Functional Disorders of the Pelvic Floor

Assessment of quality of life and management strategies

ELAINE UTOMO

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Colofon

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Functional Disorders of the Pelvic Floor
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Functionele klachten van de bekkenbodem
beoordeling van kwaliteit van leven en management strategieën

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Lieve pap, voor altijd in mijn hart.

CONTENTS

General introduction

FUNCTIONAL PELVIC FLOOR DISORDERS

Symptoms related to the dysfunction of the pelvic floor can disrupt dramatically the lives of the men and women who are affected by it. In clinical practice, functional disorders are conditions impairing the normal function and are not primarily due to a mechanical disorder or anatomical abnormality. Symptoms relating to dysfunction of the pelvic floor include involuntary loss of urine, pelvic organ prolapse, inability to control the passage of stool or flatus, and sexual dysfunction.

A few of the most commons symptoms are described:

Urinary incontinence: The loss of bladder control leading to persistent involuntary urine leakage is a symptom caused by underlying physical problems or changes, for instance after treatment of prostate cancer; an obstruction (e.g. enlarged prostate or tumor) hindering the normal flow of urine; aging of the bladder muscle resulting in a decrease of the bladder's capacity to store urine; damage of the supporting pelvic floor muscles (e.g. due to childbirth or surgery); or spinal injury (e.g. spinal cord injury, multiple sclerosis) interfering with nerve signals involved in bladder control. Different types of urinary incontinence can be distinguished, that is: stress urinary incontinence with symptoms of occasionally leaking of urine upon elevated abdominal pressure (for instance during coughing or sneezing); urge urinary incontinence with symptoms of having suddenly a strong urge to urinate leading to involuntarily urine loss; or a variation of both (mixed urinary incontinence).

Pelvic floor disorders: A weakening of the muscles and ligaments supporting women's pelvic organs – including uterus, vagina, bladder, small bowel or rectum – can lead to vaginal bulging due to sliding of these organs (prolapse). Pelvic floor disorders are seen usually years after childbirth, hysterectomy, menopause, or any combination of the above. Conditions associated with pelvic floor disorders include underactive bladder, obstructed urination or urinary incontinence, constipation, obstructed defecation or fecal incontinence, and sensation of prolapse (e.g. feeling of heaviness).

Fecal incontinence: The inability to control bowel movements can cause stool (feces) to leak from the rectum unexpectedly. Fecal incontinence ranges from an occasional leakage of stool while passing gas to a complete loss of bowel control. Common causes include diarrhea, constipation, and muscle or nerve damage of the anal sphincter. The muscle or nerve damage may be associated with aging, vaginal child delivery, pelvic surgery or spinal trauma.

Sexual dysfunction: Problems in any phase of the sexual response cycle, which consists of desire, excitement, sensation of orgasm and satisfaction,[1] can cause sexual dysfunction. In both men and women the origin of sexual dysfunction can be physical

(e.g. erectile dysfunction or ejaculation problems, pelvic floor disorders), psychological (e.g. stress, anxiety, past sexual trauma), or both.

Although above described functional disorders of the pelvic floor are as a rule not life-threatening, they often limit daily activities and may significantly influence physical, psychological, and social well-being of the affected individuals.[2] In the general population - depending on age, etiology, and the definition used - urinary incontinence affects approximately 30% to 60% of women and up to 29% of men[3,4], prolapse approximately 4-15% of women[3], and fecal incontinence up to 15% of both men and women[5]. Based on the considerable prevalence and clinical consequences, functional disorders of the pelvic floor are a serious health problem.

COMPONENTS OF ADEQUATE PATIENT CARE

Outcomes are fundamental measures of success in health care to provide for adequate patient care. When evaluating the efficacy of patient care for those with pelvic floor dysfunction, studies focused on measurable (objective of semi-objective) symptoms are useful to estimate disease burden and the effect of medical interventions. Examples of such *traditional outcome measures* are parameters obtained from urodynamic studies, voiding diaries and ultrasound results. *Patient reported outcome measures* (PROMs) are often standardized, validated questionnaires which are completed by patients to measure their perception of their functional well-being and health status.[6] PROMs represent patient's health-related quality of life (HRQOL), and provide as such another dimension of the efficacy of various treatment modalities than traditional outcome measures. Moreover, PROMs could assist to manage patient expectation and improve patient satisfaction.[7] Consequently, PROMs can be used to support shared decision-making, communication, and appropriate evaluation of individual treatment success. As physicians tend to assess superior valuation to traditional outcome measures - whereas patients tend to evaluate higher importance to the impact of symptoms on quality of life[8] - the use of PROMs has the potential to narrow the gap between the clinician's and patient's view of clinical reality and help tailor treatment plans to meet the patient's personal preferences and needs[9].

Considering that generic HRQOL measures lack sensitivity to the unique aspects of a specific disease[10,11], disease-specific HRQOL measures are regarded to be more applicable in capturing the impact of a particular disease. Suitable disease-specific PROMs have been developed and are currently recommended by the International Continence Society.[12] However, these measure tend to be English, and a measure that is valid and reliable for a particular language and culture may not prove so when used in a different population.[13] The reliability, validity, and responsiveness of a measure for

the population of interest can be assessed by testing its psychometric measurement properties.[14] So far, short, practical, and validated Dutch PROMs evaluating HRQOL of men and women with functional disorders of the pelvic floor are lacking.

Another essential contribution to adequate patient care is *evidence based medicine*. Evidence based medicine is the "conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients".[15] To address a specific research or clinical question, systematic reviews collects all evidence according to pre-specified eligibility criteria using systematic methods to minimize bias. By integrating individual clinical expertise with the best available external clinical evidence from systematic research clinical practice guidelines can be developed. To optimize treatment and promote more uniform approaches to specific aspects of patient care, evidence based guidelines are required. An example of such evidence based guidelines is the European Association of Urology (EAU) Guidelines on Neuro-Urology.[16]

AIMS OF THIS THESIS

This thesis focuses on evaluating functional disorders of the urogenital tract in men and women, using traditional outcome measures along with PROMs. In this thesis, we aim to:

1. Evaluate the urodynamic changes in patients treated with Adjustable Continence Therapy for men (ProACT) for post-prostatectomy incontinence and to explore the clinical and urodynamic preimplantation parameters as predictors of clinical outcome.
2. Develop linguistically adapted and psychometrically adequate PROMs for assessing symptom distress and HRQOL of urogenital functional disorders in Dutch.
3. Assess the effectiveness of different surgical therapies for the treatment of functional bladder outlet obstruction in adults with neurogenic bladder dysfunction.
4. Compose Dutch multidisciplinary guidelines consisting of guiding decisions and criteria regarding diagnosis, management, and treatment in patients with neurogenic bladder.

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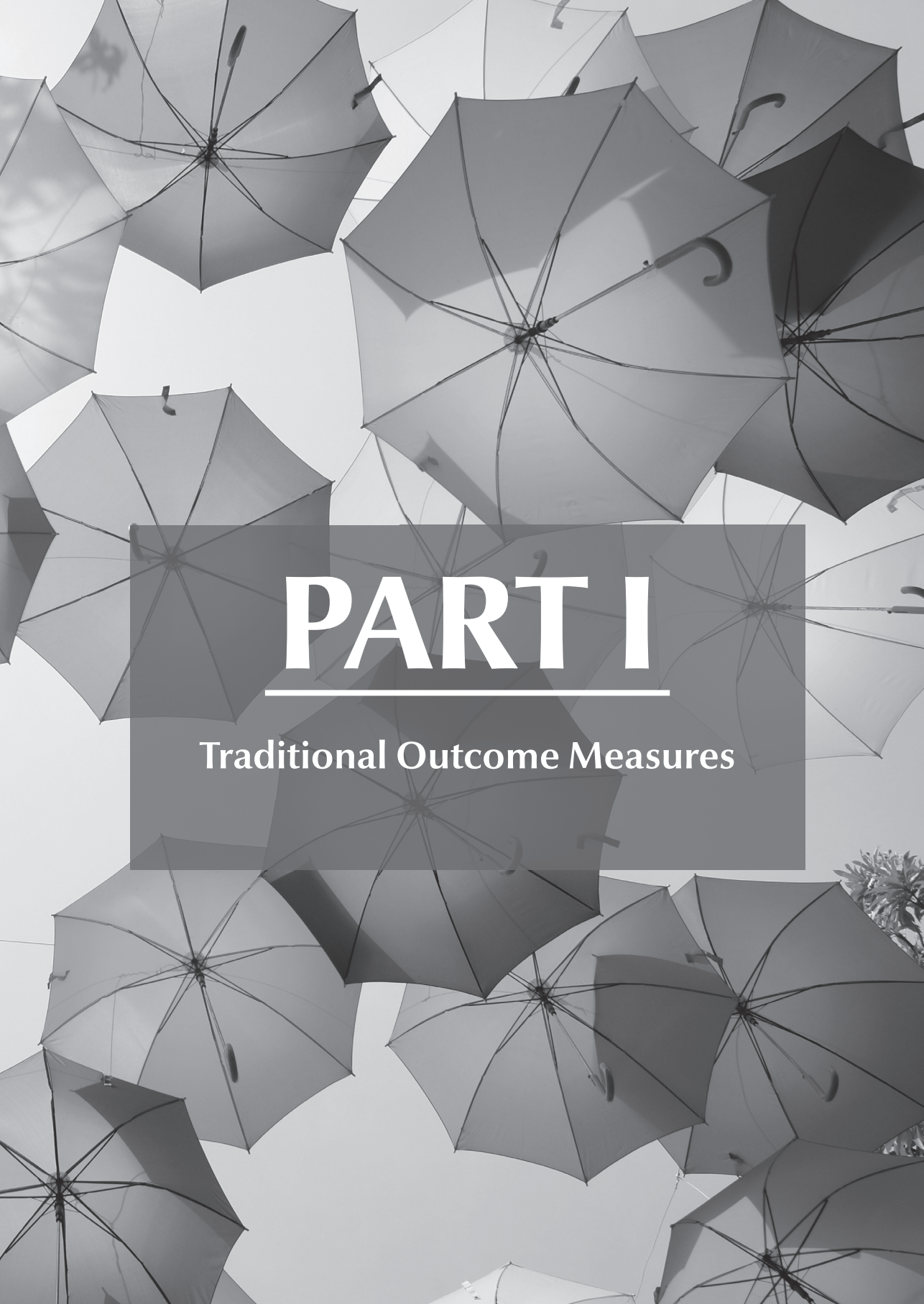

PART I

Traditional Outcome Measures

Chapter 1

Urodynamic effects of volume-adjustable balloons for treatment of post-prostatectomy urinary incontinence

Elaine Utomo, Jan Groen, Irene H. Vroom,
Ron van Mastrigt and Bertil F. M. Blok

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ABSTRACT

Aims

To evaluate the urodynamic changes in patients treated with Adjustable Continence Therapy for men (ProACT) for post-prostatectomy incontinence and to explore the clinical and urodynamic pre-implantation parameters as predictors of clinical outcome.

Methods

Patients underwent urodynamic studies before and after ProACT implantation. ProACT was considered successful if patients used none or 1 dry precautionary pad and non-successful if the patient reported ≥1 wet pad/day. The pre- and post-implantation assessments were retrospectively compared within and between the success and non-success groups. Multivariate logistic regression analysis was performed to investigate the association between the pre-implantation variables and the clinical outcomes of ProACT implantation.

Results

A total of 49 patients were included, 37 with successful and 12 with non-successful clinical outcome. Post-implantation urodynamic studies were performed a median of 9 months after ProACT implantation. In the successfully treated patients, maximum free flow rate, bladder contractility index, maximum of bladder contractility parameter w, and bladder voiding efficiency were significantly lower after implantation. The detrusor pressure at maximum flow rate, post void residual urine volume, and bladder outlet obstruction index were significantly higher. A longer duration of urinary incontinence, the use of >5 pads daily, and a smaller cystometric bladder capacity were all independently associated with non-successful clinical outcome after ProACT implantation.

Conclusion

ProACT implantation with successful clinical outcome resulted in greater urethral resistance during voiding and reduced bladder contraction strength. A longer duration of incontinence, the use of >5 pads daily, and a smaller cystometric bladder capacity were independent predictors of unsuccessful clinical outcomes, suggesting ProACT implantation should be considered sooner, rather than later, after conservative treatment of post-prostatectomy incontinence has failed.

INTRODUCTION

Men who have undergone radical prostatectomy (RP) for prostate cancer are at risk of stress urinary incontinence (SUI). The prevalence of post-prostatectomy incontinence (PPI) has ranged from 2% to nearly 60%.[1] PPI is a distressing disorder that affects men's quality of life[2] and often requires treatment. Surgical techniques can be considered if conservative treatment fails. Implantation of an artificial urinary sphincter (AUS) has been the reference standard surgical treatment of PPI; however, recently, less-invasive and less-expensive techniques have been introduced as potential alternatives.[3]

The Adjustable Continence Therapy system for men (ProACT, Uromedica, Minneapolis, MN) is a minimally invasive implant, consisting of 2 volume-adjustable balloons.[4] These balloons are placed paraurethrally just beneath the bladder neck. Each balloon is attached by a conduit to a port placed subcutaneously in the scrotum, allowing for separate volume adjustments after the initial implantation using an isotonic solution of contrast medium. The balloon volume is adjusted to create bilateral urethral compression. The balloons are adjusted until continence is achieved and the optimal balance between bladder emptying and continence has been obtained.

The clinical results of ProACT reported during the past few years have shown dry or improved rates ranging from 56% to 92%.[5-7] Nevertheless, the urodynamic working mechanism of ProACT implantation is not fully understood and needs additional elucidation. For instance, it is unknown whether the bilateral compression causes greater urethral resistance, and whether this resistance affects bladder contractility.

Various studies have shown acceptable to good reproducibility in diagnosing bladder outlet obstruction using urodynamic studies (UDS), varying from same session testing[8-10] to repeated testing within 6 months.[8,10] We, therefore, performed a study to evaluate the urodynamic changes in patients treated with ProACT for PPI and to explore which clinical and urodynamic pre-implantation parameters are associated with the non-successful clinical outcome of ProACT implantation.

METHODS

Since May 2007, ProACT balloons have been used at our department for the treatment of male SUI. The ProACT implantation procedure has been previously described.[4] In brief, using fluoroscopic guidance, 2 balloons were placed immediately adjacent to the urethra at the level of the bladder neck by way of 2 small incisions in the perineum. Each balloon was then filled with 1 mL of isotonic contrast medium solution. All implantation procedures were performed by the same surgeon. The patients were assessed after implantation at regular 3-4-week intervals. If required, we adjusted the balloon

volume with a maximum of 1 mL in each balloon per visit by way of the subcutaneous port sited in the scrotum.

The local ethical committee approved the retrospective analysis of the data from all patients who had undergone Pro-ACT implantation for PPI. All patients who had undergone ProACT implantation for PPI in our clinic until June 2012 with UDS available before and after ProACT implantation, were eligible for inclusion in the present analysis. The exclusion criteria for ProACT implantation included external radiotherapy for positive margins, salvage radiotherapy for increased prostate-specific antigen levels after RP,[4,11] and bladder neck sclerosis or urethral stenosis. The data collected from the patient medical charts included date of birth, date of RP, previous treatment of SUI, the use of anticholinergics, the reported number of incontinence pads used daily (PPD) before ProACT implantation, the date of ProACT implantation, the number of ProACT balloon adjustments and total ProACT balloon volume after implantation; the reported use of PPD after Pro-ACT balloon adjustments, and a non-validated Dutch translation of the bother question[12] of the International Prostate Symptom Score[13] (IPSS-BQ). The IPSS-BQ is a single disease-specific quality-of-life question that assesses the degree to which patients find their symptoms bothersome. The score of the IPSS-BQ ranges from 0 to 6, with a greater score indicating more bother from the patient's urinary condition. Patients were defined as having "mild" urinary incontinence if the PPD usage was 1 or 2, "moderate" if it was >2-5, and "severe" if >5 or if a condom catheter was needed.

After the volume adjustments, ProACT implantation was either "successful" or "non-successful." We defined "successful" if the patient was subjectively dry (i.e., if he used 0 PPD or 1 precautionary PPD). This precautionary pad is the smallest male incontinence pad available. "Non-successful" was defined as patients reporting the use of ≥1 wet PPD. Patients were excluded if a surgical intervention, other than ProACT implantation, had occurred between the pre-implantation and post-implantation UDS, such as internal urethrotomy, an AUS was in situ, or if the patient had a neurologic disease that could affect voiding function.

Before implantation of the ProACT balloons, the UDS was performed to determine the bladder and sphincter function. This was repeated after the balloon volume adjustments were completed. The latter, post-implantation UDS was a part of the standard evaluation protocol in our clinic either to detect bladder outlet obstruction in successful patients or to evaluate the persistence of incontinence in non-successful patients (e.g., urge incontinence).

Each UDS was performed according to the International Continence Society standards[14] and included free uroflowmetry, 2 filling cystometries, and subsequent pressure-flow studies (PFS). The maximum flow rate (Q_{max}) and average flow rate were measured using a rotating disk flow meter. A 7F double-lumen transurethral catheter was used for cystometry and PFS and were left in situ during voiding. The bladder was

filled to the maximum cystometric capacity at a medium rate (50 mL/min) using filling fluid at room temperature.[14] When filling the bladder was not possible because of total incontinence, the patient was asked to manually squeeze the urethra. The intravesical pressure transducers were placed at the level of the superior edge of the pubic symphysis. The pressure was zeroed to the atmospheric pressure.

The outcome variables derived from the cystometric studies were the parameters characterizing detrusor overactivity (DO) and compliance. DO was defined as the occurrence of involuntary detrusor contractions during the filling phase of the bladder, without a lower limit for the amplitude of an involuntary detrusor contraction.[15] Compliance was calculated at cystometric capacity[15] or at 500 mL if the capacity was >500 mL. The outcome variables derived from the PFS were Q_{max}, detrusor pressure at Q_{max} ($P_{detQmax}$), and parameters of urethral resistance and bladder contraction strength. The parameter for urethral resistance was the bladder outlet obstruction index ($BOOI=P_{det.Qmax}-2*Q_{max}$).[16] The parameters for bladder contraction strength were the bladder contractility index ($BCI=P_{detQmax}+5*Q_{max}$)[16] and parameter w[17] an approximation of the power generated by the detrusor muscle per unit of bladder wall area. The maximum of w (w_{max}) and the value of w at Q_{max} (w_{Qmax}) were used as contractility parameters.[17,18] Additionally, we determined the voided volume, postvoid residual urine (PVR) volume, cystometric bladder capacity (sum of the voided and PVR volume during PFS), and bladder voiding efficiency (BVE=(voided volume/bladder capacity)*100).[16] In the case of repeated PVR measurements, we used the lowest value measured.

The measurement with the largest cystometric capacity was used to assess the filling phase. The PFS with the greatest Q_{max} was used to assess the voiding phase. Artefacts were corrected manually. The urodynamic data were analysed using AUDACT software, version 4.50 (Andromeda Medizinische Systeme GmbH, Taufkirchen, Germany).

Statistical analysis was performed using SPSS Statistics, release 20.0.0.1 (IBM, Armonk, NY). Statistical significance was defined as p <.05. The median and interquartile range (lower quartile to upper quartile) are reported for continuous data. For discrete data, counts and percentages are reported.

To assess the change in outcome before and after ProACT implantation within the success and non-success group, the Wilcoxon signed rank test was used for continuous variables and McNemar's test for categorical variables. The Mann-Whitney U test was used to compare the pre-implantation urodynamic parameters between the success and non-success groups for continuous variables and the chi-square test for categorical variables.

Multivariate logistic regression analysis was conducted using the backward likelihood ratio method. All pre-implantation patient characteristics and pre-implantation urodynamic parameters with p <.05 on univariate analysis were considered in building the model to investigate the association between these variables and a non-successful outcome.

RESULTS

From May 2007 to June 2012, 81 patients with PPI received implantation of the ProACT balloons (Figure 1.1). At the last follow-up visit, 8 patients were still in the process of post-implantation balloon adjustments and had not yet undergone the post-implantation UDS. Another 8 patients had their ProACT devices removed because of infection (n=2), dislocation of the device (n=3), or tissue erosion (n=3). A final 8 patients met an exclusion criterion: 2 had undergone surgical intervention between the pre-implantation and post-implantation UDS, 3 had an AUS in situ, and 3 developed a neurologic disease (2 experienced a stroke and 1 developed Alzheimer's disease). Thus, 49 of the 57 patients (86%) completed the post-implantation UDS and were included in our study.

ProACT was the first surgical SUI therapy after failed pelvic floor muscle training in 38 of the 49 patients (78%). Of the 49 patients, 15 (31%) had mild, 18 (37%) had moderate, and 16 (33%) had severe SUI.

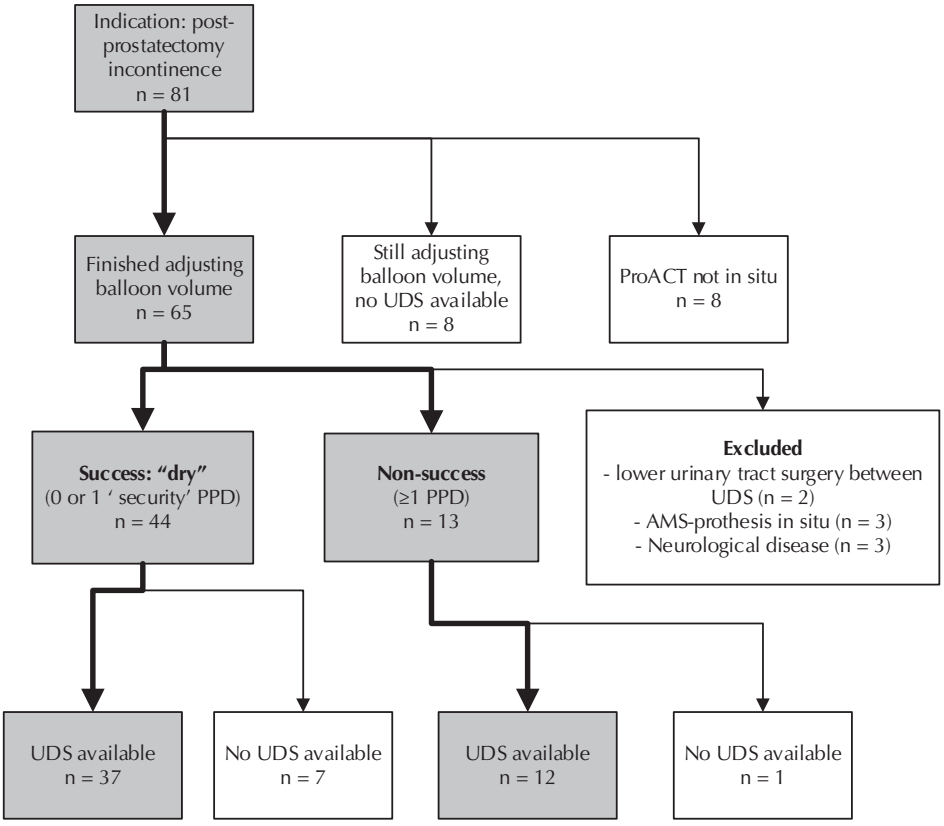

Figure 1.1 Flowchart of inclusion process of ProACT patients
Abbreviations: *UDS* urodynamic studies, *PPD* incontinence pads per day

After implantation, none of the 49 included patients had symptoms of persistent urinary retention or symptomatic urinary tract infection. ProACT implantation was successful in 37 patients and not successful in 12, although 4 of these 12 patients had a reduction in PPD of ≥50%. These 12 unsuccessfully treated patients had either received the maximal allowed filling volume (n=8) or had noted absolutely no improvement after several adjustments (n=4). The success rate was 93% (14 of 15) in patients with mild incontinence, 83% (15 of 18) in those with moderate incontinence, and 50% (8 of 16) in those with severe incontinence.

The patient characteristics were compared between the success and non-success groups (Table 1.1). In the non-success group, the median age was 7.5 years older (p=.001), the median duration of urinary incontinence was 7.5 years longer (p=.001), and the incontinence was more severe (p=.01). As expected, the patients in the non-success group had a greater balloon volume (p<.001) and a greater IPSS-BQ score (p<.001) than did the patients in the success group.

The urodynamic outcomes before and after implantation for the successful and unsuccessful groups are listed in Table 1.2. The pre-implantation cystometric bladder capacity and free flow Q_{max} were significantly lower in the non-success group than in the success group. The other parameters, including BCI (p=.06), were not significantly different between the 2 groups.

In the non-success group, only the average flow rate was significantly lower after implantation. We did not find any other significant differences between the urodynamic parameters before and after ProACT implantation. In the success group, 8 patients (22%) had DO during the pre-implantation UDS, of whom 3 continued to have DO during the post implantation UDS. Also, 7 patients showed de novo DO with threshold volumes of ≥250 mL. No statistically significant differences were found before and after implantation in the proportion of patients with DO, the cystometric bladder capacity, or bladder compliance (p=.77, p =.31, and p=.79, respectively). The urethral resistance during voiding, as described by BOOI, was significantly greater after implantation (p <.001). The BOOI increased in most patients after implantation (Figure 1.2). In 3 patients, the BOOI was lower after ProACT implantation. Four patients had a post-implantation BOOI >40 but had no clinical symptoms of symptomatic urinary retention or persistent urinary tract infection. The maximum free flow rate and average flow rate were significantly lower after implantation, and the PVR volume was significantly greater, with a median of 0 mL (interquartile range 0-25). Five patients (14%) had a PVR volume >100 mL. Consequently, the bladder voiding efficiency was significantly lower after implantation (p<.001). The proportion of patients who had to strain during the PFS (35%) was not significantly increased after implantation (32%). The bladder contraction strength, characterized by the BCI and w_{max}, was significantly lower after implantation (p<.001 and p=.004, respectively); however, w_{Qmax} was not (p=.09).

Table 1.1 Patient characteristics

Characteristic	Success (n=37)	Non-success (n=12)	*p*-value*
Before implantation			
Age, years	68.0 (63.5 – 72.5)	75.5 (69.5 – 79.8)	.001
Previous treatment of SUI			.22
Only PFMT	29 (78%)	9 (75%)	
Bulking agent	0 (0%)	1 (8%)	
AUS	2 (5%)	1 (8%)	
Unknown	6 (16%)	1 (8%)	
Urinary incontinence duration, years	3.0 (1.0 – 6.0)	10.5 (6.0 – 13.5)	.001
Incontinence severity			.01
Mild (1 or 2 PPD)	14 (38%)	1 (8%)	
Moderate (>2 to 5 PPD)	15 (41%)	3 (25%)	
Severe (>5 PPD)	8 (22%)	8 (67%)	
After implantation and balloon adjustments			
Interval between ProACT and UDS, months	7.0 (5.0 – 9.0)	13.5 (10.3 – 22.0)	<.001
Interval between last balloon adjustment and UDS, months	3.0 (2.0 – 3.0)	2.5 (1.0 – 4.0)	.87
Balloon volume, mL	4.0 (2.9 – 6.0)	7.5 (6.5 – 8.9)	<.001
Adjustments, number	3.0 (2.0 – 5.5)	6.0 (5.0 – 7.0)	.002
Incontinence severity			*NA*
No incontinence (0 or 1 security PPD)	37 (100%)	0	
Mild (1 or 2 PPD)	0	4 (33%)	
Moderate (>2 to 5 PPD)	0	2 (17%)	
Severe (>5 PPD)	0	6 (50%)	
IPSS-BQ "If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?"			<.001
Delighted	13 (35%)	0 (0%)	
Pleased	13 (35%)	0 (0%)	
Mostly satisfied	5 (14%)	1 (8%)	
Mixed	2 (5%)	5 (42%)	
Mostly dissatisfied	1 (3%)	1 (8%)	
Unhappy	1 (3%)	4 (33%)	
Terrible	1 (3%)	1 (8%)	
Missing	1 (3%)	0 (0%)	

Abbreviations*: AUS* artificial urinary sphincter, *IPSS-BQ* International Prostate Symptom Score bother question, *NA* not applicable, *PFMT* pelvic floor muscle training, *PPD* incontinence pads per day, *RP* radical prostatectomy, *UDS* urodynamic studies

Data in median (lower quartile to upper quartile) or number (%)
*Mann-Whitney U test used for continuous variables and Chi-square test for categorical variables.

Table 1.2 Urodynamic data before and after ProACT implantation

Parameter	Success-group (n=37)			Non-success group (n=12)			
	Before implantation	After implantation	*p*- value*	Before implantation	After implantation	*p*-value*	*p*-value**
Storage							
Cystometric bladder capacity (mL)	514.0 (416.5 – 574.0)	504.0 (396.5 – 607.0)	.31	384.5 (257.0 – 425.5)	367.5 (278.8 – 528.8)	.27	.003
Compliance (mL/cmH_2O)	34.9 (18.6 – 94.0)	44.3 (22.1 – 70.8)	.79	26.5 (16.4 – 46.4)	17.1 (12.3 – 24.7)	.16	.33
DO (no.)	8 (22%)	10 (27%)	.77	5 (42%)	7 (58%)	.50	.17
Voiding							
Straining (no.)	13 (35%)	12 (32%)	.13	5 (42%)	7 (58%)	.22	.91
Free flow Q_{max} (mL/s)	18.2 (11.7 – 24.9)	9.9 (6.9 – 14.1)	<.001	9.6 (6.0 – 19.7)	5.5 (3.3 – 8.4)	.07	.01
Q_{ave} (mL/s)	10.5 (6.2 – 13.7)	5.1 (3.2 – 6.8)	<.001	5.7 (3.7 – 12.1)	2.9 (1.7 – 4.9)	.03	.12
P_{det} at Q_{max} (cm H_2O)	25.9 (19.1 – 31.5)	38.6 (31.4 – 46.2)	<.001	25.3 (13.8 – 42.9)	34.3 (11.4 – 44.4)[a]	.33	.85
PVR (mL)	0 (0 – 0)[a]	0 (0 – 25)	.005	0 (0 – 0)	0 (0 – 0)	.18	.56
Urethral resistance							
BOOI	-7.4 (-22.3 – 4.2)	23.1 (6.0 – 34.3)	<.001	-0.9 (-12.8 – 27.6)	16.2 (-23.7 – 34.5)[a]	.16	.19
Bladder contraction strength							
BCI	107.3 (81.9 – 135.8)	81.2 (68.3 – 102.8)	<.001	85.5 (63.5 – 104.1)	72.7 (68.3 – 100.4)[a]	.96	.06
w_{max} (W/m^2)	9.9 (7.1 – 14.9)	7.1 (6.0 – 11.1)	.004	8.4 (7.2 – 10.2)	8.3 (5.9 – 11.0)[a]	.53	.30
w_{Qmax} (W/m^2)	6.2 (5.0 – 8.9)	6.0 (5.0 – 6.9)	.09	7.0 (3.4 – 7.9)	5.1 (3.7 – 7.1)[a]	.72	.74
Bladder emptying function							
BVE (%)	100.0 (94.7 – 100.0)	80.0 (56.6 – 100.0)	<.001	97.3 (93.3 – 99.9)	95.4 (88.8 – 100.0)	.29	.14

Abbreviations*: BCI* Bladder Contractility Index, *BOOI* Bladder Outlet Obstruction Index, *BVE* Bladder Voiding Efficiency, *DO* detrusor overactivity, *PVR* post-void residual (urine volume), $P_{det}Q_{max}$ detrusor pressure at maximum flow-rate, Q_{ave} average flow-rate, Q_{max} maximum flow-rate, w_{max} maximum of bladder contraction strength parameter w , w_{Qmax} bladder contraction strength parameter w at Q_{max}

Data are presented as median (lower quartile – upper quartile) or number (%)

*Wilcoxon signed rank test used for continuous variables and McNemar's test for categorical variables to assess the changes in outcome before and after ProACT implantation.

**Statistical significances of pre-implantation variables between success and non-success groups explored using Mann-Whitney *U* test for continuous variables and Chi-square test for categorical variables.

[a] missing data for 1 patient

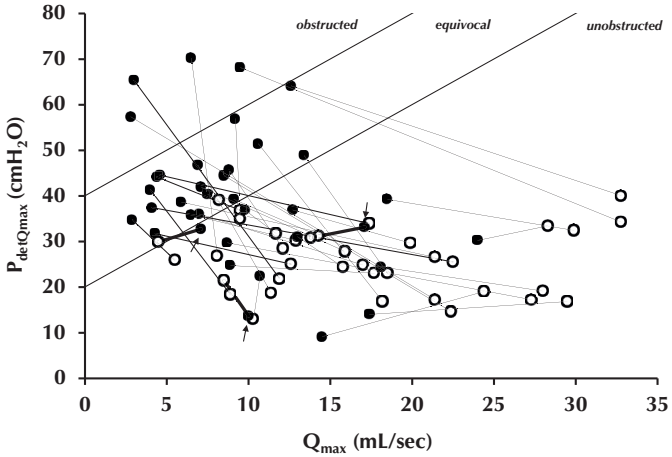

Figure 1.2 Graph showing detrusor pressure at maximum flow rate ($P_{det}Q_{max}$) and maximum flow rate (Q_{max}) before (open circles) and after (black circles) implantation of Adjustable Continence Therapy for men (ProACT). Bold lines and arrows indicate that bladder outlet obstruction index was lower after ProACT implantation.

Multivariate logistic regression analysis was performed to explore both the clinical and the urodynamic pre-implantation parameters as predictors of outcome. A longer duration of urinary incontinence (p=.007), severe incontinence (p=.02), and smaller cystometric bladder capacity (p=.05) were all independently associated with a non-successful outcome of ProACT implantation (Table 1.3). Patient age and free flow Q_{max} were not independently associated with the clinical outcome.

Table 1.3 Results of multivariate analysis for non-successful outcome

	Odds ratio	**95% CI**	***p*-value**
Duration of incontinence, *each year*	1.83	1.17 – 2.83	.007
Incontinence severity			
Mild (1 or 2 PPD)			Reference
Moderate (>2-5 PPD)	1.55	0.06 – 39.41	.79
Severe (>5 PPD)	136.42	2.10 – 9075.82	.02
Cystometric bladder capacity, *each 10 mL*	0.91	0.82 – 1.0	.05

Abbreviations: *CI* confidence interval, *PPD* incontinence pads per day, *RP* radical prostatectomy

Candidates for inclusion in the model: age, duration of urinary incontinence, severity of incontinence, maximum free flow-rate (Q_{max}), cystometric bladder capacity

DISCUSSION

The present study was designed to describe the urodynamic changes after implantation of ProACT for PPI. Our results have shown that successful treatment with ProACT increased urethral resistance and could affect the parameters of bladder contraction strength. In the successfully treated patients, a clear shift could be seen from the unobstructed area toward the equivocal and—to a lesser extent—to the obstructed area of the provisional International Continence Society nomogram (Figure 1.2). Nevertheless, no signs of clinical obstruction were found, because the proportion of patients who had to strain during voiding did not differ after ProACT implantation, and none of our patients had persistent urinary retention or symptomatic urinary tract infections during our follow-up period. Also, treatment success was demonstrated by patient-reported PPD use and IPSS-BQ, both important for quality of life. In 3 patients, the BOOI was lower after implantation, although the absolute differences were small and did not result in a clear change in the BOOI category assignments (Figure 1.2).

The BCI and w_{max}, representing bladder contractility, were significantly lower after ProACT implantation with a successful outcome. Several explanations are possible for this unexpected observation. First, the bladder can use its muscle contractility to generate a high pressure at low flow rate or a high flow rate at a low pressure.[19] Therefore, a contractility parameter should combine these 2 properties in an equation, such that when the muscle contractility does not change but the balance between the pressure and flow rate changes from external causes (e.g., a change in urethral resistance), the contractility parameter would remain constant. It might be that in the equations that define w_{max} and BCI, the decrease in Q_{max} caused by the balloon volume is not adequately compensated by the accompanying increase in $P_{detQmax}$. This would result in a decrease in contractility parameter value, which would not represent a true decrease in muscle contractility. Second, in patients with urethral obstruction from benign prostatic hyperplasia, the bladder contractions might slowly decline prematurely, leaving a PVR volume.[20] This decline could cause a lower w_{max}. It is likely that the decline does not affect the value of w at Q_{max} because the value of w at Q_{max} is usually attained earlier during the course of micturition than is w_{max}. This was also observed in our group. Parameter w_{Qmax} was not significantly lower after ProACT implantation. Third, it is physiologically plausible that our finding of lower bladder contraction strength could be caused by the decreased Q_{max} owing to the urethrovesical reflex. This reflex is responsible for the maintenance of the detrusor contraction in the normal bladder.[21] The reduced urine flow after ProACT implantation could thus lead to reduced stimulation of the bladder and, consequently, to a decreased bladder contraction strength. For these reasons, the lower bladder contraction strength we found could have resulted

from an inadequacy of the equation used to estimate the bladder contractility in urinary incontinence or might have a physiologic explanation.

Our second objective was to explore the clinical and urodynamic pre-implantation parameters as predictors of a non-successful outcome after ProACT implantation. A longer duration of urinary incontinence and severe incontinence (>5 PPD) were independent clinical predictors of a non-successful outcome. Possibly, scarred tissue around the neobladder neck from RP becomes less distensible as it ages. Consequently, inflation of the balloons might not result in sufficient urethral compression. Perhaps, ProACT treatment should be considered sooner, rather than later, after conservative treatment of PPI has failed. Patients with severe incontinence were more likely to have an unsuccessful outcome after Pro-ACT implantation than patients with either mild or moderate incontinence. Still, 50% of patients with severe PPI achieved continence with ProACT implantation. ProACT implantation has been suggested as a part of a "step-up" approach[22] before opting for AUS, which can be considered in the case of more severe incontinence. Of the urodynamic parameters, only a smaller pre-implantation cystometric bladder capacity was independently associated with non-success. This finding is in line with the results from Warner et al[23] on the urodynamic effects of transobturator male slings in the treatment of SUI. They also found that a small bladder capacity might be a predictor of an unsuccessful outcome.[23]

DO is a urodynamic diagnosis and is not necessarily symptomatic or clinically relevant. Therefore, only patients who experienced urgency in everyday life were treated with anticholinergic agents. Of the 3 patients who continued to have DO after implantation, 2 were treated with anticholinergic agents, the third patient had a threshold volume of 500 mL and no urge symptoms in daily life. Of the 7 patients had de novo DO, only 1 required treatment with anticholinergic agents; the remaining 6 patients were asymptomatic and did not need treatment. The "de novo" DO might have been already present but missed by the UDS before ProACT implantation.[24,25]

Various studies on the operative and clinical results of ProACT implantation have been published.[4,5,22,26,27] These studies were all cohort and/or feasibility studies, and our study focused on the urodynamic outcomes. Although some studies have evaluated leak point pressures and uroflowmetry,[5,26] important urodynamic outcomes of ProACT implantation such as urethral resistance and bladder contraction strength have never before been evaluated after implantation.

The limitations of our study included the use of a non-validated IPSS-BQ and the lack of a cough stress test as outcome measures. Although other ProACT studies used the same classification for incontinence severity,[27-30] it might be somewhat arbitrary, because it can vary by merely volume intake. The relatively short follow-up and small number of patients were other limitations of our study.

Still, to our knowledge, ours is the first study to review the urodynamic changes after ProACT implantation. Our results have provided a clear impression of the increased urethral resistance due to the paraurethrally placed balloons to achieve continence. Studies with longer follow-up are needed to determine the effects of chronically increased urethral resistance on bladder function from ProACT implantation. For now, individual follow-up is important to achieve the right balance between patient satisfaction and urethral resistance.

CONCLUSION

Our data have suggested that urethral resistance is increased to achieve continence with ProACT implantation without symptoms of clinical bladder outlet obstruction. We also found a decreased bladder contraction strength after continence was achieved with Pro-ACT, which could be either an artefact or part of a physiologic phenomenon. A longer incontinence duration, severe incontinence (defined by the use of >5 PPD), and a smaller cystometric bladder capacity were important predictors of a non-successful clinical outcome in patients undergoing ProACT implantation. Therefore, ProACT treatment should be considered sooner, rather than later, after conservative treatment of PPI has failed.

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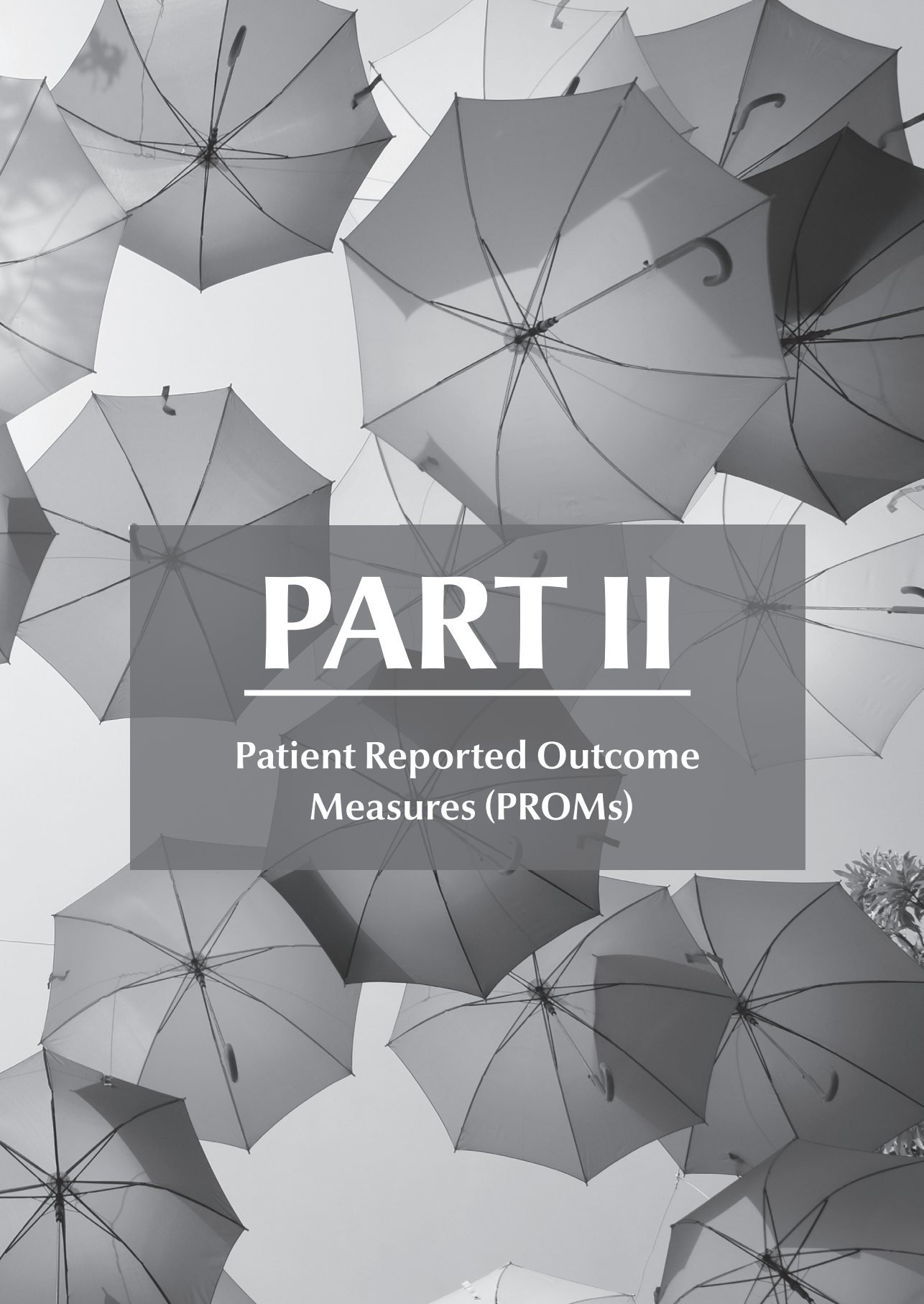

PART II

Patient Reported Outcome Measures (PROMs)

Chapter 2

Validation of the Urogenital Distress Inventory (UDI-6) and Incontinence Impact Questionnaire (IIQ-7) in a Dutch Population

Elaine Utomo, Ida J. Korfage, Mark F. Wildhagen, Anneke B. Steensma, Chris H. Bangma and Bertil F.M. Blok

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ABSTRACT

Aims

The Urogenital Distress Inventory (UDI-6) and Incontinence Impact Questionnaire (IIQ-7) assess symptom distress and the impact on daily life of urinary incontinence. The UDI-6 has not been validated before in males. Our aim was to validate the UDI-6 and IIQ-7 in Dutch men and women.

Methods

The translation to Dutch followed standardized procedures. We validated the IIQ-7 with and without an additional gender-neutral item (IIQ-SF). Adults with urinary incontinence for at least three months, completed the measures at inclusion; one week after inclusion to evaluate the test-retest reproducibility; and six months after inclusion with the addition of the RAND-36 health transition item to assess responsiveness and interpretability. To assess the discriminate ability, a reference population was enrolled. To assess construct validity, the urodynamic diagnosis was used.

Results

Questionnaire data of 160 patients were analysed. Patients reported more symptoms and bother than the reference population (p<.001). The internal consistency was good in the IIQ-SF baseline scores (Cronbach's alphas 0.86-0.92); though moderate in the UDI-6 (Cronbach's alphas 0.44-0.66). Both measures showed good reproducibility at the test-retest (Intraclass Correlations Coefficients 0.75-0.85). Construct was adequate with 75% confirmed hypotheses of urodynamic data with measure scores. The measures were responsive after treatment with smaller measurement errors than the minimal important change. No floor or ceiling effects were observed in baseline data.

Conclusion

The Dutch UDI-6 and IIQ-7 are reliable, valid, and responsive instruments for assessing symptom distress of urinary incontinence and its impact on daily life in both men and women.

INTRODUCTION

Urinary incontinence (UI) affects approximately 30% to 60% of women and 1% to 39% of men, depending on age, aetiology, and the definition of incontinence used.[1] Various measures are available to assess the impact of UI on health related quality of life (HRQOL). Generic HRQOL measures lack sensitivity to the unique aspects of a specific disease[2,3], therefore disease-specific HRQOL measures can be considered more applicable in capturing the impact of a specific disease such as UI. These measures may also serve to assess the impact of treatment on UI and to facilitate future research in incontinence treatment.

The urogenital distress inventory (UDI) and incontinence impact questionnaire (IIQ) were both developed to assess the impact of UI on HRQOL.[4,5] Short versions of the UDI and IIQ, UDI-6 and IIQ-7, were developed to reduce the respondents' burden.[6] The UDI-6 and IIQ-7 are both "A grade" recommended by the Fourth International Consultation on Incontinence.[7] A measure that is valid and reliable for a particular language and culture may not prove so when used in a different population.[8] The UDI and IIQ long forms were previously translated and revisited in Dutch[9], and are nowadays widely used in the Netherlands in urogynecology clinical practice and research.[10-12] An unvalidated Dutch translation of the UDI-6 and IIQ-7 is also commonly used.[13,14] However, by using a questionnaire without the measurement properties tested[15], it remains unknown whether a reliable, valid, and responsive measure for the population of interest is used. Though not yet in Dutch, the UDI-6 and IIQ-7 have been translated and validated in other languages.[16-22] Although both measures[6] were developed for female patients, we aimed to validate these in both sexes. Unlike the UDI-6, the IIQ-7 has earlier been validated in men.[23] The objective of this study was to validate the UDI-6 and IIQ-7 in Dutch to provide a useful evaluation tool for the use in both men and women suffering from UI.

METHODS

This observational study was conducted at a tertiary Urology and Gynaecology centre as part of a larger validation study of HRQOL pelvic floor measures. The study was approved by the Institutional Ethical Committee (MEC-2008-376).

Questionnaires

The UDI-6 is a six item symptom inventory, specific to symptoms associated with lower urinary tract dysfunction, and combines information on irritative, stress and obstructive/discomfort symptoms.[6] The IIQ-7 is a seven item life-impact assessment

instrument specific to UI, and covers separate domains of physical activity, travel, social/relationships, and emotional health.[6] Both measures were developed for self-administration and are intended to be used in combination. Patients rated how much they experience impaired function of UI and the extent to which this UI affects their daily functioning with four response options per item ((0) "not at all"; (1) "slightly"; (2) "moderately"; (3) "greatly"). We maintained the scoring procedure as described by the original developer: if more than two items are missing, a total score is not to be calculated.[6] The mean score of items is multiplied by 33 1/3 to convert to a 0–100 scale.[6] Higher scores indicates more symptom distress (UDI-6), or more impact on daily life (IIQ-7).

In consultation with the original developer we concluded that the UDI-6 had good face validity concerning male patients, i.e. the questions seemed plausible, relevant, and to span the domain adequately. In the IIQ-7 however, the item addressing household chores ("Has urine leakage affected your ability to do household chores (cooking, housecleaning, laundry)?") might be related more to females. Therefore, based on the factor loadings of the IIQ long form[4] and as suggested by the original developer, we added a question about employment ("Has urine leakage affected your employment (work) outside the home?"). The addition of this "employment" item resulted in three versions of the IIQ-7 completed by both men and women: (1) *IIQ-7 original* [6]*;* (2) *IIQ-7 adjusted*; in which the item addressing "household chores" was substituted by the item "employment" ("Has urine leakage affected your employment (work) outside the home?")[4] (3) *IIQ-8*; in which the item "employment" was added to the original IIQ-7. We refer to these versions as the IIQ-short forms (IIQ-SF). Referring to the IIQ long form[4], the "employment" item was part of the "travel" domain while the "household chose" item was part of the "physical activity" domain. However, unlike the IIQ long form, the IIQ-7 does not contain separate domain scores,[6] and therefore only total scores of the IIQ-SF are reported.

Linguistic Validation

The translation of the measures to Dutch followed standardized forward-backward procedures[8]: three independent forward translations, and backward translation by a native speaker. The Dutch versions of the measures were tested in 10 patients with UI, where potential problems were explored and discussed guided by a checklist. UI was defined according to the International Continence Society, thus "the complaint of any involuntary leakage of urine".[24] As a result, the lay-out was adapted to clarify the instructions on how to indicate the chosen answer. Several minor problems were identified which did not indicate a need to adapt the content. The Dutch versions of UDI-6 and IIQ-SF were then finalized (See 'Vragenlijsten').

Study population and study design

Inclusion criteria included males and females aged 18 years or older, symptoms of UI for at least three months, and fluent and literate in the Dutch language. Exclusion criteria were symptomatic urinary tract infections, neurologic diseases (except diabetic neuropathy), active malignant tumours, dementia, and mental retardation. At the initial physician office visit, the treating physician explained the study to all consecutive patients potentially eligible for inclusion. The physician logged the name and gender of patients who were interested in participation, and gave an information package including two sets of questionnaires. These patients were phoned by the principal investigator for further explanation, and were instructed to complete the first set of questionnaires (baseline) at home, and to return it by postal mail directly after completion, together with a signed informed consent form. The second set of questionnaires were completed one week after baseline, and returned by postal mail. Six months after baseline, patients received through postal mail a third set of questionnaires to be completed at home and returned by postal mail. Age and education were documented through the questionnaire. Educational level was classified as "low" (primary school), "intermediate" (high school) or "high" (college or university degree). The test-retest period of one week between the repeated administrations was long enough to prevent recall, though short enough to ensure that clinical change had not occurred. During this period no treatment was initiated or changed. Given the observational nature of the study, the treating physician was free to perform any investigation (e.g. urodynamic studies) and prescribe any treatment after completion of the second round of questionnaires, for individual patient care.

The third questionnaire included the health transition item of the RAND 36-Item Health Survey (RAND-36-HTI)[25], in which patients were asked to score the change in their general health compared to one year ago. The response options were: (1) 'much better'; (2) 'a little better'; (3) 'same'; (4) 'a little worse'; (5) 'much worse'. This RAND-36-HTI was used as the anchor (external criterion)[26] for the evaluation of responsiveness and interpretability.

Urodynamic studies

Because of the observational nature of this study, multichannel urodynamic testing was only carried out if indicated according to the standard evaluation protocol of our clinic as recommended by the Fourth International Consultation of Incontinence Recommendations.[27] Urodynamic testing was performed according to the International Continence Society standards.[28] Using urodynamic studies, patients were categorized into groups: no urodynamic abnormality detected, stress urinary incontinence (SUI), detrusor overactivity (DO), and detrusor underactivity. When mixed SUI/DO incontinence was detected the type of treatment patient received during follow-up determined the classification for analysis.

Reference group

Baseline data from a reference group were collected using a random subsample of an ISO-certified (ISO 26362) Dutch panel[29]. This subsample was stratified by gender, age, educational level and residential area, and therefore representative for the Dutch population above the age of 18. No medical data was available for this internet panel. A total of 450 panel participants were invited in order to meet our targeted sample size of 250 participants.

Statistical methods

Statistical analysis was conducted using IBM® SPSS-software 20.0. Statistical significance was defined as *p*-value <.05. The mean and standard deviation (SD) are reported for continuous data. For discrete data, the count and percentage are reported.

