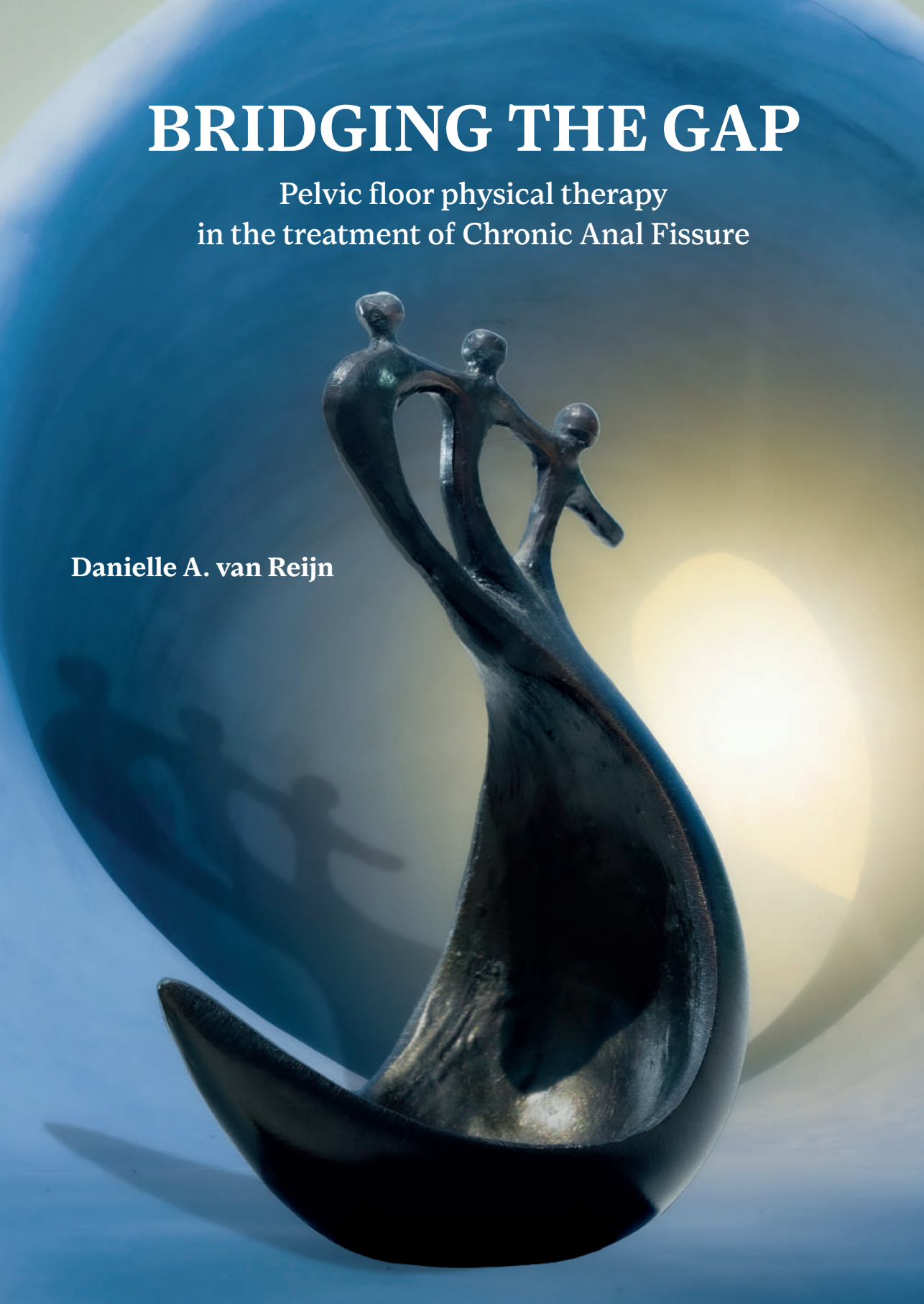
BRIDGING THE GAP

Pelvic floor physical therapy in the treatment of Chronic Anal Fissure



Danielle A. van Reijn

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Thesis, Leiden University

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Voor mijn geliefden,
Steven, Josephine, Emma, Pepijn, Olivier en Sebastiaan
Mijn ouders Aad† en Toos

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Outline of the thesis

This thesis is divided in four parts.

In **part I, chapter 1,** the general introduction**,** we described the definition, symptoms, epidemiology, and pathophysiology of chronic anal fissure including an overview of relevant anatomy of the anorectum and pelvic floor musculature.

We further outlined the current diagnostics, the relevant relationship between chronic anal fissure and pelvic floor dysfunction, and management of chronic anal fissure.

Chapter 2 presents the results of a national survey on management of chronic anal fissure among gastrointestinal surgeons in the Netherlands. **Chapter 3** reveals the results of a systematic review on the treatment efficacy of pelvic floor physical therapy for increased pelvic floor muscle tone. **Chapter 4** outlines the results of a study comparing digital rectal examination, anal electromyography, 3-dimensional high-resolution anal manometry and transperineal ultrasound.

Part II, consist of four chapters focussing on the efficacy of treatment of pelvic floor physical therapy in patients with chronic anal fissure and pelvic floor dysfunction.

In **Chapter 5** we described the study protocol of a randomized controlled trial, the Pelvic floor Anal Fissure (PAF)-study. **Chapter 6** presents the results of the PAF-study from pre-to posttreatment at 8-and 20-week follow-up and the response from a letter to the editor to our manuscript. The results from the PAF-study on quality of life are presented in **chapter 7. Chapter 8** outlines the results of the PAF-study at 1-year follow-up.

Part III, **chapter 9** contains the summary and implications of this thesis on future practice. In **Chapter 10,** the summaries of the studies are reported in Dutch.

PART I

CHAPTER 1

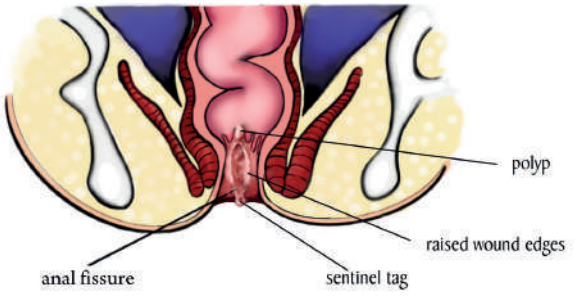
General introduction

General introduction

Chronic anal fissure (CAF) is a debilitating, painful anorectal condition associated with reduced quality of life.[1,2] Searching for medical care is often deferred due to embarrassment.[3] Prolonged persistence of symptoms and high recurrence rates indicate that present treatment modalities are not always sufficient. At present, there is a gap in treatment modalities between conservative management and surgery.
This general introduction gains more knowledge on CAF, the relevant relationship between CAF and pelvic floor dysfunction, the current diagnostics and (conservative) management in patients with CAF.

Definition, epidemiology, symptoms, anatomy, and pathophysiology

Chronic anal fissure (CAF) is defined as a longitudinal tear in the anoderm with one or more signs of chronicity including hypertrophied anal papilla, sentinel pile and exposed internal sphincter muscle with symptoms present for longer than 4-6 weeks or recurrent fissures.[4,5]
The earliest known description dates from 1934 by Lockhart-Mummery.[6]
The classical symptom is pain during and immediately after defecation, caused by an injury of the multilayer squamous epithelium of the anoderm, which is richly innervated with pain fibers through the inferior rectal nerve. The pain can persist for hours and is often accompanied by bleeding.[7,8]
The majority of the fissures (80-90%) is located in the posterior midline. Approximately 10% of the fissures are affected in the anterior midline, mostly in female patients.[9] It is theorized that the predisposition for the posterior midline has to do with the fact that specifically this area is poorly perfused.[10] Fissures located off the midline position are considered atypical fissures and are more often associated with human immunodeficiency virus, syphilis, tuberculosis, herpes, leukaemia, Crohn's disease, ulcerative colitis, and anal cancer.[5]

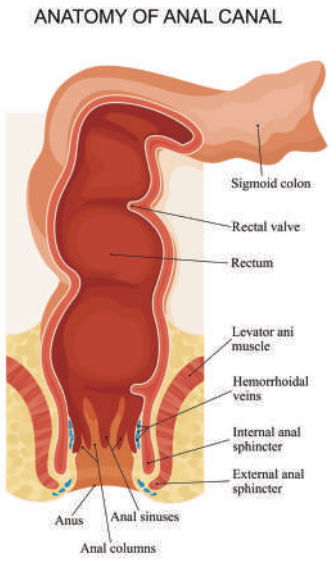


CAF is one of the most common proctological problems. In a study by Mapel,[11] in patients in the United States, the overall annual incidence was 0.11% (1.1 cases per 1000 persons). In the Netherlands, the incidence is 0.25% (2.5 cases per 1000 persons), with the highest incidence (4.3 per 1000) in women between 25-44 years.[12]

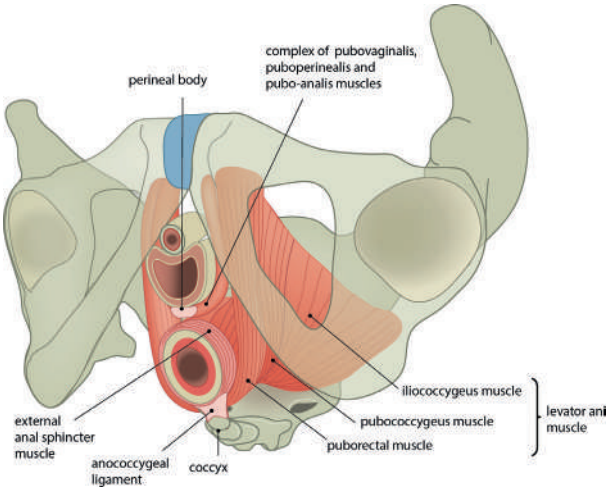
Anatomy of the anorectum

The rectum comprises the most distal end of the gastrointestinal tract. It is a hollow tube, 12 to 15 cm long, composed of a layer of longitudinal muscle woven with the underlying circular muscle.[13] The anal canal is defined as the beginning of the dentate line and ending of the anal verge, forming a transitional zone between the epithelium and perianal skin.[14] The length of the anal canal is approximately 4 cm.[15] At the dentate line, the columns of Morgagni begin with anal crypts at the base. The inner layer of the anal canal is composed of the internal anal sphincter (IAS), the outer layer of the anal canal consists of the external anal sphincter (EAS) and puborectalis muscle. In between these layers there is a fat containing intersphincteric space with the conjoined longitudinal muscle.[16] The IAS ends about 1 cm proximal to the distal edge of the EAS and is a smooth muscle sphincter, innervated by the sympathic fibers from the inferior pelvic plexus and the parasympathic nerve fibers (S2-S4).[16]

The IAS is the main contributor to the anal resting pressure and contributes up to 80% of the anal resting pressure (50-70mmHg). Other contributors to anal resting pressure include the anal mucosal folds, the anal vascular cushions, the EAS and puborectalis muscle.[17]

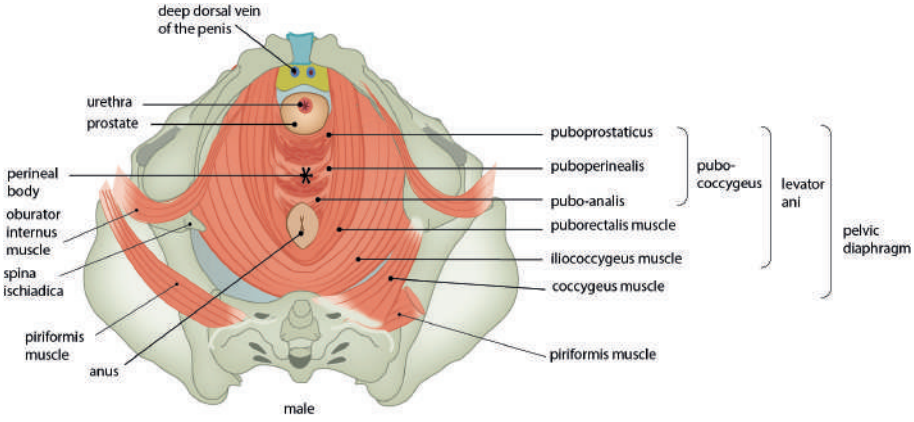


Another study by Penninckx et al.[18] found that the estimated anal resting tone was generated by the nerve-induced activity in the IAS for 45%, myogenic tone for 10%, tonic activity of the EAS (30%) and anal haemorrhoidal plexus for 15%.
The perineal body lies between the upper end of the anterior anal canal and the posterior wall of the urethral membrane. It serves as an intersection of the EAS, the bulbospongiosus muscle, the external urethral sphincter, and the levator ani muscle. The pelvic floor is a multifunctional complex of muscle fibers, fascia, ligaments, and connective tissue that form a hammock at the bottom of the abdomino-pelvic cavity.



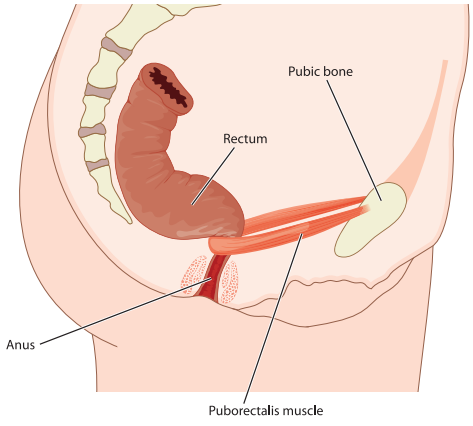
"Left inferior view of levator ani and external anal sphincter muscles -English labels" at AnatomyTOOL.org by Ron Slagter, LUMC and Marco DeRuiter, LUMC, license: Creative Commons Attribution-NonCommercial-ShareAlike

The muscles of the pelvic floor consist of superficial muscles including the m. bulbospongiosus, m. ischiocavernosus, the perineal muscles and EAS.
The deep pelvic floor muscles are the levator ani muscles composed of the puborectalis, pubococcygeus and iliococcygeus. These muscles are attached to the pubic bone, the ischial spine, and the arcus tendinous, a condensation of the obturator fascia in between these areas.[17]
The puborectalis muscle arises from the symphysis pubis and forms a loop around the recto-anal flexure.[19] The puborectalis muscle acts together with the external anal and urethral sphincters to close the urinary and anal openings and contracts the sphincters rapidly in response to an increase of intra-abdominal pressure to prevent incontinence.[16]



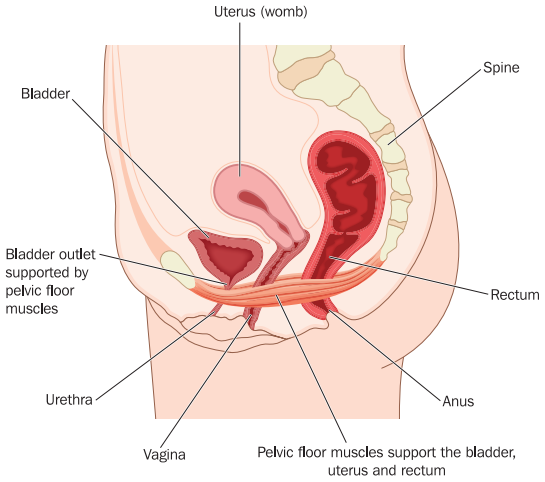
"Slagter - Drawing Inferior view of the male pelvic diaphragm 2 - English labels" at AnatomyTOOL.org by Ron Slagter, LUMC and Marco DeRuiter, LUMC, license: Creative Commons Attribution-NonCommercial-ShareAlike

At rest, the pelvic floor muscles remain in a state of continuous contraction (postural reflex) and the contractile traction of the puborectalis maintains the anorectal angle at approximately 90^0.[20] This function creates a mechanical barrier for the flow of stool and maintenance of continence.[21] Contraction of the puborectalis muscle displaces the anorectum anteriorly and changes the anorectal angle.

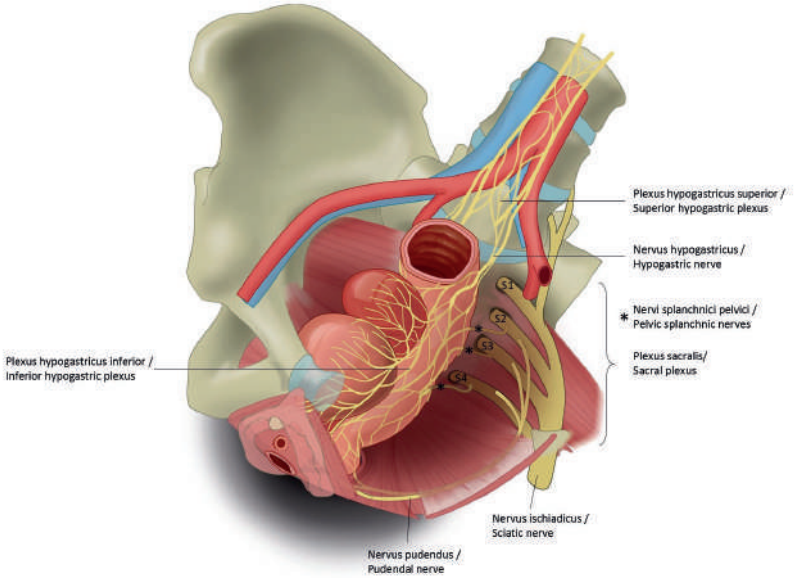


The functions of the pelvic floor include anatomic support for the pelvic and abdominal organs, storage and voiding and the pelvic floor plays an important role in sexual function.[22-25]

The levator ani together with the diaphragm, the deepest abdominal muscle, the transversus abdominus, generates and controls intra-abdominal pressure and contributes to lumbar spine stiffness.[26,27]



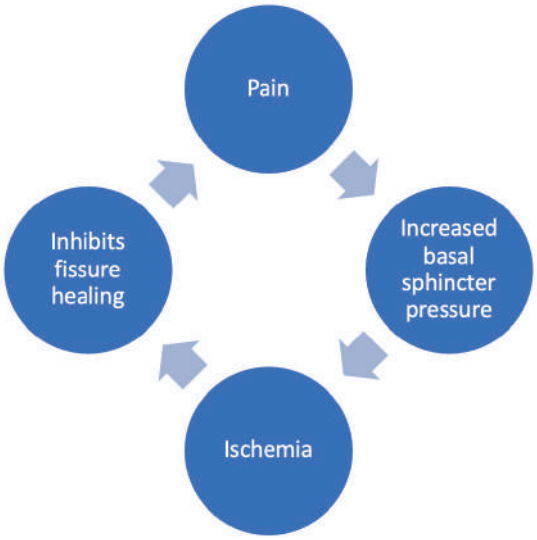
The pelvic floor is innervated by the branches of the sacral plexus S2, S3 and S4.[19]



"Anterior view of female pelvis; internal organs and innervation - Latin and English labels" at AnatomyTOOL.org by Ron Slagter, LUMC, Marco DeRuiter, LUMC and O. Paul Gobée, LUMC, license: Creative Commons Attribution-NonCommercial-ShareAlike

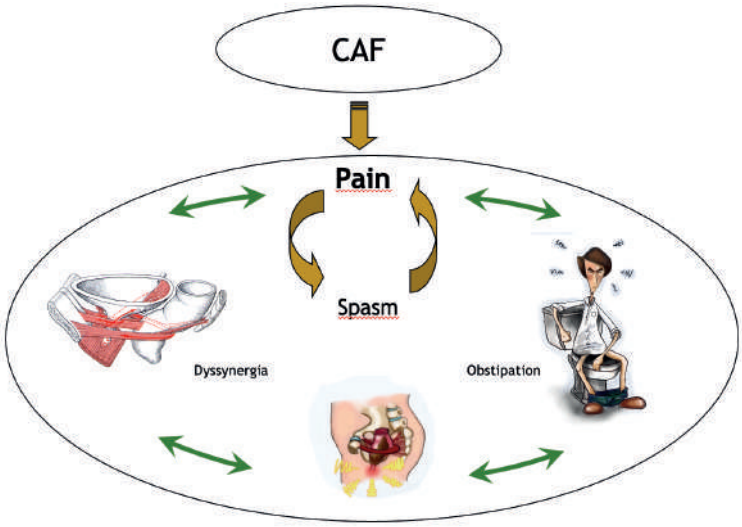
Pathophysiology

Although the etiology of CAF is uncertain, it is assumed that pain causes an increased sphincter pressure leading to diminished anodermal blood flow and local ischemia.[9,10] Besides that, passing of hard stools or sudden evacuation of liquid stool can lead to mucosal damage, resulting in an overreaction of the external anal sphincter (EAS) continence reflex and an increase of basal resting pressure.[28] This could lead to spasm which prevents CAF from healing.[28,29]



It is also theorized that insufficient stretchability of the anal sphincters leads to mucosal tears during defecation and this mucosa releases vasoconstrictors which arrests the healing process.[30]

Another hypothesis is that pelvic floor dysfunction may be part of the pathophysiology. In a retrospective study among 179 patients diagnosed with CAF, it was found that a large percentage of the patients had pelvic floor complaints such as obstructive defecation, sexual complaints, and pelvic floor dysfunction.[31] Chronic constipation is also a predisposing factor.[32]



Pelvic floor (dys)function and defecation

Defecation is the term given for the act or process of expelling feces from the digestive tract via the anus.[33] The integrity of the defecation and continence mechanism is a multifactorial process that involves somatic and visceral functions.[34]

Normal defecation requires anorectal synchronisation, an intact rectal sensation and perception, a contraction of the abdominal muscles and relaxation of the EAS and puborectalis muscle.[20] During defecation, the voluntary effort of bearing down increases the intra-abdominal pressure, together with contraction of the rectum and the perineal muscles. To evacuate stool, the anal sphincters relax and the puborectalis muscle relaxes for straightening the anorectal angle.[20] When the EAS and puborectalis muscle do not relax or even contract during attempted defecation this could result in an increase in the anorectal angle and hence prohibits the normal passage of stool.[35] Preston,[36] was the first describing the association of paradoxal anal contraction during attempted defecation and called the term ‘anismus’. The Rome-criteria advocated the term dyssynergic defecation.[37] Dyssynergic defecation or dyssynergia is an acquired behavioral disorder and can be characterized by inadequate anal relaxation, paradoxical anal contraction, or inadequate rectal propulsive forces.[38] Patients experience complaints of excessive straining, a feeling of incomplete evacuation, abdominal pain, abdominal discomfort, and anorectal pain.[39,40] According to the ROME IV criteria, dyssynergia is established by 2 out of 3 anorectal function tests:

first; abnormal anorectal evacuation pattern with manometry or electromyography, second; abnormal balloon expulsion test and third; impaired rectal evacuation by imaging (e.g. defecography).[40]

Anorectal pain could also result in increased tone (non-neurogenic hypertonicity) of the pelvic floor muscles, and this is typically associated with symptoms of post-defecatory pain which can last for hours.[41,42] Levator ani syndrome is associated with tenderness to palpation on the levator ani muscle and increased anal resting pressures and there is an overlap between increased pelvic floor muscle tone and dyssynergia.[37,40] This chronic anal pain resulting from tension or spasms in the levator muscles leads to compression of nerve endings and pain via peripheral sensitization.[43] Myofascial pain is expressed in dysfunction in the muscle and surrounding connective tissues [44] and in the levator ani syndrome, the pain can radiate into the vagina, gluteal area or the thighs.[43]

Dyssynergia and/or increased tone of the pelvic floor may probably lead to a vicious circle of pain and be an underlying cause of delayed healing in patients with CAF.[45]

Impact on quality of life

CAF is associated with reduced quality of life and can be influenced by physical, psychological, and social factors.[1] Continuing complaints may lead to functional and psychosocial impairment.[2] Patients with CAF show a high comorbidity of psychopathology, depression, and anxiety disorders with stress acting as a trigger and/or exacerbating factor.[1] Symptomatic improvement with successful nonsurgical treatment, beneficially affects health-related quality of life.[2]

Diagnostics

The diagnosis of CAF is based on medical history taking and a thorough physical exam should be performed to rule out other pathology. Before performing a digital rectal examination, it is important to explain the procedure to the patient and why, to diminish any fears and anxiety. Patients should be reassured that the digital examination will only last for a couple of minutes.[46]

During the assessment the patient lies on his/her left lateral position with the knees flexed at 90^0. The examiner uses non-allergic gloves lubricated with water-based gel or vaseline.

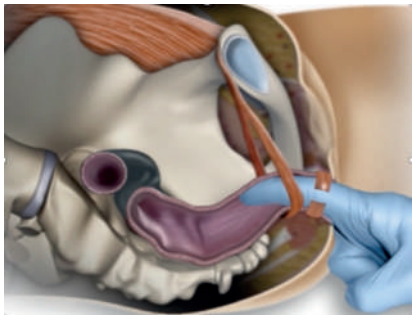
First, the anus and surrounding tissue is carefully inspected for skin excoriation, condyloma, skin tags, scars or external hemorrhoids, gaping anus, prolapsed hemorrhoids, or prolapse of the rectum and anal fissure.

Chronic anal fissure could present as a wide and deep ulcer, sometimes with visible sphincter fibers, the presence of a sentinel polyp, keratinous edges, and hypertrophied anal papillae.[47] The perineal sensation and anocutaneous reflexes are assessed by stroking the perianal skin in all four quadrants around the anus with a cotton bud. A normal response consists of a brisk contraction of the perianal skin, the anoderm, and the EAS. The anocutaneous reflex examines the integrity between the sensory nerves, S_2, S_3, S_4 neurons and motor innervation of the anal sphincter.[46]

A careful internal digital rectal examination combined with a vaginal examination is an another essential component of clinical investigation, to inquisite anal sphincter pressure, pelvic floor muscle tone- and function and dyssynergia.[48-50] However, it should be mentioned that during medical school there is a lack of emphasis on the use of digital rectal examination and it is inadequately used, nor performed in clinical practice in patients with functional anorectal complaints.[50] Besides that, the use of digital rectal examination is often delayed because of the assumption that it is contradicted or should be kept to a minimum because of associated pain.

Starting digital rectal examination, the gloved finger should be placed in the center of the anus with the finger parallel to the skin of the perineum in the midline. It is important to wait for several seconds for the IAS to relax. Then slowly advance the lubricated finger into the anus. The resting pressure is predominantly attributed to the IAS. The sphincter pressure can be assessed in rest and scored as low, normal, or high. Any presence of tenderness, mass, stricture, stool, and its consistency should be noticed. The pelvic floor muscle tone is assessed (resistance provided by a muscle when a pressure/deformation or a stretch is applied to it) on the levator ani muscle on both the right and left sides of the rectum and scored as decreased, normal or increased.[48,49,51] Tenderness to palpation with traction on the puborectalis muscle is an important feature of levator ani syndrome.[8,42] Tenderness can be scored according to each patients' reactions: 0, no pain; 1, painful discomfort; 2, intense pain; with a maximum total score of 12.[52]

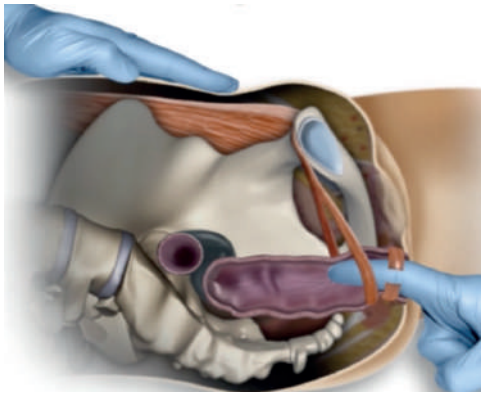
To investigate the function of the pelvic floor muscles, the patient is asked to squeeze the pelvic floor muscles as hard as possible (maximum strength), to sustain the squeeze contraction (30 seconds) (endurance), or to repeat squeeze contractions (repetitions). Measurement of squeeze pressure involves the exertion of pressure, compressing the assessor's finger during digital palpation.[52]



Digital rectal examination (Rao®)

Next, the patient is asked to bear down (push). The examiner places his/her left hand on the patient's abdomen and the patient is asked to push and bear down. Repeat this maneuver once or twice to make sure the patient understands the order and complied with the request, and that the responses are consistent.[50] Push effort is scored as relaxation, indifferent or paradoxical contraction.

To clinically diagnose dyssynergia, the presence of any two of the following findings can be used: the inability to contract the abdominal muscles, inability to relax the anal sphincter and puborectalis muscle, a paradoxal contraction of the anal sphincter and puborectalis muscle, or the absence of perineal descent.[50] The sensitivity of digital rectal examination in diagnosing dyssynergia is 71% and the specificity is 76%.[53] The current Rome criteria recommends the use of additional tests for diagnosing dyssynergia.[54]



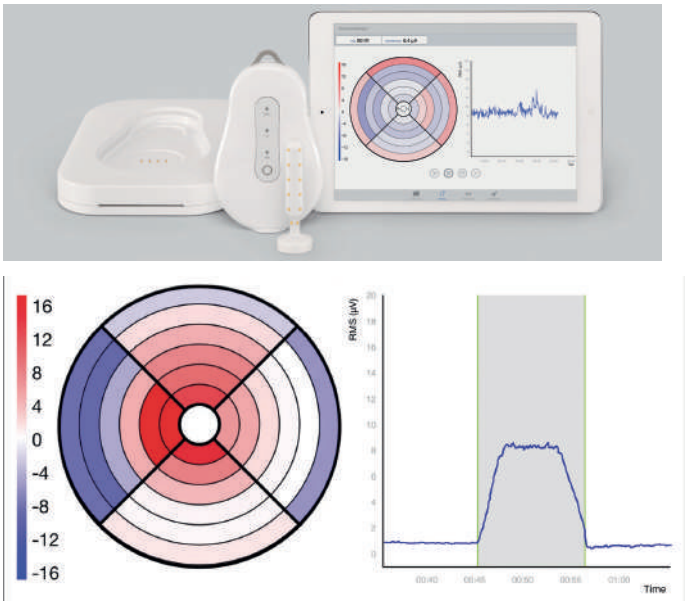
Push effort (Rao®)

When finishing the digital rectal exam, it is important to inspect the finger for obvious blood, mucus or pus and note the color of the feces. Gaping of the anal canal is suggestive of a neurological or sphincter defect.[55]

Surface electromyography (s-EMG)

Pelvic floor muscle tone and function could also be measured with surface electromyography (s-EMG) (μV),[49] with intravaginal or-anal probes.[56,57] s-EMG is the only tool that can directly assess the pelvic floor muscle activity by measuring electrical signals which is generated along muscle fibers after depolarization of their motor nerve.[58] s-EMG is used to evaluate motor control patterns, coordination and location of the pelvic floor muscles and gives the practioner and patient information about the ability to contract and relax and whether there is an increase or decrease in activity during a particular task.[59] The use of down training, has been proven effective in creating awareness to avoid holding tension.[57,60]

A validated EMG electrode, the Multiple Array Probe (MAPLe®), was used in the present study. The MAPLe® probe uses a unipolar configuration, a validated location, is not sensitive for crosstalk and is capable of registering EMG-activity on all sides and depths of the pelvic floor during diagnosis and treatment.[61]



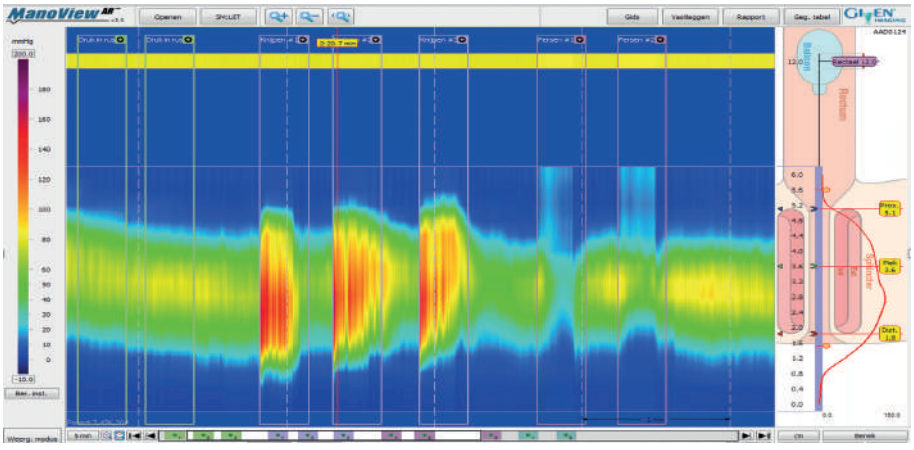
Biofeedback MAPLe®

Anorectal manometry

Anorectal high-resolution manometry (HRM) and three-dimensional high-definition manometry (3D-HRAM) are the 'gold standard' in investigating anorectal disorders.[62] The International anorectal physiology working group (IAPWG) recommends anorectal manometry in the assessment of symptoms of functional anal pain for identification of anal sphincter hypertonicity and abnormalities of rectoanal coordination and parameters of evacuation.[63] Manometry provides a comprehensive assessment of pressure activity in the rectum and sphincter complex with an assessment of rectal sensation, reflexes and rectal compliance.[21] It can be used as a component of clinical evaluation for patients in whom advanced management strategies are regarded especially in disordered evacuation.[64]

In patients with CAF, anal manometry has demonstrated high anal basal pressures.[65,66] Dyssynergia is defined by the absence of pressure reduction or an increase in the residual anal pressure during straining.[67]

Rao et al.[68] classified 4 patterns: rectal pressure > 40 mmHg and paradoxical anal contraction (type I); rectal pressure < 40 mmHg and paradoxical anal contraction (type II); rectal pressure > 40 mmHg and incomplete anal relaxation (type III); and rectal pressure < 40 mmHg and incomplete anal relaxation (type IV). In a study of Jain,[66] dyssynergic defecation was investigated with ARM and was more common in patients with CAF.



3D-HRAM resting pressure, squeezing, and straining

Defecation not only involves correct anorectal synchronisation but also a correct thoraco-abdominoperineal dynamic and vertebral position.[69] Alterations of pelvic statics may be a cause for dyssynergia. Lumbar hyperlordosis causes a horizontally position of

the sacrum, resulting in an increased distance between rectum and coccyx and opening of the anorectal angle. This can cause an increased pelvic floor muscle tone and stretch on the posterior sacrococcygeal ligament.[69,70] Thus, a comprehensive evaluation of the chest, including respiratory function, abdomen, vertebral column, pelvis, and hips is important to determine the underlying cause of pelvic floor dysfunction.[26,71]
To exclude other pathology including abscess and/or fistula, endo-anal ultrasound can be used if that is possible and otherwise examination under anesthesia is indispensable.

Conservative treatment

Over the years, a broad spectrum of non-surgical options has been introduced aimed at alleviation of symptoms, achieving reduction of anal pressure, and ameliorating the healing process.
Initial conservative management is comprised of lifestyle advice, fibre intake and/or use of laxatives and ointments. The use of fiber is effective in healing in acute fissures by using extra 20-25gr/d of fiber to normalise the defecation pattern and should be recommended to ensure avoidance and constipation.[72,73]
Improvement of toilet behaviour is important because of the anxiety of patients to go to the toilet in expectance of pain, and to prevent recurrence.
Defecation could more easily be achieved by the squatting than by the sitting position. During the squatting position, a larger anorectal angle is achieved by relaxation of the pelvic floor muscles and less strain will be required for defecation.[74]
To make defecation easier, the legs could be raised by putting the feet on a small bench of 12-16 cm height[75] and/or in a position bending forward in the "thinker" position.[76]

The "Thinker" by Rodin®

The use of 'sitz baths' is believed to help by improving hygiene and decreasing the IAS-tone mediated through sensory perianal skin receptors getting stimulated by warm water. The decrease in spasm and pain relief is attributed to this 'thermosphincteric reflex' through the activation of non-adrenergic and non-cholinergic neural release of nitric oxide.[77,78]

Gupta[79] found a significant relief in anal burning and higher satisfaction score, but no significant pain relief and wound healing. It is advised to use the sitz bath only to cover the perineum and lower pelvis (with max.40^{0}C), and not whole baths because this could lead to vasodilatation and a decrease of circulation in the perineal area.[80]

Guideline recommendations differ on this subject. Sitz baths are recommended in international clinical guidelines,[8,81] but not in the Dutch guideline.[82]

The use of ointments is aimed at reducing elevated sphincter tone and consequently increase the anodermal vascular blood flow, for which nitro-glycerine as well as calcium channel blockers may be prescribed.[5,81] Topical glyceryl dinitrate, is a nitrogen donor that works by increasing nitric oxide, which induces relaxation of the IAS. Glycerine nitrate is better than placebo in healing CAF, however recurrence occurred in around 50% of those initially cured.[7]

Calcium channel blockers (diltiazem) achieve healing rates of 80.4%,[83] but side-effects e.g., mainly pruritis may occur. Recurrence of 60% was found in patients within 2 years after end of therapy.[84] Both treatments have been shown effective although glyceryl nitrate has more side effects including headache.[81]

Botulinum toxin can be considered as an alternative or as a step-up approach when standard conservative therapy fails.[81,82] Botulinum toxin is an exotoxin produced by the bacterium clostridium botulinum. Botulinum toxin blocks nerve conduction by preventing acetylcholine release from the presynaptic nerve endings resulting in temporary muscle paralysis and to improve local vascularity.[85] Botulinum toxin is considered as a minimal invasive procedure with minor adverse effects which can be performed in an outpatient setting, however the recurrence rates vary between 18-50%.[7,86,87]

Posterior tibial nerve stimulation

Posterior tibial nerve stimulation is an office-based device to deliver retrograde electrostimulation to the sacral nerve. The tibial nerve is a mixed nerve containing L4–S3 fibers and originates from the same spinal segments as the innervations to

the bladder and pelvic floor. The mechanisms of its effect are not fully elucidated, but stimulation of peripheral fibers transmits impulses to the sacral nerves and neuromodulates the lower urinary tract, rectum, and anal sphincters.[88] It has been proven successful in the treatment of CAF,[89,90] although there is lack of related articles and data regarding this subject with methodological limitations. Posterior tibial nerve stimulation is not recommended in the Dutch guideline.[82]

Pelvic floor physical therapy

Pelvic floor physical therapy (PFPT) is an important part of treatment of pelvic floor dysfunctions and includes strategies to optimize lumbopelvic and spinal function and to improve bowel, bladder, and sexual function.[91,92] The aim of PFPT is to increase awareness and proprioception, to improve muscle relaxation and elasticity of the pelvic floor muscles, to restore abdominopelvic coordination, pelvic floor muscle function, rectal sensitivity and to reduce pain.[93,94] Interventions consist of education about pelvic floor musculature and related symptoms, behavioural modifications, exercises aimed at pelvic floor awareness and relaxation combined with soft-tissue manipulation and myofascial release.[95-97] These pelvic floor soft-tissue techniques can be performed from external and internal in the pelvis.

