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Summary and future perspectives

This thesis covers the anatomical and pathophysiological aspects of fecal incontinence faced during clinical practice with a focus on impact of quality of life and potential future treatment strategies. FI is defined in the most recent Rome IV criteria as the uncontrolled passage of solid or liquid stool (1). Its median prevalence is about 7.3% in the general population, and ranges from 2.0 to 13.2% (2-4). It has been believed that FI affects mainly women however differences between the sexes tend to decrease with age (2, 5, 6). Continence is maintained by coordination of a functioning anal sphincter complex, intact sensation of the anorectum, rectal compliance, and the ability to consciously control defecation. Pathophysiologic mechanisms often overlap and can be categorised into; anal sphincter dysfunction, pudendal neuropathy, impaired rectal sensation and poor rectal compliance (7). The additional presence of diarrhoea can overwhelm sphincter function, impairing continence even further. In men anorectal surgery such as hemorrhoidectomy, prostatectomy or perianal fistula repair is the most common cause (8). Besides a good clinical examination with rectal palpation, additional testing with anal manometry or endoanal sonography may be indicated.

Perianal fistula

Detailed knowledge of the anatomy of the rectum, anus, and perineum is indispensable in understanding the pathogenesis and pathology of FI. In **chapter 2** we provide a review on the clinical relevance of (three-dimensional hydrogen peroxide enhanced) endoanal ultrasound in perianal fistulas and abscesses in both cryptoglandular and perianal Crohn's disease. Treatment of cryptoglandular perianal fistulas and abscesses is surgical, and efficiently eradicating perianal sepsis whilst preserving anal sphincter integrity the main goal. Preoperative imaging can provide precise fistula classification, and therefore guide treatment and help avoid missing tracks during surgery, which is considered the main reason for the tract to persist or recur (9, 10). Furthermore, high recurrence rates are seen in unclassified fistula indicating that uncertainty regarding the precise relationship of the fistula track with adjacent anatomic structures reduces the effectiveness of treatment (11).

Three-dimensional hydrogen peroxide enhanced endoanal ultrasound (3D-HPUS) and MRI can both reliably delineate anatomy in cryptoglandular and Crohn's perianal fistula and abscess (12-15). In perianal Crohn's disease the introduction of biologicals offered physicians the first treatment that could potentially result in complete cessation of perianal fistula drainage. However, during treatment healing of the external opening precedes fistula tract healing, which contributes to abscess formation and fistula recurrence after discontinuation. Besides its accuracy in the

assessment of fistulas and abscesses in Crohn's disease 3D-HPUS might identify patients who can discontinue treatment without recurrence and would therefore be an excellent technique for following these fistulae rather than using MRI each time. EAUS is relatively easy to learn and perform. However, endoanal MRI is preferred by most physicians even though costs are higher and demand can outgrow availability. Yet when fistula tracts or abscesses are thought to be located above the puborectal muscle, an MRI should be performed. Furthermore, in patients with anal fibrosis or severe anal pain endoanal imaging may be impossible.

In **Chapter 3** we report on predictive factors for recurrence of cryptoglandular fistulae characterised by preoperative 3D-HPUS. We studied 143 patients undergoing preoperative evaluation between 2002 and 2012 in our tertiary centre and in a private centre specialised in proctology. In total, 96 had a low fistula treated by fistulotomy (FT), 28 a high fistula treated by fistulectomy (FC) and closure of the internal opening, and 19 a high fistula treated by fistulectomy combined with a mucosal advancement flap (MP) after being treated with a draining seton for 3-4 months. Recurrence rates after FT were 11% after 12 months, 16% after 24 months and 16% after 36 months. After undergoing surgical FC, perianal fistula recurrence rates were 42% after 12 months, 56 % after 24 months and 59 % after 36 months. Recurrence rates after undergoing FC with adjacent mucosal advancement flap placement were 25% after 12 months, 32% after 24 months and 33% after 36 months. We analysed the retrospectively collected data for gender, type of centre (academic or private), previous fistula operation, presence of secondary fistula track(s) and fistula classification. Besides a prior surgical procedure, the strongest independent predictor for recurrence was the identification of secondary tracts in the fistula pattern during preoperative 3D-HPUS. This stresses the importance of both preoperative imaging and the thorough search for these secondary tracts during surgery.