As described by the original developer[6], if one or two items were missing in the measures, they were replaced by the average of the respondent's observed values (unconditional mean imputation[30]). The UDI-6 or IIQ-7 scores were not calculated if more than two items were missing.[6]

To assess the differences between patient and reference group, the Student's T-test was used for continuous data, and the Chi-squared test for categorical variables. General linear models were used to compare measure scores, controlling for variables that differed significantly between the patient and reference group in univariate analysis.

The Welch's F statistic was used as a single global test to compare means between groups, since homogeneity was not assumed. In case of significant differences between means, pairwise comparisons using Games-Howell analysis was performed.

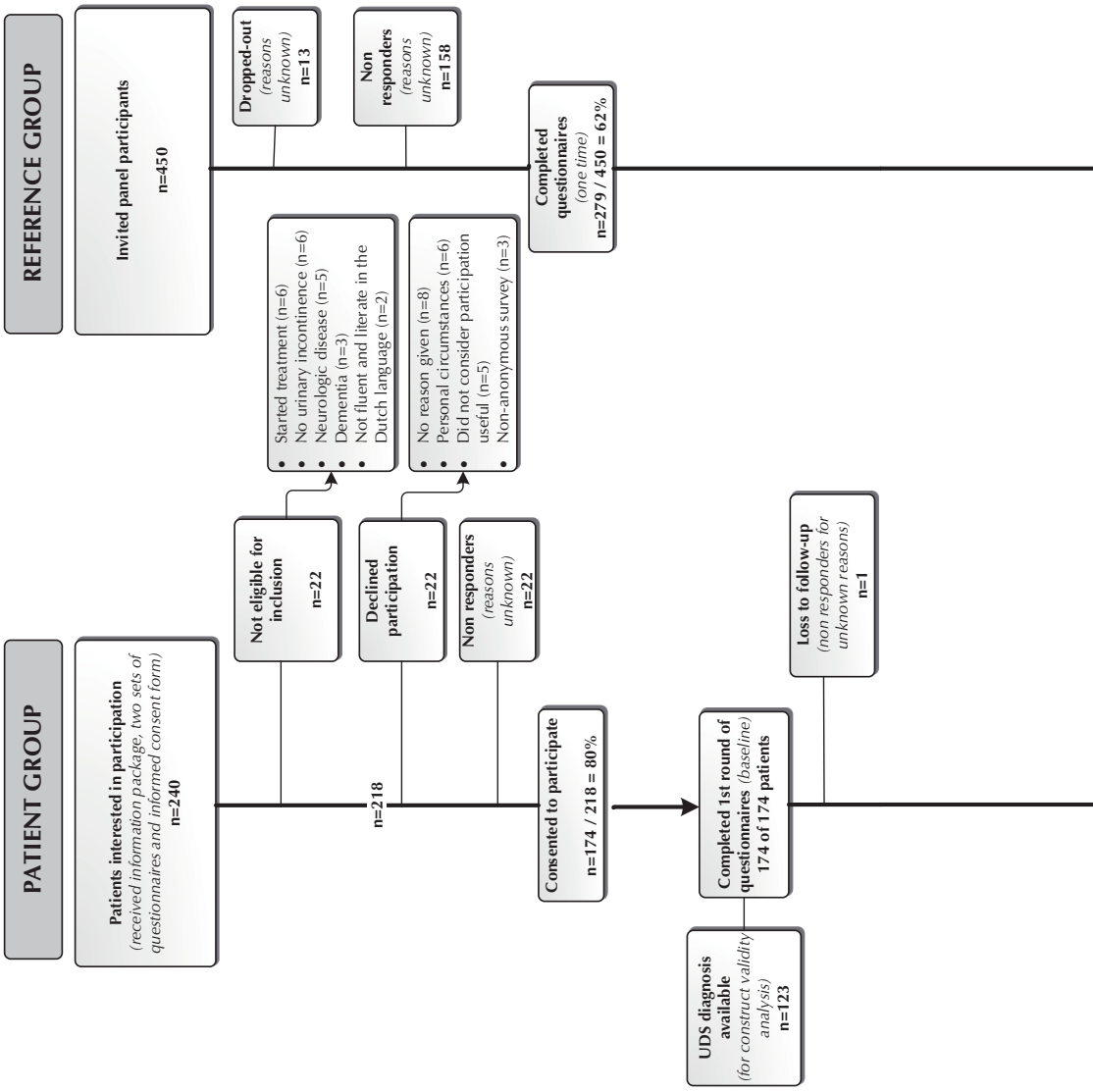
For receiver operating characteristics (ROC) analysis the anchor RAND-36-HTI was dichotomized: patients who reported that they were "a little better" and "much better" were classified as "improved", while "same", "a little worse", and "much worse" were classified as "not improved".

We tested the measurement properties of the measures[31]:

- The **internal consistency**, i.e. the extent to which the items are measuring the same underlying construct, was tested by calculating Cronbach's alpha using baseline scores. A Cronbach's alpha between 0.70 and 0.95 was considered to reflect good internal consistency.[31]
- The **reproducibility**, i.e. the degree to which repeated measurements in the test-retest period provide similar answers, concerns reliability and agreement. The **reliability**, i.e. the extent to which patients can be distinguished from each other despite measurement errors, was calculated with the Intraclass Correlation Coefficient (ICC) according to McGraw and Wong for agreement[32], and was considered acceptable when the ICC was ≥0.70.[31] **Agreement**, i.e. the extent to

which the scores on repeated measures are close to each other, was quantified using the limits of agreement (LOA) as described by Bland and Altman.[33] The LOA were calculated as the absolute mean change in scores ($mean_{change}$) of repeated measurements during the test-retest period ±1.96*SD (SD_{change}). The LOA estimates where 95% of individual differences fall, that is the absolute measurement error. Agreement is considered good if the LOA are smaller than the minimal important change (MIC; see interpretability).[31]

- The **construct validity**, i.e. the extent to which the scores relate to other measures, was verified by urodynamic diagnosis for discriminative validation. We formulated specific hypotheses and expected at least 75% of the results to be in accordance with these hypotheses[31]:
  1. We expect patients without an abnormality detected on urodynamic studies, to have significantly better IIQ-SF scores than patients with a urodynamic diagnosis;
  2. We expect patients with DO to score significantly worse in the irritative domain of the UDI-6, than patients with other urodynamic diagnoses;
  3. We expect patients with SUI to score significantly worse in the stress domain of the UDI-6, than patients with other urodynamic diagnoses;
  4. We expect patients with dysfunctional voiding or underactive detrusor, to score significantly worse in the obstructive domain of the UDI-6, than patients with other urodynamic diagnoses.
- To assess **responsiveness**, i.e. the ability of a measure to detect clinically important changes over time, in treated patients we firstly evaluated the linear relationship of the $mean_{change}$ in measure scores between baseline and 6 month follow-up with the RAND-36-HTI score, using the Pearson correlation coefficient. In addition, the area under the ROC curve (AUC) for the UDI-6 and IIQ-SF measures was determined. The AUC indicates the probability that a measure correctly classified patients as improved, using the RAND-36-HTI as an anchor. The AUC was considered adequate if ≥0.70. [15]
- To assess **interpretability**, i.e. the degree to which one can assign qualitative meaning to quantitative scores, the anchor based ROC method was used to assess the MIC.[15] The MIC was defined as the optimal ROC cut-off point, i.e. the value for which the sum of the proportions of misclassifications ([1-sensitivity]+[1-specificity]) is smallest.[15]
- **Floor and ceiling effects** occur when high proportions of respondents report scores at the lower or upper end of the scale, indicating limited content validity, and thus may lead to a reduced reliability and limited responsiveness.[15] Floor or ceiling effects are considered to be present if more than 15% of respondents achieve the lowest or highest possible score.[31]


REFERENCE GROUP
Invited panel participants
n=450
Dropped-out (reasons unknown) n=13
Non responders (reasons unknown) n=158
Completed questionnaires (one time) n=279 / 450 = 62%
PATIENT GROUP
Patients interested in participation (received information package, two sets of questionnaires and informed consent form) n=240
Not eligible for inclusion n=22
Started treatment (n=6)
No urinary incontinence (n=6)
Neurologic disease (n=5)
Dementia (n=3)
Not fluent and literate in the Dutch language (n=2)
Declined participation n=22
No reason given (n=8)
Personal circumstances (n=6)
Did not consider participation useful (n=5)
Non-anonymous survey (n=3)
Non responders (reasons unknown) n=22
n=218
Consented to participate n=174 / 218 = 80%
Completed 1st round of questionnaires (baseline) 174 of 174 patients
Loss to follow-up (non responders for unknown reasons) n=1
UDS diagnosis available (for construct validity analysis) n=123

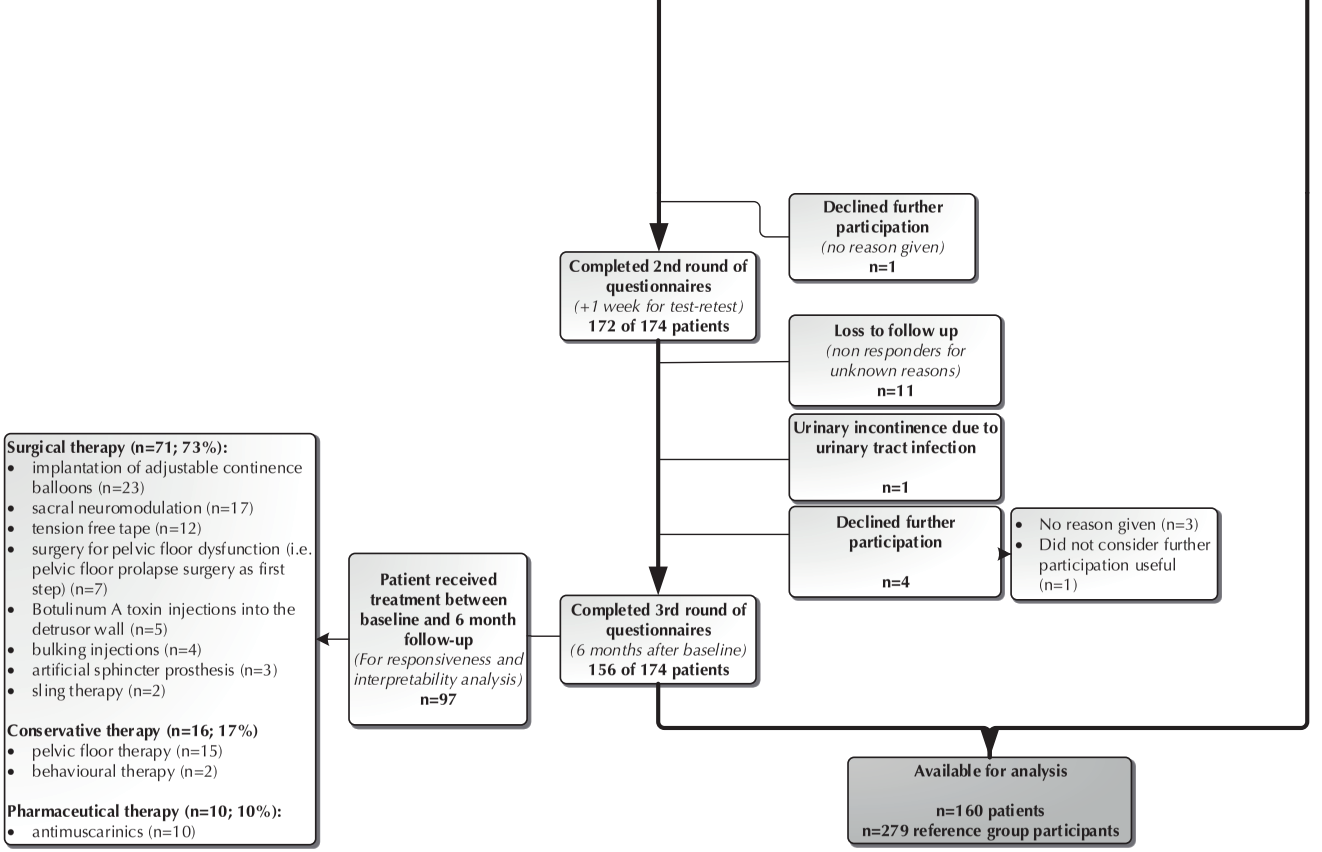


Figure 2.1 Study flowchart
Abbreviations: *UDS* urodynamic studies

RESULTS

Of 240 male and female consecutive patients, 218 were found to be eligible for inclusion (Figure 2.1). Of the 218 patients, 174 (80%) consented to participate. After three rounds of questionnaires data were available for 160 out of 174 patients (92%) to test at least one measurement property (i.e. patients completed the questionnaires at baseline and at least at one additional time-point) of at least one questionnaire (i.e. patients completed the UDI-6 and/or IIQ-7). Regarding the reference group, the measures were sent out to 450 panel participants of which 279 (62%) responded.

The study population had a mean age of 62±12 years, and 59% were female (Table 2.1). At baseline, patients reported significantly more symptoms of UI (UDI-6, $p<.001$) and more impact of these symptoms on daily life (IIQ-7 original, IIQ-7 adjusted and IIQ-8 all $p<.001$) than the reference group. After adjusting for age and educational level, these differences remained significant ($p<.001$).

Table 2.1 Characteristics of the respondents and questionnaires scores

	Patients (n = 160)	**Reference group** (n = 279)	***p*-value** univariate	***p*-value** GLM***
Age (years)	62 ± 12	49 ± 16	<.001	
Gender			.08	
Males	65 (41%)	138 (50%)		
Females	95 (59%)	141 (51%)		
Educational level*			<.001	
Low	59 (37%)	21 (8%)		
Intermediate	73 (46%)	172 (62%)		
High	28 (18%)	86 (31%)		
Scores at baseline (0-100)**				
UDI-6	46.4 ± 16.8	12.2 ± 12.7	<.001	<.001
IIQ-7 original	38.4 ± 24.6	4.0 ± 10.9	<.001	<.001
IIQ-7 adjusted	39.4 ± 25.4	4.2 ± 11.2	<.001	<.001
IIQ-8	37.3 ± 24.2	12.2 ± 12.7	<.001	<.001

Data in mean ± standard deviation or number (%).
*missing n=2
**higher scores indicate more symptom distress (UDI-6) or more impact on daily life (IIQ-SF)
****p*-value: corrected for age and educational level with general linear model (GLM)

Internal consistency

In the patient group, Cronbach's alpha was 0.49 for the UDI-6 total score and the domains ranged between 0.46–0.65, indicating moderate internal consistency (Table 2.2). In the reference group, Cronbach's alpha was 0.66 for the UDI-6 total score, and

the domains ranged between 0.44–0.58, also indicating moderate internal consistency. Internal consistency remained moderate after stratification by gender (not in table).

The Cronbach's alpha of the IIQ-7 original, IIQ-7 adjusted, and IIQ-8 were respectively 0.87, 0.86, and 0.87 in the patient group, indicating good internal consistency. In the reference group, these were 0.91, 0.91, and 0.92 respectively, also indicating good internal consistency.

Table 2.2 Internal consistency and reproducibility

	Patients	**Reference group** (n = 279)	**Patients Test-retest reliability**		
	Internal consistency (Cronbach's alpha)		**$ICC_{agreement}$**	**$mean_{change}$ ± SD_{change}**	**Limits of agreement***
UDI-6	0.49 (n=149)	0.66	0.84 (n=152)	6.3 ± 7.0	-7.42 to 20.0
Irritative	0.65 (n=155)	0.53	0.83 (n=152)	8.9 ± 13.1	-16.8 to 34.6
Stress	0.46 (n=152)	0.58	0.83 (n=152)	8.4 ± 11.5	-14.1 to 30.9
Obstructive/discomfort	0.54 (n=154)	0.44	0.85 (n=152)	7.3 ± 11.8	-15.8 to 30.4
IIQ-7 original	0.87 (n=147)	0.91	0.76 (n=153)	9.9 ± 14.1	-17.7 to 37.5
IIQ-7 adjusted	0.86 (n=132)	0.91	0.77 (n=150)	10.2 ± 14.1	-17.4 to 37.8
IIQ-8	0.87 (n=131)	0.92	0.75 (n=149)	10.0 ± 14.1	-17.6 to 37.6

All scale scores are transformed to a 0 – 100 point scale.
Higher scores indicate more symptom distress (UDI-6) or more impact on daily life (IIQ-SF).
* Limits of agreement described by Bland and Altman[33] = $mean_{change} \pm 1.96 * SD_{change}$

Reproducibility (reliability and agreement)

The retest assessments were completed on average 10±25 days after baseline assessment. The $ICC_{agreement}$ was 0.84 for the UDI-6, and the domains ranged between 0.83–0.85, indicating good reliability (Table 2.2). The $ICC_{agreement}$ of the IIQ-7 original, IIQ-7 adjusted, and IIQ-8 were 0.76, 0.77, and 0.75 respectively, also indicating good reliability.

The $mean_{change}$ and the LOA in the test-retest period are also presented in Table 2.2. The LOA are smaller than the MIC (see also results *Interpretability*), indicating good agreement.

Construct validity

In 124 patients urodynamic data were available and classified according to urodynamic diagnosis. Sixteen of 124 patients were diagnosed with mixed incontinence and were classified into either SUI (n=11) and DO (n=4), while one was treated for mixed incontinence and therefore not included in this analysis. Table 2.3 presents the measure scores in 123 patients stratified into urodynamic diagnosis.

Table 2.3 Construct validity

	No urodynamic abnormality (n = 9)	**Detrusor overactivity** (n = 34)	**Stress Urinary Incontinence** (n = 59)	**Dysfunctional voiding** (n = 9)	**Underactive Detrusor** (n = 12)	***p*-value**[#]
UDI-6 (total score)	39.5 ± 12.5	48.1 ± 13.1	48.2 ± 18.9	37.6 ± 17.9	43.5 ± 12.0	.22
Irritative	37.0 ± 23.2*	**68.6 ± 23.1**	51.6 ± 26.0*	37.0 ± 23.2*	55.5 ± 27.8	.003
Stress	50.0 ± 23.5*	50.9 ± 24.2*	**66.9 ± 22.8**	50.9 ± 24.2	45.8 ± 21.4*	.006
Obstructive/discomfort	31.5 ± 24.2	23.7 ± 22.8	25.0 ± 25.8	31.5 ± 24.2	29.1 ± 33.4	.90
IIQ-7 original	**14.8 ± 15.3**	41.0 ± 22.4**	38.8 ± 25.0**	24.9 ± 19.3	33.7 ± 17.0	.004
IIQ-7 adjusted	**15.3 ± 15.2**	41.7 ± 21.9**	39.2 ± 25.8**	25.5 ± 18.9	35.3 ± 16.3	.003
IIQ-8	**13.9 ± 13.3**	39.9 ± 22.2**	37.5 ± 24.5**	23.0 ± 17.9	33.0 ± 16.0	.001

Measure scores according to urodynamic diagnosis at baseline in mean ± SD
All scores are transformed to a 0 – 100 point scale
Higher scores indicate more symptom distress (UDI-6) or more impact on daily life (IIQ-SF)
[#]Welch's F was used for comparing means
Data **in bold** were used for pair wise comparisons of hypotheses using post hoc Games-Howell with mean difference significant at level *p<.05; **p<.01

The distribution of the mean scores of the UDI-6 irritative domain, UDI-6 stress domain, IIQ-7 original, IIQ-7 adjusted and IIQ-8, differed significantly between the urodynamic groups. Pairwise comparisons of predefined hypotheses on outcome resulted in 75% (3 out of 4) confirmed hypotheses indicating acceptable construct validity. Our confirmed hypotheses were:

- The mean score of the irritative domain of the UDI-6 was significantly higher in the DO group than in patients with SUI (p=.02), dysfunctional voiding (p=.04), or without urodynamic abnormality (p=.02).
- The mean score of the stress domain of the UDI-6 was significantly higher in the SUI group than in patients with DO (p=.02) or underactive detrusor (p<.05).
- The mean scores of the IIQ-7 original, IIQ-7 adjusted and IIQ-8 were significantly lower in the group of patients without urodynamic abnormality than in patients with SUI (p<.01) or DO (p<.01)

Responsiveness

The treatment work-up was individually determined for each patient by the treating physician after completion of the second round of questionnaires. Thus, 97 patients were treated and completed the third round of questionnaires on average 5.7±1.3 months after baseline assessment. Treatment consisted of surgery (n=71, 73%), conservative therapy (n=16, 17%), or pharmaceutics (n=10, 10%).

Table 2.4 shows the $mean_{change}$ between baseline and six month follow-up of each measure classified by the responses of the RAND-36-HTI. Since two patients (2%) reported their health was "much worse", and 10 patients (11%) reported it was "a little worse" compared to one year ago, we combined those categories. The relationships between the $mean_{change}$ of measure scores and the RAND-36-HTI as anchor were significantly linear (Table 2.4). The AUC for the UDI-6 was 0.81 (p<.001) indicating good responsiveness. The AUC for the IIQ-7 original was 0.65 (p=.02); for the IIQ-7 adjusted 0.70 (p=.004); and for the IIQ-8 0.66 (p=.02), indicating acceptable responsiveness.

Interpretability

The MIC was -16.7 for the UDI-6 with a sensitivity of 0.76 and specificity of 0.78. The MIC was -19.0 for the IIQ-7 original, -26.2 for the IIQ-7 adjusted, and -28.8 for the IIQ-8, with sensitivity ranging from 0.38–0.43 and specificity ranging from 0.84–0.90 (Table 2.4).

All MIC fell outside the LOA (Table 2.2), indicating acceptable measurement errors which are smaller than the values for MIC.[15]

Table 2.4 Responsiveness and interpretability

	Number (%) n = 97	**UDI-6** n = 80	**IIQ-7 original** n = 81	**IIQ-7 adjusted** n = 80	**IIQ-8** n = 80
Health transition item (RAND-36)*:					
A little worse / much worse	12 (12%)	5.8 ± 19.7	-2.8 ± 34.2	0.3 ± 30.5	-1.8 ± 31.8
Same	40 (41%)	-7.8 ± 17.5	-1.8 ± 22.2	-1.7 ± 21.3	-1.1 ± 21.8
A little better	13 (13%)	-19.3 ± 15.3	-18.3 ± 20.6	-20.1 ± 21.6	-18.9 ± 21.0
Much better	17 (18%)	-27.6 ± 14.8	-16.8 ± 28.6	-21.2 ± 28.1	-18.2 ± 27.0
Missing	15 (16%)				
Pearson correlation coefficient *r*		0.54	0.25	0.34	0.29
p-value		<.001	.03	.002	.01
Area under the ROC curve		0.81	0.65	0.70	0.66
p-value		<.001	.02	.004	.02
Minimal important change		-16.7	-19.0	-26.2	-28.8
Sensitivity; specificity		0.76; 0.78	0.43; 0.84	0.41; 0.88	0.38; 0.90

Data presented in number (%) or $mean_{change} \pm SD_{change}$ between baseline and six month follow-up
Negative scores indicate improvement of urinary incontinence symptoms (UDI-6) and impact on daily life (IIQ-SF)
* *"Compared to one year ago, how would you rate your health in general now?"*

Floor and ceiling effects

We observed no floor or ceiling effects in the baseline data of our patient group. The lowest score was reported by at most 5% of respondents (IIQ-SF), and the highest score by at most 0.6% or respondents (IIQ-7 adjusted).

As expected in the reference group, no ceiling effects were observed, though floor effects were present in the UDI-6 (n=76; 27%); IIQ-7 original (n=212; 76%); IIQ-7 adjusted (n=211; 76%); and IIQ-8 (n=211; 76%).

DISCUSSION

The objective of this study was to validate the UDI-6 and IIQ-7 in Dutch to provide a useful evaluation tool for the use in both men and women suffering from UI. In our population, the UDI-6 and IIQ-SF had good discriminant ability. The reproducibility (reliability and agreement) and construct validity of these measures were good, and both measures proved to be responsive and interpretable. By using the values of the MIC we determined, a decrease of ≥16.7 points in the UDI-6 score and a decrease of ≥19.0 points in the IIQ-7 original, ≥26.2 in the IIQ-7 adjusted, and ≥28.8 in the IIQ-8, can be considered as "clinically relevant" in patients undergoing any treatment for UI.

The internal consistency of the IIQ-SF in the patient group was good with Cronbach's alphas of 0.91 and 0.92. However, analysis of the UDI-6 showed moderate internal consistency of the total score and the domains, in both patient and reference group. Other validation studies found comparable Cronbach's alphas for the UDI-6.[20,21] A possible explanation is the use of unconditional mean imputation[30] for measure scores, which is the scoring procedure as described by the developer.[6] This procedure allows imputing a score of one UDI-6 domain into another UDI-6 domain, e.g. missing items of the irritative domain may be imputed by scores of the stress domain. As a consequence, domain scores might be 'contaminated'. Another possible explanation of a moderate internal consistency of the UDI-6 was suggested by Franzén et al.[20] The UDI-6 contains items assessing symptoms of disease called "causal indicators". These are called "causal indicators" since the occurrence of these symptoms can cause deterioration on HRQOL, but the impact of these symptoms on HRQOL may vary from patient to patient. Furthermore, the patient's perception of the severity of their symptoms may be influenced by other factors and concomitant symptoms.[34] The IIQ-SF contains items measuring effects of UI on HRQOL, which reflect the level of HRQOL, and are regarded as "effect indicators".[34] Scales based on causal indicators are more heterogeneous than scales based on effect indicators. For example, a patient with family problems may perceive UI as having a greater effect upon their HRQOL than usual. Since psychometric analysis is based on the assumption that all items are

effect indicators reflecting the same latent HRQOL construct, the properties of causal items (UDI-6) affect reliability measures such as Cronbach's alpha leading to a lower internal consistency.[34]

We recognize several limitations to this study. First, we recruited patient data from a tertiary urology and gynaecology centre. In this setting we expect more patients with severe symptoms of UI, and therefore the extent to which the results of this study can be generalized to other settings may be limited. Second, we did not validate the measures separately for men and women. A comparison between the two genders is desirable since health-seeking behaviour and bother from lower urinary tract symptoms (LUTS)[35] and UI[36,37] differs significantly between men and women. Twenty-five present of women were bothered by the presence of LUTS compared to 18% men, with equal prevalence of treatment seeking of 28% and 24% respectively, however in the absence of evaluation of the effect of incontinence.[35] In this hospital-based survey, men were more likely than women to seek treatment as age and severity of LUTS increased.[35] When urinary incontinence was taken into account in a community based survey, 45% of women versus 22% of men suffering from incontinence had sought medical care for their problem.[36] However in a different community based study, men with incontinence reported a higher rate of healthcare seeking of 56% compared to 46% of women.[37] Even though we did not intend to compare sexes and their urological functioning as mirrored by the questionnaires, we can highly recommend this for future research. This study was not designed for this purpose as we would have taken gender distribution into account in our sampling procedure.

The strength of this study is the study design, which enabled us to address almost all quality criteria for measurement properties of Terwee et al.[31] An exception was the criterion validity, which requires the availability of a gold standard. Since there are no gold standards of symptoms and bother of UI, we were not able to test this property. Our study design also allowed us to test the UDI-6 and IIQ-SF in male patients. As suggested in an earlier study[23], we revised the gender-specific items of the IIQ-7. Hence, we studied the original IIQ-7 along with two variants: the IIQ-7 "adjusted" and the IIQ-8. The psychometric properties of these variants of IIQ-SF were equally good. Therefore we would like to recommend using the "original" IIQ-7 in women as well as in men, to allow better international comparison of research and treatment outcome data.

CONCLUSION

In conclusion, the UDI-6 and IIQ-7 in Dutch are reliable, valid and responsive instruments, and therefore suitable for assessing symptom distress and HRQOL of UI in both men and women, as well as evaluating outcome of treatment.

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Chapter 3

Validation of the Pelvic Floor Distress Inventory (PFDI-20) and Pelvic Floor Impact Questionnaire (PFIQ-7) in a Dutch population

Elaine Utomo, Bertil F.M. Blok, Anneke B. Steensma and Ida J. Korfage

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ABSTRACT

Aims

The objective of this study was to validate the Pelvic Floor Distress Inventory (PFDI-20) and Pelvic Floor Impact Questionnaire (PFIQ-7) in Dutch women.

Methods

Patients with pelvic floor dysfunction completed the Dutch questionnaires at (1) inclusion to evaluate internal consistency, (2) 1 week later to assess test-retest reliability, and (3) 6 months later to assess responsiveness and interpretability of change. To assess validity, floor and ceiling effects and construct validity were tested. A population-based sample (reference group) completed the questionnaires once.

Results

Data of 111 patients and 283 reference group participants were analysed. Internal consistency of baseline scores in patient and reference groups was moderate (Cronbach's alpha 0.52–0.60) to adequate in the PFDI-20 (Cronbach's alpha 0.71–0.84) and adequate in the PFIQ-7 (Cronbach's alpha 0.88–0.94). Both measures presented adequate test-retest reliability (intraclass correlation coefficient 0.79–0.91) and adequate responsiveness (area under the receiver-operating characteristic curve both 0.77). Interpretability was adequate for PFDI-20 and acceptable for PFIQ-7 with a clinically relevant minimally important change of –23 and –29 points, respectively. At baseline, the scales of the PFIQ-7 showed floor effects (44–55 %) in patients, though the PFIQ-7 summary score did not. No ceiling effects were observed. Construct validity was adequate with all predefined hypotheses confirmed regarding subgroup discrimination using pooled patient and reference group baseline data.

Conclusions

For assessing distress and health-related quality of life of pelvic floor dysfunction, the Dutch PFDI-20 and PFIQ-7 are reliable and valid in the general Dutch population, and also responsive and interpretable among tertiary care seeking women.

INTRODUCTION

Women with complaints of pelvic floor dysfunction may present a variety of symptoms relating to lower urinary tract dysfunction, pelvic organ prolapse, and anorectal dysfunction.[1] Given the coexistence and complex interaction of these symptoms, comprehensive condition-specific health-related quality of life (HRQOL) questionnaires are needed to measure severity and impact of pelvic floor dysfunction in a standardized and reproducible manner.[2]

The Pelvic Floor Distress Inventory (PFDI) and Pelvic Floor Impact Questionnaire (PFIQ)[3] were developed and validated to measure symptom distress and impact on HRQOL, focusing on pelvic organ prolapse (POP), urinary incontinence (UI), and fecal incontinence (FI). Short versions of the PFDI (i.e., PFDI-20) and PFIQ (i.e., PFIQ-7) were developed to reduce respondent's burden.[4,5] The PFDI-20 and PFIQ-7 have been validated in different languages[6-14] though not yet in Dutch. We therefore translated the PFDI-20 and PFIQ-7 into Dutch. Since measures must adequately address measurement properties to be useful in research or in practice[15, 16] we tested their reliability, validity, responsiveness, and interpretability in Dutch women with symptoms of pelvic floor dysfunction.

METHODS

This observational study was conducted at a tertiary urology and gynaecology centre as part of a larger validation study of HRQOL pelvic floor measures. The study was approved by the Institutional Ethics Committee (MEC-2008-376).

Questionnaires

In both PFDI-20 and PFIQ-7, patients reported whether they experienced symptoms of pelvic floor dysfunction, and if so, the extent to which these symptoms were bothersome to them. The PFDI-20 has three scales: Pelvic Organ Prolapse Distress Inventory (POPDI-6), Colorectal-Anal Distress Inventory (CRADI-8), and Urinary Distress Inventory (UDI-6). Response options for rating distress associated with each symptom ranged from 0 ("no" as in no symptoms) to 1 ("not at all" as in symptoms are present but not bothered at all) to 4 ("quite a bit" as in symptoms are present and quite a bit bothered). Per scale, the mean score of answered items is multiplied by 25 to obtain the scale score (range 0–100).[4] Summary scores are calculated by adding up the scale scores (range 0–300). Higher scores indicate more symptom distress.[4] The PFIQ-7 measures impact of bladder, bowel, and vaginal symptoms on daily physical activity, travel, social/relationships, and emotional health. The PFIQ-7 has three scales: the Urinary Impact Questionnaire (UIQ-7), the Colorectal-Anal Impact Questionnaire

(CRAIQ-7), and the Pelvic Organ Prolapse Impact Questionnaire (POPIQ-7). Response options range from 0 ("not at all") to 3 ("quite a bit"). Per scale, the mean score of answered items is multiplied by 33.3 to obtain the scale score (range 0–100).[4] Summary scores are calculated by adding up the scale scores (range 0–300).[4] Higher scores indicate more impact on daily activity.

Linguistic validation

The measures were translated into Dutch following standardized forward-backward procedures,[17] i.e., three independent forward translations, backward translation by a native speaker, and tested face-to-face in ten patients with pelvic floor dysfunction. Several minor problems were identified without the need to adapt the content of the measures. The Dutch versions of PFDI-20 and PFIQ-7 were then finalized (See 'Vragenlijsten').

Study population and study design

For the patient group, inclusion criteria were women aged 18 years or older, with at least one symptom of pelvic floor dysfunction (UI, POP, or FI) existing for at least 3 months, and fluent and literate in the Dutch language. Exclusion criteria were active malignant tumours, dementia, and mental retardation. The definitions used for UI, POP, and FI were according to the standardized International Continence Society terminology.[18, 19] Thus, UI was defined as "the complaint of any involuntary leakage of urine," POP as "the symptomatic descent of one or more of the anterior vaginal wall, the posterior vaginal wall, and the apex of the vagina or vault after hysterectomy," and FI as "any involuntary loss of fecal material".[19] At the initial office visit, the treating physician recruited all consecutive patients potentially eligible for inclusion.

Patients received the same questionnaires at three time points (1) baseline, (2) 1 week later, and (3) 6 months later, and returned them through postal mail. During the test-retest period of 1 week, no treatment was initiated or changed. One week between the repeated administrations was long enough to prevent recall, though short enough to ensure that clinical change had not occurred. Given the observational nature of this study, the treating physician was unrestricted in prescribing therapy after completion of the test-retest for individual patient care. Age and education were documented through the questionnaire. Educational level was classified as "low" (primary school), "intermediate" (high school), or "high" (college or university degree). In the third round the health transition item of the RAND 36-Item Health Survey (RAND 36-HTI)[20, 21] was included through which patients scored the change in their general health compared to 1 year ago. The response options range from 1 ("much better") to 5 ("much worse"). The prescribed treatment between baseline and the third round of the questionnaire was obtained from the patient's medical record. This was categorized into conservative, pharmaceutical, or surgical treatment.

Reference group

We collected baseline data from a representative sample of adult women in the Netherlands through an ISO-certified (ISO 26362) Dutch panel.[22] This subsample was stratified by gender, age, educational level, and residential area and therefore representative of the Dutch population above the age of 18. No medical data were available for this panel, and thus the presence or absence of pelvic floor dysfunction was unknown.

Measurement properties

The psychometric measurement properties addressing the quality domains reliability, validity, and responsiveness were tested, and we assessed interpretability which is an important characteristic of measures.[15]

- Internal consistency (i.e., the degree of interrelatedness among the items) was assessed with Cronbach's alpha. Cronbach's alpha was determined for the summary score as well as for the scale scores. The scales intend to measure a single underlying concept by using multiple items. A high Cronbach's alpha indicates high correlations between the multiple items in a scale, i.e., redundancy of one or more items thus measuring the same concept. Values between 0.70 and 0.95 were considered to reflect adequate internal consistency.[16, 23]
- Test-retest reliability (i.e., the degree to which repeated measurements in stable persons provide similar answers) was assessed through the intraclass correlation coefficient (ICC) for agreement.[24] We used the two-way mixed single measures model in IBM® SPSS software 20.0 to calculate this. Values ≥0.70 were considered to reflect adequate reliability.[16]
- Measurement error (i.e., the systematic and random error of a patient's score not attributed to true changes) was quantified using the limits of agreement (LOA) by Bland and Altman.[25] The LOA were calculated as the absolute mean change in scores ($mean_{change}$) of repeated measurements during the test-retest period ±1.96 SD (SD_{change}). The absolute change in mean scores of the test-retest was presented without a specific direction of change.
- Content validity (i.e., the degree to which the content of a measure is an adequate reflection of the target construct) was subjectively assessed and verified ("face validity") by examining whether the items appeared to be measuring what they are intended to measure. We also assessed floor and ceiling effects. These occur when ≥15 % of scores are at the lower or upper end of the scale.[16, 23]
- Construct validity (i.e., the degree to which measure scores are consistent with hypotheses based on the assumption that the measure validly measures the target construct) was verified by hypotheses testing of the measures using known groups based on patient and reference group baseline scores.[23] Since no medical back-

ground information was available for the reference group (e.g., care-seeking or not, presence or absence of symptoms of pelvic floor dysfunction), we defined the presence of symptoms according to the response options given in the measures. The PFIQ-7 scale scores were used to assess PFDI-20 construct validity, i.e., the presence of POP, FI, or UI was defined as a score above zero on the POPIQ-7, CRAIW-7, or UIQ-7 scale, respectively. Specific items of the PFDI-20 scores were used to assess PFIQ-7 construct validity, i.e., an affirmative response to any of the items of the PFDI-20 indicating a sensation of a "*bulge*" in the pelvic area was defined as presence of POP; an affirmative response to any of the items of the PFDI-20 indicating "*stool loss*" was defined as presence of FI; and an affirmative response to any of the items of the PFDI-20 indicating "*urine leakage*" was defined as presence of UI. We formulated the following hypotheses:

1. The subgroup with POP symptoms will report significantly higher POPDI-6 and POPIQ-7 scale scores than the subgroup without POP symptoms.
2. The subgroup with symptoms of FI will report significantly higher CRADI-8 and CRAIQ-7 scale scores than the subgroup without FI symptoms.
3. The subgroup with symptoms of UI will report significantly higher UDI-6 and UIQ-7 scale scores than the subgroup without UI symptoms.
   Construct validity was considered adequate when at least 75 % of these hypotheses were confirmed.[16]

- The responsiveness (i.e., the ability of a measure to detect changes over time) was assessed in all patients who received any treatment during follow-up. We evaluated the linear relationship of the $mean_{change}$ in measure scores between baseline and 6-month follow-up with the RAND 36-HTI score using the Pearson correlation coefficient (*r*). Additionally, the area under the receiver-operating characteristic (ROC) curve (AUC) for the measures was determined.[23] By determining the AUC, the measures are considered as a diagnostic test, and the RAND 36-HTI functions as the gold standard. The AUC indicates the probability that a measure correctly classifies patients as improved using the RAND 36-HTI as an anchor. The AUC was considered adequate if ≥0.70.[23]
- The interpretability (i.e., the degree to which one can assign qualitative meaning to a measure's quantitative score or change in scores) was tested using the anchor-based ROC method to assess the minimally important change (MIC).[23] As in diagnostic studies, the optimal ROC cut-off point is chosen, i.e., the value for which the sum of the proportions of misclassifications [(1-sensitivity) + (1-specificity)] is smallest. In analogy, the MIC is defined as this optimal ROC cut-off point.[23]

Statistical methods

Statistical analysis was performed using IBM® SPSS software 20.0. Significance was set at a *p*-value <.05. For comparison of two independent groups we used the unpaired *t* test when numerical data were considered and the chi-square test when categorical data were considered. For comparison of more than two independent groups, we used the one-way analysis of variance (ANOVA). General linear models were used to compare measure scores, controlling for variables that differed significantly between patient and reference groups in univariate analysis.

The anchor RAND 36-HTI was dichotomized for ROC analysis: patients reporting to be "a little better" or "much better" were classified as "improved," while "same," "a little worse," or "much worse" were classified as "not improved."

RESULTS

Of 187 consecutive female patients, 161 (86%) were eligible for inclusion of which 117 (73%) consented to participate (Figure 3.1). After three rounds of questionnaires, data were available for 111/117 (95%) patients to test at least one measurement property (i.e., patients completed a questionnaire at baseline and at least at one additional time point) of at least one measure (i.e., patients completed the PFDI-20 and/or PFIQ-7). Regarding the reference group, the measures were sent out to 450 panel participants of which 283 (63 %) responded.

The mean age was higher (p<.001) in the patient group (59±12 years) than in the reference group (47±15 years, Table 3.1). When completing the PFDI-20, 96% of the patients reported symptoms of UI, 57% symptoms of POP, and 47% symptoms of FI. These prevalence rates were lower (p<.001) in the reference group. Of the patients, 74% (n=82) had more than one symptom of pelvic floor dysfunction (i.e., UI, or POP, or FI), compared to 17% (n=49) in the reference group.

Patients reported more symptom distress (PFDI-20) and more impact on daily activity (PFIQ-7) than the reference group (both p<.001). After adjusting for age and educational level, these differences remained significant.

Internal consistency

The PFDI-20 summary score demonstrated adequate internal consistency with Cronbach's alphas of 0.74 and 0.84 in patient and reference groups, respectively (Table 3.2). The scales of the PFDI-20 demonstrated moderate internal consistency for both patient (Cronbach's alpha 0.52–0.71) and reference groups (Cronbach's alpha 0.60–0.74). The PFIQ-7 summary and scale scores demonstrated adequate internal

Table 3.1 Characteristics and measure scores of respondents

Demographics	**Patients** (n = 111)	**Reference group** (n = 283)	***p*-value** univariate	***p*-value** GLM**
Age (years)	58.6 ± 12.2	47.0 ± 15.3	<.001	
Educational level			<.001	
Low	45 (41%)	84 (30%)		
Intermediate	51 (46%)	47 (17%)		
High	15 (14%)	152 (54%)		
Parity	2.3 ± 1.2	NA		
missing	*25 (23%)*	*NA*		
Urinary Incontinence[a] (%)	106 (96%)	128 (45%)	<.001	
Pelvic Organ Prolapse[b] (%)	63 (57%)	59 (21%)	<.001	
Faecal Incontinence[c] (%)	51 (47%)	24 (9%)	<.001	
missing	*2 (2%)*	*0 (0%)*		
Symptoms of pelvic floor dysfunction per patient (n)[d]			<.001	
0	0 (0%)	109 (39%)		
1	29 (26%)	125 (44%)		
2	55 (50%)	34 (12%)		
3	27 (24%)	15 (5%)		
Scores at baseline*				
PFDI-20 (0-300)	93.4 ± 41.5	27.1 ± 31.7	<.001	<.001
missing	*1 (1%)*	*0 (0%)*		
POPDI-6 (0-100)	22.2 ± 16.5	5.6 ± 9.8	<.001	<.001
CRADI-8 (0-100)	26.7 ± 19.5	9.3 ± 12.4	<.001	<.001
missing	*1 (1%)*	*0 (0%)*		
UDI-6 (0-100)	44.7 ± 20.7	12.3 ± 16.1	<.001	<.001
PFIQ-7 (0-300)	69.0 ± 52.5	12.7 ± 27.0	<.001	<.001
missing	*14 (13%)*	*0 (0%)*		
POPIQ-7 (0-100)	14.6 ± 22.4	3.4 ± 10.0	<.001	<.001
missing	*14 (13%)*	*0 (0%)*		
CRAIQ-7 (0-100)	20.9 ± 27.2	4.3 ±11.9	<.001	<.001
missing	*12 (11%)*	*0 (0%)*		
UIQ-7 (0-100)	35.1 ± 26.3	5.0 ± 11.3	<.001	<.001
missing	*6 (5%)*	*0 (0%)*		

Data in mean ± standard deviation or number (%). No data was missing unless otherwise indicated.
Abbreviations: *GLM* general linear models; *NA* not available

*A higher score indicates greater symptom distress or impact on health-related quality of life
***p*-value: corrected for age and educational level with general linear modelling (GLM)
[a]Defined as affirmative response to any of the items based on *"urine leakage"* (i.e. items 15, 16, 17 or 18 of the PFDI-20).

[b]Defined as affirmative response to any of the items based on a sensation of *"a bulge"* in the pelvic area (i.e. items 3, 4, 6 or 14 of the PFDI-20).
[c] Defined as affirmative response to any of the items based on *"stool loss"* (i.e. items 9 or 10 of the PFDI-20).
[d]Pelvic floor dysfunction include urinary incontinence, pelvic organ prolapse, and faecal incontinence

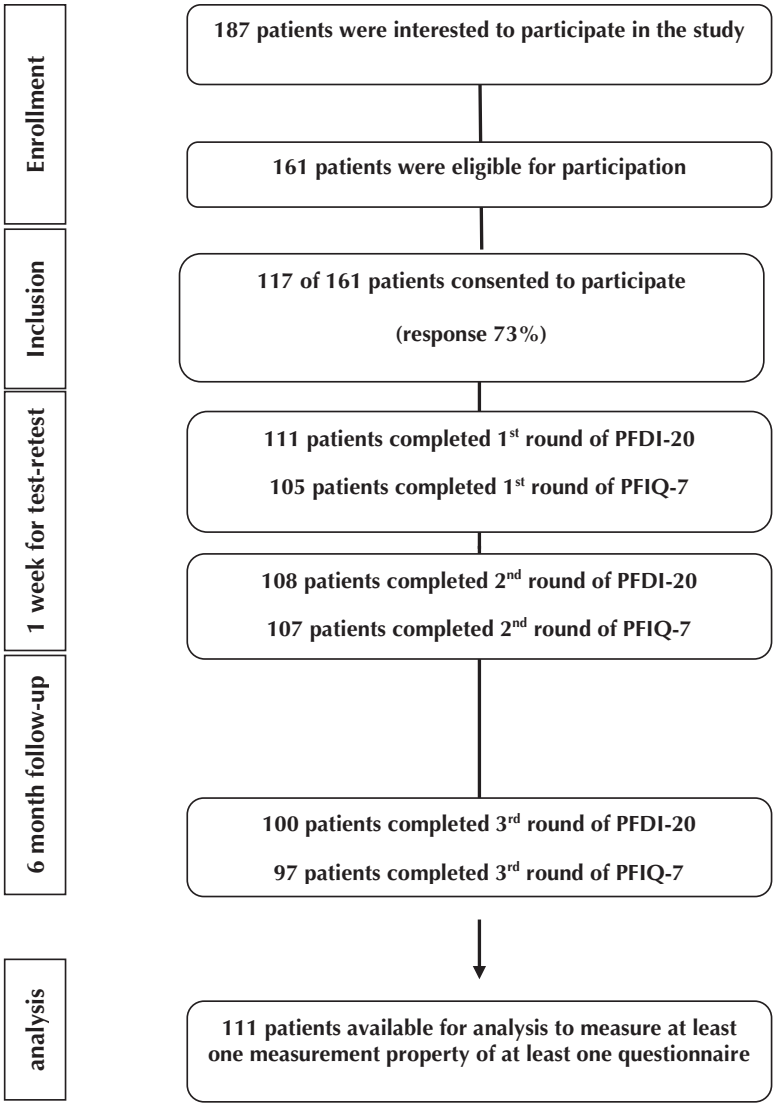

Figure 3.1 Flowchart: inclusion process of patient group

consistency in both patient (Cronbach's alpha 0.89–0.94) and reference groups (Cronbach's alpha 0.88–0.93).

Reliability

The retest assessments were completed on average 8 days after baseline measurement. The $ICC_{agreement}$ was 0.88 for the PFDI-20 summary score and ranged from 0.86 to 0.90 for the PFDI-20 scales (Table 3.2). The $ICC_{agreement}$ of the PFIQ-7 summary score was 0.83 and ranged from 0.79 to 0.91 for the PFIQ-7 scales. All retest assessments indicated adequate reliability.

Measurement error

The absolute $mean_{change}$ of repeated measurements during the test-retest period, the corresponding SD_{change}, and the LOA are presented in Table 3.2. Relating the LOA range to the range of all possible measure scores, the overall magnitude of the measurement error is 10% (59.2 of 600) for the PFDI-20 summary score and 13–14%(27, 27.4, and 26.6

Table 3.2 Internal consistency and reproducibility

Questionnaire	Internal consistency (Cronbach's alpha)		Test-retest reliability Patients		
	Patients	Reference group (n = 283)	Intraclass Correlation Coefficient	$mean_{change} \pm SD_{change}$*	Limits of agreement**
PFDI-20 (0-300)	0.74 (n=96)	0.84	0.88 (n=99)	13.3 ± 15.1	-16.3 – 42.9
POPDI-6 (0-100)	0.52 (n=103)	0.60	0.86 (n=100)	5.6 ± 6.9	-7.9 – 19.1
CRADI-8 (0-100)	0.71 (n=106)	0.71	0.90 (n=99)	5.6 ± 7.0	-8.1 – 19.3
UDI-6 (0-100)	0.60 (n=104)	0.74	0.89 (n=100)	6.8 ± 6.8	-6.5 – 20.1
PFIQ-7 (0-300)	0.89 (n=89)	0.93	0.83 (n=85)	19.2 ± 26.0	-31.8 – 70.1
POPIQ-7 (0-100)	0.92 (n=90)	0.92	0.79 (n=86)	7.3 ± 13.3	-18.8 – 33.4
CRAIQ-7 (0-100)	0.94 (n=94)	0.92	0.91 (n=86)	5.8 ± 10.2	-14.2 – 25.8
UIQ-7 (0-100)	0.90 (n=101)	0.88	0.82 (n=95)	9.9 ± 12.7	-15.0 – 34.8

*Higher scores indicate greater symptom distress or impact on health-related quality of life
** Limits of agreement described by Bland and Altman[25]= $mean_{change} \pm 1.96 * SD_{change}$

of 200 for the POPDI-6, CRADI-8, and UDI-6, respectively) for scale scores, 17% (101.9 of 600) for the PFIQ-7 summary score, and 20–26% (52.2, 40, and 49.8 of 200 for the POPIQ-7, CRAIQ-7, and UIQ-7, respectively) for scale scores.

Floor and ceiling effects

No ceiling effects were observed in the PFDI-20 and PFIQ-7 summary and scale scores, either in the patient or reference group. In patients, floor effects were found in two

Table 3.3 Floor and ceiling effects of baseline scores

Questionnaire	Patients (n=111)				Reference group (n=283)			
	Floor		Ceiling		Floor		Ceiling	
	n	Cumulative %	n	Cumulative %	n	Cumulative %	n	Cumulative %
PFDI-20 (0 – 300)	0	0	0	0	64	23	0	0
POPDI-6 (0 – 100)	14	13	0	0	177	63	0	0
CRADI-8 (0 – 100)	10	9	0	0	127	45	0	0
UDI-6 (0 – 100)	4	4	0	0	117	41	0	0
PFIQ-7 (0 – 300)	5	5	0	0	172	61	0	0
POPIQ-7 (0 – 100)	53	55	1	1	237	84	0	0
CRAIQ-7 (0 – 100)	44	44	1	1	225	80	0	0
UIQ-7 (0 – 100)	14	13	1	1	205	72	0	0

scales of the PFIQ-7, i.e., POPIQ-7 and CRAIQ-7, with 55 and 44% of subjects, respectively, exhibiting the most favourable low score of zero (Table 3.3). No floor effects were observed in the PFIQ-7 summary score. In the reference group, the PFDI-20 and PFIQ-7 summary and scale scores had floor effects ranging from 23 to 84%.

Construct validity

We appropriately confirmed all three predefined hypotheses (Figure 3.2):

1. The subgroup with POP symptoms (symptoms of vaginal bulge) reported higher scores on the POPDI-6 (23.3±17.9) and POIQ-7 (12.8±20.6) scales than the subgroup without symptoms (5.7±9.3 and 3.4±10.7, respectively), (p<.0001).
2. The subgroup with FI symptoms (stool loss) reported higher scores on the CRADI-8 (30.0±18.7) and CRAIQ-7 (30.2±28.4) scales than the subgroup without symptoms (7.0±9.4 and 3.6±10.7, respectively), (p<.0001).
3. The subgroup with UI symptoms (urine leakage) reported higher scores on the UDI-6 (39.1±21.8) and UIQ-7 (19.3±23.7) scales than the subgroup without symptoms (7.2±9.5 and 1.3±6.0, respectively), (p<.0001).

Responsiveness

A total of 100 patients completed the PFDI-20 and 97 patients the PFIQ-7 on average 5.7 months after baseline assessment (third round, Figure 3.1). Of 111 patients, 67 (60%) received treatment during follow-up as determined by the treating physician. Patients received conservative (n=50, 75 %), pharmaceutical (n=11, 16 %), and/or surgical treatment (n =44, 66 %). Table 3.4 presents the $mean_{change}$ in measure summary scores between baseline and 6-month follow-up of the measures, stratified by the responses of the RAND 36-HTI. We combined the categories of patients reporting their health

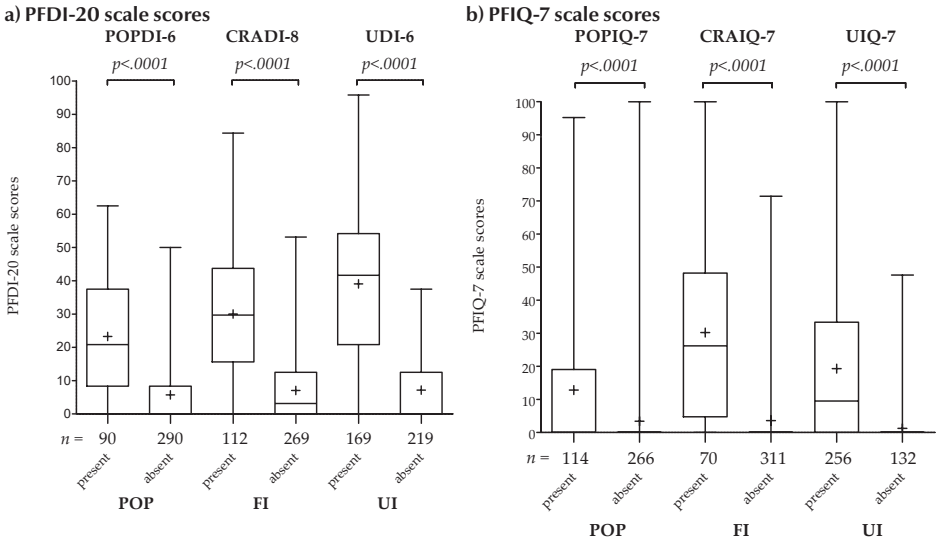

Figure 3.2 Construct validity. Pooled patient and reference baseline scales scores with comparisons between known groups. The bold lines indicates the median scale score and the box the interquartile range, the whiskers presenting the min.-max. The mean is indicated with a plus sign.

compared to 1 year ago as "much worse" (n=4) or "a little worse" (n=9). The relationships between the $mean_{change}$ of the summary scores of the measures and the RAND 36-HTI as anchor were linear (PFDI-20 r =0.49, p<.001; PFIQ-7 r =0.41, p=.002). The AUC for both measures was 0.77 (p<.001 for PFDI-20 and p=.001 for PFIQ-7), demonstrating adequate responsiveness.