Dyssynergia and increased pelvic floor muscle tone can effectively be treated with PFPT including biofeedback therapy and/or electro galvanic stimulation,[94,98-103] and are recommended in clinical guidelines.[104,105]

Biofeedback is a behavioral learning process that relies on operant conditioning; visual, auditory, or verbal feedback from instruments that measure anorectal activity.[101] Several techniques can be used, solid-state manometry systems, surface electromyography, rectal balloons, and home devices. The aim is to improve muscle tone, voluntary contraction, and abdominopelvic coordination (abdominal push effort without excessive straining), to coordinate outward motion of the abdominal wall with relaxation of the pelvic floor and modulating rectal sensation.[106] Manometry and rectal balloon training have the opportunity to display rectal and anal pressures, whereas surface electromyography provides information on the pelvic floor muscles.[105] The feedback from the devices is used to identify the disordered function and used to guide the pelvic floor muscle exercises to learn how to transform and control the disordered function.[101]

Electro galvanic stimulation is used to improve muscle proprioception and relaxation of the pelvic floor muscles and is used as form of neuromodulation for pain relief.[103,107-109]

Brown et al.[110] found that patients are more likely to attend PFPT when referred on their initial consultation with the physician than those who were referred later. A multidisciplinary setting was associated with higher rates of PFPT attendance.
Currently, PFPT is not recommended in the guidelines as a treatment option for CAF.[8,81,82]

Surgical options

Although this thesis is only focused on the conservative management of CAF, various surgical procedures should be mentioned. Fissurectomy is the surgical procedure of choice in the Netherlands, followed by lateral internal sphincterotomy.[111] Lateral internal sphincterotomy is the preferred treatment for refractory anal fissures and is still considered the golden standard because of superior healing rates,[81,82] although fecal incontinence is a potential risk.[7,86,112-114] In this regard, the development of new treatment possibilities having the same or better outcome but with less side effects remains an actual assignment.
Pelvic floor physical therapy could bridge the gap between conservative management and surgery.

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CHAPTER 2

Management of chronic anal fissure, results of a national survey among gastrointestinal surgeons in the Netherlands

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Abstract

Background

Chronic anal fissure (CAF) is a common, bothersome condition frequently accompanied by pelvic floor complaints. Despite current guidelines, optimal management is challenging. The aim of this study is to evaluate current management of CAF among gastrointestinal surgeons in the Netherlands.

Methods

Dutch gastrointestinal surgeons and residents were sent a survey invitation by email, which was available online between June 2021 and September 2021. The questionnaire consisted of 21 questions concerning work experience, physical examination, diagnostic- and surgical techniques and follow-up.

Results

Overall, 106 (33%) respondents completed the survey. Most respondents (59%) had at least 10 years of experience in treating CAF. Only 23% always addressed pelvic floor complaints. Fifty-one percent performed digital rectal examination and 22% always, or almost always, examined the pelvic floor muscles. Most respondents started treatment with fibers and/or laxatives and ointment (96%). Diltiazem was in 90% the preferred ointment. Twenty-two percent referred patients for pelvic floor physical therapy. Botulinum toxin was in 54% performed under general- or spinal anesthesia or sedation. The surgical procedure of choice was fissurectomy (71%) followed by lateral internal sphincterotomy (27%). Fissurectomy was in 51% always combined with botulinum toxin. Fifty-seven percent of the respondents preferred a physical follow-up appointment.

Conclusion

Guideline recommendations are largely followed in the Netherlands, starting with conservative measures followed by surgical procedures. Surgeons do not consistently assess pelvic floor complaints, nor do they routinely examen the pelvic floor muscles. Awareness of pelvic floor dysfunctions is important to refer patients for pelvic floor physical therapy.

Introduction

Chronic anal fissure (CAF) is defined as a longitudinal ulcer in the squamous epithelium with persisting symptoms for longer than four to six weeks or recurrent fissures.[1,2] Patients usually experience anal pain, during and immediately after defecation, which may last several hours and therefore has a substantial impact on daily activities and quality of life.[3,4]

Despite current Dutch and international guidelines optimal management of CAF is quite challenging, mainly because of its recurrent nature, therapy compliance and the variety of non-operative and operative treatments.[5,6]

Treatment of CAF has undergone an alteration in the last two decades from invasive to non-invasive, reserving surgical interventions for lesions refractory to conservative therapy.[7] Initial conservative management are comprised of lifestyle advice, fibre intake and/or use of laxatives and ointments. The use of ointments is aimed at reducing elevated internal sphincter tone and consequently increase the anodermal vascular blood flow, for which nitro-glycerine as well as calcium channel blockers may be prescribed. Botulinum toxin can be considered as an alternative or as a next step when standard conservative therapy fails.[5,6] In addition, various surgical procedures are possible such as fissurectomy, advancement flap repair and lateral internal sphincterotomy (LIS). Currently, LIS is considered the golden standard[6,8] with healing rates of 90-100% but with a potential risk of incontinence.[1,9-12]

Although most anal fissures probably heal spontaneously or with conservative measures, a percentage tend to recur or persist. A proportion of these patients have a history of constipation and obstructed defecation due to an unrecognized pelvic floor dysfunction. Consequently, these patients have complaints of excessive straining, incomplete evacuation, and hard stools together with infrequent stooling which might be due to, for instance, dyssynergia.[13,14] Dyssynergia can primarily lead to anorectal pain but can also evolve secondary to disorders causing anorectal pain.[15]

Pelvic floor dysfunctions are associated with urological, bowel, gynecological and sexual complaints, and chronic pelvic pain[16,17] and can be treated with pelvic floor physical therapy. It is unknown if surgeons treating these patients are sufficiently aware of this condition in patients with CAF. Although Dutch and international guidelines are largely based on high-quality evidence, recommendations are ambiguous. As a result, there is variation in clinical practice. The aim of this study is to evaluate current practice in the management of CAF among gastrointestinal surgeons in the Netherlands.

Materials and Methods

Design of the survey and participants

This survey study was performed and reported according to the Checklist for Reporting Results of Internet E-Surveys (CHERRIES).[18] As this study did not apply the Medical Research Involving Human Subjects Act (WMO), approval by the ethics committee was not required.

The survey was written in Dutch, consisted of 21 questions, and was created using a web-based program called Survio.[19] The closed-survey (i.e., only accessible through invitation) was sent by email to all members of the Dutch Working Group Coloproctology as well as to gastrointestinal surgeons, fellows, and residents of each hospital in the Netherlands. We used the email database of our previous survey among Dutch gastrointestinal surgeons concerning the management of anal fistulas.[20] Known invalid domains were removed and the list was checked globally by contact information that was retrieved from the Dutch Association of Surgery. The survey was accompanied by an invitation email explaining the objectives of the study and length of time of the survey (<10 min). One reminder email was sent after 4 days, the second after 10 weeks. No time limit was set for filling in the survey. The survey was available online from June 25th, 2021, to September 30th, 2021.

Survey

The survey consisted of 3 pages and a total of 21 questions, formulated by all five authors. The questions were reviewed by two colorectal surgeons and one urologist, after which the survey was edited. All authors conducted a pilot for testing validity. The survey consisted of topics concerning baseline characteristics such as respondents' function, type of hospital, years of experience in treating CAF and number of surgical procedures – including botulinum toxin injections – per year. Other questions assessed medical history and physical examination with attention to pelvic floor complaints and dysfunctions; diagnostics techniques; surgical approaches; follow-up and presumed effect of treatment. Seventeen questions were single-choice, two were multiple-choice and two questions required a number. The participants were given the chance to review and change their answers. The survey was tested for completeness, usability, and technical functionality before submission. The survey was voluntary, and no incentives were offered.

Statistical analysis

All statistical analyses were performed using Statistical Packages for Social Sciences (SPSS, Chicago, II, USA, version 26.0). To prevent missing data, all questions were mandatory with automated skip logic. The web-based program Survio automatically collected all data after which the data were exported to a Microsoft Excel spreadsheet and then imported to SPSS. Descriptive analyses were performed on all data. Categorical outcome data across groups were analysed using the Chi-square test.

Results

Respondents' characteristics

In total, 329 invitations were sent by email to gastrointestinal surgeons, fellows, and residents. Nine email addresses with an invalid domain did not receive the invitation. Hundred-and-six (33%) surveys returned and were completely answered. Forty- one responses were excluded since they did not complete. Respondents' characteristics are shown in table 1. Eighty-one percent of the respondents were gastrointestinal surgeons and 89% worked in a general hospital. Fifty-nine percent of the responders had at least 10 years of experience with treating CAF and 61% performed more than 10 procedures for CAF per year, including botulinum toxin (BT).

Medical history and physical examination

From the respondents, 28% never or almost never asked and only 23% always or almost always asked for complaints in other domains of the pelvic floor. A subgroup analysis showed that respondents with more than 10 years of experience in treating CAF slightly more often asked for pelvic floor complaints than respondents with less than 10 years of experience, although not significant.

Half of the respondents performed digital rectal examination and 23% performed proctoscopy. Only 22% of the respondents indicated that they always, or almost always, performed physical examination of the pelvic floor muscles, whilst 37% never or almost never did (Table 1).

Treatment

Ninety-six percent started treatment with fibers and/or laxatives and ointment. In 90% of the respondents, diltiazem was the preferred ointment. Fifty-six percent prescribed

ointment for a period of 6 weeks followed by 27% who continued ointment for 12 weeks. Most of the respondents (72%) felt they had enough time to give the patient instructions or advice regarding the use of laxatives, lifestyle, and ointment.
Twenty-two percent of the respondents referred to a pelvic floor therapist and they always combined this with fibers and/or laxatives.
Botulinum toxin injections were given by 77% of the respondents mainly under general- or spinal anesthesia or sedation (42%). Almost half of the respondents repeated botulinum toxin injections twice and more than 76% never performed botulinum toxin in the levator ani muscle.
Fissurectomy was the most popular operative procedure (71%), followed by LIS (27%). More than half of the respondents always, or almost always, used botulinum toxin intersphincteric in case they performed a fissurectomy. When botulinum toxin injections were performed under anesthesia, only 27% performed a fissurectomy simultaneously (Table 1).

Follow-up

Fifty-seven percent scheduled a physical follow-up check in the outpatient clinic. Forty-three percent referred a patient with CAF to another specialist at least once. A percentage of 57% estimated their patients to be symptom-free after 1 year in 50-75% of the cases.
Thirty percent of the respondents had the feeling they always or almost always treat these patients satisfactorily (Table 1).

Discussion

Implementation of Dutch and international guidelines for chronic anal fissure in daily practice varies. The present study provides an overview of the current approach in management of CAF amongst gastrointestinal surgeons in the Netherlands.
The pelvic floor plays a major role in defecation and continence. Furthermore, pelvic floor dysfunctions are prevalent in patients with chronic anal pain syndromes.[21,22] However, 28% of the respondents never or almost never asked for any pelvic floor complaints in patients with CAF and only 23% always asked about this topic.
Complaints of pelvic floor disorders vary and are often complex, making these disorders less widely recognized.[23] A survey by Nicolai et al. about addressing pelvic floor complaints among Dutch gastroenterologists showed that one of the reasons

for not asking about pelvic floor complaints was a lack of knowledge about pelvic floor disorders.[24] In our survey we did not inquire the reason for not asking for pelvic floor complaints, but this would be probably the same in gastrointestinal surgeons. We feel that knowledge about pelvic floor dysfunctions is beneficial in the treatment of anorectal disorders since this might result in a referral to another specialist in an early stage.

The study shows that there is moderate consensus among the respondents concerning performing physical examination in patients with CAF. Only half of the respondents performed digital rectal examination and 37% never or almost never examined the pelvic floor muscles. Seniority in experience did not differentiate. In case of expecting a CAF, reason for not performing digital rectal examination could be the assumption that its contradicted or should be kept to a minimum because of associated pain. However, careful digital rectal examination is important to obtain information on anorectal anatomy and function.[25,26] When identifying pelvic floor muscle dysfunction, patients can be appropriately referred to a pelvic floor physical therapist.

Most of the respondents is accustomed to start with conservative measures, which is according to current guidelines.[5,6,27-29] Diltiazem ointment was the preferred local treatment. Duration of application varies in studies and guidelines, but mostly a duration of at least 6 weeks is recommended.[30-32] In our study 56% of the respondents indicated to prefer a duration of 6 weeks. Forty percent preferred a longer therapy duration, except for 4 respondents.

Most respondents did have enough time to give instructions in the consulting room. This is important, since information about patient' complaints, lifestyle advice, laxative- or ointment and its use require an explanation by the clinician.[2,33]

Pelvic floor dysfunctions can effectively be treated with pelvic floor physical therapy, but only 22% of the respondents referred to this treatment modality, a missed opportunity. The clinical effect of pelvic floor physical therapy in patient with CAF is investigated by the Pelvic floor Anal Fissure (PAF) study.[34]

Botulinum toxin injections were performed in the outpatient's clinic by less than half of the respondents of whom 90% performed this without local anesthetics, excluding the 23 respondents who did not perform this procedure at all. More than half of the respondents (54%) performed botulinum toxin injections under general- or spinal anesthesia or sedation which is in accordance with a recent survey among members of the American Society of Colon and Rectal Surgeons (ASCRS).[35] In current literature, there is no consensus on dose, site, or number of injections.[29,36] This corresponds

with the results of our study showing no consensus on how often one should repeat botulinum toxin. Nevertheless, botulinum toxin remains an effective treatment in recurrent anal fissures as well as in patients with therapeutic failure of prior botulinum toxin injection.[7,37]

In case botulinum toxin was performed under anesthesia, only 27% always or almost always simultaneously performed fissurectomy and another 27% does this in more than half of the cases. This is comparable to the results of a survey among members of the ASCRS.[35]

When performing fissurectomy, 51% always or almost always simultaneously injected botulinum toxin and 23% did this in more than half of the patients. The clinical effect of this combined procedure was recently confirmed by Roelandt et al.[38] They found that botulinum toxin injections significantly increased the efficiency of fissurectomy, with a healing rate of 90%, compared to 81% in fissurectomy alone.[38]

Fissurectomy was the surgical procedure of choice in our study (71%), followed by LIS (27%). LIS is the preferred treatment for refractory anal fissures and is still considered the golden standard since LIS has superior healing rates,[5,6] although fecal incontinence is a potential risk.[8-11] Guideline recommendations differ on this subject. The ASCRS guideline favours LIS,[6] the Dutch guideline, however, recommends LIS only for refractory fissures when previous treatment fails.[5]

The follow-up was diverse in our survey. Twenty-one percent of the respondents stated that they scheduled a telephone call follow-up check after starting the treatment. This is quite interesting given the fact that it concerns a chronic disorder which has a large impact on quality of life and increased health care utilization.[39] Besides that, chronic pelvic pain is often accompanied by pelvic floor dysfunctions.[40] A physical diagnostic follow-up should be performed since physical rectal examination is important to monitor clinical healing of the fissure and investigation of anal sphincter tone. A physical follow-up will probably better monitor patients' wellbeing and subsequently ensure that the patient does not end up in a vicious circle of pain again.

Forty-three percent referred a patient to another specialist at least once last year. No recommendations are made in clinical guidelines concerning follow-up period or when to refer a patient to another specialist.

This study has some limitations that should be mentioned. First, the response rate of 33% may have caused non-response bias. However, this response rate was less compared to earlier published response rates of online surveys.[41,42] Second, the questionnaire was sent to all members of the Dutch Coloproctology Working group

that consists of members that have large experience and affiliation in treating anorectal diseases. Of all respondents, 33% came from this group. This may have caused selection bias. Third, we used a non-validated questionnaire and respondents were self-reported. Self-reports may have resulted in an overestimation of history-taken practices and to our knowledge, validated questionnaires are not available in this field.

Conclusion

Guideline recommendations in treating CAF are largely followed and consistent among most gastrointestinal surgeons in the Netherlands. Initial treatment consists of conservative measures followed by surgical procedures. Surgeons do not consistently assess pelvic floor complaints, nor do they routinely examen the pelvic floor muscles. Awareness of pelvic floor dysfunctions in patients with CAF is important to refer patients for pelvic floor physical therapy.

What does this paper add to the literature?

Gastrointestinal surgeons in the Netherlands have not yet been surveyed regarding their current management concerning chronic anal fissure. The paper discusses similarities and discordances between surgeons and compare these to current Dutch and international guidelines. Furthermore, it emphasizes the focus on the pelvic floor in current management of CAF.

Table 1. Results

Respondents' characteristics	**N (%)**
What is your medical specialty?	
Gastrointestinal surgeon	86 (81)
General surgeon	7 (7)
Fellow	2 (2)
Resident in training	8 (7)
Physician assistant/nurse practitioner	3 (3)
What type of hospital are you working?	
Academic	4 (4)
Non-academic (peripheral)	94 (89)
(Private) clinic	8 (7)
How many years of work experience do you have as a medical specialist in the treatment of CAF?	
1-5 years	19 (18)
5-10 years	24 (23)
10-20 years	35 (33)
>20 years	28 (26)

Table 1. Continued

Respondents' characteristics	N (%)
How many procedures for CAF (incl botulinum toxin) do you perform per year?	
0-10	41 (39)
10-30	41 (39)
30-50	19 (18)
>50	5 (5)
Medical history and physical examination	
How often do you ask a patient with CAF about pelvic floor complaints (gynaecology, urology, sexuology)? **SC?*	
Never/almost never	30(28)
In less than half of the cases	38 (36)
In more than half of the cases	14 (13)
Almost always/always	24 (23)
In case you expect CAF by medical history, which physical examination and/or diagnostics do you do? **MC*	
None	1 (1)
Inspection	103 (97)
Digital rectal examination	54 (51)
Proctoscopy	24 (23)
Endo-anal ultrasound	6 (6)
Do you examine the pelvic floor muscles by a patient with CAF (squeeze, relaxation and push of the levator ani muscle and external anal sphincter)? **SC*	
Never/almost never	39 (37)
In less than half of the cases	26 (24)
In more than half of the cases	18 (17)
Almost always/always	23 (22)
Treatment	
Which treatment do you initiate when treating a patient with CAF? (assuming the general practitioner has not already done this) **MC*	
Lifestyle advice by nutrition advice and toilet behaviour	79 (74)
Fibers/laxatives and ointment	102 (96)
Pain medication (local and/or systemic)	43 (41)
Pelvic floor physical therapy	23 (22)
Botulinum toxin	2 (2)
Which ointment do you prescribe for CAF? **SC*	
Lidocaine	1 (1)
Isosorbide dinitrate	9 (8)
Diltiazem	96 (90)
Other	0 (0)
In case of isosorbide dinitrate or diltiazem, what was your recommendation concerning duration of application? (number)	
16 weeks	1 (1)
12 weeks	29 (27)
8 weeks	13 (12)
6 weeks	59 (56)
4 weeks	1 (1)
3 weeks	1 (1)
2 weeks	2 (2)

Table 1. Continued

Respondents' characteristics	N (%)
Do you feel you have enough time to instruct and advice the patient regarding the use of laxatives, lifestyle, and ointment? *SC	
Never/almost never	4 (4)
In less than half of the cases	7 (7)
In more than half of the cases	19 (18)
Almost always/always	76 (72)
How do you perform the botulinum toxin (BT) injections? *SC	
Outpatient clinic, without anesthesia	34 (32)
Outpatient clinic, with local anesthesia	4 (4)
General- or spinal anesthesia or sedation	45 (42)
Not applicable, I do not perform this procedure	23 (22)
How often do you repeat BT injections? *SC	
One time	16 (19)
Two times	41 (49)
More than two times	22 (27)
I do not repeat	4 (5)
Do you simultaneously give BT in the levator ani muscle when treating CAF? *SC	
Never/almost never	63 (76)
In less than half of the cases	13 (16)
In more than half of the cases	6 (7)
Almost always/always	1 (1)
What is your preferred surgical procedure for CAF (except BT)? *SC	
Fissurectomy	59 (71)
Lateral internal sphincterotomy (LIS)	22 (27)
Advancement flap repair	2 (2)
In case you perform a fissurectomy, do you simultaneously give BT intersphincteric? *SC	
Never/almost never	15 (18)
In less than half of the cases	7 (8)
In more than half of the cases	19 (23)
Almost always/always	42 (51)
In case you perform BT under anesthesia, do you simultaneously perform a fissurectomy? *SC	
Never/almost never	24 (29)
In less than half of the cases	15 (18)
In more than half of the cases	22 (27)
Almost always/always	22 (27)
Follow-up	
How do you manage the follow-up after starting a treatment? *SC	
No follow-up	0 (0)
Physical appointment	60 (57)
Telephone call	22 (21)
According to the needs of the patient	24 (23)
How many times did you refer a patient with CAF to another specialist last year? (number)	
0 times	61 (58)
1-5 times	42 (40)
6-10 times	3 (3)

Table 1. Continued

Respondents' characteristics	N (%)
What percentage of your patients do you estimate to be symptom-free a year after starting the treatment? *SC	
0-25%	0 (0)
25-50%	9 (8)
50-75%	60 (57)
75-100%	33 (31)
I do not know	4 (4)
Do you feel you can treat patients with CAF satisfactorily? *SC	
Never/almost never	0 (0)
In less than half of the cases	2 (2)
In more than half of the cases	72 (68)
Almost always/always	32 (30)

CAF= Chronic Anal Fissure; BT=botulinum toxin; SC= Single Choice; MC= Multiple Choice

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CHAPTER 3

Pelvic floor physical therapy for pelvic floor hypertonicity: A systematic review of treatment efficacy

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Abstract

Background

Hypertonicity of the pelvic floor (PFH)[1] is a disabling condition with urological, gynaecological, and gastrointestinal symptoms, sexual problems, and chronic pelvic pain, impacting quality of life. Pelvic floor physical therapy (PFPT) is a first-line intervention, yet no systematic review on the efficacy of PFPT for the treatment of PFH has been conducted.

Objectives

To systematically appraise the current literature on efficacy of PFPT modalities related to PFH.

Methods

PubMed, Embase, Emcare, Web of Science and Cochrane databases were searched from inception until February 2020. A manual search from reference lists of included articles was performed. Ongoing trials were reviewed using clinicaltrial.gov. Randomized controlled trials (RCTs), prospective - and retrospective cohorts and case-study analyses were included.

Outcome measures were pelvic floor muscle tone and function, pain reports, sexual function, pelvic floor symptom scores, quality of life and patient's perceived effect.

Results

The literature search resulted in 10 eligible studies including 4 RCTs, 5 prospective studies and 1 case study published between 2000 and 2019. Most studies had a high risk of bias associated with the lack of a comparison group, insufficient sample sizes and non-standardized interventions. Six studies were of low and 4 of medium quality. All studies were narratively reviewed. Three of 4 RCTs found positive effects of PFPT compared to controls on five out of 6 outcome measures. The prospective studies found significant improvements in all outcome measures that were assessed. PFPT seems to be efficacious in patients with chronic prostatitis, chronic pelvic pain syndrome, vulvodynia, and dyspareunia. Smallest effects were seen in patients with interstitial cystitis and painful bladder syndrome.

Conclusion

The findings of this systematic review suggest that PFPT can be beneficial in patients with PFH. Further high-quality RCTs should be undertaken to confirm the effectiveness of PFPT in the treatment of PFH.

[1]An update on the terminology by the International Continence Society was conducted and published in 2021 after this systematic review. 'Hypertonicity' is changed into 'increased pelvic floor muscle tone' and is further used in this thesis.
Frawley H, Shelly B, Morin M, et al. An International Continence Society (ICS) report on the terminology for pelvic floor muscle assessment. Neurourol Urodyn. Jun 2021;40(5):1217-1260.

Introduction

The pelvic floor is a multifunctional complex of muscle fibers, fascia, ligaments, and connective tissue that form a hammock at the bottom of the abdomino-pelvic cavity. The muscles of the pelvic floor consist of superficial muscles including the m. bulbospongiosus, m. ischiocavernosus, the perineal muscles and external anal sphincter muscle. The deep pelvic floor muscles are the levator ani composed of the puborectalis, pubococcygeus and iliococcygeus. The pelvic floor provides anatomical support for the pelvic and abdominal viscera and is involved in urinary, defecatory and sexual function.[1-4] The pelvic floor is capable of generating and controlling intra-abdominal pressure together with other muscles surrounding the abdominal cavity and contributes to lumbar spine stiffness.[5,6]

Pelvic floor hypertonicity (PFH) is often associated with urological, gynaecological, gastrointestinal, and sexual problems as well as chronic pelvic pain. Prevalence ranges from 50-90%.[7,8] These complaints have a profound impact on quality of life.[9-12]

Several terms are used for PFH in the literature, such as pelvic floor spasm, non-relaxing pelvic floor, and overactivity. Currently, the International Urogynecological Association (IUGA)/International Continence Society (ICS) defines the term "non-neurogenic hypertonicity" as an increase in muscle tone related to the contractile or viscoelastic components that can be associated with either elevated contractile activity and/or passive stiffness in the muscle.[13] In addition, the hypertonic muscle tissue may contain myofascial trigger points (MTrPs).[14] A MTrP is a discrete, hyperirritable nodule in a taut band of a skeletal muscle which is palpable and tender during physical examination. An active MTrP is clinically associated with spontaneous pain in the surrounding tissue and/or to distant sites in specific referred pain patterns.[15,16]

PFH can be a primary problem or a secondary adaptation to an acute or chronic injury to one or more musculoskeletal components in the pelvic floor and surrounding structures. Pelvic surgery, traumatic vaginal delivery, traumatic injury of the back or pelvis, gait disturbances, pelvic pain, experienced threat and (chronic) stress are found to be associated with PFH.[17-20]

PFH is assumed to be related to learned behaviour, otherwise acquired in adulthood through voluntary holding to inhibit micturition or defecation or to avoid incontinence. This might be related to habit, lifestyle and/or stressful occupation.[9]

A history of physical or sexual abuse or insecure attachment is common among women with PFH and is associated with impaired sexual arousal, desire, and orgasm.[21,22]

Laan et al.[23] conceptualized PFH as a symptom of chronic activation of the defensive

stress-system and should thus be regarded as a physical manifestation of emotional dysregulation.

Clinically, PFH is diagnosed by digital palpation of the pelvic floor. This includes assessment of muscle tone (resistance provided by a muscle when a pressure or a stretch is applied to it) and muscle function (voluntary contractility, strength, endurance, repeatability, co-contraction, and relaxation ability).[8,13,24,25]

There is no single accepted or standardized way of measuring muscle tone and there are no normative values.[13] Digital palpation can be combined with the use of surface electromyography (s-EMG) and dynamometry.[8,26] To access pain and MTrPs, patient-reported outcome measures can be used and include numerical rating scales, visual analog scales (VAS) [27,28] and simple verbal pain rating scales.[13]

Pelvic floor physical therapy (PFPT) is considered to be an important part of treatment of PFH and includes strategies to optimize lumbopelvic, spinal and pelvic floor muscle function and to improve urinary, defecatory and sexual function.[29-31] The aim of PFPT for PFH is to increase awareness and proprioception, to improve muscle relaxation and elasticity of the pelvic floor and to reduce pain. Interventions consist of education about the pelvic floor and related symptoms, behavioural modifications, exercises aimed at pelvic floor awareness and relaxation combined with soft-tissue manipulation and myofascial release.[30,32-35] Another frequently used treatment modality is s-EMG to register pelvic floor muscle activation with intravaginal or-anal electrode probes.[36,37] Electrogalvanic stimulation is used to improve muscle proprioception and relaxation of the pelvic floor muscles and is used as form of neuromodulation for pain relief.[38-41]

To date, efficacy of this range of treatments is not yet well established. Investigation by systematically reviewing the effectiveness of PFPT for PFH as a stand-alone entity has not yet been performed. The goal of this review was to systematically appraise the current literature on the effectiveness of PFPT for the treatment of PFH.

Material and Methods

Search strategy

This systematic review adhered to guidelines detailed in the Preferred reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[42]

A comprehensive literature search was conducted using the following electronic databases: MEDLINE, Embase, Emcare, and the Cochrane Central Register of Controlled Trials (Wiley Interface, current issue) from inception until February 2020.

Protocol registry (http://www.clinicaltrials.gov) was screened for upcoming trials. The search strategy was developed by a health science librarian with experience in systematic review searching. Different relevant search terms (thesaurus terms and terms in title, abstract or both) concerning PFH and PFPT were used. The following medical subject headings and text words were used: hypertonicity of the pelvic floor, overactive pelvic floor, non-relaxing pelvic floor, micturition disorder, defecation disorder, sexual dysfunction, chronic pelvic pain, physical therapy, myofeedback and electrogalvanic stimulation. The reference lists of eligible studies and relevant systematic reviews were searched for additional articles that were not found in the main search. Search strings are listed in Appendix 1.

Inclusion and exclusion criteria

Randomized control trials (RCTs), cross-over studies, prospective and retrospective cohort studies and case studies involving PFPT in patients with PFH were included in the review. Inclusion criteria were men and/or women (>18 years) with pelvic floor problems and complaints suggestive of PFH; muscle tone diagnosed by palpation and/or s-EMG; adequate description of the intervention. Studies with the following outcome measures were eligible: pelvic floor muscle tone, pain, sexual function, quality of life, pelvic floor symptoms and patient's perceived effect. Studies had to be original, available as full-text and written in English. Studies with patients with neurological diseases, low pelvic floor muscle tone, medication, surgery, sacral neuromodulation, and percutaneous tibial nerve stimulation were excluded.

Data collection and analysis

Two authors independently selected studies by screening titles and abstracts followed by full text screening. Any discrepancies were resolved by discussion until consensus. The following data were extracted: first author, year of publication, country, inclusion and exclusion criteria, sample size, participants characteristics (such as age, gender, sample size), study design, details of the pelvic floor interventions, outcomes measurements, and outcome. Level of bias was evaluated using the Cochrane Collaboration's Risk of Bias criteria. For each of these risk domains, studies were categorized as at low, uncertain, or high risk of bias based on random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other bias.[43]

Outcome measures

All outcome measures of included studies are listed in Table 1.

Table 1. Outcome measures

Muscle tone and function	◊ Modified Oxford-scale[50] ◊ 7-point digital palpation scale muscle tone (-3 to +3)[45] ◊ 4-point digital palpation score for muscle flexibility and muscle relaxation (0-4)[45] ◊ Vulvalgesiometer [45] ◊ Rest s-EMG-values[44,45,48] ◊ Modified Oxford-scale (0-5)[45,46] ◊ The New PERFECT-scale [48]
Pain	◊ Digital palpation of the pelvic floor muscles (levator, obturator internus, diaphragm urogenital) [51] ◊ Visual analog scales (VAS)[35,46,47,49] ◊ the National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI)[35,44,49,51] ◊ Pelvic pain symptom scale (PPSS)[35,49] ◊ Likert visual analog scale[50-52] ◊ VAS-scores to assess vulvar pain[45] ◊ Degree of pain during sexual intercourse[48]
Sexual Function	◊ Female Sexual Function Index (FSFI)[46,48,51,52] ◊ Cervantes scale measuring sexual response cycle on Quality of Life (QoL)[48] ◊ Sexual health domain of the PPSS[35,49] ◊ Sexual Health Inventory for Men (SHIM)[51]
Pelvic floor symptoms	◊ O'Leary-Sant IC Symptom/Problem Index (ICSI/ICPI)[50-52] ◊ NIH-CPSI [35,44,49,51] ◊ American Urological Association (AUA) symptom and bother score[47] ◊ VAS-urgency[47] ◊ Likert visual analog scale urgency[50,52] ◊ Likert visual analog scale frequency[52] ◊ Pelvic pain symptom scale (PPSS)[35,49]
Quality of life	◊ Cervantes QoL[48] ◊ VAS-QoL[45] ◊ NIH-CPSI domain QoL[35,44,49,51] ◊ 12-item Short Form survey (SF-12)[50-52]
Patient's perceived effect	◊ Global Response Assessment (GRA)[35,49,51,52]

Treatments

The duration of treatment varied between 5-12 sessions, with sessions lasting between 30-75 minutes, over a period varying from 5 days to 3 months. PFPT protocols in the studies consisted of at least 3 of the following interventions: education about anatomy and function of the pelvic floor and related symptoms;[44-47] digital vaginal palpation of the pelvic floor for proprioception and to guide home exercises;[46,48] manual techniques to release MTrPs of the pelvic floor and soft-tissue massage, including stretching,

external manipulation of the pelvic floor and surrounding muscles;[35,45,46,48-52] insertion techniques using dilatators,[45] muscle exercises focused on awareness and relaxation;[35,44,46,48,49,51,52] infrared thermotherapy,[48] home exercises[35,45-49,51,52] and bladder training.[47] Four studies used s-EMG[44,45,47,48] and 2 studies used electrogalvanic stimulation.[45,46] Treatment in the control-arm of the 4 RCTs consisted of no-treatment,[46] western massage of lower back muscles,[51,52] heat applied to lower back and myofascial release of the abdominal diaphragm, piriformis and iliopsoas muscles.[48]

Results

Search results

In total, 570 studies were identified through electronic searches of which 237 duplicates were removed. Of the remaining 333 studies, 298 were excluded based on title and abstract screening. Thirty-five references were read in full, after which 25 references were excluded (see Figure 1 for exclusion reasons). A total of 10 studies met the inclusion criteria. Four studies were RCTs,[46,48,51,52] there was one case study[35] and 5 prospective cohort studies.[44,45,47,49,50] No ongoing studies were found. Studies represented a total of 581 participants, samples sizes in the studies varied from 19 to 138 patients. Patients with sexual problems were investigated in 2 RCTs[46,48] and in one prospective cohort study.[45] These studies involved patients with dyspareunia and provoked vestibulodynia (PVD). Patients with interstitial cystitis and painful bladder syndrome (IC/PBS) were investigated in 2 RCTs[51,52] and 1 prospective study.[50] Patients with chronic prostatitis and chronic pelvic pain syndrome (CP/CPPS) were studied in one RCT,[51] 3 prospective studies[44,47,49] and in the case study.[35] Given the marked heterogeneity of the studies, with different indications, outcome measurements and interventions, all studies were narratively reviewed.

Study quality assessment

A summary of study design, patient characteristics, sample size, interventions, outcome assessments and findings are listed in Table 2.

The quality assessment (see Figure 2) related to selection bias indicated a high risk of bias for six studies due to the absence of randomization or a comparison group. Blinding of participants and personnel for treatment received was feasible in none of the studies. Blinding of outcome assessment was at high risk in eight studies.[35,44-48,50,51]

Attrition bias (dropout) was high in three studies.[35,47,50] Risk of reporting bias was high due to insufficient information about the exact treatment protocol in two studies,[35,50] and high due to insufficient information about interpretation of the results.[52] Eight of the 10 studies described their treatment protocols in detail.[44-49,51,52] Sample-size calculation was reported in the 4 RCTs.[46,48,51,52] Other risks of bias concerned loss of funding or insurance to complete the study. We considered six studies to be of low quality, with only zero to two low bias risks.[35,44,45,47,49,50] The other four studies were of medium quality.[46,48,51,52]

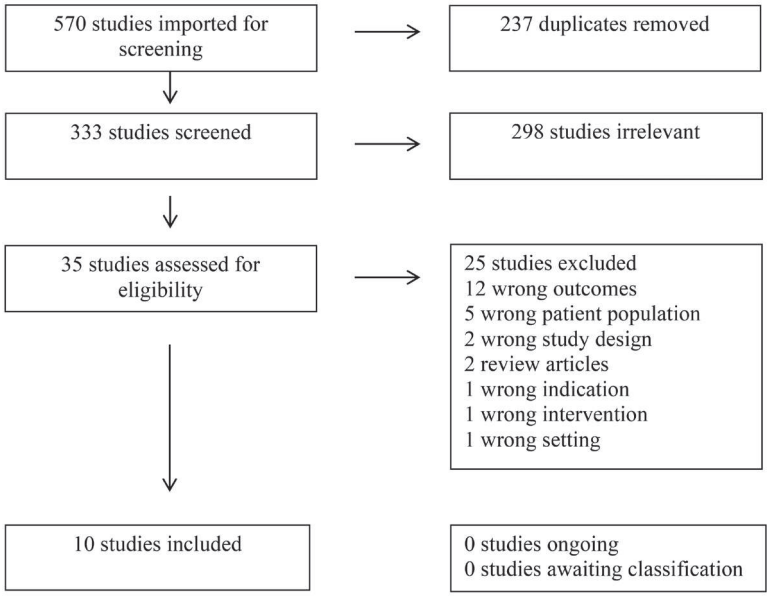

Figure 1. PRISMA flowchart

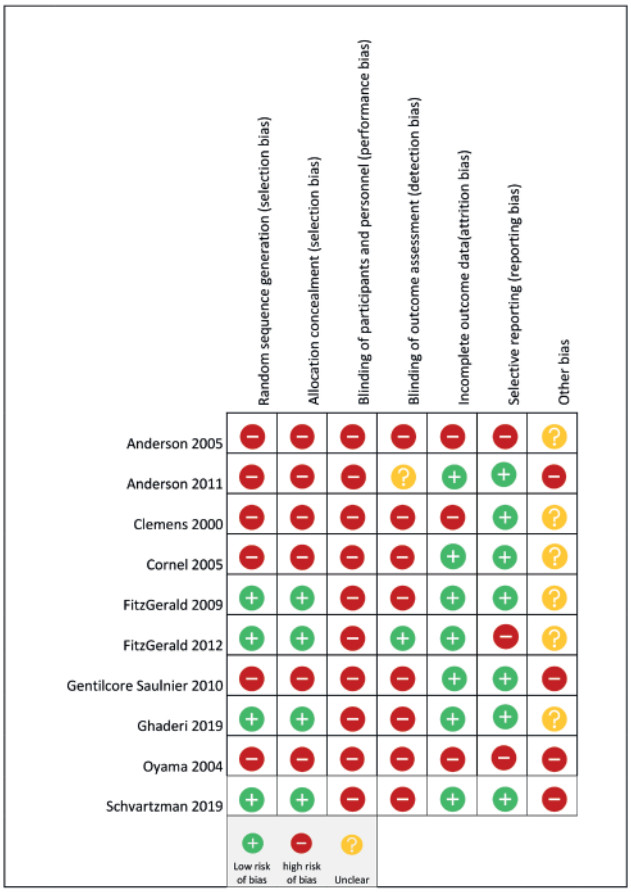

Figure 2. Risk of bias assessment

Outcome assessments

Pelvic floor muscle resting tone and function

Changes in muscle tone as a result of PFPT were directly measured in one RCT[48] and in 3 prospective cohort studies.[44,45,50] The RCT[48] involved patients with dyspareunia and found that PFPT did not significantly decrease resting activity from baseline to post-treatment using s-EMG. In one prospective study[44] in men with CPPS, the mean value of the muscle tone measured with s-EMG decreased significantly from pre- to post-treatment. The second prospective cohort study[45] in women with PVD found a significant reduction in muscle tone, measured with the 7-point digital palpation scale,

a significant increase from pre- to post-treatment in pelvic floor muscle flexibility and in the ability to relax the pelvic floor muscles after contraction measured with 4-point digital palpation scale. S-EMG demonstrated a higher tonic rest activity at pre-treatment in the superficial layer of pelvic floor muscles in the patient group compared to controls but not in the deeper layer of the pelvic floor muscles. The last prospective study[50] in women with IC showed significant improvement in muscle tone after PFPT in all pelvic floor muscles except for the coccygeus, using the modified Oxford Scale. Pelvic floor muscle function was measured in 2 RCTs[46,48] and one prospective study.[45] One RCT[48] involving patients with dyspareunia found that PFPT significantly increased sustained contractions from baseline to post-treatment and the number of peaks were significantly higher in the PFPT-group using s-EMG and compared to control who received heat applied to lower back and myofascial release of the abdominal diaphragm, piriformis and iliopsoas muscle. A significant improvement was found in post-treatment pelvic floor muscle function measured with New-PERFECT scores in the PFPT- group and relative to baseline. The second RCT[46] involved patients with dyspareunia and found significant improvement in pelvic floor muscle strength and endurance in the PFPT group in comparison with a no-treatment control group using the modified Oxford-scale. One prospective cohort study[45] found a significant increase in pelvic floor muscle strength from pre-to post-treatment but not compared to control measured with the modified Oxford scale.