Recurrence of perianal fistulas or abscesses is often followed by an additional surgical intervention, further increasing changes of developing FI. In **Chapter 4** we investigated what fistula characteristics and surgical procedures were associated with the presence and severity of FI during long term follow up in a group of non IBD patients in our tertiary centre, and in a private centre specialised in proctology. The majority of the 118 patients included was male (64%) and after a mean of 9.8 years follow up (SD 4.2), 40 patients experienced FI (34%). We focused on gender, age of first perianal sepsis related surgery, age during follow up in October 2013, fistula classification, the presence of multiple fistula tracts, number of perianal abscesses surgically incised and drained (0, 1, > 1), number of FT's received (0, 1, > 1) and the number of sphincter sparing procedures received (0, 1, > 1). Independent risk factors for the presence of FI were one, or > 1 surgical FT, multiple abscess drainages, and the presence of a high trans-sphincteric or

supra-sphincteric fistula tract. Management of anal fistulae by FT is a delicate balance between cure and continence, especially in slightly higher more complex fistulae (16, 17). Risk of postoperative FI is believed to be minimal, taken into account patient specific related factors such as age, parity and preoperative continence, if less than one third of the lower external anal sphincter is treated by FT (18). However unfortunately, incontinence rates after FT might be higher than we assume (19). Therefore, a shift towards performing more sphincter sparing procedures is warranted. For the future, the relatively novel ligation of the intersphincteric fistula tract procedure (LIFT) seems promising (20, 21). A major advantage seems the type of recurrence after LIFT. More complex fistulas treated by LIFT tend to return or persist as intersphincteric, original trans- or suprasphincteric, or as a residual external tract. Therefore, the minority of patients need more complex surgery to solve their pathology. They can subsequently be cured by low FT or repeated LIFT procedure (22, 23). However ambiguous results have been reported (24) and there is a paucity of data on long term outcome. Besides experiencing more severe FI (Wexner incontinence score 1.2 (SD 2.1) versus 4.5 (SD 6.2)) compared to those with simple fistula, patients with more complex fistula reported lower QOL regarding lifestyle, depression, and embarrassment. We should be aware of the fact that FI remains an under treated condition as only one-third of those affected receive medical evaluation and treatment (25, 26). Therefore, special attention should be paid to these patients in order to better mitigate symptoms in life.

Impact on quality of life

Quality of life in patients with FI is usually disadvantageously affected. Patients tend to prevent social consequences of FI by limiting their activities and remain tethered to their toilet. This may lead to social isolation, depression, and loss of employment, intimate relations or self-esteem (27) (28, 29). In **Chapter 5** we evaluated QOL, FI, sexual dysfunction, and alteration of anorectal function five years after anal sphincteroplasty for third degree obstetric anal sphincter injury (OASI) in 66 women. In women, vaginal delivery (especially forceps-assisted), median episiotomy, fetal macrosomia, and increased maternal age are the most important risk factors for FI (30, 31). In the majority of women FI resolves within the first 12 months after delivery. However, some women will (again) develop complaints later in life attributed to OASI, aging, sphincter atrophy, or subsequent deliveries with concomitant damage. It seems logical to assume that more extensive tearing of the anal sphincters relates to more severe FI. However, the association between FI and the degree of OASI are not conclusive (32). In First and second degree OASI the perianal skin, respectively perianal muscles are torn, the anal sphincters however remain intact. Third degree OASI is stratified into partial rupture of the EAS <50% (grade 3a), total rupture of the EAS >50% (grade 3b), or combined EAS and IAS rupture (3c). In a fourth degree OASI; EAS, IAS and anal epithelium are torn. In our study 26 had grade 3a, 24 had grade 3b and 16 women had grade 3c OASI. Follow up after

OASI suggests poor anorectal function. We found overall FI prevalence rates of 20%, 50% and 63% for solid stool, liquid stool and flatus, respectively. Fortunately, over 50% of experienced FI was seldom present (less than once per month). However, women with a grade 3a OASI without FI two months after anal sphincteroplasty were excluded from the study, therefore overall FI might be overestimated. We found that sexual dysfunction including arousal, orgasm, satisfaction or pain was present in 59% of women. Dysfunction was more prominent in women with larger OASI. We found a clear trend suggesting that women with larger OASI experience lower QOL. This was most pronounced in experienced role limitations due to emotional problems, ($p = 0.062$) underlining the social stress and invalidating character of FI as a complaint.