Interpretability

Using ROC analysis, the optimum cut-off point was used to determine the MIC. Thus, with 73% correctly identified as improved and 75%as not improved, the MIC for the PFDI-20 summary score was –22.9 (Table 3.4). According to the lower limit of the LOA (Table 3.2), improvements in PFDI-20 summary scores of ≤16.3 cannot be attributed to a true improvement of the respondent, but should be attributed to a measurement error. The MIC of the PFDI-20 (–22.9) lies adequately outside the LOA (–16.3 to 42.9), meaning an improvement of ≥22.9 points on the PFDI-20 summary scale is a true clinically relevant change in score. Treated patients reporting "a little better" on the RAND 36-HTI 6 months after baseline showed mean changes of –32.3 on the PFDI-20 summary score, which indicates a true clinically relevant improvement.

The MIC for the PFIQ-7 summary score was –28.6, with 75% correctly identified as improved and 77 % as not improved (Table 3.4). This MIC (–28.6) lies between the LOA (Table 3.2: –31.8 to 70.1) and therefore cannot be detected as a true clinically relevant improvement, since an improvement of ≤31.8 points should be attributed to

Table 3.4 Responsiveness and Interpretability

Health transition item (RAND-36)*	**Number (%) n = 67**	**PFDI-20 Summary score (0 – 300)**	**PFIQ-7 Summary score (0 – 300)**
Much worse / A little worse	13 (16%)	-1 ± 18.4	-23.2 ± 52.6
Same	31 (39%)	-13.3 ± 25.3	-1.8 ± 40.7
A little better	9 (11%)	-32.3 ± 40.2	-31.3 ± 36.4
Much better	14 (18%)	-47.7 ± 39.6	-73.6 ± 51.7
p-value between RAND-36 items**		.001	.001
Pearson correlation coefficient *r*		0.49	0.41
p-value		<.001	.002
Area under the ROC curve		0.77	0.77
p-value		<.001	.001
Minimal important change		-22.9	-28.6
Sensitivity; specificity		0.73 ; 0.75	0.75 ; 0.77

Data presented in number (%) or $mean_{change} \pm SD_{change}$ between baseline and 6-month follow-up. Negative scores indicate an improvement in pelvic floor distress and/or impact.
Abbreviation: *ROC* receiver-operative characteristic
* *"Compared to one year ago, how would you rate your health in general now?"*
** Analysis of variance (ANOVA) was used

a measurement error. The change values lying between the lower LOA (–31.8) and the MIC (–28.6) are considered important by patients, but cannot be distinguished from measurement error. Treated patients reporting "a little better" on the RAND 36-HTI 6 months after baseline showed mean changes of –31.3 for the PFIQ-7 (Table 3.4), which is close to the lower limit of the LOA.

DISCUSSION

The objective of this study was to validate the PFDI-20 and PFIQ-7 in Dutch to provide an adequate tool to assess symptom distress and impact of pelvic floor dysfunction on HRQOL. Our findings regarding the reliability, construct validity, and responsiveness were generally very positive.

Both summary scales and four of six scales scores showed adequate internal consistency. The POPDI-6 and UDI-6 showed low to moderate internal consistency with Cronbach's alphas of 0.52 and 0.60 in patient groups, respectively, indicating

low homogeneity. Similar alphas were found in the Turkish[11] and Swedish[10] versions. As expected, floor effects were present in the reference group (23–84%) and ceiling effects were absent (0%) in summary and scale scores of both measures. In patients, we observed substantial floor effects in the POPIQ-7 (55%) and CRAIQ-7 scales (44%), indicating a not normal score distribution towards the most favourable low score of zero. The PFIQ-7 summary score did not demonstrate floor effects. Potentially patients typically experience different types of pelvic floor dysfunction (Table 3.1), but not necessarily *all* possible symptoms, e.g., POP and FI without UI.

The MIC of the PFIQ-7 indicated that the measurement error was too wide to detect clinically relevant improvement. However, the LOA are group averages, and just as the normal distribution, the measurement error range is bell-shaped and balances out towards the outer limits and therefore possibly less clinically relevant at the lower limit. Furthermore, the MIC lies close to the lower limit of agreement, with a small difference of 3.2 points on a scale of 0–300 which represents meaningful improvement, but cannot be distinguished from measurement error. We therefore recommend using the lower limit of agreement of −31.8 as MIC for PFIQ-7.

Our study has some limitations. First, it is desirable to have a correlation of 0.5–0.6 between the anchor and the meanchange in scores at the 6-month follow-up[23], while our anchor had a correlation of r =0.49 and r =0.41 for the PFDI-20 and PFIQ-7, respectively. This can be because generic measures, such as our RAND 36-HTI anchor, may not reveal the impact of sexual, urinary, and bowel dysfunctions on patients, because such dysfunctions tend not to be perceived as health problems.[26] Furthermore, it is preferable to measure the change in health prospectively. Second, since medical information about the reference group was not available, we determined the prevalence rates of symptoms of pelvic floor dysfunction using self-reported items of the PFDI-20. Third, this validation study applies to measurements in groups of patients, thus not directly to individual patients for individual measurements. Nevertheless, these questionnaires may create the opportunity to discuss certain important, but possibly less obvious, topics (e.g., emotional health) with the patient. Fourth, our study setting allowed us to determine the MIC of improvement, though not of deterioration. Only patients after treatment were included for analysis of responsiveness and interpretability. These patients were treated with the intention to improve their condition. We therefore did not determine the MIC of deterioration. And lastly, our study lacks the use of objective measures for assessment of symptoms of pelvic floor dysfunction.

The strengths of our study are the extensive assessment of measurement properties, covering the reliability (test-retest), validity, and—in particular—the responsiveness and interpretability of the measures in women after any treatment of pelvic floor dysfunction. An exception is the criterion validity, which requires the availability of a gold standard. Since there are no gold standards of symptoms and bother of pelvic

floor dysfunction, we were not able to test this property. We also included a reference population which is an important addition for the interpretation of the score distribution of the general population. The prevalence rates we found were comparable to the reported rates in the literature. In our study, the prevalence rates of UI and FI in the reference group were 45 and 9%, respectively, and are similar to the reported prevalence of UI in women in the general population (30–60%)[27,28] and FI in men and women in the general population (0–15.2% without significant gender differences).[29] The prevalence of POP in our reference group (21%) was higher than the reported prevalence of 4–15%.[27] Though this may be explained by the definition used by Milsom[27]: the reported rates are based on pelvic heaviness, genital bulge, and digital pressure on the vagina or perineum by defecation, and we included the need for digital pressure in the vaginal area for urination in the definition of POP. Ultimately, we had a high response rate of 73% with a limited dropout rate at 6 months of only 17%.

In conclusion, our findings provide positive evidence for the appropriateness of the Dutch PFDI-20 and PFIQ-7 to measure symptom distress and quality of life changes in women with pelvic floor dysfunction. With this study we validated the Dutch versions of the PFDI-20 and PFIQ-7 allowing use of these short forms for clinical or research purposes.

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Chapter 4

The Fecal Incontinence Quality of Life Scale (FIQL) and Fecal Incontinence Severity Index (FISI): Validation of the Dutch Versions

Lisette A. 't Hoen, Elaine Utomo, Willem R. Schouten, Bertil F.M. Blok and Ida J. Korfage.

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ABSTRACT

Aims

Fecal incontinence (FI) is known to have a major impact on quality of life. The Fecal Incontinence Quality of Life scale (FIQL) and Fecal Incontinence Severity Index (FISI) have been developed to assess this impact. The aim of this study was to validate the FIQL and FISI in the Dutch language.

Methods

The study population consisted of women and men experiencing FI and a reference group. The FIQL (four domains) and FISI questionnaires were validated by testing standardized measurement properties: discriminative ability, internal consistency, reproducibility, construct validity, and responsiveness.

RESULTS

A total of 55 patients and 277 reference participants were included. Patients had significant lower and higher scores at the FIQL and FISI, respectively, than references (FIQL: 2.58±0.70 and 3.92±0.36, FISI: 38.57±10.73 and 23.17±15.01; p<.001), indicating worse functioning in patients and with this the discriminative abilities of the measures. The FIQL demonstrated adequate internal consistency on all domains (0.72–0.96), except for the embarrassment domain (0.55). The reproducibility was good for both measures. A negative correlation was found between the FIQL and FISI. Furthermore, the FIQL showed a positive (0.77) and the FISI a negative correlation -0.31) with the Mental Component Summary scale of the SF-12. Responsiveness analysis showed a minimal important change of 0.40 points for the FIQL.

CONCLUSION

Validity and reliability were good in the Dutch FIQL, but inconclusive in the FISI. The Dutch FIQL can support physicians in determining the impact of FI on patient's quality of life.

INTRODUCTION

The spectrum of fecal incontinence (FI) comprises the involuntary loss of gas, liquid, and solid stool.[1] Prevalence figures differ from 1.4% to 42%, depending on the age and sex of the population and the definition of incontinence.[2-4] The incidence of FI is higher in women and higher with age. FI is known to have a major impact on the quality of life (QoL) in patients, resulting in psychological symptoms, functional loss in daily life, and even social isolation.[5] Furthermore, FI is associated with other pelvic floor disorders such as urinary incontinence and pelvic organ prolapse.[6]

To assess the severity of FI and its impact on QoL, standardized and validated instruments are needed, which can also be used to diagnose FI and to assess the effectiveness of FI therapy. It is important to establish that measures adequately evaluate the topic of interest before they can be used in clinical practice. Standardized validation processes have been developed to assess this ability.[7] Several validated questionnaires are available in English, such as the International Consultation on Incontinence Modular Questionnaire-Bowel symptoms (ICIQ-BS),[8] Manchester Bowel Questionnaire, [9] Fecal Incontinence Quality of Life scale (FIQL)[10] and the Fecal Incontinence Severity Index (FISI).[11]

We have chosen to use the FIQL and the FISI because of the grade B recommendation by the International Continence Society, prevalent use in clinical research about pelvic floor disorders, and personal preference. The FIQL was also validated in various other languages.[12–17] The FIQL is a condition-specific quality of life measure to assess FI.[10] The FISI is a scoring system to assess the severity of symptoms of FI.[11] To enable the use of proper measures in Dutch clinical practice, versions of the FISI and FIQL have yet to be translated and validated. The aim of this study is to provide validated versions of the Dutch FISI and FIQL following a standardized procedure to evaluate the measurement properties.[18]

METHODS

This study is part of a large health-related QoL study among patients visiting a tertiary pelvic floor center.[19–21] Approval was obtained by the local medical research ethics committee (MEC-2008-376) and guidelines following good clinical practice were followed.

Linguistic Validation

A standardized guideline was used for the translation of the FIQL and the FISI measures.[22] Three native Dutch each independently translated the English FIQL and FISI to

Dutch. After discussion and revision of differences, a native English speaker performed a backward translation. In a pilot study, 10 patients participated in a face-to-face validation and changes were made according to their feedback. The final versions of the FISI and FIQL were then used for this study (See "Vragenlijsten").

Study Population

Patient group

Women and men were eligible for inclusion when they experienced symptoms of FI for at least 3 months, spoke fluently Dutch, and were over 18 years old. Patients with current malignancy, dementia, mental retardation, and/or another neurological disease were excluded. Eligible patients were informed about this study by their physician during a regular outpatient visit. If interested in participation, they received an information package containing the consent form and the first two questionnaires. After written informed consent was given, these questionnaires were to be filled out during the inclusion visit, and 1 week after inclusion. The second set of questionnaires was sent out through postal mail and completed 6 months after inclusion. Treatment was not initiated during the first week of study participation. An extra question taken from the RAND 36-Item Health Survey, the RAND 36- Health Transition Item (RAND 36-HTI), was added to the last questionnaires.[23] This question compares the general health of patients to 1 year ago.

Reference group

An ISO-certified (ISO 26362) panel was used as a reference group. Stratification for age, educational level, and residence was performed to create a representative group of the Dutch general population. Beforehand, the presence of FI was unknown.

Questionnaire

The questionnaire consisted of three measures:

- The FIQL is a condition-specific measure that evaluates QoL in patients who experience FI. The measure consists of 29 questions, subdivided into four subscales: Lifestyle, Coping/Behaviour, Depression/Self-perception, and Embarrassment. With a few exceptions, responses are graded on a 4-point Likert-scale ranging from 1 ''strongly agree'' to 4 ''strongly'' disagree. The additional response option ''not applicable'' is graded with a score of 4, in concordance with Dr. Rockwood, developer of the FIQL.[10] Question 1, general health, is graded from 1 ''excellent'' to 5 ''poor'' and is reversely scored. Question 4, FI specific depression, is graded from 1 ''extremely so'' to 6 ''not at all.'' The scale scores are calculated by adding the numerical values of all responses in that specific scale and then dividing by its

number of items. Scale scores are only calculated if at least half of the items have been answered. Higher scores indicate a better QoL.[10]

- The FISI is a severity rating score for FI. This score evaluates the frequency of four types of FI: gas, mucus, and liquid and solid stool. Frequency options range from "two or more times a day" to "never." Surgeon and patient specific ratings are available. In this study, the scores were based on patient specific ratings. Higher scores indicate more severe FI.[11]
- The Short Form Health Survey (SF-12) is a general health QoL questionnaire. Based on the responses two summary measures can be calculated, the physical component summary (PCS-12) and the mental component summary (MCS-12).[24] The SF-12 was distributed to the patient group only.

Measurement Properties

The following measurement properties were evaluated following standardized quality criteria[18]:

Reliability

Internal consistency

This indicates the extent to which the items in a (sub) scale assess the same construct. A Cronbach's alpha of >0.70 was considered to show adequate and >0.50 to show moderate internal consistency.[18]

Reproducibility

This indicates the degree to which scores in a stable patient remain similar on repeated measurements. The intraclass correlation coefficient (ICC) was calculated to evaluate test-retest reliability, that is, the extent to which patients can be differentiated from each other, despite measurement error. A value of at least 0.70 was required for adequate test-retest reliability.[25] Agreement concerns the similarity between scores on repeated measures. The measurement error (systematic and random error of a score not due to true changes) was quantified as limits of agreement (LOA). The LOA represent the range of a specific percentage of the differences between two sets of scores and are calculated as the mean change in score ±1.96 * standard deviation (SD) of the changes.[26] The impact of the measurement error has been calculated by relating the range of the LOA to the range of the total score of the measure.

Validity

Content validity

This is the extent to which the measure addresses the concepts of interest in the target population. Face validity is the degree to which the measures indeed presents an ad-

equate reflection of the construct to be measured, in this case clinical symptoms and quality of life dependent on FI.[18] Floor or ceiling effects are present if more than 15% of the responders reported the highest or the lowest score.[18] Floor and ceiling effects were determined for total and scale scores.

Criterion validity

This is the correlation between the measure of interest and a gold standard. No perfect gold standard exists for the FIQL or FISI. The SF-12 was chosen as a substitute, because it is a commonly used generic health-related QoL measures and consists of a physical and a mental component scale, which could correspond to the FISI and FIQL, respectively. The correlation between the FIQL and FISI was determined as well. Pearson's *r* was used to calculate the correlations between the different measures.[18]

Construct validity

This is the extent to which predefined hypotheses about the scores of the FIQL and FISI measures in relation to other measurements could be confirmed. If at least 75% of these hypothesis were correct, construct validity was considered adequate.[18] We formulated the following hypotheses:

a. FISI and FIQL scores will be negatively correlated.
b. FISI scores will be higher in patients than in the reference group.
c. FIQL scores will be lower in patients than in the reference group.
d. In patients FIQL scores will be positively correlated with MCS-12 scores.

Responsiveness

This is the ability of a measure to detect clinical important change over time. This was only calculated for patients who received treatment. The area under the receiver operating characteristic (ROC) curve (AUC) shows the ability of a measure to distinguish patients who have improved from those who have not. The RAND 36-HTI was used as an external criterion to determine the AUC for the FIQL and FISI scores. An AUC of at least 0.50 was considered adequate.[18]

Interpretability

This is the degree to which a qualitative meaning can be assigned to the quantitative scores of the measure. To indicate a true clinical relevant improvement we used the minimal important change (MIC), defined as the optimal ROC cut-off point; the value for which the sum of proportions for misclassifications ([1-sensitivity]+[1-specificity]) was smallest.[7] The LOA should be smaller than the MIC.[18]

Statistical Methods

To determine an adequate sample size quality criteria were followed, which stated that at least 50 patients were required.[18] We reported continuous data as mean and SD and the categorical data as numbers and percentages. Differences between patient and reference group were evaluated using the Student's t-test and Chi-square test for continuous and categorical variables, respectively. One-way analysis of variance (ANOVA) was used for the evaluation of more than two independent groups. Treatment options were divided into three subgroups; conservative, pharmaceutical, and surgical. A two-sided *p*-value of <.05 was considered significant. Statistical analysis was performed using SPSS version 21.0 (IBM Crop., Armonk, NY).

RESULTS

Out of the 91 patients interested in study participation, 55 (60%) completed the first questionnaire (Figure 4.1). Table 4.1 displays the characteristics of patient and reference group (n=277) and shows a higher percentage of women in the patient group than in the reference group. The total score and four subscale scores of the FIQL are significantly lower in the patient group, indicating a worse quality of life due to FI. The FISI score is significantly higher in the patient group, indicating more severe symptoms of FI.

Reliability

Internal consistency

For the FIQL the Cronbach's alpha ranged from 0.55 to 0.96 on the total score and on the four separate domains in the patient group. It was below 0.70 for the embarrassment domain only, indicating moderate internal consistency for that domain and adequate internal consistency for the total score and the three other domains. For the reference group the Cronbach's alpha for the FIQL were adequate as well (Table 4.2). The FISI had a low Cronbach's alpha of 0.22 in patients, while it had a moderate Cronbach's alpha of 0.66 in the reference group (Table 4.2).

Reproducibility

The test retest period had a mean duration of 7.5 days. Table 4.2 demonstrates the excellent reliability for the total (ICC 0.95) and domain scores (ICC 0.80–0.95) of the FIQL. A good reliability was shown for the FISI (ICC 0.72) as well. The impact of the measurement error is expected to be 25% when relating the range of the LOA (-0.51 to 0.47) to the range of the total FIQL score (0–4). For the FISI the impact of the measurement error is expected to be 48%, LOA (-16.26 to 13.02).

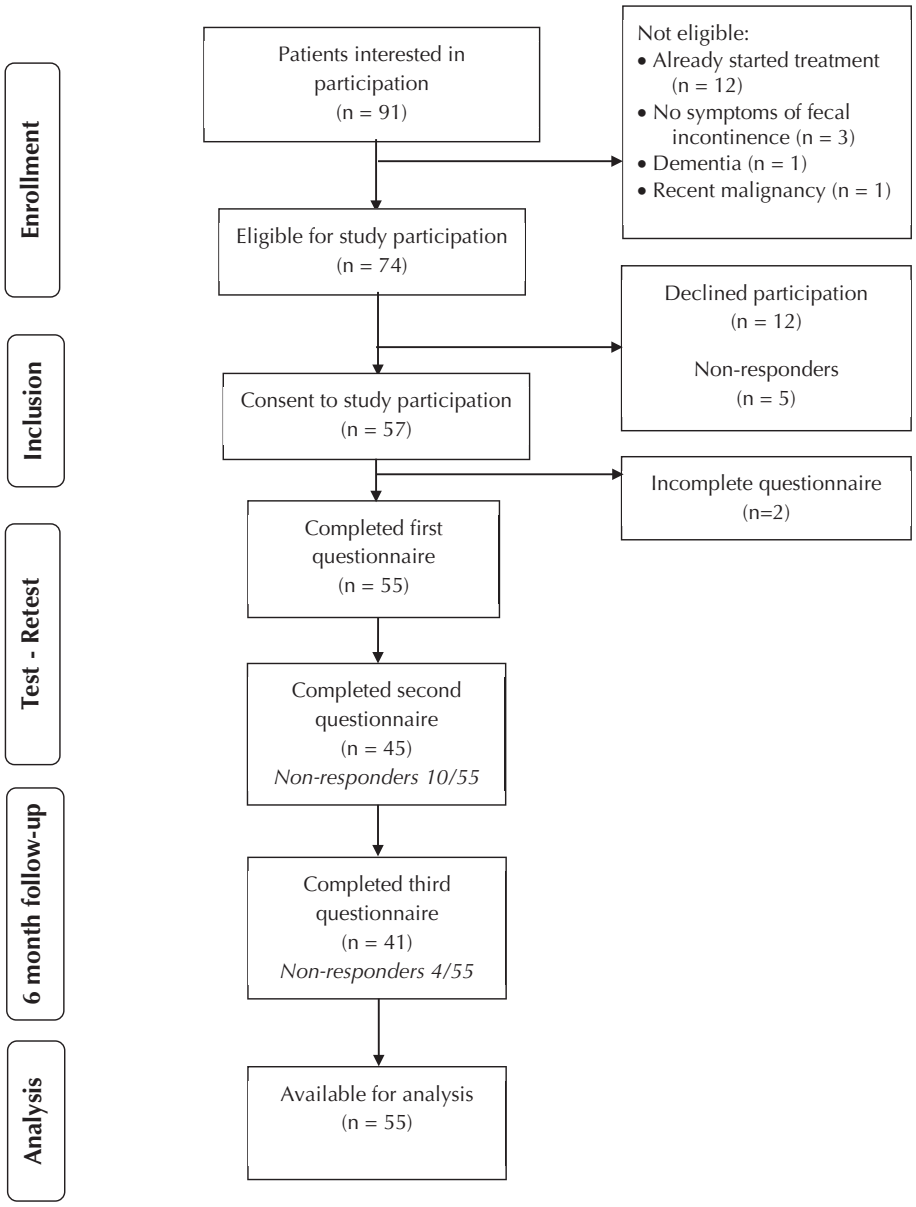

Figure 4.1 Flowchart: inclusion process of patient group

Validity

Content validity

Face validity was considered adequate for the FIQL and FISI by the researchers and 10 patients during the pilot study. For the total score of the FIQL, a ceiling effect was observed in 68% of the reference group, reflecting the low prevalence of FI in this group.

Table 4.1 Demographic and Clinical Characteristics of the Study Group (Patient vs Reference).

	Patient group (n=55)	Reference group (n=277)	*p*-value
Gender, number of women (%)	52 (95)	141 (51)	< .001
Age (years), mean±SD	59.3 ± 12.45	48.7 ± 16.2	< .001
Educational level, number(%)			
Lower	20 (36)	59 (21)	.01
Middle	25 (45)	133 (48)	
Higher	10 (18)	85 (31)	
Scores, mean ± SD			
FISI[a]	38.57 ± 10.73	23.17 ± 15.01	<.001
FIQL[b]	2.58 ± 0.70	3.92 ± 0.36	<.001
Lifestyle	2.82 ± 0.93	3.92 ± 0.33	<.001
Coping/behaviour	2.07 ± 0.73	3.85 ± 0.43	<.001
Depression/self-perception	3.20 ± 0.98	4.04 ± 0.41	<.001
Embarrassment	2.23 ± 0.80	3.86 ± 0.43	<.001
Scores at 6 month follow-up, mean±SD	(n=45)		
FISI[a]	35.91 ± 14.41		.16[d]
FIQL[b]	2.72 ± 0.66		.01[d]
Lifestyle	2.97 ± 0.76		.02[d]
Coping/behaviour	2.24 ± 0.77		.01[d]
Depression/self-perception	3.33 ± 0.79		.17[d]
Embarrassment	2.37 ± 0.89		.06[d]
Scores SF-12, mean±SD	(n = 23)		
PCS-12[c]	41.50 ± 11.66		
MCS-12[c]	46.26 ± 13.39		

[a] Higher FISI scores indicate more severe FI.
[b] Higher FIQL scores indicate a better FI quality of life.
[c] Scores higher than 50 indicates better quality of life, scores lower than 50 indicates poorer quality of life.
[d] Difference between baseline and 6 month follow-up.

For the FISI, a floor effect was observed in the reference group (16%), again reflecting the low prevalence of FI.

Criterion validity

In the patient group no correlation was found between FIQL (or any of its domain scores) and FISI, while in the reference group significant negative correlations were found (Table 4.3). Correlations of the FIQL and the FISI with the PCS-12 were insignificant (Table 4.3). Significant positive correlations were found for all four domains and total score of the FIQL with the MCS-12, and a significant negative correlation was found for the FISI and MCS-12.

Table 4.2 The Internal Consistency is presented with the Cronbach's alpha for total and domain scores

	Cronbach's alpha Patients	Referents	Test	Retest	Intraclass correlation coefficient (95%CI)	Mean change ± SD	Limits of agreement[a]
FIQL Total (n=40)	0.95	0.96	2.61 ± 0.69	2.64 ± 0.71	0.95 (0.90 – 0.97)	-0.02 ± 0.25	-0.51 – 0.47
Lifestyle	0.93	0.94	2.82 ± 0.93	2.78 ± 0.97	0.94 (0.89 – 0.97)	0.04 ± 0.33	-0.61 – 0.68
Coping/behaviour	0.86	0.93	2.08 ± 0.76	2.17 ± 0.82	0.93 (0.88 – 0.96)	-0.09 ± 0.29	-0.66 – 0.48
Depression/self-perception	0.89	0.79	3.27 ± 0.92	3.26 ± 0.89	0.95 (0.90 – 0.97)	0.01 ± 0.30	-0.58 – 0.60
Embarrassment	0.55	0.72	2.30 ± 0.80	2.36 ± 0.88	0.80 (0.67 – 0.89)	-0.07 ± 0.53	-1.11 – 0.97
FISI Total (n=42)	0.22	0.66	37.83 ± 10.18	39.45 ± 9.57	0.71 (0.53 – 0.84)	-1.62 ± 7.47	-16.26 – 13.02

The ICC and LOA scores reflect the reproducibility of both questionnaires. [a] Limits of agreement is calculated as: mean *change* ± 1.96 * SD*change*

Table 4.3 The correlation between FIQL total, FIQL domains, and FISI in the patient group (n=55) and the reference group (n=277), *the numbers in italic* presents the clinical correlation of the FIQL.

	FIQL Total	Lifestyle	Coping / behavior	Depression/self-perception	Embarrassment	FISI
FIQL Total	1.00					
	1.00					
Lifestyle	0.87[a]	1.00				
	0.57[a]	*1.00*				
Coping/behavior	0.82[a]	0.81[a]	1.00			
	0.66[a]	*0.71[a]*	*1.00*			
Depression/self-perception	0.89[a]	0.69[a]	0.67[a]	1.00		
	0.86[a]	*0.37[a]*	*0.37[a]*	*1.00*		
Embarrassment	0.64[a]	0.32[b]	0.30[b]	0.48[a]	1.00	
	0.57[a]	*0.56[a]*	*0.59[a]*	*0.32[a]*	*1.00*	
FISI	-0.17[c]	-0.16[c]	-0.22[c]	-0.22[c]	-0.02[c]	1.00
	-0.25[a]	*0.28[a]*	*-0.32[a]*	*-0.30[a]*	*-0.25[a]*	*1.00*
PCS-12	0.15[c]	0.18[c]	0.19[c]	0.28[c]	-0.36[c]	-0.36[c]
MCS-12	0.77[a]	0.58[a]	0.68[a]	0.70[a]	0.46[b]	-0.31[c]

The correlation between the FIQL and FISI, and PCS-12 and MCS-12 in the patient group only (n=23) was calculated to reflect the criterion validity.
[a] $p < .01$ [b] $p < .05$ [c] $p > .05$

Construct validity

Three of four predefined hypotheses were confirmed, indicating good construct validity.

a. An insignificant correlation was found between FIQL and FISI scores, and the hypothesis could therefore not be confirmed.
b. FISI scores of patients were higher than those of the reference group.
c. FIQL scores of patients were lower scores than those of the reference group.
d. The MCS-12 was positively correlated with the FIQL on all domains.

Responsiveness

At 6 month follow-up 45 patients completed the FIQL and FISI, of whom 32 patients had received treatment. Treatment was conservative in 17 patients, pharmaceutical in nine patients and surgical in six patients. The change in scores is shown in Table 4.1. The AUC for the FIQL in this group was 0.69, with a *p*-value of .08 (Table 4.4). For the FISI an AUC of 0.45 was found, with a *p*-value of .62.

Interpretability

Table 4.4 displays a MIC for the FIQL of 0.40 with 63% correctly identified as improved and 75% as not improved. The MIC is just within the range of the LOA, indicating that a change of 0.40 points could possibly be attributed to measurement error. For the FISI a MIC of 11.50 with 100% correctly identified as improved and 16% as not improved is found. This MIC is within the LOA range, indicating that with a change of 11.50 points a true improvement cannot be de distinguished from a measurement error.

Table 4.4 The FIQL and FISI scores in patients who have received treatment and their corresponding RAND-36 response reflect the responsiveness and interpretability.

	Number (%) (n=31)[a]	**FIQL scores (n=31)[b]**	**FISI scores (n=31)[c]**
RAND-36 health transition item			
Much worse / a little worse	5 (16)	0.23 ± 0.88	2.80 ± 9.42
Same	15 (48)	0.28 ± 0.34	-8.21 ± 15.85
A little better	5 (16)	0.40 ± 0.39	1.60 ± 6.43
Much better	6 (19)	0.74 ± 0.45	-11.67 ± 15.27
Area under the ROC curve		0.69	0.45
p-value		.08	.62
Minimal important change		0.40	11.50
Sensitivity; specificity		0.63 ; 0.75	1.00 ; 0.16

The RAND-36 functions as an anchor.

Data presented are in number (%) or $mean_{change}$ ±SD_{change} between baseline and follow-up at 6 months.

[a]Responsiveness has only been reported for the 31 patients who received treatment.

[b]Positive scores indicate an improvement in quality of life.

[c]Negative scores indicate an improvement in symptoms.

DISCUSSION

With this study, we have addressed the need for validated measures in the Dutch language for the assessment of the impact and severity of FI. We found an adequate reliability and validity for the FIQL, for the FISI these remain inconclusive. The results differed significantly between patient and reference groups for both measures, indicating worse quality of life and more severe symptoms of FI in the patient group, thereby demonstrating their discriminative power.

The Cronbach's alpha ranged between 0.55 and 0.95 for the total score and the four separate domains, which is similar to other validation studies.[12,13,15,17] The internal consistency was, therefore, adequate for all but one domain. The Cronbach's alpha for the embarrassment scale of 0.55 was below the minimum of 0.70 that is considered adequate. Such a low Cronbach's alpha has previously also been reported in other validation studies.[12,15,17] This embarrassment scale consists of (only) three questions. It addresses two unrelated aspects of shame, which may have led to a diverse pattern of answers and thus a relatively low Cronbach's alpha. In our opinion, the lower internal consistency for this scale is not problematic.

The low internal consistency we found for the FISI could (partially) be explained by the fact that the FISI is a scoring system for symptoms of FI. The construct measured by the FISI is observable and it is therefore clear that each item of the FISI contributes to the construct of FI. Guidelines state that low internal consistency does not have to be problematic if the construct to be measured is evident.[7]

For both measures the high ICC indicates an excellent reproducibility. The ICC for the FIQL total score and its four different domain scales range from 0.80 to 0.95, similar to previous validation studies.[12–14,17] The embarrassment scale showed a good reproducibility (ICC 0.80), even though it showed a sub adequate internal consistency (Cronbach's alpha 0.55). This strengthens the earlier assumption that the low internal consistency is acceptable. Future research could focus on this embarrassment scale by assessing the impact of redistribution of the scale items, deletion of the scale or patient interviews.

Similar to other validation studies, a scoring system was used to assess the correlation between clinical symptoms and the FIQL questionnaire. The FISI measure was chosen for this study, other studies have used both the FISI and Wexner scores.[13,15,17] Negative correlations between the FIQL and FISI were seen in both patient and reference groups, however, these were only significant in the reference group. The insignificant correlation in the patient group might be explained by the small sample size. This is the only predefined hypothesis that was not confirmed for the construct validity.

We found a good correlation for the FIQL and the FISI with the MCS-12. This was expected, given that the four domains of the FIQL mainly address the experience of

FI and not so much the (physical) symptoms. In other validation studies, which used the SF-36 to determine criterion validity,[13,15] positive correlations were found between the FIQL and some of the physical domain scores of the SF-36, however, we could not repeat this since we used the PCS-12. Therefore, an adequate comparison with the other validation studies cannot be made.

Responsiveness analysis of the FIQL showed a borderline significant AUC of 0.69 (p=.08), indicating a good correlation of the FIQL with clinical change determined with the RAND 36-HTI. The small number of patients available for this analysis might have contributed to the borderline significant p-value for the FIQL, and also have caused the AUC of 0.45 for the FISI. In addition, the weak correlation between the FISI and the RAND 36-HTI could be caused by the more divergent FISI scores. However, we could not elucidate the cause of this weak correlation. The difference between the constructs to be measured, that is, the experience versus the actual severity of the FI symptoms, could explain the difference found during the responsiveness and interpretability analysis with the RAND 36-HTI for the FIQL and FISI.

The strengths of this study are the use of standardized measurement properties to evaluate the quality of the Dutch versions of the FIQL and FISI and the use of a reference group to assess the ability of both measures to detect clinically relevant differences. Limitations of this study include the small number of patients who received treatment during the 6 months follow-up. This complicated the adequate evaluation of responsiveness and interpretability for the FISI.

CONCLUSION

The Dutch version of the FIQL showed good reliability and validity for use in patients with FI. The measurement properties of the FISI were found to be inconclusive. It is recommended to confirm the responsiveness of the FIQL and measurement properties of the FISI in a bigger cohort in future research.

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Chapter 5

The Pelvic Organ Prolapse/ Urinary Incontinence Sexual Questionnaire (PISQ-12): validation of the Dutch version

Lisette A. 't Hoen, Elaine Utomo, Anneke B. Steensma, Bertil F.M. Blok and Ida J. Korfage.

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ABSTRACT

Aims

To establish the reliability and validity of the Dutch version of the Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) in women with pelvic floor dysfunction.

Methods

The PISQ-12 was translated into Dutch following a standardized translation process. A group of 124 women involved in a heterosexual relationship that have had symptoms of urinary incontinence, fecal incontinence and/or pelvic organ prolapse for at least 3 months were eligible for inclusion. A reference group was used for assessment of discriminative ability. Data were analysed for internal consistency, reproducibility, construct validity, responsiveness, and interpretability. An alteration was made to item 12 and was corrected for during the analysis.

Results

The patient group comprised 70 of the 124 eligible women, and the reference group comprised 208 women from a panel representative of the Dutch female population. The Dutch PISQ-12 showed an adequate internal consistency with a Cronbach's alpha of 0.57 – 0.69, increasing with correction for item 12 to 0.69 – 0.75, for the reference and patient group, respectively. Scores in the patient group were lower (32.6±6.9) than in the reference group (36.3±4.8; p=.0001), indicating a lower sexual function in the patient group and good discriminative ability. Reproducibility was excellent with an Intraclass correlation coefficient for agreement of 0.93 (0.88 – 0.96). A positive correlation was found with the Short Form-12 Health Survey (SF-12) measure representing good criterion validity. Due to the small number of patients who had received treatment at the 6-month follow-up, no significant responsiveness could be established.

Conclusion

This study showed that the Dutch version of the PISQ-12 has good validity and reliability. The PISQ-12 will enable Dutch physicians to evaluate sexual dysfunction in women with pelvic floor disorders.

INTRODUCTION

Women who suffer from pelvic floor disorders (PFD) generally experience a reduced quality of life.[1] PFD includes urinary incontinence (UI), pelvic organ prolapse (POP) and/or fecal incontinence (FI). The prevalence of PFD in adult women has been estimated to be 23.7% and increases with age up to 49.7% in women aged 80 years or older.[2] Several studies have shown that women suffering from UI and POP experience a deterioration in sexual function,[3-5] and FI has also been associated with poorer sexual function.[6] Given the number of women suffering from PFD, it is important to evaluate their sexual function. Questionnaires can be used to assess the necessity for treatment of sexual dysfunction, and to determine treatment effectiveness.

The Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ-12) is a validated condition-specific quality of life questionnaire.[7] The International Continence Society recommends this questionnaire (with grade A) to assess sexual function with urinary symptoms.[8] In recent years the PISQ-12 has been validated in different languages: Arabic, Chinese, French, Persian, Portuguese, Swedish, and Turkish.[9-15] The increased awareness of sexual dysfunction in association with PFD strengthens the need for a validated Dutch measurement tool for sexual function.[16] A recent study has used a Dutch translation of the PISQ-12 to evaluate sexual function in the Dutch population.[17] However, this version was not validated and the results can therefore not be considered internationally compatible. The aim of this study is to develop a validated Dutch version of the PISQ-12 measure.

METHODS

This observational study was performed at a tertiary pelvic floor centre. It is part of a larger health-related quality of life study, which was approved by the medical research ethics committee (MEC-2008-376).[18,19]

Study populations

Patient group

Women were eligible for inclusion if they spoke Dutch fluently, were aged over 18 years, and in a heterosexual relationship. Also, they needed to have been experiencing symptoms of UI, POP stage 2 or higher and/or FI for at least 3 months. Exclusion criteria consisted of dementia, mental retardation, active malignant tumours, and no sexual activity during the past 6 months. During a regular outpatient visit all potentially eligible patients were informed about the study, and invited to participate by their treating physician. A patient information package containing the consent form

and the first two sets of measures were handed out. Patients were asked to fill in the questionnaires at three predetermined time-points (during the inclusion visit, and at 1 week and 6 months after inclusion), and to return the questionnaires by post directly after completion. The patients' educational levels were determined and classified as "lower" (primary school), "middle" (high school), and "higher" (college or university). The final questionnaire contained an extra question taken from the RAND 36-Item Health Survey (RAND 36-HTI). Patients were asked to compare their current general health status to their status 1 year ago.[20] No treatment was initiated during the first week following inclusion. Physicians and patients were unrestricted in the choice of treatment given the observational character of this study. For treatment evaluation we distinguished conservative, pharmaceutical and surgical treatments.

Reference group

The reference group in this study was taken from an ISO-certified (ISO 26362) panel of Dutch women 18 years of age or older. This group was stratified for age, educational level and residence to act as a representative group of the Dutch female population. Beforehand, the presence of pelvic floor symptoms in this group was unknown.

Questionnaire

The questionnaire consisted of two measures:

- The PISQ-12 is a short-form of the PISQ-31 measure.[21] It is a condition-specific measure that evaluates sexual function in heterosexual women who suffer from UI and/or POP. The PISQ-12 measures three domains: behavioural-emotive (items 1 – 4), physical (items 5 – 9) and partner-related (items 10 – 12). It is a self-administered questionnaire, and responses are graded on a five-point Likert scale ranging from 0 (always) to 4 (never). Items 1 – 4 are reversely scored and a total of 48 is the maximum score[22]; higher scores indicate better sexual function. Up to two missing responses are accepted. The total score sum with missing values is calculated by multiplying the number of items by the mean of the responses to the items reported by that person. The PISQ-12 is reported as a single sexual function score. It does not report the separate domains.[7]
- The Short Form-12 Health Survey (SF-12) consists of two summary measures, physical component scores (PCS-12) and mental component scores (MCS-12).[23] It is the short-form of the SF-36 measure and is frequently used as a gold standard for health-related quality of life questionnaires.[10,14] The SF-12 was distributed to the patient group only.

Linguistic validation

The translation process of the PISQ-12 was performed according to a standardized guideline.[24] First the English PISQ-12 was forward-translated by three independent native Dutch speakers. Differences were discussed and consensus was reached on the final version, which was then backward-translated by a native English speaker. A face-to-face test with ten patients was performed, and small textural changes were made accordingly without the need to adapt the content, resulting in the final Dutch version (See "Vragenlijsten").

Measurement properties

The questionnaire was validated according to the following measurement properties:

Content validity

Content validity is the extent to which the questionnaire measures the concepts of interest in the target population. The correspondence between the questionnaire items and clinical symptoms was subjectively assessed by the researchers. Face validity was determined by the researchers and a selected group of patients during linguistic validation.[25]

Internal consistency

Internal consistency is the correlation between different items in a questionnaire for the total and subscale scores, i.e. do the questions measure the same construct? A Cronbach's alpha was calculated for the total score and three subscale scores separately. Internal consistency is considered good if the Cronbach's alpha was between 0.70 and 0.95.[25] For study-related reasons we also calculated the Cronbach's alpha of the PISQ-12 minus item 12 for total score and the partner-related subscale score.

Reproducibility

Reproducibility is the degree to which scores on a questionnaire are similar in a stable person on repeated measurements. This can be reported through reliability and agreement.[25]

Reliability

Reliability considers the degree to which patients can be differentiated from each other, despite measurement error. The Intraclass correlation coefficient (ICC) for agreement was calculated to assess the test–retest reliability. A value of at least 0.70 is the minimum standard.[26]

Agreement

Agreement concerns the similarity in scores when measured on separate occasions, i.e. the measurement error. The limits of agreement (LOA) were reported and equal the mean change in scores of repeated measurements±1.96*standard deviation (SD) of the changes.[27]

Criterion Validity

Criterion validity is the degree to which questionnaire scores correlate with a gold standard. For the PISQ-12 no perfect gold standard exists. Therefore, criterion validity was determined using the SF-12, a quality of life measure resulting in physical and mental summary scores, which was also used in the Chinese validation.[10] Spearman's correlation was determined with values ranging from –1 to +1. A stronger negative or positive correlation is found when values are close to the extremes.[25]

Construct Validity

Construct validity is the extent to which hypotheses about the scores of a questionnaire in relation to other measures are valid. If at least 75% of the predefined hypotheses are correct, construct validity is considered adequate.[25]

The predetermined hypotheses were:

1. Women with lower scores on the PCS-12 have lower scores on the PISQ-12.
2. Women in the patient group will have lower PISQ-12 scores than women in the reference group.
3. PISQ-12 scores will increase after women have received treatment.

Responsiveness

Responsiveness is the extent to which a questionnaire is able to detect clinically important changes over time. This was calculated for all patients who had received treatment. The RAND 36-HTI was used as an external criterion in the determination of the area under the receiver operating characteristic (ROC) curve (AUC) for the PISQ-12 measurements. The AUC shows the ability of a questionnaire to distinguish patients who have improved. An AUC of at least 0.50 is considered adequate.[25]

Interpretability

Interpretability is the degree to which a qualitative meaning can be assigned to the quantitative questionnaire scores. The minimal important change (MIC) is the minimal change required to indicate a true clinically relevant improvement. The LOA should be smaller than the MIC.[25] The anchor-based ROC approach was used to determine the MIC. The MIC is the optimal ROC cut-off point and is defined as the value for which the sum of the proportions for misclassifications ((1 – sensitivity)+(1– specificity)) is smallest.[28]

Floor and ceiling effects

Floor and ceiling effects occur when more than 15% of the women have received the lowest or highest possible score.[25] Floor and ceiling effects were assessed at the total and subscale levels.

Statistical methods

To determine the sample size the quality criteria proposed by Terwee et al.[25] were followed. These state that a sample size of at least 50 patients is considered adequate to validate the questionnaire in Dutch. For continuous data we report the mean and standard deviation (SD). For categorical data we report counts and percentages. To evaluate the differences between the patient and reference group Student's *t* test and the chi-squared test were used for continuous and categorical variables, respectively. One-way analysis of variance (ANOVA) was used for the evaluation of more than two independent groups. A two-sided *p*-value of <.05 was considered significant. The anchor RAND 36-HTI was dichotomized to "improved" and "not improved"; "a little better" and "much better" were classified as "improved", while "same", "a little worse" and "much worse" were classified as "not improved". Statistical analysis of the data was done using SPSS version 21.0 (IBM Corp., Armonk, NY)

RESULTS

Of the 124 consecutive patients who were interested in participation in the study, 100 were found to be eligible and 70 of these patients consented to participate after receiving further information. During analysis, data from 70 patients were available, and consisted of at least one completed measure at one time-point (Figure 5.1). The reference group consisted of 208 women who had responded of 450 Dutch women contacted. Table 5.1 displays the nature of PFD in the patient group. The women in the reference group were younger than the women in the patient group (45.1±14.2 years and 53.6±12.3 years, respectively; $p<.001$). There was also a significant difference in educational level, with an average higher level of education in the reference group ($p=.004$). During the layout process of the PISQ-12 the answers to item 12 were incorrectly altered from "much less intense to much more intense" to "always to never". This unfortunate alteration resulted in suboptimal answer options. Therefore, we calculated the total score without item 12 as well. The reference group showed a significantly overall higher scores on the PISQ-12 measure than the patient group, indicating better sexual function in this group. After correcting for the altered item 12, the difference between the patient and reference group remained significant (Table 5.1).

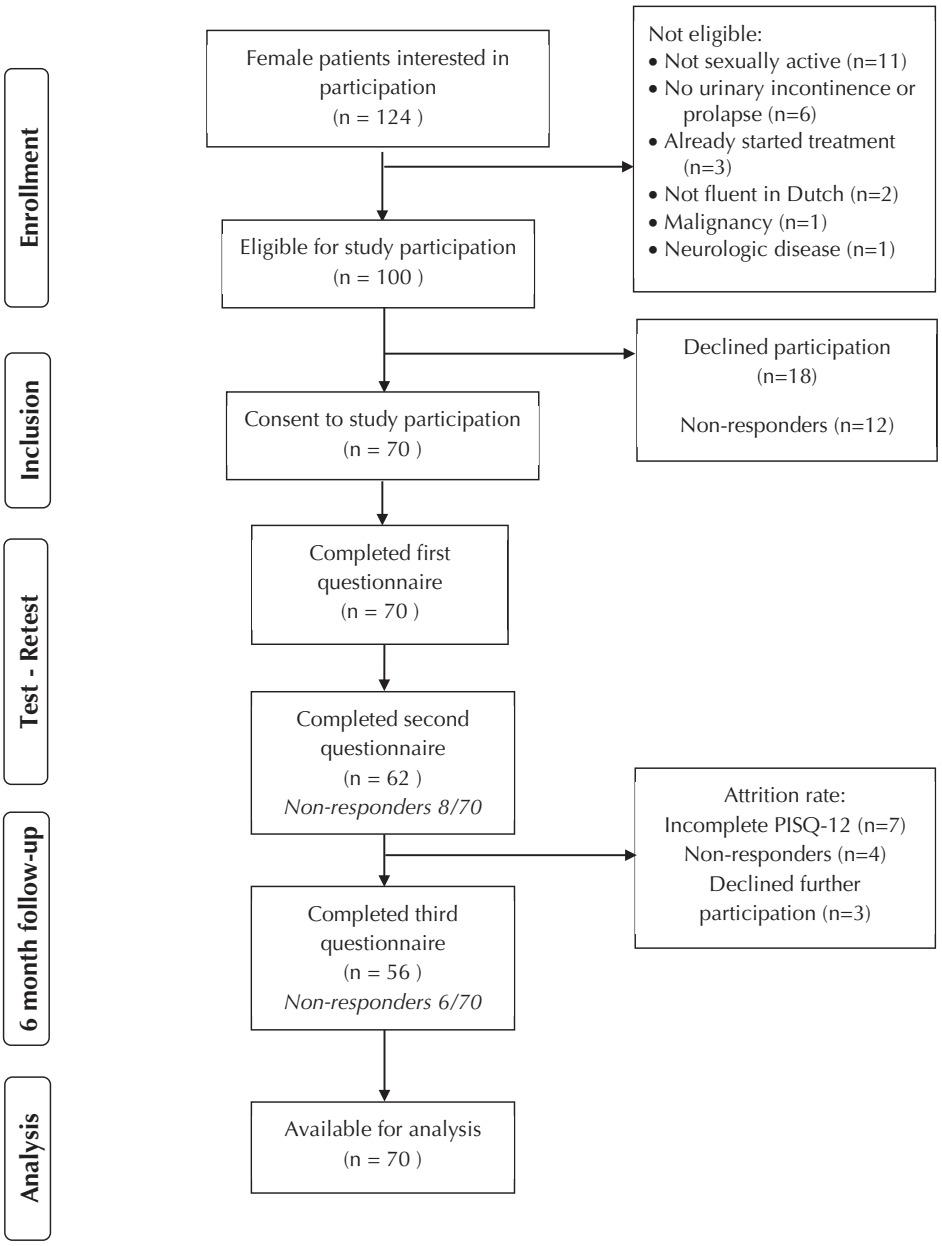

Figure 5.1 Flowchart: inclusion process of patient group

Measurement properties

Content validity

The content validity was determined to be adequate by the researchers and the selected patient group during the linguistic validation process.

Table 5.1 Demographic and clinical characteristics of the study population (patient and reference groups)

	Patient group (n=70[a])	Reference group (n=208)	*p*-value
Age (years), mean ± SD	53.6 ± 12.3	45.1 ± 14.2	<.001[d]
Education, n (%)			.004[e]
Lower	21 (31)	60 (29)	
Middle	38 (57)	86 (41)	
Higher	8 (12)	62 (30)	
Type of PFD, n (%)			
UI	60 (86)		
POP	24 (34)		
FI	17 (24)		
Treatment, n (%)			
Conservative	11 (31)		
Pharmaceutical	3 (8)		
Surgical	21 (61)		
PISQ-12 scores, mean ± SD[b]			
Baseline	32.7 ± 7.0	36.3 ± 4.7	.001[d]
Baseline, minus item 12	30.7 ± 7.1	34.8 ± 5.1	.01[d]
6 months (n=56)	33.5 ± 6.5		
6 months, minus item 12	31.4 ± 7.0		
SF-12 scores, mean ± SD[c]			
Baseline (n=56)			
PCS-12	41.7 ± 12.0		
MCS-12	48.1 ± 10.5		
6 months (n=46)			
PCS-12	44.6 ± 10.9		
MCS-12	45.4 ± 12.0		

[a]Unless stated otherwise
[b]Higher scores indicate better sexual function
[c]All scores higher than 50 indicates better quality of life, all scores lower than 50 indicates poorer quality of life.
[d]Students *t* test
[e]Chi² test

Internal consistency

Table 5.2 shows that the PISQ-12 total score had an adequate internal consistency in the patient group, with a Cronbach's alpha of 0.69. In the reference group the internal consistency showed a moderate Cronbach's alpha of 0.57. The domain scales differed between the patient and reference groups from 0.37 – 0.85 and 0.13 – 0.72, respectively. In addition, we calculated the Cronbach's alpha without item 12. The PISQ-12

showed an adequate internal consistency of 0.75 and 0.69 for the patient and reference groups, respectively. For the partner-related scale internal consistency improved from 0.37 to 0.55 for the patient group, and from 0.13 to 0.49 for the reference group.

Reproducibility

A total of 62 patients completed the questionnaires at baseline and the retest after a week (Table 5.2). The average test–retest period was 6.8±2.6 days. For the PISQ-12 ICC for agreement was 0.93 (range 0.88 – 0.96). This indicates adequate reliability. The ICC for agreement remained adequate after correction for item 12: 0.94 (range 0.90 – 0.96). Relating the LOA range (10.6) to the total PISQ-12 score range (48) resulted in an expected measurement error of 22 %.