Pain

Pain scores were assessed in all studies. In one RCT[51] in patients with CP/CPPS and IC/PBS, PFPT resulted in significant relief of tenderness/pain in 4 muscle groups (levator ani posterior and anterior, obturator internus and urogenital diaphragm) from pre-to post-treatment in both groups measured with digital examination. In the IC/PBS group a significant relief of tenderness/pain was found compared to controls who received full body global therapeutic massage. This study also found reduced pain scores measured with Likert pelvic pain score to be significantly reduced from pre-to post-treatment in both groups but not compared to controls. The second RCT[48] found a significant reduction in post-treatment dyspareunia pain scores using VAS in the PFPT group relative to controls. The third RCT[46] found post-treatment VAS pain scores in the genital area before, during, and after vaginal intercourse to be significantly decreased compared to no-treatment controls, which sustained after

follow-up of three months. Only 1 RCT[52] was unable to show a decrease in pelvic/bladder discomfort and/or pain after PFPT compared to controls who received full body global therapeutic massage. One prospective study[50] in women with IC, found a significant decrease in pelvic pain measured with Likert scores compared to baseline. The second prospective cohort study,[45] in women with PVD demonstrated significant reduce of pain in the superficial pelvic floor muscles to a painful pressure stimulus induced with a vulvalgesiometer. Vulvar pain intensity ratings were also significantly decreased after treatment and no longer differed from non-affected controls. The third prospective study,[47] in men with CPPS, found significantly lower pelvic pain-scores after PFPT measured with VAS. The fourth prospective study[44] in men with CP/CPPS found a significant decrease in the subdomain pain of the National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) after PFPT. The fifth prospective study[49] in men with CP/CPPS also found significant improvement in pain from pre- to post-treatment in the subdomain of the NIH-CPSI and Pelvic Pain Symptom Scale (PPSS). Finally, the case study[35] demonstrated a more than 25% reduction in pelvic pain symptom scores using VAS-scores.

Sexual function

Sexual function was investigated in all 4 RCTs,[46,48,51,52] in one prospective study[49] and the case study.[35] One RCT[51] found significantly higher post-treatment Female Sexual Function Index (FSFI) total scores for women in the IC/PBS patient group compared to pre-treatment, no significant differences were found relative to control. In men with CP/CPSS, no significant differences in sexual function were found from pre-to post-treatment and relative to controls using the Sexual Health Inventory for Men. In the second RCT[52] no significant changes in FSFI total scores were observed from pre-to post-treatment, the same was true for controls. In the third RCT[46] in women with dyspareunia, the FSFI total scores were significantly improved after PFPT compared to no treatment controls. In the fourth RCT[48] in women with dyspareunia, the FSFI-scores improved significantly from pre-to post-treatment, FSFI-lubrication and pain improved significantly compared to controls. Cervantes QoL-sexuality improved significantly from pre-to post-treatment but not compared to controls. The prospective study[49] found significant improvement in sexual function measured with the sexual health domain of the PPSS. The case study[35] demonstrated an improvement in sexual function measured with PPSS of more than 50% in 51% of the patients after PFPT.

Improvement of pelvic floor symptoms

Symptom improvement was investigated in 2 RCTs,[51,52] 4 prospective studies[44,47,49,50] and the case study.[35] One RCT[51] found equal and significant improvement in urinary symptoms in the CP/CPSS group measured with the NIH-CPSI. Interstitial Cystitis Symptom Index/Interstitial Cystitis Problem (ICSI/ICPI) scores also showed improvement in urinary symptoms but only in the IC/PBS patient group. Another RCT[52] was unable to demonstrate a decrease in urgency and frequency ratings and ICSI/ICPI scores after PFPT. In a prospective study[49] in patients with CP/CPPS, NIH-CPSI total scores significantly decreased with approximately 30% after treatment. The second prospective study[44] in CP/CPPS patients showed significant symptom improvement in the subdomain NIH-CPSI-micturition. The third prospective study[47] found significant improvement in the American Urological Association Symptom and Bother Score and VAS urgency and VAS voiding frequency scores in patients with CP/CPPS. Significant improvement in symptoms measured with ICSI/ICPI was seen in the fourth prospective study[50] in patients with IC. At long-term follow-up, the improvement in ICPI and ICSI scores remained statistically significant. The case study[35] found that overall 72% of patients reported marked (46%) or moderate (26%) improvement after PFPT. Urinary symptoms decreased significantly in patients reporting marked improvements. More than half of the patients treated with PFPT had a 25% or greater decrease in urinary symptom scores, as assessed by the PPSS.

Quality of life

Quality of life was measured in 3 RCTs,[48,51,52] and 4 prospective studies[44,45,49,50] and the case study.[35] One RCT[48] in patients with dyspareunia found significant improvement in QoL from pre-to post-treatment but not compared to controls measured with the Cervantes scale. Another RCT[52] in IC/PBS patients found no significant improvement relative to controls in quality of life using the 12-item Short Form Survey (SF-12). In the RCT[51] with CP/CPPS and IC/PBS patients no differences were found between treatment groups in the QoL-domain of the SF-12, whereas a significant pre-post treatment improvement was found using both the SF-12 and NIH-CPSI, but in the CP/CPPS group only. One prospective study[45] found a significant decrease in the perceived negative impact of PVD on QoL measured with a VAS-scale. Two prospective studies[44,49] in men with CP/CPPS found a significant improvement in the NIH-CPSI subdomain QoL scores. Another prospective study[50] in women with

IC showed significant improvements in the physical component summary score and mental component summary score of the SF-12. The case study[35] found significant improvement in quality of life domain of the NIH-CPSI after PFPT.

Patients' perceived effect

Patients' perceived effect was measured in 2 RCTs[51,52] one prospective study[49] and the case study.[35] In a RCT[52] comparing PFPT with lower back massage, a significantly larger proportion of patients than controls reported having benefited from treatment (59% vs 26%, respectively). Likewise, another RCT[51] found a significantly larger proportion of patients (57%) reporting benefit relative to controls (21%). In one prospective study,[49] 59% of the patients with CP/CPPS reported symptoms as moderately or markedly improved. In the case study,[35] 72% of patients had higher global response assessment scores indicating global improvement.

Table 2. Study characteristics of the included studies.

Study	Design/N	Population/ Mean age SD/ range)	Interventions/Duration	Outcome Measures (muscle tone/ function, pain, sexual function, pelvic floor symptoms, QoL, PPE)	Results
Fitzgerald et al.(2009)	RCT N=47	Women and men with IC/PBS and CP/CPPS PFPT: 41.1(11.4) Controls: 44.9(14.0)	PFPT Internal(pelvic) and external MTrP and connective tissue manipulation PF, hip girdle and abdomen Neuromuscular education Proprioceptive awareness exercises/ home exercises	PF digital palpation tenderness/pain	Pre-to post-treatment: IC/PBS (p<.001) CP/CPPS (p<.001) PFPT vs control: IC/PBS (p<.05) CP/CPPS: ns
			Control Full body Western massage	Likert pelvic pain	Pre-to post-treatment: IC/PBS (p<.01) CP/CPPS (p<.001) PFPT vs control: IC/PBS: ns CP/CPPS: ns
			10 weekly 1-hour sessions	NIH-pain	Pre-to post-treatment: CP/CPPS (p<.001) PFPT vs control: ns
				SHIM	Pre-to post-treatment:ns PFPT vs control:ns
				FSFI	Pre-to post-treatment: IC/PBS (p<.01) PFPT vs control: ns
				ICSI	Pre-to post-treatment: IC/PBS (p<.05) CP/CPPS (p<.01) PFPT vs control: IC/PBS (p<.05) CP/CPPS ns

Table 2. Continued

Study	Design/N	Population/ Mean age SD/ range)	Interventions/Duration	Outcome Measures (muscle tone/ function, pain, sexual function, pelvic floor symptoms, QoL, PPE)	Results
				ICPI	Pre-to post-treatment: IC/PBS (p<.01) CP/CPPS (p<.01) PFPT vs control: IC/PBS (p<.05) CP/CPPS: ns
				NIH-CPSI total	Pre-to post-treatment: CP/CPPS (p<.001) PFPT vs control: ns
				NIH-urinary	Pre-to post-treatment: CP/CPPS (p<.001) PFPT vs control (p<.01)
				NIH- QoL	Pre-to post-treatment: CP/CPPS (p<.05) PFPT vs control: ns
				Likert urinary urgency score	Pre-to post-treatment: IC/PBS (p<.01) PFPT vs control: ns
				Likert urinary frequency score	Pre-to post-treatment: IC/PBS (p<.05) PFPT vs control: ns

Table 2. Continued

Study	Design/N	Population/ Mean age SD/ range)	Interventions/Duration	Outcome Measures (muscle tone/ function, pain, sexual function, pelvic floor symptoms, QoL, PPE)	Results
				SF-12 physical scale	Pre-to post-treatment: IC/PBS ns CP/CPPS (p<.05) PFPT vs control: IC/PBS ns CP/CPPS ns
				SF-12 mental scale	Pre-to post-treatment: IC/PBS ns CP/CPPS ns PFPT vs control: IC/PBS ns CP/CPPS ns
				GRA	PFPT vs control: IC/PBS (p<.05) CP/CPPS ns
Schvartz-man et al.(2019)	RCT N=42	Pre- and postmenopausal women with dyspareunia PFPT: 51.9 (5.3) Controls: 50.6 (4.7)	PFPT PF digital palpation using NEW PERFECT scale Myofascial release PF PF infrared thermotherapy Hold/relax exercises Myofascial release of abdominal diaphragm, piriformis and iliopsoas S-EMG biofeedback training	New PERFECT scale	Pre-to post-treatment: P-mean (p<001) E-mean (p<.001) R-mean (p<.001) F-mean (p<.001) E-mean: NA C-mean (p≤.001) T-mean: ns PFPT vs control: P-mean (p<.005) E-mean (p<.005) R-mean (p<.05) F-mean (p<.01) E-mean: NA C-mean (p<.001) T-mean: (p<.05)

Table 2. Continued

Study	Design/N	Population/ Mean age SD/ range)	Interventions/Duration	Outcome Measures (muscle tone/ function, pain, sexual function, pelvic floor symptoms, QoL, PPE)	Results
			Control Heat applied to lower back and myofascial release of abdominal diaphragm, piriformis, m. iliopsoas	S-EMG resting tone (uV)	Pre-to post-treatment ns
				S-EMG sustained contraction duration	PFPT vs control ns Pre-to post-treatment ns
			7 one-hour sessions	VAS pain during sexual intercourse	PFPT vs control (p< .05) Pre-to post-treatment p<.001 PFPT vs control p<.001
				FSFI	Pre-to post-treatment: Desire (p<.05) Arousal (p<.05) Lubrication (p<.05) Orgasm (p<.001) Satisfaction (p<.001) Pain (p<.001) Total Score (p<.001) PFPT vs control: Desire ns Arousal ns Lubrication (p<.05) Orgasm ns Satisfaction ns Pain (p<.05) Total Score ns

Table 2. Continued

Study	Design/N	Population/ Mean age SD/ range)	Interventions/Duration	Outcome Measures (muscle tone/ function, pain, sexual function, pelvic floor symptoms, QoL, PPE)	Results
				Cervantes QoL	Pre-to post-treatment: Menopause Health (p<.001) Sexuality (p<.001) Couple relationship ns Physical ns Total Score (p<.001) PFPT vs control: Menopause Health ns Sexuality ns Couple relationship ns Physical ns Total Score ns
Ghaderi et al.(2019)	RCT N=64	Premenopausal women with dyspareunia PFPT: 34.9 (9.2) Controls: 35.7 (8.0)	PFPT Explanation of pelvic anatomy and function PF digital palpation proprioception Manual techniques PF Intravaginal EGS (110Hz, 80ms) PF home exercises	Modified Oxford -scale	PFPT vs control: PF muscle strength: (p<.001) PF muscle endurance (p<.05)
			Control No treatment	VAS pain	PFPT vs control: (p<.05) Significant difference remains at 3-months follow-up
			10 sessions in 3 months	FSFI	PFPT vs control: Desire (p<.05) Arousal (p<.05) Lubrication (p<.05) Orgasm (p<.05) Satisfaction (p<.05) Pain (p<.05) Total Score (p<.05)

Table 2. Continued

Study	Design/N	Population/ Mean age SD/ range)	Interventions/Duration	Outcome Measures (muscle tone/ function, pain, sexual function, pelvic floor symptoms, QoL, PPE)	Results
Fitzgerald et al. (2012)	RCT N=81	Women with IC/ PBS PFPT: 43.1 (15.1) Controls: 43.0 (12.9)	PFPT Internal(pelvic) and external MTrP and connective tissue manipulation PF, hip girdle and abdomen Neuromuscular education Proprioceptive awareness exercises/ home exercises	Likert bladder pain score	PFPT vs controls ns
				FSFI Total Score	PFPT vs controls ns
			Control Full body global therapeutic massage		
			10 weekly 1-hour sessions	ICSI	PFPT vs controls ns
				ICPI	PFPT vs controls ns
				Likert urgency score	PFPT vs controls ns
				Likert frequency score	PFPT vs controls ns
				SF-12 physical scale	PFPT vs control ns
				SF-12 mental scale	PFPT vs control ns
				GRA	PFPT vs control ($p<.005$)

Table 2. Continued

Study	Design/N	Population/ Mean age SD/ range)	Interventions/Duration	Outcome Measures (muscle tone/ function, pain, sexual function, pelvic floor symptoms, QoL, PPE)	Results
Gentilcore –Saulnier et al.(2010)	Prospective cohort study N=22	Women with and without PVD PFPT: 22.0 (2.0) Controls: 21.0 (1.0)	PFPT Explanation of pelvic anatomy and function Digital intravaginal techniques Insertion techniques using dilatators S-EMG- biofeedback training and EGS (15Hz,250msec) PF home exercises and dilator insertion	Vaginal palpation general tone	Pre-treatment group difference (p<.05) Post-treatment group difference ns PFPT pre-post-treatment (p<.01)
			Control No treatment	Vaginal palpation flexibility at the vaginal opening	Pre-treatment group difference (p<.01) Post-treatment group difference ns PFPT pre-post-treatment (p<.01)
			8 one-hour treatments in 12 weeks	Vaginal palpation relaxation capacity after contraction	Pre-treatment group difference (p<.05) Post-treatment group difference ns PFPT pre-post-treatment (p<.05)

Table 2. Continued

Study	Design/N	Population/ Mean age SD/ range)	Interventions/Duration	Outcome Measures (muscle tone/ function, pain, sexual function, pelvic floor symptoms, QoL, PPE)	Results
				Vaginal palpation strength	Pre-treatment group difference ns Post-treatment group difference ns PFPT pre-post-treatment ($p<.05$)
				S-EMG PFM tonic activity at rest	
				Deep PF muscles	Pre-treatment group difference ns Post-treatment group difference ns PFPT pre-post-treatment ns
				Superficial PF muscles	Pre-treatment group difference ($p<.05$) Post-treatment group difference ns PFPT pre-post-treatment ns
				S-EMG PF maximum voluntary contractile activity	Pre-treatment group difference ns Post-treatment group difference ns PFPT pre-post-treatment ns

Table 2. Continued

Study	Design/N	Population/ Mean age SD/ range)	Interventions/Duration	Outcome Measures (muscle tone/ function, pain, sexual function, pelvic floor symptoms, QoL, PPE)	Results
				S-EMG At rest and during painful pressure stimulus	Pre-treatment group difference (p<.005)
					Post-treatment group difference ns
					PFPT pre-post-treatment (p<.01)
				S-EMG PF pain responses	
				Deep PF muscles	Pre-treatment group difference ns
					Post-treatment group difference ns
				Superficial PF muscles	PFPT pre-post-treatment ns
					Pre-treatment group difference (p<.05)
					Post-treatment group difference ns
					PFPT pre-post-treatment (p<.0001)
				Pain intensity	Pre-treatment group difference (p<.01)
					Post-treatment group difference ns
					PFPT pre-post-treatment (p<.01)

Table 2. Continued

Study	Design/N	Population/ Mean age SD/ range)	Interventions/Duration	Outcome Measures (muscle tone/ function, pain, sexual function, pelvic floor symptoms, QoL, PPE)	Results
				Pain unpleasantness	Pre-treatment group difference ns Post-treatment group difference ns PFPT pre-post-treatment (p<.001)
				QoL	PFPT pre-post-treatment (p<.01)
Oyama et al. (2004)	Prospective pilot study N= 21	Women with IC PFPT: 42 (21-64)	PFPT Intravaginal massage and MTrP-release No control group	Modified Oxford scale muscle tone m iliococcygeus m pubococcygeus m obturator internus m coccygeus	 Pre-to post-treatment (p <.05) Pre-to post-treatment (p <.05) Pre-to post-treatment (p <.05) Pre-to post-treatment ns
			10 sessions for period of 5 weeks	Likert pain	Pre-to post-treatment (p < .01) Pre-treatment-to follow-up (p<0.01)
				Likert urgency	Pre-to post-treatment (p<.001) Pre-treatment-to follow-up (p<0.005)
				ICPI	Pre-to post-treatment (p<.05) Pre-treatment-to follow-up (p<0.05)

Table 2. Continued

Study	Design/N	Population/ Mean age SD/ range)	Interventions/Duration	Outcome Measures (muscle tone/ function, pain, sexual function, pelvic floor symptoms, QoL, PPE)	Results
				ICSI	Pre- to post-treatment (p<.05) Pre-treatment-to follow-up (p< .05)
				SF-12 physical scale	Pre-to post-treatment (p<.05) Pre-treatment-to follow-up ns
				SF-12 mental scale	Pre-to post-treatment (p<.05) Pre-treatment-to follow-up ns
Cornel et al. (2005)	Prospective cohort study N= 31	Men with CP/CPPS PFPT: 43.9 (23-70)	PFPT Explanation of pelvic anatomy and function s-EMG biofeedback training PF exercises	s-EMG rest uV	Pre-to post-treatment (p<.001)
			No control group	NIH-CPSI pain	Pre-to post-treatment (p<.001)
			6-8 sessions initially once a week later on every 2-4 weeks	NIH-CPSI micturition	Pre-to post-treatment (p<.001)
				NIH-CPSI total	Pre-to post-treatment (p<.001)
				NIH-CPSI QoL	Pre-to post-treatment (p<.001)

Table 2. Continued

Study	Design/N	Population/ Mean age SD/ range)	Interventions/Duration	Outcome Measures (muscle tone/ function, pain, sexual function, pelvic floor symptoms, QoL, PPE)	Results
Clemens et al. (2000)	Prospective cohort study N=19	Men with CP/CPPS PFPT: 36 (18-67)	PFPT Explanation of pelvic anatomy and function s-EMG biofeedback training Bladder training Hold/relax PF home exercises	VAS pain score	Pre-to post-treatment (p<.001)
				AUA bother score	Pre-to post-treatment (p<.001)
			No control group	AUA symptom score	Pre-to post-treatment (p<.001)
				VAS urgency	Pre-to post-treatment (p<.005)
			6 biweekly 1-hour sessions	VAS voiding frequency	Pre-to post-treatment (p<.005)
Anderson et al. (2011)	Prospective cohort study N=116	Men with CP/CPPS PFPT: 48 (19-80)	PFPT Internal manual techniques PF home exercises Psychologist daily instructions on reducing nervous system	VAS pelvic pain	Pre-to post-treatment (p<.001)
			No control group	PPSS sexuality	Pre-to post-treatment (p<.001)
				PPSS symptom severity	Pre-to post-treatment (p<.001)

Table 2. Continued

Study	Design/N	Population/ Mean age SD/ range)	Interventions/Duration	Outcome Measures (muscle tone/ function, pain, sexual function, pelvic floor symptoms, QoL, PPE)	Results
			5 (30 to 60 min) sessions for 6 days	NIH-CPSI Total Score	Pre-to post-treatment ($p<.001$) Pre-treatment-to follow up ($p<.001$)
				NIH-CPSI QoL	Pre-to post-treatment ($p<.001$)
				GRA	59% of patients reported symptoms as moderately or markedly improved
Anderson et al.(2005)	Case study N= 138	Men with CP/CPPS PFPT: 40.5 (16-79)	PFPT Internal manual techniques Deep tissue mobilisation Relaxation exercises Daily PF home relaxation exercises	VAS-pelvic pain	Pre-to post-treatment: Markedly improved group ($p<.01$) Moderately improved group ns
			No control group	PPSS pain	Pre-to post-treatment: Markedly improved group ($p<.01$) Moderately improved group ns
			8 biweekly sessions and 4 weekly sessions	NIH CPSI pain	Pre-to post-treatment: Markedly improved group ($p<0.001$) Moderately improved group ($p<.05$)
				PPSS sexual function	63% of the patients had a 25% or greater improvement in sexual function; 56(43%) achieved a 50% or greater response after PFPT

Table 2. Continued

Study	Design/N	Population/ Mean age SD/ range)	Interventions/Duration	Outcome Measures (muscle tone/ function, pain, sexual function, pelvic floor symptoms, QoL, PPE)	Results
				PPSS urinary symptoms	Pre-to post-treatment: Markedly improved group ($p<.001$) Moderately improved group ns
				NIH-CPSI Total score	Pre-to post-treatment: Markedly improved group ($p<.001$) Moderately improved group ($p<.01$)
				NIH-CPSI urinary symptoms	Markedly improved group ($p<.05$)
				NIH-CPSI QoL	Moderately improved group ns
					Markedly improved group ($p<.001$) Moderately improved group ($p<.05$)

RCT=Randomized Controlled Trial; PFPT=Pelvic Floor Physiotherapy; PF= pelvic floor; IC/PBS=Interstitial Cystitis/Painful Bladder Syndrome; CP/CPPS=Chronic Prostatitis/Chronic Pelvic Pain Syndrome; MTrP=Myofascial Trigger Point; PPE=patient's perceived effect; QoL=Quality of Life; SHIM=Sexual Health Inventory for Men; FSFI=Female Sexual Function Index; ICSI=Interstitial Cystitis Symptom Index; ICPI=Interstitial Cystitis Problem Index; NIH/CPSI=National Institute of Healh Chronic Prostatitis Symptom Index; GRA=Global Response Assessment; NEW-PERFECT=Performance/Endurance/Repetition/Fast/Elevation/Co-contraction/Timing; NA=not applicable; s-EMG=surface Electromyography; MVC=Maximum Voluntary Contraction; EGS=Electrogalvanic Stimulation; TENS=Transcutaneous Electroneurostimulation; SF-12=12-item Short Form Survey; VAS=Visual Analogue Scale; PVD=Provoked Vulvodynia; AUA=American Urological Association Symptom and Bother Score; PPSS=Pelvic Pain Symptom Scale.

Note. ns=non-significant

Discussion

Three of 4 RCTs found positive effects of PFPT compared to controls on five of six outcome measurements (pelvic floor muscle resting tone and function, various features of pain, sexual function, pelvic floor symptoms, and patient's perceived effect). QoL remained unchanged in 2 of 3 RCTs. The 5 prospective studies found significant improvements from pre- to post-treatment on all the outcome measures that they assessed (pelvic floor muscle resting tone and function in 3 studies; pain in all studies; sexual function in one study; pelvic floor symptoms in 4 studies, QoL in 4 studies and patients perceived effect in 1 study). Finally, the case study found positive effects on all outcome measures that were assessed (pain, sexual function, symptoms, QoL and patients perceived effect). Taken together, the findings of this systematic review suggest that PFPT can be beneficial in patients with PFH.

However, it should be noted that the RCT[52] with the largest sample size demonstrated an effect of PFPT in only 1 of 5 outcome measures, namely patient's perceived effect. This was 1 of 2 RCTs[51,52] that measured the least effect of PFPT in patients with IC/PBS. It is not entirely clear why this particular RCT yielded negative results. Possibly, PFH in these patients is secondary to a visceral abnormality and therefore they may benefit less from PFPT than other PFH patient groups. The treatment modalities of PFPT used in this protocol may have been insufficient for this patient group, or perhaps the pain and urological complaints in this patient group was unrelated to PFH. This was also the study in which a substantial proportion of the participants (62%) reported at least one adverse event, the most common adverse event being pain in the bladder or pelvis. The high pain ratings may have negatively influenced the other outcome measurements. The other RCT[51] had post treatment data of only 11 participants with IC/PBS and should therefore be considered less reliable.

Treatment of PFPT proved to be most efficacious in improving muscle resting tone and function and pain. The 5 studies that measured muscle resting tone and function directly, all found significant improvements,[44-46,48,50] and for pain 9 of 10 studies found pain to significantly decrease with PFPT. Interestingly, the 2 RCTs[46,48] in women with dyspareunia found treatment effects in muscle function, a reduction in pain, as well as improvements in sexual function. Muscle function may be an important variable involved in sexual function. In an experimental study in women with PVD, Naess and Bø[53] found maximal voluntary pelvic floor muscle contraction to reduce vaginal resting pressure and resting s-EMG activity. Their findings suggest that improving maximal voluntary pelvic floor muscle contractions are instrumental in treating PFH. In a study

in patients with PVD[45] pain and muscle resting tone improved but unfortunately, sexual function was not investigated. Three studies[45,46,48] showed that PFPT decreased vulvar pain and pain during intercourse. These findings suggest that PFH is a maintaining factor in vulvar pain syndromes. Sexual function was also improved in patients who did not present with sexual problems as their primary complaint.[35,49]

QoL improved significantly in 6 of 8 studies,[35,44,45,48-50] but no improvement was seen in the 2 RCTs that measured QoL.[51,52] These were the RCTs in patients with IC/PBS, the majority of whom had high pain ratings during treatment. Possibly other contributing factors may be involved that affect their QoL, such as depression and anxiety as a consequence of chronic pain.[54] An outcome measure related to QoL, self-reported global perceived effect, improved significantly in all four studies that assessed this variable.[35,49,51,52] Surprisingly, the RCT[52] with the largest sample of IC/PBS patients did report greater global perceived effect than the controls. Even though their symptoms did not improve significantly, patients apparently did feel that the treatment was worthwhile. The authors of the study neither noted nor discussed this discrepancy. Other than a possible placebo effect, we have no explanation for this finding.

Several limitations of the studies in this systematic review impede the interpretation of the findings, such as the heterogeneity of patient groups and outcome measures, the small number of RCTs that met our inclusion criteria and the wide range of treatment modalities. In addition, an RCT is a prerequisite for preventing selection bias, performance bias and detection bias which was a common limitation in most of the studies reviewed. Treatment programmes varied considerably in their content and duration and some data were incompletely reported. Most studies did not present follow-up data of adequate duration. In addition, none of the 10 studies were of high quality.

Although muscle resting tone improved in most studies that measured this, these findings should be interpreted with caution. Muscle resting tone was mostly quantified by digital palpation using various scales. These scales require a subjective interpretation on the part of the assessor and in some studies, the physical therapist providing the treatment was also the one assessing improvement. This may have biased the findings towards a positive outcome. In three studies muscle resting tone and function was established using more objective measures such as s-EMG,[44,45,48] but caution is warranted in clinical use and interpretation of this measure as well. Many factors influence amplitude, skin conductance and artefacts. Other common problems

with s-EMG include a wide variation in equipment and electrodes, protocols and non-standardized normal rest s-EMG values.[55] It would be advisable to use s-EMG measures in conjunction with other muscle resting tone measures.[13,48]
Overall, it is clear that better outcome measures are needed. Another issue concerns the use of questionnaires. The wide range of conditions in which PFH seems to be involved as well as the wide range of PFH symptoms render the decision about which questionnaires to include in a study, a difficult one. Only validated patient related outcome measures will bring this field further along.

Conclusion

The findings of this systematic review suggest that PFPT can be beneficial in patients with PFH. Given the low to moderate study quality, more high-quality RCTs with standardized treatment protocols, validated outcome measures, sufficient sample sizes and long-term follow-ups should be undertaken to confirm the effectiveness of PFPT in the treatment of PFH.

Appendix 1.

Search strategy

((((“Pelvic floor”[ti] OR “Pelvic Diaphragm”[ti] OR “Pelvic Floor”[majr] OR “Pelvic Floor/physiopathology”[mesh] OR “Pelvic Floor Disorders”[majr] OR (“Practice Guideline”[ptyp] AND “pelvic”[ti]) OR “pelvic”[ti]) AND (Overactivity OR hypertonicity OR hypertonic OR hypertonic* OR tone OR tonicity OR tonic OR relaxation OR Non-relaxing OR Nonrelaxing OR spasm OR spasms OR stiffness OR stiff OR contracture OR contracting OR cramp OR cramps OR cramp OR “levator ani”[tw] OR “levator ani syndrome” OR “levator syndrome”[tw] OR “muscle activity”[tw] OR “Practice Guideline”[ptyp] OR “tenderness”[tw])) OR “pelvic floor hypertonia” OR “pelvic floor hypertonicity” OR “pelvic floor hypertonus”) AND (micturition OR micturit* OR defecation OR defaecation OR defecat* OR defaecat* OR sexual function OR sexual dysfunction OR sexual function* OR sexual dysfunction* OR prolapse OR prolaps* OR stress Urinary incontinence OR Urge urinary incontinence OR mixed incontinence OR incontinence OR incontin* OR overactive bladder OR urgency OR frequency OR obstructed micturition OR constipation OR constipat* OR dyssynergia OR dyssynerg* OR obstipation OR obstipat* OR vulvodinia OR vulvodynia OR vulvodin* OR vulvodyn* OR dyspareunia OR vaginism OR vaginismus OR vaginism* OR erectile dysfunction OR chronic testicular pain OR chronic pelvic pain OR chronic pelvic pain syndrome OR CPPS OR ejaculation OR premature ejaculation OR premature ejacul* OR Provoked vestibulodynia OR Dysfunctional voiding OR Voiding dysfunction OR Obstructed defaecation OR Obstructed defecation OR Coccygodynia OR Anal pain OR Chronic anal fissure OR Chronic anal fissures OR Proctalgia OR Ejaculation precox OR Ejaculation praecox OR Scrotal pain) NOT (((“Child”[mesh] OR “child”[ti] OR “children”[ti] OR “girl”[ti] OR “girls”[ti] OR “boy”[ti] OR “boys”[ti] OR pediatr*[ti] OR paediatr*[ti]) NOT (“Adult”[mesh] OR “adult”[ti] OR “adults”[ti])) OR “Pharmaceutical Preparations”[majr] OR “medication”[ti] OR “medications”[ti] OR “drug”[ti] OR “drugs”[ti] OR “Drug Therapy”[majr] OR pharmaco*[ti] OR “Botulinum Toxins”[majr] OR “Botulinum Toxins”[ti] OR “Botulinum Toxin”[ti] OR “botox”[ti] OR “Cholinergic Antagonists”[majr] OR “Cholinergic Antagonists”[ti] OR “Cholinergic Antagonist”[ti] OR anticholinergic*[ti] OR anti-cholinergic*[ti] OR ((“Nervous System Diseases”[majr] OR “Nervous System Diseases”[ti] OR “Nervous System Disease”[ti] OR “neurological diseases”[ti] OR “neurological disease”[ti]) NOT (“Spasm”[majr] OR “spasm”[ti] OR “spasms”[ti])) OR ((“Surgical Procedures, Operative”[majr] OR “surgery”[ti] OR surgical*[ti]) NOT “after”[ti]) OR “Implantable Neurostimulators”[majr] OR “Implantable Neurostimulators”[ti] OR “Implantable Neurostimulator”[ti] OR neuromodulat*[ti] OR rehabilitat*[ti] OR “Rehabilitation”[majr] OR “rehabilitation”[Subheading] OR “physical therapy modalities”[majr] OR “physical therapy”[ti] OR “physiotherapy”[ti] OR physiotherap*[ti] OR “exercise”[majr] OR “exercise”[ti] OR “exercises”[ti] OR “exercise therapy”[majr] OR “biofeedback, psychology”[majr] OR “biofeedback”[ti] OR “bio-feedback”[ti] OR bio-feedback*[ti] OR “myofeedback”[ti] OR myofeedback*[ti] OR “myo-feedback”[ti] OR myo-feedback*[ti] OR “electrostimulation”[ti] OR electrostimulat*[ti] OR “electric stimulation”[majr] OR “electric stimulation”[ti] OR “electrical stimulation”[ti] OR “life style”[majr] OR “life style”[ti] OR “lifestyle”[ti] OR “Conservative Treatment”[majr] OR “conservative management”[ti] OR “conservative treatment”[ti] OR “muscle therapy”[ti] OR “Electromyography”[majr] OR “electromyography”[ti] OR electromyogr*[ti] OR “EMG”[ti] OR “EMGs”[ti] OR “magnetic resonance imaging”[majr] OR “magnetic resonance”[ti] OR “Ultrasonography”[majr] OR ultrasoun*[ti] OR ultrason*[ti] OR “mapping”[ti]) AND english[la]) AND (“2009/01/01”[PDAT] : “3000/12/31”[PDAT])

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CHAPTER 4

To what extent are anorectal function tests comparable?
A study comparing digital rectal examination, anal electromyography, 3-dimensional high resolution anal manometry and transperineal ultrasound

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Abstract

Background

Anorectal function tests are helpful for objective investigation of anorectal (dys) function. A variety of tests are available, but there is no recommendation when to perform which test. Furthermore, which test is the most accurate is controversial and the correlation between these tests is not very clear. The aim of our study was to examine the correlation of anal pressures and the possibility to diagnose pelvic floor dyssynergia between digital rectal examination (DRE) and several anorectal function tests.

Methods

Between January 2020 and April 2022, all men and women aged 18 to 80 years, treated at the Proctos Clinic, who were referred for pelvic floor physical therapy (PFPT) by the surgeon and underwent anorectal function tests, were included. DRE was performed to establish the anal pressure at rest, and during squeeze and straining. Anorectal function tests included 3D High- resolution anal manometry (3D-HRAM), balloon expulsion test (BET), transperineal ultrasound (TPUS) and surface electromyography (s-EMG).

Results

A total of 50 patients, 37 (74%) females, were included. Median age was 51 years. Twenty-three (62%) females had a history of two or more vaginal deliveries. The most frequent reason for referral for PFPT was fecal incontinence in 27 (54%) patients. The assessed pressures and pelvic floor function measured with DRE by the surgeon and the pelvic floor physical therapist during rest, squeeze and straining correlated in 78%, 78% and 84%, respectively. Correlation between DRE and 3D-HRAM or s-EMG, was better for squeeze pressures than resting pressures. The correlation between s-EMG and 3D-HRAM was better during squeeze than at rest with an agreement of 59% and 37% respectively.

Conclusion

DRE by an experienced investigator is of sufficient value for daily clinical practice to detect dyssynergia and to measure sphincter tone. Commonly performed anorectal

function tests correlate poorly with DRE and with other anorectal function tests. When conservative treatment fails, further investigation is warranted, however these results should be interpreted with caution.

What does this paper add to the literature?

Anorectal function tests as the 3D high resolution anorectal manometry, balloon expulsion test, surface electromyography and transperineal ultrasound are all frequently performed in the diagnostic work-up in patients with defecation disorders. No previous study has compared these tests regarding their outcomes, nor has the interrater agreement been measured regarding the digital rectal examination by two experienced observers. Furthermore, transperineal ultrasound is in all probability not frequently used and therefore underexposed in the diagnostic workup of patients with dyssynergic defecation.

Introduction

Anorectal function disorders like fecal incontinence and chronic constipation are very common. Generally, a conservative approach with lifestyle advice, fibers, laxative and pelvic floor physical therapy will improve complaints in many patients. When unsuccessful, or the underlying cause seems unclear, these patients are referred to a specialist for further evaluation of anorectal function and possible therapy.[1] Besides digital rectal examination (DRE), a variety of tests are available to evaluate anorectal function. One may then objectively assess e.g., low, or high tone of the anal sphincter, paradoxical contraction, or inadequate relaxation of the pelvic floor.

Available tests are for example, anorectal manometry (ARM), 3-dimensional high-resolution anorectal manometry (3D-HRAM), balloon expulsion test (BET), surface electromyography with or without an intra anal probe (s-EMG), transperianal ultrasound defecography and the classical defecography. Although some studies suggest that DRE alone is a useful tool to identify anorectal disorders,[2,3] others propose that anorectal function tests objectively evaluate anorectal function and might provide a predictive value for treatment results and influence management.[4-9] Which anorectal function test is the most accurate, is under debate.

The s-EMG with intra-vaginal or -anal electrode probes is commonly utilized by the pelvic floor physical therapist to confirm DRE and evaluate therapy.[5,10] ARM is often considered the gold standard to measure anal pressures, however lack of reproducibility mentioned in several studies makes the test questionable.[11-16] Few studies compared ARM with anal s-EMG and showed limited concordance.[17-19] A more recent study compared ARM with DRE to determine dyssynergia and concluded that there was a moderate agreement.[20]

According to the ROME IV criteria dyssynergia is established by two out of three anorectal function tests: first; abnormal anorectal evacuation pattern measured with ARM or s-EMG, second; abnormal BET, and third; impaired rectal evacuation diagnosed on imaging studies (e.g., defecography).[7] Furthermore, examinations as DRE and transperineal ultrasound are not mentioned in this context and a clear gold standard for one of these tests is not suggested. One could wonder whether a restricted use of these additional tests is justified.

Could we rely on DRE and use additional tests only in complex patients?

Another reason to perform anorectal function tests is an attempt to objectively measure the anal pressures. Since there is no gold standard, a reappraisal for DRE by experienced investigators seems worthwhile investigating.

The Proctos Clinic is a tertiary referral center for specialized proctological care with experienced surgeons, a pelvic floor physical therapist and a fully equipped anorectal function laboratory. The aim of our study was to examine the correlation of the anal pressures between DRE, 3D-HRAM and the s-EMG. DRE, 3D-HRAM, s-EMG, BET and the trans-perineal ultrasound were compared to diagnose dyssynergia. Furthermore, we sought to assess the level of agreement between DRE performed by the surgeon and the pelvic floor physical therapist.

Material and Methods

Study population

The Proctos Clinic is a tertiary referral center for anorectal function complaints. Between January 2020 and April 2022, men and women aged 18 to 80 years, who underwent anorectal function tests and were referred for pelvic floor physical therapy (PFPT), were invited to participate in the study. Exclusion criteria were noncompliance with verbal instruction in Dutch and current psychiatric disorders. Patients in whom the timeframe was more than 4 weeks between the tests were excluded as the measurements may not be comparable.

Patients first visited the surgeon, who performed a DRE and a transperineal ultrasound and counseled the patients for the study. Subsequently, patients were asked to participate in case they were referred for 3D-HRAM, BET and pelvic floor physical therapy. The pelvic floor physical therapist also performed DRE and s-EMG at first visit. The pelvic floor physical therapist was blinded for the DRE of the surgeon and also for the results of de 3D-HRAM, BET and transperineal ultrasound. All appointments were scheduled within 4 weeks. Results of the different tests were prospectively recorded. All patients signed a written informed consent before entering the study. The study was approved by the Medical Ethics Review Committee of the Amsterdam University Medical Centres, location AMC.

