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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