Table 5.2 Internal consistency and reproducibility
The Cronbach's alpha reflects the internal consistency for the total and subscale scores.
The reproducibility is presented with the intraclass correlation coefficient and limits of agreement

	Internal consistency		Reproducibility (n=62)				
	Cronbach's alpha		Test score (mean ± SD)	Retest score (mean ± SD)	Intraclass correlation coefficient(95% CI)	Change (mean± SD)	Limits of agreement[a]
	Patient group	Reference group					
PISQ-12 total	0.69	0.57	32.6 ± 7.1	33.0 ±7.1	0.93(0.88-0.96)	-0.32 ± 2.71	-5.63 to 4.99
Minus item 12	0.75	0.69	30.7 ± 7.3	31.0 ± 7.3	0.94(0.90-0.96)	-0.32 ± 2.52	-5.26 to 4.62
Behavioral emotive	0.85	0.72	9.58 ± 3.86	9.68 ± 3.69	0.90(0.84-0.94)	-0.05 ± 1.45	-2.89 to 2.79
Physical	0.71	0.62	14.48 ± 4.53	14.71 ± 4.38	0.94(0.90-0.96)	-0.23 ± 1.54	-3.25 to 2.79
Partner-related	0.37	0.13	8.58 ± 2.27	8.63 ± 2.31	0.80(0.69-0.87)	-0.05 ± 1.67	-3.32 to 3.22
Minus item 12	0.55	0.49	6.66 ± 1.80	6.71 ± 2.00	0.85(0.77-0.91)	-0.05 ± 1.03	-2.07 to 1.97

[a] Calculated as: $mean_{change} \pm 1.96 * SD_{change}$

Criterion validity

The PISQ-12 scores showed positive correlations with the two summary scores of the SF-12 (PCS-12 and MCS-12; Figure 5.2). For the PISQ-12 and PCS-12 adequate agreement was found at baseline and the 6-month follow-up (Spearman's rho 0.41 and 0.34, respectively). The PISQ-12 and MCS-12 showed only adequate agreement at baseline (Spearman's rho 0.32).

Construct validity

Two of our three predefined hypotheses were confirmed:

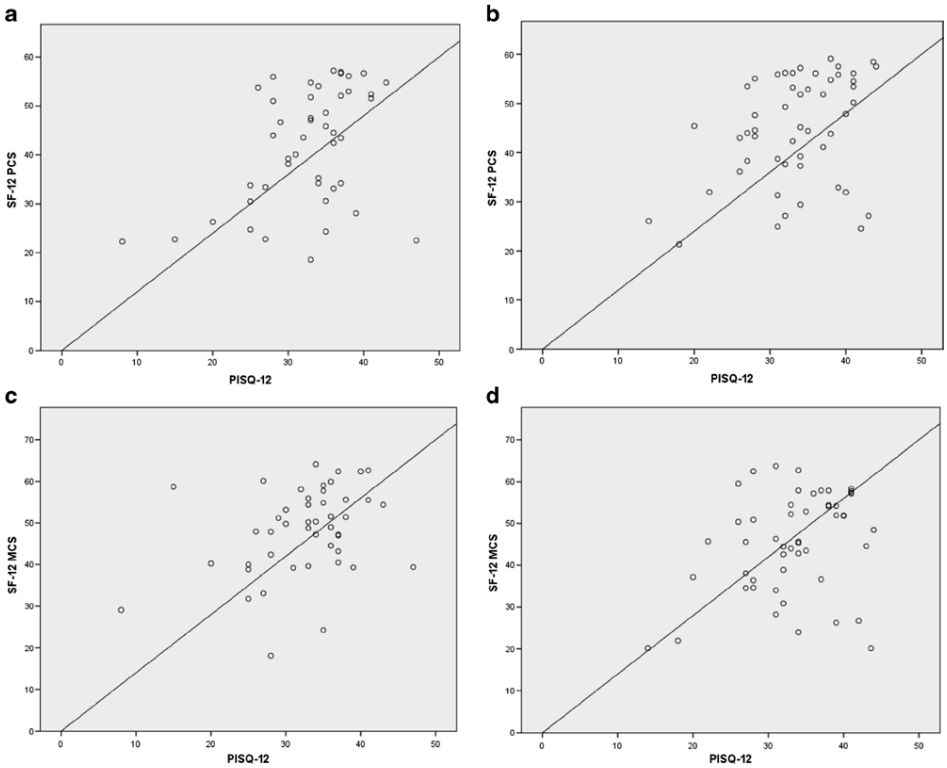

Figure 5.2 Correlations between PISQ-12 and SF-12 scores to establish the criterion validity.
a) PISQ-12 vs. PCS-12 at baseline (n=56; Spearman's rho 0.41; *p*=.005)
b) PISQ-12 vs. PCS-12 at 6 months (n=46; Spearman's rho 0.34; *p*=.02)
c) PISQ-12 vs. MCS-12 at baseline (n=56; Spearman's rho 0.32; *p*=.03)
d) PISQ-12 vs. MCS-12 at 6 months (n=46; Spearman's rho 0.26; *p*=.07)

1. A significant correlation was found between the PCS-12 score and the PISQ-12 score (Figure 5.2).
2. Women in the patient group did indeed have lower PISQ-12 scores than women in the reference group (Table 5.1).
3. Women who received treatment did not show a significant improvement in PISQ-12 score compared to before treatment (Table 5.3).

Responsiveness

At the 6-month follow-up, 56 patients completed the third round of questionnaires as shown in Table 5.1. Of these patients, 27 had received treatment for either UI, POP or FI. This treatment consisted of surgical treatment in 15 patients (56 %), conservative treatment in 9 patients (33 %) and pharmaceutical treatment in 3 patients (11 %). Of these 27 patients, 24 answered the RAND 36-HTI question. The AUC for the PISQ-12 in this group was 0.69 (*p*=.14, not significant; Table 5.3).

Table 5.3 PISQ-12 scores in patients who received treatment and their corresponding RAND-36 response reflect responsiveness and interpretability of the PISQ-12.
The RAND-36 functions as an anchor.

	Number (%) (n=24[a])	PISQ-12 scores[b]
RAND-36 health transition item		
Much worse / a little worse	5 (21)	2.60 ± 8.38
Same	10 (42)	-0.10 ± 5.97
A little better	5 (21)	2.20 ± 3.27
Much better	4 (17)	5.00 ± 4.97
Area under the ROC curve		0.69
p-value		.14
Minimal important change		-0.50
Sensitivity; specificity		0.89 ; 0.60

Data presented are in number (%) or mean change ±SD change between baseline and follow-up at 6 months
[a]Responsiveness reported only for the 24 patients who received treatment
[b]Positive scores indicate an improvement in sexual function

Interpretability

The MIC was −0.50 with a sensitivity of 0.89 and a specificity of 0.60 (Table 5.3). This corresponds with 89 % correctly identified as improved and 60 % as not improved. The MIC was inside the range of the LOA, indicating that the change in score of −0.50 in treated patients who have reported an improvement on the RAND 36-HTI was not clinically relevant.

Floor and ceiling effects

The distribution of floor and ceiling effects for the patient and reference groups is shown in Table 5.4. No floor and ceiling effects were reported in the patient group or the reference group for the PISQ-12 total score. Furthermore, no floor and ceiling effects were reported in the patient group on the scale level. In the reference group, only a ceiling effect on the physical scale was reported.

Table 5.4 The floor and ceiling effects at baseline for the patient and reference groups

	Patient group (n = 70)		Reference group (n = 208)	
	Floor	Ceiling	Floor	Ceiling
PISQ-12 Total score	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Behavioral emotive	3 (4%)	0 (0%)	1 (0.5%)	2 (1%)
Physical	0 (0%)	10 (14%)	0 (0%)	53 (25%)
Partner-related	0 (0%)	7 (10%)	0 (0%)	13 (6%)

DISCUSSION

In response to the growing need for a validated measure for sexual dysfunction in women with PFD, the aim of this study was to provide a validated Dutch version of the PISQ-12 measure. In women with PFD significantly lower PISQ-12 scores were observed than in the reference group representing the Dutch female population. This indicates poorer sexual function in the patient group, as expected, confirming the discriminative ability of the PISQ-12 measure. It also stresses the need to consider treatment options for sexual dysfunction in addition to treatment options for PFD alone.

The study showed that the Dutch version of the PISQ-12 has moderate internal consistency. Cronbach's alpha was 0.69 in the patient group and 0.57 in the reference group. Other studies validating the PISQ-12 in different languages have shown higher Cronbach's alpha values, ranging from 0.71 to 0.79.[10, 13,-15] The lower value found in this study originated from the partner-related item scale, probably due to the alteration of item 12. A Cronbach's alpha for the partner-related scale of 0.37 was found in the patient group, in contrast to 0.13 in the reference group when no adjustment for item 12 was performed. With correction for item 12, Cronbach's alpha scores for both the total score and the partner-related score increased to values comparable to those found for the earlier translated PISQ-12 versions. The internal consistency of the PISQ-12 then showed an adequate value of 0.75 for the patient group and 0.69 for the reference group. The big discrepancy found between the patient and reference group at the scale level was also resolved with the correction. This suggests that the incorrect answer options for item 12 caused the lower values before correction. Overall, the PISQ-12 showed an adequate consistency for the remaining 11 items.

The internal consistency of the partner-related scale was lower than that of the total score and both the behavioural-emotive scale and the physical scale, even after correction for item 12. This was also found in previous translations of the PISQ-12.[10, 15] It should be noted that the partner-related scale evaluates the physical sexual function related to the partner. However, even though sexual function is related to the partner, a poorer physical sexual function in the partner will not automatically result in a similar sexual dysfunction in the woman. A lower partner-related scale score does not need to be correlated with the behavioural-emotive and physical scale scores.

The reproducibility for the Dutch PISQ-12 in terms of the test–retest scores was excellent. The ICC for agreement was 0.93, comparable to that of the Swedish PISQ-12[14], confirming the reproducibility of this measure. With correction for item 12 the reliability remained stable, as expected, since patients received the same version of the measure at both time-points. The good ICC value enables the use of the PISQ-12 as a measure for distinguishing the severity of sexual dysfunction between patients.

The criterion validity of a questionnaire is preferably determined by the degree of its correlation the gold standard. Since no gold standard is available to determine sexual dysfunction in women with PFD we chose to use the SF-12[23] to assess the criterion validity of the PISQ-12. The SF-12 is a commonly used generic measure for health-related quality of life and was also used in the Chinese validation study of the PISQ-12.[10] We found a positive correlation between sexual dysfunction as assessed with the PISQ-12 and both summary scores of the SF-12 at baseline. However, at the 6-month follow-up the PISQ-12 showed a significant correlation with the PCS-12, but not with the MCS-12. This weakened correlation at follow-up could potentially be explained by the fact that the group of patients was smaller at 6 months. It is also possible that the SF-12 was not the right choice to assess the criterion validity because the SF-12 is a generic measure: changes in quality of life unrelated to sexual dysfunction might have influenced the SF-12 score without influencing the PISQ-12 score (criterion contamination). We are thus unable to conclude that the PISQ-12 has a good criterion validity using the SF-12. Therefore, we recommend the use of a larger patient group to determine the criterion validity of the PISQ-12.

The responsiveness and interpretability reported were not adequate. Of the 35 patients who did receive treatment during the 6-month follow-up, only 24 completed the third questionnaire including RAND 36-HTI. This small number of patients could explain why the AUC and MIC were not significant. Furthermore, the study was conducted at a tertiary centre, where women might present with more severe symptoms of PFD. Treatment options might therefore be more limited, which could explain the only slight overall improvement of PISQ-12 scores after treatment. This probably also contributed to the inability to confirm hypothesis 3 for the construct validity. In addition, the anchor used for responsiveness evaluation, the RAND 36-HTI, solely addresses one aspect of general health, while sexual function is multifactorial. It might therefore not provide an adequate comparison for this specific evaluation.

No floor or ceiling effects were found for the total score of the PISQ-12 for the patient group or the reference group. The complexity of symptoms of PFD could have contributed to the lack of floor and ceiling effects in the patient group. In the reference group ceiling effects were found only on the physical subscale. This has previously also been demonstrated in patients.[29] After treatment the physical subscale showed ceiling effects, while the other subscales did not.

The strength of this study was the use of the quality criteria for the evaluation of the measurement properties tested, as proposed by Terwee et al.[25] Also, the use of a reference group enabled clarification of differences in sexual function between patients with PFD and a reference population. There are some limitations to this study. First, item 12 was altered during the layout process. In our opinion, errors can (and will) always occur. If an error does occur, we think it best to acknowledge it and try to correct

for it in the analysis. Second, the small number of patients during our 6-month follow-up made it difficult to properly assess the responsiveness of the Dutch PISQ-12. Third, the PISQ-12 can only be used in sexually active women. Consequently, an assessment of sexual dysfunction in sexually inactive women cannot be performed. The PISQ-IR is a new questionnaire that does take sexual function and activity or inactivity into account [30]. Therefore, the PISQ-IR can be used in all patients presenting with symptoms of PFD. However, currently no validated Dutch version is available. The actual use of the Dutch PISQ-12 might affect treatment in sexually active women. It would be worthwhile to evaluate the impact of the use of the Dutch PISQ-12 in clinical practice.

In conclusion, this Dutch version of PISQ-12 was tested following well-established guidelines on measurement properties. It was demonstrated to have adequate validity and reproducibility, especially after correction for item 12 on the partner-related scale. The use of this measure in clinical practice will enable Dutch physicians to assess the impact of sexual dysfunction on women with PFD who are sexually active. It is recommended that responsiveness be determined in a larger group of patients.

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Chapter 6

The measurement properties of the five-item International Index of Erectile Function (IIEF-5): a Dutch validation study

Elaine Utomo, Bertil F.M. Blok, Hester Pastoor, Chris H. Bangma and Ida J. Korfage

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ABSTRACT

Erectile dysfunction, affecting men worldwide, is associated with worse mental health. The severity of erectile dysfunction as well as the effect of its treatment can be assessed using valid self-reported outcome measures. A widely used measure is the International Index of Erectile Function short form (IIEF-5) which is not yet validated in Dutch. The objective of this study was to translate the IIEF-5 into Dutch and to investigate its reliability and validity to provide a useful evaluation tool. The IIEF-5 was translated into Dutch following standardized forward-backward procedures. To conduct this observational study, men with symptoms of erectile dysfunction completed the Dutch IIEF-5 at inclusion, one week later, and six months after inclusion. A population-based sample (reference group) completed the IIEF-5 once. The quality domains reliability and validity were addressed by testing the measurement properties internal consistency, reliability, measurement error, and content validity. Data of 82 patients and 253 reference group participants were analysed. Internal consistency was adequate with Cronbach's alpha of 0.94 in both patient and reference group. In patients, the test-retest reliability was adequate with an Intraclass correlation coefficient for agreement of 0.88. A floor effect was present in the patient group (42%), though not in the reference group (3%). There was no ceiling effect in patients (0%), while this was present in the reference group (17%). Analysis of responsiveness was not possible due to the limited number of patients receiving treatment. The Dutch IIEF-5 is a reliable and valid measure to determine severity of symptoms of erectile dysfunction. This evaluation tool is valuable for clinical use and interpreting results across international clinical studies. The context of a patient's sexual life is however indispensable and should be taken in mind.

INTRODUCTION

The estimated overall prevalence rate of erectile dysfunction (ED) ranges from 10% to 20% worldwide, considering variations in definitions, methodology, and study population.[1] A population-based study in the Netherlands - the Krimpen study - determined a crude incidence of 14.1 cases per 1,000 person years for clinically relevant ED.[2] We defined ED as a man's consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual activity.[3] Erectile dysfunction, as well as satisfaction with sex life, were found to be related with worse mental health in men of all ages.[4,5] As help seeking behaviour of Dutch men with ED slightly increased in the past 20 years[6], valid self-reported measures are important to evaluate symptoms associated with ED as well as to evaluate treatment effect. The International Index of Erectile Function (IIEF) is such a measure.[7,8] The widely used IIEF was "Grade A" recommended in erectile function assessment by the International Consultation of Sexual Medicine in 2010.[9] The demand for a brief, easily administered measure resulted in an abridged five-item version of the 15-item IIEF: the IIEF-5, also known as the Sexual Health Inventory for Men (SHIM).[10,11] It was developed for screening and diagnostic severity assessment in clinical practice and in clinical trials. Although the IIEF-5 has been validated in other languages,[12-15] a Dutch version is still lacking. We therefore translated the IIEF-5 into Dutch. For translated measures to be useful in research or clinical practice, they must adequately address measurement properties, including reliability, validity, responsiveness, and interpretability.[16,17]

This study was designed to translate the IIEF-5 into Dutch and to investigate its reliability and validity to provide a useful evaluation tool for men reporting symptoms of ED.

METHODS

We conducted this observational study at a tertiary urology centre as part of a larger validation study of health-related quality of life (HRQOL) pelvic floor measures.[18,19] The study was approved by the Institutional Ethics Committee (MEC-2008-376) and pre-registered at The Netherlands National Trial Register (NTR2355).

Study population and study design

Patient inclusion criteria were men aged 18 years or older with self-reported ED, and fluent and literate in the Dutch language. As described by the original developer, men were also supposed to be in a stable relationship with a female partner and to have the

possibility to engage in sexual activity and intercourse.[20] Exclusion criteria were active malignant tumours, dementia, and mental retardation.

At the initial visit, the treating practitioner explained the study to each consecutive patient potentially eligible for inclusion. The practitioner provided an information package including two sets of questionnaires to patients who were interested in participation. As this study was part of a larger validation study of HRQOL pelvic floor measures, the practitioner specified on the cover of the sets of questionnaires for which measure or measures the patient was eligible. The patients were then phoned by the investigator for further explanation, and were asked to complete the informed consent form and the first questionnaire immediately (baseline) and the second questionnaire one week later (T1). Six months after baseline patients received a third questionnaire to be completed at home through postal mail (T2). After each completion patients returned the questionnaires through postal mail using a return envelope. No treatment was initiated or changed during the test-retest period of one week. This one week period was long enough to prevent recall, though short enough to ensure that clinical change had not occurred. Information from the patient's medical record was retrieved about the cause of ED and the applied treatment, if any. Treatment was categorized into "conservative", "pharmaceutical", or "surgical". Date of birth and education were documented through the questionnaire. Educational level was classified as "low" (primary school), "intermediate" (high school), or "high" (college or university degree). The third questionnaire included a question about the change in patient's general health compared to one year ago. This health transition item of the RAND 36-Item Health Survey[21-23] contained the following response options: "much better", "a little better", "same", "a little worse", and "much worse". Patients who did not return the questionnaire were sent a reminder including a reply form where they could indicate if they required a replacement questionnaire, or if they refrained from further participation with the option to motivate. If questions were skipped or questionnaires were left empty without providing any reasons, a copy of the uncompleted questionnaire was sent immediately to the patient with the request to fully complete the questionnaire. Also, patients were then asked to motivate if they intentionally skipped a question or questions.

Reference data

Data from a representative sample of men aged 18 years or older in the Netherlands were collected through an ISO-certified Dutch online panel (ISO 26362).[24] This sample was stratified by age, educational level and residential area, and therefore representative for the Dutch male population above the age of 18. The presence or absence of ED in the participants was unknown beforehand. No inclusion or exclusion criteria were applied.

Questionnaire

The IIEF-5 consists of five items originating from the IIEF. Four of its five items were taken from the six-item erectile function domain of the IIEF which is a validated measure as a diagnostic evaluation tool.[25] The fifth item of the IIEF-5 concerns intercourse satisfaction.

Response options are based on rating scales from 0 to 5 or 1 to 5. The responses are summed resulting in a total IIEF-5 score ranging from 1 to 25, with lower values representing poorer sexual function. Erectile dysfunction can be classified into five severity grades: absence of ED (IIEF-5 score 22-25), mild (17-21), mild to moderate (12-16), moderate (8-11), and severe (1-7).[10,11]

Linguistic validation

The IIEF-5 was translated into Dutch following standardized forward-backward procedures: three independent forward translations and a backward translation by a native speaker.[26] The Dutch version of the IIEF-5 was tested in 10 patients with ED, where potential problems were explored and discussed guided by a checklist. Erectile dysfunction was defined according to the International Consultation on Sexual Dysfunctions.[9] This pilot testing led to the following adjustments: the word "penetration" (question 3) appeared too formal. We therefore used "entered" and put the word "penetration" between brackets. The words "sexual stimulation" (question 2) and "intercourse" (questions 3 to 5) were exemplified with footnotes. Some other minor textual changes were added without changing the content. The Dutch version of the IIEF-5 was then finalized and subsequently used in this validation study (See "Vragenlijsten").

Measurement properties

To address the quality domains reliability and validity, we tested the measurement properties internal consistency, reliability, measurement error, and content validity of the Dutch IIEF-5.[16]

- The **internal consistency** is the degree of interrelatedness among the items in the measure. A reliable measure assesses a single underlying concept by using multiple items. This was calculated with the Cronbach's alpha. A high Cronbach's alpha indicates high correlations between the multiple items. Values between 0.70 and 0.95 were considered to reflect adequate internal consistency.[17,27]
- The **reliability** is the proportion of the total variance because of "true" differences among patients. To assess the degree to which repeated measurements in stable patients provide similar answers we performed a test-retest. An Intraclass correlation coefficient (ICC) for agreement[24] of ≥ 0.70 was considered to reflect adequate reliability.[17,27]
- The **measurement error** is the systematic and random error of a patient's score not attributed to true changes. This was quantified using the limits of agreement

by Bland and Altman.[28] The absolute mean change in scores of repeated measurements during the test-retest period ($mean_{change}$)±1.96*standard deviation of these changes (SD_{change}) were the limits of agreement.

- The **content validity** is the degree to which the content of a measure adequately reflects the target construct. This was subjectively assessed and verified by examining whether the items appeared to be measuring what they are intended to measure ("face validity"). The floor and ceiling effects were also assessed. This may occur when 15% or more of the respondents score at the lower (floor) or upper (ceiling) end of the scale, thus could indicate a limited content validity.[17,27]

Statistical methods

Statistical significance was defined as *p*-value <.05. For comparison of patient and reference group the unpaired *t* test was used for numerical variables, and the chi-square test for categorical variables. General linear models were used to compare measure scores, controlling for demographics that differed significantly between patient and reference group in univariate analysis. Statistical analysis was performed using IBM® SPSS software 21.0, SPSS Inc., Chicago, IL, USA.

RESULTS

A total of 108 consecutive patients were initially interested and eligible, of which 82 (76%) consented to participate (Flowchart, Figure 6.1). The measure was sent out to 480 panel participants of which 253 (53%) responded. In the patient group, the mean age (64.4 ± 11.5 years) was higher (*p*<.001) than in the reference group (50.6 ± 15.7 years, Table 6.1). Also, educational levels differed significantly between patient and reference group. Information from the patient's medical record indicated that symptoms of ED were mostly due to an organic cause (81%). The patient group had a significant (*p*<.001) lower score of IIEF-5 (mean 5.5 ± 6.1, Table 6.2), indicating worse sexual health than the reference group (mean 18.8±7.2). The IIEF-5 score was used to classify the severity of ED: the majority of the patients (71%) versus 13% of the participants of the reference group were classified as "severe" ED. Most participants of the reference group had no ED (53%). These differences remained significant after adjusting for age and educational level.

Before reminders were sent, the missing item rate was highest in the questionnaire after one week follow-up (Table 6.3): 15% of patients left at least one item empty (three questionnaires were left completely empty). The final missing rates and the missing rates at other time-points were 6 to 7%. Missing items were balanced in numbers across the different items of the IIEF-5.

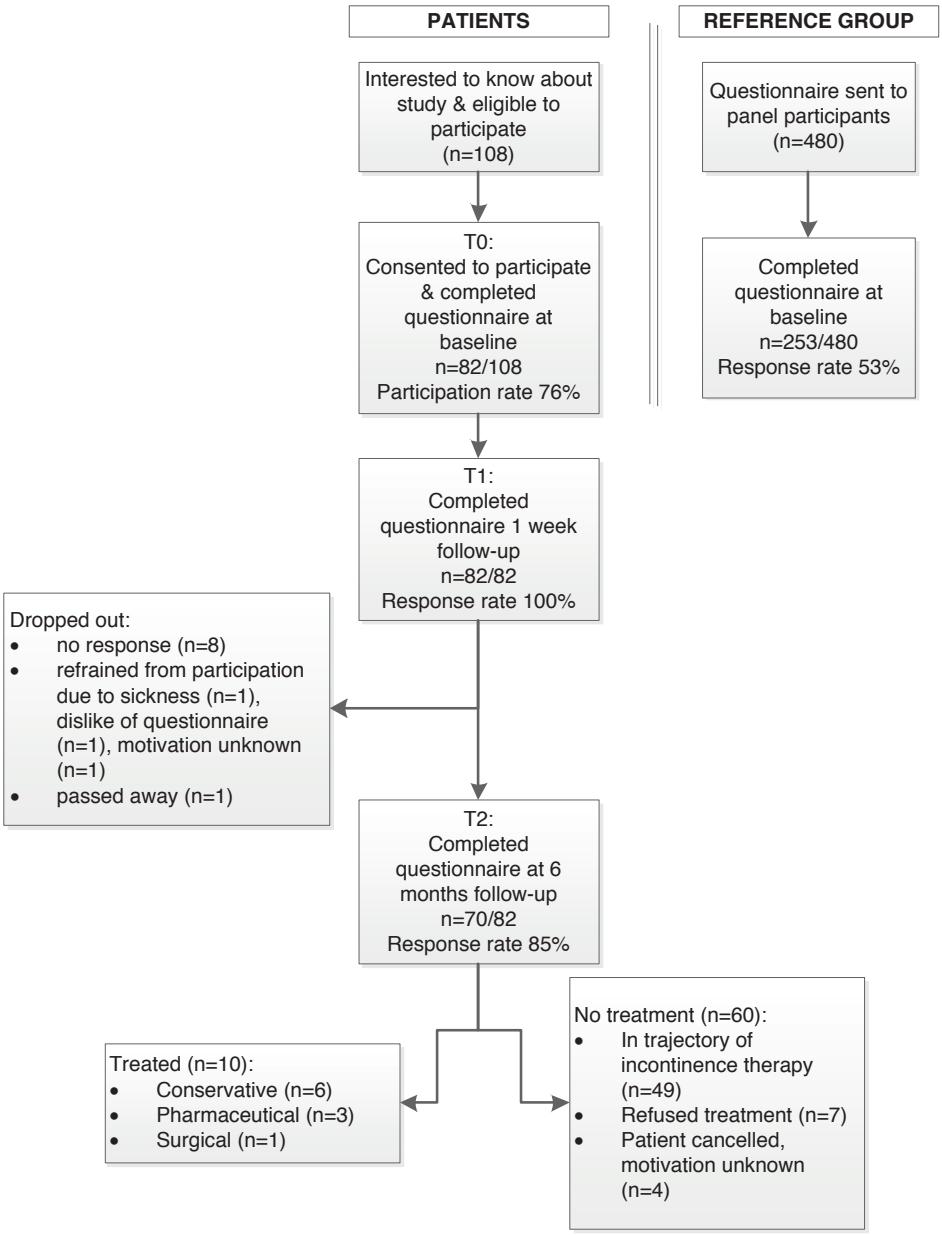

Figure 6.1 Study flowchart

Internal consistency, reliability and measurement error

The IIEF-5 score demonstrated adequate internal consistency with a high Cronbach's alpha of 0.94 in both patient and reference group (Table 6.4). On average, the retest assessments were completed nine days after baseline measurement. The $ICC_{agreement}$

Table 6.1 Characteristics of respondents

Demographics	**Patients** (n = 82)	**Reference group** (n = 253)	***p*-value**[a]
Age (years)	64.4 ± 11.5	50.6 ± 15.7	<.001
Educational level			<.001
Low	23 (29%)	24 (10%)	
Intermediate	36 (45%)	166 (66%)	
High	21 (26%)	63 (25%)	
Primary cause of ED		NA	
Organic	66 (81%)		
Psychogenic	8 (10%)		
Mixed	6 (7%)		
Unknown/missing	2 (2%)		

Data are mean ± standard deviation or number (%).
Abbreviations: *GLM* general linear models; *NA* not available
[a]*p*-value: corrected for age and educational level with general linear modeling

Table 6.2 IIEF-5 scores

	Patients (n = 82)	**Reference group** (n = 253)	***p*-value** univariate	***p*-value** GLM[b]
Score IIEF-5[a] at baseline ± SD (range 1 – 25)	5.5 ± 6.1	18.8 ± 7.2	<.001	<.001
Missing	5 (6%)	0 (0%)		
Score IIEF-5 after 1 week ± SD (range 1 – 25)	5.5 ± 5.6	NA		
Missing	6 (7%)	NA		
Score IIEF-5 after 6 months ± SD (range 1 – 25)	4.6 ± 5.4	NA		
Missing	4 (6%)	NA		
Classification of severity of ED at baseline[c], number (%)			<.001	
Severe (score 1-7)	55 (71%)	32 (13%)		
Moderate (score 8-11)	8 (10%)	15 (6%)		
Mild to moderate (score 12-16)	7 (9%)	20 (8%)		
Mild (score 17-21)	7 (9%)	52 (21%)		
No ED (22-25)	0	134 (53%)		

[a]Total score of IIEF-5 was only calculated if there were no missings, higher scores indicates better sexual health
[b]*P*-value: corrected for age and educational level with general linear model (GLM)
[c]Classification according to total score IIEF-5[20, 11]

of the IIEF-5 score was 0.88 (Table 6.4) and indicates adequate reliability. Table 6.4 also presents the absolute $mean_{change}$ of repeated measurements during the test-retest period, the corresponding SD_{change}, and the limits of agreement. Relating the range of the limits of agreement (10.1) to the range of the possible test-retest scores on the IIEF-5, that is -25 to +25 (50), the magnitude of the measurement error is 20%.

Table 6.3 Number of times missing per item

Item of IIEF-5	Baseline[a]	1 week follow-up[b]	6 months follow-up[c]
	(n)	(n)	(n)
1	3	6	4
2	3	7	1
3	2	3	2
4	2	4	2
5	1	6	2
% (number) of patient who skipped an item after reminder	6% (5/82)	7% (6/82)[d]	6% (4/70)[e]

[a]One questionnaire was left completely empty: unknown reason
[b]Three questionnaires were left completely empty: unknown reason, all were completed after sending reminder
[c]One questionnaire was left completely empty: not sexually active because ED after radical prostatectomy
[d]At one week follow-up, six patients initially skipped an item before reminder was sent
[e]At six months follow-up, one patient initially skipped an item before reminder was sent

Table 6.4 Internal consistency and reliability

	Internal consistency (Cronbach's alpha)		Test-retest reliability Patients (n = 73)		
	Patients	Reference group	Intraclass Correlation Coefficient	$mean_{change} \pm SD_{change}$[a]	Limits of agreement[b]
	n = 77	n = 253	n = 73		
IIEF-total score (1-25)	0.94	0.94	0.88	1.4 ± 2.6	-3.7 – 6.4

[a]Higher scores indicate better sexual health
[b]Limits of agreement described by Bland and Altman[28] = $mean_{change} \pm 1.96 * SD_{change}$

Content validity

In patients, no ceiling effect (0%) was observed in the IIEF-5 score, while floor effect was present in 42%, exhibiting a non-normal score distribution towards the less favourable low score of one (Table 6.5). In the reference group, the contrary was seen: the floor effects were acceptably low (3%) while a ceiling effect (17%) was present.

Follow-up

A total of 70 patients completed the IIEF-5 on average 5.9 months after baseline assessment (T2, Figure 6.1 Flowchart). Of these patients, 10 received treatment during follow-up and 60 men were untreated because they received urinary incontinence therapy (n=49), refused surgical treatment (n=7), or they cancelled surgery due to unknown reasons (n=4). The change in IIEF-5 score in treated patients after six months was 2.2 ± 3.9 compared to -0.6 ± 2.8 in untreated patients (p=.007). The change seen is in accordance with the hypothesis that IIEF-5 scores of treated patients will increase,

and therefore suggestive of sensitivity. Analysis of responsiveness and interpretability was not possible because of the limited number of treated patients.

Table 6.5 Floor and ceiling effects at baseline

Questionnaire	Patients (n=77)				Reference group (n=253)			
	Floor		Ceiling		Floor		Ceiling	
	n	%	n	%	n	%	n	%
IIEF-5 total score (1-25)	32	42	0	0	7	3	42	17

DISCUSSION

The objective of this study was to validate the Dutch version of the IIEF-5 and thereby to provide a useful measure for use in men with symptoms of ED. Generally, our findings regarding the internal consistency, reliability, and measurement error were very positive. Cronbach's alphas of 0.94 in both patient and reference group are considered high. We found an $ICC_{agreement}$ of 0.88 (test–retest) for the five items of the Dutch translation of the IIEF-5, which demonstrates adequate reliability. Furthermore, the $mean_{change}$ after one week was ± 1.4 IIEF-5 score points, demonstrating adequate agreement. Finally, comparing patient and reference group mean scores, the IIEF-5 had adequate discriminative ability (p<.001). Results obtained in our study were similar to previously reported findings in other studies. *Shamloul et al*. reported adequate internal consistency with high Cronbach's alpha of 0.91 and adequate test-retest reliability with a high $ICC_{agreement}$ of 0.92.[14]

Ceiling effects were high in the reference group and floor effects were low, while in patients ceiling effects were absent but substantial floor effects were observed. This means that 42% of patients, who were all in a stable relationship, actually did not attempted sexual intercourse. *Cappelleri et al.* stated that the IIEF-5 score range of 1 to 7 - representing severe ED - indicates sexual functioning that is so poor that men do not bother to attempt sexual activity and intercourse.[20] We agree with *Cappelleri et al.* that the IIEF-5 should not be used blindly and should be placed in context. More important, it is intended to complement clinical judgment and diagnostic assessment, and the practitioner should explore patient's desire and opportunity for sexual activity to ensure that low IIEF-5 scores are truly indicative of severe ED.[29] In other words, the sexual response cycle of the patient consisting of sexual desire and erection (excitement phase); sensation of orgasm and contentment of ejaculation (orgasmic phase); and detumescence including satisfaction (resolution phase); should be examined.[30]

Furthermore, sexual activity consists of more than intercourse alone and therefore assessment should also include solo sexual activity like masturbation. Regarding the importance of clinical judgment, we were not able to propose any inclusion criteria for the reference group. This group could have been comprised of respondents who are able to have and maintain an erection, but do not have a partner; do not have sexual contact with their partner; or do have sexual contact but no sexual intercourse. Such men will have a score of 21 or lower, indicating ED according to the IIEF-5 classification, while they actually do not have an erection problem. Such an IIEF-5 classification will thus give the wrong impression.

Concerning our evaluation of the measurement properties; unfortunately we were not able to assess convergent and discriminant validity. To assess convergent validity we need to assess its positive correlation with measures of similar constructs. To our knowledge there are no other Dutch validated measures available with similar construct as the IIEF-5, and therefore we were not able to assess convergent validity. For discriminative validity we needed to be able to assess the ability of the measure to differentiate between expected differences between subgroups of patients. We actually found a significant difference in IIEF-5 score between our patient and reference group. However, as discussed earlier, the IIEF-5 classification in the reference group may be not correctly classified as the context of the presence or absence of sexual activity is unknown. Another limitation of our study was that analysing responsiveness and interpretability appeared to be impossible since only 10 patients received treatment during follow-up. During six months of follow-up, the number of men who actually started treatment for ED was limited. Using the IIEF-5 as a measure of responsiveness of ED treatment is debatable. Treatment of ED, with, for example a phosphodiesterase type 5 inhibitor, entails that patients are encouraged to at least attempt sexual activity and/or intercourse. If a patient who presents with ED did not engage in sexual activity and/or intercourse before ED treatment, his IIEF-5 score will improve with at least four points after the initiation of treatment since the attempt in itself will result in better IIEF-5 scores. This may suggest that treatment worked while the treatment did not necessarily result in better erectile function. Finally, the absence of a comorbidity index to assess and score any potential comorbid condition, as outcomes of a chronic condition represents another limitation; indeed, ED may be affected by coexisting comorbid chronic conditions.

In conclusion, our findings support positive evidence for the appropriateness of the Dutch IIEF-5 to evaluate severity of ED symptoms allowing to be used in clinical decision making as a diagnostic aid. This cultural and linguistic adjustment provides opportunity to compare self-reported ED status in international research and analysis of treatment. It seems however necessary to use this measure complementary to the

context of a patient's sexual life. The suitability of the IIEF-5 as a measure of responsiveness remains open to discussion.

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PART III

Evidence based medicine in functional urology

Chapter 7

Surgical management of functional bladder outlet obstruction in adults with neurogenic bladder dysfunction

Elaine Utomo, Jan Groen en Bertil F.M. Blok

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ABSTRACT

Background

The most common type of functional bladder outlet obstruction in patients with neurogenic bladder is detrusor-sphincter dyssynergia (DSD). The lack of co-ordination between the bladder and the external urethral sphincter muscle (EUS) in DSD can result in poor bladder emptying and high bladder pressures, which may eventually lead to progressive renal damage.

Objectives

To assess the effectiveness of different surgical therapies for the treatment of functional bladder outlet obstruction (i.e. DSD) in adults with neurogenic bladder dysfunction.

Search methods

We searched the Cochrane Incontinence Group Specialised Register, which contains trials identified from the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, MEDLINE In-Process, and hand searching of journals and conference proceedings (searched 20 February 2014), and the reference lists of relevant articles.

Selection criteria

Randomised controlled trials (RCTs) or quasi-RCTs comparing a surgical treatment of DSD in adults suffering from neurogenic bladder dysfunction, with no treatment, placebo, non-surgical treatment, or other surgical treatment, alone or in combination.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data.

Main results

We included five trials (total of 199 participants, average age of 40 years). The neurological diseases causing DSD were traumatic spinal cord injury (SCI), multiple sclerosis (MS), or congenital malformations.

One trial compared placement of sphincteric stent prosthesis with sphincterotomy. For urodynamic measurements, results for postvoid residual urine volume (PVR) and cystometric bladder capacity were inconclusive and consistent with benefit of either sphincteric stent prosthesis or sphincterotomy at three, six, 12, and 24 months. Results for maximum detrusor pressure ($P_{det.max}$) were also inconclusive at three, six, and 12 months; however, after two years, the $P_{det.max}$ after sphincterotomy was lower than after stent placement (mean difference (MD) -30 cmH_2O, 95% confidence interval (CI) 8.99 to 51.01).

Four trials considered botulinum A toxin (BTX-A) injection in the EUS, either alone or in combination with other treatments. The comparators included oral baclofen, oral alpha blocker, lidocaine, and placebo. The BTX-A trials all differed in protocols, and therefore we did not undertake meta-analysis. A single 100 units transperineal BTX-A injection (Botox®) in patients with MS resulted in higher voided urine volumes (MD 69 mL, 95% CI 11.87 to 126.13), lower pre-micturition detrusor pressure (MD -10 cmH_2O, 95% CI -17.62 to -2.38), and lower $P_{det.max}$ (MD -14 cmH_2O, 95% CI -25.32 to -2.68) after 30 days, compared to placebo injection. Results for PVR using catheterisation, basal detrusor pressure, maximal bladder capacity, maximum urinary flow, bladder compliance at functional bladder capacity, maximal urethral pressure, and closure urethral pressure at 30 days were inconclusive and consistent with benefit of either BTX-A injection or placebo injections. In participants with SCI, treatment with 200 units of Chinese manufactured BTX-A injected at eight different sites resulted in better bladder compliance (MD 7.5 mL/cmH_2O, 95% CI -10.74 to -4.26) than participants who received the same injections with the addition of oral baclofen. Results for maximum uroflow rate, maximal cystometric capacity, and volume per voiding were inconclusive and consistent with benefit of either BTX-A injection or BTX-A injection with the addition of oral baclofen. However, the poor quality of reporting in this trial caused us to question the relevance of bladder compliance as an adequate outcome measure.

In participants with DSD due to traumatic SCI, MS, or congenital malformation, the results for PVRs after one day were inconclusive and consistent with benefit of either a single 100 units transperineal BTX-A (Botox®) injection or lidocaine injection. However, after seven and 30 days of BTX-A injection, PVRs were lower (MD -163 and -158 mL, 95% CI -308.65 to -17.35 and 95% CI -277.57 to -39.03, respectively) compared to participants who received lidocaine injections. Results at one month for $P_{det.max}$ on voiding, EUS activity in electromyography, and maximal urethral pressure were inconclusive and consistent with benefit of either BTX-A or lidocaine injections.

Finally, one small trial consisting of five men with SCI compared weekly BTX-A injections with normal saline as placebo. The placebo had no effect on DSD in the two participants allocated to the placebo treatment. Their urodynamic parameters were unchanged from baseline values until subsequent injections with BTX-A once a week for three weeks. These subsequent injections resulted in similar responses to those of the three participants who were allocated to the BTX-A treatment. Unfortunately, the report presented no data on placebo treatment.

Only the trial that compared sphincterotomy with stent placement reported outcome measures renal function and urologic complications related to DSD. Results for renal function at 12 and 24 months, and urologic complications related to DSD at three, six, 12, and 24 months were inconclusive and consistent with benefit of either sphincteric stent prosthesis or sphincterotomy.

Adverse effects reported were haematuria due to the cystoscopic injection and muscle weakness, of which the latter may be related to the BTX-A dose used.

All trials had some methodological shortcomings, so insufficient information was available to permit judgment of risk of bias. At least half of the trials had an unclear risk of selection bias and reporting bias. One trial had a high risk of attrition bias, and another trial had a high risk of reporting bias.

Authors' conclusions

Results from small studies with a high risk of bias have identified evidence of limited quality that intraurethral BTX-A injections improve some urodynamic measures after 30 days in the treatment of functional bladder outlet obstruction in adults with neurogenic bladder dysfunction. The necessity of reinjection of BTX-A is a significant drawback; a sphincterotomy might therefore be a more effective treatment option for lowering bladder pressure in the long-term.

However, because of the limited availability of eligible trials, this review was unable to provide robust evidence in favour of any of the surgical treatment options. More RCTs are needed, measuring improvement on quality of life and on other types of surgical treatment options for DSD since these are lacking. Future RCTs assessing the effectiveness of BTX-A injections also need to address the uncertainty about the optimal dose and mode of injection for this specific type of urological condition.

BACKGROUND

Description of the condition

The central nervous system controls urination. Normal urination requires a synergic action between the detrusor muscle (smooth muscle) and the external urethral sphincter (striated muscle). To expel urine from the bladder, the external urethral sphincter relaxes, which is followed by a detrusor contraction. The pontine micturition centre controls this synergy between the detrusor muscle and the external urethral sphincter.[1] Disruption of the pathways between the pontine micturition centre and the caudal part of the spinal cord often results in detrusor-sphincter dyssynergia (DSD). In this condition, a detrusor contraction occurs concurrently with an inappropriate contraction of the urethral striated muscle, the periurethral striated muscle, or both, thus, blocking the bladder outlet.[2]

The most common form of bladder outlet obstruction (BOO) in people with neurogenic bladder is DSD. Detrusor-sphincter dyssynergia typically occurs in people with traumatic supra-sacral spinal lesions (spinal cord injury). Other common causes of DSD are multiple sclerosis (MS), acute transverse myelitis, and myelomeningocele.[3-7] Detrusor-sphincter dyssynergia can result in poor bladder emptying and high bladder pressures, which in turn can cause recurrent urinary tract infections, high intravesical pressures, vesico-ureteral reflux, and hydronephrosis. If untreated, progressive renal damage may occur.[8]

Several authors have attempted to classify DSD. For instance, *Blaivas et al.*[9] defined three types of DSD depending on electromyography (EMG) findings. Type three was the predominant type, characterised by a sustained sphincter contraction that coincided with the detrusor contraction. Another classification was proposed by *Yalla et al.*[10] who described three DSD types based on clinical and urodynamic observations. There is a significant overlap between these two classification schemes, and their clinical relevance has been questioned. A simpler way of describing the results of EMG trials is to describe the frequency of external urethral sphincter contraction during detrusor contraction as either intermittent or continuous.[8]

The symptoms associated with DSD represent a functional disability that may result in considerable impairment of a person's quality of life (QoL). Neurogenic bladder problems were associated with lower QoL scores in people with traumatic spinal cord injury.[11] Therefore, QoL is a very important consideration in the management of people with neurogenic bladder dysfunction. Moreover, a relationship between bladder management methods and QoL in people with spinal cord injury was found: Those who were able to void normally had the best QoL in both physical and mental component scores.[12]

Management of DSD is aimed at reducing intravesical pressure and promoting bladder emptying. First-line conservative treatment includes an optimised combination of antimuscarinic agents (anticholinergic drugs) and clean intermittent self-catheterisation. The effect on the bladder pressure should be strictly monitored urodynamically after initiation of antimuscarinic treatment.[13] However, more invasive treatment is necessary in people in whom bladder pressure is pathologically elevated with antimuscarinics, who cannot tolerate antimuscarinic agents, or who are unable to perform clean intermittent self-catheterisation (e.g. people with quadriplegia).

The optimal surgical management of BOO secondary to DSD remains unknown and is the focus of this review. Other causes of BOO, such as benign prostatic enlargement and urethral stricture, are out with the scope of the review.[14-16] Furthermore, we have not addressed the treatment of high bladder pressure in patients with only detrusor overactivity and not DSD. Upper urinary tract diversion is usually reserved as a last resort[17] and was not considered as a part of this review, but we did include suprapubic catheterisation.

Description of the intervention

1. Sphincterotomy

External sphincterotomy is a transurethral treatment of the sphincteric hypertonicity, which is present in DSD by disrupting, either partially or totally, the continuity of the external urethral sphincter. It is performed either with the use of electrocautery[18] or a contact laser.[19,20] The goal is to reduce the intravesical voiding pressure and to lower detrusor leak-point pressure. Sphincterotomy should prevent urologic complications, such as urosepsis and deterioration of renal function; reduce vesico-ureteral reflux; and eliminate the need for chronic indwelling catheterisation. A degree of continence may be maintained if bladder neck function can be preserved. Sphincterotomy can provide an extended period of satisfactory bladder emptying.[21] However, on-going revision may be required and a number of complications have been described, principally postoperative haemorrhage, erectile dysfunction (complete or partial loss of tumescence), urine extravasation, urethral stricture, and fistula formation.[21,22]

2. Implantable urethral stents

Urethral stents mechanically keep open the external urethral sphincter and thereby lower the detrusor leak-point pressure. The stents are either permanent or temporary.

The permanent UroLume® prosthesis (also known as Wallstent in Europe, AMS Medinvent SA, Lausanne, Switzerland) was initially developed as a self-expanding prosthesis used to maintain the patency of stenotic arteries after balloon angioplasty. *Milroy et al.*[23] first described the use of this stent in the treatment of recurrent urethral strictures. The stent is made of a stainless steel super alloy, which is corrosion-resistant

and non-magnetic. This alloy is woven into a braided, pliable, self-expanding cylindrical mesh. After insertion, the mesh exerts a strong, continuous, outward force against the wall of the urethra (lumen) and maintains a patent diameter of up to 42 F. The mesh becomes epithelialized by urothelium and is considered to be permanent. *Shaw et al.*[24] were the first to use this urethral stent as a successful alternative to external sphincterotomy in the treatment of DSD. Since then, studies have confirmed its long-term clinical benefit and safety, by showing improvements in maximum detrusor pressure and postvoid residual urine volume, alongside unchanged bladder capacity and reduced hydronephrosis.[25,26]

Soni et al.[27] first described the use of the Memokath® temporary stent (Engineers & Doctors A/S, Hornbaek, Denmark) to treat DSD. The stent is composed of a nickel-titanium alloy with 'shape memory'. The stent will return to a preformed shape after deformation when heated to 45 ºC or above. When cooled (10 ºC or below), the stent becomes soft and easy to remove. Because of its closed, tight, spiral structure, urothelial ingrowth is prevented, and this allows the stent to be easily removed if required. It has shown short-term success in patients with DSD in terms of decreasing the detrusor pressure and postvoid residual urine volume.[28]

3. Urethral balloon dilatation

Balloon dilatation of the external urethral sphincter was first introduced as a treatment for benign prostatic hyperplasia. *Chancellor et al.*[29] reported on their technique and early experience with balloon dilatation of the external urethral sphincter in seven spinal cord-injured men with DSD. Balloon dilatation of the external urethral sphincter uses placement of the Optilume Prostate Dilator® (American Medical Systems Inc, Minnesota, USA) under fluoroscopic guidance. The balloon is inflated to a diameter of 90 F under a pressure of three to four atmospheres for 10 minutes. Balloon dilatation was effective in significantly reducing postvoid residual urine volume.[30] Balloon dilatation and UroLume® stenting both proved to be as effective as external sphincterotomy in the treatment of DSD.[31] In contrast, *McFarlane et al.*[32] reported a lower success rate than both sphincterotomy and sphincter stenting and did not recommend balloon dilatation for the treatment of DSD.

4. Intraurethral botulinum A toxin (BTX-A) injection

Botulinum A toxin (BTX-A) is a protein neurotoxin produced by a bacterium of the *Clostridium* genus. It is an inhibitor of acetylcholine release at the neuromuscular junction. BTX-A is injected directly into the target muscle, and the clinical effect is to induce relaxation of the injected striated muscle. The clinical effects begin within two to three days and are reversible as terminal nerve resprouting occurs within three to six months. BTX-A has previously been used successfully in the management of muscular

disorders, including strabismus, focal dystonia, skeletal muscle spasms, and spasticity. Application of BTX-A in the lower urinary tract has produced promising results in treating lower urinary tract dysfunction.[33] Its use for the treatment of DSD was first reported by *Dykstra & Sidi*[34] BTX-A was injected once a week for three weeks into the external urethral sphincter of 11 spinal cord-injured men with DSD.

Currently, two preparations of BTX-A are commercially available: onabotulinumtoxinA or Botox® (Allergan Inc., Irvine, California, USA) and abobotulinumtoxinA or Dysport® (Ipsen Ltd, Slough, UK). BTX-A treatment has the advantage of being minimally invasive, can be injected on an outpatient basis, and has a good safety profile. However, it provides only temporary relief of symptoms, because the BTX-A-treated nerve terminals do not degenerate and axonal resprouting and formation of new neuromuscular junctions occurs.[35] As a result of this regeneration, repeat BTX-A sphincter injections are necessary. The duration of effect of a single treatment is two to three months, whereas repeat treatments appear to have cumulative efficacy lasting nine to 13 months.[36]

5. Intrathecal baclofen

Baclofen is a well-recognised option for the treatment of skeletal muscle spasticity.[37] It acts by activating gamma-aminobutyric acid-B receptors, by normalising and decreasing interneuron and motor neuron activity in the spinal cord. Although baclofen has been used for over two decades as an oral preparation, its difficulty in passing through the blood-brain barrier limited its usefulness for the treatment of DSD. Intrathecal baclofen delivery systems were developed to circumvent this problem: Patients receive a continuous intradural administration of baclofen via an implanted pump. Thus, it can be delivered directly into the spinal fluid to allow higher concentrations in the spinal cord. The rationale behind this modality is to minimise the systemic baclofen side-effects from higher oral doses (weakness, dizziness, drowsiness, rash, and hallucinations), while enhancing its therapeutic benefit. After intrathecal application of baclofen, urethral pressure shows urethral relaxation during isovolumetric bladder contractions in spinal cord-injured rats.[38] It has been proposed that baclofen activates inhibitory interneurons that, in turn, inhibit directly external urethral sphincter motoneurons in the nucleus of Onuf.[39] *Steers et al.*[40] showed a 40% decrease of DSD in people with severe spasticity due to spinal cord pathology after intrathecal baclofen.

6. Pudendal nerve block

The pudendal nerve contains the motor axons to the external urethral sphincter as well as other nerve fibres innervating the external anal sphincter and other pelvic floor muscles. By blocking the pudendal nerve, action potential propagation in the nerve is blocked and thus reduces or blocks unwanted external urethral sphincter activity.

Pudendal nerve block using phenol solution has been widely used as a neurolytic agent for the relief of spasticity. Pudendal neurolysis can be done in a relatively non-invasive way and can be easily performed on an outpatient basis. Treatment of DSD with this technique was first described in 1979.[41] Other clinical studies showed that pudendal nerve block performed by phenol solution was safe, easy to perform, and effective as a treatment for DSD in selected people with spinal cord injury.[42,43] However, a number of authors have reported that the duration of the effect of the nerve block was unpredictable.