Anorectal investigations

Digital rectal examination

DRE was performed by all five surgeons and the pelvic floor physical therapist in the same standardized way. The procedure of DRE was explained to the patient. During the assessment the patient was lying on his/her left side with the knees flexed at 90.$^{0.}$ The examiners used non-allergic gloves lubricated with water-based gel. All patients

were asked to empty their bladder before the assessment. After careful insertion of the index finger, the sphincter tone was assessed at rest and scored as low, normal- or high (Table 1). Squeeze tone was evaluated as the increment in pressure and scored similar. Then the patient was asked to squeeze for 30 seconds. The squeeze pressure was scored as low, normal, or high. Subsequently, the examiner placed his/her left hand on the patient's abdomen and the patient was asked to push and bear down. Push effort was scored as relaxation, indifferent or paradoxical contraction.

Surface electromyography (s-EMG)

Pelvic floor muscle tone and function were measured with s-EMG (μV) [10] with an intra-anal probe (MAPLe® Novuqare Pelvic Health B.V. CE 0344, Rosmalen, the Netherlands). This is a probe with a matrix of 24 electrodes enabling measuring EMG signals from the different sides and layers of the pelvic floor muscles. The EMG probe is placed intra-anal, with the reference electrode placed on the spina iliaca anterior superior. Patients were asked to perform four consecutive tasks: 1) one minute rest where patients were instructed to feel the pelvic floor in rest 2) three maximum voluntary contractions where patients were instructed to perform a controlled contraction and relaxation of the pelvic floor muscles 3) one endurance contraction where patients were instructed to contract the pelvic floor muscles at such a level that they could hold for 30 seconds and 4) one push effort where the patient was asked to bear down. The examiner was holding the probe to keep it in place. From these s-EMG measurements, mean s-EMG amplitudes per electrode were calculated. A sustained increase in surface s-EMG activity (>50% increase from baseline) on attempted bearing down was defined as dyssynergia. The EMG values are presented as absolute values (μV). Normal values have not been published yet. For this reason, the pelvic floor physical therapist estimated the normal values for men and women on clinical experience and a recent study where EMG values were measured during PFPT in patients with a chronic anal fissure[21] (Table 1). Results of the one year follow-up will be published shortly.

3D high resolution anal manometry (3D-HRAM)

The 3D-HRAM was performed by a nurse continence specialist and, the methods are previously described.[22] The anorectal probe has 256 pressure sensors on 16 lines, each line having 16 circumferential sensors. The probe, which is covered by a disposable sheath, has a diameter of 10.75 mm, a length of 64 mm and an internal lumen to inflate the balloon (3.3 cm long with a capacity of 400cc). Patients underwent the test in the

left lateral position. Patients were asked to use a MICROLAX® enema the night before and the morning of the test. Pressures were measured at rest, during squeeze and during straining according to the London protocol (Carrington IAPWG 2019). Analysis of the manometry data was performed with ManoView (Given Imaging, Duluth, GA, USA). The mean resting pressure (MRP) and mean squeeze pressure (MSP) were measured by the software and were additional visually reviewed by the gastroenterologist RF. Fig 1 and fig 2 shows examples of the pressure profile during rest (MBP) and during squeeze (MSP) with ManoView. Normal values have been published by several authors and show a large range.[14,23-28] Based on these studies we considered an anal rest or squeeze pressure lower than 50 mmHg as 'low'. For comparison with the other tests, the anal pressures were categorized as described in Table 1.

Figure 1. 3D-HRAM. Normal pressure profile during rest (MBP), increase during squeeze (MSP) and decrease during straining (ST).

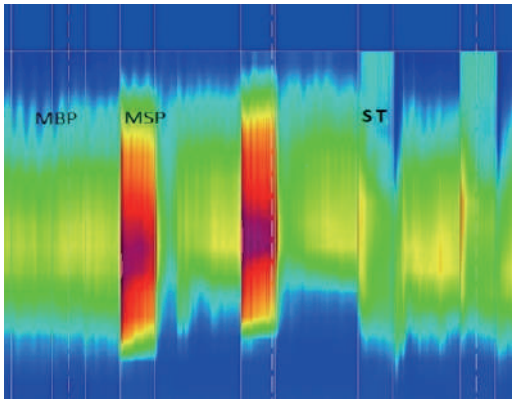
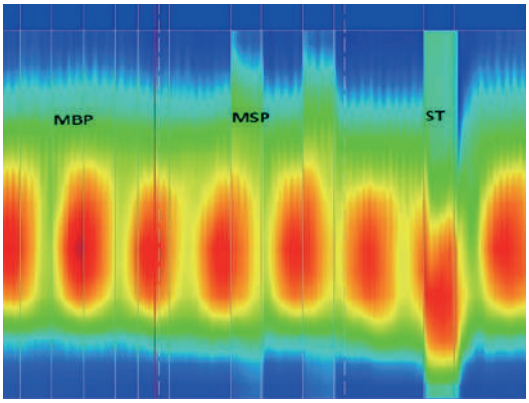


Figure 2. 3D-HDRAM. Dyssynergia. A high basal pressure (MBP) profile is seen with no changes in pressure during maximal squeeze (MSP) and straining (ST).



Balloon expulsion (BET)

A non-sterile disposable balloon (BARD, Covington, USA) was filled with 50cc water or until the patients felt a desire to defaecate. Balloon expulsion time differs in literature. According to several studies, evacuation within 1 minute was considered as normal.[28-30] The BET was performed by a nurse continence specialist in our clinic and results were scored <1 minute or >1 minute[1] (Table 1).

Transperineal ultrasound (TPUS)

Transperineal ultrasound was performed with a standard BK Medical scanner (BK Medical ApS, Herlev, Denmark) and a transducer (BK Medical, type 2C9, 13 MHz). The patient was lying supine with the legs flexed. As with the 3D-HRAM, patients were asked to use a MICROLAX® enema the night before and the morning of their appointment. Transperineal ultrasound was performed using a conventional curved array probe rested on the perineum to gain dynamic two-dimensional mid plane sagittal views. For the real time movement 50 ml echo lucent gel was introduced in the rectum. The patient was asked to squeeze, bear down and cough while views were digitally recorded. The movements during straining were categorized as relaxation, indifferent and paradoxical contraction. Evacuation of gel during straining was categorized as yes or no (Table 1).

Table 1. Summary of anorectal function tests and their categorized outcomes

	Mean resting pressure	Mean squeeze pressure	Push	Evacuation
DRE surgeon	1. Low 2. Normal 3. High	1. Low 2. Normal 3. High	1. Relaxation 2. Indifferent 3. Paradoxical	-
DRE Pelvic floor physical therapist	1. Low 2. Normal 3. High	1. Low 2. Normal 3. High	1. Relaxation 2. Indifferent 3. Paradoxical	-
3D-HRAM	1. Low: 0-49 mmHg 2. Normal: 50-100 mmHg 3. High: >100 mmHg	1. Low: 0-49 mmHg 2. Normal: 50-200 mmHg 3. High: >200 mmHg	1. Relaxation 2. Indifferent 3. Paradoxical	-
s-EMG	<u>Women</u> 1. Low: 0-2.0 2. Normal:2.1-5.0 3. High: > 5.1 <u>Men</u> 1. Low: 0-3.0 2. Normal 3.1-6.0 3. High: > 6.1	<u>Women</u> 1. Low: 0-6.0 2. Normal: 6.1-15.0 3. High: > 15.1 <u>Men</u> 1. Low: 0-9.0 2. Normal: 9.1-18.0 3. High: > 18.1	1. Decrease of electrical activity (relaxation) 2. Indifferent 3. Increase of electrical activity (paradoxical)	-

Table 1. Continued

	Mean resting pressure	Mean squeeze pressure	Push	Evacuation
Trans perianal echo	-	-	1. Relaxation 2. Indifferent 3. Paradoxical	1. Yes 2. No
BET	-	-	-	1. <1 min = normal 2. >1 min = abnormal

DRE digital rectal examination*; 3D-HRAM* 3-dimensional high resolution anorectal manometry*; s-EMG* surface electromyography*; BET* balloon expulsion test.

Statistical analysis

All statistical analyses were performed using SPSS (IBM, SPSS Statistics 28). Continuous data were described as mean or median depending on the distribution, including range and standard deviation. Statistical analysis was performed by comparing categorical results of anal pressures with descriptive statistics using crosstabs, namely, the resting and squeeze pressures and straining movement of DRE by the surgeon and pelvic floor physical therapist, 3D-HRAM, s-EMG, transperineal ultrasound (with echo lucent gel) and BET. The interrater agreement for DRE, which included tone during rest and squeeze and straining movement, between the referring surgeon and the pelvic floor physical therapist was assessed by using the Cohen's Weighted Kappa test. Agreement was classified as follows: poor agreement (0.00-0.20), fair (0.21-0.40), moderate (0.41-0.60), substantial (0.61-0.80), and almost perfect agreement (0.81-1.00). p values of <0.05 were considered significant.

Results

Patients, demographics, and clinical characteristics

Between January 2020 and April 2022, 56 patients were referred for PFPT by the surgeon and underwent anorectal function tests in the diagnostic work-up. Six patients were excluded due to incomplete data because the patient cancelled an appointment or when treatment started between the different tests. The appointment for the 3D-HRAM was always prior to, or at the same day as the pelvic floor physical therapist. Demographics and clinical characteristics of the study group are detailed in Table 2. A total of 37 (74%) females were included and median age was 51 years. Twenty-three (62%) females had two or more vaginal deliveries. Thirty-one (62%)

patients previously received PFPT. Most frequent indication for referral for PFPT was fecal incontinence in 27 patients (54%).

Table 2. Patient characteristics.

	No. patients
Gender	
Male, n (%)	13 (27)
Female, n (%)	37 (74)
Median age, years (SD)	51 (15)
Indication, n (%)	
Fecal incontinence	27 (54)
Obstructed defecation	10 (21)
Chronic anal fissure	3 (6)
Haemorrhoidal disease	2 (4)
Other	8 (17)
Vaginal parity, n (%)	
0	7 (19)
1	7 (19)
2	14 (38)
>3	9 (24)
Rectal surgery in the past, n (%)	9 (18)
Radiotherapy in de past, n (%)	1 (2)
Urologic or gynecologic surgery in the past, n (%)	10 (20)
Neurological or connective tissue disease, n (%)	3 (6)
Pelvic floor physical therapy in the past, n (%)	31 (62)

Interrater agreement digital rectal examination

The assessed sphincter tone and pelvic floor muscle function with DRE by the surgeon and the pelvic floor physical therapist during rest, squeeze and straining correlated in 78%, 78% and 84%, respectively. This resulted in substantial agreement for assessing the resting tone with a Cohen's Weighted Kappa (κ) of 0.749 (95% CI 0.612-0.886). In the assessment of the squeeze tone this was somewhat lower, but still substantial, with a (κ) of 0.620 (95% CI 0.432-0.807). When assessing straining, they agreed almost perfect with a (κ) of 0.819 (95% CI 0.700-0.938).

The prolonged squeeze (30 seconds) was only performed by few surgeons and therefore, we omitted this variable from the analysis.

Digital rectal examination by the surgeon and pelvic floor physical therapist and anorectal manometry (n=46 and n=45)

When classifying the resting tone and pressure as low, normal, or high, 23 (47%) patients were assessed similar by the surgeon's DRE and the 3D-HRAM. In the assessment of squeeze tone and pressures this was somewhat better with 31 (65%)

patients. DRE of the pelvic floor physical therapist was similar to 3D-HRAM in 26 (53%) and 32 (65%) patients in the assessment of the resting and squeeze tone and pressure respectively.

Digital rectal examination by the surgeon and pelvic floor physical therapist and surface electromyography (n=49 and n=50)

The resting tone assessed by the surgeon's DRE and s-EMG activity was similar in only 18 (36%) patients. For squeeze this was 32 (65%). DRE by the pelvic floor physical therapist correlated in 18 (36%) and 41 (82%) patients with s-EMG in the assessment of resting tone and squeeze tone. The surgeon and the pelvic floor physical therapist both classified the resting tone with DRE in respectively three and four patients as 'low' while s-EMG activity assessed 'high'. One patient with a chronic anal fissure was classified 'high' for squeeze tone with DRE by both the surgeon and pelvic floor physical therapist but classified 'low' with s-EMG.

Anorectal manometry and surface electromyography (n=49)

When the results are categorized as low, normal, and high, the 3D-HRAM and s-EMG correlated well in only 18 (37%) patients when comparing the resting pressure and electric activity. With 29 (59%) patients this was better when comparing the squeeze tone and electric activity. Overall, four patients who were classified as 'low' on the 3D-HRAM were classified 'high' with s-EMG activity concerning resting pressure and one patient vice versa during squeeze pressure.

Comparing detecting dyssynergia

Balloonexpulsion test and evacuation of gel during TPUS (n=19)

Four patients were not able to evacuate the gel despite being able to expel the balloon within one minute. Three patients evacuated the gel – of whom two not completely – while they were not able to expel the balloon within one minute (Table 3).

Table 3. Balloon expulsion test (BET) versus evacuation of gel during transperineal ultrasound

		Evacuation of gel during TPUS		
		Yes	**No**	**Total**
BET	<1 minute	5	4	9
	>1 minute	3	7	10
Total		8	11	19

TPUS and evacuation of gel during TPUS (n=24)

Half of patients who underwent TPUS with echo lucent gel evacuated the gel (Table 4). Nineteen patients were classified as 'indifferent' regarding the straining movement.

Table 4. Transperineal ultrasound (TPUS) versus evacuation of gel during TPUS

		Evacuation of gel during TPUS		
		Yes	**No**	**Total**
TPUS	Relaxation	3	0	3
	Indifferent	9	10	19
	Paradoxical	0	2	2
Total		12	12	24

TPUS and BET (n=23)

Eighteen patients were classified 'indifferent' on the transperineal ultrasound (Table 5). Almost half of them expelled the balloon within one minute and the other half in more than one minute or not at all. One patient showed normal 'relaxation' of the puborectalis muscle when straining on TPUS, whereas he was not able to expel the balloon within one minute.

Table 5. Transperineal ultrasound (TPUS) versus balloon expulsion test (BET)

		BET		
		< 1 minute	**> 1 minute**	**Total**
TPUS	Relaxation	1	3	4
	Indifferent	10	8	18
	Paradoxical	0	1	1
Total		11	12	23

S-EMG versus BET (n=37)

Thirteen patients (35%) were classified as 'paradoxical' of whom almost half was able to expel the balloon within one minute and half could not (Table 6). Fourteen patients were classified as 'indifferent' of whom nine was not able to expel the balloon within one minute.

Table 6. Surface electromyography (s-EMG) versus balloon expulsion test (BET)

		BET		
		< 1 minute	**> 1 minute**	**Total**
s-EMG	Relaxation	7	3	10
	Indifferent	5	9	14
	Paradoxical	6	7	13
Total		18	19	37

3D-HRAM with BET (n=37)

Four out of 10 patients (40%) who showed paradoxical straining on the 3D-HRAM were able to expel the balloon within one minute while five out of the 16 patients (31%) who showed normal relaxation could not expel the balloon within one minute (Table 7).

Table 7. 3D high resolution anorectal manometry (3D-HRAM) versus balloon expulsion test (BET)

		BET		
		< 1 minute	**> 1 minute**	**Total**
3D-HRAM	Relaxation	11	5	16
	Indifferent	3	8	11
	Paradoxical	4	6	10
Total		18	19	37

DRE by the surgeon versus BET (n=37)

Half of the 10 patients who were classified as ‘indifferent’ were able to expel the balloon within one minute (Table 8). Of the patients who were assessed as normal ‘relaxation’ or ‘paradoxical’ respectively 9 of 15 (67%) and 4 of 12 (33%) were able to expel the balloon within one minute.

Table 8. Digital rectal examination (DRE) of the surgeon versus balloon expulsion test (BET)

		BET		
		< 1 minute	**> 1 minute**	**Total**
DRE surgeon	Relaxation	9	6	15
	Indifferent	5	5	10
	Paradoxical	4	8	12
Total		18	19	37

DRE by the pelvic floor physical therapist versus BET (n=37)
Results are almost similar with the DRE by the surgeon.

S-EMG versus TPUS (n=32)
Twelve patients (37%) showed the same results concerning classifying the puborectalis muscle movement in these tests (Table 9).

Table 9. Surface electromyography (s-EMG) versus transperineal ultrasound (TPUS)

		TPUS			
		Relaxation	**Indifferent**	**Paradoxical**	**Total**
s-EMG	Relaxation	2	6	0	8
	Indifferent	3	9	1	13
	Paradoxical	0	10	1	11
Total		5	25	2	32

S-EMG versus evacuation of gel during TPUS (n=24)
Two patients were not able to evacuate the gel while they showed a decrease in electric activity which corresponds with relaxation of the pelvic floor muscles (Table 10). One patient evacuated the gel completely during TPUS but showed an increase in electric activity with the s-EMG. This patient did not show paradoxical movement on the other tests.

Table 10. Surface electromyography (s-EMG) versus evacuation of gel during transperineal ultrasound (TPUS)

		Evacuation of gel during TPUS		
		Yes	**No**	**Total**
s-EMG	Relaxation	6	2	8
	Indifferent	5	4	9
	Paradoxical	1	6	7
Total		12	12	24

3D-HRAM versus TPUS (n=32)
In 8 (25%) patients the test showed the same results (Table 11). TPUS was often classified as ‘indifferent’ in 25 (78%) patients.

Table 11. 3D high resolution anorectal manometry (3D-HRAM) versus transperineal ultrasound (TPUS)

		TPUS			
		Relaxation	**Indifferent**	**Paradoxical**	**Total**
3D-HRAM	Relaxation	3	13	0	16
	Indifferent	2	3	0	5
	Paradoxical	0	9	2	11
Total		5	25	2	32

3D-HRAM versus evacuation of gel during TPUS (n=24)

Two patients were classified as 'paradoxical' but were able to evacuate the gel during TPUS (Table 12). Also, three patients could not evacuate while they showed normal 'relaxation' on the 3D-HRAM.

Table 12. 3D dimensional high resolution anorectal manometry (3D-HRAM) versus evacuation of gel during transperineal ultrasound (TPUS)

		Evacuation of gel during TPUS		
		Yes	**No**	**Total**
3D-HRAM	Relaxation	8	3	11
	Indifferent	2	3	5
	Paradoxical	2	6	8
Total		12	12	24

3D-HRAM versus s-EMG (n=50)

Twenty-six (52%) patients showed similar results in both tests (Table 13). S-EMG was more often classified as 'indifferent', and one patient was classified 'paradoxical' while normal 'relaxation' was measured using 3D-HRAM.

Table 13. 3D dimensional high resolution anorectal manometry (3D-HRAM) versus surface electromyography (s-EMG)

		s-EMG			
		Relaxation	**Indifferent**	**Paradoxical**	**Total**
3D-HRAM	Relaxation	9	13	1	23
	Indifferent	3	5	3	11
	Paradoxical	0	4	12	16
Total		12	22	16	50

TPUS versus DRE by the surgeon (n=32)

In 17 patients (52%) the tests showed similar results. Twenty-five (78%) patients were classified 'indifferent' with TPUS (Table 14).

Table 14 Transperineal ultrasound (TPUS) versus digital rectal examination (DRE) by the surgeon.

		DRE surgeon			
		Relaxation	**Indifferent**	**Paradoxical**	**Total**
TPUS	Relaxation	5	0	0	5
	Indifferent	6	10	9	25
	Paradoxical	0	0	2	2
Total		11	10	11	32

TPUS versus DRE by the pelvic floor physical therapist (n=32)

Results are almost similar with the DRE by the surgeon.

DRE by the surgeon versus evacuation of gel during TPUS (n=24)

One patient showed 'paradoxical' straining during DRE by the surgeon but could evacuate the gel during the TPUS at the same day (Table 15). One patient could not evacuate the gel while the surgeon classified 'relaxation' with DRE.

Table 15. Digital rectal examination (DRE) by the surgeon versus evacuation of gel during transperineal ultrasound (TPUS)

		Evacuation of gel during TPUS		
		Yes	**No**	**Total**
DRE surgeon	Relaxation	7	1	8
	Indifferent	4	5	9
	Paradoxical	1	6	7
Total		12	12	24

DRE by the pelvic floor physical therapist versus evacuation of gel during TPUS (n=24)

Results are almost similar with DRE by the surgeon except that DRE in two patients were classified as 'relaxation' while they could not evacuate the gel.

S-EMG versus DRE by the surgeon (n=50)

In 26 (52%) patients the test results were similar. S-EMG classified 'indifferent' in 22 (44%) patients (Table 16). One patient was classified 'paradoxical' with s-EMG but classified 'relaxation' by the surgeons' DRE.

Table 16. Surface electromyography (s-EMG) versus digital rectal examination (DRE) by the surgeon

		DRE surgeon			
		Relaxation	**Indifferent**	**Paradoxical**	**Total**
s-EMG	Relaxation	9	3	0	12
	Indifferent	7	8	7	22
	Paradoxical	1	6	9	16
Total		17	17	16	50

S-EMG versus DRE by the pelvic floor physical therapist (n=50)

In 31 (62%) patients the test results were similar (Table 17).

Table 17. Surface electromyography (s-EMG) versus digital rectal examination (DRE) by the pelvic floor physical therapist

		DRE pelvic floor physical therapist			
		Relaxation	**Indifferent**	**Paradoxical**	**Total**
s-EMG	Relaxation	12	0	0	12
	Indifferent	6	10	6	22
	Paradoxical	0	7	9	16
Total		18	17	15	50

3D-HRAM versus DRE by the surgeon (n=50)

In 26 (52%) patients the test results were similar (Table 18). Five patients were classified as 'paradoxical' straining by the surgeon while these patients showed 'relaxation' on 3D-HRAM. The other way around; one patient was classified 'paradoxical' with 3D-HRAM but the surgeon classified DRE as 'relaxation'.

Table 18. 3D high resolution anorectal manometry (3D-HRAM) versus digital rectal examination (DRE) by the surgeon

		DRE surgeon			
		Relaxation	**Indifferent**	**Paradoxical**	**Total**
3D-HRAM	Relaxation	12	6	5	23
	Indifferent	4	5	2	11
	Paradoxical	1	6	9	16
Total		17	17	16	50

3D-HRAM versus DRE by the pelvic floor physical therapist (n=50)

Results were almost similar to the surgeon's DRE.

Discussion

The present study provides an overview of the correlation between outcomes of frequently performed anorectal function tests and compare their ability to measure dyssynergia. Furthermore, this study measured the level of agreement between DRE performed by the surgeon and the pelvic floor physical therapist in a tertiary referral center.

Despite the surgeons and the pelvic floor physical therapist being experienced, performing several digital rectal examinations per day, the agreement of the anal pressure between their DRE was not perfect. The assessed tone during rest, squeeze and straining did not correlate in 22%, 22% and 16% respectively. To the best of our knowledge no literature concerning the interrater agreement of DRE has been published. Interrater agreement has only been studied in vaginal digital assessment concerning the pelvic floor function and digital rectal examination in the context of prostate cancer.[31-33] Overall, the agreement was substantial to almost perfect. The small differences in classification of DRE between the surgeon and pelvic floor physical therapist may be explained by differences in interpretation of the indifferent movement of the pelvic floor. Not a single examination was classified both as relaxation and paradoxical movement.

The correlation between the surgeons' DRE, pelvic floor physical therapists' DRE and the 3D-HRAM in our study was moderate and somewhat better for squeeze tone/pressures than resting tone/pressures. Several studies compared DRE with ARM and showed an overall good agreement of pressures, however similar to our study, slightly better for squeeze pressures, but results are not consistent.[9,15,34-39] For example, the study by Beatrice et al. showed that DRE correlates well, but not perfectly, with the ARM for resting pressures, r=0.71 (p<0.001).[9] However, Orkin et al. observed an excellent agreement between DRE and the ARM for resting pressures (r=0.82) and for squeeze pressures (r=0.81).[34] In contrast, Soh et al. described a poor agreement between DRE and ARM for resting pressures with a k-coefficient of 0.01 and a moderate agreement for squeeze pressure with a k-coefficient of 0.42.[35] Pinto et al. showed a moderate to strong agreement for resting pressure with a Gamma index of 0.7 and a strong correlation of the squeeze pressures with a Gamma of 0.96.[37] All studies – including ours – report that the examinations were performed by experienced examiners but the results vary considerably. Nevertheless, ARM can be performed with a variety of types of equipment, techniques, and study protocols, making results less reproducible and thus difficult to compare.[40,41] A recent study by Prichard et al. described even significantly different results during ARM between operators despite

using similar instructions to patients.[16] Even a small difference in outcome could lead in a different interpretation. It must be noted that in contrast to most ARM studies we used the 3D probe.

DRE correlated better with 3D-HRAM in patients referred for fecal incontinence. With 54% this was the largest group in this study. However, defining 'normal' resting and squeeze pressures for ARM values is quite difficult. There is obviously an overlap since several studies showed different values for normal and abnormal resting and squeeze pressures for ARM.[14,23-28] To be accurate in comparing between groups, the pressures should be adjusted according to age, gender, and parous and nulliparous females. But these differences were small and to make comparisons between tests manageable in this study we did not differentiate.

The surgeons' DRE and the pelvic floor physical therapist's DRE were compared to the s-EMG and showed some discrepancies. The surgeon's DRE and the pelvic floor physical therapist's DRE were categorized as 'low' whereas the s-EMG categorized 'high' in three and four patients, respectively. However, one patient was categorized 'high' with DRE and 'low' with s-EMG. This can probably be explained by the fact that patients who can hardly control their external anal sphincter might overcompensate with their levator muscle. As we measured with s-EMG, the mean of the total electrical activity of the external anal sphincter including the levator muscle, the EMG activity might be higher than expected. When retrospectively assessing the 3D-HRAM, these patients showed indeed higher pressures of the posterior levator muscle on the 3D image in contrast to the sphincter and vice versa for the patient with a chronic anal fissure. Furthermore, high tone on the levator muscle with DRE might be turgor which is not measured with s-EMG. For this reason, comparing s-EMG with other tests might not be appropriate and should probably be used only to confirm physical examination and biofeedback registration.

The correlation between s-EMG and the 3D-HRAM was better for squeeze pressures and electric activity than resting pressures and electric activity with an agreement of 59% and 37% respectively. A study from 1989 also showed limited concordance with a correlation coefficient of 0.55 ($p<0.001$) between the maximum squeeze pressure with ARM and maximum contraction pattern with de EMG.[17] Regarding diagnosing dyssynergia while straining with s-EMG and 3D-HRAM, our results were not in line with the results by Chiarioni et al.[30] In our study, s-EMG and ARM were concordant in 52% while Chiarioni et al. described an agreement of 88% for classifying patients' dyssynergic or not dyssynergic. Both tests are used to test the anorectal function but

are used for different purposes in clinical practice. The question that remains is how relevant small differences are in clinical practice.

The results of the six different function tests used to diagnose pelvic floor dyssynergia, namely DRE by both the surgeon and the pelvic floor physical therapist, 3D-HRAM, s-EMG, BET and transperineal ultrasound (with echo lucent gel) were to some extent comparable. Although most comparisons were statistically significant, the correlation remained low. Discrepancies with TPUS could be explained by the non-anatomical supine position of the test and the fact that the patient is not in private environment. Three patients who evacuated the gel – although not completely – but were not able to expel the balloon within 1 minute, were referred for PFPT because of fecal incontinence. It is very likely that these patients lost the gel by leaking, not because of the push effort. This makes these tests not suitable to compare.

Furthermore, the tests are performed in different postures; the balloon expulsion is performed in a private setting, in sitting position, whereas the other tests are performed by an examiner with the patient lying in the left lateral position. 3D-HRAM measures the anorectal pressures, s-EMG measures electrical activity and TPUS is visually assessed by the doctor were evacuating echo lucent gel might support their findings. Some discrepancies cannot be explained except the snapshot nature of the tests. It is known that the diagnostic accuracy of ARM is limited for discriminating between healthy people and patients with functional constipation.[42] Unfortunately, previous studies with TPUS assessed its accuracy for detecting rectocele, intussusception or enterocele, or used a total pelvic floor ultrasound without echo lucent gel. No previous studies reported its accuracy to diagnose dyssynergia. However, based on our experience the TPUS is a low cost and easy tool for surgeons to perform. Surgeons are able to perform their own test in the outpatient clinic and, moreover, it has comparable results with the classical defecography [43] which makes it worth considering it a relevant anorectal function test.

The BET is a frequently used test for assessing defecatory dysfunction since it is a simple and low-cost procedure. Different protocols are used to perform the procedure; air filled or water-filled balloon, lying or seated position. Time values that are considered abnormal range from 1 till 5 minutes.[28-30,44,45] In our study, a balloon expulsion time of more than 1 minute was considered prolonged. This was categorized as dyssynergia by the 3D-HRAM in 32% of the cases. In contrast to older studies more recent studies demonstrated poor agreement between BET and ARM.[46,47] According to the ROME IV criteria, dyssynergic defecation is established by two out of three tests: 1) ARM

or s-EMG; 2) balloon expulsion test or 3) defecography. Remarkable is that the ARM or the s-EMG should be abnormal and that DRE and the transperineal ultrasound are not mentioned in this work-up.[7] This might be confusing and suggests that none of the tests can be considered as golden standard. Furthermore, anorectal function tests provide additional workload and costs whereas DRE is widely available and dyssynergia is a widespread phenomenon. The ROME IV criteria are merely used to standardize patients in an attempt to objectivize dyssynergia. Also, Bordeianou et al. had their doubts about which test to assign highest value, the s-EMG, BET or ARM, prior to referral to the pelvic floor physical therapist with dyssynergia.[48]

Undoubtedly this study has several limitations which should be acknowledged. First, the surgeons and the pelvic floor physical therapist were unblinded to the patients' medical history when performing the DRE which likely has influenced the results by information bias. Secondly, although all surgeons and the pelvic floor physical therapist were given instructions before the study started on how to perform a complete structured DRE and systematically describe the physical examination in the electronic health record, variety in performing and assessing DRE is insurmountable. The single observer for all 3D-HRAM results might be a lowness or a strength in this study. A considerable limitation of this study is that we were not able to use controlled normal s-EMG values since they have not yet been published. Furthermore, the results of the study would have had more relevance if there was a gold standard or known sensitivity of the tests. This issue is also reflected in the ROME IV criteria for dyssynergic defecation as mentioned above. Unfortunately, not all patients underwent all tests due to logistic problems in the outpatient clinic concerning the tests in the context of the study. Consequently, some patients did not undergo the BET or the TPUS. Lastly, there might have been interpretation bias by assessing straining movement of the pelvic floor. It is not known how 'indifferent' movement of the pelvic floor is defined among the examiners; does this mean 'no movement' or also 'relaxation but not enough'? This probably resulted in different outcomes.

This study showed that squeeze pressures were more often similarly categorized than resting pressures in anorectal function tests. It further shows that the surgeons' DRE and the pelvic floor physical therapist's DRE more often similar assessed in comparison to anorectal functions tests as 3D-HRAM, s-EMG or TPUS. Still, the correlation between all tests is quite disappointing and this raises questions regarding when to perform these tests in addition to DRE. Or does this mean that we can suffice with an expert's DRE when referring to the pelvic floor physical therapist for

dyssynergia? The pelvic floor physical therapist will evaluate therapy with his/her own DRE with or without s-EMG, not with ARM or transperineal ultrasound. Perhaps we should only perform anorectal function tests in patients who are refractory to conservative treatment like lifestyle and pelvic floor physical therapy, or when more invasive procedures like surgery or botulinum toxin e.g., are considered. Furthermore, these tests are valuable when evaluating new (surgical) therapies.

Conclusion

This study shows that DRE has a good correlation amongst experienced investigators. Since commonly performed anorectal function tests correlate poorly with DRE, and with other anorectal function tests, DRE by an experienced investigator suffices in daily clinical practice. When conservative treatment fails, further investigation is warranted, however these results should be interpreted with caution.

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PART II

CHAPTER 5

Pelvic floor physical therapy in the treatment of chronic anal fissure (PAF-study): study protocol for a randomized controlled trial

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Abstract

Background

Chronic anal fissure (CAF) is a common cause of severe anorectal pain with a high incidence rate. Currently, a wide range of treatment options are available with recurrence rates varying between 7-42%. Pelvic floor physical therapy (PFPT) is a treatment option for increased pelvic floor muscle tone and dyssynergia which often accompanies CAF. However, literature on this subject is scarce. The Pelvic Floor Anal Fissure (PAF)-study aims to determine the efficacy and effectiveness of PFPT on improvement on pelvic floor muscle tone and function, pain, healing of the fissure, quality of life and complaint reduction in patients with CAF.

Methods

The PAF-study is a single-centre, two armed, randomized controlled trial. Patients with CAF and pelvic floor dysfunction are eligible for inclusion. Exclusion criteria include abscess, fistula, Crohn's disease, ulcerative colitis, anorectal malignancy, prior rectal radiation, and pregnancy. A total of 140 patients will be randomized for either PFPT or postponed treatment of PFPT.

The primary outcome is tone at rest during electromyographic registration of the pelvic floor before and after therapy. Secondary outcomes consist of healing of the fissure, pain ratings, improvement of pelvic floor function, complaint reduction and quality of life. Primary and secondary endpoints are measured at 8 and 20 weeks and at 1-year follow-up.

Discussion

Currently, there is a gap in treatment modalities between conservative management and surgery. This manuscript prescribes the rationale, design, and methodology of a randomized controlled trial investigating PFPT as a treatment option for patients with CAF.

Introduction

A chronic anal fissure (CAF) is a longitudinal tear in the anoderm with one or more signs of chronicity including hypertrophied anal papilla, sentinel tag and exposed internal sphincter muscle with symptoms present for longer than 4-6 weeks.[1,2] CAF is a common cause of severe anorectal pain in adults, with a high incidence rate[3] and negatively impacts quality of life.[4,5] Patients with CAF usually experience anal pain, during and immediately after defecation, which may last for several hours. The pathophysiology of CAF is not fully understood, and treatment varies. Conservative management consists of lifestyle advice, high fiber diet and relaxation of the internal sphincter tone with ointment, thus improving blood flow and symptom relief.[2,6] When this conservative treatment fails, the next step can be botulinum toxin injections or lateral internal sphincterotomy (LIS). Botulinum is used as an effective treatment modality for anal fissure. It is considered as a minimal invasive procedure with minor adverse effects but has a recurrence rate of 41,7%.[7]

The cure rate of LIS is higher than botulinum toxin and has a recurrence rate of 6.9%,[7] however there is a potential risk of incontinence.[7-10] Nevertheless, LIS is the golden standard of care for surgical treatment of CAF.[6,11]

A proportion of patients with CAF have concomitant pelvic floor dyssynergia.[12] Dyssynergia typically present with defecation difficulties consisting of prolonged straining, frequent attempts of evacuation, a feeling of incomplete evacuation and anorectal pain because of incomplete relaxation of the puborectalis muscle.[13,14]

Anorectal pain could also result in increased tone of the pelvic floor muscles, and this is typically associated with symptoms of post-defecatory pain which can last for hours.[15,16] Dyssynergia and/or increased tone of the pelvic floor may probably lead to a vicious circle of pain and delayed healing.[17] These pelvic floor dysfunctions can effectively be treated with pelvic floor physical therapy (PFPT) including biofeedback therapy and/or neuromuscular electrical stimulation[18-24] and are recommended in current clinical guidelines.[25,26]

In addition, PFPT including biofeedback therapy and/or neuromuscular electrical stimulation is a minimal invasive treatment with a low risk of adverse events.[25,27-29]

CAF is a debilitating and bothersome condition, particularly because of its recurrent nature. Prolonged persistence of symptoms and recurrence indicate that present treatment modalities are not always sufficient. Currently, there is a gap in treatment modalities between conservative management and surgery. Therefore, we aim to provide a management protocol for PFPT to bridge this gap. We hypothesise that treatment with PFPT in patients with CAF and concomitant pelvic floor dysfunction will result in improvement of pelvic floor muscle tone and function, pain, healing of the fissure, quality of life and complaint reduction.

Material and Methods

Objectives

Primary Objective: To establish the efficacy and effectiveness of treatment of CAF and pelvic floor dysfunction with PFPT including surface electromyography (s-EMG)- biofeedback.
Secondary objectives: - Prevalence of pelvic floor dysfunction in chronic anal fissure; - relation between CAF and other pelvic floor dysfunctions; - pain reports; - healing of the fissure; - quality of life; - complaint reduction with a proctology specific patient reported outcome measurement.

Study design

The PAF-study is a single-centre, parallel, randomized controlled trial (RCT). This superiority trial is designed to detect a difference of PFPT including biofeedback and no PFPT at first follow-up. The overall design is shown in figure 1. The design involves allocation of all appropriate consecutive patients with CAF and pelvic floor dysfunction. Eligible patients will be randomly assigned to an intervention group, which will receive 8 weeks of PFPT or assigned to a control group which will receive postponed PFPT.
A complete list of items from the World Health Organization Trial Registration Data Set is provided in Appendix 1.