The prevalence of FI in patients with Crohn's disease (CD) has barely been studied. During exacerbations prevalence might be higher than during remission, presumably because liquid stool is more difficult to control than solid stool. Little is known about factors predicting FI or FI-related QOL in patients with inflammatory bowel disease (IBD). Ileo-anal pouch surgery may induce mild daytime or night-time FI, and has been reported to occur in more than 17% of patients (33). The association between previous performed perianal fistula surgery and FI verifies that sphincter injury may play a major role in the development of FI in CD patients (34). The association of FI with anal fissures underlined prior data (35). Fissures that are resistant to conservative treatment may require surgery such as lateral internal sphincterotomy, which in itself may induce FI, particularly in women (36). These findings imply that patients with perianal disease are exposed to a high risk of FI, which may help clinicians to detect patients with FI and set a goal to diagnose and treat the underlying cause to improve patients QOL. Anorectal function investigations (endoanal ultrasound and anorectal manometry) can be used to detect the underlying cause of FI and can give more information on functional and anatomical abnormalities. In a multivariate analysis older age, female gender, ileo-anal pouch surgery, other IBD-related bowel surgery, anal fistula surgery, anal stretch, anal fissure and urinary continence were all associated with FI (35). In **chapter 6** we assessed the prevalence of FI in a tertiary population with Crohn's disease and set out to validate its risk factors. In this retrospective and cross-sectional study a questionnaire was sent out to 528 patients with CD to evaluate perianal disease, FI and its impact on QOL. Median age was 42 years (range 18-91), 215 (66% of the 325 respondents) were female and diagnosis of CD was established for a median period of 12 years (interquartile range 6-21). Sixty-five patients (20%) of all responders reported FI for liquid or solid stools, at least once in the past 4 weeks. However, 29 patients reported incontinence for flatus only, increasing the prevalence of incontinence of any type of stool to 29%. FI was associated with liquid stools ($p = 0.001$), previous IBD-related bowel resections ($p = 0.001$), stricturing behavior of disease ($p = 0.020$) and perianal disease ($p = 0.030$). Quality of life (lifestyle, coping, depression, embarrassment) was poor in patients with fecal

incontinence, particularly in patients with more frequent episodes of FI. In our multivariate model there was a strong association of liquid stools with FI. Liquid stools occur frequently during exacerbations. It should be noted that we did not correct for disease activity in the multivariate regression analysis, since no recent standardized assessment of disease activity including endoscopy was available in all patients. Occurrence of liquid stools was highly correlated to previously performed bowel resections (particularly ileocecal resections with or without additional small bowel resections), presuming that besides disease activity, impaired (inadequate or incomplete) fluid absorption and bile acid malabsorption might contribute to the origin of liquid stools (37). Identification of presence and subsequent treatment of liquid stools associated with bowel resections can be a simple way to improve the FI and QOL. It should be noted that only a minority of the IBD patients appear to seek help for FI (38). Major reasons for not seeking help are embarrassment, anxiety for invasive tests or surgery. Furthermore the lack of awareness regarding where and how to ask for help, or the services available for them. Concerning these data, and the fact that the prevalence of FI in CD patients is high if compared to the percentages reported in the community-dwelling population, increase of awareness of this embarrassing complaint seems to be pivotal. Therefore, considering the reduced QOL in incontinent patients with CD, active questioning to identify FI is recommended, especially in those with liquid stools, perianal disease or previous (intestinal or perianal) surgery.

Future treatment strategies

Conservative treatment is the first step in patients with FI. It includes dietary adaptations, medication use, stool bulking agents, physiotherapy and different modalities of biofeedback. Patients with decreased rectal capacity often benefit by reducing dietary fibre intake combined with the use of anti-diarrhoea drugs. This decreases the amount of stool to better accommodate reduced rectal capacity. Patients with normal storage capacity may benefit from fibre supplements such as psyllium, with or without anti-diarrheal agents (39). When FI is caused by chronic diarrhea, treatment is directed towards the possible underlying case (bile acid malabsorption, IBD, IBS or overflow incontinence) or otherwise aimed at thickening the stool. Next in line or combined with the use of bulking agents or anti-diarrhoea drugs are behavioral interventions. Depending on the definition of success, patient characteristics and modality used, physiotherapy and biofeedback are deemed effective in up to 78% of patients (40, 41). In addition, rectal cleansing can be added which has shown moderate results varying from 40-45 % (42). When conservative management fails or is insufficient, more invasive treatment options such as sacral neurostimulation (SNS), with success rates of 60 to 89%, can be considered (43, 44). Another minimally invasive potential treatment option is the controlled delivery of radio frequent energy into the anorectum, also known as the Secca procedure. The Secca procedure is an ambulatory procedure and has been suggested