A relatively recent approach involves the use of high-frequency stimulation to block the pudendal nerve. Several animal studies have demonstrated high-frequency stimulation as a potential method for suppressing DSD and improving effective voiding.[44-47]

7. Suprapubic catheterisation

In a small subset of people with DSD, insertion of an indwelling transurethral or suprapubic catheter is necessary. Insertion of a suprapubic catheter is a simple form of urinary diversion, which involves inserting a catheter directly into the bladder through the abdominal wall. The handling and long-term risks of a suprapubic catheter are often the subject of debate.[48]

Compared to clean intermittent self-catheterisation, the use of an indwelling catheter (either suprapubic or transurethral) significantly increases the risk of bladder and renal stones, complicated urinary tract infections, urethral fistulas, renal failure, strictures, and erosions.[48,49] A controversial issue is the association of long-term use of an indwelling catheter and squamous cell carcinoma of the bladder.[50] There are several advantages of a suprapubic catheter compared to a transurethral catheter: reduced risk of urethral trauma, destruction, or both; less risk of prostatitis or epididymitis; and less urethral pain. However, it requires a minimal 'surgical' intervention to insert the suprapubic catheter, with potential to injure structures adjacent to the bladder, especially the bowel. The preferred insertion technique appears to be quite variable, and there is no evidence of any one best way to insert the suprapubic catheter.[51]

An epidemiological follow-up study found that suprapubic catheters were more frequently used at follow up compared to an initially placed transurethral catheter.[52] This could be due to a shift from the indwelling transurethral catheter towards the suprapubic catheter because of complications related to these, but it is also more convenient as it permits sexual function.[53]

Why it is important to do this review

The wide variety of surgical treatments available for curing or improving BOO in adults with neurogenic bladder dysfunction indicates a lack of consensus for what is optimal treatment. Provided that sufficient numbers of trials of adequate quality have been

conducted, the most reliable evidence is likely to come from the consideration of randomised controlled trials, and this will be the basis for this review. The aim is to help identify optimal practice and to highlight where there is need for further research. Other relevant Cochrane reviews that may be of interest to the reader include the following:

- Intermittent catheterisation for long-term bladder management;[54]
- Which anticholinergic drug for overactive bladder symptoms in adults;[55]
- Catheter policies for management of long term voiding problems in adults with neurogenic bladder disorders;[56]
- Urinary diversion and bladder reconstruction/replacement using intestinal segments for intractable incontinence or following cystectomy;[17] and
- Washout policies in long-term indwelling urinary catheterisation in adults.[57]

OBJECTIVES

To assess the effectiveness of different surgical therapies for the treatment of functional bladder outlet obstruction (i.e. DSD) in adults with neurogenic bladder dysfunction. We considered the following comparisons:

1. Sphincterotomy
    - Sphincterotomy versus no intervention or placebo
    - Sphincterotomy versus non-surgical therapy
    - Sphincterotomy versus other surgical therapy
2. Implantable urethral stents
    - Implantable urethral stents versus no intervention or placebo
    - Implantable urethral stents versus non-surgical therapy
    - Implantable urethral stents versus other surgical therapy
3. Urethral balloon dilatation
    - Urethral balloon dilatation versus no intervention or placebo
    - Urethral balloon dilatation versus non-surgical therapy
    - Urethral balloon dilatation versus other surgical therapy
4. Intraurethral botulinum A toxin (BTX-A) injection
    - Intraurethral BTX-A injection versus no intervention or placebo
    - Intraurethral BTX-A injection versus non-surgical therapy
    - Intraurethral BTX-A injection versus other surgical therapy
5. Intrathecal baclofen
    - Intrathecal baclofen versus no intervention or placebo
    - Intrathecal baclofen versus non-surgical therapy
    - Intrathecal baclofen versus other surgical therapy

6. Pudendal nerve block
    - Pudendal nerve block versus no intervention or placebo
    - Pudendal nerve block versus non-surgical therapy
    - Pudendal nerve block versus other surgical therapy
7. Suprapubic catheterisation
    - Suprapubic catheterisation versus no intervention or placebo
    - Suprapubic catheterisation versus non-surgical therapy
    - Suprapubic catheterisation versus other surgical therapy

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCT) or quasi-randomised controlled clinical trials in which at least one arm is a surgical method of managing functional BOO in adults suffering from neurogenic bladder dysfunction, including cross-over trials.

Types of participants

All adult men and women with functional BOO due to neurogenic bladder dysfunction, diagnosed either by symptom and history-taking or urodynamic studies. We accepted the trialists' definition of an adult and their diagnosis and classification of DSD.

Types of interventions

At least one arm of the trial included a surgical treatment for functional BOO due to neurogenic bladder dysfunction:

- sphincterotomy;
- implantable urethral stents;
- urethral balloon dilatation;
- intraurethral BTX-A injection;
- intrathecal baclofen;
- pudendal nerve block; or
- suprapubic catheterisation.

These interventions were compared with no treatment or placebo; non-surgical treatment; or with each other, alone, or in combination.

The review did not address the following:

- urinary retention as a result of failure of the detrusor muscle to contract (areflexia);

- non-functional causes of BOO (e.g. benign prostatic enlargement and urethral stricture);
- treatment of high bladder pressure in people who do not also have DSD, such as using intravesical botulinum A toxin (BTX-A) with clean intermittent self-catheterisation and bladder augmentation; and
- urinary diversion, which is usually reserved as a last resort and was not considered as a part of this review.

Types of outcome measures

Primary outcomes

1. Clinicians' observations

- Urodynamic measurements/studies (e.g. detrusor leak-point pressure, bladder pressure, postvoid residual urine volume, bladder capacity)
- Renal function
- Adverse effects: number of urologic complications related to DSD (e.g. urinary tract infections)

Secondary outcomes

1. Quantification of symptoms

- Frequency of incontinent episodes from self-report or voiding diary
- Frequency of urinary retention rates
- Clean intermittent self-catheterisation rates
- Use of rescue antibiotics

2. Quality of life

- Acceptability of procedure or satisfaction with outcome (e.g. Patient Global Impression of Improvement (PGI-I)[58])
- Condition-specific health measures (e.g. Qualiveen[59])
- Other condition-specific quality of life questionnaires related to urinary incontinence or voiding symptoms (e.g. Bristol Female Lower Urinary Tract Symptoms (BFLUTS) Questionnaire, Incontinence Impact Questionnaire (IIQ), King's Health Questionnaire (KHQ), Overactive Bladder Questionnaire (OAB-q), International Consultation on Incontinence Modular Questionnaire (ICIQ modules)) or sexual matters (e.g. International index of Erectile Function Questionnaire (IIEF), Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire (PISQ), ICIQ modules)
- Generic quality of life or health status measures (e.g. Short-Form 36[60], EuroQol[61])
- Psychological outcome measures (e.g. Hospital Anxiety Depression Scale (HADS)[62])

3. Measures of associated symptoms (objective or subjective)

- Bladder symptoms (including symptomatic and occult incontinence)
- Sexual symptoms

4. Surgical outcome measures

- Operating time
- Blood loss
- Need for transfusion
- Additional surgery or other treatment for DSD
- Length of inpatient hospital stay
- Use of antibiotic prophylaxis

5. Adverse effects

- Infection related to the procedure
- Number with perioperative surgical complications (e.g. infection, haemorrhage, etc.)
- Number of urethral strictures due to the procedure with the need of further treatment
- Number with other complications inherent to the procedure

6. Socioeconomic measures

For example, catheter days, inpatient days, days to return to activities of daily living.

- Use of resources
- Cost of interventions or resources
- Resource implications of effects of treatment
- Formal economic evaluations

7. Other outcomes

- Non-prespecified outcomes judged important when performing the review

Search methods for identification of studies

We did not impose any language or other restrictions on the searches, and we identified the trials from the sources listed below.

Electronic searches

Relevant trials were identified from the Cochrane Incontinence Group Specialised Register (date of last search: 20 February 2014). The Register contains trials identified from the Cochrane Central Register of Controlled Trials (CENTRAL) (1999 onwards), MEDLINE (1966 onwards), MEDLINE In-Process (2001 onwards), and hand searching

of journals and conference proceedings. The methods used to derive this, including the search strategy, are described under the Group's module in *The Cochrane Library*[63]. The terms used to search the Incontinence Group Specialised Register are given below:

({DESIGN.CCT*} OR {DESIGN.RCT*}) AND {TOPIC.URINE.NEUROGENIC*} AND {INTVENT.SURG*})

All searches were of the keyword field of Reference Manager (Reference Manager Professional Ed. version 2012, New York; Thomson Reuters).

Searching other resources

We searched the reference lists of all relevant reviews and trial reports to identify further relevant trials.

Data collection and analysis

We processed included trial data as described in the *Cochrane Handbook for Systematic Reviews of Interventions*.[64] We resolved any differences of opinion related to trial inclusion, methodological quality, or data extraction by discussion with a third party. We described comparability of trial groups in terms of potential confounding variables, such as use of antimuscarinics, age, and gender.

When appropriate, we undertook meta-analysis. For categorical outcomes, we related the numbers reporting an outcome to the numbers at risk in each group to derive a relative risk (RR). For continuous variables, we used means and standard deviations to derive a mean difference (MD). We used a fixed-effect model for calculation of 95% confidence intervals (95% CI). We had planned to investigate differences between trials if significant heterogeneity was found or appeared obvious from visual inspection of the results.

Where reports included insufficient data for use in the review or where we required further information or clarification on any matters, we made attempts to contact the trial authors.

Selection of studies

Two review authors independently screened the trials identified by the literature search for eligibility by title and abstract, excluding obviously irrelevant reports. For the trials considered eligible, we obtained full-text papers. If there was any uncertainty about the eligibility of the trials based on title and abstract, the same two reviewers reviewed the full paper, resolving any disagreements by discussion and consulting the third review author when disagreement arose. We have listed trials formally consid-

ered for the review but excluded in Table 7.1 'Characteristics of excluded studies' with reasons given for their exclusion.

We used Early Review Organizing Software (EROS 2013, Buenos Aires, Argentina) to perform the selection of the trials. EROS is a web-based program for the initial phases of a systematic review. It facilitates independent revision of references and immediate resolution of discrepancies.

Data extraction and management

Two reviewers independently undertook assessment of methodological quality and data extraction using data extraction forms, based on the Incontinence Group's assessment criteria, which include quality of random allocation and concealment, description of dropouts and withdrawals, analysis by intention-to-treat, and 'blinding' during treatment and at outcome assessment. Extracted data and quality assessment were cross-checked and any disagreements discussed and, if necessary, resolved by a third reviewer.

RESULTS

Description of studies

The characteristics of included studies are described in Table "Characteristics of included studies" which is available online http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004927.pub4/full at *The Cochrane Library*.[65]

The characteristics of excluded studies are described in Table 7.1.

Results of the search

The search strategy (first run in October 2011) identified 43 records. An updated search run in December 2012 retrieved five additional records, and another updated search run in February 2014 retrieved four additional records. This resulted in a total of 52 records (Figure 7.1). After examination of the titles and abstracts of these references, we removed one duplicate and excluded 33; thus, we accessed 18 trials for eligibility. We obtained full-text copies of these trials, which we subjected to further assessment.

Included studies

The further assessment of the 18 full-text reports identified five trials evaluating surgical management of functional BOO in adults with neurogenic bladder dysfunction.[66-70] One trial was published in Chinese[67] and translated by a native Chinese urologist-in-training with Dutch as a second language. We have provided further details in the 'Characteristics of included studies' which is available online.[65]

Table 7.1 Characteristics of excluded studies

Study	Reasons for exclusion
Chancellor MB, Rivas DA, Abdill CK, *et al*[31]. *Arch Phys Med Rehabil. 1994 Mar;75(3):297-305*	Not a RCT. Quote: "Each patient selected his own form of treatment"
Dunn MD, Portis AJ, Kahn SA Yan Y, *et al.*[81] *J Endourol. 2000 Mar;14(2):195-202.*	Not urethral stents, but ureteral pigtail stents. Not on functional BOO in adults with neurogenic bladder dysfunction
Herschorn S, Gajewski J, Ethans K, et al.[72] *Neurourology and Urodynamics 2009;28(7):608–9*	Not intraurethral BTX-A injection but intradetrusor injection for the treatment of neurogenic urinary incontinence
Herschorn S, Gajewski J, Ethans K, *et al.*[71] *Neurourology and Urodynamics 2009;28(2):138–9.*	Not intraurethral BTX-A injection but intradetrusor injection for the treatment of neurogenic urinary incontinence
Loubser PG, Narayan RK, Sandin KJ, *et al.*[77] *Paraplegia 1991;29(1):48–64.*	7 participants underwent urodynamics in this trial, 1 participant continued to have detrusor hyperreflexia with DSD, but this 1 participant cannot be randomised
Mehta S, Hill D, Foley N, *et al*[78] *Arch Phys Med Rehabil. 2012 Apr;93(4):597-603.*	Non-randomised: review paper for the treatment of incomplete voiding after SCI. The authors reviewed 2 studies on DSD,[68,69] which we already included
Meythaler JM, Guin-Renfroe S, Brunner RC, *et al*[80] *Stroke 2001;32(9):2099–109.*	Treatment of spasticity of extremities with intrathecal baclofen; no evaluation of lower urinary tract function
Naumann M, So Y, Argoff CE, *et al.*[79] *Neurology 2008;70(19):1707–14.*	Non-randomised; review paper on BTX-A for the treatment of autonomic disorders and pain. They reviewed 3 studies on DSD,[68-70] which we already included
Schurch B, de Seze M, Denys P, *et al.*[74] *Neurourology and Urodynamics. 2004; Vol. 23, issue 5/6:609–10.*	Not intraurethral BTX-A injections but intradetrusor injections for the treatment of neurogenic urinary incontinence
Schurch B, de Sèze M, Denys P, *et al.*[73] *Neurourology and Urodynamics 2005;24(5/6):545–6.*	Not intraurethral BTX-A injections but intradetrusor injections for the treatment of neurogenic urinary incontinence
Schurch B, Denys P, Kozma CM, *et al.*[75] *European Urology 2007;52(3):850–8.*	Not intraurethral BTX-A injections but intradetrusor injections for the treatment of neurogenic urinary incontinence
Steers WD, Meythaler JM, Haworth C, *et al.*[40] *Journal of Urology 1992;148(6):1849–55.*	Not a RCT
Thavaseelan JT, Burns-Cox N, Jordan K, *et al.*[76] *BJU International 2005;95 (Suppl 1):4–5.*	RCT. However, no intra-urethral BTX-A injections but intra-detrusor injections for the treatment of neurogenic urinary incontinence

The characteristics of included studies are described in Table "Characteristics of included studies" which is available online at http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004927.pub4/full at *The Cochrane Library*.[65]

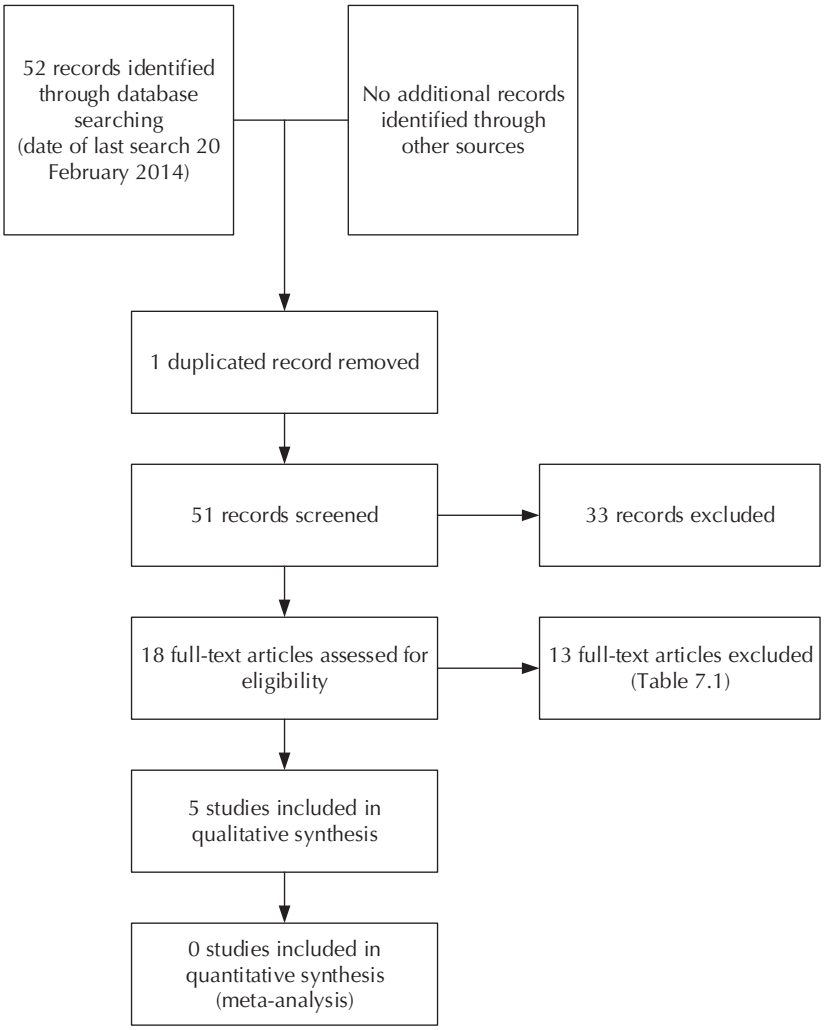

Figure 7.1 PRISMA study flow diagram

The surgical treatments studied in the included trials were as follows:

- sphincterotomy[66] ;
- placement of sphincteric stent prosthesis[66] ;
- BTX-A injection into the external urethral sphincter[67-70] ; and
- lidocaine injection in the external urethral sphincter.[68]

Two trials included placebo as a comparator,[69,70] and two added oral medication to the surgical intervention.[67,70]

Design

All included trials were RCTs with two arms, of which two trials[66,70] were parallel-arm trials of two interventions. In *Cui et al.*[67] all included participants received the same surgical intervention, and on the second day, only a randomised subgroup received a pharmaceutical treatment. In *de Sèze et al.*[68] participants who reported a negative result at the end of the trial received treatment from the other arm, and in *Dykstra & Sidi*[69] the participants who were allocated to the placebo arm received the actual intervention after completion of the study.

Setting

Care was provided in a hospital setting in four trials: in a urology department in China,[67] at the physical medicine unit of two different centres in France,[68] in a university clinic on an outpatient basis in the United States,[69] and in an outpatient setting of five university hospitals and one rehabilitation clinic in France.[70] One trial provided care at three spinal cord injury centres in the United States.[66]

Participants

The trials enrolled a total of 199 participants. The number of participants in individual trials ranged from five to 86.

- One trial only enrolled participants with DSD due to MS.[70]
- Three trials[66,67,69] only enrolled participants with DSD due to traumatic spinal cord injury.
- One trial[68] included participants with different reasons for cord lesion (traumatic, MS, and congenital malformation).

Duration of neurological disease

The average duration of onset of underlying neurological disease was 10 years[66-70] and ranged from 2.5[67] to 16 years.[70] The presence of DSD was urodynamically confirmed in all trials,[66-70] of which two added needle-electrode EMG to diagnose DSD,[68,69] and *de Sèze et al.*[68] added also voiding cystourethrography to confirm DSD.

Age and gender

The average age of the study participants overall was 40 years, ranging from 32[69] to 50[70] years. Two trials[66,69] enrolled only men. In one trial[67], we found a discrepancy between the reported gender in the abstract and in the main text: The abstract reported 31 men and seven women, while the main text reported 28 men and seven women. The remaining trials included either more men (92%)[68] or more women (67%).[70]

Other concurrent treatment

Two trials[68,70] made statements about the use of other treatments or medication during the trial. Participants from *de Sèze et al.*[68] discontinued use of forms of treatment that interfered with bladder function during the trial, except in two participants for whom oral antispastic medication (baclofen) was maintained at a constant dose throughout the study. Participants from *Gallien et al.*[70] were excluded if they took any treatment that could have altered neuromuscular transmission.

Interventions

There were no trials evaluating urethral balloon dilatation, intrathecal baclofen, pudendal nerve block, or suprapubic catheterisation. The trials tested the following surgical interventions.

Sphincterotomy

- External urethral sphincterotomy versus implantable urethral stent placement[66]

Intraurethral botulinum A toxin (BTX-A) injection

- BTX-A injection into the external urethral sphincter with and without oral baclofen[67]
- BTX-A injection versus lidocaine injection into the external urethral sphincter[68]
- BTX-A injection versus placebo (saline) injection into the external urethral sphincter[69]
- BTX-A injection versus placebo (saline) injection into the external urethral sphincter with all participants also having oral alpha blockers[70]

Intraurethral botulinum A toxin (BTX-A) injection protocols

The variety in single and repeat injections and mode of BTX-A injection differed between trials:

- *De Sèze et al.*[68] and *Gallien et al.*[70] administered BTX-A injections one time with a single injection transperineally;
- *Cui et al.*[67] also administered BTX-A injections one time, but with a cystoscope transurethrally at eight different sites into the external urethral sphincter; and
- *Dykstra & Sidi*[69] administered BTX-A injections once a week for three weeks, using a cystoscope transurethrally to inject at three to four different sites into the external urethral sphincter.

Cui et al.[67] used BTX-A produced in China (Lanzhou Biotechnology). The other three trials used onabotulinumtoxinA.[68-70]

Also, the dose in units (U) of BTX-A differed between trials:

Table 7.2 Adverse effects

Included studies	Reported adverse events	Details of reported adverse events
Chancellor et al.[66]	**1**. device removal (stent) **2**. additional insertion procedures (stent) **3**. requirement of repeat sphincterotomy due to restenosis of the sphincter **4**. bladder neck obstruction **5**. no alterations in erectile function or ejaculation in both groups	**1**. Stent explantation in 6 of 31 participants (19%) due to the following: - stent migration detected at 3-month follow up (n =3); - incorrect placement of stent at insertion (n = 1); - participant's own request because he did not like using the condom catheter to collect urine (n = 1); and - pain and symptoms of dysreflexia during reflex voiding (n = 1) **2**. Additional insertion procedures of stent (i.e. more than 1 insertion procedure) in 7 participants (23%): - 2 procedures (n = 6); and - 3 procedures (n = 1) **3**. Repeat sphincterotomy in 2 of 26 participants (8%) 6 months postoperatively **4**. Of all participants, 9% required urethrotomy because of a urethral stricture (Analysis 1.14*), and 21% were treated for bladder neck obstruction (Analysis 1.12*)
Cui et al.[67]	**1**. haematuria **2**. muscle weakness and central nervous system symptoms in BTX-A with oral baclofen group	Toxic and adverse events were recorded between 2 to 9 months postoperatively **1**. all participants in both groups had varying degrees of haematuria **2**. after 1 week of oral baclofen, **3** participants reported muscle weakness and central nervous system symptoms like dizziness, malaise, and weakness
De Sèze et al.[68]	**1**. faecal incontinence after lidocaine injection **2**. transitory exacerbation of urinary incontinence for 2 weeks after BTX-A **3.** no complications involving haemorrhaging or infection **4**. no systemic side-effects (e.g. nausea, vomiting, dry mouth, dysphagia, weakness in the respiratory muscles, or paresis of the extremities) in both groups	Adverse effects were evaluated at the end of the study (30 days)
Dykstra and Sidi[69]	**1**. mild, generalised upper extremity weakness **2**. mild haematuria after cystoscopic injections **3**. no urinary tract infections due to cystoscopic injections **4**. no adverse effects, such as nausea, vomiting, dry mouth, diplopia, blurred vision, photophobia, dysphonia, dysarthria, dysphagia, or subjective weakness of the respiratory muscles	**1**. mild generalised upper extremity weakness in 3 participants, of which in 1 participant - 3 weeks after the last injection single-fiber electromyography studies revealed increased fiber density and a small increase in jitter at slow-firing rates (3 Hz) in the left deltoid **2**. haematuria resolved within 24 hours

Consequences for participants	Trial author's conclusions
1. stents were removed without difficulty (despite epithelialisation) or longterm complications; prosthesis migration was easily diagnosed in all cases **2**. consequences not mentioned **3**. consequences not mentioned **4**. consequences not mentioned	No author's conclusions concerning adverse effects
1. haematuria resolved without additional treatment after 2 to 3 days in all but 1, who received haemostatic agents and required hospitalisation for observation **2**. discontinued the use of baclofen after 1 week but continued follow up	BTX-A with baclofen is relatively safe with few complications, which are easily accepted by the participants; however, the long-term toxicity is unknown
1. consequences not mentioned **2**. consequences not mentioned	BTX-A is safe because of the very scarce side-effects reported by the participants
1. caused difficulty with transfers and some activities of daily living; these gradually subsided over a 2- to 3-week period, after which the strength returned to normal **2**. consequences not mentioned	The transient weakness suffered by 3 participants was probably caused by receiving a too-large toxin dose in a 3-week period. An initial dose of 140 units of toxin was injected, followed by 2 doses of 240 units each week. To prevent weakness from the initial 3 injections, the trial authors now wait 2 weeks between injections

Table 7.2 Adverse effects (continued)

Included studies	Reported adverse events	Details of reported adverse events
Gallien et al.[70]	Serious adverse events: **1**. multiple sclerosis attack **2**. pyelonephritis **3**. lumbar radicular pain **4**. femoral fracture **5**. uterine leiomyoma **6**. drug-induced confusion **7**. dyspnoea Non-serious adverse events: **8**. urinary tract infections **9**. multiple sclerosis attack **10**. urinary leakages **11**. faecal incontinence	12 serious adverse events in 11 different participants during follow-up: **1**. 2 and 4 participants in the placebo and BTX-A group, respectively **2**. 1 participant in placebo group **3**. 1 participant in placebo group **4**. 1 participant in placebo group **5**. 1 participant in BTX-A group **6**. 1 participant in BTX-A group **7**. 1 participant in BTX-A group 64 non-serious adverse events were reported in 45 participants during follow- up: **8**. urinary tract infections in 38 participants (placebo n = 12; 29%, and BTX-A n = 16; 36%; RR 1.24, 95% CI 0.67 to 2. 29, Analysis 2.11.1) **9.** multiple sclerosis attack in 9 participants (placebo n = 3; 7%, and BTX-A n = 6; 13%; RR 1.86, 95% CI 0.50 to 6.95, Analysis 2.8*) **10**. urinary leakages in 4 participants (placebo n =2; 5%, and BTX-A n = 2; 4%; RR 0.93, 95% CI 0.14 to 6.30, Analysis 2.11.2*) **11**. 1 participant in BTXA group (placebo n = 0, and BTX-A n = 1; RR 2.80, 95%CI 0.12 to 66.70, Analysis 2.11.3*)

***)** The details of the statistical data analyses are available online at *The Cochrane Library*.[65] http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004927.pub4/full

- 100 U[68,70] ;
- 200 U[67] ; and
- 140 U initially, and subsequent injections of 240 U.[69]

Outcomes

Primary outcomes

All trials reported urodynamics measurements, including the postvoid residual urine volume - either measured urodynamically or using catheterisation. Other reported urodynamic outcomes were as follows: detrusor pressure, bladder capacity, bladder compliance, uroflow rate, voided volume, urethral pressure profile, and EMG of external urethral sphincter activity.

The urodynamic outcomes were all measured at different time points. Three trials[67,68,70] measured primary outcomes one month after injection and one trial,[69] a week after each injection. *Chancellor et al.*[66] considered primary outcomes at three, six, 12, and 24 months postoperatively.

Consequences for participants	Trial author's conclusions
All 11 participants with a serious adverse event were declared in the context of hospitalisation	No serious adverse event could be attributable to BTX-A

Only one trial[66] reported renal function, in terms of hydronephrosis and vesico-ureteric reflux, and urologic complications related to DSD (e.g. urinary tract infection).

Secondary outcomes

Chancellor et al.[66] quantified DSD symptoms by reporting the catheterisation rates. Four trials reported quality of life,[66-68,70] using different instruments to measure satisfaction rate[67,68] and condition-specific quality of life.[66,67,70] However, no trial reported if the instruments (questionnaires) were validated measures. Only *Chancellor et al.*[66] described associated symptoms, such as alterations in erectile function or ejaculation. Four trials reported associated symptoms of the underlying neurologic disease, such as autonomic dysreflexia symptoms[66,68,69] or MS attacks.[70] All trials reported surgical outcomes, consisting of blood loss, infection related to the procedure, hospital-stay length, occurrence of urethral strictures, complications, toxic effects, adverse events, tolerance, and side-effects.[66-70] Further details on adverse effects can be found in Table 7.2.

No trial reported socioeconomic measures, and therefore we did not describe these measures in the results. Other important outcomes reported were the need for re-intervention[68] and participant-reported days of effect.[68,69]

Excluded studies

We excluded 13 trials after further assessment of the 18 full-text reports.

- Six trials compared surgical interventions on detrusor overactivity but not functional BOO.[71-76]
- Five trials were not randomised.[31,40,77-79]
- *Meythaler et al.*[80] determined the effect of intervention on spasticity of extremities, but not on the urological tract.
- *Dunn et al.*[81] compared stents for the upper urinary tract (ureteric stents) instead of the lower urinary tract (urethral stents).

We provide further details in the 'Characteristics of excluded studies' tables (Table 7.1).

Risk of bias in included studies

We present specific characteristics, details of assessment, methodological quality, and risk of bias of the included trials in the 'Characteristics of included studies' tables available online[65] and in Figure 7.2 and Figure 7.3.

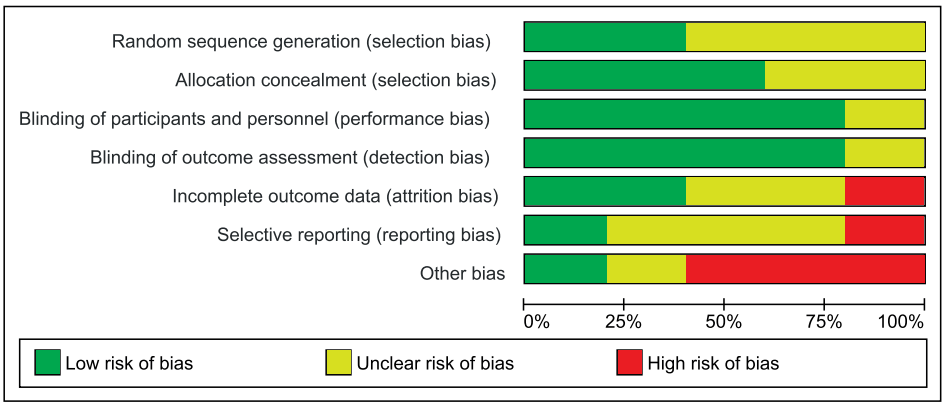

Figure 7.2 Risk of bias graph
review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies

Allocation (selection bias)

Random sequence generation (selection bias)

The method used for random sequence generation was unclear in three of five trials[66-68]: All three trials simply stated the trial was randomised, but provided no further

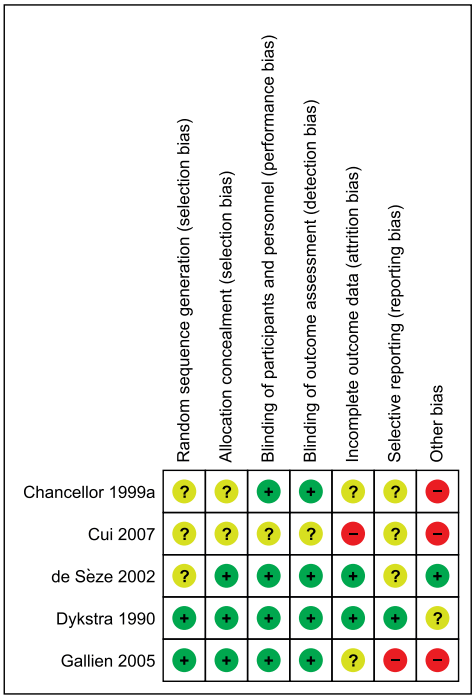

Figure 7.3 Risk of bias summary
review authors' judgements about each 'Risk of bias' item for each included study

details about the sequence generation process. We judged two trials to be at low risk: both *Dykstra & Sidi*[69] and *Gallien et al.*[70] used a computer random number generator.

Allocation concealment (selection bias)

We judged three of five trials[68-70] as having an adequate method of concealment of allocation prior to assignment since they used central allocation. The remaining two[66,67] did not provide details about allocation concealment; hence, we judged them as 'unclear' risk of bias.

Blinding (performance bias and detection bias)

We judged the performance bias due to knowledge of the allocated interventions by participants and personnel during the study and the detection bias during outcome assessment as 'low' risk of bias in four of five trials: Three trials[68-70] stated that they were 'double-blind' and provided a clear description of the blinding of the participants and personnel and outcome assessment, whereas due to specific surgical approaches, blinding in *Chancellor et al.*[66] was not possible. However, the review authors judged that the outcomes of *Chancellor et al.*[66] were not likely to be influenced by lack of blinding.

One trial[67] did not provide details about blinding of participants and personnel, nor about blinding of outcome assessment, so we therefore judged as 'unclear' risk of performance and detection bias.

Incomplete outcome data (attrition bias)

Two trials[68,69] did not contain missing data; therefore, we judged them to be at low risk of attrition bias. Two trials[66,70] did not provide a satisfactory explanation for the missing of data, and therefore there was insufficient information available to permit judgement of 'low' or 'high' risk of attrition bias. We judged one trial to be at high risk of bias because there was dropout due to adverse events only in the experimental group.[67] Only one trial[70] reported that they had performed an intention-to-treat analysis. However, they did not report how they handled missing values. The other trials[66-69] did not report how they handled data from participants who deviated from the protocol, but we assumed that they were analysed in the groups to which they were randomised.

Selective reporting (reporting bias)

It was unclear if there was selective reporting of the outcomes in three trials, because the protocols were not available.[66-68] However, it has to be noted that the trials reported the outcomes of all study parameters mentioned in the Methods section. Even though no trial protocol was available for *Dykstra & Sidi*,[69] the review authors judged the risk of selective reporting as 'low' since correspondence with a trial author assured that all of the trial's prespecified outcomes were reported in the prespecified way. We judged one trial[70] as high risk for reporting bias since the report provided no result for an outcome of interest mentioned in the methods section.

Effects of interventions

The details of the following statistical data analyses are available online at *The Cochrane Library*.[65] http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004927.pub4/full

Comparison 01: implantable urethral stent versus sphincterotomy

One small trial addressed this comparison.[66] All participants had traumatic spinal cord injury with urodynamically verified DSD. *Chancellor et al.*[66] compared implantation of the UroLume® sphincteric stent prosthesis with conventional external sphincterotomy.

Primary outcome measures

Urodynamic measurements

Postvoid residual urine volume (Analysis 1.1) and cystometric bladder capacity (Analysis 1.2) were not statistically significantly different between the interventions at either time-point.

The maximum detrusor pressure measured at three, six, or 12 months (Analysis 1.3) was relatively stable and low in both groups without statistically significant differences between the groups. However, at 24 months, the maximum detrusor pressure significantly increased in the participants who received an implantable stent, compared to the participants after sphincterotomy (MD 30.00 cmH_2O, 95% CI 8.99 to 51.01, Analysis 1.3.4).

Renal function

The occurrence of vesico-ureteral reflux was not statistically significantly different between the groups at 12 and 24 months (Analysis 1.4).

Hydronephrosis using radiography was reported per renal unit, although we have strong indications that the reported number of evaluated renal units was incorrectly reported. The report describes an evaluation of 52 renal units in the sphincterotomy group and 69 renal units in the stent group. Further in the report, 59 renal units were evaluated in the stent group. We assumed 59 units was correct since this could be confirmed by the associated reported percentage. The occurrence of hydronephrosis was not statistically significantly different between the groups at 12 and 24 months (Analysis 1.5). The confidence intervals were wide, reflecting few events and small groups.

The occurrence of urinary tract infections as a complication related to DSD was more common, but also not statistically significantly different between the groups at three, six, 12, and 24 months, neither in terms of positive urine culture (Analysis 1.6), nor in terms of symptomatic urinary tract infections (Analysis 1.7).

Secondary outcome measures

Quantification of symptoms

The participant-reported disappearance of autonomic dysreflexia symptoms was not statistically significantly different between groups at 24 months (Analysis 1.8). The catheterisation rates also were not statistically significantly different between groups at three, six, 12, and 24 months (Analysis 1.9).

Quality of life

The trial did not report which questionnaires it used to evaluate bladder emptying and quality of life with respect to the urological condition and if these questionnaires were validated. Exact data of the number of participants worrying about DSD, noticing bothersomeness with urination, the number who were hampered in their daily activities, and the participants reporting that the urological condition interfered with social life were lacking. We were therefore not able to analyse the effect of the intervention on quality of life.

Measures of associated symptoms (objective or subjective)

Participants reported their bladder-emptying ability as "much better", "somewhat better", "no change", "somewhat worse", and "much worse". For the current review, "much better" and "somewhat better" defined improvement, while "no change", "somewhat worse", and "much worse" defined no improvement. No statistically significant difference of the improvement rate of the bladder-emptying ability was observed between groups at three, six, 12, and 24 months (Analysis 1.10).

The report stated that no alterations in erectile function or ejaculation were noted in men who underwent sphincterotomy or stent placement at any time. The report provided no data.

Surgical outcome measures

Surgical measures were reported in all 26 participants who underwent sphincterotomy and in 30 of 31 participants who underwent stent placement.

More participants after sphincterotomy (23/26, 88.5%) than after stent placement (19/30, 63.3%) were hospitalised for two days or longer after the surgical intervention, in favour of stent placement (RR 0.72, 95% CI 0.53 to 0.97, Analysis 1.11). There were no statistically significant differences between groups in the number of participants with bladder neck obstruction requiring treatment (Analysis 1.12).

Adverse effects

(See Table 7.2.)

There were no statistically significant differences between groups in outcomes of haemorrhaging (one-day postoperative bleeding as quantified by haemoglobin value, Analysis 1.13) or number of participants with urethral strictures requiring surgical treatment (Analysis 1.14). Re-stenosis of the sphincter in two participants who underwent sphincterotomy required repeat sphincterotomy six months postoperatively.

Comparison 02: botulinum A toxin injection versus placebo

Two trials addressed this comparison.[69,70]

The extremely small trial from *Dykstra & Sidi*[69] in five men with spinal cord injury compared sphincter injections with either a dose of BTX-A (n = 3) or normal saline as placebo (n = 2), applied once a week for a total of three weeks. The initial dose of BTX-A was 140 U on a botulinum A toxin, with subsequent injections of 240 U. In the three participants allocated to the BTX-A treatment, an average decrease of 25 cmH_2O was seen in the maximal urethral pressure, an average decrease of 125 mL was seen in their postvoid residual urine volume, and an average decrease of 30 cmH_2O was found in the maximum bladder pressure during voiding. After completion of the study, participants who had received placebo were offered the opportunity to undergo the same

injections with BTX-A. The report mentions that in participants who received placebo injections, all outcomes were unchanged from baseline values until the subsequent injection with BTX-A once per week for three weeks. This resulted in similar responses to those of the other three participants who initially received BTX-A. The effects of the BTX-A injection lasted an average of 60 days in all five participants. All participants continued to use condom catheters after injection. Three participants had suffered from autonomic dysreflexia symptoms during voiding, of which all reported a noticeable improvement in their autonomic dysreflexia symptoms after toxin injections. Unfortunately, the report presented no data on placebo treatment, and therefore we could not make quantitative comparison between active and placebo treatment.

Gallien et al.[70] compared a single transperineal injection of BTX-A (Botox®, Allergan Inc.) into the external urethral sphincter with a single placebo (saline) transperineal injection into the external urethral sphincter in MS patients. In addition, participants in both groups were prescribed an alpha blocker (5 mg tablet slow-release alfuzosin twice a day) over four months. All results mentioned below in this comparison originate from *Gallien et al.*[70]

Primary outcome measures

Urodynamic measurements

The postvoid residual urine volume measured using catheterisation at 30 days did not differ statistically significantly between groups (Analysis 2.1). However, the voiding volume at 30 days was statistically significantly larger in the BTX-A group (MD 69 mL, 95% CI 11.87 to 126.13, Analysis 2.2).

At 30 days, the BTX-A group had a statistically significant lower pre-micturition detrusor pressure (MD -10.00 cmH_2O, 95% CI -17.62 to -2.38, Analysis 2.3.2) and maximum detrusor pressure (MD -14.00 cmH_2O, 95% CI -25.32 to -2.68, Analysis 2.3.3) compared to the placebo group. All other urodynamic outcomes at 30 days did not differ statistically significantly between groups: basal detrusor pressure (Analysis 2.3.1), maximal bladder capacity (Analysis 2.4), maximal urinary flow (Analysis 2.5), bladder compliance at functional bladder capacity (Analysis 2.6), and maximal and closure urethral pressure (Analysis 2.7).

Renal function

No data were available for analysis of any of the outcomes relating to renal function.

Secondary outcome measures

Quantification of symptoms

The occurrence of MS attacks was reported in both groups and did not differ statistically significantly between groups (Analysis 2.8).

Quality of life

The International Prostate Symptoms Score (IPSS) was measured as a condition-specific quality of life questionnaire related to lower urinary tract symptoms. This IPSS score did not differ statistically significantly between groups (Analysis 2.9). The variables assessing the quality of voiding (obstructive symptoms, urinary frequency, urgency, and incontinence) were assessed using 10 cm visual analogue scales (VAS). The VAS scores were not statistically significantly different between groups (Analysis 2.10).

Measures of associated symptoms (objective or subjective)

No data were available for analysis of any of the outcomes relating to symptoms associated with DSD.

Surgical outcome measures

The trials reported no relevant data regarding any surgical outcome measures.

Adverse effects

(See Table 7.2.)

Outcomes reported that related to the surgical intervention were the number of people with urinary tract infections, urinary leakage (incontinence), and faecal incontinence. There were no statistically significant differences between groups (Analysis 2.11). Serious adverse events and non-serious adverse events were reported, though exact data were not available.

Comparison 03: botulinum A toxin injection combined with non-surgical therapy

We identified one small trial[67] comparing a single 200 U BTX-A injection combined with oral baclofen versus a single 200 U Chinese-manufactured BTX-A injection without oral baclofen, in patients after spinal cord injury.

Primary outcome measures

Urodynamic measurements

The study measured the postvoid residual urine volume, though no data were available from the report to analyse the effect of intervention on postvoid residual urine volume.

Urodynamics were performed in both groups one month after the injections. The maximum uroflow rate (Analysis 3.1), maximal cystometric capacity (Analysis 3.2), and volume per voiding (Analysis 3.3) were not significantly different between groups. The bladder compliance was significantly higher (better) in the BTX-A group without oral baclofen group than in the BTX-A group with oral baclofen. Participants after BTX-A with baclofen had a lower (worse) compliance with a MD of -7.50 mL/cmH_2O, 95% CI

-10.74 to -4.26 (Analysis 3.4), compared to participants after BTX-A without baclofen. The report does not describe at which bladder volume the compliance was calculated. This is important because the bladder compliance describes the relationship between change in bladder volume and change in detrusor pressure. Furthermore, this trial did not report the detrusor pressure, which is a shortcoming since it is an important urodynamic measure when evaluating renal function. Therefore, the value of compliance as an outcome in this report may be limited.

Renal function
No data were available for analysis of any of the outcomes relating to renal function.

Secondary outcome measures

Quantification of symptoms
No data were available for analysis of any of the outcomes that quantifies symptoms. The report describes the measurement of the urinary frequency per 24 hours, though no data were available.

Quality of life
The amelioration degree was not statistically significantly different between groups (Analysis 3.5). The report did not describe how the amelioration degree was measured. The IPSS was administered in men, and the Urogenital Distress Inventory (UDI) was administered in women, though no data were available from the report. We were therefore not able to analyse the effect of intervention regarding the quality of life.

Measures of associated symptoms (objective or subjective)
No data were available for analysis of any of the outcomes relating to associated symptoms of DSD.

Surgical outcome measures
No data were available for analysis of any of the outcomes relating to surgical outcome measures.

Adverse effects
Reported adverse events were haematuria and muscle weakness (Table 7.2). However, no data were available for analysis of any of the outcomes relating to adverse effects.

Comparison 04: botulinum A toxin injection versus other surgical therapy

One very small trial[68] addressed this comparison; participants with spinal cord lesions (due to traumatic spinal cord injury, MS, or congenital malformation) received either a single 100 U BTX-A injection (Botox®, Allergan Inc.) or a lidocaine injection into the external urethral sphincter via the transperineal route. Participants who had a negative result at the end of the trial (30 days) received the other treatment. The results presented below only include data from the first period, since only this information was available from the report.

Primary outcome measures

Urodynamic measurements

The postvoid residual urine volume measured by catheterisation was significantly lower (better) after seven days (MD -163 mL, 95% CI -309 to -17, Analysis 4.1.2) and 30 days (MD -158 mL, 95% CI -278 to -39, Analysis 4.1.3) in favour of the group who received BTX-A injections. These differences were not quite statistically significantly different in the short-term (one day after treatment) (Analysis 4.1.1).

Reported urodynamic outcomes 30 days after injection were maximal detrusor pressure on voiding (Analysis 4.2), maximal urethral pressure (Analysis 4.3), and improvement in Blaivas classification of DSD (Analysis 4.4). None of these urodynamic outcomes were statistically significantly different between groups.

Renal function

No data were available for analysis for any of the outcomes relating to renal function.

Secondary outcome measures

Quantification of symptoms

No data were available for analysis of any of the outcomes that quantified symptoms of DSD.

Quality of life

The satisfaction score with treatment, using a question ("Do you find this treatment to be efficacious?") with response options from 0 (no efficacy) to 10 (maximal efficacy), was measured 30 days after injection. This was statistically significantly higher (better) in the participants who received BTX-A injections (MD 3.41, 95% CI 0.93 to 5.89, Analysis 4.5).

Measures of associated symptoms (objective or subjective)

The disappearance of symptoms of autonomic dysreflexia was not statistically significantly different between groups (Analysis 4.6). The report described the assessment of

the participant's personal opinion about the evolution of the voiding difficulties (time to induce voiding), but no data were available from the report for quantitative analysis. All participants in the BTX-A group reported an improvement in voiding difficulties, whereas the voiding difficulties remained unchanged in the lidocaine group.

Surgical outcome measures

At the end of the trial (30 days), one of five participants from the BTX-A group and all eight participants from the lidocaine group required another injection. The difference did not however reach statistical significance (Analysis 4.7).

Tolerance assessed by a quantitative tolerance score was not significantly different between groups (Analysis 4.8). Forty-six per cent of the participants reported that the BTX-A injection was efficacious for three months, and in 23% of the participants, the effect lasted longer than three months. The efficacy was shorter than three months in 31% of participants.

Adverse effects

There were no events of haemorrhaging or infections related to the procedure in either group and no systematic side-effects. One participant in each group reported side-effects, involving faecal incontinence after lidocaine and transitory exacerbation of urinary incontinence for two weeks after BTX-A (Table 7.2).

DISCUSSION

Summary of main results

In patients with neurogenic bladder dysfunction, the first aim of any therapy is protection of the upper urinary tract.[13] In patients with detrusor-sphincter dyssynergia (DSD), a high detrusor pressure during the voiding phase can result in a pathologic high-pressure bladder, which needs to be converted into a low-pressure reservoir. In patients for whom conservative treatment (i.e. clean intermittent self-catheterisation and pharmaceutical treatment (e.g. antimuscarinics)) is not possible or feasible, surgical treatment options should be considered. According to the European Association of Urology Guidelines,[13] sphincterotomy is the standard surgical treatment for DSD. Since the introduction of sphincterotomy in 1958 as a treatment of obstruction at the level of the external urethral sphincter in people suffering from neurogenic bladder,[82] improvements in surgical care and the development of new surgical options have been developed. However, consensus on what defines optimal surgical management seems to be lacking. This was the background of the current systematic review.

Only a limited number of small randomised controlled trials (RCTs) comparing a surgical approach with any other intervention in the treatment of functional bladder outlet obstruction (BOO) in adults with neurogenic bladder dysfunction was available. Also, the most recent included trial was performed no less than six years ago.[67]

Primary outcomes: urodynamic measurements

In the only trial comparing sphincterotomy with urethral stent placement,[66] the maximum detrusor pressure was lower (mean difference (MD) of -30.00 cmH_2O, 95% confidence interval (CI) 8.99 to 51.01, Analysis 1.3.4) in the sphincterotomy group compared to the stent group, but only at two years.

Interestingly, this was due to an increase of maximum detrusor pressure in the stent group, rather than because of a decrease in the sphincterotomy group. Results for maximum detrusor pressure were inconclusive at three, six, and 12 months. Results for postvoid residual urine volume and cystometric bladder capacity were inconclusive and consistent with benefit of either sphincteric stent prosthesis or sphincterotomy at three, six, 12, and 24 months.

Four of five included trials assessed intraurethral botulinum A toxin (BTX-A) injections as a surgical option. Unfortunately, we could not combine these in a meta-analysis as the comparator treatment differed in these trials. Comparing a single intraurethral 100 U BTX-A injection (Botox®, Allergan Inc.) with a placebo injection, while administering concomitant alfuzosin in multiple sclerosis (MS) patients,[70] voiding volume was higher after BTX-A (MD of 69.00 mL, 95% CI 11.87 to 126.13, Analysis 2.2). Also, both pre-micturition and maximal detrusor pressure were lower after BTX-A. A mean difference of -10.00 cmH_2O, 95% CI -17.62 to -2.38 and -14.00 cmH_2O, 95% CI -25.32 to -2.68, respectively, was found after 30 days (Analysis 2.3). However, postvoid residual urine volume as measured by catheterisation, basal detrusor pressure, maximal bladder capacity, maximal urinary flow, bladder compliance at functional bladder capacity, maximal urethral pressure, and closure urethral pressure at 30 days were inconclusive and consistent with benefit of either BTX-A or placebo injections. *Cui et al.*[67] compared 200 U intraurethral BTX-A injection (Lanzhou Biotechnology, China) with or without concomitant oral baclofen in spinal cord injury patients. Bladder compliance was better in patients who received BTX-A injections without oral baclofen, compared to the patients who received BTX-A injections with oral baclofen. Compared to the BTX-A group without baclofen, the BTX-A group with baclofen had a MD of -7.50 mL/cmH_2O, 95% CI -10.74 to -4.26 after one month (Analysis 3.4). Results for maximum uroflow rate, maximal cystometric capacity, and volume per voiding were all inconclusive and consistent with benefit of either BTX-A injection or BTX-A injection with the addition of oral baclofen. We believe that the relevance of bladder compliance as an outcome measure in this setting should be questioned. First, the authors did not report at which

bladder volume the compliance was calculated. Second, the trial authors did not provide data for comparison of detrusor pressure, which is a more important parameter for the effectiveness of treatment. Third, the trial authors did not provide a theoretical explanation of why particularly the addition of oral baclofen - which is supposed to act as an antispasticity agent - is not favoured in this trial.

The trial of *de Sèze et al*[68] compared a single 100 U intraurethral BTX-A injection (Botox®, Allergan Inc.) with a single intraurethral lidocaine injection in participants with DSD of mixed aetiology (i.e. traumatic spinal cord injury, MS, or congenital malformation). Botulinum A toxin injections resulted in lower postvoid residual urine volumes with MDs of -163.00 mL, 95% CI -308.65 to -17.35 and -158.30 mL, 95% CI -277.57 to -39.03 after seven and 30 days, respectively (Analysis 4.1), though not yet after one day. Results at one month for maximal detrusor pressure on voiding, EUS activity in electromyography, and maximal urethral pressure were inconclusive and consistent with benefit of either BTX-A or lidocaine injections. In addition, participants were significantly more satisfied 30 days after BTX-A injections (Analysis 4.5).

Finally, *Dykstra & Sidi*[69] performed a trial involving five men with spinal cord injury. These men were injected with either BTX-A (initial dose of 140 U onabotulinumtoxinA with subsequent injections of 240 U) or placebo (saline) once a week for three weeks at three or four sites in the external urethral sphincter. The placebo had no significant effect on DSD in the two participants allocated to the placebo treatment. Their urodynamic parameters were unchanged from baseline values until subsequent injections with BTX-A once a week for three weeks. These subsequent injections resulted in similar responses to those of the three participants who were allocated to the BTX-A treatment.

However, it is unclear how relevant changes in urodynamic parameters, such as postvoid residual urine volumes, are to participants' satisfaction with treatment and particularly whether beneficial urodynamic changes translate into reduced effect on damage to the kidneys, as none of the trials reported this crucial outcome.

Primary outcomes: renal function and urologic complications related to DSD

The remaining two primary outcome measures, renal function and urologic complications related to DSD, were only reported in the trial that compared sphincterotomy with stent placement. Results for renal function vesico-ureteric reflux and hydronephrosis, Analysis 1.4; Analysis 1.5) at 12 and 24 months, and urologic complications related to DSD (e.g. urinary tract infection, Analysis 1.6; Analysis 1.7) at three, six, 12, and 24 months were inconclusive and consistent with benefit of either sphincteric stent prosthesis or sphincterotomy.

Participant-reported outcomes and quality of life

Despite the major impact of neurogenic bladder dysfunction on quality of life (QoL), only two trials[67,70] used questionnaires as a patient-reported outcome measure. Both used the International Prostate Symptom Score (IPSS), which is a seven-item symptom score originally developed for men with benign prostatic hyperplasia,[83] the addition of a QoL question. Where *Gallien et al.*[70] used this prostate symptom score in both male and female patients, *Cui et al.*[67] used the Urogenital Distress Inventory (UDI)[84] in female participants, which lacks a specific QoL question. Since both trials did not report the data of the QoL question of the IPSS separately, we were not able to draw any conclusions regarding the improvement of QoL after intervention. *Chancellor et al.*[66] reported surveying participants regarding the QoL with respect to the urogenital condition, but the lack of data and information regarding if and which questionnaires were used does not provide us with any meaningful data. In the trial of *de Sèze,*[68] a treatment satisfaction score was determined using a single question. However, this single question ("Do you find this treatment to be efficacious?") may not be specific enough and can be interpreted as an improvement in symptoms as well as an improvement in QoL.

Duration of effect

The findings of the aforementioned trials evaluating BTX-A injections suggest that BTX-A may be useful in the treatment of DSD in adults with neurogenic bladder dysfunction. The duration of effectiveness of BTX-A injections is however limited. *Dykstra & Sidi*[69] reported an effect of BTX-A of an average of 60 days after the third (last) injection, and *de Sèze et al.*[68] reported BTX-A was efficacious for at least three months in the majority of participants (69%).