Eligibility

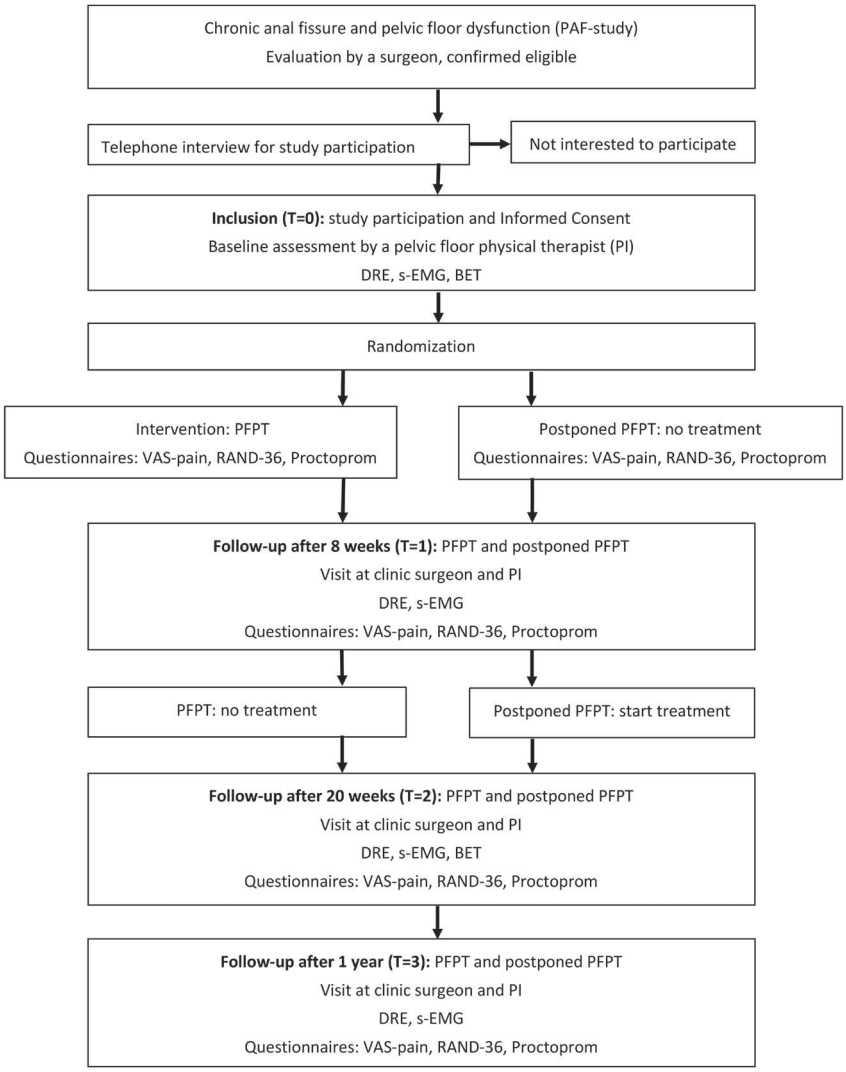
The study population will consist of all patients >18 years old, presenting with CAF and pelvic floor dysfunction.
Inclusion criteria:

- Complaints of more than 6 weeks and all patients failed conservative treatment with ointment, fibers and/or laxatives
- Sufficient understanding of the Dutch written language (reading and writing)
- Able to complete online questionnaires
- Written informed consent

Exclusion criteria:

- Presenting an abscess or fistula
- Crohn's disease or ulcerative colitis
- Anorectal malignancy
- Previous rectal radiation
- Pregnancy

Figure 1. Study design flow diagram



PI= Principal Investigator; DRE= Digital Rectal Examination; s-EMG = surface-electromyography; BET= Balloon Expulsion Test; PFPT= Pelvic Floor Physical Therapy; VAS = Visual Analog Scale; RAND-36 = 36-short-form health survey

Trial recruitment and consent

Patients will be recruited at a specialized multidisciplinary proctology clinic in the Netherlands. The surgeon, coordinating investigator and/or the principal investigators (PI),

a pelvic floor physical therapist, will approach the patient and inform him/her about the study. It is the responsibility of the surgeon and the PI to provide the patient with detailed information, both orally and writing, about the aims and design of the study, as well as the medical procedures involved. If necessary, the patient will have the opportunity to ask all possible questions and receive additional information throughout enrolment in the study. If eligible, the PI will provide the patient with an information letter and informed consent form, explaining the purpose of the study, study design, benefits, and patient risks. According to Good Clinical Practice, a patient is asked for formal consent prior to participation. Patients who decide to participate will bring the signed consent form at first visit with the PI. The PI is assigned for inclusion and informed consent and will be responsible for storing the signed informed consent forms. For those patients who do not consent to participate, the reason(s) for declining will be anonymously recorded in a database.

Follow-up procedure

Follow-up for all patients will consist of an appointment with the surgeon and PI, at 8 weeks from baseline. Clinical examination will be provided through inspection and digital rectal examination to investigate the improvement of healing of the fissure and pelvic floor function. Patients are requested to fill in the validated questionnaires at this timepoint. Patients who were allocated to postponed PFPT will start their treatment after this first follow-up assessment. Patients from both groups will visit the surgeon and PI and fill in the questionnaires at 20 weeks and 1-year follow-up.

Withdrawal

Patients can leave the study at any time for any reason without any consequences. This will have no consequences for their further treatment. The PI or surgeon can decide to withdraw a patient from the study for urgent medical reasons. Patients will not be replaced in this study after withdrawal.

Randomization and blinding

After obtaining fully written informed consent, patients will be randomly assigned to be treated with PFPT or assigned to a control group which will receive postponed PFPT (1:1 allocation, random block sizes of 4, 6 and 8). The randomization will be computer generated using Castor EDC (www.castoredc.com). A unique record number will be generated, and the allocation will be disclosed. The PI will not be able to access

the randomization sequence. The PI, who will also be involved in the data analysis is not blinded for allocation. The PI will inform the patient about group allocation and follow-up appointments. The PI will also be responsible for communication with the collaborating pelvic floor physical therapist and inform them by telephone call about allocated intervention and other complementary information of the patient. The letter of referral will be sent by a secure online mail system.

Baseline

Demographics and physical examination

Demographic characteristics will be collected including age, gender, and relevant history.

Clinical data will be collected including previous treatment, duration of symptoms and findings on clinical examination regarding fissure and pelvic floor dysfunction.

To examine pelvic floor muscle tone, strength, endurance and relaxation of the pelvic floor muscles, a careful functional digital rectal examination will be performed.[30-32] Dyssynergia is detected by rectal examination [33] and balloon expulsion test.[34,35] Besides that, pelvic floor muscle tone and function is measured with s-EMG[30,36] with an intra-anal probe (MAPLe®).[37] This probe has a matrix of 24 electrodes and is capable of providing electro galvanic stimulation and registering s-EMG-activity nearest to the individual muscles of the pelvic floor during diagnosis and treatment.[37] Patients are asked to perform four consecutive tasks: one-minute rest, ten maximum voluntary contractions, one endurance contraction of thirty seconds and one push effort where the patient is asked to bear down. The MAPLe® system is validated for its purpose.[37,38]

Questionnaires

Patients are asked to fill in three validated questionnaires online. To quantify the average intensity of pain during defecation, a visual analog scale (VAS) will be used on a 11-point scale from 0 (no pain) to 10 (most intense pain).[39]

Quality of life is measured using the RAND-36 Health Status Inventory.[40] The RAND-36 questionnaire entails nine domains of health-related quality of life pertaining to both physical health (physical functioning, role limitations resulting from physical health, pain, general health perceptions), mental health (emotional well- being, role limitations resulting from emotional problems, social functioning, energy/fatigue) and health change. The score for each scale is obtained by the sum of the scores for

each item and linearly transformed into a range from 0 to 100 where a higher score denotes a better level of functioning.

The Proctoprom, a patient related outcome measurement was developed by Van der Mijnsbrugge et al.,[41] to assess the impact of proctologic complaints on different domains of a patient's life and evaluates the effect of treatment. This questionnaire consists of 5 items using a scale of 0-10 (0 = no complaints and 10 = maximum complaints), with a maximum score of 50. All items but one (item 4) are mandatory.

An overview of the assessment and questionnaires is shown in Table 1.

Table 1. Assessment schedule and questionnaires

	Baseline	8 wk.	20 wk.	1 year
Digital rectal examination (surgeon/PFPT)	•	•	•	•
Proctoscopy/Endoanal ultrasound (surgeon)[1]	•	•	•	
Surface-electromyography (s-EMG) (PFPT)	•	•	•	•
Balloon expulsion test (BET) (nurse)	•		•	•
Proctoprom	•	•	•	•
Quality of Life (RAND-36)	•	•	•	•
VAS-pain	•	•	•	•

[1.] if neccessary

Trial interventions

The description of the intervention follows the Template for Intervention Description and Replication (TIDieR) checklist (Appendix 2).

Referral

Patients are referred to an extra mural private practice, preferably nearby patients' home address. The pelvic floor physical therapists providing the treatment are all certified and trained. They all receive the treatment protocol prior treatment and have access to peer consultation when needed. The modalities composing the treatment protocol were selected to reflect clinical practice in the Netherlands.

Interventions

At baseline all patients receive information about the pelvic floor and related symptoms, defecation physiology, behavioural modifications and lifestyle advice and continue ointment, fibers and/or laxatives.

The treatment consists of 5 sessions of a mean of 45-minutes in a period of 8 consecutive weeks. The treatment protocol is comprised of intrarectal myofascial techniques, such as stretching the puborectalis muscle and myofascial release on identified trigger points in the pelvic floor to increase flexibility, release muscle tension and improve circulation. Manual techniques are tailored to the patient and based on results and findings of the diagnostic evaluation of the pelvic floor at every visit. To gain awareness, patients are taught how to contract and relax the pelvic floor muscles and are learned how to incorporate these into daily life. Breathing and pelvic floor muscle exercises are combined with surface electromyography (s-EMG)-biofeedback with an intra-anal probe (MAPLe®).[37] The sessions are performed to increase awareness and monitor pelvic floor (dys)function.[21,30,42,43]

Patients with pelvic floor dyssynergia learn how to relax the pelvic floor during straining. If patients are unable to contract or relax the pelvic floor, neuromuscular electrical stimulation will be applied intra-anally during the biofeedback session.

The home exercise program incorporates stretching the puborectalis muscle during the application of ointment, and pelvic floor muscle - and breathing exercises to improve relaxation. Furthermore, patients use thermotherapy with a heat blanket or sitz baths for relaxation.[44] Additionally, information will be provided with folders and videos to guide the home exercises. Therapy compliance is encouraged because the daily home exercises determine to a great extent the success rate.[45] The collaborating pelvic floor physical therapist will evaluate the patients' compliance of home exercises at every visit.

Patients who are assigned to postponed PFPT will not receive additional treatment besides the use of ointment and fibres/laxatives until first follow-up at 8 weeks after inclusion.

Harms

Adverse Events (AE) are defined as any undesirable experience occurring to a subject during the study, whether considered related to the trial procedure or to an already existing condition. All (serious) adverse events suspected unexpected serious adverse reactions (SUSAR) and any other significant problems are reported to the Medical Ethics Review Committee (MERC) using an online submission system. All adverse events will be described in the final analysis. No adverse events are expected since PFPT including biofeedback and/or neuromuscular electrical stimulation is usual care in the Netherlands. The expected burden for the participants is very low.

Main study outcomes

Primary outcome

The primary outcome measurement is tone at rest (μV) during s-EMG registration of the pelvic floor before and after therapy.
Secondary outcomes consist of prevalence of pelvic floor dysfunction in CAF; relation between CAF and other pelvic floor dysfunctions, pelvic floor muscle function before and after PFPT; VAS-pain during defecation before-and after PFPT, healing of the fissure (complete re-epithelisation), quality of life (the Short-Form 36 Health Survey, RAND-36) and complaint reduction with a proctology specific patient reported outcome measurement (Proctoprom) before and after PFPT.
The effect analyses adhere to the design of an RCT and measures at baseline, after 8, 20 weeks and 1-year follow-up.

Statistical analysis

Data are analysed using Statistical Packages for Social Sciences (SPSS, Chicago, II, USA, version 26.0). Descriptive methods will be used to assess quality of data, homogeneity of treatment groups and endpoints. Normality of the data will be analysed with histograms. Data are presented using mean (SD), median (min-max) for the numeric and non-normal variables and frequency (percentages) for categorical variables. A paired *t*-test or Wilcoxon signed-rank test will be used to compare continuous variables within groups. The two-sample *t*-test or the Mann-Whitney-U test for quantitative data and the chi-square test or Fisher's exact test for qualitative data will be performed to test differences between groups. The analysis of covariance (ANCOVA) is used to assess the effect of intervention and to control for baseline measures and confounders. Repeated measure analysis of variance (ANOVA) will be performed for the different time points assessments between groups and interaction between groups and observed time. All *p*-values will be two-tailed and statistical significance will be taken as a *p*-value of less than 0.05. In case of incomplete records, missing data will be imputed using multiple imputation to accommodate intention to treat analysis when more than 5% data is missing. The number of imputations will be defined by the percentage of incomplete patients with respect to the variables of interest. An interim analysis will not be performed for this study.

Sample size

The primary outcome of the study is the tone at rest during s-EMG registration of pelvic floor. In preliminary studies we found a mean of 1.75 in rest, with a standard deviation of 1.75. Based on a slightly conservative standard deviation of 1.8, and a difference to be detected of 1.0, 70 patients in each treatment arm are required to detect a difference of 1.0 between the treatment group and the control group with postponed treatment, with a nominal alpha level of 5% and a power of 90%.

Data management and data protection

All medical data will be collected at the clinic before entry into the trial database. After fully signed written informed consent, data collection will be facilitated by case record forms in Castor EDC. Each participant will receive an identification code. Patients' name and other information that can directly identify the patient, will be omitted. The PI will have a decoding list with randomization numbers and patient identification numbers in the investigator site file. Only the coordinating surgeon and PI will have access to the key to the code. All data concerning patients or their participation in this trial will be considered confidential and handled in compliance with all applicable regulations. Data will be stored in a password protected digital database. The data will be archived for 15 years after completion of the study.

Data safety monitoring

The Committee in Research Involving Human Subjects Leiden approved this study and declared it as a "negligible risk" study and therefore no Data Safety Monitoring Board is needed and no interim analysis or formal stopping rules for the trial are needed to be conducted or formulated. No anticipated harms exist, nor will compensation be provided for trial participation.

Ethical approval and dissemination

The study is conducted in accordance with the principles of the Declaration of Helsinki, the Medical Research Involving Human Subjects Act (WMO) and the General Data Protection Regulation. The protocol has been approved by the Medical Ethics Review Committee of the Leiden University Medical Centre (P18.090).

Two dissemination meetings were arranged before the study started at the Proctos Clinic with collaborating pelvic floor physical therapists. The meeting provided general background and developed further knowledge in the specialty of anorectal dysfunction. During the pandemic of COVID-19, three online meetings were held to mentor these meeting.
Findings of the study will be disseminated in peer-reviewed journals and presented at conferences, whether they are positive, negative, or inconclusive.

Discussion

To our knowledge, the PAF-study is the first RCT investigating the efficacy and effectiveness of PFPT with s-EMG biofeedback in patients with CAF.
In the development and implementation of this RCT, several methodological issues were considered such as the design, the duration of the treatment and choice of PFPT modalities. Our treatment protocol consists of a combination of PFPT modalities to promote clinical improvement in patients with CAF which has proven effective in the treatment of pelvic floor disorders.[21,24,46]
The distressing and bothersome condition of CAF has a considerable impact on QoL. PFPT already have been proven effective in QoL in patients with pelvic pain and sexual complaints.[22,47] To assess the impact of several proctologic complaints on different aspects of a patient's life, the Proctoprom was developed and evaluates disease burden and effect of treatment.[41] The Proctoprom is a valid and reliable tool that is responsive to change and that meets consensus-based standards for the selection of health measurement instruments. The use of this questionnaire will give more rise to burden patients experience in this debilitating problem.
This manuscript presents and discusses the rationale, design, and methodology of a randomized controlled trial investigating PFPT as a treatment option for patients with CAF. Finally, short- and long-term outcome of treatment of CAF using this regime will be described. Findings from this trial will provide a complementary treatment option and could probably become a recommendation in clinical guidelines.

Appendix 1. Items World Health Organization Trial registration Data Set

Data category	Information
Primary registry and trial identifying number	The Dutch Trial registry; NTR7581
Date of registration in primary registry	12-01-2018
Secondary identifying numbers	Ethical committee, NL65658.058.18 METC-nr. P18.090
Sources of monetary or material support	The Dutch Association for Pelvic Physiotherapy (NVFB)
Primary sponsor	Proctos Clinic, Bilthoven, the Netherlands
Secondary sponsor	Leiden University Medical Centre, Leiden, the Netherlands
Contact for public queries	davr@me.com; + 31622141471; Proctos Clinic, Professor Bronkhorstlaan 10, 3723 MB Bilthoven, the Netherlands
Contact for scientific queries	D.A.van Reijn MSc; davr@me.com; + 31622141471; Proctos Clinic, Professor Bronkhorstlaan 10, 3723 MB Bilthoven, the Netherlands
Public title	Pelvic floor physical therapy in patients with chronic anal fissure
Scientific title	Pelvic floor physical therapy in patients with chronic anal fissure: a randomized controlled trial
Country of recruitment	The Netherlands
Health condition or problem studied	Chronic anal fissure
Intervention(s)	*Baseline*: all patients received information about the pelvic floor and related symptoms; -explanation about relevant anatomy and defecation (patho) physiology; -behavioural modifications and lifestyle advice. *Intervention*: 5 face-to-face appointments of a mean of 45-minutes in a period of 8 consecutive weeks; -intrarectal myofascial techniques; -pelvic floor - and breathing exercises; -surface electromyography biofeedback with an intra-anal probe (MAPLe®); neuromuscular electrical stimulation intra-anally if applicable *Home exercise programme: s*tretching the puborectalis muscle during the application of ointment; -pelvic floor - and breathing exercises; -thermotherapy Control group: no additional treatment besides the use of ointment and fibres/laxatives. Start same treatment protocol at first follow-up (8 weeks after inclusion)
Key inclusion and exclusion criteria	Ages eligible for inclusion: >18 years Sexes eligible for study: both *Inclusion criteria*: Patients presenting chronic anal fissure and pelvic floor dysfunction; -complaints for more than 6 weeks and failed conservative treatment with ointment, fibers and/or laxatives; -sufficient understanding of the Dutch written language (reading and writing); -able to complete online questionnaires; -written informed consent *Exclusion criteria*: Presenting an abscess or fistula; - Crohn's disease or ulcerative colitis; - anorectal malignancy; -previous rectal or anal surgery; -previous rectal radiation; -pregnancy

Appendix 1. Continued

Data category	Information
Study type	Interventional Allocation: randomized Intervention model: parallel assignment Sequence generation: 1:1 allocation, random block sizes of 4,6 and 8 No blinding: the principal investigator, collaborating pelvic floor physical therapists, patients Blinding: surgeon
Date of first enrolment	10 December 2018
Target sample size	140
Recruitment status	Complete
Primary outcome(s)	Tone at rest (μV) during surface electromyographic registration of the pelvic floor before and after therapy.
Key secondary outcomes	Prevalence of pelvic floor dysfunction; -pelvic floor muscle function; -VAS-pain; -healing of the fissure (complete re-epithelisation and absence of pain); -quality of life (RAND-36); - complaint reduction with proctology specific patient reported outcome measurement (Proctoprom)

Appendix 2. TIDieR checklist Pelvic floor physical therapy in Chronic Anal Fissure (PAF-study)

Brief name	**Pelvic floor physical therapy in patients with chronic anal fissure: a randomized controlled trial**
1. Intervention	PFPT including biofeedback vs postponed PFPT
2. Why	To determine the efficacy and effectiveness of PFPT on improvement on pelvic floor muscle tone and function, pain, healing of the fissure, quality of life and complaint reduction in patients with CAF.
3. What	*Baseline information by pelvic floor physical therapist/PI for all patients:* Information about the pelvic floor and related symptoms, defecation physiology, behavioural modifications, and lifestyle advice (s.e toilet advice, stress reduction). Patients continue fibers and/or laxatives. Patients use ointment 2-3 times a day, before and after defecation and before sleep. *Baseline diagnostics by PI for all patients:* *Digital rectal examination*: the patient placed in left lateral position hip flexed at 70^0 and knees flexed at $90.^0$ After inspection of the anus, the inserted finger is carefully and slowly advanced into the rectum. The resting sphincter tone is assessed in rest and scored as normal, decreased, or increased. Pelvic floor muscle tone is scored as; normal, decreased, or increased. The patient is asked to squeeze as strong and fast as possible for 10 times, and to squeeze and hold as long as possible (up to 30 seconds). In addition to the finger in the rectum, a hand is placed over the patient's abdomen to assess the push effort. The patient is asked to push and bear down as if to defecate. Push effort of the anal-and pelvic floor muscles is scored as relaxation, indifferent or paradoxal contraction. *S-EMG measurement:* S-EMG is performed with an anal probe (MAPLe®). This is a probe with a matrix of 24 electrodes enabling measuring EMG-signals from the different sides and layers of the PF muscle. The probe is placed intra-anal, the grounding electrode placed on the spina iliaca anterior superior. The patient is asked to perform four consecutive tasks according to a standardized protocol: 1) one-minute rest where participants are instructed to relax and breathe normally; 2) ten maximum voluntary contractions (MVC) where the patient is verbally instructed to perform a short controlled (maximum) contraction for one second without contracting the muscles surrounding the pelvic floor and relax the pelvic floor muscles between the MVC contractions for 3 seconds; 3) one endurance contraction where the patient is instructed to contract the pelvic floor muscles at such a level that they could hold for 30 seconds, without contracting the muscles surrounding the pelvic floor; 4) one push effort where the patient is asked to push and bear down. The investigator is holding the probe to keep it in place. During these examinations, no instructions were given on how to perform a correct pelvic floor muscle contraction. From these s-EMG measurements, mean EMG amplitudes per electrode are calculated. The EMG mean values are presented as absolute values (μV).

Appendix 2. Continued

Brief name	**Pelvic floor physical therapy in patients with chronic anal fissure: a randomized controlled trial**
	Treatment PFPT: - 5 sessions of a mean of 45-minutes in a period of 8 consecutive weeks. - Different treatment modalities are combined in one session and all treatments are tailored to the patient. - Intrarectal myofascial techniques: stretching the puborectalis muscle and myofascial release on identified trigger points (first 3 sessions for a maximum of 10 minutes). - Pelvic floor muscle exercises: contraction and relaxation combined with breathing exercises (first 3 sessions maximum of 10 minutes) - Breathing exercises and learn how to push (2 sessions), lying down and sitting - Surface electromyography (s-EMG)- biofeedback with an intra-anal probe (MAPLe®). Relaxation with breathing techniques, maximum contractions and sets of endurance contractions are used to achieve the treatment goals (3 sessions for 15-20 minutes). - The therapist monitors the adequate relaxation of the pelvic floor muscles throughout the sessions. - If patients are unable to relax the pelvic floor, neuromuscular electrical stimulation will be applied intra-anally during the biofeedback session (15-20 minutes about 45 contractions; 35Hz/250 μsec fade in, fade out 2 sec, hold 4-6 sec, pause 10-16 sec). - If patients are unable to contract neuromuscular electrical stimulation will be applied intra-anally during the biofeedback session (20 minutes/30-45 contractions; 35Hz/250-600 μsec; fade in, fade out 2 sec, hold 4-6 sec, pause 8-12 sec). *Home exercise program:* - Stretching the puborectalis muscle during the application of ointment (2-3 times a day, 5 minutes); pelvic floor muscle - and breathing exercises to improve relaxation (2-3 times a day, 15 minutes); thermotherapy with a heat blanket three times a day for 15 minutes, preferable at fixed time points or sitz baths for relaxation. - Information is provided with folders and videos to guide the home exercises. - The collaborating pelvic floor physical therapist will ask the patient about the compliance of home exercises and supports correct behaviour at every visit Changes and improvements are noted the patient file. Patients who are assigned to postponed PFPT will not receive additional treatment besides the use of ointment and fibres/laxatives until first follow-up at 8 weeks and start with the same treatment protocol.
4. Procedures	Training before the PAF-study started was carried out by an experienced PF physical therapist/principal investigator at a meeting at the Proctos Clinic in the Netherlands. The training provided general background and the developed further knowledge in the specialty of anorectal dysfunction. In total 12 of the collaborating pelvic floor physical therapists from every part of the country providing the treatment attended the meeting. All pelvic floor physical therapists are certified and trained and have at least 3 years of experience in the field of anorectal problems. They all received the treatment protocol prior treatment and have access to peer consultation when needed. To mentor these meetings, we arranged 3 on-line sessions during the COVID-19 pandemic.

Appendix 2. Continued

Brief name	**Pelvic floor physical therapy in patients with chronic anal fissure: a randomized controlled trial**
5. Who provided	PFPT is provided by pelvic floor physical therapists in the Netherlands. They are registered at the Dutch Association for Pelvic Physiotherapy (NVFB). They are all trained and educated in the performance of invasive techniques, as is used during digital rectal examination, rectal techniques, and biofeedback in men and women. All therapists had training in the use of biofeedback with the MAPLe®. The pelvic floor physical therapist of the Proctos Clinic and principal investigator of the study was responsible for the first diagnostic evaluation of the pelvic floor including EMG-measurement, baseline information and follow-up appointments at 8 - and 20 weeks and 1 year.
6. How	Face-to face
7. Where	First meeting and follow-up appointments at 8 -and 20 weeks and 1-year follow-up at the Proctos Clinic in the Netherlands Treatment with pelvic floor physical therapist in a private practice, near patients' residence.
8. When, and how much	Baseline and follow- up: at 8, 20 weeks and one year: 4 appointments of 45 minutes PFPT: 5 sessions in a period of 8-10 weeks (30-45 minutes) Postponed PFPT: at first follow-up, at 8 weeks after inclusion start treatment with the same treatment protocol
9. Tailoring	The interventions are tailored to the patient based on results and findings of the diagnostic evaluation of the pelvic floor at every visit.
10. Modifications	No modification was made
11. How well	Appointments at the private practices are monitored by clinicians delivering the intervention. Monitoring at fixed time points (follow-up) includes an appointment with the surgeon and pelvic floor physical therapist/PI at the Proctos Clinic.

PAF-study= Pelvic floor Anal Fissure- study; *PFPT*= Pelvic Floor Physical Therapy; *CAF*= chronic anal fissure; *PI*= principal investigator; *s-EMG*= surface electromyography

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CHAPTER 6

Pelvic floor physical therapy in patients with chronic anal fissure: a randomized controlled trial

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Abstract

Background

A chronic anal fissure is a common, painful condition with great impact on daily life. The exact pathogenesis has not been fully elucidated, and treatment varies. A large percentage of patients experience pelvic floor dysfunction (dyssynergia and increased pelvic floor muscle tone). The aim of our study was to investigate the effect of pelvic floor physical therapy in patients with chronic anal fissure.

Methods

Between December 2018 and July 2021, at the Proctos Clinic in the Netherlands, patients with chronic anal fissure and pelvic floor dysfunction were randomly assigned to an intervention group, receiving 8 weeks of pelvic floor physical therapy including electromyographic biofeedback or assigned to a control group receiving postponed pelvic floor physical therapy. The primary outcome was muscle tone at rest during electromyographic registration of the pelvic floor before and after pelvic floor physical therapy. Secondary outcomes contained healing of the fissure, pain ratings, improvement of pelvic floor function and complaint reduction measured with a proctology specific patient-reported outcome measurement. Endpoints were measured at 8- and 20 - week follow-up.

Results

One hundred forty patients were included in the study, 68 men (48.6%) and 72 women (51.4%) with a mean age of 44.5 ±11.1 (range 19-79) years.

Mean resting electromyographic values of the pelvic floor in the intervention group significantly improved from pre-to post- treatment (p<0.001) and relative to controls (mean estimated difference between groups -1.88 μV; 95% CI, -2.49 to -1.27 (p<0.001) at first follow-up and remained significant from baseline at 20-week follow-up (p<0.001). The intervention group performed better compared to the control group on all secondary outcomes i.e., healing of the fissure (55.7% of the patients vs 21.4% in control), pain ratings (p<0.001), diminished dyssynergia (p<0.001), complaint reduction (p<0.001), and decrease of pelvic floor muscle tone (p<0.05) at first follow-up.

Conclusions

The findings of this study provide strong evidence that pelvic floor physical therapy is effective in patients with chronic anal fissure and pelvic floor dysfunction and supports its recommendation as adjuvant treatment besides regular conservative treatment.

Introduction

Background and objectives

Chronic anal fissure (CAF) is one of the most common proctological problems. It causes significant morbidity and has a large impact on quality of life.[1,2] An anal fissure refers to a longitudinal ulcer in the squamous epithelium, generally located in the posterior midline.[3] The classical symptom is pain during defecation, which may persist for hours.[3,4]

The exact pathogenesis of CAF is debatable. Passing of hard stools or sudden evacuation of liquid stool can lead to mucosal damage, resulting in an overreaction of the external anal sphincter (EAS) continence reflex and an increase of basal resting pressure. This could lead to spasm, thus leading to reduced blood flow and ischaemia, which prevents CAF from healing.[5-8] Defecation is a complex function. Normal defecation requires anorectal synchronisation, an intact rectal sensation and perception, a contraction of the abdominal muscles and relaxation of the EAS and puborectalis muscle. To evacuate stool, it is essential that the puborectalis muscle relaxes for straightening the anorectal angle.[9] When the pelvic floor muscles do not relax or even contract (dyssynergia) during attempted defecation this could result in an increase in the anorectal angle and hence prohibits the normal passage of stool.[10]

Dyssynergia and increased pelvic floor muscle tone are likely to be factors contributing to delayed healing and pain in patients with CAF.[11,12]

Initial treatment of CAF is based on conservative management with fiber and /or laxatives to alleviate constipation. Treatment with ointment is directed toward relieving internal sphincter spasm, thus improving circulation and pain relief.[13] If unresponsive to conservative management including ointment, botulinum toxin injections may be considered, however this is associated with recurrence rates of 18-50%.[3,14,15] Another option and currently the gold standard of surgical intervention is lateral internal sphincterotomy.[16] Nevertheless, its potential risk of causing incontinence, 3.4 - 14%, should be kept in mind when considering this treatment.[14,16-18]

In patients with CAF, who have also been diagnosed with pelvic floor dysfunction, pelvic floor physical therapy (PFPT) may add to adequate treatment. The aim of PFPT is to increase awareness and proprioception, to improve muscle relaxation, elasticity of the pelvic floor muscles, to restore abdominopelvic coordination, and reduce pain.[19,20] PFPT including biofeedback therapy has already been proven effective in the treatment of increased pelvic floor muscle tone and dyssynergia,[19,21-24] but has not been investigated in patients with CAF.

We hypothesised that treatment with PFPT including biofeedback in addition to regular conservative management will result in an improvement of pelvic floor muscle tone and function, pain, healing of the fissure and increased satisfaction in patients with CAF and concomitant pelvic floor dysfunction.

Materials and Methods

Study design

The PAF-study is a single-centre, parallel, randomized controlled trial. This superiority trial was designed to detect a difference of PFPT including surface electromyographic biofeedback (EMG) versus no PFPT at first follow-up. The design involved allocation of all appropriate consecutive patients with CAF and pelvic floor dysfunction. Eligible patients were randomly assigned, after providing written informed consent, to an intervention group receiving 8 weeks of PFPT including EMG-biofeedback or assigned to a control group receiving postponed PFPT.

Baseline and follow-up

Baseline and follow-up appointments at 8 and 20 weeks from baseline with the surgeon and principal investigator, an experienced pelvic floor physical therapist, consisted of a clinical examination provided through inspection to investigate the healing of the fissure. If necessary, proctoscopy was performed to exclude other pathology. Resting anal sphincter pressure, pelvic floor muscle tone and function were measured by a careful digital rectal examination and scored as decreased, normal and increased.[25,26] Pelvic floor dysfunction was defined by the presence of dyssynergia and/or increased pelvic floor muscle tone.

Besides that, pelvic floor muscle tone was measured with EMG (μV) [25] with an intra-anal probe (MAPLe,® Novuqare Pelvic Health B.V. CE 0344, Rosmalen, the Netherlands). This probe has a matrix of 24 electrodes and is capable of registering EMG-activity nearest to the individual muscles of the pelvic floor during diagnosis and treatment. The MAPLe® system is validated for its purpose.[27] In addition, muscle tone of the EAS was measured with EMG (circle 1, MAPLe®).

Dyssynergia was detected by digital rectal examination and balloon expulsion test.[28,29] The balloon expulsion test provides an assessment of the patient's ability to evacuate artificial stool during simulated defecation. A non-sterile disposable balloon (BARD,

Covington, USA) was filled with 50ml water or until the patient felt an urge to defecate. Evacuation of the balloon after more than 2 minutes was seen as impossible to expulse and was considered dyssynergic defecation.[28] The balloon expulsion test was performed at baseline and 20-week follow-up by the nurse in our clinic.
Patients were requested to fill in 2 validated self-administered questionnaires at baseline, and at 8- and 20-week follow-up. To quantify the average intensity of pain during defecation, a visual analog scale (VAS) from 0 (no pain) to 10 (most intense pain) was used.[30]
The Proctoprom, a patient related outcome measurement was used to assess the impact of proctologic complaints on different aspects of a patient's life and to evaluate the effect of treatment.[31]

Participants

Men and women aged 18 years or older presenting CAF and pelvic floor dysfunction were recruited at the Proctos Clinic in the Netherlands from December 2018 until July 2021. CAF was defined as a longitudinal ulcer with symptoms presenting longer than 6 weeks or recurrent fissures.
All patients had failed conservative treatment with fiber and/or laxatives and ointment (diltiazem or isosorbide dinitrate) used for at least 6 weeks and with accurate instructions about how to apply. All patients had sufficient understanding of the Dutch language (reading and writing) and were able to complete online questionnaires. We considered patients who were not able to undergo a digital rectal examination, not eligible for this study. Patients with an abscess or fistula, Crohn's disease or ulcerative colitis, anorectal malignancy, prior rectal radiation, and pregnancy were excluded from the study.

Interventions

At baseline, patients in both groups received information about the pelvic floor and related symptoms, explanations about relevant anatomy and defecation (patho) physiology, behavioural modifications, and lifestyle advice. All patients continued their conservative measures including the use of ointment (diltiazem or isosorbide dinitrate).
PFPT consisted of 5 face-to-face appointments of a mean of 45 minutes in a period of 8 consecutive weeks, using a treatment protocol.[32] Patients were referred to an extra-mural private practice, preferably nearby patients' home address.

The treatment protocol was comprised of intrarectal myofascial techniques, such as stretching the puborectalis muscle and myofascial release on identified trigger points in the pelvic floor to increase flexibility, release muscle tension and improve circulation. Manual techniques were tailored to the patient and based on results and findings of the diagnostic evaluation of the pelvic floor at every visit. To gain awareness, patients were taught how to contract and relax the pelvic floor muscles and were learned how to incorporate these into daily life. Breathing and pelvic floor muscle exercises were combined with EMG-biofeedback with an intra-anal probe (MAPLe®).[27] The sessions were performed to increase awareness and monitor pelvic floor (dys)function.[19,20] Patients with pelvic floor dyssynergia learned how to relax the pelvic floor during straining. If patients were unable to contract or relax the pelvic floor muscles, neuromuscular electrical stimulation was applied intra-anally during the biofeedback session. The home exercise program incorporated stretching the puborectalis muscle during the application of prescribed ointment, and pelvic floor muscle - and breathing exercises to improve relaxation. Furthermore, patients used thermotherapy with a heat blanket or sitz baths for relaxation.[33] Additionally, information was provided with folders and videos to guide the home exercises.

Patients who were assigned to postponed PFPT did not receive additional treatment besides their conservative measures until first follow-up at 8 weeks after inclusion.

All medical data were collected at the clinic before entry into the trial database, data collection was facilitated by case record forms in Castor EDC.[34] We recorded all adverse events and serious adverse events.

Outcome measures

The primary outcome was muscle tone at rest during EMG-registration of the pelvic floor before and after PFPT.

Secondary outcomes contained clinical healing of the fissure (complete re-epithelisation), average pain intensity during defecation on a VAS-scale, improvement of pelvic floor muscle function and complaint reduction measured with the Proctoprom before and after PFPT.

All outcomes were measured at baseline, at 8- and 20-week follow-up.

Sample size

The sample size of the study was based on the primary outcome of the study, the tone at rest during EMG registration of the pelvic floor. In preliminary studies we found

a mean of 1.75 (μV) at rest, with a standard deviation of 1.75. Based on a slightly conservative standard deviation of 1.8, and a difference to be detected of 1.0 between the treatment group and the control group, we concluded that at least 70 patients in each treatment arm was required to detect a difference of 1.0 between the treatment group and the control group with postponed treatment. This sample size provided ample power (>90%) to detect a moderate effect size with a nominal alpha level of 5%.

Randomization

The surgeon and the principal investigator approached the patient and informed the patient about the study. Patients who met the eligibility criteria were randomly assigned to the PFPT treatment group or to the control group receiving postponed PFPT (1:1 allocation, random block sizes of 4,6 and 8). The randomization was computer generated using Castor EDC.[34]

A unique record number was generated, and the allocation was disclosed. The principal investigator was not able to access the randomization sequence and had a decoding list with randomization numbers and patient identification numbers in the investigator site file. Only the coordinating surgeon and principal investigator had access to the key to the code. The principal investigator informed the patient about group allocation and follow-up appointments.

Blinding

The principal investigator, who was also involved in the data analysis was not blinded for allocation. Because of the nature of the intervention, the principal investigator, collaborating pelvic floor physical therapists and patients could not be blinded. However, the surgeon performing the 8- and 20-week follow-up to investigate the healing of the fissure, resting anal sphincter pressure and pelvic floor dyssynergia was blinded to group allocation.

Statistical analysis

Data were analysed using Statistical Packages for Social Sciences (SPSS, Chicago, II, USA, version 26.0). Descriptive methods were used to assess quality of data, homogeneity of treatment groups and endpoints. Normality of the data were analysed with histograms. Data are presented using mean (SD), median (min-max) for the

numeric and non-normal variables and frequency (percentages) for categorical variables. A paired *t* test and Wilcoxon signed rank was used to compare continuous variables within groups. McNemar was used to compare categorical variables within groups. Comparison between groups for continuous variables was made by repeated measure analysis of variance using a mixed model after transformation of the data to enhance normality, with treatment, time (categorical) and their interaction as fixed effects and with random patient effects. In addition, data at each time point were compared with independent samples *t* tests, Mann-Whitney *U* test and Chi-square test depending on the variables. All *p* values were two-tailed and statistical significance was taken as a *p* value of less than 0.05. Multiple imputation for incomplete records was not needed because less than 5% of the data was missing. An interim analysis was not performed for this study.

Results

Between 10 December 2018 and 13 July 2021, 155 patients with CAF were found eligible. 140 patients, 68 men (48.6%) and 72 women (51.4%) with a mean age of 44.5 ±11.1 (range 19-79) years were randomized to PFPT (n=70) or a control group (postponed PFPT) (n=70). Baseline characteristics were similar between the 2 groups (Table 1). After randomisation, one patient in the PFPT group and 2 patients in the control group withdrew after inclusion.

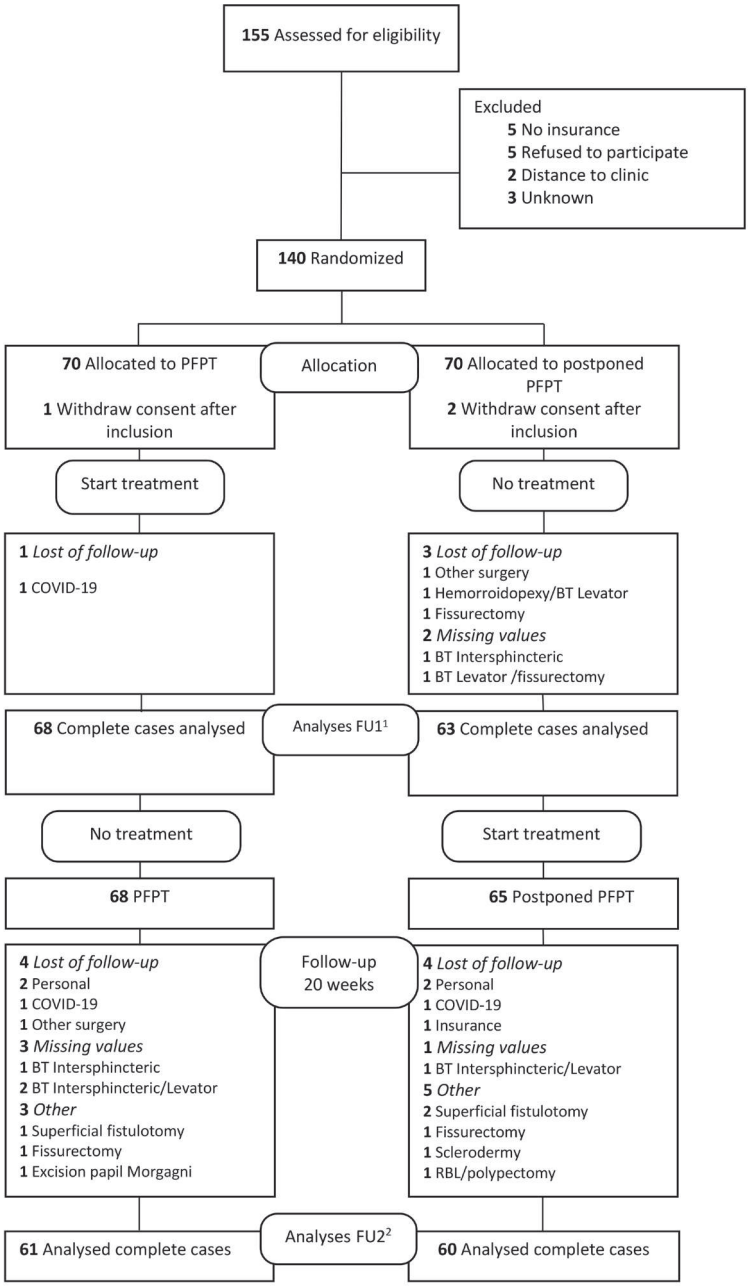
During the study, 4 patients were lost of follow-up at 8 weeks, one patient in the PFPT group and 3 in the control group. At 20 weeks after inclusion, 4 patients were lost of follow-up in the PFPT- group and 4 in the control group (Figure 1. CONSORT diagram).