as a treatment option for FI. Up to date an estimated 6000 procedures have been performed in the US, UK, Italy, France, The Netherlands, Germany, Turkey and the Middle East. The supposed mechanism of action of Secca is tightening the anal canal by inducing collagen deposition and subsequent scarring. This remodeling of the anal canal is alleged to increase one's ability to recognize and retain stool, improving continence. According to the American Society of Colon and Rectal surgeons clinical practice guidelines for the treatment of FI 2015, the application of temperature-controlled radiofrequency energy to the sphincter complex may be used to treat FI (45). In **chapter 7** we report the results of the first randomised sham controlled clinical trial investigating this modality. 40 patients with FI in which maximal conservative management had failed were randomised to receiving either Secca or sham procedure. Mean age was 62 years (SD 9) and complaints were present for a mean 9 years. At baseline, VS was 16.8 (SD 2.9). At t = 6 months both groups reported a significantly lower Vaizey incontinence score. However, the Secca group improved 2,4 VS points more than the Sham group, (13.2 (SD 3.1) versus 15.6 (SD 3.3), $p = 0.02$). FIQL at t = 6 months was not statistically different and anorectal function did not show any alteration. The procedure was well tolerated and there were no serious adverse events. Patients who randomized into the sham group were offered true Secca procedure at t= 6 months. In **chapter 8** we provide the clinical response and sustainability of the Secca procedure with up to 3 years follow-up. In total 31 patients were included. A clinically significant response to Secca was defined as $\geq 50\%$ reduction in VS. Data was obtained at baseline, 6 months, 1 year and 3 years. During follow-up, 5/31 (16%), 3/31 (10%) and 2/31 (6%) of patients maintained a clinically significant response while reporting the following Vaizey incontinence scores, 18 (SD 3), 14 (SD 4), 14 (SD 4), 15 (SD 4). No predictive factors for success were found. So even though the Secca procedure is minimally invasive, safe, inexpensive, easy to perform and to learn, the improvement of FI and QOL are poor or non-existent. Compared to other less invasive and properly studied alternatives such as sacral nerve stimulation improvement of FI after Secca procedure seems trivial. We therefore believe that, although Secca procedure shows a minimal improvement in FI score compared to placebo, its clinical relevance is negligible. Therefore, the Secca procedure should not have a place in the current treatment algorithm of FI. However, what do we offer those who refuse or are ineligible for an invasive or experimental treatment? Teaching and motivating patients to cope with their health problem and inspiring them not to give up on conservative management is important. However there is a paucity of data on the effect of repetitive conservative management when it has previously been deemed unsatisfactory. Therefore, in **chapter 9** we evaluated the effect of nurse and pelvic floor physiotherapist led bowel training sessions in a challenging tertiary group of patients with, and without a medical history of combined conservative treatment. Combined conservative treatment was defined as the use stool-bulking agents (psyllium fibers) with or without antidiarrheal medication (loperamide) in combination with biofeedback or pelvic floor muscle training. In this prospective study we assessed Vaizey incontinence score and QOL in 50 patients

after repetitive nurse and physiotherapist led bowel training sessions. Mean time period between the first and the last consultation session was 4.9 months, 95% CI (3.1 – 7.2). A decrease in VS of ≥ 5 points was, in concordance with other Dutch studies, deemed to be clinically significant and achieved in 42% of patients. In the 21 with previous combined conservative treatment mean VS decreased from 16.1 (SD 4.7) to 10.9 (SD 3.8), $p < 0.001$. In those (29/50) without, VS declined from 13.9 (SD 3.1) to 9.2 (SD 3.3), $p < 0.001$. These satisfactory results were present in 39/48 (81%) during long term follow up. Every consecutive treatment aimed to improve functionality of the continence maintaining mechanisms could have an additive affect. However, in our study there was no difference in improvement between those with, or those without previous combined conservative treatment. This might be explained by the inadequacy of previous treatment sessions or the lack of focus and commitment at the patients end. We believe that personal contact by motivated healthcare workers is pivotal for the effect of conservative management, especially in tertiary patients with a lot of comorbidity. In our study this approach resulted in an improved QOL regarding; role limitations due to physical problems, social functioning, mental health and role limitations due to emotional problems. Therefore, nurse and physiotherapist led bowel training sessions could be considered in patients with FI who refuse or are ineligible for minimally invasive surgical procedures such as SNS. Even though previous conservative management was considered unsuccessful, another effort may still be worthwhile.

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