Adverse effects

See Table 7.2 on adverse effects.

Twenty-three per cent of participants needed more than one stent insertion procedure, and 19% of participants required a stent explantation. This was in contrast to the adverse effects of sphincterotomy, where a repeat sphincterotomy after six months was required in only 8% of participants. Treatment for bladder neck obstruction was necessary in one out of five of all participants.

Concerning the adverse events in the BTX-A trials, haematuria was reported in two trials,[67,69] but this was due to the cystoscopic injection and not necessarily due to the injected agent. More important are the effects of BTX-A on muscle weakness. This seem related to the dose of BTX-A used.

Two trials using more than 100 U BTX-A reported muscle weakness;[67,69] this was in contrast to the two trials using 100 U (single dose) BTX-A, in which no muscle weakness was observed[68] or reported.[70] However, the last two trials reported both incontinence

for faeces[68] and urine.[68,70] The serious adverse events as reported by *Gallien et al.*[70] were not attributable to BTX-A.

Quality of the evidence

In general, the included trials were small, diversely designed, and reported outcomes were defined in different ways. Therefore, due to paucity of evidence, the results should be interpreted cautiously. The risk of selection bias and reporting bias (Figure 7.3) is certainly present, mainly because of insufficient information to permit judgement. Contacting trial authors resulted in additional information for one trial,[69] though initially three of five trials did not provide enough information in their report.[66,67,69] These potential risks may be related to inadequate reporting common in older trials,[66,69] or to publication in a non-English language journal,[67] rather than to methodological shortcomings.

Potential biases in the review process

We applied no language or other restrictions in the search for trials. Despite the comprehensive search, we may still have missed unreported trials or trials only reported in conference abstracts, causing publication bias.

We added the following non-prespecified outcomes in the protocol to the review as secondary outcomes, since we judged these important during this review:

- The occurrence of autonomic dysreflexia symptoms and MS attacks as associated symptoms of neurogenic lower urinary tract dysfunction.
- The need for reinjection of intraurethral BTX-A.
- Participant-reported days of effect

This may have introduced unintentional outcome reporting bias in the review process with the possibility of biased and misleading interpretation of the results.[85] However, we added these outcomes because of knowledge of studies that existed, not necessarily because of knowledge of the results.

Agreements and disagreements with other studies or reviews

We identified two systematic reviews that systematically reviewed surgical treatment options in the treatment of DSD.[78,79]

Mehta et al.[78] conducted a systematic review and meta-analysis to assess the effect of intraurethral BTX-A injections on improving bladder emptying in patients with spinal cord injury. They pooled data from two RCTs[68,69] and six uncontrolled trials, and concluded that BTX-A was effective in significantly reducing postvoid residual urine volume, detrusor pressure, and urethral pressure after one month. They made no statements about the clinical utility of BTX-A. Because this review included non-

randomised controlled trials, the data used for meta-analysis were pre-intervention versus postintervention.

Naumann et al.[79] conducted an evidence-based review of the safety and efficacy of BTX-A in the treatment of autonomic and urologic disorders and low back and head pain. The conclusions and recommendation of the safety and efficacy of BTX-A in the treatment of DSD were based on the quality of the trials.[86] *Gallien et al.*[70] received the highest classification based on the quality of the trial, and *de Sèze et al.*[68] and *Dykstra & Sidi*[69] received the second best classification. Based on these three trials, *Naumann et al.*[79] recommended that BTX-A should be considered for DSD in people with spinal cord injury with a level B rating for recommendations.[86] No effects of interventions were analysed.

AUTHORS CONCLUSIONS

Implications for practice

At present, there are insufficient data available to determine the optimal surgical treatment of BOO in adults with neurogenic bladder dysfunction. Four out of five of the trials focused on BTX-A treatment. This review has found evidence of limited quality that BTX-A injection - either administered by itself or in combination with another treatment - confers benefit with regard to increasing voided urine volume, lowering detrusor pressure, and decreasing postvoid residual bladder urine volume. In addition, one small study found that it appears to lead to a higher satisfaction than lidocaine injection. However, the necessity of regular reinjection of BTX-A is a significant drawback. A sphincterotomy might be a more effective treatment option for lowering bladder pressure in the long-term; however, results from one small study comparing sphincterotomy versus sphincteric stent prosthesis on urodynamic measures were inconclusive.

Implications for research

Unfortunately, this review failed to provide robust evidence in favour of any of the surgical treatment options, because of the limited availability of eligible trials, the variability in the interventions (e.g. dose and mode of injection of BTX-A) of the included trials, and particularly because of their small size (ranging from five to 86 participants). Also, the duration of follow-up of the included trials was limited, with an average of eight months.

Therefore, more and larger RCTs are needed to evaluate the most effective surgical intervention for functional BOO in adults with neurogenic bladder dysfunction. Furthermore, RCTs of specific surgical treatment options for DSD (i.e. urethral balloon

dilatation, intrathecal baclofen, pudendal nerve block, suprapubic catheterisation) are lacking. Randomised controlled trials assessing the effectiveness of BTX-A need to address the remaining uncertainty about the optimal dose and mode of injection, keeping in mind the possible dose-related adverse events.

Trials should use standardised terminology and outcomes in accordance with International Continence Society (ICS) standards[2] and the Consolidated Standards of Reporting Trials (CONSORT) statement[87] improve the quality of the reports and draw meaningful conclusions. In addition, further trials are advised to select outcomes that really matter to patients and practitioners, which is facilitated by the Core Outcome Measures in Effectiveness Trials (COMET) initiative.[88]

The lack of trials assessing QoL from the patient's point of view as an outcome is worrying, as the medical (technical) success does not necessarily correspond with the emotional judgement of success reported by the patient. Health-related QoL should receive much more attention in future trials. Furthermore, none of the included trials addressed socioeconomic outcomes. In future trials, the duration of effectiveness of BTX-A injections should be considered as a socioeconomic outcome.

This systematic review included only RCTs and quasi-RCTs. However, because of the limited availability of eligible trials, future reviews should consider including evidence from non-randomised trials for outcomes, although this will introduce bias.

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Chapter 8

Multidisciplinaire richtlijnen neurogene blaas *(in Dutch)*

Elaine Utomo (projectbegeleiding werkgroep)

Richtlijnen Nederlandse Vereniging voor Urologie (NVU), 2012

EXCERPT

Multidisciplinary guidelines in managing patients with neurogenic bladder dysfunction

Multidisciplinary evidence based clinical guidelines for management of patients with symptoms of neurogenic bladder in the Netherlands are provided. Information for Dutch clinical practitioners is provided about the incidence, definitions, diagnosis, therapy, and follow-up of neuro-urological disorders.

These guidelines were made in collaboration with the Dutch associations of urologists (Nederlandse Vereniging voor Urologie), neurologists (Nederlandse Vereniging voor Neurologie), rehabilitation physicians (Nederlandse Vereniging van Revalidatieartsen), Elderly Care Physicians and Social Geriatricians (Verenso), Continence Nurses and Carers (Continentie Verpleegkundigen & Verzorgenden), and patient support groups for people with paraplegia (Dwarslaesie Organisatie Nederland) and for people with congenital physical disabilities (BOSK).

Neurogenic bladder dysfunction is a condition with many aspects. Comprehensive and specific diagnostics are needed to determine an individual treatment plan. During treatment the medical and physical condition of the patient needs to be taken into account. Furthermore, the patients' expectations concerning social, physical and medical health occupy an important role. A considerable amount of different therapeutic options are available which needs to be personalized for each individual patient. Equally important as treatment success is the requirement of lifelong guidance's and follow-up. These Dutch guidelines serve to support both clinician and patient to provide for treatment and follow-up tailored to the needs of the individual patient.

INLEIDING

Aanleiding voor het maken van de richtlijn

Elke schade aan de zenuwcontrole van de lage urinewegen kan leiden tot neurogeen blaaslijden. Een patiënt met neurogeen blaaslijden kan last hebben van onder andere urine incontinentie door onder- of overactieve blaas, infecties en steenvorming in de urinewegen en verslechtering van de nierfunctie. In de afgelopen vier decennia is de prognose bij patiënten met een neurogeen gestoorde blaas sterk verbeterd. Dit is deels het gevolg van maatregelen in de preventieve zorg zoals de introductie van intermitterende katheterisatie en de controle en behandeling van de hoge drukblaas (LE: 3, Tabel 8.1).[1,2] Het niet consequent toepassen van preventieve maatregelen kan leiden tot complicaties en verkort de levensverwachting. Het merendeel van de patiënten met neurogeen blaaslijden vereist dus levenslange zorg met als doel een optimale kwaliteit van leven en maximalisatie van de levensverwachting. De onduidelijkheid over de meest effectieve manier van diagnostiek en behandeling van neurogeen blaaslijden is echter blijven bestaan door het gebrek aan richtlijnen.

De *"European Association of Urology (EAU) Guidelines Working Panel for NLUTD"* heeft voor het eerst in de wereld richtlijnen betreffende neurogene blaas opgesteld en gepresenteerd tijdens het 23e jaarlijkse EAU congres in 2008.[3] Deze richtlijnen bieden betrokken specialisten de gelegenheid hun behandeling van het neurogeen blaaslijden te toetsen aan die van experts. De EAU richtlijnen zijn weinig evidence based en alleen urologen zijn geconsulteerd bij de opstelling van het document. De hierbij gepresenteerde richtlijnen zijn deels gebaseerd op de EAU richtlijnen en opgesteld met de consensus van vier betrokken beroepsverenigingen.

Tabel 8.1 Levels of Evidence

Level	Type of evidence
1a	Conclusie gebaseerd op meta-analyse of gerandomiseerde onderzoeken
1b	Conclusie gebaseerd op minstens één gerandomiseerd onderzoek
2a	Conclusie gebaseerd op één goed uitgevoerd gecontroleerd onderzoek zonder randomisatie
2b	Conclusie gebaseerd op minimaal één ander soort goed uitgevoerd kwasi-experimenteel onderzoek
3	Conclusie gebaseerd op goed uitgevoerd niet-experimenteel onderzoek, zoals vergelijkende onderzoeken, correlatie onderzoeken en case reports
4	Conclusie gebaseerd op mening van deskundigen of klinische ervaringen

Naar Sackett et al. [5]

Doelstelling van de richtlijn

Klinische richtlijnen zijn gedefinieerd als 'systematisch ontwikkelde aanbevelingen bedoeld om hulpverleners en patiënten te helpen bij het nemen van beslissingen over de gewenste zorg bij concrete gezondheidsproblemen'. [4]

Deze richtlijn biedt ondersteuning bij het beantwoorden van de volgende vragen:

a) wat is neurogeen blaaslijden?
b) wanneer moet neurogeen blaaslijden worden vastgesteld?
c) met welke onderzoeken kan neurogeen blaaslijden worden aangetoond?
d) hoe moeten asymptomatische patiënten met neurogeen blaaslijden worden behandeld?
e) hoe moeten symptomatische patiënten met neurogeen blaaslijden worden behandeld?
f) is preventieve behandeling van neurogeen blaaslijden nodig?
g) wanneer is nader onderzoek naar neurogeen blaaslijden vereist?
h) wanneer moet naar tweede- en derdelijnszorg worden verwezen?
i) wat is het schema van lange termijn follow-up bij patiënten met hoog risico neurogeen blaaslijden?
j) welke adviezen aan verzorgers dienen te worden gegeven?

Betrokken patiëntengroep

De richtlijn is relevant voor alle patiënten met bewezen of mogelijk neurogeen blaaslijden. Het betreft zowel klinische als ambulante patiënten.

Voor wie is de richtlijn bedoeld?

Deze richtlijn is bedoeld voor:

- alle zorgverleners die betrokken zijn bij de zorg voor patiënten met een neurogene blaas, zoals huisartsen, verpleegkundigen, revalidatieartsen, neurologen, urologen en specialisten ouderengeneeskunde.
- patiënten met een neurogene blaas en hun familieleden en/of verzorgers

Methode richtlijnontwikkeling

Deze richtlijn volgt de criteria zoals beschreven voor *Evidence Based Medicine*. Patiënten met neurogeen blaaslijden krijgen weinig aandacht in medisch onderzoek. Het gevolg is dat literatuur met betrekking tot deze doelgroep schaars is en de beschikbare literatuur betreft zelden niveau 1 bewijs (gerandomiseerde trials). Desondanks heeft de werkgroep gemeend de bewijskracht indien mogelijk te scoren en te vermelden door gebruik te maken van "levels of evidence" (LE) en/of "grades of recommendations" (GR) gebaseerd op 'expert opinion' [5] (Tabel 8.2).

Tabel 8.2 Gradering van aanbevelingen

Graad	Aanbevelingen gebaseerd op
A	Klinische onderzoeken van goede kwaliteit met specifieke aanbevelingen en minimaal één gerandomiseerd onderzoek
B	Goed uitgevoerde klinische onderzoeken, maar zonder gerandomiseerde onderzoeken
C	Geen gepaste klinische onderzoeken beschikbaar van goede kwaliteit

Naar Sackett et al. [5]

Juridische betekenis van richtlijnen

Richtlijnen zijn geen juridische voorschriften, maar indien mogelijk op wetenschappelijk bewijs gebaseerde inzichten om kwalitatief goede zorg te verlenen. Indien beargumenteerd kan worden, kunnen zorgverleners op basis van hun autonomie afwijken van de richtlijn en toepassing hiervan is zijn of haar verantwoordelijkheid. De richtlijn is pas geldig indien geaccordeerd door de betrokken beroepsvereniging.

Wie hebben de richtlijn ontwikkeld?

De richtlijn is ontwikkeld door een multidisciplinair samengestelde werkgroep, waarbij het initiatief is genomen door de Nederlandse Vereniging voor Urologie. De Orde van Medisch Specialisten bood methodologische en financiële ondersteuning bij de richtlijnontwikkeling en bij het beoordelen en samenvatten van de wetenschappelijke evidentie.

Samenstelling van de werkgroep:
Dr. B. Blok, uroloog, voorzitter
Drs. M. de Beer, revalidatiearts
Dr. E. Birnie, epidemioloog
Dr. J. Heesakkers, uroloog
Prof. dr. R. Hintzen, neuroloog
Dr. L. de Kort, uroloog
Drs. H. van de Sande, specialist ouderengeneeskunde namens Verenso
Dr. J.R. Scheepe, kinderuroloog
Drs. T.A.M. Siepman, neuroloog
Mw. J. Bergman, Verpleegkundig Specialist Continentiezorg namens CV&V
Dhr. M. Klem, directeur BOSK
Mw. W. de Moes, namens Dwarslaesie Organisatie Nederland
Drs. E. Utomo, projectleider

SAMENVATTING AANBEVELINGEN EN CONCLUSIES

Classificatie van neurogeen blaaslijden

De functionele classificatie wordt aanbevolen. Deze classificatie is gebaseerd op symptomatologie tijdens de vullings- of mictiefase (GR: C).

Diagnostiek

Anamnese

- Een uitgebreide algemene anamnese moet worden verricht met de nadruk op huidige klachten van urinewegen, darmstelsel, en seksuele en neurologische functies als klachten in het verleden (GR: C).
- Speciale aandacht moet worden besteed aan het bestaan van alarmverschijnselen, zoals pijn, infectie, hematurie en koorts, toename van spasme en tekenen van autonome disregulatie, die verdere specifieke diagnostiek rechtvaardigen (GR: C).
- Het wordt geadviseerd om een mictiedagboek bij te houden omdat deze waardevolle informatie kan geven (GR: C).

Lichamelijk onderzoek

- De individuele beperkingen van de patiënt moeten worden meegewogen in de planning van nader onderzoek (GR: C).
- Alvorens diagnostische onderzoeken plaatsvinden, wordt geadviseerd de neurologische status zo compleet mogelijk te omschrijven. Alle sensaties en reflexen in het urogenitale gebied worden getest (GR: C).
- Voor het vaststellen van de sensibiliteit bij dwarslaesie patiënten is de ASIA classificatie te prefereren.

D. Bij lichamelijk onderzoek moet extra aandacht worden gegeven aan aanwijzingen voor aangeboren afwijkingen die neurogene blaasklachten kunnen veroorzaken zoals spina bifida en scoliose (GR: C).

Aanvullend onderzoek

- Urinesediment, bloedonderzoek, residu na mictie en vrije uroflowmetrie en beeldvorming van de (hoge) urinewegen moeten aanvullend worden onderzocht.

Urodynamisch onderzoek

- Urodynamisch onderzoek is noodzakelijk om de eventuele disfunctie van de lage urinewegen vast te stellen (GR: B).
- Uroflowmetrie en meting van het residu na mictie moeten worden uitgevoerd voordat invasieve urodynamica worden verricht (GR: B).

- Video-urodynamisch onderzoek is de gouden standaard van invasieve urodynamica bij patiënten met neurogeen blaaslijden (GR: B).
- Specifieke uro-neurofysiologische onderzoeken worden alleen op indicatie verricht (GR: B).

Behandeling

- Neurogeen blaaslijden wordt behandeld ter bescherming van de nierfunctie, verbetering van de urine incontinentie en optimalisatie van de kwaliteit van leven (LE: 3).
- Bij een te hoge detrusordruk moet deze worden verlaagd om schade aan de hoge urinewegen te voorkomen (GR: B).

Conservatieve behandeling

Geassisteerde blaasontlediging

- Elke methode van geassisteerd legen van de blaas moet worden gebruikt met de grootste voorzichtigheid (GR: B).
- Gedragsmodificatie kan de continentie bevorderen (LE: 2b; GR: B).

Blaasrevalidatie

- Bekkenbodemfysiotherapie met biofeedback en blaasrevalidatie is mogelijk effectief gebleken in geselecteerde MS patiënten (LE 1b).

Elektrostimulatie

- Chronische nervus pudendus stimulatie geeft significante urodynamische verbeteringen (LE: 3).
- Sacrale neuromodulatie is effectief gebleken bij dwarslaesiepatiënten, maar is wel afhankelijk van de onderliggende neurologische aandoening en of deze progressief is (LE: 3).
- Niet-chronische elektrische stimulatie kan gunstige effecten hebben op neurogene blaas (LE: 2b).
- Transcraniale magnetische stimulatie verbeterde mictiesymptomen bij MS en Parkinson patiënten (LE: 3).

Externe hulpmiddelen

- Een condoom katheter of incontinentiemateriaal kan de effecten van urine-incontinentie verminderen tot een maatschappelijk aanvaardbare situatie (GR: B).

Medicamenteuze behandeling

Keuze anticholinergicum

- De lange termijn werkzaamheid en veiligheid van anticholinerge therapie voor neurogene detrusor activiteit is goed gedocumenteerd (LE: 1a).
- Een combinatie van medicamenteuze therapieën kan worden overwogen om het behandelingsresultaat te maximaliseren, echter wees hierin terughoudend bij ouderen met comorbiditeit (LE: 2a; GR: B).
- Oxybutynine chloride en tolterodine tartraat zijn geaccepteerde en effectieve anticholinergica (LE: 1a).

Detrusor onderactiviteit

- Er bestaat geen bewijs voor de werking van medicijnen bij een onderactieve detrusor (LE: 2a).

Verlaging blaasuitgangsweerstand

- Alfa-blokkers zijn gedeeltelijk succesvol gebleken bij het verminderen van de urethrale weerstand (LE: 2a).

Minimaal invasieve behandelingen

Katheterisatie

- Intermitterende katheterisatie (IC) is de standaard behandeling voor patiënten die niet in staat zijn om hun blaas spontaan en volledig te legen. Zij moeten echter lichamelijk en cognitief in staat zijn tot (zelf)katheterisatie (GR: A).
- Patiënten moeten goed worden geïnstrueerd in de techniek en de risico's van IC (GR: B).
- Aseptische IC is de methode van keuze (GR: B).
- De gewenste kathetergrootte is 12 tot 14 Charrière (GR: B).
- De gemiddelde frequentie van de IC is 4 tot 6 keer per dag (GR: B).
- Het gekatheriseerde blaasvolume moet lager blijven dan 400 ml (GR: B).
- Transurethrale en suprapubische verblijfskatheters dienen slechts in uitzonderlijke gevallen te worden gebruikt onder strikte controle. De katheter moet vaak worden vervangen.
- Siliconen katheters hebben de voorkeur en moet worden vervangen om de 6-12 weken; (gecoate) latex katheters moeten worden vervangen om de 6 à 12 weken (GR: B).

Botulinetoxine A injecties in de blaas

- Botulinum toxine injecties in de detrusor is de meest effectieve minimaal invasieve behandeling om overactiviteit te verminderen bij neurogeen blaaslijden (GR: A),

voor onabotuline toxine A (Botox ®) worden 200 EH geadviseerd (GR: A) en voor abobotulinum toxine A (Dysport ®) 500 EH (GR: A).

Intravesicale vanilloïden

- Intravesicale vanilloïden zorgen voor een tijdelijke afname van detrusor overactiviteit (LE: 1a).

Blaashals en urethrale behandelingen

- De blaasuitgangsweerstand kan worden verlaagd ter bescherming van de bovenste urinewegen door sfincterotomie of botulinum toxine A in de sfincter (GR: C).
- Urethrale stents worden afgeraden vanwege de substantiële complicaties en risico's op herhaaldelijke interventies (GR: B).
- Bij vesicoureterale reflux moet de intravesicale druk worden verlaagd (GR: B).

Chirurgische behandelingen

Overactieve detrusor

- Detrusormyectomie is een aanvaardbare optie voor de behandeling van een overactieve blaas wanneer een meer conservatieve aanpak heeft gefaald. Het is beperkt invasief en heeft een minimale morbiditeit (GR: B); dit kan echter op de lange termijn leiden tot een verminderde blaascontractiliteit.
- Sacrale rhizotomie met sacrale anterior wortel stimulatie (SARS) in complete laesies en sacrale neuromodulatie in incomplete laesies zijn effectieve behandelingen in geselecteerde patiënten (GR: B).
- Blaasaugmentatie is een aanvaardbare optie voor het verminderen van detrusordruk wanneer minder invasieve ingrepen hebben gefaald. Voor de behandeling van een ernstig verdikte of fibrotische blaaswand kan blaassubstitutie worden overwogen (GR: B).

Onderactieve blaas

- Sacrale neuromodulatie (bij incomplete laesies) kan bij geselecteerde patiënten een effectieve behandeling zijn (GR: B).

Urethrale sfincter insufficiëntie

- De artificiële urinaire sfincter (AUS) verdient de voorkeur bij patiënten met neurogeen blaaslijden (GR: B).
- De plaatsing van een urethrale sling is een geaccepteerde procedure bij onderactieve urethrale sfincter (GR: B).

Urinedeviaties

- Continente of incontinente stoma's kunnen worden overwogen bij therapieresistente patiënten.
- In geselecteerde patiënten (bijv. rolstoel gebonden patiënten) kan een katheteriseerbaar stoma waardevol zijn.

Urineweginfecties bij neurogeen blaaslijden

De meeste kennis betreffende urineweginfecties (UWI) bij neurogene blaas is verkregen uit studies bij patiënten met een dwarslaesie en niet direct toepasbaar op andere populaties, zoals MS, CVA of morbus Parkinson.

- Recidiverende UWI's kunnen een teken zijn van een slechte techniek van zelfkatheterisatie of een suboptimale behandeling van een onderliggend probleem, bijvoorbeeld een hoge drukblaas, residu na mictie of urinewegstenen. Het bevestigen of uitsluiten van deze oorzaken is noodzakelijk.
- Een asymptomatische bacteriurie moet niet worden behandeld bij patiënten met een dwarslaesie; ook niet bij intermitterende katheterisatie (GR: B).
- Gebruik van antibiotica bij recidiverende urineweginfecties kan leiden tot bacteriele resistentie; gericht antibiotica gebruik wordt daarom geadviseerd (GR: C).

Seksuele functie en vruchtbaarheid bij dwarslaesie

Erectiele disfunctie (ED)

- Orale PDE5Is zijn de eerstelijns behandeling voor ED bij mannen met een dwarslaesie (GR: A).
- Mechanische hulpmiddelen zoals een vacuümpompen en ringen kunnen effectief zijn maar zijn niet praktisch in het gebruik (GR: C).
- Intracaverneuze injecties met vasoactieve medicijnen (alleen of in combinatie) zijn de tweedelijns behandeling als orale medicatie niet heeft gewerkt (GR: A).
- Chirurgische peniele protheses kunnen worden gegeven aan geselecteerde patienten die niet reageren op conservatieve behandelingen (GR: B).

Mannelijke vruchtbaarheid

- Spermawinning kan door middel van prostaatmassage, vibrostimulatie, transrectale electro-ejaculatie of PESA (GR: B).
- Medisch geassisteerde voortplanting (IUI, IVF, ICSI) zijn geaccepteerde behandelingen bij dwarslaesiepatiënten (GR: B).

Vrouwelijke seksualiteit

- PDE5I's kunnen gedeeltelijk de subjectieve seksuele problemen bij vrouwen met een dwarslaesie oplossen (GR: C).

- Reflex lubricatie en orgasme kunnen worden opgewekt bij vrouwen met een dwarslaesie boven het sacrale ruggenmerg (GR: B).
- Orgasme en opwinding kunnen worden opgewekt bij vrouwen met schade aan de sacrale reflexboog door stimulatie van erogene zones boven het niveau van de laesie (GR: B).

Vrouwelijke vruchtbaarheid

- Het reproductieve vermogen van vrouwen wordt slechts tijdelijk beïnvloed door de dwarslaesie (GR: B).
- De zwangerschap heeft een normaal verloop maar er bestaat meer kans op complicaties zoals blaasproblemen, spasticiteit, doorligplekken door gewichtstoename en autonome dysreflexie tijdens zwangerschap en bevalling (GR: B).

Kwaliteit van leven

- Een van de hoofddoelen is het verbeteren van de kwaliteit van leven (LE: A).
- Beschikbare instrumenten zijn: Qualiveen, een specifiek instrument voor dwarslaesie en multiple sclerose patiënten, Visuele Analoge Schaal (VAS) voor de hinder. De Qualiveen is echter nog niet vertaald en gevalideerd in het Nederlands. Generieke (SF-36) of specifieke vragenlijsten voor incontinentie (UDI-6, IIQ-7, I-QOL) kunnen ook gebruikt worden (GR: B).

Follow-up

- Afhankelijk van de neurologische pathologie en de huidige toestand van het neurogeen blaaslijden kan het controle interval variëren, maar bij patiënten met hoge blaasdrukken wordt geadviseerd eens in de 1 tot 2 jaar te controleren.
- Geïndividualiseerde follow-up is noodzakelijk om de KvL en levensverwachting te monitoren.

DEFINITIES

Intermitterende katheterisatie (IC)

Het legen van de blaas door een katheter die na de procedure wordt verwijderd. De procedure gebeurt meestal met gelijkmatige intervallen, bijvoorbeeld vier maal per dag.

Aseptische IC

De katheters blijven tijdens de katheterisatie steriel, de genitaliën worden gedesinfecteerd en een (desinfecterend) glijmiddel wordt gebruikt.

Clean IC (CIC)

Voor de katheterisatie worden wegwerpkatheters gebruikt en de genitaliën worden tevoren gereinigd.

Intermitterende zelf-katheterisatie

Intermitterende katheterisatie door de patiënt zelf.

Lower motor neuron laesie

Laesie ter hoogte van de segmenten S1-S2 of lager in het ruggenmerg, waarbij de motoneuronen van blaas en sfincter uitgevallen zijn.

Upper motor neuron laesie

Laesie boven de segmenten S1-S2 in het ruggenmerg.

Mictie, gebalanceerd

Bij patiënten met neurogeen blaaslijden (post-mictie residu <80 ml of <20% van het totale blaasvolume). Mictie met fysiologische detrusordruk en laag residu na mictie. De hoogte is afhankelijk van de urethrale weerstand en blaascontractiekracht.

Mictie, getriggerd

Mictie, op gang wordt gebracht door te kloppen. Er ontstaat reflexmatig een blaascontractie door stimulatie van drukreceptoren.

Detrusor lekdruk

De laagste waarde van de detrusordruk waarbij urine lekkage wordt gezien zonder een blaascontractie of verhoging van de abdominale druk bij urodynamisch onderzoek.

ACHTERGROND

Patiënten met schade aan het zenuwstelsel hebben vaak last van een neurogene blaas. Er zijn ongeveer een half miljoen mensen met een neurogene blaas in Nederland. De bekendste oorzaken van neurogene blaas zijn dwarslaesie, multiple sclerose (MS), beroerte (CVA) en cauda equina syndroom (CES). Echter, ook minder voor de hand liggende aandoeningen die zenuwweefsel aantasten kunnen leiden tot een neurogene blaas, zoals diabetes mellitus. Neurogeen blaaslijden komt ook vaak voor in verpleeghuizen, voorbeelden zijn eindstadia van MS en morbus Parkinson. Ook bij CVA-patiënten en dementerenden komt veelvuldig neurogeen blaaslijden voor.[6]

Neurogeen blaaslijden kan leiden tot verschillende soorten complicaties. Urine-incontinentie treedt op door detrusoroveractiviteit (=overactieve blaas), overloop door acontractiele blaas (=verlamde blaas) en/of sfincterinsufficiëntie (sluitspier-insufficiëntie). Stoornissen in de blaaslediging kunnen leiden tot residu en retentie met als gevolg urineweginfecties met steenvorming. Een ernstige complicatie is nierschade door een hoge druk in de blaas in combinatie met of door opstijgende infecties. Verder kunnen verlies van kwaliteit van leven (KvL), hogere gezondheidszorgkosten ten gevolge van frequente ziekenhuisopnamen, minder arbeidsparticipatie en sociale isolatie optreden als gevolg van neurogene blaasfunctiestoornissen. Het merendeel van de patiënten met neurogeen blaaslijden vereist levenslange zorg om de kwaliteit van leven te behouden en de levensverwachting te maximaliseren. Patiënten na een CVA of patiënten met dementie kunnen (weer) onzindelijk worden. Zij hebben het besef van toiletgang niet meer (decorumverlies), maar dit hoeft niet altijd gepaard te gaan met over- of onderactiviteit van de blaas. Dit is dus een speciaal soort categorie patiënten.

In de afgelopen jaren zijn er monodisciplinaire richtlijnen ontwikkeld voor de diagnostiek en behandeling van de neurogene blaas door de Europese Associatie voor de Urologie.[7] Gezien de grote verschillen tussen de diverse Europese landen, de inrichting van het zorgstelsel, de beschikbaarheid van apparatuur en de financiering, kan deze richtlijn niet automatisch gebruikt worden voor de Nederlandse situatie. In Nederland zijn er helaas nog geen relevante mono- of multidisciplinaire richtlijnen beschikbaar. Dit initiatief tracht multidisciplinaire richtlijnen te ontwikkelen door middel van samenwerking van vier beroepsverenigingen, te weten de Nederlandse Vereniging voor Urologie (NVU), Nederlandse Vereniging voor Neurologie (NVVN), Vereniging voor Revalidatie Artsen (VRA) en Vereniging voor Specialisten Ouderengeneeskunde (Verenso).

De noodzaak van een landelijke multidisciplinaire richtlijn werd bevestigd door een enquête onder Nederlandse urologen die werd gehouden bij de aanvang van het opstellen van deze richtlijn.[8] Daaruit bleek dat er een zeer grote verscheidenheid bestaat in de diagnostiek en de behandeling van de neurogene blaas.

Classificatie neurogeen blaaslijden

Classificatie van neurogeen blaaslijden draagt bij tot beter begrip en behandeling van neurogeen blaaslijden. Diverse classificatiesystemen zijn voorgesteld voor de indeling van neurogeen blaaslijden.[9-12] Een eenvoudig classificatie systeem is weergegeven in tabel 8.3 (LE: 4).[13] Het is gebaseerd op symptomatologie tijdens de vullingsfase of tijdens de mictiefase.

Tabel 8.3 De functionele classificatie

Onvermogen tot opslag, veroorzaakt door:
• Blaas
• Blaasuitgang
• Combinatie van blaas en blaasuitgang
Onvermvogen tot ledigen, veroorzaakt door:
• Blaas
• Blaasuitgang
• Combinatie van blaas en blaasuitgang

**Naar* Wein et al. [13]

Tijdens de vullingsfase kunnen deze symptomen veroorzaakt worden door disfunctie van de blaas, de blaasuitgang of beide. De blaas kan bijvoorbeeld onwillekeurige contracties vertonen of een veranderde sensatie hebben. Een afwijking van de blaasuitgang kan zich presenteren als een intermitterend verlaagde uitgangsweerstand.

Het onvermogen om de blaas te legen tijdens de mictiefase kan eveneens komen door disfunctie van de blaas, de blaasuitgang of beide. De blaas kan bijvoorbeeld niet of onvoldoende contraheren; de blaasuitgang kan een anatomische obstructie hebben of vertoont detrusor-sfincter dyssynergie (DSD). Bij DSD is de coördinatie tussen detrusor en sfincter verloren en dit kan resulteren in een onwillekeurig, onvolledig en regelmatig onderbroken mictie of zelfs in urine retentie. Aandoeningen, waarbij zowel de opslag als het legen van de blaas is aangedaan, kunnen ook eenvoudig met de voorgestelde classificatie worden ingedeeld.

De functionele classificatie kan worden uitgebreid naar bijvoorbeeld een (video) urodynamische classificatie onderverdeeld in blaas of blaasuitgangsactiviteit tijdens de vullings- of de mictiefase. Eveneens kunnen behandelingen op deze manier worden ingedeeld. Een bepaalde therapie kan de vullings- of de mictiefase bevorderen. Het is een eenvoudige en informatieve indeling die naar eigen inzicht kan worden uitgebreid.

Gecombineerde problemen kunnen ook goed met de functionele classificatie worden ingedeeld. Voorbeelden van gecombineerde problemen zijn:

- verminderde blaascontractiliteit of blaasoveractiviteit gecombineerd met sfincter disfunctie
- blaasuitgangsobstructie gecombineerd met blaasoveractiviteit
- blaasuitgangsobstructie met een niet werkende sfincter
- blaasoveractiviteit met een verminderde blaascontractiliteit

DIAGNOSTIEK

Het tijdig stellen van een diagnose en classificeren van de blaasfunctie is van belang bij zowel het congenitale als het verworven neurogeen blaaslijden. Er kunnen namelijk onherstelbare veranderingen in de lage urinewegen optreden en het is belangrijk om de patiënt goed te evalueren en zo nodig te behandelen.[14] Schade kan al zijn opgetreden als neurologisch gerelateerde symptomen slechts in geringe mate aanwezig zijn (LE: 3).[9,15] Tevens kan neurogeen blaaslijden het eerste symptoom zijn van een onderliggende neurologische aandoening (LE: 3).[16,17]

Diagnostiek naar neurogeen blaaslijden moet bestaan uit zowel neurologische als niet-neurologische onderzoeken (GR: C). Verder moet er navraag gedaan worden naar de voorgeschiedenis van de patiënt en lichamelijk onderzoek en urineonderzoek worden verricht (GR: C).

Anamnese

Een uitgebreide algemene en speciële anamnese is essentieel voor een goede evaluatie (Tabel 8.4). Navraag moet worden gedaan naar zowel huidige als vroegere symptomen en ziekten (LE: 4).[18] Speciaal moet worden gevraagd naar het functioneren van het urogenitaal stelsel, defecatiepatroon, seksuele en neurologische functies. Aandacht moet worden gegeven aan mogelijke alarmsymptomen (zoals pijnklachten, infecties, hematurie, koorts, toename van spasme en tekenen van autonome disregulatie) die verder onderzoek vereisen. In de anamnese wordt gevraagd naar (GR: C):

- verworven of aangeboren neurologische afwijkingen
- neurologische symptomen (somatisch en sensorisch), inclusief luxerend moment, verloop en eventuele behandeling
- spasticiteit (alle suprasacrale laesies)
- autonome dysreflexie (laesie boven T6)
- mentale gesteldheid en begripsvermogen
- eerdere operaties
- medicatie
- mobiliteit, handfunctie
- socio-economische situatie

Een 24-uurs dagboek is een betrouwbaar en consistent diagnosticum bij vrouwen met urine incontinentie (LE: 3),[20,21] dit is echter niet onderzocht bij patiënten met een neurogene blaas. Desondanks wordt geadviseerd een mictiedagboek 2 tot 3 dagen bij te houden (GR: C). Indien een mictiedagboek nauwkeurig wordt bijgehouden, kan deze waardevolle informatie geven over de klachten die dagelijks worden ondervonden. Het mictiedagboek is ook nuttig voor patiënten die intermitterend katheteriseren (LE: 4).[19]

Tabel 8.4 Anamnese bij neurogeen blaaslijden*

Voorgeschiedenis

- Kinderleeftijd – adolescentie – volwassen
- Erfelijke of familiaire risicofactoren
- Menarche (leeftijd)*; kan passen bij metabole afwijking*
- Obstetrische voorgeschiedenis
- Geschiedenis van diabetes; *soms kan correctie het neurologische probleem oplossen*
- Specifieke ziekten, *bijv. syfilis, Parkinson, multiple sclerose, encephalitis*
- Traumata en operaties, *vooral aan de wervelkolom en het centrale zenuwstelsel*

Heden

- Medicatie
- Leefstijl (roken, alcohol en drugs); *mogelijke invloed op urineren en defecatie*
- Kwaliteit van leven
- Levensverwachting

Specifieke urologische voorgeschiedenis

- Begin van urologische klachten
- Verlichting na de mictie/gevoel van residu; *mate van neurologische laesie bij het ontbreken van obstructieve uropathie*
- Blaassensatie
- Start van de mictie *(normaal, reflex, persen, Credé, katheteriseren)*
- Onderbreking van de mictie *(normaal, paradoxaal, passief)*
- Enuresis
- Manier van mictie (zittend, staand, katheterisatie)
- Urineweginfecties
- Mictiedagboek; (semi)objectieve informatie over het aantal keren mictie, dag en nacht frequentie, geplaste volumina, incontinentie, urge episoden

Defecatie-anamnese

- Frequentie en fecale incontinentie/soiling
- Aandrang tot defecatie
- Defecatie patroon
- Rectale sensatie
- Start van defecatie *(manuele rectale stimulatie of (micro)klysma)*

Seksuele anamnese

- Genitale seksuele disfunctie symptomen
- Sensatie in genitaal gebied
- Specifiek man: erectie, (ontbreken van) orgasme, ejaculatie
- Specifiek vrouw: dyspareunie, (ontbreken van) orgasme, lubricatie

Neurologische anamnese

- Verkregen of congenitale neurologische aandoening
- Mentale status en begrip (ook via hetero-anamnese)
  Neurologische symptomen (somatisch en sensorisch), met begin, beloop en eventueel behandeling
- Spasticiteit (alle suprasacrale laesies)
- Autonome dysreflexie (laesie boven niveau Th6)
- Mobiliteit en handfunctie

** Bors en Turner[18] (LE: 4; GR: C) en Stöhrer et al.[19] (LE: 4; GR: C).*

De darmfunctie is vaak bij neurogene patiënten gestoord. Dit resulteert meestal in constipatie en in mindere mate in fecale incontinentie. Verder geeft persen bij geconstipeerde patiënten overmatige belasting op de bekkenbodem, wat een verhoogde kans geeft op verzakkingsklachten en urine incontinentie.[22] Darmontlediging moet daarom worden bevorderd, bijvoorbeeld door middel van laxantia, klysmata of darmspoelingen.[22] Een landelijke richtlijn over obstipatie is beschikbaar en onderdeel van de richtlijnen palliatieve zorg van het Integraal Kankercentrum Midden-Nederland.[23]

Lichamelijk onderzoek

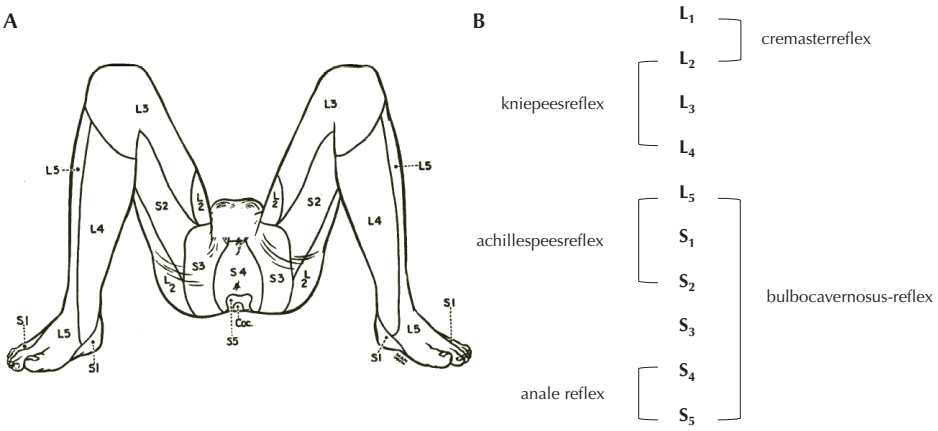
Om het (lichamelijk) onderzoek zo goed mogelijk te laten verlopen, is het belangrijk om aandacht te besteden aan mogelijke lichamelijke en geestelijke beperkingen. Dit kan worden gedaan door de neurologische status zo uitvoerig mogelijk in kaart te brengen (Tabel 8.5) (GR: C). De sensibiliteit en reflexen van het hele urogenitale gebied worden uitgebreid onderzocht evenals de anale sfincter en bij vrouwen de bekkenbodemspieren (Figuur 8.1).[24,25] Bij patiënten met een dwarslaesie is voor het vaststellen van de sensibiliteit in de betreffende dermatomen zoals weergegeven in figuur 8.1 de ASIA classificatie[26] te prefereren. Hierbij wordt in elk relevant dermatoom op een vast punt de tastzin en de pijnzin volgens vaste criteria gescoord. Bij een veranderd neurologisch beeld is het vervolgonderzoek dan betrouwbaarder.

Uitgebreid lichamelijk onderzoek is van belang voor een betrouwbare interpretatie van de komende diagnostische onderzoeken. Voor het behandelplan is het belangrijk de mobiliteit en handfunctie van de patiënt goed te documenteren (GR: C). Verder moet gezocht worden naar aanwijzingen van aangeboren afwijkingen zoals voetafwijkingen, spina bifida occulta en scoliose (GR: C).

Tabel 8.5 Specifieke uro-neurologische onderzoeken*

- Sensaties S2-S5 (beide kanten)
  - conform de ASIA richtlijnen [26]
- Reflexen (verhoogd/normaal/verminderd/afwezig)
  - Bulbocavernosus reflex
  - Perianale reflex
  - Knie en enkel reflexen
  - Plantair respons (Babinski)
- Anale sfincter tonus
  - Aanwezigheid (verhoogd/normaal/verminderd/afwezig)
  - Vrijwillige contracties van anale sfincter en heupmusculatuur (verhoogd/normaal/verminderd/afwezig)
- Specifiek mannen: prostaat palpatie
- Specifiek vrouwen: descensus (prolaps) van bekkenorganen

**Naar* Stöhrer et al.[19] *(LE: 4; GR: C).*



Figuur 8.1 (a) dermatomen van de spinale zenuwen L2-S4; (b) urogenitale en andere reflexen van de caudale spinale zenuwen. Uit: Stöhrer et al.[7]

Autonome dysreflexie (AD) betreft een plotseling versterkte autonome reactie op potentieel pijnlijke stimuli onder het laesie niveau bij patiënten met een dwarslaesie of disfunctie van het myelum boven het niveau Th-6. Hypertensie komt hierbij vaak voor en kan levensbedreigend zijn indien onvoldoende behandeld [27-29] (LE: 3).

Aanvullend onderzoek

Aanvullend onderzoek moet worden uitgevoerd. Essentiële onderzoeken zijn:[19]

- Urinesediment
- Bloedonderzoek (o.a. kreatinine)
- Mictiedagboek
- Meting van urine residu na mictie, indien mogelijk ook vrije uroflowmetrie (zie: 'Urodynamische testen')
- Indien van toepassing: kwantificatie van urineverlies door middel van padtest
- Beeldvorming hoge urinewegen (met name echografie)

Urodynamisch onderzoek

Het urodynamische onderzoek (UDO) is de enige methode die objectief de (dis)functie van de lage urinewegen kan weergeven. Het is essentieel om de status van de lage urinewegen te beschrijven bij patiënten met een neurogene blaas. Het onderzoek kan worden gebruikt in combinatie met aanvullende diagnostische toetsen om het type neurogeen blaaslijden te beschrijven (Tabel 8.6). Een kanttekening moet worden gemaakt bij kwetsbare ouderen met neurogeen blaaslijden (bijvoorbeeld diep dementen) en patiënten met een slechte prognose. Een UDO voor deze doelgroep kan te belastend zijn en de symptomatische behandeling kan worden gegeven zonder aanvullende diagnostiek.

Tabel 8.6 Karakteristieke bevindingen bij neurogeen blaaslijden*

Vullingscystometrie
- toegenomen, afgenomen, of afwezig aandranggevoel
- vegetatieve niet-specifieke sensaties
- lage blaascompliantie
- (kleine of grote) blaascapaciteit
- detrusor overactiviteit; spontaan of opwekbaar
- incompetent urethraal sluitingsmechanisme (incontinentie)
Druk-flowcurve**
- verminderde detrusoractiviteit (hypocontractiele blaas) of acontractiele blaas
- blaasuitgangsobstructie
- detrusor/sfincter dyssynergie

* Gemodificeerd van Abrams et al [40].
** Deze kenmerken vereisen neurologische evaluatie; deze klachten kunnen de eerste tekenen zijn van een neurologische aandoening [15].

De International Continence Society (ICS) heeft technische richtlijnen van het UDO beschreven en aanbevelingen gedaan voor het rapporteren van UDO resultaten (LE: 4).[19]

Urodynamische testen

Vrije flowmetrie en bepaling van residu na mictie geven een eerste indruk van de mictie (LE: 3).[30,31] Als de conditie van de patiënt deze niet-invasieve onderzoeken toelaat moet dit gebeuren voordat het invasieve UDO wordt verricht.[19]

Vullingscystometrie betreft het eerste deel van het UDO en kwantificeert de cystometrische capaciteit van de blaas; ook wel de blaascapaciteit. Vullingscystometrie als alleenstaand onderzoek heeft slechts een beperkte waarde (LE: 3).[30] Tijdens dit onderzoek kunnen afwijkingen worden gezien zoals detrusoroveractiviteit, lage blaascompliantie (stugge blaas, waarbij toename van de blaasvulling resulteert in abnormale stijging van de blaasdruk), DSD, een incompetente urethrale sfincter, abnormale blaassensaties en andere sensaties (zoals autonome dysreflexie) en incontinentie (LE: 3).[30,32]

De detrusor leak point pressure (DLPP) of detrusor lekdruk is de laagste waarde van de detrusordruk waarbij urineverlies optreedt tijdens vullingsfase zonder dat er abdominale druk is of een detrusor contractie. Met de DLPP kan een schatting worden gemaakt van het risico voor de hoge urinewegen.[33,34] Het is meer een screenende test vanwege de beperkte diagnostische waarde.[19,35] Er zijn aanwijzingen dat een hoge DLPP (40 cm H_2O of hoger) verder onderzoek vereist middels video urodynamisch onderzoek (VUDO) vanwege het risico op beschadiging van de hoge urinewegen (LE: 3).[33]

De Valsalva leak point pressure (VLPP) of valsalva lekdruk is de laagste detrusordruk waarbij urineverlies optreedt zonder dat er een detrusorcontractie optreedt. De druk

die wordt opzettelijk veroorzaakt door te hoesten of de Valsalva manoeuvre. Het geeft een indruk van de ernst en soort stress urine incontinentie.[19]

Druk-flowcurven betreffen het tweede deel van het UDO en geven een indruk van de functie van de blaas en onderste urinewegen. Afwijkende bevindingen die tijdens dit onderzoek kunnen worden gezien zijn: detrusor onderactiviteit of acontractiliteit, DSD, obstructie door niet-relaxerende sfincter, te groot residu na mictie.

Video urodynamisch onderzoek (VUDO) combineert vulllingscystometrie en druk-flowcurven met radiologische beeldvorming. Dezelfde afwijkingen kunnen worden gezien zoals eerder beschreven bij de vullingscystometie en druk-flowcurven, maar daarnaast geeft het extra informatie over de morfologie van de blaas en onderste urinewegen. In het bijzonder vesico-ureterale reflux (VUR) kan goed worden aangetoond. VUDO is momenteel het onderzoek dat de meest uitgebreide informatie geeft wat gebruikt kan worden voor de evaluatie van neurogeen blaaslijden (LE: 3).[19,36,37] VUDO is met name geïndiceerd bij verdenking van een hoge drukblaas, VUR, DSD, congenitale of verworven anatomische afwijkingen. In andere gevallen volstaat meestal een UDO.

Elektromyografie (EMG) is een semi kwantitatieve meting van de bekkenbodemactiviteit en kan worden gebruikt om DSD en verhoogde bekkenbodemcontracties te diagnosticeren. Gecombineerd met een VUDO kan meer accuraat DSD worden opgespoord (LE: 3).[38]

Ambulant urodynamisch onderzoek maakt het mogelijk de werking van de blaas te bestuderen tijdens normale blaasvulling. Het onderzoek vindt plaats in de eigen - en daarmee weinig stressvolle - omgeving tijdens normale dagelijkse bezigheden. Echter, onderzoek heeft aangetoond dat ambulant urodynamisch onderzoek niet noodzakelijk is bij dwarslaesie patiënten als standaard UDO adequaat wordt uitgevoerd. Ambulante urodynamica kunnen wel geïndiceerd zijn bij patiënten waarbij standaard urodynamica niet conclusief blijken te zijn.[39]

Specifieke uro-neurofysiologische onderzoeken

Specifieke uro-neurofysiologische onderzoeken worden geadviseerd als onderdeel van de neurologische evaluatie van de patiënt. Electieve onderzoeken worden op specifieke indicatie verricht (GR: C)[19]:

- Elektromyografie van de bekkenbodemspieren, urethrale sfincter en/of anale sfincter
- Zenuwgeleidingsonderzoek van de nervus pudendus
- Meten van reflextijden van de bulbocarvernosus en anale reflexbogen
- Opgewekte potentialen van clitoris of glans penis
- Sensorische testen van de blaas en urethra

BEHANDELING

De doelen van de behandeling van neurogeen blaaslijden zijn als volgt [41-44]: behoud van nierfunctie, verbetering van de urine continentie, verbetering van de blaasontlediging en optimalisatie van de kwaliteit van leven (LE: 3). Hierbij zijn van belang de beperkingen van de patiënt, kosteneffectiviteit, technische complexiteit en mogelijke complicaties [44]. Het behoud van de functie van de hoge urinewegen is van het grootste belang bij patiënten met neurogeen blaaslijden.[2,41-43,45-47] Vroeger was nierfalen een belangrijke doodsoorzaak bij chronische dwarslaesiepatiënten.[2,46,47] Dit heeft geleid tot de gouden regel in de behandeling van neurogeen blaaslijden: garandeer dat de detrusordruk binnen een veilige limiet blijft tijdens de vullings- en mictiefase (LE: 3).[41-44] Als er bij vullingscystometrie een hoge detrusordruk wordt gezien moet worden getracht deze druk te verlagen, zeker als deze aanwezig is vanaf geringe vulling en persisteert tot aan de maximale capaciteit. Persisterend hoge blaasdruk tijdens de vullingsfase is een belangrijke risicofactor voor beschadiging van de hoge urinewegen, een DLPP > 40 cmH_2O wordt gezien als directe een oorzaak voor nierschade (LE: 3).[33]

De kwaliteit van leven is een belangrijke richtlijn waarop een therapiekeuze wordt gebaseerd. Ook is het ziektebeeld en leeftijd van belang bij de keuze van therapie.

Conservatieve behandeling

Geassisteerde blaasontlediging

Stimulatie van de sacrale of lumbale dermatomen bij patiënten met een suprasacrale dwarslaesie kan een *reflex contractie* van de detrusor opwekken (LE: 3).[41,48] Dit reflexmatig opwekken van de mictie (bijvoorbeeld door suprapubisch kloppen) kan gebeuren onder strikte urodynamische controle vanwege de verhoogde morbiditeit die hiermee is geassocieerd (LE: 3; GR B).[49-52]

Blaascompressie technieken om urine uit te drijven (Credé manoeuvre) en mictie door gebruik te maken van buikpers (Valsalsva manoeuvre) zorgen voor hoge drukken en zijn mogelijk schadelijk voor de hoge urinewegen en moeten daarom worden afgeraden (LE 3; GR: B).[53,54] Verder kan een al verzwakte bekkenbodemfunctie door de passieve druk achteruitgaan en eventueel bestaande incontinentie verergeren.[48]

Gedragsmodificatie kan de continentie bevorderen door bijvoorbeeld direct te urineren bij aandrang, op de klok urineren (blaastraining) en leefstijlmodificatie (LE: 2B; GR: B).[55-58]

Bekkenbodemfysiotherapie (BBFT) met eventueel biofeedback kan helpen bij geselecteerde patiënten met neurogene blaas.[59-63] In een geblindeerde gerandomiseerde studie met vrouwelijke MS patiënten bleek dat na BBFT met biofeedback de incontinentie en nycturie significant afnamen, ten opzichte van de groep die een

pseudo-behandeling met biofeedback onderging (LE 1b).[64] Derhalve kan BBFT met biofeedback bij MS patiënten worden geïndiceerd.