There were no reported negative side effects or serious adverse events in both groups.

Table 1. Demographics at baseline

Variable	PFPT group (n=70)	Postponed PFPT (n=70)
Age, years mean ±SD, (range)	44.2±10.7, (23-66)	44.7±11.6, (19-79)
Sex, women/men, n (%)	37(52.9)/33(47.1)	35(50.0)/35(50.0)
Partus, yes/no (%)	31.4/21.4	30/20
Vaginal/C-section (%)	28.6/2.9	25.7/4.3
Duration of complaints (%)		
0-2 months	12.9	11.4
2-6 months	18.6	27.1
6-12 months	12.9	15.7
12-36 months	24.3	20.0
>3 years	31.4	25.7
Smoking, yes/no (%)	7.1/92.9	11.4/88.6
Gastric bypass, yes/no (%)	2.9/97.1	4.3/95.7
Previous treatment:		
Botulinum toxin, yes/no (%)	10/90	5.7/94.3
Lateral internal sphincterotomy, yes/no (%)	1.4/98.6	0.0/100
Alternate, yes/no (%)	37.1/62.9	32.9/67.1
Obstipation, yes/no (%)	12.9/87.1	17.1/82.9
Use of laxatives/fiber, yes/no (%)	44.3/55.7	47.1/52.9
Sexual complaints, yes/no (%)	27.1/72.9	24.3/75.7
Psychological consultant, yes/no (%)	37.1/62.9	27.1/72.9
Urological complaints, yes/no (%)	25.7/74.3	28.6/71.4
Location of fissure (%)		
Anterior	12.9	15.7
Posterior	78.6	77.1
Other	8.6	7.1
Anal sphincter pressure (%)		
Decreased	1.4	1.4
Normal	12.9	10,0
Increased	85.7	88,6
Pelvic floor resting tone (%)		
Decreased	2.9	4.3
Normal	10.0	15.7
Increased	87.1	80.0
Squeeze pressure (%)		
Decreased	34.3	31.4
Normal	48.6	50.0
Increased	17.1	18.6
Traction puborectalis painful, yes/no (%)	70/30	80/20
Dyssynergia digital rectal examination, yes/no (%)	67.1/32.9	78.6/21.4
Proctoscopy, yes/no (%)	45.7/54.3	42.9/57.1
Ointment (%)		
Diltiazem	94.3	88.6
Isosorbinedinitrate (ISDN)	4.3	10.0
Other	1.4	1.4

Figure 1. CONSORT diagram



[1]Timepoint 8 weeks after inclusion; [2]Timepoint 20 weeks after inclusion
PFPT=Pelvic Floor Physical Therapy; BT= Botulinum Toxin; RBL=Rubber Band Ligation

Primary outcome

Regarding the analysis of repeated measures, the PFPT group was found to be more effective for reducing pelvic floor muscle tone measured with EMG compared to control group (p<0.001) (Figure 2; Table 2). The mean estimated difference between groups post-treatment at first follow-up, at 8 weeks from baseline was -1.88 μV; 95% CI, -2.49 to -1.27 (p<0.001). At 20 weeks, when both groups had received PFPT, the mean difference between PFPT and control group showed no significance (- 0.05 μV; 95% CI. -.82 to .71; p=0.889) (Table 2).

The mean tone of the pelvic floor at rest measured with EMG, decreased significantly from pre-to post-treatment in the PFPT- group (p<0.001) and remained significant from baseline to 20-week follow-up (p<0.001) (Table 2). In the control group, the mean resting tone of the pelvic floor did not decrease significantly at first follow-up (p=0.192). At 20-week follow-up the control group showed a significant decrease in mean resting tone of the pelvic floor after treatment (p<0.001) (Table 2).

Regarding the analysis of repeated measures, the PFPT group was found to be more effective for reducing EAS-tone measured with EMG, compared to control group (p<0.001) (Figure 2; Table 2). The mean estimated difference between groups at post-treatment was -1.44 μV; 95% CI. -2.77 to -.12 (p<0.05). At 20 weeks, no significant difference was found between groups (0.61 μV; 95% CI. -.62 to 1.84; p=0.331) (Table 2).

The mean score, tone at rest of the EAS in the PFPT- group, decreased significant from pre-to post-treatment (p<0.001) and remained significant at 20-week follow-up (p<0.05). No significant decrease was found in the mean resting tone of the EAS at first follow-up in the control group (p=0.173). After intervention at 20-week follow-up, the mean resting tone of the EAS decreased significant in the control group (p<0.001) (Table 2).

Table 2. Study measures at baseline, 8-week and 20 -week follow-up. Comparison within and between treatment groups and repeated measurements

	PFPT group					Control group				Between groups 8 weeks	Between groups 20 weeks	Group vs Time	
	Baseline	8 weeks	*p* value	20 weeks	*p* value	Baseline	8 weeks	*p* value	20 weeks	*p* value	*p* value	*p* value	*p* value
EMG PF resting tone (μV), mean (SD)	6.9(2.9)	4.8(1.9)	<0.001*	5.0(1.7)	<0.001*	6.5(2.8)	6.1(2.3)	0.192*	4.2(1.7)	<0.001*	<0.001§	0.889§	<0.001@
EMG EAS resting tone (μV), mean (SD)	6.1(2.8)	4.5(2.1)	<0.001*	5.4(2.7)	<0.05*	6.0(2.8)	5.8(2.7)	0.173*	4.5(2.3)	<0.001*	<0.05§	0.331§	<0.001@
Fissure healed yes (%)	0.0	55.7	<0.001y	55.7	<0.001y	0.0	21.4	<0.001y	60.0	<0.001y	<0.001c	0.333c	NA
VAS pain score, mean (SD)	5.5(1.6)	2.3(1.9)	<0.001*	1.5(1.6)	<0.001¢	5.2(1.6)	4.6(1.8)	<0.001*	1.5(1.6)	<0.001¢	<0.001§	0.425a	<0.001@
Increased tone PF (%)	87.1	28.6	<0.001y	22.9	<0.001y	81.4	77.1	0.980y	20.0	<0.001y	<0.05c	0.750c	NA
Proctoprom mean (SD) ¥	5.2(2.0)	2.8(2.1)	<0.001¢	1.9(1.9)	<0.001¢	5.0(2.2)	3.8(2.2)	<0.05¢	2.4(2.1)	<0.001¢	<0.001a	0.118a	<0.001@
Dyssynergia DRE yes (%)	67.1	25.7	<0.001y	24.3	<0.001y	78.6	64.3	0.092y	22.9	<0.001y	<0.001c	0.964c	NA
Dyssynergia BET yes (%) ¥	38.6	NA	NA	5.7	<0.001y	45.7	NA	NA	4.3	<0.001y	NA	0.566c	NA

Proctoprom sample sizes are 64 and 61 PFPT and control respectively at baseline, 58 and 54 respectively at 8 weeks follow-up and 44 and 45 respectively at 20 weeks follow up

Dyssynergia BET sample sizes are 34 and 35 for PFPT and control respectively. At 20 weeks sample sizes are 18 PFPT vs 20 control.

PFPT=Pelvic Floor Physical Therapy; EMG=Electromyography; EAS=External Anal Sphincter; VAS=Visual Analog Scale; NA= not applicable; PF=Pelvic Floor; DRE= Digital Rectal Examination; BET=Balloon Expulsion Test; PF=Pelvic Floor

*	Paired t-test, comparison of scores between baseline and 8 weeks and 20 weeks
§	Unpaired t-test comparison of change scores from baseline to week 8 and 20 weeks
@	Repeated measurement analyses
¢	Wilcoxon signed rank test
a	Mann-Whitney U test
y	McNemar
c	Chi-square test
¥	The sample sizes shown are slightly smaller for some secondary outcomes due to missing values.

Secondary outcomes

Clinical healing of the fissure

In the PFPT group, the fissure was healed in 55.7% of the patients vs 21.4% in control group at 8-week follow-up (p<0.001). At 20-week follow-up healing of the fissure did not further improve in the PFPT but was healed in 60% in the control group after treatment (p<0.001). No significant differences were found in fissure healing between groups at 20-week follow-up (p= 0.333) (Table 2).

Pain

Regarding the analysis of repeated measures, the PFPT group was found to be more effective for reducing VAS pain score compared to control group (p<0.001) (Figure 2, Table 2). The mean estimated difference between groups at 8 weeks from baseline was -2.47; 95% CI. -3.05 to -1.89 (p<0.001). At 20 weeks no significance in mean difference in VAS pain scores was found between groups (-0.17; 95%CI. -.89 to .54; p=0.425) (Table 2).

VAS pain was significantly reduced in both the PFPT and the control group at 8 weeks from baseline (p<0.001). At 20-week follow-up, VAS pain in PFPT-group and control group further decreased and remained significant from baseline (p<0.001) (Table 2).

Pelvic floor function

Dyssynergia measured with digital rectal examination was found in 67.1% in the PFPT group vs 78.6% in control group before treatment. After intervention at 8 weeks from baseline, dyssynergia was found in 25.7% in the PFPT group vs in 64.3% in control group (p<0.001). At 20-week follow-up, when both groups received treatment, the difference in dyssynergia was no longer significant between groups (p=0.964) (Table 2).

At baseline, dyssynergia measured with the balloon expulsion test was found in 38.6% in PFPT group vs 45.7% in control group. After 20 weeks no significance was found in dyssynergia measured with the balloon expulsion test in the PFPT group vs the control group (p=0.566) (Table 2).

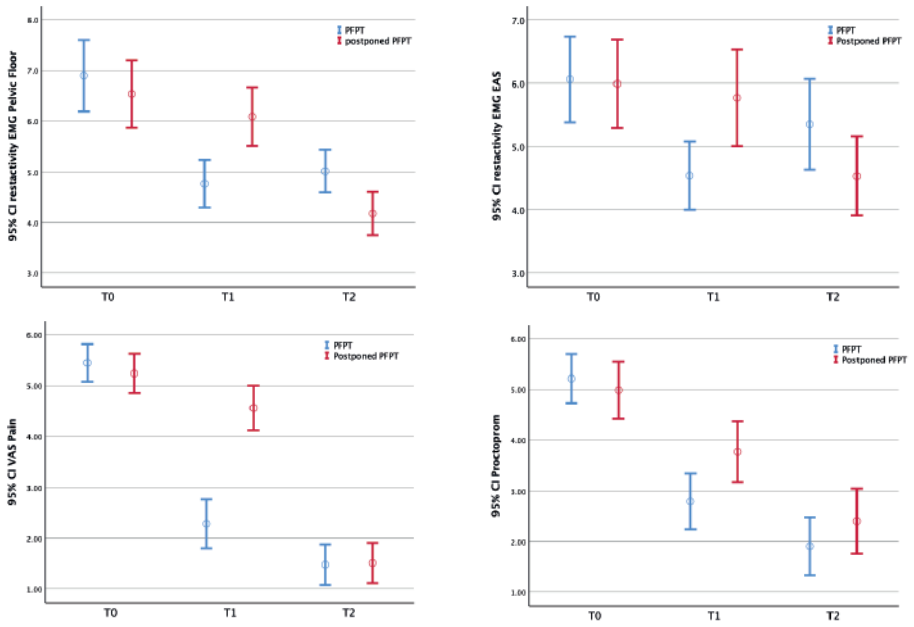
Increased pelvic floor muscle tone measured with digital rectal examination was found in 87.1% of the patients in the PFPT group vs 81.4% in control group before treatment. After intervention at 8 weeks from baseline, increased pelvic floor muscle tone was found in 28.6% in the PFPT group vs 77.1 % in the control group (p<0.05). At 20-week follow-up no significance was found in increased pelvic floor muscle tone between the two groups after treatment (p=0.750) (Table 2).

Patient related outcome measurement

According to repeated measurement analysis, complaints were more effectively reduced in the PFPT-group compared to the control group at 8 weeks from baseline (p<0.001) (Figure 2; Table 2). The mean estimated difference between groups at 8 weeks from baseline was -1.56; 95% CI. -2.24 to -.88 (p<0.001). At 20 weeks no significant difference in Proctoprom scores was found between groups (-0.66; 95%CI. -1.59 to .28; p=0.118) (Table 2).

The Proctoprom scores in the PFPT -group decreased significantly from pre-to post-treatment at 8 weeks from baseline (p<0.001). In the control group the Proctoprom scores also decreased (p<0.05). Improvement of Proctoprom scores were maintained in both groups at 20-week follow-up (p<0.001) (Table 2).

Figure 2. Repeated measurement analyses



Discussion

The present study is the first randomized clinical trial of EMG-biofeedback-assisted PFPT for CAF. The results of our study show a significant decrease in mean resting tone of the pelvic floor measured with digital rectal examination and EMG, improvement of healing of the fissure, pelvic floor function, pain, and complaint reduction. These results confirm our hypothesis that PPFT is effective in patients with CAF.

Pelvic floor muscle tone measured with EMG-biofeedback decreased from pre-to post-treatment and between groups and has been proven an effective and efficient treatment modality. Biofeedback is a neuromuscular training approach in which patients learn how to appropriately contract or relax muscles, aided by visual or auditory feedback of muscle activity. It is the mainstay in the treatment of anorectal dysfunctions and is commonly utilized in PFPT.[35] The efficacy of PFPT including biofeedback on pelvic floor dysfunction has already been proven in randomized control trials,[19,36,37] although the success depends on motivation of the patient and skills of the therapist.[22]

Muscle tone measured with EMG, also improved in the EAS from pre-to post-treatment and compared to controls. These results confirm the role of the EAS in patients with CAF, which correlates with findings of Grimaud.[38] In this study, including patients with chronic idiopathic anal pain, biofeedback was used for relaxation of the EAS. A significant decrease in resting pressure was observed in the anal canal measured with manometry, which was accompanied by a relief in anal pain, suggesting that the pain was due to abnormal chronic contraction of the EAS.

Pelvic floor muscle tone, based on digital rectal examination significantly decreased from pre- to post-treatment and between groups. A comprehensive careful digital rectal examination is an important topic to obtain information on anorectal anatomy and function.[22,26] Besides that, the use of quantified digital palpation to measure muscle tone and dyssynergia, is recommended in clinical guidelines.[4,25] Although no normative values on pelvic floor muscle tone exits, it appears that patients with CAF have higher levels of tonic activation of the pelvic floor. Furthermore, tenderness to palpation often accompanied with increased pelvic floor muscle tone is a feature of levator ani syndrome [4,39] and was found in 75% of our patients. Increased tone or spasm of the levator ani, probably leading tot ischemia could be a contributing factor in the pain patients experience.[40] Tenderness to palpation is a predicting factor of response to biofeedback treatment.[41]

Fourteen percent of the fissures were anterior, mainly in women (70%), 35% of whom had had a vaginal delivery. Anterior fissures are associated with low anal sphincter

pressure in the presence of anal sphincter defects,[42] but a subgroup analysis showed high anal sphincter pressure in 90% of these women. In contrast, high anal sphincter pressure was found in 87% of posterior fissures. This outcome is quite interesting, although it should be mentioned that we investigated anal sphincter pressure with digital rectal examination and not with manometry. The presence of pain and an alteration of anal sensibility,[43] could blur correct anal sphincter pressure and result in a higher pressure. Several studies about comparison between digital rectal examination show an overall good agreement in pressures with manometry but the results are not consistent.[43-47] These results should be interpreted with care.

Dyssynergia of the pelvic floor was found in a large percentage (72.9%) of our patients at baseline. Subgroup analyses showed less dyssynergia (56%) in patients with low/normal pressures compared to patients with high anal sphincter pressures (76%). This is comparable to the study of Jain et al.,[48] in which 426 patients with fecal evacuation disorders were investigated with anorectal manometry. Dyssynergia was more common in patients with CAF. Whether CAF is secondary to dyssynergic defecation or responsible for an abnormal defecation pattern is still under debate.

Treatment with biofeedback for dyssynergia is highly recommended in clinical guidelines [4,23] and was also successful in our study, considering the improvement in dyssynergic pattern of the pelvic floor after treatment, although 22% of the patients did not improve.

Dyssynergia is affected by alterations of the chest, abdominal wall and vertebral column and pelvic floor that may be functional, anatomical, or behavioural which may influence the outcome of PFPT. [20,49] It is important to perform a comprehensive evaluation of these alterations with a multidimensional approach to define which patients will benefit most from PFPT.[50]

The Proctoprom was used to detect changes over time, the patient's state of health measures and the effect of treatment.[31] This study showed a significant effect of disease burden and treatment from the patient's point of view.

Although the PFPT group improved in all the outcome measures, patients in the control group also improved significant in pain and Proctoprom-scores, at first follow-up. The first step in treatment is re- education and understanding defecation disorders.[51] Probably the information all patients receive about their complaints, instruction about toilet behaviour and lifestyle advice contribute to this improvement.

An evident decrease of pelvic floor muscle tone, improvement of fissure healing and pelvic floor function at 20-week follow-up indicated that patients from the postponed

PFPT group also benefited from PFPT. Although patients from the early PFPT group improved quickly, it is still worthwhile initiating PFPT at any time during treatment.
The main strengths of this study are the prospective randomized control trial design, sufficiently powered intent-to treat analyses and the design of the study in which all patients received PFPT. In addition, the use of a PFPT- protocol performed by large group of collaborating pelvic floor physical therapist in the Netherlands makes this treatment suitable in all clinical settings. All pelvic floor physical therapists involved in the study were highly trained and had access to equipment for EMG-biofeedback. The use of a validated EMG electrode[27] to measure pelvic floor muscle tone, the use of a standardised measurement protocol by the same investigator in the same environment diminished information bias.[52]
The willingness to participate and adherence of the patients to the trial procedures and the intervention was high, evidenced by the low rate of loss of follow-up. The use of this clinical trial set up with a postponed PFPT- group may have also positively influenced the adherence rate. Patients knew they would start with PFPT, albeit 8 weeks later.
Our population was real world; we enrolled patients of all ages and both sexes with duration of complaints varying from 2 months to more than 3 years and living in different parts of the Netherlands. Thus, the results may be generalizable to the CAF population at large.
There were several limitations in our study. The first concerns the risk of detection bias; we were unable to mask group allocation from patients, collaborating pelvic floor physical therapist and principal investigator, because of the trial design and the nature of the intervention. Second, the pelvic floor physical therapist was also the principal investigator and consequently investigator's bias could not be ruled out.
The balloon expulsion test, to identify patients with pelvic floor dyssynergia was only performed in 69 patients at inclusion with a high rate of loss to follow-up at 20 weeks. The main reason was a logistic one. It was not always possible to combine an appointment in the clinic with the nurse and principal investigator, especially during the COVID-19 pandemic. In addition, in a large percentage the balloon expulsion test failed. This could be a result of fear of patients with CAF in expelling a balloon.
COVID-19 did have some influence on our study. During the first pandemic in 2020 we were not able to include patients in the study for 4 months and a small number of patients were lost to follow-up because they were diagnosed with COVID-19 at the follow-up appointment.

Clinical guidelines of leading societies do not recommend PFPT as a treatment option for CAF. Our findings provide strong evidence that PFPT is effective in the treatment of CAF and pelvic floor dysfunction. PFPT has no side-effects, low potential for complications, and low costs.

Conclusions

Our findings confirm that PFPT is effective in patients with CAF and concomitant pelvic floor dysfunction in improving pelvic floor muscle tone and function, healing of the fissure, reducing pain and complaint reduction. This study provides evidence that PFPT can be used as adjuvant treatment in CAF and pelvic floor dysfunction besides regular conservative treatment.

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The authors reply to "Pelvic floor dysfunction and chronic anal fissure: a dog chasing its tail."

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Dear Sir,

We would like to thank Dr Pietroletti and collegues for their interest in our manuscript and the thoughtful comments concerning the role of pelvic floor physical therapy in patients with chronic anal fissure (CAF).[1]

Although the etiology CAF is uncertain, it is assumed that pain causes an increased sphincter tone leading to ischemia of the anal sphincter. This inhibits fissure healing, generating a vicious circle of pain and constipation thus prolonging the healing process as Pietroletti and colleagues mentioned.

We hypothesized that pelvic floor dysfunction may be part of the pathophysiology and reason for unresponsiveness to some current treatment. In a retrospective study we found that a large percentage of patients with CAF had pelvic floor complaints such as dyspareunia and obstructive defecation and pelvic floor dysfunction (dyssynergia and/or increased pelvic floor muscle tone).[2]

Increased tone of the pelvic floor can be a primary problem or a secondary adaptation to an acute or chronic injury such as CAF or to musculoskeletal components in the pelvic floor and surrounding structures. Pelvic surgery, traumatic vaginal delivery, chronic pelvic disorders, experienced threat and (chronic) stress are found to be associated with increased pelvic floor muscle tone and related to habit, lifestyle and/or stressful occupation.[3] The long duration of continuing fissure symptoms may lead to functional and psychosocial impairment,[4] and seeking medical care is often delayed due to embarrassment. These underlying factors should be kept in mind when treating patients with CAF.

Although the title may not fully cover the whole scope of the manuscript, we think that the pelvic floor anal fissure (PAF)-study shows a broader perspective on patients with CAF.

As mentioned in both the study protocol and in the abstract, the primary objective of our study was to establish the effectiveness of pelvic floor physical therapy in the treatment of CAF and pelvic floor dysfunction such as dyssynergia and/or increased pelvic floor muscle tone.

All patients used ointment for at least 6 weeks prior to the treatment protocol and had applied the ointment internally at least 3 times a day. This could have positively decreased the visual analogue scale (VAS)-pain score during defecation at baseline. In addition, a large percentage of our population (51%) had fissure-related complaints for more than 6 months and only 12% had complaints for less than 2 months. The complaint duration may have influenced the (subjective) VAS-pain scores.

Patients were only included in this trial when digital rectal examination could be performed. In our experience, patients tolerate the examination well after careful counselling, and are reassured that other anorectal disease is excluded. During a careful digital rectal examination, the pelvic floor muscles and anorectal anatomy and function can be evaluated properly. Additionally, we objectively evaluated pelvic floor muscle tone electromyographically with an intra-anal probe. Patients not included in the study were treated with other surgical procedures such as botulinum toxin and/or fissurectomy.

The anal stretching technique prescribed in the treatment protocol were focused on the pelvic floor muscles. The stretching technique combined with soft-tissue manipulation and myofascial release is aimed at pelvic floor awareness and relaxation.[3] These techniques cannot be compared to digital anal stretching treatment under sedation.

Treatment with percutaneous nerve stimulation (PTNS) has been proven effective in the treatment of overactive bladder, fecal incontinence, pelvic pain [5] and non-operative treatment of CAF.[6]

The tibial nerve is a mixed nerve containing L4–S3 fibers and originates from the same spinal segments as the innervations to the bladder and pelvic floor. The mechanisms of its effect are not fully elucidated, but stimulation of peripheral fibers transmits impulses to the sacral nerves and neuromodulates the lower urinary tract, rectum, and anal sphincters.[5] PTNS could probably be combined with our treatment program to improve efficacy but warrants further investigation in well-designed randomized controlled trials Our study tried to fill the gap for treatment modalities between conservative management and surgery in patients with CAF and concomitant pelvic floor dysfunction.

When a dog is chasing his tail, there is a lot of effort made with little effect. We believe that the positive outcomes from the use of this rehabilitative approach in patients with CAF is not time consuming and can help to improve healing of the fissure, complaint reduction, and quality of life. Additionally, the awareness by the patient of the influence of the pelvic floor muscles in anal pain might help to prevent recurrence. The PAF-study can pave the road for further research in this field.

References

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CHAPTER 7

Pelvic floor physical therapy in the treatment of chronic anal fissure (PAF-trial): outcome of Quality of Life

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Abstract

Background

Chronic anal fissure (CAF) is one of the most common anorectal diseases and is associated with reduced quality of life. The aim of this study was to investigate the effects of pelvic floor physical therapy on quality of life in patients with CAF using the Short-Form 36 Health Survey (RAND-36).

Methods

Adult patients with CAF and concomitant pelvic floor dysfunction such as dyssynergia and increased pelvic floor muscle tone were randomly assigned to an intervention group, receiving 8 weeks of pelvic floor physical therapy, or assigned to a control group receiving postponed pelvic floor physical therapy (PAF-trial). Quality of life and pain ratings were outcomes of the study and were measured at 8- and 20-week follow-up.

Results

One hundred patients (50 women and 50 men, median age 44.6 years [range 19–68 years]), completed the RAND- 36 questionnaire and visual analog (VAS) pain scale score at admission. A significant improvement was found at 20-week follow-up in all domains of the RAND-36; physical functioning, pain, health change ($p< 0.001$); physical role, vitality, general health, social functioning, emotional role, mental health ($p< 0.05$). VAS pain was significantly reduced at 8 weeks (mean estimated difference 1.98; 95% CI 1.55–2.42, $p< 0.001$) and remained significant at 20-week follow-up ($p< 0.001$). The difference between the groups as regards change in the mean pain intensity scores at 8 weeks was 2.48 (95% CI − 3.20 to − 1.75; $p< 0.001$). Compared to the reference values of the general Dutch population, the patients in our study with a chronic anal fissure and pelvic floor dysfunction reported an impaired quality of life in 8 of 9 domains of the RAND-36. After treatment, significant lower scores were found in 2 out of 9 domains.

Conclusions

The results of this study provide evidence that treatment by pelvic floor physical therapy improves quality of life and reduces pain, making it an important tool in management of CAF and concomitant pelvic floor dysfunction.

Introduction

Chronic anal fissure (CAF) is a common proctological problem associated with reduced quality of life.[1] CAF is defined as a longitudinal ulcer in the squamous epithelium[2] and gives rise to distressing symptoms of bleeding and pain during and after defecation. The incidence of CAF is nearly 0.11% (1.1 cases per 1000 persons) and varies considerably according to age and sex.[3] Persistence of symptoms for long periods may lead to functional and psychosocial impairment,[4] and seeking medical care is often delayed due to embarrassment.[5] Furthermore in patients with CAF, there is a high degree of depression, anxiety disorders and stress.[1]

Health related quality of life (QoL) can be influenced by physical, psychological, and social factors, an individual's life experience and general well-being.[1,6] The purpose of health related QoL evaluations is to move beyond clinical symptoms by examining how patients perceive and experience the impact on well-being and daily life.[6,7]

The most common generic instrument to measure QoL is the validated Medical Outcomes 36-Item Short-Form Health Survey (SF-36) used for decision-making for health care policies and clinical interventions.[8] Although there is a need to integrate aspects of functional and psychosocial impairment into medical care,[9] only a few studies studied QoL in patients with CAF.

Recently, the Pelvic floor Anal Fissure study (PAF-trial) was completed, which is a randomized controlled trial demonstrating the beneficial effects of pelvic floor physical therapy (PFPT) on an improvement of pelvic floor muscle tone and function, VAS pain scores, fissure healing and complaint reduction.[10] The aim of PFPT is to increase awareness and proprioception, to improve muscle relaxation, elasticity of the pelvic floor muscles, to restore abdominopelvic coordination and reduce pain.[11,12]

In the PAF-trial we also hypothesised that treatment of PFPT will improve QoL. Here, we present the results of QoL measured with the Short-Form RAND-36 (RAND-36)[13] and VAS-pain ratings in patients with CAF and pelvic floor dysfunction who were included in the PAF-trial. Furthermore, to better elucidate the results, the study compares baseline and post-treatment values with reference values of the RAND-36 of the general Dutch population.[13]

Materials and Methods

Study design

Quality of life was assessed with the RAND-36 in the PAF-trial.[14]

The PAF-trial is a single-centre, parallel, randomized controlled trial. The design involved allocation of all appropriate consecutive patients older than 18 years with

CAF and pelvic floor dysfunction. Eligible patients were randomly assigned, after providing written informed consent to an intervention group receiving 8 weeks of PFPT or assigned to postponed PFPT (1:1 allocation).

Participants

Men and women aged 18 years or older presenting CAF and pelvic floor dysfunction were recruited by the surgeon at the Proctos Clinic in the Netherlands. CAF was defined as a longitudinal ulcer in the squamous epithelium with one or more signs of chronicity including hypertrophied anal papilla, sentinel pile and exposed internal sphincter muscle. Patients had fissure complaints of more than 6 weeks and all patients failed conservative treatment with fibers and/or laxatives and had applied the ointment (diltiazem or isosorbide di-nitrate) internally for at least 6 weeks. Pelvic floor dysfunction was defined by the presence of dyssynergia and/or increased pelvic floor muscle tone.

All patients had sufficient understanding of the Dutch language (reading and writing) and were able to complete the online questionnaires. Patients who were not able to undergo a digital rectal examination, patients presenting an abscess or fistula, Crohn's disease or ulcerative colitis, anorectal malignancy, previous rectal radiation and pregnancy were excluded from the trial.

Physical examination and questionnaires

The diagnosis of CAF was based on medical history taken and a thorough local inspection of the anus. Resting anal sphincter pressure was measured by a careful digital rectal examination and scored as decreased, normal and increased.[15] Pelvic floor dysfunction was defined by the presence of dyssynergia and/or increased pelvic floor muscle tone. Pelvic floor muscle tone was measured with a digital rectal examination[16] and surface electromyography (μV)[16] with an intra-anal probe (MAPLe,®Novuqare Pelvic Health B.V. CE 0344, Rosmalen, the Netherlands), which is validated for its purpose.[17] Pelvic floor dyssynergia was detected by digital rectal examination [18] and balloon expulsion test.[19]

If necessary, proctoscopy was performed to exclude other pathology.

To access the impact of global QoL, the validated Dutch version of Short-Form RAND-36, Health Status Inventory, version 2.[13] was used.

The RAND-36 consists of 36 items and 9 subscales: physical functioning, bodily pain, role limitation due to physical health problems, vitality, general health perception,

social functioning, role limitation due to emotional problems, mental health, and health change perception. The RAND-36 consist of the same sets of items as the SF-36,[20] although the scoring procedure differs between the RAND-36 and SF-36 on the domains of general health and bodily pain. The score for each scale is obtained by the sum of the scores for each item linearly transformed into a range from 0 to 100. Higher score indicates more favorable QoL.

To quantify the average intensity of pain during defecation, a visual analog scale (VAS) from 0 (no pain) to 10 (most intense pain) was used.[21] Patients were requested to fill in the RAND-36 and VAS-score at baseline, and at 8- and 20-week follow-up.

Interventions

At baseline, patients in both groups received information about the pelvic floor and related symptoms, explanation about relevant anatomy and defecation (patho) physiology, behavioural modifications, and lifestyle advice. All patients continued their conservative measures including the use of ointment (diltiazem or isosorbide di-nitrate). PFPT consisted of 5 face-to-face appointments of 45-minutes in a period of 8 consecutive weeks, using a treatment protocol. Details of this treatment protocol were prescribed earlier.[14] Patients who were assigned to postponed PFPT did not receive additional treatment besides their conservative measures and the use of ointment until first follow-up at 8 weeks after inclusion. Patients from the postponed PFPT group followed the same treatment protocol after first follow-up.

Data collection of the RAND-36 was facilitated by a secure on-line system called Castor EDC.[22] Patients received the questionnaire by e-mail through the Castor system at 3 timepoints; at baseline, at 8- and 20-week follow-up.

Outcome measures

The primary outcome of this study was QoL in patients with CAF and pelvic floor dysfunction before and after PFPT and compared to reference values of the general Dutch population. The other outcome measure was the average pain intensity during defecation on a VAS-scale.

The sample size of the PAF-study was based on the primary endpoint, the tone at rest during electromyographic registration of the pelvic floor and consisted of 140 patients.[14] The data from the questionnaires that were at least 75% completed at baseline and follow-up were used for the analysis of this study.

Statistical analysis

Data were analysed using Statistical Packages for Social Sciences (SPSS, Chicago, II, USA, version 28.0). Descriptive methods were used to assess quality of data, homogeneity of treatment groups and endpoints. Normality of the data were analysed with histograms. Data are presented using mean (SD), median (min-max) for the numeric and non-normal variables and frequency (percentages) for categorical variables. A paired *t*-test or Wilcoxon signed-rank test was used to compare continuous variables within groups. An independent *t*-test or Mann- Whitney *U* test for quantitative data was performed to analyse statistical differences between groups. For each of the dimensions of the RAND-36, items scores were coded, summed, and transformed on to a scale of 0 to 100. Statistical analyses consisted of estimating means and standard deviations for each of the RAND-36 scale scores. Comparison between groups for continuous variables was made by repeated measure analysis of variance using a mixed model after transformation of the data to enhance normality, with treatment, time (categorical) and their interaction as fixed effects and with random patient effects. To acquire an indication of the QoL of life of patients with CAF as compared to the reference group of the Dutch population, we calculated for each dimension the significance from the norm score[13] with the one-sample *t*-test.
In case of missing data, we excluded that specific case in total from further analyses when less than 75% of the questionnaire was filled out. All *p* values were two-tailed, and statistical significance were taken as a *p* value of less than 0.05.

Results

Between December 2018 and July 2021, 140 patients, were randomized to PFPT or postponed PFPT. After randomisation, 3 patients withdrew.
The RAND-36 was adequately completed by 100 patients at baseline, of whom 50 women and 50 men with a mean age of 44.6±11.1 (range 19-68). The results from the questionnaires at baseline of 37 patients were excluded because less than 75% of the form had been completed.
The participants' demographic and clinical characteristics of the total group of patients from the PAF-study, those who completed the baseline questionnaire adequately and individual treatment groups, are presented in Table 1.
There were no significant differences in terms of demographic or clinical parameters between the groups at baseline (Table 1).

The non-response rate at 20-week follow-up was 31%. The results of the mean RAND-36 subscores from the different domains and the mean VAS pain scores, per time point from the total group and individual treatment groups, are presented in Table 2.

Table 1. Baseline demographics

Variable	Total group PAF-study (n=140)	Total with adequate baseline data RAND-36 (n=100)	PFPT RAND-36 (n=52)	Postponed PFPT RAND-36 (n=48)
Age, years, median (range)	44.5 (19-79)	44.6 (19-68)	44.4 (23-66)	44.8 (19-68)
Sex: women/men (%)	51.4/48.6	50/50	53.8/46.2	45.8/54.2
Duration of complaints (%)				
0-2 months	12.1	15.0	13.5	16.7
2-6 months	22.9	26.0	25.0	27.1
6-12 months	14.3	12.0	13.5	10.4
12-36 months	22.1	26.0	25.0	27.1
>3 years	28.6	21.0	23.1	18.8
VAS-pain score (mean, SD)	5.3±1.6	5.5±1.7	5.6±1.6	5.4±1.8

VAS visual analog scale, *PFPT* pelvic floor physical therapy, *RAND-36* short-form health survey

QoL pre-and post-treatment

For the group who adequately completed the questionnaire, the mean scores significantly improved in all domains of the RAND-36 from baseline to 20-week follow-up; physical functioning, bodily pain, health change (p<0.001); physical role, vitality, general health, social functioning, emotional role, and mental health (p<0.05) (Table 2, Fig. 1).

QoL pre-and post-treatment for individual treatment groups

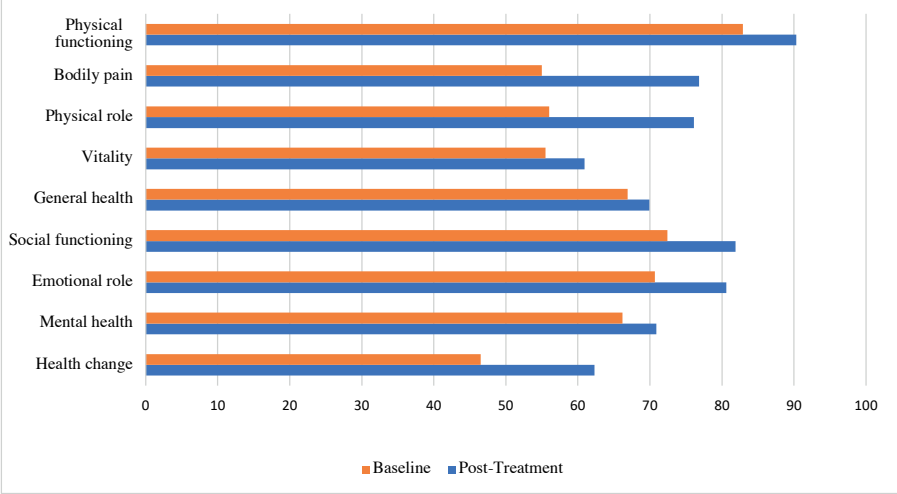
At 8-week follow-up, the PFPT group had significantly improved as regards bodily pain (p<0.001), physical role, social functioning, mental health, and health change (p<0.05) and the effect remained significant at 20-week follow-up. No significant improvement was found in vitality, general health, and emotional role at 8- and 20-week follow- up (Table 2). The postponed PFPT group significantly improved in the domains, pain (p<0.001), physical functioning, physical role, mental health, and health change (p<0.05) at first follow-up and remained significant at 20-week follow-up. At 20 weeks, the postponed group significantly improved in general health and emotional role (p<0.05) post-treatment. No significant improvements were found in the postponed group in the domain vitality and social functioning at this timepoint (Table 2).