Urotherapie van de lage urinewegen, inclusief elektrostimulatie

Urotherapie

Urotherapie is een niet-farmacologische, niet-chirurgische behandeling gericht om de verstoorde blaasfunctie zo goed mogelijk te reguleren om zoveel mogelijk medische complicaties te beperken die negatieve effecten op de kwaliteit van leven kunnen hebben. Het terugkeren van de vrijwillige controle over de lage urinewegen en het verdwijnen van de disfunctie is beschreven bij patiënten met niet-neurogene blaasdisfunctie. Dit gebeurt door gedragstherapie bij patiënten met urge incontinentie en biofeedback training bij stress incontinentie. Een recente gerandomiseerde gecontroleerde studie liet zien dat een uitgebreid urotherapie-programma van 12 maanden bij MS patiënten, de mictieklachten significant deed afnemen. Tevens was er een toename van de kwaliteit van leven, gemeten door niet gevalideerde vragenlijsten.[65]

Elektrostimulatie

Elektrische stimulatie van specifieke zenuwen of zenuwgebieden kan leiden tot een direct gewenst effect op blaasklachten. Verschillende vormen van elektrische stimulatie zullen worden besproken.

<u>*Chronische pudendus of sacrale elektrische stimulatie*</u>

Bij chronische elektrische stimulatie wordt gebruikt gemaakt van een implanteerbaar apparaat die elektrische pulsen stuurt naar zenuwen die de blaasfuncties regelen. Een proefstimulatie met apparaat buiten het lichaam *perifere zenuw evaluatie* (PNE) (1e fase) gaat voorafgaand aan de definitieve implantatie (2e fase).

Chronische stimulatie van de *nervus pudendus* bij patiënten met een neurogene blaas gaf in een pilot studie significante subjectieve en urodynamische verbeteringen (LE: 3)[66].

Bij s*acrale neuromodulatie* (SNS) worden de sacrale zenuwen elektrisch gestimuleerd. Bij dwarslaesie patiënten is SNS effectief gebleken (>50% verbeterd) bij een follow-up duur van 2,5 jaar (LE 3).[67] De effectiviteit van SNS is afhankelijk van de onderliggende neurologische aandoening; met name of het een progressieve aandoening betreft of niet. MS patiënten hebben minder baat bij een SNS behandeling (LE: 3).[68]

<u>*Niet-chronische elektrische stimulatie*</u>

Bij niet-chronische elektrische stimulatie wordt gebruikt gemaakt van een tijdelijk apparaat buiten het lichaam wat elektrische pulsen stuurt naar zenuwen die de blaasfuncties regelen.

Er werden therapeutische effecten gezien na stimulatie van de *nervus tibialis posterior* (PTNS) bij multiple sclerose (MS) patiënten.[69] Echter, acute effecten tijdens urodynamisch onderzoek werden wisselend aangetoond in deze patiëntengroep (LE: 2b).[70,71]

Continue elektrische stimulatie van *nervus dorsalis penis/clitoris* (DPN) onderdrukt detrusor contracties en vergroot de blaascapaciteit bij patiënten met een dwarslaesie en MS (LE: 2b).[72,73] De DPN kan ook conditioneel worden gestimuleerd. Zodra er een onwillekeurige detrusor contractie optreedt (gemeten door een toename van intravesicale druk) wordt er elektrisch gestimuleerd zolang als deze detrusor contractie duurt. Conditionele elektrische stimulatie van de DPN onderdrukt effectief detrusor contracties en vergroot eveneens de blaascapaciteit van patiënten met een dwarslaesie en MS (LE: 2b).[73-76]

Transcutane elektrische stimulatie (TENS) van de sacrale dermatomen had geen tot minimaal effect op de urodynamische uitslagen, maar het leidde wel tot significant gunstige klinische effecten bij patiënten met neurogene detrusor overactiviteit (LE: 2b).[74,77]

Neuromusculaire stimulatie met bekkenfysiotherapie kan bij MS patiënten ook een substantiële vermindering van blaasfunctiestoornissen geven (LE: 2b).[78]

Repetitieve transcraniale magnetische stimulatie

Transcraniale magnetische stimulatie verbeterde mictiesymptomen bij patiënten met Parkinson en MS, hoewel het niet duidelijk is hoe lang en met welke parameters gestimuleerd moet worden (LE: 3).[79,80]

Externe hulpmiddelen

Opvangmateriaal kan het middel zijn om sociale continentie te verkrijgen.[41,48] Condoomkatheters met opvangzak zijn een praktische methode bij de man. Ook kunnen incontinentieverbanden een oplossing bieden. In beide gevallen is het van belang goed toezicht te houden met het oog op het verhoogde risico op infectie[48] en decubitus.[81]

Een penisklem kan hoge druk in de blaas en op het urethrale weefsel veroorzaken en is daarom gecontraïndiceerd.[82]

Medicamenteuze behandeling

Er bestaat nog geen optimaal medicament tegen neurogene detrusor overactiviteit (NDO). Anticholinergica worden het meest voorgeschreven hoewel niet alle geregistreerd zijn voor neurogene blaas (Tabel 8.7). Patiënten met neurogeen blaaslijden hebben meestal een hogere dosis anticholinergica nodig dan patiënten met idiopathische detrusoroveractiviteit (LE: 1b; GR: A).[83-88] Hogere doseringen zijn echter wel geassocieerd met meer bijwerkingen.[89] Voorzichtigheid en oplettendheid is geboden

gezien de meerdere bijwerkingen en potentiële interacties. Vooral ouderen met co-morbiditeit zijn zeer kwetsbaar voor de bijwerkingen van polyfarmacie. Anticholinergica moeten zeer terughoudend in combinatie met elkaar worden gebruikt om stapeling van anticholinergische bijwerkingen te voorkomen.[90] Anticholinergica kunnen ook intravesicaal worden toegediend Dit kan een alternatief zijn bijvoorbeeld bij kinderen met neurogene blaas, die onvoldoende reageren op orale anticholinergica of bijwerkingen hebben.[91,92] De bijwerkingen zijn minder bij intravesicale toediening maar kunnen nog steeds optreden.[92] Een systematische review toonde aan dat na intravesicale toediening de maximale blaascapaciteit toenam en de blaasdruk afnam. Er is echter onvoldoende wetenschappelijk bewijs om deze therapie te adviseren.[92]

Tabel 8.7 Anticholinergica voor de behandeling van neurogene detrusor overactiviteit

Geneesmiddel	Referenties	Opmerking	LE	GR
Oxybutynine	Block et al.[103], Granata et al.[104]	-	1b	A
Trospium chloride	Dykstra en Sidi.[105], Wilson et al.[106]	-	1b	A
Tolterodine	Dykstra en Sidi[105], Ströher en Pannek[107]	-	1b	A
Propiverine	Granata et al[104], Ströher et al[108]	-	1b	A
Darifenacine	-	Nog geen data	-	-
Solifenacine	Van Rey et al[102]	-	3	C
Fesoterodine	-	Nog geen data	-	-

LE = level of evidence; GR = grade of recommendation.

Uit: Stöhrer et al. [7]

Keuze van anticholinergicum

Oxybutynine chloride (LE: 1a)[84,85,88,89,93-96] en tolterodine tartraat (LE: 1a)[97-99] zijn geaccepteerde en effectieve medicamenteuze behandelingen. Deze anticholinergica worden goed verdragen en zijn veilig, ook op lange termijn. Gezien het verschillende tolerantieprofiel kan een ander anticholinergicum worden voorgeschreven in het geval van bijwerkingen.[87] Darifenacine,[100,101] fesoterodine en solifenacine[102] worden goed getolereerd en zijn effectief bij patiënten met overactieve blaas, maar er zijn slechts enkele onderzoeken uitgevoerd bij patiënten met neurogene blaasklachten.

Medicamenteuze behandeling van neurogene detrusor onderactiviteit

Er zijn geen medicamenten die bewezen effectief zijn in de behandeling van detrusor onderactiviteit (LE: 2a; GR: B).[45] Het wordt niet aangeraden cholinerge medicatie, zoals bethanechol chloride en distigmine bromide, voor te schrijven voor dit doel (LE: 1a).[109]

Medicamenteuze behandeling ter verlaging van de blaasuitgangsweerstand

Selectieve en niet-selectieve α-blokkers, zoals alfusozine en tamsulosine, hebben bewezen gedeeltelijk de blaasuitgangsweerstand te verlagen en residu na mictie te verkleinen (LE: 2a; GR: B).[45,110-114] In geselecteerde patiënten kan dit worden voorgeschreven.

Minimaal invasieve behandelingen

Katheterisatie

Intermitterend katheteriseren (IC) (zowel zelf-katheterisatie als gekatheteriseerd worden door een ander)[1,115] is de gouden standaard voor de behandeling van onderactief en overactief neurogeen blaaslijden onder de voorwaarden dat overactiviteit kan worden gecontroleerd en de patiënt cognitief en lichamelijk in staat te katheteriseren.[41,45]

Steriele IC vermindert significant het risico op een urineweginfectie (UWI) en/of bacteriurie[45,115,116] vergeleken met IC met behulp van een schone, niet-steriele katheter. In de dagelijkse praktijk is routinematig steriel IC echter niet haalbaar en aseptische IC of IC met behulp van een schone katheter is dan een goed alternatief.[117,118] Aseptische IC geeft in vergelijking met 'schone IC' een significant kleiner risico op contaminatie.[117]

Inadequate instructies en onvolledige blaaslediging bij patiënten met neurogeen blaaslijden spelen een rol bij het risico op infectie.[45,118] Gemiddeld wordt 4 tot 6 keer per dag gekatheteriseerd met een 12 of 14 Charrière katheter. Minder vaak katheteriseren verhoogt de kans op UWI's omdat de urine langer in de blaas aanwezig is.[118] Vaker katheteriseren zorgt echter weer voor een toename van infecties.[118] Het gekatheteriseerde blaasvolume moet lager zijn dan 400 ml.

Transurethrale verblijfkatheters en – in mindere mate – suprapubische katheters moeten zoveel mogelijk worden vermeden omdat zij een risicofactor vormen op UWI's en lange termijn complicaties.[45,119-121] Indien verblijfkatheters toch moeten worden gebruikt dan wordt de voorkeur gegeven aan siliconen boven latex katheters.[122] In de praktijk verwisselt men één keer per 6 à 12 weken een siliconen katheter.[123]

Botulinetoxine A injecties in de blaas

Botulinetoxine A zorgt voor een langdurige (ongeveer 9 maanden), reversibele, chemische denervatie.[124,125] Botulinetoxine A heeft bij een aantal kleine, gerandomiseerde, placebo-gecontroleerde onderzoeken bewezen effectief te zijn in de behandeling van neurogeen blaaslijden (LE: 1a).[126,127] De injecties kunnen herhaaldelijk worden gegeven zonder dat het de effectiviteit doet afnemen.[124,128,129] Sporadisch wordt er als bijwerking gegeneraliseerde spierzwakte gezien.[124,128,130] Histologische onderzoeken hebben geen elektronen microscopische veranderingen in de blaaswand kunnen aantonen na injectie.[131] In heel Europa, behalve in Zwitserland, is Botulinetoxine A slechts "*off-label*" verkrijgbaar. Onlangs werd aangetoond in een gerandomiseerd,

gecontroleerd onderzoek (RCT) dat voor onabotuline toxine A (Botox®) injecties in de neurogene blaas 200 E en 300 E even effectief zijn en goed werd getolereerd. Echter 200 E onabotuline toxine A had minder bijwerkingen dan 300 E (LE: 1b). Voor abobotulinum toxine A (Dysport®) geldt dat 500 E en 750 E even effectief met een vergelijkbaar bijwerkingsprofiel (LE: 1b).[132] Op grond van deze RCT is registratie voor onabotuline toxine A aangevraagd en verwacht wordt dat deze in 2012 wordt toegekend. Aangezien Botulinetoxine A meerdere toepassingen heeft en ook voor andere indicaties wordt gebruikt, moet er altijd worden geïnformeerd of de patiënt hier recent mee is behandeld. Hoewel er geen consensus beschikbaar is over de tussentijd tussen twee verschillende behandelingen, wordt in praktijk minimaal 4 tot 6 weken gewacht tot de tweede injectie.

Intravesicale vanilloïden

De vanilloïden capsaicine en resiniferatoxine worden in de blaas als spoeling gegeven en desensitiseren de C-vezels met als effect een tijdelijke afname van detrusor overactiviteit (LE: 1a).[133-137] Resiniferatoine en capsaïcine hebben echter slechts een beperkte effectiviteit vergeleken met botulinetoxine A injecties in de musculus detrusor.[138,139] Deze middelen worden in Nederland nauwelijks gebruikt.

Blaashals en urethrale behandelingen

De blaasuitgangsweerstand kan worden verlaagd ter bescherming van de bovenste urinewegen. Dit kan worden bewerkstelligd door sfincterotomie[140,141] of door middel van chemische denervatie van de sfincter met behulp van botulinetoxine A.[105,142,143]

Na sfincterotomie namen hydronefrose (70-90%), aantal recidiverende urineweginfecties (75%) en autonome dysreflexie (>90%) af.[140] Tevens verbeterden de urodynamische parameters.[140] Het is echter een onomkeerbare procedure waarbij de normale sfincter permanent wordt beschadigd en complicaties zoals bloedingen kunnen optreden.[140,144] Het succespercentage van chemische denervatie van de sfincter met botuline toxine A varieert van 59-100%.[144]

Sfincterotomie en chemische denervatie van de sfincter zal tot incontinentie leiden maar kan worden gehanteerd door gebruik te maken van externe hulpmiddelen. In uitzonderlijke gevallen kan een semi-rigide penisprothese worden geplaatst indien de condoomkatheter niet op de penis kan blijven zitten.

Plaatsing van urethrale stents wordt afgeraden omdat deze procedure geassocieerd is met substantiële complicaties en risico's op herhaaldelijke interventies.[106,145] De blaasuitgangsweerstand verhogen door middel van bulkinjecties, urethrale stents of alternatieve hulpmiddelen wordt niet aangeraden voor langdurige behandeling (LE: 2a; GR: B).[103,146]

Neurogene detrusor overactiviteit en vesicoureterale reflux

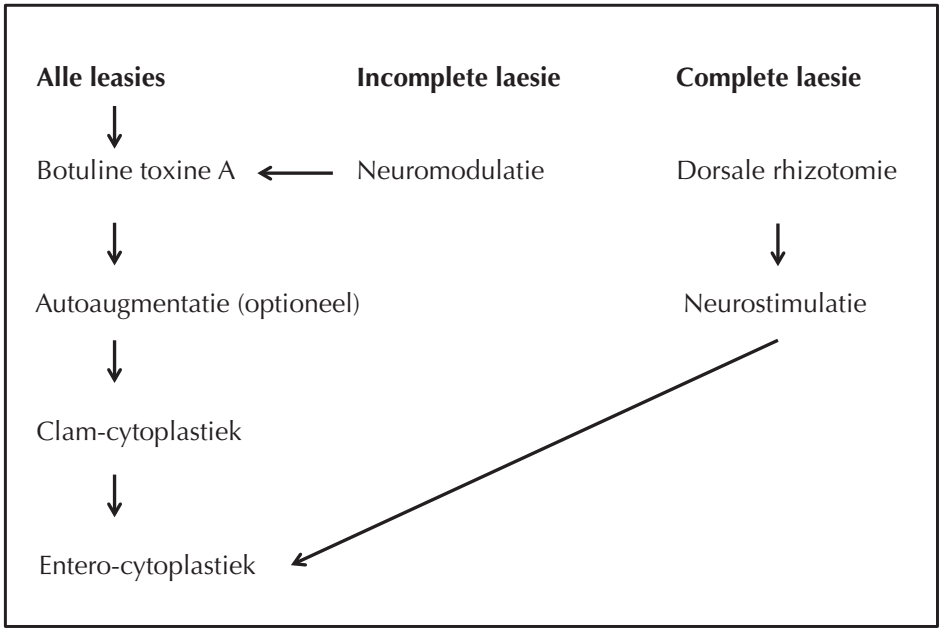
Vesicoureterale reflux (VUR) moet worden behandeld door de intravesicale drukken te verlagen. Indien de reflux aanhoudt ondanks urodynamisch bewezen lage druk in de vulfase, kunnen bulkinjecties of een ureterreïmplantatie worden overwogen.[104,147]

Chirurgische behandelingen

Overactieve detrusor

Blaasaugmentatie (bijv. ileocystoplastiek) is geïndiceerd bij een overactieve detrusor wanneer andere behandelingen geen effect hebben gehad.[107,148] (Figuur 8.2)

Alternatieve opties zijn autoaugmentatie (myomectomie)[108], dorsale rhizotomie met of zonder *"sacral anterior root stimulator"* (SARS) (bij complete laesies)[149,150] en neuromodulatie (bij incomplete laesies).[151] Deze behandelingen blijken significant de kwaliteit van leven te verbeteren.[149,152] Detrusor myectomie kan echter wel tot een verminderde contractiliteit leiden, en bijna de helft van de patiënten moet om deze reden zelf-katheteriseren.[153]



Figuur 8.2 Chirurgische behandeling van neurogene detrusor overactiviteit.
Uit: Stöhrer et al.[7]

Onderactieve detrusor

Sacrale neuromodulatie (bij incomplete laesies)[151] kan bij geselecteerde patiënten een effectieve behandeling zijn (LE: 2; GR: B).

Urethrale sfincter insufficiëntie

De artificiële urinaire sfincter (AUS) verdient de voorkeur bij patiënten met neurogeen blaaslijden (LE: 2; GR: B).[154] Echter, na implantatie van een AUS, is bijna de helft afhankelijk van zelf-katheterisatie om de blaas volledig te legen.[155-157] De ideale kandidaat voor een AUS is een patiënt die voor implantatie een goede blaasontlediging heeft.[155]

Een alternatieve en minimaal invasieve behandeling is de plaatsing van een midurethrale sling bij de vrouw of para-urethrale ballon bij de blaashals bij de man (LE: 3, GR: B).[158-160] Diverse soorten materialen zijn ontwikkeld voor een midurethrale sling.[161] Afhankelijk van de wens van de patiënt, ervaring van de operateur, de handfunctie, de mate van incontinentie en de blaasfunctie wordt de keuze gemaakt tussen een AUS of een andere methode.

Een voorwaarde van de behandeling van sfincter insufficiëntie is aanwezigheid van detrusor activiteit, of controle over de detrusor zonder significante vesicoureterale reflux. Het gelijktijdig uitvoeren van blaasaugmentatie en autologe fasciesling of implantatie van een artificiële urinaire sfincter is een optie bij patiënten met neurologische afwijkingen.[162]

Urinedeviaties

Plaatsing van een continent[163] of incontinente deviatie[164-166] kan worden overwogen bij neurogeen blaaslijden. Het aanleggen van een stoma wordt meestal gezien als laatste optie bij therapieresistente patiënten. De nierfunctie wordt op deze manier beschermd en de incontinentie wordt verholpen. Een incontinent stoma (Bricker) is geïndiceerd bij patiënten die niet in staat zijn te katheteriseren. Een katheteriseerbaar stoma (appendicovesicostoma volgens Mitrofanoff of getapert ileum volgens Monti) kan een goed alternatief zijn bij mensen die in staat zijn te katheteriseren. Specifiek kan deze optie geïndiceerd zijn bij rolstoelgebonden vrouwelijke patiënten en bij mannen met een urethrale strictuur.

URINEWEG INFECTIES BIJ NEUROGEEN BLAASLIJDEN

De meeste kennis betreffende urineweginfecties (UWI) bij neurogene blaas is verkregen uit studies bij patiënten met een dwarslaesie en niet direct toepasbaar op andere populaties, zoals MS, CVA of morbus Parkinson. Bacteriurie zonder symptomatologie moet niet worden behandeld, ook niet bij intermitterende katheterisatie.[167]

Recidiverende urineweginfecties

Recidiverende UWI's kunnen een teken zijn van een slechte techniek van zelfkatheterisatie of een suboptimale behandeling van een onderliggend probleem, bijvoorbeeld

een hoge drukblaas, residu na mictie of urinewegstenen. Het bevestigen of uitsluiten van deze oorzaken is noodzakelijk.[167]

Preventie

De beste preventie van UWI bij patiënten met neurogene blaas bestaat uit een evenwichtige behandeling van de disfunctie van de lage urinewegen. Hierbij is het belangrijk te streven naar een lage drukblaas tijdens de vulling en mictie en residuloze lediging van de blaas. Aseptische CIC wordt gebruikt met steriele gelubriceerde of hydrofiele katheters.[168-170]

Mictie op de klok en een minimale dagelijkse vloeistofinname van 30 ml/kg lichaamsgewicht worden gezien als ondersteunende factoren in de preventie van UWI.

Er is op diverse manieren geprobeerd om de UWI's in de neurogene blaas te minimaliseren. Gerandomiseerd gecontroleerde studies geven wisselende resultaten over de meerwaarde cranberry extracten.[171-173] Methenamine hippuraat[174] en blaasspoelen zijn ineffectief gebleken.[175] Het aminozuur L-methionine is mogelijk een belangrijk component in de profylaxe van recidiverende urineweginfecties. Het gunstige effect van L-methionine is te wijten aan een uitscheiding van zure valenties in de urine en het verlaagt de bacteriële cyto-adherentie.[176,177] L-methionine kan worden toegepast bij neurogene blaaspatiënten als andere maatregelen en onderhoudsantibiotica niet werken.[177] Er is weinig wetenschappelijk bewijs voor de preventieve werkzaamheid.

De aanbevelingen over het gebruik van antibiotische profylaxe door de Nederlandse Vereniging voor Urologie zijn beschreven in de richtlijn *Bacteriële urineweginfecties bij adolescenten en volwassenen*.[167] Een asymptomatische bacterurie moet niet worden behandeld. Er wordt geadviseerd bij drie of meer ongecompliceerde UWI's binnen één jaar antibiotische profylaxe voor te schrijven om recidieven te beperken. Deze richtlijn is ook van toepassing op patiënten met neurogeen blaaslijden (LE 1b)[178], echter routinematig gebruik van profylaxe heeft een nadelige invloed op de resistentie ontwikkeling.[179] Gericht gebruik wordt daarom geadviseerd.

Er is geen indicatie om routinematig antibiotische profylaxe te geven bij katheterisatie (ongeacht de duur) en bij het verwijderen van de katheter.

SEKSUELE FUNCTIE EN VRUCHTBAARHEID BIJ DWARSLAESIE

Neurologische ziektes en letsels hebben een evidente invloed op de seksuele gezondheid, echter richtlijnen voor de behandeling hiervan ontbreken nog.[180] Periodieke controles met gevalideerde vragenlijsten kunnen helpen om het probleem inzichtelijk te maken en dragen hiermee bij aan de seksuele revalidatie (LE:3).[181]

Erectiele disfunctie (ED)

Medicamenteuze behandeling - Phosphodiesterase type 5 inhibitors (PDE5Is)

Phosphodiesterase type 5 inhitors (PDE5Is) worden aanbevolen als eerstelijns behandeling bij mannen met een dwarslaesie en erectiele disfunctie (ED). De medicatie is veilig en effectief voor gebruik op de lange termijn (LE:1b).[182-184] De meest voorkomende bijwerkingen zijn hoofdpijn en blozen. Mannen met een tetraplegie kunnen orthostatische hypotensie krijgen gedurende enkele uren na het gebruik van een PDE5I.

Ook bij patiënten met MS en de ziekte van Parkinson zijn tadalafil, vardenafil en sildenafil citraat effectieve en veilige lange termijnbehandelingen (LE: 1b).[185-187]

De grote meerderheid van de patiënten met neurogene erectiele disfunctie vereist een lange termijn behandeling voor ED. Echter, sommige patiënten nemen hun medicatie niet trouw in of stoppen de medicatie vanwege bijwerkingen.[182] Daarnaast kunnen sommige patiënten met ernstig neurologisch letsel resistent zijn voor PDE5Is.[187]

Mechanische hulpmiddelen

Mechanische hulpmiddelen (vacuümpompen en penisringen) kunnen effectief zijn[188,189] maar zijn vaak niet praktisch in het gebruik.

Intracaverneuze injecties

Patiënten die niet reageren op orale medicatie kunnen intracaverneuze injecties (ICI) met fentolamine/papaverine toegediend krijgen. Deze zijn zeer effectief bij de behandeling van ED bij mannen met een dwarslaesie, maar het gebruik vereist een nauwkeurige dosering met lage startdosis en enige voorzorgsmaatregelen. De bekendste complicaties bij intracaverneuze medicatie zijn priapisme en fibrose van de corpora cavernosa.

Een intracaverneuze injectie met vasoactieve medicatie is de eerste therapeutische optie bij patiënten die medicatie met nitraat gebruiken, bij medicatie met mogelijke interactie met PDE5Is, of bij patiënten voor wie PDE5Is ineffectief zijn.

Topische applicatie van middelen voor gladde spier relaxatie van de penis (prostaglandine) of intra-urethrale plaatsing van prostaglandine E1 (MUSE) blijken minder effectief te zijn bij dwarslaesie patiënten die lijden aan ED.[190]

Peniele prothesen

Een peniele prothese kan effectief zijn bij de behandeling van ED bij mannen met een dwarslaesie en wordt aangeboden als alle conservatieve behandelingen hebben gefaald. Ernstige complicaties, waaronder infectie en prothese perforatie, komen voor bij ongeveer 10% van de patiënten, afhankelijk van het type implantaat.[191-193]

Neurologische bypass

In enkele klinieken wordt de ilioinguinale zenuw verbonden met de ipsilaterale nervus dorsalis penis (TOMAX procedure). Hierdoor kan de sensibiliteit aan de geopereerde zijde in de glans penis worden hersteld bij dwarslaesie en spina bifida patiënten met een lage laesie.[194] Deze procedure is nog niet veelvuldig uitgevoerd, maar de resultaten zijn veelbelovend. Vijftien maanden na de ingreep waren alle mannen seksueel actief.

Mannelijke vruchtbaarheid

Verminderde vruchtbaarheid bij mannen met een dwarslaesie is een veel voorkomend verschijnsel en komt door een combinatie van ED, anejaculatie en abnormaal semen. De precieze oorzaak van deze afgenomen vruchtbaarheid is niet bekend (LE: 3).[195] Vaak zijn geassisteerde reproductieve technieken (ART) noodzakelijk om tot een succesvolle bevruchting te komen.[196]

De kans op zwangerschap is lager dan in de algemene populatie. Sinds de introductie van medisch geassisteerde voortplantingstechnieken (met name intracytoplasmische sperma injectie (ICSI)) hebben mannen met een dwarslaesie een goede kans om biologische vaders te worden.[196-198] Afhankelijk van de kwaliteit van het sperma kan er middels een beslisboom een behandelplan worden gemaakt.[196]

Er zijn diverse methodes beschreven om retrograad sperma goed op te vangen. Bij retrograde ejaculatie kan een ballonkatheter worden gebruikt om de blaashals af te sluiten en antegrade ejaculatie te verkrijgen.[199] Er is meer vergelijkend onderzoek nodig om het effect van intracaverneuze injecties op de ejaculatie en het orgasme te evalueren en de effectiviteit en tolerantie bij lange termijn gebruik. Ook moet er worden onderzocht of het vroege gebruik het herstel van spontane erecties verhoogt.[182] Prostaatmassage is veilig en eenvoudig uit te voeren om sperma te verkrijgen bij mannen met laesies boven Th10.[200]

De twee meest gebruikte mechanische methoden om sperma te verkrijgen zijn vibrostimulatie en transrectale electro-ejaculatie.[201-203] Bij mannen met laesies boven Th10 wordt sperma beter verkregen middels vibrostimulatie.[204-206] Als vibrostimulatie niet succesvol is, kan dit eventueel met midodrine worden gecombineerd. Electro-ejaculatie is echter de tweede keus voor spermawinning als herhaalde pogingen met vibrostimulatie zijn mislukt.[207] Bij intacte sensibiliteit moet electro-ejaculatie onder narcose plaatsvinden in verband met pijn bij deze behandeling.

Chirurgische procedures, zoals epididymale (PESA/MESA) of testiculaire (TESE) spermawinning, kunnen gebruikt worden als vibrostimulatie en electro ejaculatie niet hebben geholpen.[208,209]

Sperma kwaliteit en motiliteit

Studies over sperma kwaliteit en motiliteit hebben het volgende aangetoond:

- Vibrostimulatie geeft ejaculaat met betere sperma-motiliteit dan verkregen door middel van electrostimulatie.[202,210]
- Antegraad sperma heeft een betere kwaliteit dan retrograad verkregen sperma.
- Electro-ejaculatie waarbij intermitterend met stroom wordt gestimuleerd produceert een grotere hoeveelheid antegraad sperma dan continue stimulatie.[211]
- Blaascontrole door intermitterende katheterisatie kan de sperma kwaliteit verbeteren, vergeleken met een verblijfskatheter, reflexmictie of blaasexpressie.[212]
- Sperma kwaliteit bij patiënten met een dwarslaesie verbetert door het opwerken in seminaal plasma.[213]

Er zijn geen relevante publicaties over vruchtbaarheid bij andere neurologische ziekten.

Vrouwelijke seksualiteit

Studies hebben aangetoond dat de meeste vrouwen (65–80%) seksueel actief blijven na een dwarslaesie, maar veel minder frequent dan voor het letsel. Daarbij geeft ongeveer 25% van de vrouwen met een dwarslaesie aan minder tevreden te zijn met hun seksuele leven.[214-216]

Verder is aangetoond dat urine incontinentie de grootste blokkade voor seksuele activiteit is. Patiënten met een hoge dwarslaesie hebben vooral problemen met de positie en spasticiteit.

Met begeleiding kunnen vrouwen met een dwarslaesie zich seksueel aanpassen waardoor zij een positiever zelfbeeld krijgen, meer gevoel van eigenwaarde en het gevoel aantrekkelijk te zijn voor zichzelf en anderen.[217-220]

Het gebruik van specifieke medicatie voor seksuele disfunctie is geïndiceerd bij onvoldoende lubricatie. Sildenafil kan gedeeltelijk de subjectieve problemen met seksuele opwinding oplossen, terwijl manuele en mechanische stimulatie van de clitoris de genitale respons kan verhogen.[221,222] Neurofysiologische studies hebben aangetoond dat vrouwen die Th11-L2 speldenprik sensaties beleven, ook psychogene genitale vasocongestie kunnen hebben. Reflex lubricatie en orgasme komen vaker voor bij vrouwen met een dwarslaesie waarbij de sacrale reflexboog intact is (S2-S5). Bij een complete laesie van de sacrale reflex, kunnen opwinding en orgasme worden opgewekt door stimulatie van andere erogene zones boven het niveau van de laesies.[223-225]

Onderzoek heeft laten zien dat vrouwen met een dwarslaesie ontevreden zijn met de kwaliteit en de kwantiteit van seksueel gerelateerde revalidatie en dat zij minder vaak seksuele informatie ontvangen dan mannen.[225-227]

Vrouwelijke vruchtbaarheid

Het reproductieve vermogen van vrouwen wordt slechts tijdelijk beïnvloed door de dwarslaesie. De menstruatie stopt gedurende kortere of langere tijd na de dwarslaesie.[228] Niet bij iedereen treedt vervolgens cyclusherstel op. Circa 70% van de seksueel actieve vrouwen gebruikt een vorm van contraceptie na het letsel. Orale anticonceptie wordt minder gebruikt na dan voor de dwarslaesie.[215] Hoewel de zwangerschap doorgaans normaal verloopt, hebben vrouwen met een dwarslaesie meer kans op complicaties tijdens de zwangerschap en bevalling vergeleken met lichamelijk gezonde vrouwen. Complicaties tijdens de bevalling zijn blaasproblemen, spasticiteit, doorligplekken door gewichtstoename en autonome dysreflexie.[229,230] Obstetrisch gezien worden er in deze groep meer keizersneden uitgevoerd en is er een verhoogde incidentie van baby's met een laag geboortegewicht.[215] Epidurale anesthesie is effectief bij de meeste patiënten met autonome dysreflexie tijdens de bevalling.[231,232]

Er is zeer weinig gepubliceerd over de ervaringen van vrouwen in de menopauze na een dwarslaesie.[233] Er zijn geen relevante publicaties over seksualiteit en vruchtbaarheid bij andere neurologische ziekten.

KWALITEIT VAN LEVEN

De kwaliteit van leven (KvL) is een zeer belangrijk aspect in de gehele behandeling van de patiënt met neurogeen blaaslijden.[7] De wijze van behandeling van neurogeen blaaslijden kan sterk de gezondheid gerelateerde KvL beïnvloeden bij patiënten met een dwarslaesie.[234] Behandelingen die de continentie verbeteren en gunstige urodynamische resultaten geven zijn gecorreleerd met een betere KvL.[235] De KvL is een weergave van het coping mechanisme van het individu met de nieuwe levenssituatie.[236] De KvL kan worden beïnvloed door verschillende factoren, inclusief steun door familie, de mogelijkheid om aan te passen, productiviteit, eigenwaarde, financiele stabiliteit, opleiding en de fysieke en sociale omgeving (LE: 3).[237] Leeftijd, geslacht, ras en de acceptatie van de aandoening door de patiënt moeten ook in beschouwing worden genomen als de KvL wordt bepaald (LE: 3).[238]

Bepaling van kwaliteit van leven

Er zijn specifieke KvL vragenlijsten voor neurogeen blaaslijden. De enige gevalideerde instrumenten zijn de algemene visuele analoge schaal (VAS) voor de symptoomlast en de Qualiveen welke een specifiek instrument is voor de KvL bij patiënten met een dwarslaesie en Multiple Sclerose. Qualiveen heeft een goed onderscheidend vermogen en is een valide evaluatie instrument[235,239-241] en een verkorte versie is momenteel beschikbaar.[242] Er is echter geen gevalideerde Nederlandstalige Qualiveen

beschikbaar. Het International Consultation on Incontinence Modular Questionnaire (ICIQ) Project ontwikkelt vragenlijsten met betrekking tot incontinentie volgens een modulair systeem.[243] Een neurologische specifieke module is nog in ontwikkeling.

Meer gebruikelijk is het bepalen van de KvL met behulp van incontinentie specifieke KvL vragenlijsten zoals de Incontinence Impact Questionnaire (IIQ)[244,245], Urogenital Distress Inventory (UDI)[244,245], Incontinence Quality of Life Instrument (I-QOL)[246] of King's Health Questionnaire (KHQ)[247]. Of met behulp van algemene gezondheidsvragenlijsten zoals de Short Form 36 Health Survey Questionnaire (SF-36)[248], Euro Quality of Life-5 Domains (EQ-5D)[249], Short Form 6D Health Survey Questionnaire (SF-6D)[250] of de the Health Utilities Index 3 (HUI)[251].

Verder kan de zogenaamde QALY (quality-adjusted life year) –metrie gebruikt worden om de status van de patiënt uit te rekenen door de levensjaren doorgebracht in een specifieke gezondheidsstatus te wegen met een factor die staat voor een waarde die de maatschappij of patiënten geven aan die gezondheidsstatus (LE: 3).[252]

Invloed van therapie op kwaliteit van leven

Geschikte therapieën dienen de symptomen, de urodynamische parameters, de functionele mogelijkheden en KvL te verbeteren, en secundaire complicaties te voorkomen.[240,253] Veranderingen in neurogene blaas klachten zijn een belangrijke factor in de KvL van de patiënt (LE:2a).[254,255]

FOLLOW-UP

Neurogeen blaaslijden is een instabiele ziekte en presenteert zich zeer variabel, zelfs binnen relatief korte tijd. Nauwkeurige follow-up en regelmatige controle worden daarom sterk aanbevolen.[107] Afhankelijk van de neurologische pathologie en de huidige toestand van het neurogeen blaaslijden kan het controle interval variëren, maar bij patiënten met hoge blaasdrukken wordt geadviseerd eens in de 1 tot 2 jaar te controleren. Bij patiënten met MS of een acute dwarslaesie is het te adviseren dit interval te verkorten. In geval van een veilige blaas met lage drukken en gering residu hoeft regelmatige urodynamische controle niet worden verricht. Geïndividualiseerde follow-up is noodzakelijk om de KvL en levensverwachting te monitoren.

CONCLUSIE

Neurogeen blaaslijden is een ziektebeeld met veel aspecten. Uitgebreid onderzoek en specifieke diagnostiek zijn nodig voordat een individueel behandelplan kan worden

opgesteld. Gedurende de behandeling moet er rekening gehouden worden met de medische en fysieke conditie van de patiënt. Tevens zijn de verwachtingen van de patiënt ten aanzien van de toekomstige sociale, fysieke en medische situatie zeer belangrijk. De behandelend specialist kan kiezen uit een grote hoeveelheid therapeutische opties, elk met bepaalde voor- en nadelen. Ongeacht het succes van een ingestelde therapie, is een levenslange begeleiding essentieel voor het leven van de patiënt. Het doel van deze richtlijnen is de toestand van de neurogene blaas van een patiënt zo precies mogelijk te omschrijven. De hulpverlener kan met deze omschrijving, samen met de patiënt, een op maat gesneden optimale begeleiding en therapie kiezen.

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Summary and general discussion

In this thesis traditional and patient reported outcome measures aimed to evaluate functional disorders of the pelvic floor are presented.

TRADITIONAL OUTCOME MEASURES

Despite nowadays diagnostic and therapeutic advancements like magnetic resonance imaging and robot assistance, post-prostatectomy incontinence remains a major concern for patients. The surgical armamentarium for stress urinary incontinence in men ranges from minimally invasive procedures to artificial urinary sphincter implantation. Multiple innovative devices have been introduced in this rapidly moving field over the recent years.[1] These include the artificial urinary sphincter, bulking agent injection therapy, male slings, and balloon implantation. For severe or persistent urinary incontinence the artificial urinary sphincter is still the current standard of treatment. As the evidence for the use of these devices in daily practice is growing, the respective indications for the various surgical options are also evolving. In this respect pre-intervention evaluation, including urodynamics to assess bladder storage, is important to understand the contributing components to the patient's condition. This will also aid in the decision which intervention is best indicated for the individual patient in order to optimize treatment outcome.

In **Part I** we reported on one of the backbones of diagnostics in functional urology, the urodynamic study. This traditional outcome investigation measures physiological parameters of the urinary bladder, sphincter, and urethra during filling and voiding. These urodynamic parameters are interpreted by the physician and assist to diagnose the cause and nature of bladder dysfunction. In ***Chapter 1***, urodynamic changes after implantation of the Adjustable Continence Therapy (ProACT, Uromedica, Minneapolis, MN) were described. ProACT is a minimally invasive implant consisting of two volume-adjustable balloons.[2] The balloons are placed paraurethrally just cranial from the pelvic floor. Each balloon is attached by a plastic tube to a titanium port placed subcutaneously in the scrotum allowing for separate volume adjustments using an isotonic solution of contrast medium after the initial implantation. The balloon volume is adjusted to create bilateral urethral compression until continence is achieved and the optimal balance between bladder emptying and dryness has been obtained. The implantation of ProACT in men with post-prostatectomy incontinence was considered successful if patients used none or one dry precautionary incontinence pad per day, and not successful if the patient reported one or more wet pads per day. Men who were successfully treated with ProACT (37 out of 49 men) showed an increased urethral resistance and reduced bladder contraction strength as compared to pre-treatment urodynamic evaluation. Nonetheless, no signs of clinical obstruction were

found after successful implantation as patients did not develop significant post-void residue or symptomatic urinary tract infections during follow-up. Independent clinical predictors for a non-successful ProACT implementation were a longer duration of urinary incontinence, more severe incontinence (i.e. the need to use more than five incontinence pads per day), and a smaller cystometric bladder capacity measured before ProACT implantation. These results suggest that ProACT implantation, which is a minimal invasive and reversible treatment, may be considered as a first-line surgical option in a 'step up' approach for the treatment of post-prostatectomy incontinence after conservative treatment has failed.[3] It should at least be considered before opting for more invasive operative techniques, like the artificial urinary sphincter, especially for patients with less severe incontinence. Although more studies are required before clinical algorithms can be constructed, our results indicate that urodynamic measurements may be useful to guide the choice for an individually tailored treatment modality. It is clear that, these adjustable balloons are not an option for all men and that potentially subgroups may best benefit from implantation. The ultimate role of adjustable balloons will depend on their generalized availability and a rational treatment paradigm, which incorporates their use in appropriately selected patients. Undoubtedly, the treatment of male urinary incontinence remains a clinical problem because of the lack of a solution that is universally successful.

PATIENT REPORTED OUTCOME MEASURES (PROMs)

Urinary incontinence is a symptom of inadequate storage indicating bladder dysfunction. The *standardisation sub-committee of the International Continence Society* defined it as "the complaint of any involuntary loss of urine". [4] This definition is suitable for epidemiological studies, but when assessing the prevalence of bothersome incontinence the definition of "involuntary loss of urine that is a social or hygienic problem" seems more useful.[5] There is not a single and precise definition for incontinence which frequently limits the comparison of results derived from various studies in this field. This also applies to any measure of severity which is further complicated by subjectivity and dependence on self-report by the individual. While urinary incontinence is not a life-threatening condition, it certainly has the potential to have a negative impact on the psychological health of the patients. Furthermore, it hinders aspects of daily living, thereby having a detrimental effect on quality of life.[6] Measures incorporating the patient's perspective are called patient reported outcome measures (PROMs), which are originating from patients themselves, reporting their health condition, including symptoms, functional status and health-related quality of life (HRQL). Especially in conditions involving pelvic floor dysfunction, PROMs should be considered as impor-

tant measures of outcome when considering natural history and therapeutic efficacy. Validated PROMs for adequate assessment are, however, not generally available for patients and physicians, and were lacking in Dutch, which is the native language of the vast majority of people in the Netherlands.

Therefore, in **Part II**, commonly used English PROMs for assessing symptom distress and HRQOL of pelvic floor dysfunction, including urogenital functional disorders, were translated and adapted to Dutch after which their measurement properties were tested. The translation into Dutch followed standardized forward-backward procedures: three independent forward translations, and a backward translation by a native speaker.[7] Subsequently each Dutch PROM was pilot tested with interviews during which potential problems were explored and discussed through guidance of a checklist. Hereafter, the final versions of the questionnaires were designed. Patients with symptoms of pelvic floor dysfunction were requested to complete the questionnaires at inclusion; 1-week after inclusion; and 6 months after inclusion together with a single self-reported health *transition* question of the RAND-36.[8-10] By following the quality criteria as proposed by the EMGO Institute for Health and Care Research[11] we were able to perform a standardized assessment of the measurement properties of the following disease specific PROMs:

- the Urogenital Distress Inventory (UDI-6) and Incontinence Impact Questionnaire (IIQ-7) short forms (***Chapter 2***) to assess *urinary incontinence,*
- the Pelvic Floor Distress Inventory (PFDI-20) and Pelvic Floor Impact Questionnaire (PFIQ-7) short form (***Chapter 3***) to assess *pelvic floor dysfunction,*
- the Fecal Incontinence Quality of Life Questionnaire (FIQL) and the Fecal Incontinence Severity Index (FISI) (***Chapter 4***) to assess *fecal incontinence,*
- the Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire short form (PISQ-12) (***Chapter 5***) to assess *prolapse and sexuality*,
- the 5-item International Index of Erectile Function (IIEF-5) (***Chapter 6***) to assess *erectile dysfunction*.

All above translated PROMs had adequate internal consistency and thus proved to be reliable and valid instruments for assessing symptom distress and HRQOL of pelvic floor dysfunction. The UDI-6, IIQ-7, PFDI-20, and PFIQ-7 also showed to be responsive meaning that they have the ability to detect changes over time. The PFDI-20 and PFIQ-7 showed adequate interpretability; indicating that a qualitative meaning to the quantitative scores can be assigned. In addition, we validated the UDI-6 and IIQ-7 in male patients by revising the gender-specific items of the IIQ-7, as these were originally constructed and validated in women.

Demonstrating reliability and validity is essential in determining whether a specific PROM will be useful in the evaluation of a health-care intervention. Reliability and

validity are more accurately described as continuous rather than dichotomous psychometric indices. For this reason, claiming that an instrument is "completely reliable" or "completely valid" is inaccurate. Reliability and validity are separate psychometric properties. Measures can be highly reliable but still not able to measure what they are purported to measure. Thus, reliability is necessary but not sufficient for a measure to be valid. Similarly, saying an instrument has been "validated" conveys no information other than that its performance or psychometric properties have been evaluated. However, as this is an accustomed way to summarize the findings in PROM-based research we have formulated our conclusions concordantly. Although information about the reliability and validity of an instrument is critical, these properties must be considered in the context of the setting in which the instrument will be used. A good example is the IIEF-5 which is supposed to complement clinical judgment and diagnostic assessment, but not to replace patient history taking (*Chapter 6*).

In the field of functional urology linguistically adapted and psychometrically adequate PROMS are valuable as treatment success is dependent on the patient's perspective on their quality of life and their ability to function. Validated PROMs should thus form a key part of treatment evaluation and development, both within as well as outside of the context of clinical trials, in addition to the traditional outcome measures such as surgical complications and morbidity rates. Furthermore, PROMs could be useful for clinicians in daily practice as well, for instance in understanding the long-term results of intervention on HRQOL or the impact of pelvic floor dysfunction for the individual patient over time, which may very well fluctuate. Systematized information about the self-perceived severity of pelvic floor dysfunction could be especially relevant with respect to the decision whether to proceed or not to proceed with more invasive treatments strategies. Unfortunately, physicians are often reluctant to routinely use PROMs because of the concerns of additional workload. Also, some clinicians believe that they already understand their patients' problems by adequate history taking and that they are not in need of the additional information derived by PROMs for patient management.[12] On the other hand, patients generally welcome systems that routinely use PROMs if used well and not misdirect the focus of the clinical encounter, it not only focuses on factors that have value to clinicians, and as long as it is not too much of an inconvenience.[12] To overcome the barriers for routine use, PROMS should preferably be short and easy to use and interpret, both for patients as well as physicians. Secure electronic forms through interactive applications are probably essential before successful implementation of PROMs in daily practice can be considered.

Also needed before general implementation of the Dutch measures is validation in other clinical settings. Our studies were all conducted in a tertiary urology and gynaecology care centre, where we expect patients to have more severe symptoms of

functional disorders of the pelvic floor. The extent to which the results of our studies can thus be generalized may be limited. Firstly, in primary care practice there is a higher prevalence of community-dwelling older adults with symptoms of urogenital dysfunction. A Dutch survey study[13] among 255 women of 55 years and up found that 64% were not known by their general physician (GP) as suffering from at least one episode of involuntary loss of urine a month. These women's main reasons for not consulting a GP were: not regarding incontinence as a serious problem (73%), having found a way to cope on their own (57%), considering urinary incontinence as a normal sequel of aging (47%), and having low expectations of treatment (24%). In addition, *mentioning* the symptoms to a professional may not be enough as there are reports of GPs not responding to these complaints, either by ignoring the statement of symptoms or by providing a dismissive explanation. Patients tend to interpret a lack of response from the doctor as an indication that no treatment is available. In a study of management of incontinence in general practice, 30% of the women who had told their doctor about their symptoms perceived that they were offered no help.[14] It is probable that many primary health care providers lack confidence in managing urinary incontinence, and that this contributes to under treatment in those seeking help. Validated PROMs might actually help GPs in the interpretation of the severity of functional disorders of the pelvic floor and subsequent need for further therapy or referral. Educational outreach regarding pelvic floor disorders and the Urogynecology specialty would likely improve patient access to care.[15] The adoption of PROMs in primary care, however, poses specific challenges that are related to the specific characteristics of the patient population. For instance, primary care patients show a wide range of disease, including many early undifferentiated stages and conditions which may be mild and temporary. Therefore, disease-specific measures may be less preferable over generic measures in this setting, as the latter can be used across diseases to address a broad set of domains of general health.[16,17]

EVIDENCE BASED MEDICINE IN FUNCTIONAL UROLOGY

Part III focuses on evidence based medicine (EBM) in the clinical research of neurogenic bladder dysfunction. In this specific disease the first aim of urological treatment is protection of the upper urinary tract.[18] In patients with detrusor-sphincter dyssynergia (DSD), a high detrusor pressure during filling may result in a pathologic high-pressure bladder, which needs to be converted into a low-pressure reservoir. Surgical treatment can be considered in patients for whom conservative treatment failed or is not possible. Since the introduction of endoscopic sphincterotomy in 1958 as a treatment of functional obstruction at the level of the external urethral sphincter in neurogenic

bladder [19] new surgical options have been developed. In ***Chapter 7*** the effectiveness of different surgical therapies for the treatment of functional bladder outlet obstruction due to DSD in patients with neurogenic bladder was assessed. The wide variety of surgical treatments available for curing or improving bladder outlet obstruction in adults with neurogenic bladder dysfunction indicates a lack of consensus for what is optimal treatment. We conducted a Cochrane systematic review to help identify optimal practice in patients with DSD, and to highlight where there is need for further research. The Cochrane Collaboration is to develop systematic reviews of the strongest evidence available about healthcare interventions, with editorial teams overseeing the preparation and maintenance of the reviews.[20] We used explicit methods aimed at minimizing bias in order to produce more reliable findings that can be used to inform decision-making. In our review we identified limited quality of evidence for intraurethral Botulinum toxin A injections in improving urodynamic outcomes related to the function of the bladder and urethra 30 days after injection. Nonetheless this review did not find enough evidence to identify the most effective surgical treatment for DSD. It is often thought that due to focusing exclusively on randomized controlled trials (RCTs) a large swath of the published literature is excluded from their purview. Nevertheless, *Alper et al.* determined how often clinical conclusions derived from Cochrane Reviews have uncertain validity due to review conduct and reporting deficiencies. They concluded that Cochrane Reviews provide high-quality assessment and synthesis of evidence, with fewer than 1% of Cochrane Reviews having limitations which hinder the summary of best current evidence for clinical decision-making.[21] However, in daily practice an intervention may nevertheless be considered as an adequate patient management strategy, despite scientifically proven efficacy within placebo-controlled studies. This is especially the case in interventions with low risks and low costs.

Finally, in ***Chapter 8*** multidisciplinary evidence based clinical guidelines for management of patients with symptoms of neurogenic bladder in the Netherlands are provided. With these guidelines, we provided information for Dutch clinical practitioners about the incidence, definitions, diagnosis, therapy, and follow-up of neuro-urological disorders. The multidisciplinary guidelines serve the clinician to make decisions about appropriate health care. These guidelines were made in collaboration with the Dutch associations of urologists (Nederlandse Vereniging voor Urologie), neurologists (Nederlandse Vereniging voor Neurologie), rehabilitation physicians (Nederlandse Vereniging van Revalidatieartsen), Elderly Care Physicians and Social Geriatricians (Verenso), Continence Nurses and Carers (Continentie Verpleegkundigen & Verzorgenden), and patient support groups for people with paraplegia (Dwarslaesie Organisatie Nederland) and for people with congenital physical disabilities (BOSK).

FINAL CONCLUSION

This thesis has yielded significant results regarding the evaluation of functional disorders of the pelvic floor in both men and women, using traditional outcome measures along with PROMs, namely:

- Successful ProACT implantation resulted in greater urethral resistance during voiding and reduced bladder contraction strength.
- Independent predictors of unsuccessful clinical outcome after ProACT implantation include a longer duration of incontinence, the use of 5 or more incontinence pads a day, and a smaller cystometric bladder capacity.
- The Dutch short-form measures UDI-6 and IIQ-7 to assess *urinary incontinence,* the PFDI-20 and PFIQ-7 to assess *pelvic floor dysfunction,* the FIQL and FISI to assess *fecal incontinence,* the PISQ-12 to assess *prolapse and sexuality*, and the IIEF-5 to assess *erectile dysfunction*, all had adequate internal consistency and thus proved to be reliable and valid instruments for assessing symptom distress and HRQOL of pelvic floor dysfunction.
- Using the Cochrane methodology, evidence of limited quality was found that intraurethral Botulinum toxin A injections improve some urodynamic measures after 30 days in the treatment of functional bladder outlet obstruction in adults with neurogenic bladder dysfunction.
- Our Dutch multidisciplinary guidelines "Neurogene blaas" provide an overview of the available evidence for adequate diagnosis, treatment, and follow-up of patients suffering from neurogenic bladder.

As PROMs are designed to provide relevant insight in the self-perceived impact of pelvic floor dysfunction on the HRQOL of the individual patient, which cannot be captured with objective medical testing, we believe both should be correspondingly weighted when determining and providing good medical care. Along with the presented evidence-based management strategies in this thesis, we can contribute to shared decision making, as this is defined as: 'an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences'. [22]

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Samenvatting en discussie *(in Dutch)*

In dit proefschrift worden traditionele en patiënt gerapporteerde uitkomstmaten gepresenteerd. Deze uitkomstmaten hebben als doel om functionele klachten van de bekkenbodem te evalueren.