Table 2. Study measures at baseline, 8-week and 20 -week follow-up. Comparison within and between treatment groups and repeated measurements for all patients with adequate baseline data

Quality of Life Scale RAND-36	**Total group**			**PFPT**					**Postponed PFPT**					**MD between groups**
	Baseline mean(SD) (n=100)	**20 weeks mean(SD) (n=69)**	***p* valueS**	**Baseline mean(SD) (n=52)**	**8 weeks mean(SD) (n=45)**	***p* value¥**	**20 weeks mean(SD) (n=37)**	***p* valueS**	**Baseline mean(SD) (n=48)**	**8 weeks mean(SD) (n=40)**	***p* value¥**	**20 weeks mean(SD) (n=32)**	***p* valueS**	***p* value**
Physical functioning	82.9(20.9)	90.3(14.1)	<0.001¢	84.9(18.7)	89.2(17.1)	*p*=.124¢	91.8(14.0)	p=.052¢	80.7(23.0)	87.1(16.9)	*p*=.012¢	88.6(14.3)	*p*=.008¢	*p*=.174p
Bodily pain	55.0(26.5)	76.8(20.5)	<0.001t	54.8(25.2)	69.7(24.7)	<0.001t	78.1(19.6)	<0.001t	55.3(28.2)	74.4(21.9)	<0.001¢	75.4(21.6)	<0.001t	*p*=.339y
Physical role	56.0(44.1)	76.1(38.9)	*p*=.004¢	57.7(43.3)	78.9(35.7)	*p*=.004¢	79.7(38.6)	*p*=.022¢	54.2(45.4)	73.1(36.4)	*p*=.012¢	71.9(39.5)	*p*=.049¢	*p*=.176p
Vitality	55.5(18.7)	60.9(16.1)	*p*=.013t	55.5(20.4)	58.7(19.5)	*p*=.296t	61.1(16.8)	*p*=.054t	55.5(16.9)	57.6(15.6)	*p*=.283t	60.6(15.6)	*p*=.130t	*p*=.753y
General Health	66.9(18.8)	69.9(17.6)	*p*=.036t	71.2(17.7)	73.2(19.3)	*p*=.394¢	73.1(18.4)	*p*=.484t	62.3(19.0)	64.9(17.8)	*p*=.222t	66.3(16.2)	*p*=.029t	*p*=.469y
Social Functioning	72.4(24.2)	81.9(22.2)	*p*=.011¢	70.2(23.6)	81.4(22.2)	*p*=.010¢	84.5(21.3)	*p*=.031¢	74.7(24.8)	80.0(22.3)	*p*=.065¢	78.9(23.2)	*p*=.157¢	*p*=.455y
Emotional role	70.7(41.4)	83.6(31.1)	*p*=.043¢	76.3(36.4)	82.9(33.0)	*p*=.085¢	84.7(28.9)	*p*=.747¢	64.6(45.8)	79.2(32.6)	*p*=.072¢	82.3(33.9)	*p*=.047¢	*p*=.192p
Mental Health	66.2(14.5)	70.9(13.0)	*p*=.003t	65.9(14.6)	71.1(17.7)	*p*=.050t	71.5(11.5)	*p*=.042t	66.5(14.7)	70.5(14.0)	*p*=.035t	70.4(14.8)	*p*=.038t	*p*=.701y
Health Change	46.5(24.6)	62.3(23.3)	<0.001¢	49.5(26.4)	61.7(28.5)	*p*=.004t	64.2(25.4)	*p*=.003t	43.2(22.3)	55.6(24.3)	*p*=.004t	60.2(20.9)	<0.001t	*p*=.726y
VAS-pain score	5.5(1.7)	1.5(1.6)	<0.001¢	5.6(1.6)	2.4(2.0)	<0.001¢	1.4(1.6)	<0.001¢	5.4(1.8)	4.7(1.9)	<0.001¢	1.6(1.6)	<0.001¢	<0.001y

t Paired t-test,
¢ Wilcoxon signed rank test
p Mann Whitney U test
y Unpaired T test
¥ p- value 8 weeks vs baseline
S p- value 20 weeks vs baseline
RAND-36= Short-Form 36 Health Survey; PFPT= pelvic floor physical therapy; MD= mean difference

Figure 1. Median Short-Form Rand-36 scores total group before and after treatment.



According to the mean estimated difference between groups at 8-week follow-up, no significant differences were found in the different domains of the RAND-36 (Table 2). Repeated measurement analysis showed more improvement in all domains in time from baseline to follow-up at 20 weeks in the PFPT- group compared to postponed PFPT- group although these differences were not significant (Figure 2).

Pain

For the group as a whole, the VAS was significantly reduced from baseline to follow-up at 8 weeks (mean estimated difference 1.98; 95% CI 1.55–2.42, $p< 0.001$) and remained significant at 20-week follow-up ($p<0.001$) (Table 2). geen enter. The vas pain score moet eronder staan

The VAS pain score was significantly reduced in both the PFPT and the postponed PFPT group at 8 weeks from baseline ($p<0.001$). At 20-week follow-up, the VAS pain score in the PFPT group and postponed PFPT group further decreased and remained significant compared to baseline ($p<0.001$). The difference between the groups as regards change in the mean pain intensity scores at 8 weeks from baseline was 2.48 (95% CI − 3.20 to − 1.75; $p<0.001$) favoring the PFPT group. At 20 weeks, no significant mean difference in VAS scores was found between groups ($p=0.269$).

Figure 2. Repeated measurement analysis different domains
PFPT pelvic floor physical therapy, CI confidence interval

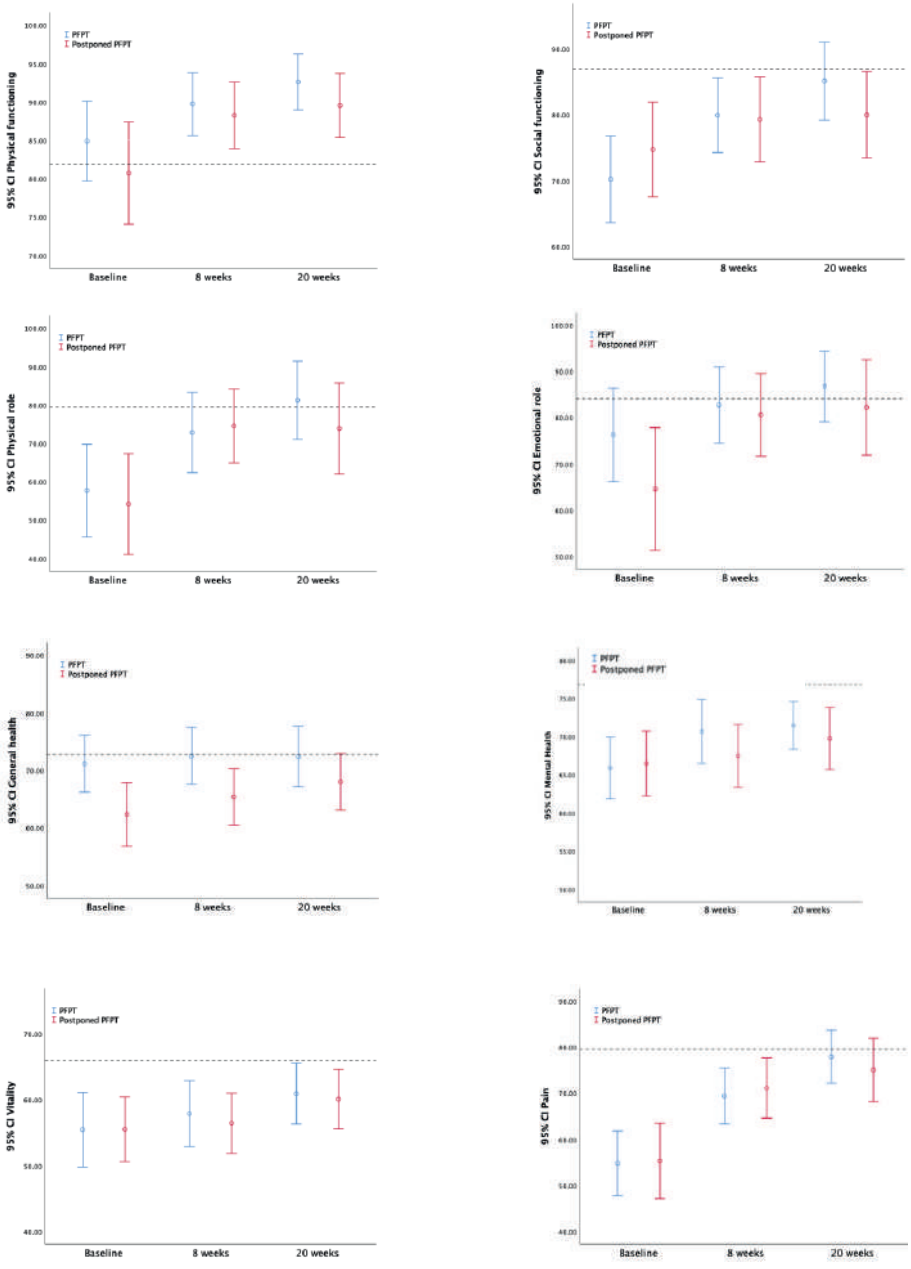
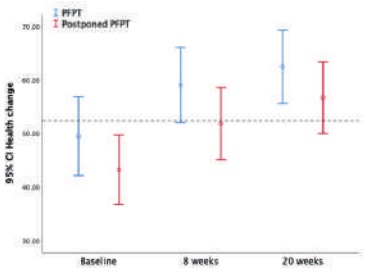


Figure 2. Continued

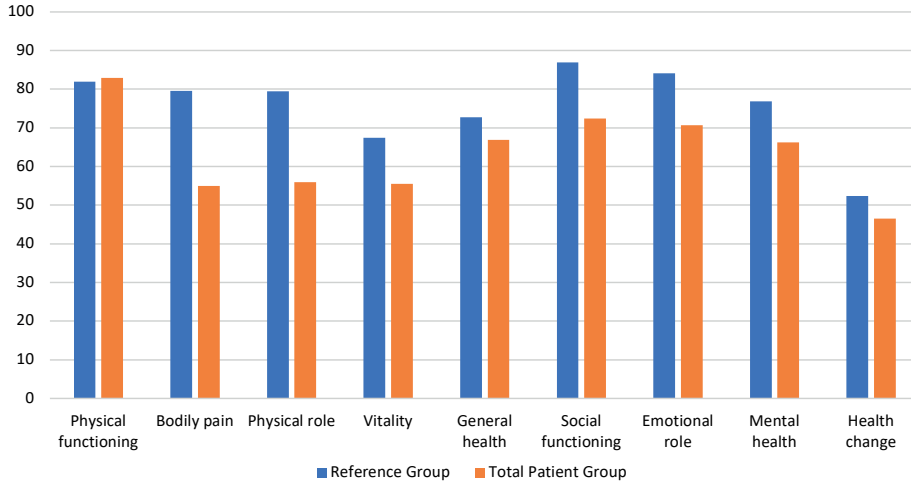


QoL in the total group compared to the Dutch population

Compared to the reference group of the general Dutch population based on a mean age of 44 years,[13] patients with CAF scored significantly lower on the subscales pain, physical role, vitality, social functioning, mental health (p<0.001) and general health, emotional role, and health change (p<0.05). No significant difference was found in the domain physical functioning (p=.633) (Figure 3).

Results showed that patients had higher post treatment scores at 20-week follow-up compared to the Dutch reference values on physical functioning and health change (p<0.001), but the scores were still significantly lower on vitality and mental health (p<0.001). No significant difference was found between the total group compared to the normal Dutch population on the other domains at this timepoint.

Figure 3. Mean Short-Form 36 Health Survey (RAND-36) scores of the total group and the reference group from the Dutch population



Discussion

Principal findings

Health related quality of life measured by the RAND-36 significantly improved in all dimensions in all patients at 20-week follow-up and confirm the efficacy of PPFT on quality of life in patients with CAF from the PAF-trial. The literature on the RAND-36 shows that very small differences in the range of 3-5 points on the survey could be interpreted as clinically important.[23,24] In all domains of the RAND-36, the minimal clinical importance was higher than 3 points, which could be interpreted as indicating that the treatment was meaningful to the patient.

Furthermore, compared to the reference values of the general Dutch population, patients with CAF and pelvic floor dysfunction reported an impaired QoL in 8 of 9 domains of the RAND-36. After treatment significant lower scores were found in 2 out of 9 domains.

The positive effect of PFPT on QoL in patients with other anorectal complaints[25,26] is already known but has never been investigated in patients with CAF.

In our study, the PFPT group significantly improved in 5 of 9 domains of the RAND-36 at 8-week follow-up. Interestingly, the postponed PFPT group also improved on 5 of 9 domains. An important aspect of treatment is re- education and improving understanding of defecation disorders.[27] It is likely that the information all patients receive about their complaints, instruction about toilet behaviour and lifestyle advice also are reflected in an improvement in quality of life in the postponed PFPT group, explaining our results.

Neither group improved in the domains, general health, vitality, and emotional role at 8-and 20-week follow-up. One of the reasons could be that RAND-36 is not sensitive enough to pick up changes in these domains in a relative short period of time (i.e., 20 weeks). More studies with a long-term follow-up are needed to confirm this.

In the domain bodily pain, all patients significantly improved post-treatment compared to baseline. The same results were found for VAS pain scores. Reduction of pain is likely to have a positive reflection on QoL. Results from a study by Griffin et al.[4] in patients with CAF who were treated with topical ointment, confirm this assumption. Higher VAS-pain scores were associated with worse outcome in all aspects of health-related QoL, with pain influencing many psychosocial and functional activities. A study by Tsunoda et al.[28] examining the treatment of CAF with diltiazem found that pain had a negative impact on the domains bodily pain and social functioning at

baseline. Patients with healed fissures after treatment, reported an improvement in bodily pain, vitality, general health, and mental health. The PAF-study[10] found that the fissure was healed in 60% of all patients at 20-week follow-up. Significant lower scores were found in patients with non-healed fissures in the domains, bodily pain, social functioning, and emotional role at that time-point.

In a study of Bagul et al.[29] in patients with CAF who received botulinum toxin injections, pain scores improved in 74% of the patients. QoL improved in patients in the domains of physical functioning, bodily pain, social functioning, and mental health. The study demonstrated that pain was a significant factor influencing the outcome of QoL scores. Another study investigating QoL after lateral internal sphincterotomy in 58 patients[30] found improvement in pain symptoms although not all domains of health related QoL were similarly positively affected. Smaller gains were reported among younger participants, women, participants with no comorbidities and those participants who waited the longest for their surgery.

Patients with CAF in our study scored overall lower than the reference group of the Dutch population. One of the reasons could be the chronicity of the problem. In our population, 65% of the patients had complaints for more than 6 months, which would have a negative influence on the patient, family members and other relations.[31] Other factors influencing the outcome of treatment should be investigated in further studies with a long-term follow-up.

The conclusions of this study are strengthened by the response rate of 71% at baseline, the high sample size and prospective design of the study. We enrolled patients of all ages and both sexes from different parts of the Netherlands. Thus, the results may be generalizable to the CAF population at large.

This study has some limitations. Currently, there is no disease-specific tool for assessing QoL in patients with CAF and therefore a generic instrument was used. The RAND-36 was chosen because it is one of the most used questionnaires measuring QoL, and it is translated in Dutch.[13] Its reliability has been proven in a post-rehabilitation Dutch population[32] but may not be specific enough to fully analyze the QoL in patients with CAF.

The non-response rate was 31% at 20-week follow-up. This may have caused bias if non-or partial- respondents differ from respondents as concerns QoL or its determinants or confounders.[33] Reasons for non-completion at 20-week follow-up were surgery including Botulinum toxin, fissurectomy, fistulotomy, sclerodermy and other surgery (breast cancer). Other reasons were COVID-19, pregnancy, loss

of follow-up for logistical reasons (distance, insurance, other) and personal. We did not find significant baseline differences between those followed up and those lost to follow-up.

Although the results show a significant improvement in a short period of time (e.g.,20 weeks), it is unknown what the long-term outcome of PFPT on QoL will be. In the PAF-trial, patients also visited the clinic at 1-year follow-up. At the time of submitting this manuscript the results of the 1-year follow-up were not completed. Hence, they could not be incorporated.

Conclusions

The results of this study provide evidence that PFPT is effective in the improvement of QoL and positively influences pain in patients with CAF and pelvic floor dysfunction. Patients with CAF and concomitant pelvic floor dysfunction reported an impaired QoL compared to the reference values of the general population in the Netherlands.

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CHAPTER 8

Pelvic floor physical therapy in patients with chronic anal fissure: long term follow-up of a randomized controlled trial

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Abstract

Background

Chronic anal fissure is a common benign anorectal disease with a high recurrence rate. Pelvic floor physical therapy has been proven effective in the short-term management in patients with chronic anal fissure and pelvic floor dysfunction (PAF-trial).
The aim of this study was to determine the outcomes of the PAF-trial and fissure recurrence in patients who completed the 2 months of pelvic floor physical therapy at 1-year follow-up.

Methods

Electromyographic registration of the pelvic floor, digital rectal examination, visual analog scales, patient related outcome measurements and quality of life were assessed at baseline, and at 1 year after inclusion. The primary outcome was muscle tone at rest during electromyographic registration of the pelvic floor at baseline and at 1-year follow-up. Secondary outcomes contained fissure recurrence, pain ratings, pelvic floor dysfunction, complaint reduction measured with a proctology specific patient-reported outcome measurement and quality of life.

Results

The treatment protocol was followed by 133 patients. 97 patients (71%) completed the 1-year follow-up, 48 women (49.5%) and 49 men (50.5%) with a mean age of 44,4 ±11.6 years (range 19-68).
In the total group of patients, mean resting electromyographic values of the pelvic floor significantly improved from baseline to follow-up at 1 year (mean estimated difference 2.20 μV; 95% CI, 1.79 to 2.61; $p<0.001$). After 1 year, the fissure recurred in 15 patients (15.5%). VAS-pain significantly decreased from baseline to follow-up (mean estimated difference 4.16; 95% CI, 3.75 to 4.58; $p<0.001$). Dyssynergia was found in 72.9% at baseline and decreased to 14.4% at 1-year follow-up ($p<0.001$). Complaint reduction measured with the Proctoprom, significantly improved from baseline to 1-year follow-up ($p<0.001$). Quality of life (RAND-36) significantly improved in eight of nine domains at 1-year follow-up. No significant improvement was found in the domain vitality.

Conclusions

In the PAF-trial, we demonstrated that pelvic floor physical therapy yields a significant and clinical benefit in the time course and therefore should be advocated as adjuvant conservative treatment in patients with chronic anal fissure.

Introduction

Background and objectives

Chronic anal fissure (CAF) is a frequent and disabling anorectal disorder. Optimal management of CAF is quite challenging, mainly because of its recurrent nature. Initial conservative therapy includes normalization of the defecation pattern by a fiber-enriched diet to ensure the regular passage of soft stools.[1] Treatment with ointments is aimed at reducing elevated internal sphincter tone for which nitro-glycerine as well as calcium channel blockers achieve good results.[2] When conservative treatment fails local botulinum toxin injections and/or fissurectomy and lateral internal sphincterotomy are possible treatment options. Botulinum toxin is often used for CAF, but has a recurrence rate of 41.7%.[3] In the Netherlands the first step of surgical treatment is fissurectomy.[4] The long term-effect of fissurectomy has been proven successful with recurrence rates between 6 and 12%,[5,6] although the mean time for obtaining wound healing is about 10 weeks.[6] Lateral internal sphincterotomy remains the surgical treatment of choice for fissures that are refractory to medical treatment and is recommended in guidelines.[7,8] The recurrence rate of lateral internal sphincterotomy is low (6.9%),[3] however there is a potential risk of incontinence.[3,9-11]
To fill the gap in treatment modalities between conservative management and surgery we recently performed a randomized controlled trial to investigate the effect of pelvic floor physical therapy in the treatment of CAF (PAF-trial). This trial demonstrated that pelvic floor physical therapy was effective in patients with CAF and concomitant pelvic floor dysfunction. Patients had clinically relevant and significant improvements in all outcomes, clinical healing of the fissure, pain ratings, diminished pelvic floor dyssynergia and complaint reduction.[12]
The aim of this study was to determine the outcomes of the PAF-trial and fissure recurrence at 1-year follow-up.

Materials and Methods

Study design

This was a study of the long-term results of PFPT, originally evaluated in a single -centre randomized controlled trial (PAF-trial).[12] The PAF-trial included 140 patients with CAF and pelvic floor dysfunction. Patients were randomized to 2 study groups, an intervention group starting immediately after inclusion with PFPT and a control group receiving postponed PFPT after 8 weeks after inclusion. The present study was a long-term follow-up, using the same outcomes as in the RCT.[13]

Baseline and follow-up

Baseline and follow-up appointments at 1 year from baseline with the surgeon and principal investigator, an experienced pelvic floor physical therapist, consisted of a clinical examination provided through inspection to investigate the healing of the fissure. Resting anal sphincter pressure, pelvic floor muscle tone and function were measured by a careful digital rectal examination and scored as decreased, normal and increased.[14,15] Pelvic floor dysfunction was defined by the presence of increased pelvic floor muscle tone and/or dyssynergia detected by digital rectal examination.[14,16] Besides that, pelvic floor muscle tone was measured with EMG (mV)[14] with an intra-anal probe (MAPLe® Novuqare Pelvic Health B.V. CE 0344, Rosmalen, the Netherlands).

Patients were requested to fill in 3 validated self- administered questionnaires at baseline, and 1-year follow-up. To quantify the average intensity of pain during defecation, a visual analog scale (VAS) from 0 (no pain) to 10 (most intense pain) was used.[17] The Proctoprom, a patient related outcome measurement was used to assess the impact of proctologic complaints on different aspects of a patient's life and to evaluate the effect of treatment.[18] To access the impact of global quality of life, the validated Dutch version of Short-Form RAND-36, Health Status Inventory, version 2 was used. [19] The RAND-36 comprises of 36 items and entails 9 subscales: physical functioning, bodily pain, role limitation due to physical health problems, vitality, general health perception, social functioning, role limitation due to emotional problems, mental health, and health change perception.

Participants

Men and women aged 18 years or older presenting with CAF and pelvic floor dysfunction were recruited at the Proctos Clinic in the Netherlands from December 2018 until July 2021. CAF was defined as a longitudinal ulcer in the squamous epithelium with one or more signs of chronicity including hypertrophied anal papilla, sentinel tag and exposed internal sphincter muscle with symptoms presenting longer than 6 weeks or recurrent fissures.

All patients had failed conservative treatment with fiber and/or laxatives and ointment (diltiazem or isosorbide dinitrate) used for at least 6 weeks and with accurate instructions about how to apply. All patients had sufficient understanding of the Dutch language (reading and writing) and were able to complete online questionnaires. We considered patients who were not able to undergo a digital rectal examination, not

eligible for this study. Patients with an abscess or fistula, Crohn's disease or ulcerative colitis, anorectal malignancy, prior rectal radiation, and pregnancy were excluded from the study.

Interventions

At baseline, patients in both groups received information about toilet behaviour, the pelvic floor and lifestyle advice. All patients continued their conservative measures including the use of ointment (diltiazem or isosorbide dinitrate) during the treatment period.

PFPT consisted of 5 face-to-face appointments of 45-minutes in a period of 8 consecutive weeks, using a treatment protocol. Details of this treatment protocol were prescribed earlier.[13] Data collection of the questionnaires was facilitated by a secure on-line system called Castor EDC.[20] Patients received the questionnaires by e-mail through the Castor system at baseline and 1-year follow-up.

Outcome measures

Primary outcome was muscle tone at rest during EMG-registration of the pelvic floor at baseline and 1-year follow-up.

Secondary outcomes contained fissure recurrence, average pain intensity during defecation on a VAS-scale, pelvic floor (dys)function, complaint reduction measured with the Proctoprom[18] and quality of life measured with the Short-Form RAND-36.[19] All outcomes were measured at baseline and 1-year follow-up.

Statistical analysis

Data were analysed using Statistical Packages for Social Sciences (SPSS, Chicago, II, USA, version 26.0). Descriptive methods were used to assess quality of data, homogeneity of treatment groups and endpoints. Normality of the data were analysed with histograms. Data are presented using mean (SD), median (min-max) for the numeric and non-normal variables and frequency (percentages) for categorical variables. A paired *t* test and Wilcoxon signed rank was used to compare continuous variables within groups. McNemar was used to compare categorical variables within groups. Comparison between groups for continuous variables was made by repeated measure analysis of variance using a mixed model after transformation of the data to enhance normality, with treatment, time (categorical) and their interaction as fixed

effects and with random patient effects. In addition, data at each time point were compared with independent samples *t* tests, Mann-Whitney *U* test and Chi-square test depending on the variables. All *p* values were two-tailed and statistical significance was taken as a *p* value of less than 0.05. Multiple imputation for incomplete records was not needed because less than 5% of the data was missing. An interim analysis was not performed for this study.

Results

Between 10 December 2018 and 13 July 2021, 140 patients were randomized to PFPT (n=70) and a control group (postponed PFPT) (n=70). Baseline characteristics were similar between the 2 groups (Table 1).

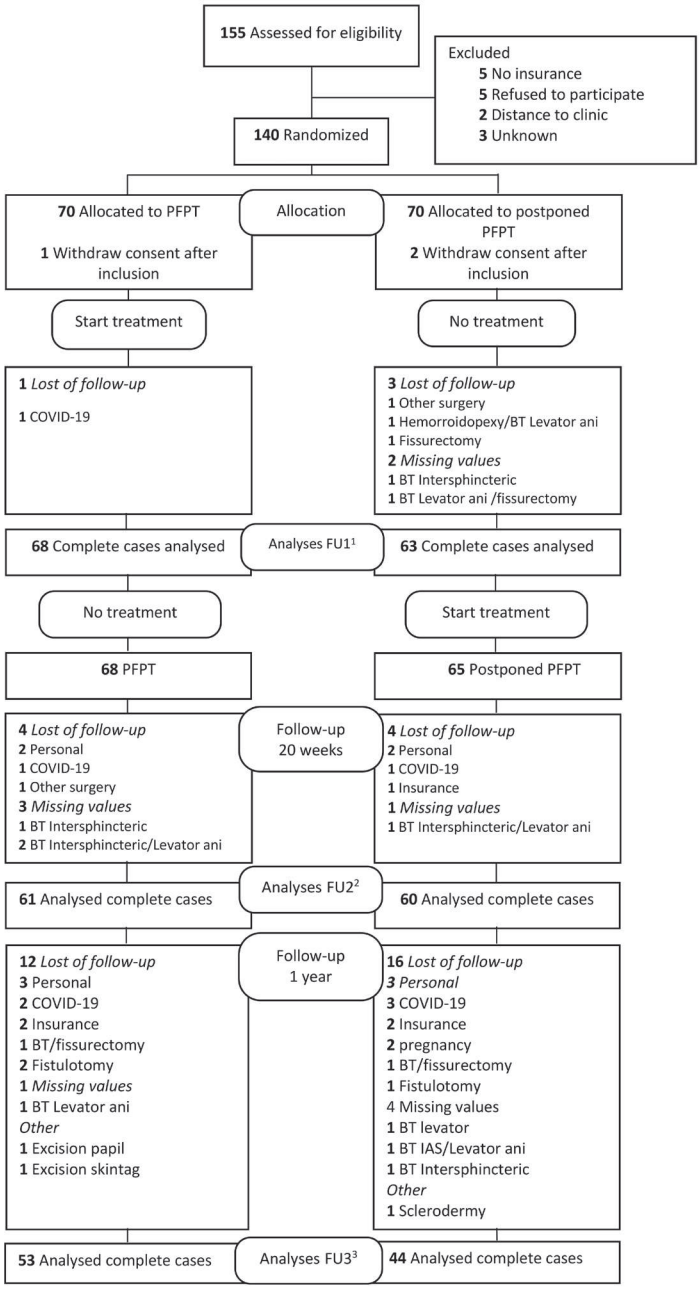
Table 1. Demographics at baseline

Variable	Total group (n=140)	PFPT group (n=70)	Postponed PFPT (n=70)
Age, years mean (SD), (range)	44.5(11.1),(19-79)	44.2(10.7),(23-66)	44.7(11.6),(19-79)
Gender, women/men, n(%)	72(51.4)/68(48.6)	37(52.9)/33(47.1)	35(50)/35(50.0)
Duration of complaints (%)			
0-2 months	12.1	12.9	11.4
2-6 months	22.9	18.6	27.1
6-12 months	14.3	12.9	15.7
12-36 months	22.1	24.3	20.0
>3 years	28.6	31.4	25.7
Lokation of fissure (%)			
Anterior	14.3	12.9	15.7
Posterior	77.9	78.6	77.1
Other	7.9	8.6	7.1

After randomisation, 1 patient in the PFPT group and 2 patients in the postponed PFPT group withdrew after inclusion. 97 patients completed the 1-year follow-up, 48 women (49.5%), 49 men (50.5%) with a mean age of 44,4 ±11,6 (range 19-68). In total, 40 patients were lost of follow-up from baseline to 1-year follow-up. Details of the loss of follow-up, missing values and other surgery are shown in Figure 1. (CONSORT diagram).

There were no reported negative side effects or serious adverse events in both groups.

Figure 1. CONSORT diagram



[1] Timepoint 8 weeks after inclusion; [2]Timepoint 20 weeks after inclusion; [3]Timepoint 1 year after inclusion
PFPT=Pelvic Floor Physical Therapy; BT=Botulinum Toxin; IAS= internal anal sphincter; RBL=Rubber Band Ligation

Primary outcome

Mean resting electromyographic values of the pelvic floor in the total group of patients significantly improved from baseline to 1-year follow-up (mean estimated difference 2.20 µV; 95% CI, 1.79 to 2.61; $p<0.001$).

In the PFPT-group the mean tone of the pelvic floor at rest measured with EMG, decreased significantly from baseline to 1-year follow-up (mean estimated difference 2.39 µV; 95% CI, 1.79 to 2.99; $p<0.001$). In the postponed PFPT-group, the mean tone of the pelvic floor at rest measured with EMG significantly decreased from baseline to follow-up at 1 year (mean estimated difference 1.97 µV; 95% CI, 1.42 to 2.52; $p<0.001$) (Table 2).

The mean estimated difference between groups at 1-year follow-up was -.427 µV; 95% CI, -1.25 to .391 ($p=.303$).

Regarding the analysis of repeated measures, pelvic floor muscle tone at 1 year from baseline, measured with EMG, was reduced in favor of the PFPT-group ($p<0.001$) (Figure 2.1; Table 2).

Figure 2.1 Repeated measures restactivity muscle tone (EMG) pelvic floor

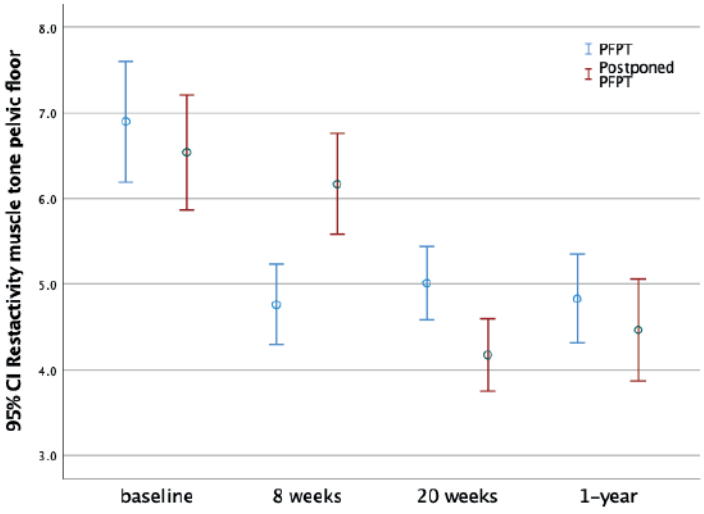


Table 2. Study measures at baseline and 1-year follow-up. Comparisons within and between treatment groups and repeated measures

	Total group			**PFPT group**			**Postponed PFPT group**			**MD between groups**	**Group vs time**
	Baseline n=140	**1- year n=97**	***p* value**	**Baseline n=70**	**1- year n=53**	***p* value**	**Baseline n=70**	**1- year n=44**	***p* value**	***p* value**	***p* value**
Rest EMG pelvic floor mean (sd) (μV),(n)	6.7(2.9)	4.7(1.9),(94)	<0.001*	6.9(2.9)	4.8(1.9),(52)	<0.001*	6.5(2.8)	4.5(1.9),(42)	<0.001*	*p*=.303[b]	<0.001[f]
VAS-pain mean (sd),(n)	5.3(1.6)	1.0(1.4),(94)	<0.001[a]	5.5(1.6)	1.1(1.2),(53)	<0.001[a]	5.2(1.6)	.93(1.6),(41)	<0.001[a]	*p*=.509[b]	<0.001[f]
Proctoprom mean (sd),(n)	5.1(2.1)	2.1(1.9),(84)	<0.001[a]	5.2(2.0)	2.1(1.9),(34)	<0.001[a]	5.0(2.2)	2.1(1.9),(30)	<0.001[a]	*p*=.662[c]	<0.001[f]
Dyssynergia DRE yes (%),(n)	72.9	14.4,(96)	<0.001[d]	67.1	9.4,(53)	<0.001[d]	78.6	20.5,(43)	<0.001[d]	*p*=.112[e]	NA
Tenderness traction puborectalis yes (%),(n)	75.0	9.3,(96)	<0.001[d]	70.0	7.5,(53)	<0.001[d]	80	11.4.(43)	<0.001[d]	*p*=.495[e]	NA

PFPT=Pelvic Floor Physical Therapy; EMG=electromyography; VAS=Visual Analog Scale; DRE= Digital Rectal Examination; NA= not applicable

*Paired t-test
aWilcoxon signed rank test
bUnpaired t-test
cMann-Whitney U test
dMcNemar
eChi-square test
fRepeated measurement analyses

Secondary outcomes

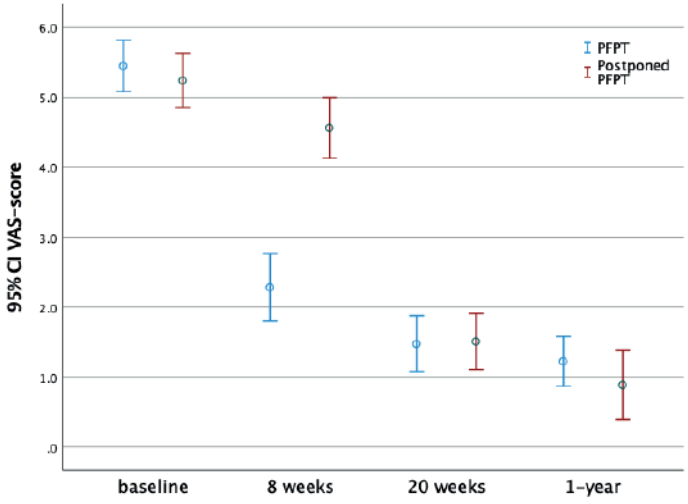
Fissure recurrence

In the total group of patients, after one year, the fissure recurred in 15 patients (15.5%), 60% women and 40% men. In the PFPT-group, in 11.3% vs 20.5% in the postponed PFPT-group. No significant difference was found between groups at 1-year follow-up.

Pain

VAS- pain was significantly reduced in the total group of patients from baseline to follow-up at 1 year (mean estimated difference 4.23; 95% CI, 3.82 to 4.66; $p<0.001$). In the PFPT group and the postponed PFPT group the pain score measured with VAS, decreased significantly from baseline to 1-year follow-up ($p<0.001$) (Table 2).
No significant differences were found between groups at 1-year follow-up (Table 2).
Regarding the analysis of repeated measures, the PFPT group was found to be more effective for reducing pain compared to the postponed PFPT group at 1 year from baseline ($p<0.001$) (Figure 2.2; Table 2).

Figure 2.2 Repeated measures pain (VAS)-score



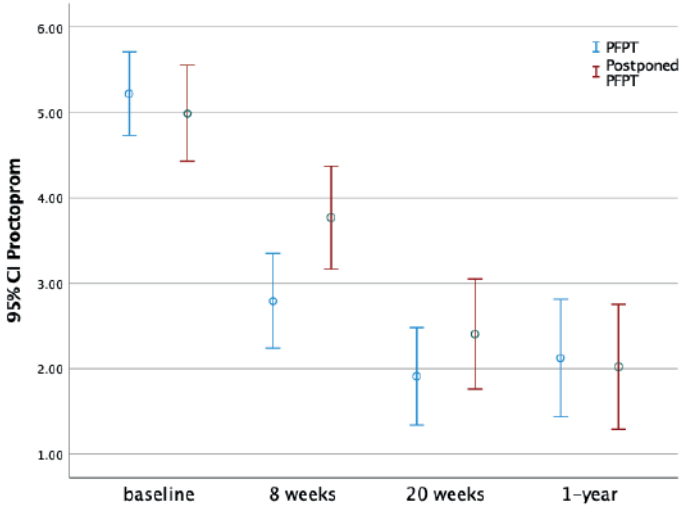
Pelvic floor function

Increased pelvic floor muscle tone measured with digital rectal examination was found in 87.1% of the total group of patients at baseline and in 19 patients (19.6%) at 1-year follow-up ($p<0.001$). 14 patients in the PFPT group vs 5 patients in the postponed

PFPT group, but there were no significant differences between groups.
Tenderness with traction on the puborectalis muscle, by digital rectal examination was found in the total group of patients in 75% at baseline vs 9.3% at 1-year follow-up (p<0.001). At 1- year follow-up tenderness with traction on the puborectalis muscle was painful in 7.5% in the PFPT group vs 11.4% in postponed PFPT group. No significant differences were found between groups at 1-year follow-up (Table 2).
Dyssynergia diagnosed by digital rectal examination was found in the total group of patients in 72.9% at baseline vs 14.4% at 1-year follow-up (p<0.001). In the PFPT-group in 9.4% vs 20.5% in the postponed PFPT-group at 1-year follow-up. No significant differences were found between groups at 1-year follow-up (Table 2).

Patient related outcome measurement
The Proctoprom scores in the total group, the PFPT-group and postponed PFPT group decreased significantly from baseline to follow-up at 1 year (p<0.001). At 1 year, no significant difference in Proctoprom scores was found between groups (Table 2).
Regarding the analysis of repeated measures, the PFPT group experienced significantly more reduction of complaints than the control group at 1 year from baseline (p<0.001) (Figure 2.3; Table 2).

Figure 2.3 Repeated measures Proctoprom



Quality of life

In the total patients' group, the mean scores significantly improved in the domains of the RAND-36 from baseline to 1-year follow-up, bodily pain, health change ($p<0.001$), physical functioning, physical role, general health, social functioning, emotional role, and mental health ($p<0.05$) (Table 3, Figure 3). No significant improvement was found in the domain vitality.