TRADITIONELE UITKOMSTMATEN

Urine incontinentie na operatieve prostaatverwijdering (prostatectomie) blijft ondanks de hedendaagse diagnostische en therapeutische innovaties, zoals de MRI-scanner (*magnetic resonance imaging*) en robot geassisteerde ingrepen, een belangrijke zorg voor patiënten. Tot op heden is de kunstmatige sfincter prothese de standaard behandeling voor ernstige of aanhoudende urine incontinentie. In de afgelopen jaren zijn op het gebied meerdere vooruitstrevende behandelingen geïntroduceerd.[1] Hieronder vallen onder andere de kunstmatige sfincter prothese, bulkinjecties, plaatsing van bandjes (*male sling)* en sluitspierballonnen (*Adjustable Continence Therapy: ProACT)*. Gezien er steeds meer wetenschappelijk bewijs is voor het gebruik en effectiviteit van deze behandelingen, worden de verschillende indicaties ook steeds specifieker. Om die reden is evaluatie vóór de interventie belangrijk, zoals urodynamisch onderzoek welke een beeld geeft van de gezondheidstoestand van de patiënt. Dit zal tevens helpen in de besluitvorming welke interventie het beste past bij de individuele patiënt om tot een zo goed mogelijk behandelingsresultaat te komen.

In het eerste deel van dit proefschrift wordt een van de belangrijkste diagnostische onderzoeken binnen de functionele urologie belicht: het urodynamisch onderzoek. Dit functie onderzoek van de lage urinewegen levert fysiologische waarden (traditionele uitkomstmaten) op van de urine blaas, sluitspier ('sfincter') en plasbuis ('urethra') tijdens blaasvulling en –lediging. Deze waarden worden door de arts geïnterpreteerd en hebben als doel om de oorzaak en de aard van de blaasdisfunctie te diagnosticeren. In ***hoofdstuk 1*** worden de urodynamische veranderingen na implantatie van de sluitspierballonnen ProACT beschreven. ProACT is een minimaal invasieve implantaat die bestaat uit twee ballonnen geplaatst aan weerszijden van de plasbuis vlak bij de blaas.[2] Het volume van de ballonnen zijn na implantatie aan te passen. Dit wordt gedaan via een slangetje met een ventiel dat aan het ballonnetje zit. Dit ventiel wordt onderhuids in de balzak geplaatst en is dan goed bereikbaar voor het bijvullen. Door het volume van de ballon aan te passen wordt er bilaterale compressie gegeven op de urethra tot een optimum tussen blaaslediging en continentie is bereikt. De implantatie van ProACT bij incontinente mannen na prostaatverwijdering was succesvol als de patiënt geen of één droge incontinentie inlegger ('voor de zekerheid') gebruikte. De behandeling werd als niet succesvol bevonden als de patiënt aangaf minimaal één natte inlegger te hebben per dag. De mannen in ons onderzoek die succesvol

werden behandeld met ProACT (37 van de 49 mannen), hadden bij het urodynamisch onderzoek ná implantatie een toegenomen urethrale weerstand en een afgenomen blaascontractiekracht vergeleken met urodynamisch onderzoek vóór implantatie. Dit leidde echter niet tot klinische blaasobstructie, daar de patiënten geen significante residu na mictie of symptomatische urineweginfecties doormaakten gedurende follow-up. Onafhankelijke factoren van niet-succesvolle ProACT implantatie waren een langere duur van urine incontinentie, ernstigere incontinentie (d.w.z. meer dan vijf incontinentie inleggers per dag) en een kleinere cystometrische blaascapaciteit voor implantatie. Deze resultaten wekken de suggestie dat ProACT implantatie – wat immers een minimaal invasieve en reversibele behandeling is – een eerste chirurgische optie is in de behandeling van incontinentie na prostaatverwijdering als conservatieve behandelingen hebben gefaald.[3] Het zou op zijn minst moeten worden overwogen alvorens er gekozen wordt voor meer invasieve operatieve technieken zoals de kunstmatige sfincter prothese, zeker voor patiënten met een minder ernstige vorm van incontinentie. Er zijn uiteraard meer onderzoeken nodig voordat klinische algoritmen kunnen worden ontworpen, maar onze resultaten laten zien dat dergelijke traditionele uitkomstwaarden belangrijk zijn voor het maken van een individuele keuze van de te vervolgen behandelstrategie. Het is duidelijke dat de aanpasbare ballonnen niet een optie zijn voor alle mannen en er hier gekeken moet worden naar de subgroepen die er het beste mee geholpen worden. De toekomstige rol die ProACT ballonnen gaan krijgen hangt af van de uiteindelijke bruikbaarheid die mede bepaald wordt door toepassing in correct geselecteerde patiëntengroepen. Ongetwijfeld blijft de behandeling van urine incontinentie bij mannen een klinisch probleem doordat er nog geen universele succesvolle oplossing voorhanden is.

PATIËNT-GERAPPORTEERDE UITKOMSTMATEN

Urine incontinentie is een symptoom van inadequate urine opslag door de blaas en daarom een teken van blaasdysfunctie. De *standardisation sub-committee of the International Continence Society (ICS)* definieert de klacht als "elke vorm van onvrijwillige urine verlies".[4] Dit is een definitie die voornamelijk geschikt lijkt te zijn voor gebruik in epidemiologisch onderzoek. De definitie "onvrijwillig urineverlies dat tot een sociaal of hygiënisch probleem leidt" legt meer de nadruk op de hinder en is daardoor geschikter als er gekeken wordt naar de prevalentie van de hinder van incontinentieklachten.[5] Een enkele en precieze definitie voor incontinentie ontbreekt en dit zorgt ervoor dat de resultaten van verschillende onderzoeken niet goed onderling te vergelijken zijn. Dit is ook het geval bij uitkomstmaten over de ernst of hinder van incontinentieklachten, daar deze veel meer subjectief zijn van aard. Urine incontinentie

is geen levensbedreigende aandoening, maar het heeft zeker een negatieve impact op de psychische gezondheid van patiënten. Het hindert aspecten van het dagelijkse leven en heeft daardoor een nadelig effect op de kwaliteit van leven.[6]

Uitkomstmaten die het perspectief van de patiënt meenemen worden patiënt-gerapporteerde uitkomstmaten *(patient reported outcome measures:* PROMs*)* genoemd. Dit zijn uitkomstmaten die door de patiënten zelf worden gerapporteerd waarin zij hun gezondheidstoestand aangeven zoals symptomen, functionele status en gezondheidsafhankelijke kwaliteit van leven *(health-related quality of life:* HROQL). PROMs zijn belangrijke maten in het beoordelen van de therapeutische effectiviteit, zeker in het geval van aandoeningen die de bekkenbodem betreffen. Gevalideerde Nederlandstalige PROMs voor gebruik bij patiënten met bekkenbodemproblematiek waren echter niet voldoende voorhanden. Om die reden zijn in het tweede deel van dit proefschrift veelgebruikte Engelstalige bekkenbodemvragenlijsten vertaald en aangepast voor de Nederlandse taal. Van deze Nederlandse PROMs hebben we de psychometrische eigenschappen getest. De cross-culturele vertaling naar het Nederlands is volgens richtlijnen uitgevoerd: drie onafhankelijke heen-vertalingen (vanuit het Engels naar het Nederlands) en een terug-vertaling (vanuit het Nederlands weer naar het Engels) door personen met de doeltaal als moedertaal.[7] Daaropvolgend werd elke Nederlandse PROM getest ('*pilot test*'): patiënten vulden de vragenlijsten in en werden achteraf geïnterviewd ondersteund door een checklist over de betekenis van de vragen en antwoorden om potentiele problemen op te sporen. Na de pilot test waren de vragenlijsten klaar voor gebruik. Patiënten met bekkenbodemklachten werden gevraagd om de vragenlijsten in te vullen op drie verschillende momenten: op de dag van inclusie, 1 week na inclusie en 6 maanden na inclusie. Bij de laatste vragenlijst was een gezondheidsverandering item toegevoegd van de RAND-36.[8-10] Door gebruik te maken van de kwaliteitscriteria zoals opgesteld door het EMGO instituut[11] hebben we de psychometrische eigenschappen getest van de door ons vertaalde ziekte-specifieke PROMs:

- De korte versie van de *Urogenital Distress Inventory* (UDI-6) en *Incontinence Impact Questionnaire* (IIQ-7) (***Hoofdstuk 2***) om urine incontinentieklachten te evalueren,
- De korte versie van de *Pelvic Floor Distress Inventory* (PFDI-20) en *Pelvic Floor Impact Questionnaire* (PFIQ-7) (***Hoofdstuk 3***) om bekkenbodemklachten te evalueren,
- de *Fecal Incontinence Quality of Life Questionnaire* (FIQL) en de *Fecal Incontinence Severity Index* (FISI) (***Hoofdstuk 4***) om klachten van ontlastingsincontinentie te evalueren,
- de korte versie van de *Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire* (PISQ-12) (***Hoofdstuk 5***) om prolaps en seksualiteitsklachten te evalueren,

- de 5-item *International Index of Erectile Function* (IIEF-5) (***Hoofdstuk 6***) om erectieklachten te evalueren.

Alle hierboven genoemde PROMs hadden een adequate interne consistentie en zijn daarom betrouwbare en valide instrumenten om de hinder van symptomen van bekkenbodemklachten en de HRQOL te evalueren. De UDI-6, IIQ-7, PFDI-20 en PFIQ-7 bleken ook responsief te zijn, dat wil zeggen dat deze vragenlijsten werkelijke veranderingen konden meten over de tijd. De PFDI-20 en PFIQ-7 hadden een adequate interpreteerbaarheid: een kwalitatieve betekenis aan een kwantitatieve score kon worden toegerekend. De UDI-6 en IIQ-7 die oorspronkelijk ontwikkeld en gevalideerd zijn voor gebruik bij vrouwen hebben we ook kunnen valideren voor gebruik bij mannen door een geslacht specifieke vraag te reviseren.

Om een PROM te kunnen gebruiken als evaluatie instrument in de gezondheidszorg dient deze betrouwbaar en valide te zijn. Betrouwbaarheid en validiteit zijn continue en eigenlijk nooit dichotome variabelen. Om die reden is het incorrect om te zeggen dat een instrument 'volledig betrouwbaar' of 'volledig valide' is. Betrouwbaarheid en validiteit zijn aparte psychometrische eigenschappen. Instrumenten zouden zeer betrouwbaar kunnen zijn en tegelijk *niet* meten wat het beoogt te meten. Daardoor is de eigenschap betrouwbaarheid noodzakelijk, doch niet op zichzelf staand voldoende om valide te zijn. Eveneens, concluderen dat een instrument is 'gevalideerd' zegt niets meer dan dat het gebruik of de psychometrische eigenschappen zijn geëvalueerd. Omdat dit echter een gebruikelijke manier is van het samenvatten van bevindingen in PROM-gerelateerd onderzoek, hebben we eveneens onze conclusies op deze manier gesteld. Informatie over de betrouwbaarheid en validiteit van een instrument is belangrijk, maar deze eigenschappen moeten wel worden beoordeel in de context waarin deze wordt gebruikt. Een goed voorbeeld is de IIEF-5 die vooral bedoeld is om het klinische oordeel te ondersteunen en als hulpmiddel voor diagnostiek, niet om de anamnese te vervangen (zie ook *Hoofdstuk 6).*

Op het gebied van functionele urologie zijn taalkundig aangepaste en psychometrisch adequate PROMs waardevol daar het behandelsucces afhankelijk is van het perspectief van de patiënt op hun kwaliteit van leven en mogelijkheden in het dagelijkse functioneren. Gevalideerde PROMs zouden daarom een sleutelrol moeten vervullen in de ontwikkeling en evaluatie van behandelingen, naast de traditionele uitkomstmaten zoals urodynamische waarden, chirurgische complicaties en morbiditeit aantallen. PROMs kunnen clinici in de dagelijkse praktijk ondersteunen om bijvoorbeeld de lange termijn resultaten van een interventie op de impact of HRQOL te beoordelen over de tijd, aangezien deze doorgaans fluctueren. Het systematisch verzamelen van informatie over subjectieve bekkenbodemklachten is vooral relevant zodra de keuze wordt gemaakt door te gaan met meer invasieve behandelingen. Helaas zijn artsen vaak terughoudend om PROMs routinematig te gebruiken omdat

er gedacht wordt dat dit extra werk met zich meebrengt. Ook zijn er artsen die menen dat ze al voldoende hebben aan de anamnese om te begrijpen welke hinder patiënten ondervinden en hier geen PROMs voor nodig hebben.[12] Aan de andere kant, patiënten staan doorgaans wel open voor een systematiek waarin routinematig PROMs worden gebruikt mits deze niet de aandacht verschuift van het klinische bezoek, niet alleen aandacht vestigt op items die voor de arts zelf interessant zijn en als het niet teveel moeite kost.[12] Om dergelijke barrières te doorbreken zouden PROMs dus kort en makkelijk in te vullen zijn. In de toekomst zijn beveiligde elektronische vragenlijsten middels interactieve programma's en toepassingen vermoedelijk een vereiste voor succesvolle implementatie van PROMs in de dagelijkse praktijk.

Een ander punt waar naar gekeken dient te worden alvorens de Nederlandse vragenlijsten kunnen worden geïmplementeerd is de toepasbaarheid in andere klinische settings. Onze studies werden allemaal verricht in een derdelijns urogynaecologische centrum waar patiënten over het algemeen ernstigere symptomen hebben van bekkenbodemklachten. De mate waarin de resultaten van onze studies doorgetrokken mogen worden naar de algehele populatie is dus beperkt. Allereerst in de eerstelijnszorg is een hogere prevalentie van thuiswonende ouderen met urogenitale klachten. Een Nederlands onderzoek liet zien dat 64% van de 255 deelnemende vrouwen van 55 jaar en ouder nooit hun klachten van urine incontinentie (minimaal één keer per maand onvrijwillig urineverlies) hadden besproken bij hun eigen huisarts.[13] De hoofdredenen hiervan waren: het gevoel hebben dat incontinentie niet een serieuze klacht is (73%), zelf een manier hadden bedacht hoe hiermee om te gaan (57%), urine incontinentie beschouwen als een normaal verloop bij het ouder worden (47%) en weinig verwachten van een behandeling (24%). Het benoemen van deze klachten aan een professional blijkt echter niet altijd afdoende te zijn; er zijn huisartsen die niet reageren als een patiënt deze klacht meldt door deze klacht te negeren of door een afwijzende reactie. Patiënten nemen dan aan dat het uitblijven van een reactie van een arts een aanwijzing is dat er geen behandeling voorhanden is. In een ander onderzoek werd aangetoond dat 30% van de vrouwen die het probleem bij hun arts neerlegden geen hulp aangeboden kregen.[14] Mogelijk weten eerstelijns hulpverleners geen raad hoe om te gaan met klachten van urine incontinentie en dit draagt weer bij aan de onderbehandeling van patiënten die wél hulp zoeken. Gevalideerde PROMs zouden huisartsen goed kunnen helpen bij het interpreteren van de ernst van de functionele bekkenbodemklachten. Dit faciliteert op zijn beurt de beslissing van de te ondernemen vervolgstappen bijvoorbeeld door te verwijzen naar een specialist. Door educatie te geven aan huisartsen over bekkenbodemklachten zou de toegang van de zorg voor de patiënt kunnen verbeteren.[15]

Alvorens PROMs in de eerste lijn kunnen worden toegepast moet er rekening gehouden worden met de specifieke karakteristieken van de patiëntenpopulatie in de

eerste lijn. Patiënten uit de eerste lijn hebben namelijk een breder scala aan klachten en aandoeningen die vaak ook nog in een vroeg ongedifferentieerd stadium worden gepresenteerd. Sommige klachten hiervan zijn slechts mild van aard en tijdelijk van duur. Algemene gezondheidsvragenlijsten hebben om deze reden waarschijnlijk de voorkeur boven ziekte-specifieke vragenlijsten, daar deze verschillende domeinen bevraagt over de algehele breedte van de gezondheid.[16,17]

EVIDENCE BASED MEDICINE IN DE FUNCTIONELE UROLOGIE

In het derde deel van dit proefschrift wordt er aandacht geschonken aan het wetenschappelijke bewijs (*evidence based medicine: EBM)* in klinisch onderzoek van neurogeen blaaslijden. Bij neurogeen blaaslijden is bescherming van de hogere urinewegen het hoofddoel van urologische behandeling.[18] Patiënten met detrusor-sfincter dyssynergie (DSD) kunnen hoge blaasdrukken ontwikkelen wat tot een pathologische hoge drukblaas kan leiden. In dat geval moet de blaas omgevormd worden naar een lage druk reservoir. Als conservatieve behandeling tekortschiet moeten chirurgische opties worden overwogen. Sinds de introductie van endoscopische sfincterotomie in 1958[19] als behandeling van functionele obstructie ter hoogte van de externe sfincter bij neurogeen blaaslijden, zijn er diverse nieuwe chirurgische opties ontwikkeld. In ***Hoofdstuk 7*** hebben we gekeken naar de effectiviteit van diverse chirurgische therapieën voor de behandeling van functionele blaasobstructie door DSD bij patiënten met neurogeen blaaslijden. Er bestaat geen consensus over de vraag wat de optimale chirurgische behandeling is van neurogeen blaaslijden door de grote verscheidenheid in mogelijkheden. Wij hebben daarom een Cochrane systematische review verricht om de optimale behandeling te identificeren voor patiënten met DSD. De *Cochrane Collaboration* is een internationale, onafhankelijke, non-profit organisatie met als missie zorgverleners, beleidsmakers en patiënten te helpen bij het nemen van beslissingen over gezondheidszorg. Zij doet dit door het maken van systematische samenvattingen van al het beschikbare wetenschappelijke onderzoek betreffende het effect (of het ontbreken daarvan) van gezondheidszorginterventies.[20] Door gebruik te maken van de Cochrane methodiek verkleinden we het risico op bias waardoor we zoveel mogelijk betrouwbare conclusies konden trekken. In ons review vonden we bewijs van beperkte kwaliteit voor de behandeling middels intra-urethrale Botulinum toxine A injecties. Urodynamische uitkomsten gerelateerd aan de blaas- en urethrafunctie verbeterden 30 dagen na injectie. Desalniettemin is er niet voldoende betrouwbaar bewijs om de meest effectieve chirurgische behandeling voor DSD aan te wijzen.

Er wordt vaak gedacht dat door alleen gerandomiseerd gecontroleerd onderzoek te includeren in Cochrane reviews er een heleboel gepubliceerde data die wel zouden kunnen bijdragen worden uitgesloten. Echter, *Alper e.a*. hebben onderzocht hoe vaak conclusies getrokken uit Cochrane reviews een twijfelachtige validiteit hadden als gevolg van de manier van het uitvoeren van de review (*review conduct en reporting deficiencies*). Zij concludeerden dat Cochrane reviews van hoge kwaliteit zijn met in minder dan 1% van de gevallen beperkingen die het beste bewijs voor het nemen van klinische beslissingen in de weg zaten.[21] Echter in de dagelijkse gang van zaken kan iets toch worden gezien als een adequate behandeloptie zonder dat dit wetenschappelijke wordt ondersteund door onderzoek naar de effectiviteit middels placebo gecontroleerd bewijs. Dit is vooral het geval bij interventies met lage risico's en lage kosten.

Tenslotte, in ***Hoofdstuk 8*** staan multidisciplinaire wetenschappelijk ondersteunde richtlijnen voor de behandeling van patiënten met klachten neurogene blaas in Nederland. Met deze richtlijnen bieden we informatie voor behandelaren over de incidentie, definities, diagnose, behandelingen en follow-up van neuro urologische aandoeningen. De richtlijnen hebben als doel om de clinicus te ondersteunen in het maken van beslissingen op dit gebied. De werkgroep bestond uit leden van de Nederlandse Vereniging van de Urologie, de Nederlandse Vereniging voor Neurologie, de Nederlandse Vereniging van Revalidatieartsen, Verenso, V&VN Continentie Verpleegkundigen & Verzorgenden en de patiëntenorganisaties Dwarslaesie Organisatie Nederland en Organisatie BOSK.

CONCLUSIE

Dit proefschrift verschaft belangrijke resultaten met betrekking tot de evaluatie van functionele stoornissen van de bekkenbodem bij zowel mannen als vrouwen. Hier is gebruik gemaakt van traditionele uitkomstmaten evenals PROMs. De conclusies die kunnen worden getrokken uit dit proefschrift zijn:

- Succesvolle ProACT-implantatie resulteerde in een toegenomen urethrale weerstand tijdens mictie en een afgenomen blaasconcentratiekracht.
- Onafhankelijke voorspellers voor een succesvolle ProACT-implantatie zijn een langere incontinentieduur, het gebruik van vijf of meer incontinentie verbanden per dag en een kleinere cystometrische blaascapaciteit.
- De gepresenteerde Nederlandse korte vragenlijsten UDI-6 en IIQ-7 voor de beoordeling van urine-incontinentie, de PFDI-20 en PFIQ-7 voor de beoordeling van bekkenbodemklachten, de FIQL en FISI voor de beoordeling van ontlastingsincontinentie, de PISQ-12 voor de beoordeling van prolaps en seksualiteit en de IIEF-5

voor de beoordeling van erectieklachten, hadden allemaal een adequate interne consistentie en zijn derhalve betrouwbare en geldige (valide) instrumenten voor het beoordelen van symptomen en HRQOL van bekkenbodemklachten.

- Er is bewijs van beperkte kwaliteit dat intra-urethrale Botulinum toxine A injecties voor de behandeling van functionele blaas obstructie na 30 dagen een aantal urodynamische waarden verbeterden bij volwassenen met neurogene blaasklachten.
- De Nederlandse multidisciplinaire richtlijnen "Neurogene blaas" geven een overzicht van het beschikbare bewijs voor adequate diagnose, behandeling en follow-up van patiënten met klachten van neurogene blaaslijden.

Daar PROMs het inzicht geven in de HRQOL van bekkenbodemklachten en traditionele onderzoeksmethoden dit niet doen, zijn wij van mening dat beide soorten uitkomstmaten naar ratio moeten worden toegepast voor adequate gezondheidszorg. Samen met de gepresenteerde EBM strategieën uit dit proefschrift leveren we een belangrijk aandeel aan gezamenlijke besluitvorming (*shared decision making).* Dit laatste is namelijk gedefinieerd als een gezamenlijk proces van zorgverlener en patiënt over gezondheids- en behandelingsdoelen welke worden gesteld op basis van wetenschappelijke kennis, ervaringskennis, waarden en wensen van de patiënt.[22]

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Vragenlijsten

UDI-6: Urogenitale Klachten Lijst

In hoeverre heeft u van het volgende last:

(Kruis één vakje per regel aan)	Helemaal niet	Een beetje	Redelijk wat	Zeer veel
1. Vaak plassen	☐	☐	☐	☐
2. Urineverlies dat verband houdt met het gevoel van aandrang	☐	☐	☐	☐
3. Urineverlies dat verband houdt met lichamelijke activiteit, hoesten of niezen	☐	☐	☐	☐
4. Kleine hoeveelheden urineverlies (druppels)	☐	☐	☐	☐
5. Moeite uw blaas te legen	☐	☐	☐	☐
6. Pijn of ongemak in de onderbuik of rond het kruis	☐	☐	☐	☐

Einde van vragenlijst UDI-6

Utomo et al. Neurourol Urodyn. 2015 Jan;34(1):24-31.

IIQ-7: vragenlijst impact van incontinentie

Sommige mensen vinden dat ongewild urineverlies invloed kan hebben op hun activiteiten, relaties en gevoelens. De onderstaande vragen gaan over facetten van uw leven die misschien zijn beïnvloed of veranderd door uw probleem.

Kruis bij elke vraag het antwoord aan, dat het best omschrijft in hoeverre uw activiteiten, relaties en gevoelens zijn beïnvloed door urineverlies.

Heeft urineverlies invloed gehad op uw….

(Kruis één vakje per regel aan)	**Helemaal niet**	**Een beetje**	**Redelijk wat**	**Zeer veel**
1. vermogen om huishoudelijke taken te doen (koken, schoonmaken, de was doen)?	☐	☐	☐	☐
2. lichamelijke activiteiten zoals bijv. wandelen of zwemmen of andere oefeningen?	☐	☐	☐	☐
3. uitgaansactiviteiten (films, concerten, etc.)?	☐	☐	☐	☐
4. vermogen om langer dan 30 minuten van uw huis met de auto of bus te reizen?	☐	☐	☐	☐
5. deelname aan sociale activiteiten buitenshuis?	☐	☐	☐	☐
6. emotionele gezondheid (nervositeit, depressie, etc.)?	☐	☐	☐	☐
7. gevoel van frustratie?	☐	☐	☐	☐

Einde van vragenlijst IIQ-7

Utomo et al. Neurourol Urodyn. 2015 Jan;34(1):24-31.

PFDI-20: inventaris van bekkenbodemproblemen

Wilt u alstublieft alle vragen van onderstaande lijst beantwoorden? Er wordt gevraagd of u bepaalde darm, blaas of bekkenbodem symptomen heeft, en zo ja, in hoeverre u daar last van heeft.

Bij het beantwoorden van de vragen moet u denken aan de klachten die u de afgelopen 3 maanden heeft gehad.

Voorbeeld:

- *Indien u gewoonlijk GEEN drukkend gevoel in de onderbuik heeft, zet dan een **X** in het vakje bij "Nee" en ga door met de volgende vraag.*
- *Indien u gewoonlijk WEL een drukkend gevoel heeft in de onderbuik, zet dan een **X** in het vakje bij "ja" én geef aan in hoeverre u daar last van heeft. Ga daarna door met de volgende vraag.*

1. Heeft u gewoonlijk een drukkend gevoel in de onderbuik?

☐ nee ☐ ja

↳ **Zo ja, in hoeverre heeft u daar last van?**

☐ helemaal niet ☐ een beetje ☐ redelijk wat ☐ vrij veel

2. Heeft u doorgaans een zwaar of verdoofd gevoel in het bekkengebied?

☐ nee ☐ ja

↳ **Zo ja, in hoeverre heeft u daar last van?**

☐ helemaal niet ☐ een beetje ☐ redelijk wat ☐ vrij veel

3. Heeft u gewoonlijk een uitstulping of komt er iets naar buiten, dat u kunt zien of voelen in het gebied van uw vagina?

☐ nee ☐ ja

↳ **Zo ja, in hoeverre heeft u daar last van?**

☐ helemaal niet ☐ een beetje ☐ redelijk wat ☐ vrij veel

4. Moet u doorgaans op de vagina of rond de endeldarm drukken om ontlasting te hebben of om het af te kunnen maken?

☐ nee ☐ ja

↳ **Zo ja, in hoeverre heeft u daar last van?**

☐ helemaal niet ☐ een beetje ☐ redelijk wat ☐ vrij veel

5. Heeft u gewoonlijk het gevoel dat u uw blaas niet volledig leeg plast?

☐ nee ☐ ja

↳ **Zo ja, in hoeverre heeft u daar last van?**

☐ helemaal niet ☐ een beetje ☐ redelijk wat ☐ vrij veel

Ga naar vraag 6
op de volgende pagina

Utomo et al. Int Urogynecol J. 2014 Apr;25(4):531-44.

6. Heeft u ooit met uw vingers op een uitstulping moeten drukken in het gebied van de vagina om te kunnen plassen of om het plassen af te kunnen maken?

☐ nee ☐ ja

↳ **Zo ja, in hoeverre heeft u daar last van?**

☐ helemaal niet ☐ een beetje ☐ redelijk wat ☐ vrij veel

7. Heeft u het gevoel dat u teveel moet persen om ontlasting te kunnen hebben?

☐ nee ☐ ja

↳ **Zo ja, in hoeverre heeft u daar last van?**

☐ helemaal niet ☐ een beetje ☐ redelijk wat ☐ vrij veel

8. Heeft u het gevoel dat uw darmen nog niet helemaal leeg zijn na de ontlasting?

☐ nee ☐ ja

↳ **Zo ja, in hoeverre heeft u daar last van?**

☐ helemaal niet ☐ een beetje ☐ redelijk wat ☐ vrij veel

9. Heeft u gewoonlijk ongecontroleerd ontlastingverlies als uw ontlasting goed gevormd is?

☐ nee ☐ ja

↳ **Zo ja, in hoeverre heeft u daar last van?**

☐ helemaal niet ☐ een beetje ☐ redelijk wat ☐ vrij veel

10. Heeft u gewoonlijk ongecontroleerd ontlastingverlies als uw ontlasting dun is?

☐ nee ☐ ja

↳ **Zo ja, in hoeverre heeft u daar last van?**

☐ helemaal niet ☐ een beetje ☐ redelijk wat ☐ vrij veel

11. Heeft u gewoonlijk ongecontroleerde winderigheid uit uw endeldarm?

☐ nee ☐ ja

↳ **Zo ja, in hoeverre heeft u daar last van?**

☐ helemaal niet ☐ een beetje ☐ redelijk wat ☐ vrij veel

12. Heeft u doorgaans pijn tijdens de ontlasting?

☐ nee ☐ ja

↳ **Zo ja, in hoeverre heeft u daar last van?**

☐ helemaal niet ☐ een beetje ☐ redelijk wat ☐ vrij veel

13. Ervaart u een sterk aandranggevoel en moet u zich haasten naar het toilet voor de ontlasting?

☐ nee ☐ ja

↳ **Zo ja, in hoeverre heeft u daar last van?**

☐ helemaal niet ☐ een beetje ☐ redelijk wat ☐ vrij veel

14. Komt een deel van uw darmen wel eens door de anus en stulpt die uit tijdens of na de ontlasting?

☐ nee ☐ ja

↳ **Zo ja, in hoeverre heeft u daar last van?**

Ga naar vraag 15
op de volgende pagina

☐ helemaal niet ☐ een beetje ☐ redelijk wat ☐ vrij veel

15. Moet u gewoonlijk vaak plassen?

☐ nee ☐ ja

↳ **Zo ja, in hoeverre heeft u daar last van?**

☐ helemaal niet ☐ een beetje ☐ redelijk wat ☐ vrij veel

16. Heeft u doorgaans urineverlies dat verband houdt met een gevoel van aandrang; oftewel een sterk gevoel dat u naar het toilet moet gaan?

☐ nee ☐ ja

↳ **Zo ja, in hoeverre heeft u daar last van?**

☐ helemaal niet ☐ een beetje ☐ redelijk wat ☐ vrij veel

17. Heeft u gewoonlijk urineverlies dat verband houdt met hoesten, niezen of lachen?

☐ nee ☐ ja

↳ **Zo ja, in hoeverre heeft u daar last van?**

☐ helemaal niet ☐ een beetje ☐ redelijk wat ☐ vrij veel

18. Heeft u doorgaans kleine hoeveelheden urineverlies (druppels)?

☐ nee ☐ ja

↳ **Zo ja, in hoeverre heeft u daar last van?**

☐ helemaal niet ☐ een beetje ☐ redelijk wat ☐ vrij veel

19. Heeft u gewoonlijk moeite uw blaas te legen?

☐ nee ☐ ja

↳ **Zo ja, in hoeverre heeft u daar last van?**

☐ helemaal niet ☐ een beetje ☐ redelijk wat ☐ vrij veel

20. Heeft u doorgaans *pijn* of *ongemak* in de onderbuik of rond het kruis?

☐ nee ☐ ja

↳ **Zo ja, in hoeverre heeft u daar last van?**

☐ helemaal niet ☐ een beetje ☐ redelijk wat ☐ vrij veel

Einde van vragenlijst PFDI-20

Utomo et al. Int Urogynecol J. 2014 Apr;25(4):531-44.

PFIQ-7: vragenlijst impact bekkenbodemklachten

Sommige vrouwen vinden dat blaas, darm of vaginale klachten invloed kunnen hebben op hun activiteiten, relaties en gevoelens.

Zet achter elke vraag een **X** bij het antwoord dat het best beschrijft in hoeverre uw activiteiten, relaties en gevoelens zijn beïnvloed door uw blaas, darm of vaginale klachten of aandoeningen in de afgelopen 3 maanden.

Mogelijk heeft u wel of geen klachten in elk van deze drie gebieden, **maar vult u alstublieft altijd een antwoord in, in alle drie de kolommen bij elke vraag**.
Indien u *geen* klachten heeft in deze gebieden dan zou het juiste antwoord *"Helemaal niet"* zijn in de bijbehorende kolom van de vraag.

In hoeverre beïnvloeden klachten of aandoeningen gerelateerd aan, uw: ↴	**Blaas of urine**	**Darm of endeldarm**	**Vagina of bekken**
1. vermogen om huishoudelijke taken te doen (koken, schoonmaken, de was doen)?	☐ Helemaal niet ☐ Een beetje ☐ Redelijk wat ☐ Vrij veel	☐ Helemaal niet ☐ Een beetje ☐ Redelijk wat ☐ Vrij veel	☐ Helemaal niet ☐ Een beetje ☐ Redelijk wat ☐ Vrij veel
2. vermogen om lichamelijke activiteiten uit te voeren, zoals bijv. wandelen of zwemmen of andere oefeningen?	☐ Helemaal niet ☐ Een beetje ☐ Redelijk wat ☐ Vrij veel	☐ Helemaal niet ☐ Een beetje ☐ Redelijk wat ☐ Vrij veel	☐ Helemaal niet ☐ Een beetje ☐ Redelijk wat ☐ Vrij veel
3. uitgaansactiviteiten (bijv. films, concerten, etc.)?	☐ Helemaal niet ☐ Een beetje ☐ Redelijk wat ☐ Vrij veel	☐ Helemaal niet ☐ Een beetje ☐ Redelijk wat ☐ Vrij veel	☐ Helemaal niet ☐ Een beetje ☐ Redelijk wat ☐ Vrij veel
4. vermogen om te reizen met de auto of bus op een afstand van meer dan 30 minuten van uw huis?	☐ Helemaal niet ☐ Een beetje ☐ Redelijk wat ☐ Vrij veel	☐ Helemaal niet ☐ Een beetje ☐ Redelijk wat ☐ Vrij veel	☐ Helemaal niet ☐ Een beetje ☐ Redelijk wat ☐ Vrij veel
5. deelname aan sociale activiteiten buitenshuis?	☐ Helemaal niet ☐ Een beetje ☐ Redelijk wat ☐ Vrij veel	☐ Helemaal niet ☐ Een beetje ☐ Redelijk wat ☐ Vrij veel	☐ Helemaal niet ☐ Een beetje ☐ Redelijk wat ☐ Vrij veel
6. emotionele gezondheid (nervositeit, depressie, etc.)?	☐ Helemaal niet ☐ Een beetje ☐ Redelijk wat ☐ Vrij veel	☐ Helemaal niet ☐ Een beetje ☐ Redelijk wat ☐ Vrij veel	☐ Helemaal niet ☐ Een beetje ☐ Redelijk wat ☐ Vrij veel
7. gevoel van frustratie?	☐ Helemaal niet ☐ Een beetje ☐ Redelijk wat ☐ Vrij veel	☐ Helemaal niet ☐ Een beetje ☐ Redelijk wat ☐ Vrij veel	☐ Helemaal niet ☐ Een beetje ☐ Redelijk wat ☐ Vrij veel

Einde van vragenlijst PFIQ-7

Utomo et al. Int Urogynecol J. 2014 Apr;25(4):531-44.

FIQL: Ontlasting (fecale) Incontinentie Kwaliteit van Leven Schaal

1. Hoe zou u over het algemeen uw gezondheid noemen:
(kruis één vakje aan)

Uitstekend	Zeer goed	Goed	Matig	Slecht
☐	☐	☐	☐	☐

De volgende uitspraken gaan over ongewild ontlastingverlies.
Wilt u voor elk van onderstaande uitspraken aangeven, hoe vaak dit een probleem voor u is?
Als één van onderstaande uitspraken een probleem voor u is vanwege een andere reden dan ongewenst ontlastingverlies, kruis dan het hokje "niet van toepassing" (n.v.t.) aan.

2. Als gevolg van ongewenst ontlastingverlies:

(Kruis één vakje per regel aan)	Meestal	Soms	Heel af en toe	Nooit	n.v.t.
a. Ben ik bang om uit te gaan.	☐	☐	☐	☐	☐
b. Vermijd ik bezoek aan vrienden.	☐	☐	☐	☐	☐
c. Vermijd ik een nacht ergens anders te slapen dan thuis.	☐	☐	☐	☐	☐
d. Vind ik het lastig uit te gaan en dingen te doen, zoals naar de bioscoop of naar de kerk gaan.	☐	☐	☐	☐	☐
e. Eet ik minder voordat ik uitga.	☐	☐	☐	☐	☐
f. Probeer ik zoveel mogelijk in de buurt van een toilet te blijven als ik van huis ben.	☐	☐	☐	☐	☐
g. Is het belangrijk dat ik mijn dagelijkse activiteiten afstem op mijn ontlastingpatroon.	☐	☐	☐	☐	☐
h. Vermijd ik reizen.	☐	☐	☐	☐	☐
i. Maak ik mij zorgen dat ik niet op tijd het toilet haal.	☐	☐	☐	☐	☐
j. Heb ik het gevoel geen controle over mijn darmen te hebben.	☐	☐	☐	☐	☐
k. Kan ik mijn ontlasting niet lang genoeg ophouden voordat ik bij het toilet ben.	☐	☐	☐	☐	☐
l. Verlies ik ontlasting zonder dat ik dit merk.	☐	☐	☐	☐	☐
m. Probeer ik ongelukjes te voorkomen door in de buurt te blijven van een toilet.	☐	☐	☐	☐	☐

De FIQL vragenlijst gaat verder op de achterzijde

't Hoen et al. Neurourol Urodyn. 2017 Mar; 36(3):710-715

De volgende uitspraken gaan over ongewild ontlastingverlies.
Wilt u voor elk van onderstaande uitspraken aangeven in hoeverre u het hiermee eens of oneens bent?
Als één van onderstaande uitspraken een probleem voor u is vanwege een andere reden dan ongewenst ontlastingverlies, kruis dan het hokje "niet van toepassing" (n.v.t.) aan.

3. Als gevolg van ongewenst ontlastingverlies:

(Kruis één vakje per regel aan)	Helemaal mee eens	Gedeeltelijk mee eens	Gedeeltelijk niet mee eens	Helemaal niet mee eens	n.v.t.
a. Schaam ik mij.	☐	☐	☐	☐	☐
b. Kan ik veel dingen niet doen, die ik wil doen.	☐	☐	☐	☐	☐
c. Maak ik mij zorgen om ongelukjes met ontlasting.	☐	☐	☐	☐	☐
d. Voel ik mij somber.	☐	☐	☐	☐	☐
e. Maak ik mij zorgen dat anderen mij naar ontlasting vinden ruiken.	☐	☐	☐	☐	☐
f. Heb ik het gevoel dat ik geen gezond persoon ben.	☐	☐	☐	☐	☐
g. Geniet ik minder van het leven.	☐	☐	☐	☐	☐
h. Heb ik minder vaak seks dan ik zou willen.	☐	☐	☐	☐	☐
i. Voel ik mij anders dan andere mensen.	☐	☐	☐	☐	☐
j. Ben ik me constant bewust van de kans op ongelukjes.	☐	☐	☐	☐	☐
k. Ben ik bang om seks te hebben.	☐	☐	☐	☐	☐
l. Vermijd ik reizen met het vliegtuig of de trein.	☐	☐	☐	☐	☐
m. Vermijd ik uit eten gaan.	☐	☐	☐	☐	☐
n. Als ik naar een onbekende plek ga, zoek ik altijd eerst uit waar het toilet is.	☐	☐	☐	☐	☐

4. Heeft u zich in de afgelopen maand zo verdrietig, ontmoedigd, hopeloos gevoeld, of heeft u zoveel problemen gehad dat u zich afvroeg of het allemaal nog wel zin had?
(Kruis één vakje aan)

☐	☐	☐	☐	☐	☐
Extreem mee eens, tot het punt dat ik het bijna op wilde geven	**Heel erg mee eens**	**Nogal ja**	**Wel wat,** genoeg om me zorgen te maken	**Een klein beetje**	**Helemaal niet**

't Hoen et al. Neurourol Urodyn. 2017 Mar; 36(3):710-715

Einde van vragenlijst FIQL

FISI: index voor de mate van ontlasting (fecale) incontinentie

Wilt u voor elk van de onderstaande vormen van ongewenst ontlastingverlies aangeven hoe vaak u er gemiddeld last van had, ongeacht de hoeveelheid.

Denk aan uw klachten van de *afgelopen maand*.

(Kruis één vakje per regel aan)	2 of meer keer per dag	1 keer per dag	2 of meer keer per week	1 keer per week	1 – 3 keer per maand	nooit
Winderigheid	☐	☐	☐	☐	☐	☐
Slijm	☐	☐	☐	☐	☐	☐
Dunne ontlasting	☐	☐	☐	☐	☐	☐
Vaste ontlasting	☐	☐	☐	☐	☐	☐

Einde van vragenlijst FISI

't Hoen et al. Neurourol Urodyn. 2017 Mar; 36(3):710-715

PISQ-12: vragenlijst over bekkenbodemverzakking/ urine-incontinentie en seksueel functioneren

Hieronder vindt u een lijst met vragen over u en uw partners seksleven. Alle informatie is strikt vertrouwelijk. Uw vertrouwelijke antwoorden zullen uitsluitend worden gebruikt om artsen te helpen begrijpen wat voor patiënten belangrijk is voor hun seksleven.

Bij het beantwoorden van de vragen moet u denken aan uw seksleven in de afgelopen zes maanden.

(Kruis één vakje per regel aan)	Altijd	Gewoonlijk	Soms	Zelden	Nooit
1. Hoe vaak heeft u behoefte aan seks? Dit gevoel kan inhouden zin in seks hebben, plannen om seks te hebben, gefrustreerd voelen door gebrek aan seks, etc.	☐	☐	☐	☐	☐
2. Komt u tot een hoogtepunt (heeft u een orgasme) als u geslachtsgemeenschap heeft met uw partner?	☐	☐	☐	☐	☐
3. Voelt u zich seksueel opgewonden wanneer u seks heeft met uw partner?	☐	☐	☐	☐	☐
4. Hoe tevreden bent u over de afwisseling van seksuele activiteiten in uw huidige seksleven?	☐	☐	☐	☐	☐
5. Heeft u pijn tijdens de geslachtsgemeenschap?	☐	☐	☐	☐	☐
6. Heeft u last van urineverlies tijdens seksuele activiteit?	☐	☐	☐	☐	☐
7. Beperkt de angst voor urine- of ontlastingverlies uw seksuele activiteit?	☐	☐	☐	☐	☐
8. Vermijdt u geslachtsgemeenschap vanwege een uitstulping in de vagina (bijvoorbeeld de blaas, de endeldarm of de vagina die naar buiten komt)?	☐	☐	☐	☐	☐
9. Wanneer u seks heeft met uw partner, ervaart u dan negatieve emotionele reacties zoals angst, walging, schaamte of schuld?	☐	☐	☐	☐	☐
10. Heeft uw partner een probleem met erecties wat uw seksuele activiteit beïnvloedt?	☐	☐	☐	☐	☐
11. Heeft uw partner een probleem met voortijdig klaarkomen wat uw seksuele activiteit beïnvloedt?	☐	☐	☐	☐	☐
12. Hoe intens zijn uw orgasmen de afgelopen 6 maanden, in vergelijking met orgasmen die u in het verleden heeft gehad?	☐	☐	☐	☐	☐

Einde van vragenlijst PISQ-12

't Hoen et al. Int Urogynecol J. 2015 Sep;26(9):1293-303.

IIEF-5: Seksuele gezondheidsinventaris voor mannen

Seksuele gezondheid is een belangrijk onderdeel van het lichamelijke en geestelijk welbevinden van een individu. Erectiestoornissen zijn veel voorkomende seksuele klachten. Er zijn veel verschillende mogelijkheden om erectiestoornissen te behandelen. Deze vragenlijst is ontwikkeld om u en uw arts te helpen ontdekken of u misschien last heeft van erectiestoornissen en om eventueel behandelingsmogelijkheden te bespreken.

In de afgelopen zes maanden:

1. Hoe beoordeelt u uw vertrouwen om een erectie te krijgen en te behouden?
(Omcirkel het juiste antwoord)

Erg laag	Laag	Gemiddeld	Hoog	Erg hoog

2. Als u erecties had met seksuele stimulatie*, hoe vaak waren uw erecties hard genoeg voor penetratie?
(Omcirkel het juiste antwoord)

Geen seksuele activiteit	Bijna nooit/nooit	Een paar keer *(veel minder dan de helft van het aantal keer)*	Soms *(ongeveer de helft van het aantal keer)*	Meestal *(veel meer dan de helft van het aantal keer)*	Bijna altijd/altijd

3. Tijdens de gemeenschap, <u>hoe vaak</u> was u in staat om uw erectie te behouden nadat u bij uw partner naar binnen was gegaan (gepenetreerd)?**
(Omcirkel het juiste antwoord)

Geen gemeenschap geprobeerd	Bijna nooit/nooit	Een paar keer *(veel minder dan de helft van het aantal keer)*	Soms *(ongeveer de helft van het aantal keer)*	Meestal *(veel meer dan de helft van het aantal keer)*	Bijna altijd/altijd

4. Tijdens de gemeenschap, <u>hoe moeilijk</u> was het om uw erectie te behouden tot het volbrengen van de geslachtsdaad?**
(Omcirkel het juiste antwoord)

Geen gemeenschap geprobeerd	Heel erg moeilijk	Erg moeilijk	Moeilijk	Een beetje moeilijk	Niet moeilijk

5. Wanneer u gemeenschap had, <u>hoe vaak</u> was het bevredigend voor u?**
(Omcirkel het juiste antwoord)

Geen gemeenschap geprobeerd	Bijna nooit/nooit	Een paar keer *(veel minder dan de helft van het aantal keer)*	Soms *(ongeveer de helft van het aantal keer)*	Meestal *(veel meer dan de helft van het aantal keer)*	Bijna altijd/altijd

*) Seksuele activiteit: Hieronder verstaan we bijv. erotisch spel met een partner, erotische afbeeldingen bekijken, etc.

**) Gemeenschap: Hieronder wordt verstaan de penetratie (binnengaan) van de vagina van de partner, oftewel neuken.

Utomo et al. Andrology 2015 Nov;3(6):1154-9

Dankwoord

Met dit laatste hoofdstuk van het proefschrift is een eind gekomen aan mijn promotietraject. Een traject dat niet succesvol afgesloten had kunnen worden zonder de bijdrage en steun van vele betrokkenen. Een aantal mensen wil ik hierbij in het bijzonder bedanken.

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About the Author

List of publications

Elaine Utomo was born in Rotterdam on October 1st 1984. After graduating from her high school Comenius College in Capelle aan den IJssel in 2002 (*vwo diploma*), she started studying Dentistry at the University of Amsterdam (ACTA). After one year, in 2003, she chose to study Medicine in Rotterdam instead, of which she obtained her medical degree *cum laude* at the Erasmus University in Rotterdam in 2010. She subsequently started as a PhD student working on her thesis at the department of Urology under the supervision of Prof.dr. C.H. Bangma, dr. B.F.M. Blok and dr. I.J. Korfage at the Erasmus MC in Rotterdam. In 2013 she combined her research with her primary-care residency training at Erasmus MC. In January 2017 she obtained her license and is currently working as a general physician. She lives with her husband Adriaan van der Meer in Berkel en Rodenrijs.

Elaine Utomo werd in Rotterdam geboren op 1 oktober 1984. Na het behalen van haar vwo-diploma aan het Comenius College te Capelle aan den IJssel in 2002, startte ze met de studie tandheelkunde aan de Universiteit van Amsterdam, ACTA. Na één jaar, in 2003, koos zij ervoor om te gaan beginnen aan de opleiding geneeskunde aan de Erasmus Universiteit Rotterdam. Zij behaalde daar haar artsendiploma *cum laude* in 2010. Aansluitend begon zij te werken als arts-onderzoeker aan haar promotieonderzoek op de afdeling urologie onder supervisie van Prof.dr. C.H. Bangma, dr. B.F.M. Blok en dr. I.J. Korfage aan het Erasmus MC in Rotterdam. In 2013 combineerde zij haar onderzoekswerkzaamheden met de huisartsenopleiding in het Erasmus MC. Zij behaalde haar huisartsendiploma in januari 2017 en werkt sindsdien als huisarts. Ze woont samen met haar echtgenoot Adriaan van der Meer in Berkel en Rodenrijs.

LIST OF PUBLICATIONS

Boxmeer JC, Smit M, Utomo E, Romijn JC, Eijkemans MJ, Lindemans J, Laven JS, Macklon NS, Steegers EA, Steegers-Theunissen RP. Low folate in seminal plasma is associated with increased sperm DNA damage. Fertil Steril. 2009 Aug;92(2):548-56.

Utomo E, Groen J, Vroom IH, van Mastrigt R, Blok BF. Urodynamic effects of volume-adjustable balloons for treatment of postprostatectomy urinary incontinence. Urology. 2013 Jun;81(6):1308-14.

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Utomo E, Blok BF, Pastoor H, Bangma CH, Korfage IJ. The measurement properties of the five-item International Index of Erectile Function (IIEF-5): a Dutch validation study. Andrology. 2015 Nov;3(6):1154-9.

't Hoen LA, Utomo E, Schouten WR, Blok BF, Korfage IJ. The fecal incontinence quality of life scale (FIQL) and fecal incontinence severity index (FISI): Validation of the Dutch versions. Neurourol Urodyn. 2017 Mar;36(3):710-15.

PhD Portfolio

Summary of PhD training and teaching

Name PhD student: Elaine Utomo	**PhD period:** February 2010 – December 2017
Erasmus MC Department: Urology	**Promotor:** prof. dr. C.H. Bangma
	Supervisors: dr. B.F.M. Blok, dr. I.J. Korfage

1. PhD training

	Year	Workload (ECTS)
General courses		
- BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	May 2010	1.0 ECTS
- Classical Methods for Data-analysis	Sept 2010	5.7 ECTS
- 2 day course Dutch Cochrane Center Development of Systematic Review	March 2011 Nov 2011	0.5 ECTS 0.5 ECTS
- Biomedical English Writing and Communication	March 2012	4.0 ECTS
- One day workshop on Indesign CS5	Dec 2012	0.15 ECTS
Seminars and workshops		
- Department Journal Club	2010 – 2013	2.0 ECTS
- Department "refereeravond"	2010 – 2013	2.0 ECTS
- Department "promovendi-avond"	2010 – 2013	2.0 ECTS
- Department Campbell Club	2010 – 2011	1.0 ECTS
- Department "heilig onderwijsuur"	2011 – 2012	1.0 ECTS
Presentations		
- Speaker podium presentation: Invasive versus non-invasive evaluation of successful Pro-ACT treatment in post radical prostatectomy stress urinary incontinence 41st annual meeting of the International Continence Society (ICS), Glasgow UK, 2011	Sept 2011	2.0 ECTS
- Speaker poster presentation: Evaluation of ProACT treatment in male stress urinary incontinence after radical prostatectomy: invasive and non-invasive urodynamics 27th Annual European Association of Urology Congress (EAU), Paris, France, 2012	Feb 2012	2.0 ECTS
National conferences		
- Voorjaarsvergadering Nederlandse Vereniging voor Urologie Speaker: Invasieve en niet-invasieve urodynamica van ProACT behandeling bij stress urine-incontinentie na radicale prostatectomie	May 2011	1.0 ECTS
- Externe refereeravond Erasmus MC Speaker: Evaluatie van ProACT behandeling bij mannen met stress urine incontinentie na radicale prostatectomie: invasieve en non-invasieve urodynamica	October 2011	2.0 ECTS
- Voorjaarsvergadering Nederlandse Vereniging voor Urologie peaker: Validatie van twee veelgebruikte vragenlijsten: Nederlandse Urogenital Distress Inventory (UDI-6) en Incontinence Impact Questionnaire (IIQ-7) voor mannen en vrouwen	May 2013	1.0 ECTS

International conferences		
- Attending symposium on prostate cancer – a multidisciplinary approach, Rotterdam, the Netherlands	2010	0.5 ECTS
- Attending 41st annual meeting of the International continence society (ICS), Glasgow UK, 2011	Aug-Sept 2011	1.0 ECTS
- Attending 27th annual European Association of Urology Congress (EAU), Paris, France, 2012	Feb 2012	1.0 ECTS
Other		
- Working at Urology ward	Jan- Feb 2012	2.0 ECTS
- Journal reviewer "The Patient: Patient-Centered Outcomes Research"	March 2014	0.25 ECTS

2. Teaching

	Year	**Workload (ECTS)**
Lecturing		
- Operating departement practitioner student at "Zorgacademie" Topic: "Ingrepen aan ureter, blaas en urethra"	2011	1.0 ECTS
- Medical students in minor week Gynecology Topic: Measures for quality of life in patients with pelvic floor dysfunction	2011 - 2012	1.0 ECTS
Supervising practicals and excursions, tutoring		
- PKV ("Practicum Klinische Vaardigheden") medical interns topic: Male Genital Examination	2011 – 2012	1.0 ECTS
- Supervising medical interns at Urology ward	2012	1.0 ECTS

"From where I stand,
the sun is shining all over the place."