Figure 3. Quality of life, at baseline and 1-year follow-up

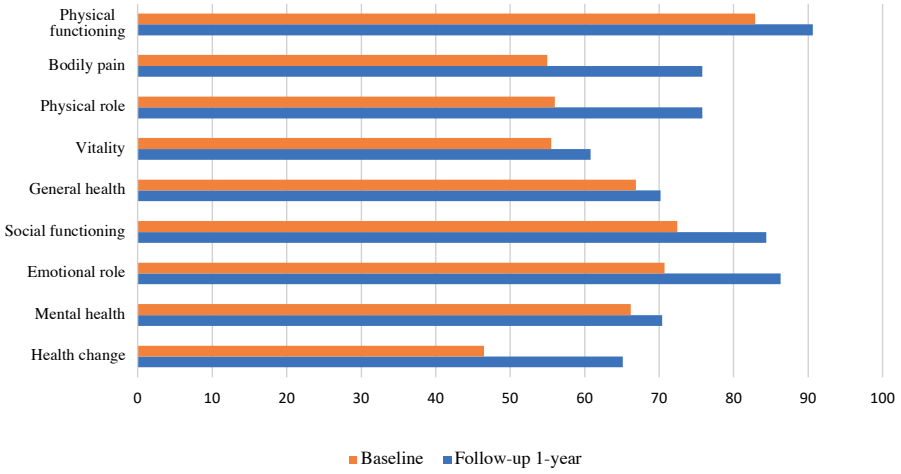


Table 3. Study measures quality of life at baseline and 1-year follow-up. Comparison within and between treatment groups

Quality of Life Scale SF-36	**Total group**			**PFPT group**			**Control Group**		
	Baseline mean(SD) n=100	**One-year mean(SD) n=61**	***p* value**	**Baseline mean(SD) n=52**	**One-year mean(SD) n=31**	***p* value**	**Baseline mean(SD) n=48**	**One-year mean(SD) n=30**	***p* value**
Physical functioning	82.9(20.9)	90.6(14.0)	*p*=.006¢	84.9(18.7)	92.1(8.3)	*p*=. 110¢	80.7(23.0)	89.0(18.1)	*p*=.031¢
Bodily pain	55.0(26.5)	75.8(22.3)	**<0.001**¢	54.8(25.2)	75.1(19.7)	*p*=.008¢	55.3(28.2)	76.5(25.0)	*p*=.003¢
Physical role	56.0(44.1)	75.8(35.6)	*p*=.047¢	57.7(43.3)	78.2(30.8)	*p*=.123¢	54.2(45.4)	73.3(40.4)	*p*=.258¢
Vitality	55.5(18.7)	60.8(16.5)	*p*=.112¢	55.5(20.4)	61.6(18.4)	*p*=.200t	55.5(16.9)	60.0(14.5)	*p*=.125t
General Health	66.9(18.8)	70.2(15.9)	*p*=.048t	71.2(17.7)	73.7(14.5)	*p*=.483¢	62.3(19.0)	66.7(16.8)	*p*=.050¢
Social Functioning	72.4(24.2)	84.4(19.5)	*p*=.005¢	70.2(23.6)	86.3(15.3)	*p*=.092¢	74.7(24.8)	82.5(23.1)	*p*=.041¢
Emotional role	70.7(41.4)	86.3(29.4)	*p*=.018¢	76.3(36.4)	84.9(32.0)	*p*=.794¢	64.6(45.8)	87.8(29.9)	*p*=.006¢
Mental Health	66.2(14.5)	70.4(14.7)	*p*=.037t	65.9(14.6)	71.7(13.1)	*p*=.302¢	66.5(14.7)	69.1(16.3)	*p*=.025¢
Health Change	46.5(24.6)	65.2(22.9)	**<0.001**t	49.5(26.4)	66.9(24.5)	*p*=.010t	43.2(22.3)	63.3(21.5)	**<0.001**t

t Paired t-test,
¢ Wilcoxon signed rank test

Discussion

Principal findings

This is the first study with a long-term follow-up demonstrating the efficacy of PFPT in patients with CAF and pelvic floor dysfunction. The results from this follow-up study show that PFPT resulted in significant and clinically relevant long-term improvement regarding mean resting tone of the pelvic floor, recurrence rate, changes in dyssynergia of the pelvic floor, pain, complaints, and quality of life. Furthermore, the improvement at the short-term follow-up at 20 weeks[12] was sustained at the long-term follow-up for all outcomes.

Pelvic floor muscle tone and function measured with EMG-biofeedback decreased from baseline to follow-up and demonstrated an effective and efficient treatment modality. Biofeedback is the mainstay in the treatment of anorectal dysfunctions[21,22] and is commonly utilized in PFPT. In this trial, we established that EMG-biofeedback in CAF with pelvic floor dysfunction yields a high percentage of clinical benefit, in the short, medium- and long-term period.

The long-term efficacy of PFPT including biofeedback on dyssynergia has already been proven in randomized control trials in patients with constipation,[23,24] although no long-term studies were performed in patients with CAF.

Pelvic floor muscle tone, based on digital rectal examination significantly decreased from baseline to follow-up after 1 year. A comprehensive careful digital rectal examination is an important topic to obtain information on anorectal anatomy and function.[15,25] Although digital rectal examination to investigate muscle tone and dyssynergia is recommended in clinical guidelines,[8,14] only 23% of the surgeons investigate the pelvic floor during digital rectal examination in patients with CAF.[4]

In our study we found that a large percentage of the patients had an increased pelvic floor muscle tone and this could be a contributing factor in the pain patients experience after defecation.[26] It is therefore important to investigate the pelvic floor muscles during digital rectal examination in patients with CAF.

In almost 75% of the patients, dyssynergia of the pelvic floor was found at baseline. Pelvic floor dyssynergia, is thought to be a learned and acquired behavioral disorder of defecation, where an inability to coordinate the abdominal, recto-anal, and pelvic floor muscles during attempted defecation exists.[27] Although patients improved in their dyssynergic pattern, it is possible that this learned behavior does tend to lose the benefit over a period of time [28] which could influence fissure recurrence. It is important to encourage patients to continue practicing their exercises and learned techniques.

A clinical follow-up could be beneficial to re-evaluate and to repeat the learned skills.[28] In our trial we scheduled at least 2 follow-up appointments after the treatment period in 1 year. This could have positively influenced the outcome of treatment. Besides that, a clinical follow-up could reinforce the adherence rate which are described in behavioural interventions such as PFPT. Important barriers to adherence are difficulties remembering to do the exercises and finding time to do them.[29]

The recurrence rate in our study was 15.5%, which is low compared to other current treatments in CAF. When clinical factors related to recurrence were analysed, gender, duration of complaints, location of the fissure and prior treatment were not significantly related to the long-term recurrence. In half of our patients the recurrence was influenced by stool changes. Special attention should be paid to avoid constipation and remain a good lifestyle to avoid recurrence. The use of extra 20-25gr/d of fiber should be recommended to ensure avoidance and constipation.[30,31]

The first results from our study[13] confirmed that both groups significantly improved at 20 weeks follow-up on all outcomes, although the PFPT-group improved faster than the postponed group.

At 1-year follow-up, no significant difference was found between groups, even though a higher recurrence rate (20.5%) was found in the postponed PFPT group. More patients from the postponed PFPT-group received botulinum toxin (3.8% vs 9.1%). Thus, we would recommend starting with PFPT as soon as possible after at least 6 weeks of using ointment (diltiazem or isosorbide di-nitrate) and good regulation of the defecation pattern.

Seven patients in our study developed a superficial fistula during the trial. Suppurative lesions are commonly found with CAF and mostly due to diseases of the anal glands, or the result of infection of the lymphoid tissues, which become chronically infected.[32] It is unknown which proportion of fistulas are due to a fissure and at what time lapse it becomes evident. In the Netherlands, only 57% of the gastrointestinal surgeons scheduled a physical follow-up after 6-8 weeks and 46% scheduled telephone call or according to the needs of the patients.[4] The development of other anorectal complaints could therefore be missed.

Conservative management of chronic anal fissure is associated with significant improvement in patients related outcome scores. In our study we used the Proctoprom to detect changes over time, the patient's state of health measures and the effect of treatment.[18] The study showed a significant effect of disease burden from the patient's point of view at long-term follow-up. In a study by Wilson et al.[33] on bowel function

reported outcome measures in 37 patients with CAF, an association was found with a statistically significant change in social impact, stool related aspects and the mean score of global functioning. The patients received counselling including fiber supplementation, toileting strategies and the use of ointment but were not treated with PFPT. These baseline strategies were also effective in the patients from the postponed PFPT who also improved on Proctoprom-scores.[12]

In the PAF-trial we found significant improvements in all nine domains of the RAND-36 at 20-week follow-up and this result sustained in eight of nine domains at 1-year follow-up, except for the domain vitality. The domain vitality measures energy/fatigue. It is possible that this domain is less influenced by this anorectal disease. On the other hand, when patients improve with 5 points on the RAND-36, this could be interpreted as clinically relevant.[34]

Strengths

This is the first study of the long-term results of using PFPT in the treatment of CAF. The main strengths of this study are, the well powered, prospective randomized control trial design, and the design of the study in which all patients received the same treatment of PFPT with a long-term follow-up.

The willingness to participate and adherence of the patients to the trial procedures and the intervention was high, which can be seen by a relatively low rate of loss of follow-up (29%) even during the COVID-19 pandemic.

Limitations

First, the pelvic floor physical therapist was also the principal investigator and consequently investigator's bias could not be ruled out. Secondly, COVID-19 did have some influence on our study. During the pandemic a small number of patients were lost to follow-up because they were diagnosed with COVID-19 at the follow-up appointment. Some of our patients were lost to follow-up because they were treated with surgery or for personal circumstances. This may have caused non-response bias.

Clinical implications

Clinical guidelines of leading societies do not recommend PFPT as a treatment option for CAF. Our findings provide strong evidence that also in the long run, PFPT is effective in the treatment of CAF and pelvic floor dysfunction.

Conclusions

Pelvic floor physical therapy provided sustained improvement in pelvic floor muscle tone, pain ratings, patients satisfaction and quality of life in patients with chronic anal fissure after 1-year follow-up.

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PART III

CHAPTER 9

Summary of results and general discussion

Chapter 1

General introduction

Anorectal disorders are common in general practice and the incidence of chronic anal fissure is 2.5 cases per 1000 persons in the Netherlands.[1]

This thesis covers the anatomical and pathophysiological aspects of CAF faced during clinical practice with the focus on treatment by pelvic floor physical therapy alongside current management.

In chapter 1 we outlined the symptoms, pathogenesis, diagnostics, and management of CAF. A chronic anal fissure (CAF) refers to a longitudinal ulcer or tear in the squamous epithelium, generally located in the posterior midline with symptoms present for longer than 4-6 weeks or recurrent fissures.[2,3] The classical symptom is pain during defecation, which may persist for hours,[4,5] and has a significant impact on quality of life.[6]

Although some debate exists on the pathogenesis of CAF, it is assumed that pain causes an increased anal sphincter tone leading to ischemia which inhibits fissure healing, generating a vicious circle of pain and constipation.[7-10]

Pelvic floor dysfunction e.g., dyssynergia and/or increased pelvic floor muscle tone may also be an underlying cause and part of the pathophysiology and a reason for unresponsiveness to treatment.

We described the importance of performing a digital rectal examination including examination of the pelvic floor muscles and a comprehensive evaluation of the pelvis and surrounding structures to determine the underlying cause of pain and pelvic floor dysfunction.[11,12]

Recent technological advances (electromyography and anorectal manometry) were described in this thesis. Electromyography can be used to assess motor control patterns, coordination, and pelvic floor muscle function.[13] Manometry can be used as a component of clinical evaluation for patients in whom additional management strategies are considered.[14]

According to current guidelines, the initial conservative management is comprised of fibre intake and/or use of laxatives, toilet behaviour, lifestyle advice, sitz baths, and ointments.

Pelvic floor physical therapy (PFPT) is an important part of a multidisciplinary treatment approach and could be added to conservative management.

When conservative treatment fails, botulinum toxin can be applied.[15,16] which is a safe alternative to surgery.[17] Various surgical procedures are possible such as fissurectomy and lateral internal sphincterotomy. Although lateral internal sphincterotomy is the

preferred surgical treatment in guidelines,[15,16] there is a potential risk of incontinence.[18-21] Therefore the need for conservative management cannot be overemphasized.

Chapter 2

Management of chronic anal fissure, results of a national survey among gastrointestinal surgeons in the Netherlands

The knowledge among clinicians across medical community concerning the pelvic floor and pelvic floor disorders and regarding when and how to refer to pelvic floor physical therapy (PFPT) varies.[22] Our aim was to evaluate current practice in the management of CAF amongst gastrointestinal surgeons in the Netherlands. A 21-item questionnaire was sent by email to Dutch gastrointestinal surgeons and residents between June 2021 and September 2021.

The questionnaire consisted of questions concerning work experience, physical examination, diagnostic- and surgical techniques and follow-up. Overall, 106 (33%) surgeons completed the survey and 59% had at least 10 years of experience in treating CAF. Only 23% always addressed pelvic floor complaints. Fifty-one percent performed digital rectal examination and 22% always, or almost always, examined the pelvic floor muscles. Most respondents started treatment with fibers and/or laxatives and ointment (96%) and diltiazem was in 90% the preferred ointment. Twenty-two percent referred patients for PFPT. Botulinum toxin was in 54% performed under general- or spinal anesthesia or sedation. The first surgical procedure of choice was fissurectomy (71%) followed by lateral internal sphincterotomy (27%). Fissurectomy was in 51% always combined with botulinum toxin. Fifty-seven percent of the respondents preferred a physical follow-up appointment.

Guideline recommendations are largely followed in the Netherlands, starting with conservative measures followed by surgical procedures. Surgeons do not consistently assess pelvic floor complaints, nor do they routinely examen the pelvic floor muscles. Awareness of pelvic floor dysfunctions is important to refer patients for pelvic floor physical therapy.

Chapter 3

*Pelvic floor physical therapy for pelvic floor hypertonicity**1**: a systematic review of treatment efficacy*

Increased pelvic floor muscle tone (non-neurogenic hypertonicity) is a disabling condition with urological, gynaecological, and gastrointestinal symptoms, sexual

problems, and chronic pelvic pain. Increased tone of the pelvic floor may be a cardinal factor contributing to delayed healing and pain in patients with CAF.[23,24] To gain more knowledge on the effect of treatment on increased pelvic floor muscle tone, we systematically reviewed the treatment efficacy of PFPT. The outcome measures were pelvic floor muscle tone and function, pain reports, sexual function, pelvic floor symptom scores, quality of life and patient's perceived effect.

The literature search resulted in 10 eligible studies published between 2000 and 2019. Most studies had a high risk of bias associated with the lack of a comparison group, insufficient sample sizes and non-standardized interventions. Six studies were of low and 4 of medium quality. All studies were narratively reviewed. Three of 4 RCTs found positive effects of PFPT compared to controls on 5 out of 6 outcome measures. The prospective studies found significant improvements in all outcome measures that were assessed. PFPT seems to be efficacious in patients with chronic prostatitis, chronic pelvic pain syndrome, vulvodynia, and dyspareunia. Smallest effects were found in patients with interstitial cystitis and painful bladder syndrome. No studies were found in patients with a chronic anal fissure and the use of PFPT. The findings of this systematic review suggest that PFPT can be beneficial in patients with increased pelvic floor muscle tone.

[1]An update on the terminology by the International Continence Society was conducted and published in 2021 after this systematic review. 'Hypertonicity' is changed into 'increased pelvic floor muscle tone' and is further used in this thesis.

Chapter 4

To what extent are anorectal function tests comparable? A prospective study comparing digital rectal examination, anal electromyography, 3-dimensional high resolution anal manometry and transperineal ultrasound

Anorectal function tests are helpful objectivizing anorectal (dys)functions, but there is no recommendation when to perform which test. The aim of our prospective study was to examine the correlation of anal pressures and diagnosing pelvic floor dyssynergia between digital rectal examination (DRE) and several anorectal function tests.

Between January 2020 and April 2022, all men and women aged 18 till 80 years, treated in the Proctos Clinic, who were referred to PFPT by the surgeon and underwent anorectal function tests in their diagnostic work-up, were included. Digital rectal examination was performed to establish the anal pressure in rest, and during squeeze and straining. Anorectal function tests included 3D-High resolution anal

manometry (3D-HRAM), balloon expulsion test, transperineal ultrasound and surface electromyography (s-EMG).

A total of 50 patients, 37 (74%) females, were included with a median age of 51 years. Twenty-three (62%) females had two or more vaginal deliveries in the past. Most frequent indication for referral for PFPT was fecal incontinence in 54% of the patients. The assessed pressures and pelvic floor function measured with digital rectal examination by the surgeon and the pelvic floor physical therapist during rest, squeeze and straining correlated in 78%, 78% and 84%, respectively. Correlation between digital rectal examination and 3D-HRAM or s-EMG, was better for squeeze pressures than resting pressures. The correlation between surface electromyography and 3D-HRAM was better during squeeze- than in rest with an agreement of 59% and 37% respectively. Digital rectal examination by an experienced investigator is of sufficient value for daily clinical practice to detect dyssynergia and measuring sphincter tone. Commonly performed anorectal function tests do not correlate with digital rectal examination, nor with other anorectal function tests. Although anorectal function tests can allay anxiety, these tests are invasive to the patient and expensive for health insurances.[25] They can however give some clarity in specific complex combined incontinence and obstructive defecation complaints. Perhaps we should reserve anorectal function tests for these kinds of patients and to those who are refractory to conservative treatments, where more invasive procedures, surgery, botulinum toxin e.g., are considered. Furthermore, these tests are valuable when evaluating new (surgical) therapies.

Chapter 5

Pelvic floor physical therapy in the treatment of chronic anal fissure (PAF-study): study protocol for a randomized controlled trial

Prolonged persistence of symptoms and recurrence in patients with CAF indicate that present treatment modalities are not always sufficient. Currently, there is a gap in treatment modalities between conservative management and surgery. We aim to provide a management protocol for PFPT to bridge this gap. The protocol prescribes the rationale, design, and methodology of a randomized controlled trial investigating PFPT as a treatment option for patients with CAF. The Pelvic Floor Anal Fissure study (PAF-study) is a single-centre, two armed, randomized controlled trial. The PAF-study aims to determine the efficacy and effectiveness of PFPT on improvement

on pelvic floor muscle tone and function, pain, healing of the fissure, quality of life and complaint reduction in patients with CAF. Patients with CAF and pelvic floor dysfunction will be recruited by surgeons of the Proctos Clinic. Exclusion criteria included abscess, fistula, Crohn's disease, ulcerative colitis, anorectal malignancy, prior rectal radiation, and pregnancy. A total of 140 patients are randomized for either PFPT or postponed treatment of PFPT. The primary outcome is tone at rest during electromyographic registration of the pelvic floor before and after therapy. Secondary outcomes consist of healing of the fissure, pain ratings, improvement of pelvic floor function, complaint reduction and quality of life. Primary and secondary endpoints are measured at 8 -and 20 week and at 1-year follow-up.

Chapter 6

Pelvic floor physical therapy in patients with chronic anal fissure: a randomized controlled trial

This chapter outlines the results of the PAF-study at 8- and 20-week follow-up.

Between December 2018 and July 2021, at the Proctos Clinic in the Netherlands, patients with chronic anal fissure and pelvic floor dysfunction were randomly assigned to an intervention group, receiving 8 weeks of PFPT including electromyographic biofeedback or assigned to a control group receiving postponed PFPT.

Endpoints were measured at 8- and 20-week follow-up. 140 patients were included in the study, 68 men (48.6%) and 72 women (51.4%) with a mean age of 44,5 ±11.1 (range 19-79) years. Mean resting electromyographic values of the pelvic floor in the intervention group significantly improved from pre-to post-treatment (p<0.001) and relative to controls (mean estimated difference between groups -1.88 μV; 95% CI, -2.49 to -1.27 (p<0.001) at first follow-up and remained significant from baseline at 20-week follow-up (p<0.001).

The intervention group performed better compared to the control group on all secondary outcomes i.e., healing of the fissure (55.7% of the patients vs 21.4% in control, pain ratings (p<0.001), diminished dyssynergia (p<0.001), complaint reduction (p<0.001) and decrease of pelvic floor muscle tone (p<0.05) at first follow-up.

The findings of this study provide strong evidence that PFPT is effective in patients with CAF and pelvic floor dysfunction and supports its recommendation as adjuvant treatment besides regular conservative treatment.

Chapter 7

Pelvic floor physical therapy in the treatment of chronic anal fissure (PAF-trial): outcome of Quality of Life

CAF is associated with reduced quality of life.[6] This chapter outlines the results of the effects of PFPT on quality of life in patients with CAF who were included in the PAF-trial using the Short-Form 36 Health Survey (RAND-36). Quality of life and pain ratings were outcomes of the study and were measured at 8- and 20-week follow-up.
Between December 2018 and July 2021, 100 patients, (50 women and 50 men, with a median age of 44.6 years [range19-68]), completed the RAND-36 questionnaire and visual analog (VAS) pain score at admission. A significant improvement was found at 20-week follow-up in all domains of the RAND-36; physical functioning, pain, health change (p<0.001); physical role, vitality, general health, social functioning, emotional role, mental health (p<0.05). VAS pain was significantly reduced at 8 weeks (mean estimated difference 1.98; 95% CI. 1.55 to 2.42, p<0.001) and remained significant at 20-week follow-up (p<0.001). The difference between the groups as regards change in the mean pain intensity scores at 8 weeks was 2.48 (95% CI. -3.20 to -1.75; p<0.001). Compared to the reference values of the general Dutch population, the patients in our study with a CAF and pelvic floor dysfunction reported an impaired quality of life in 8 of 9 domains of the RAND-36. After treatment significant lower scores were found in 2 out of 9 domains.
The results of this study provide evidence that treatment by PFPT improves quality of life and reduces pain, making it an important tool in management of CAF and concomitant pelvic floor dysfunction.

Chapter 8

Pelvic floor physical therapy in patients with chronic anal fissure: long term follow-up of a randomized controlled trial

The optimal management of CAF is quite challenging, mainly because of its recurrent nature. Our aim was to determine the outcomes of the PAF-trial and fissure recurrence in patients who completed the 2 months of PFPT at 1-year follow-up.
The treatment protocol was followed by 133 patients. 97 patients (71%) completed the 1-year follow-up, 48 women (49.5%) and 49 men (50.5%) with a mean age of 44,4 ±11.6 years (range 19-68). In the total group of patients, mean resting electromyographic values of the pelvic floor significantly improved from baseline to follow-up at 1 year (mean estimated difference 2.20 μV; 95% CI, 1.79 to 2.61; p<0.001).

After 1 year, the fissure recurred in 15 patients (15.5%). VAS-pain significantly decreased from baseline to follow-up (mean estimated difference 4.16; 95% CI, 3.75 to 4.58; $p<0.001$). Dyssynergia was found in 72.9% at baseline and decreased to 14.4% at 1-year follow-up ($p<0.001$). Complaint reduction measured with the Proctoprom, significantly improved from baseline to 1-year follow-up ($p<0.001$). Quality of life (RAND-36) significantly improved in eight of nine domains at 1-year follow-up. No significant improvement was found in the domain vitality.
In the PAF-trial, we demonstrated that PFPT yields a significant and clinical benefit in the time course and should be advocated as adjuvant conservative treatment in patients with chronic anal fissure.

Discussion and recommendations

Conservative treatment is the first step in patients with CAF. It includes dietary adaptations, the use of (extra) fibers and/or laxatives, toilet behaviour, lifestyle advice, ointment and PFPT.
A selective approach is recommended based on the patient's medical history and physical examination. We strive for a greater understanding and recognition of CAF leading to, at an early stage, a better outcome for the patient.
Digital rectal examination including investigating of the pelvic floor muscles should be performed in routine clinical practice in the chronic phase, to distinguish between different causes of anorectal pain[26] aiming to adequately refer patients for PFPT.
To make the correct diagnosis and to reduce various treatment options, a local and/or regional partnership between a general practitioner (and collective) and a pelvic floor physical therapist is a desirable future perspective. The pelvic floor physical therapist as a practice assistant could be a possibility. But we also see a further development of 1.5-line care with the pelvic floor physical therapist in a one-off consultation in the role of consultant specialist as a renewed option to optimize the care for this anorectal disorder.
In this thesis we have proven the effect of PFPT in patients with CAF and concomitant pelvic floor dysfunction. Pelvic floor physical therapists are trained to diagnose and treat a wide range of diagnoses related to pelvic floor dysfunctions. The personal contact and skills of the therapist are pivotal for the effect of conservative management in this debilitating disease. In addition, to optimize the outcome, it is essential to actively listen to the patient to identify patients concerns, to provide education about CAF and the use of ointment (when, how and why), to set realistic goals,[27]

manage comorbid conditions that may interfere with therapy compliance and manage expectations.[25] The success rate of PFPT depends on a careful diagnosis and patient selection,[28] evaluation concerning patients' motivation and commitment to treatment. The use of behaviour training with biofeedback was effective and durable in our study, but it should be mentioned that it is a labour-intensive treatment, treatment protocols vary among centers, and it is not universally available.

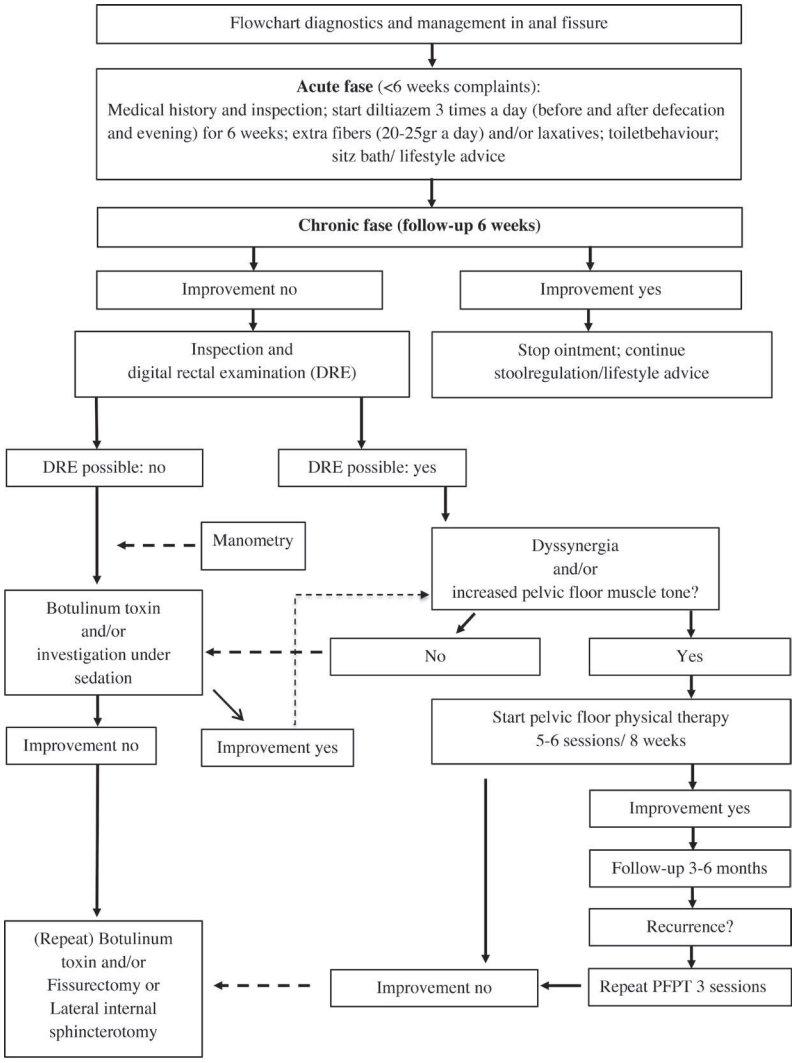
Brown et al.[29] found that adherence and completion of the treatment are critical for maintaining effectiveness. Monitoring sessions could be performed after the PFPT sessions to verify correct performance of exercises. Studies on effective implementation are the next step.

There is evidence of a strong and consistent relationship of sexual and/or physical abuse history in gastro intestinal disorders.[30-33] Besides that, increased pelvic floor muscle tone is associated with sexual abuse.[34,35] A history of sexual and/or physical abuse may play a role in the divergence between the symptoms patients report and objective measurements and may alter treatment recommendations.[36] Besides that, there is a high comorbidity of psychological disorders e.g. anxiety and depression in patients with CAF which could have a negative influence on quality of life and sexual function.[6,37-39] More attention should be paid for addressing the issue of sexual health and other associated psychological factors in clinical practice and implementing questions concerning these topics and pelvic floor dysfunction in history taken. Further studies are needed to establish the effect of the underlying psychological mechanisms and the use of additional behavioral interventions including psychoeducation besides PFPT to identify targeted efficacious interventions in patients with CAF.

Although we did not perform an evaluation of the actual costs of each treatment including PFPT, we should take this into account. Treatment of CAF is a balance between efficacy, adverse events, risk of recurrence and costs. Improving daily functioning and reducing recurrence rates has cost implications and it is likely that the integrated nature of our conservative treatment is more cost-effective because of the diminishing need for surgery. A cost consideration study would be sensible calculating costs in time, effort, and finance for undergoing PFPT.

The findings of our study highlight the feasibility and effectiveness of a multidisciplinary treatment and points out the importance of integrating across health care professionals to improve the treatment in patients with CAF. The treatment of CAF should be sequential and tailored to the patients' needs and a holistic and multimodal approach is a requisite.

Referral to a gastrointestinal surgeon is essential when a digital rectal examination is not possible to perform, and when patients fail to respond to conservative measures including PFPT. A tailored approach is reflected in the proposed algorithm.
Although more high-quality studies are warranted to determine the effect of PFPT in patients with CAF and implementing these in guidelines, we are convinced that PFPT fills the gap between conservative treatment and surgery.



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CHAPTER 10

Dutch summary

Nederlandse samenvatting

Een chronische anale fissuur (CAF) is een veel voorkomende pijnlijke anorectale aandoening met een incidentie van 0.25% (2.5 per 1000 patiënten per jaar) in Nederland. Dit proefschrift behandelt de anatomische en pathofysiologische aspecten van een CAF, de relatie met de bekkenbodem, de diagnostiek en de huidige (conservatieve) behandeling. In dit proefschrift bespreken we de rol van bekkenfysiotherapie en tonen we het effect aan van bekkenfysiotherapeutische interventie op korte en lange termijn en op kwaliteit van leven bij patiënten met een CAF.

Hoofdstuk 1

Algemene introductie

Een CAF wordt gedefinieerd als een kloofje of scheurtje in het anoderm, meestal posterieur gelegen, met meerdere kenmerken van chroniciteit zoals opgeworpen wondranden, het à vue zijn van sfinctervezels, een 'sentinal pile' en een inflammatoire poliep waarbij de symptomen langer dan 4-6 weken bestaan. Het klassieke symptoom is pijn tijdens de ontlasting, die daarna uren kan aanhouden en dit heeft een aanzienlijke invloed op kwaliteit van leven.

De exacte pathogenese van een CAF is nog niet volledig opgehelderd, maar er wordt aangenomen dat pijn een verhoogde sfinctertonus veroorzaakt, wat leidt tot ischemie met als gevolg een verminderde genezingstendens van de fissuur. Hierdoor kan er een vicieuze cirkel van pijn en obstipatie ontstaan.

Een groot percentage van de patiënten met een CAF laat ook bekkenbodemdysfuncties zien. De bekkenbodem is een complexe structuur bestaande uit bindweefsel, ligamenten, fasciae en spieren. In rust hebben de bekkenbodemspieren een basisspanning waardoor er steun gegeven wordt aan de bekkenorganen. Voor mictie, defecatie, gemeenschap en de baring moet de bekkenbodem ontspannen. Een verhoogde tonus van de bekkenbodem en/of dyssynergie (het onvermogen om de bekkenbodem te relaxeren en/of een gebrek aan coördinatie van de abdominale, rectale en bekkenbodemmusculatuur tijdens defecatie) kan deel uitmaken van de pathofysiologie en een onderliggende oorzaak zijn voor het suboptimaal reageren op de ingestelde behandeling.

De diagnose van een CAF wordt gesteld door anamnese en lichamelijk onderzoek. We beschrijven het belang van het uitvoeren van een zorgvuldig digitaal rectaal onderzoek, inclusief onderzoek van de bekkenbodem. Daarnaast is het van belang om het bekken en de omliggende structuren te onderzoeken om een eventuele onderliggende oorzaak van pijn en bekkenbodemdysfunctie te bepalen.

In dit proefschrift worden recente technologische ontwikkelingen (elektromyografie en anorectale manometrie) beschreven. Elektromyografie kan worden gebruikt om de elektrische activiteit van de bekkenbodemmusculatuur in kaart te brengen en inzicht te krijgen in tonus en functie van de bekkenbodem. Anale manometrie meet en objectiveert de anale druk in rust, tijdens aanspannen en persen en kan worden gebruikt als onderdeel van klinische evaluatie voor patiënten bij wie aanvullende behandelstrategieën worden overwogen. Endo-anale echografie kan worden verricht bij verdenking op andere onderliggende pathologie.
De conservatieve behandeling van een CAF, volgens de huidige richtlijnen, bestaat uit het reguleren van de ontlasting door de inname van (extra) vezels en/of het gebruik van laxeermiddelen, leefstijladviezen, verbeteren van toiletgedrag, eventueel het gebruik van warmte ter relaxatie en het gebruik van medicatie in de vorm van zalf (diltiazem of isosorbine dinitraat). Medicatie wordt gebruikt ten behoeve van relaxatie van de sfincter, het verbeteren van de doorbloeding en voor pijnbestrijding. Het op de juiste wijze (inwendig) aanbrengen van de zalf is hierbij van cruciaal belang.
Bekkenfysiotherapie als behandeloptie zou kunnen worden toegevoegd aan de conservatieve behandeling maar is nog niet opgenomen in de huidige richtlijnen.
Wanneer de conservatieve behandeling faalt, kan een injectie met botulinetoxine worden gegeven welke een veilig alternatief is voor een chirurgische interventie.
Verschillende chirurgische ingrepen zijn mogelijk, zoals fissurectomie en laterale interne sfincterotomie. Hoewel laterale interne sfincterotomie in de huidige richtlijnen de aanbevolen chirurgische behandeling van een CAF is, met een hoge succeskans, bestaat er een potentieel risico op incontinentie.
We kunnen de noodzaak van het inzetten van de optimale conservatieve behandeling dan ook niet genoeg benadrukken.

Hoofdstuk 2

Behandeling van een chronische anale fissuur: een survey onder gastro-intestinaal chirurgen in Nederland

De behandeling van een CAF laat ondanks de richtlijnen verschillen zien onder zorgverleners. Daarbij varieert binnen de huidige zorgverleners de kennis over de bekkenbodem en bekkenbodemdysfuncties en wanneer te verwijzen naar een bekkenfysiotherapeut. Ons doel was de huidige werkwijze onder gastro-intestinale chirurgen en arts-assistenten met betrekking tot de behandeling van een CAF in Nederland in kaart te brengen.

Een vragenlijst met 21 items werd tussen juni 2021 en september 2021 verzonden per e-mail naar 329 respondenten (gastro-intestinale chirurgen en arts-assistenten) in Nederland. De vragenlijst bestond uit vragen over werkervaring, het lichamelijk onderzoek, de diagnostische en chirurgische technieken en de follow-up bij de diagnostiek en behandeling van een CAF. In totaal vulden 106 (33%) respondenten de enquête in, waarvan meer dan de helft (59%) ten minste 10 jaar ervaring had in de behandeling van een CAF. Een kwart van de respondenten (23%) vroeg naar bekkenbodemklachten. Digitaal rectaal onderzoek werd uitgevoerd door 51% van de respondenten, waarbij 22% van de respondenten de bekkenbodem altijd of bijna altijd onderzocht. De meeste respondenten startten de behandeling met vezels en/of laxeermiddelen en zalf. Diltiazem werd aangegeven als de zalf van voorkeur. 22% van de respondenten verwees patiënten met een CAF naar een bekkenfysiotherapeut. Wanneer er werd behandeld met botulinetoxine werd dit in meer dan de helft van de gevallen (54%) toegediend onder algehele of spinale anesthesie of sedatie. De eerste chirurgische behandeling van voorkeur was voor 71% van de respondenten een fissurectomie. Dit werd gevolgd door een laterale interne sfincterotomie (27%). Fissurectomie werd gecombineerd met botulinetoxine door de helft (51%) van de respondenten. In 57% werd de voorkeur gegeven aan een fysieke vervolgafspraak en 22% van de respondenten gaf de voorkeur aan een telefonische vervolgafspraak.
Concluderend kan gesteld worden dat de aanbevelingen vanuit de huidige Nederlandse richtlijn grotendeels worden gevolgd. Er wordt gestart met conservatieve maatregelen, gevolgd door chirurgische interventies. Echter, chirurgen vragen bekkenbodemklachten niet consequent uit, onderzoeken niet routinematig de bekkenbodem en verwijzen in een klein percentage naar een bekkenfysiotherapeut voor deze aandoening.

Hoofdstuk 3

*Bekkenfysiotherapie voor verhoogde tonus**1** (hypertonie) van de bekkenbodem, een systematisch onderzoek naar de effectiviteit van bekkenfysiotherapeutische behandeling*

Een verhoogde tonus van de bekkenbodem kan een belangrijke factor zijn die bijdraagt aan een vertraagde genezing en pijn bij patiënten met een CAF. Om de bijdrage van bekkenfysiotherapie aan de optimale behandelstrategie voor patiënten met een CAF te onderzoeken, hebben we de effectiviteit van bekkenfysiotherapie bij een verhoogde tonus van de bekkenbodem systematisch beoordeeld. Als uitkomstmaten waren gekozen bekkenbodemspiertonus en -functie, pijnrapportages, seksuele functie, kwaliteit van leven, en het klinisch waargenomen effect.

De literatuursearch resulteerde in 10 studies gepubliceerd tussen 2000 en 2019. De meeste studies hadden een hoog risico op bias in verband met het ontbreken van een vergelijkingsgroep, onvoldoende steekproefgrootte en niet-gestandaardiseerde interventies. Zes studies waren van lage, en 4 van gemiddelde kwaliteit. Alle studies werden narratief beoordeeld. In 3 van de 4 gerandomiseerde studies (RCT's) werden positieve effecten gevonden van bekkenfysiotherapie in vergelijking met een controlegroep op 5 van de 6 uitkomstmaten. In de prospectieve studies werden significante verbeteringen gevonden op alle uitkomstmaten. Bekkenfysiotherapie laat positieve resultaten zien bij patiënten met chronische prostatitis, chronisch bekkenpijnsyndroom, vulvodynie en dyspareunie. De geringste effecten werden gezien bij patiënten met interstitiële cystitis en blaaspijnsyndroom.
Er werden geen studies gevonden waarbij patiënten met de diagnose CAF waren geïncludeerd.
De bevindingen van deze systematische review tonen aan dat bekkenfysiotherapie effectief kan zijn bij patiënten met een verhoogde tonus van de bekkenbodem.

[1]*De terminologie is in 2021 aangepast door de International Continence Society (ICS). 'Hypertoniciteit' is veranderd in 'verhoogde tonus'.*

Hoofdstuk 4

In hoeverre zijn anorectale functietesten vergelijkbaar? Een prospectieve studie waarbij digitaal rectaal onderzoek, anale electromyografie, drie-dimensionale anale hoge resolutie manometrie en transperianale echografie worden vergeleken

Anorectale functietests zijn nuttig bij het objectiveren van anorectale (dys)functies, maar er zijn geen duidelijke aanbevelingen wanneer welke test uitgevoerd zou moeten worden en wat de onderlinge verbanden in uitkomst zijn.
Het doel van onze studie was het onderzoeken van de correlatie tussen digitaal rectaal onderzoek en verschillende anorectale functietesten met betrekking tot de anale druk en het diagnosticeren van bekkenbodemdysfunctie (dyssynergie).
Tussen januari 2020 en april 2022 werden in de Proctoskliniek mannen en vrouwen van 18 tot 80 jaar, die door de chirurg waren verwezen naar de bekkenfysiotherapeut en anorectale functietests ondergingen, geïncludeerd. Digitaal rectaal onderzoek werd uitgevoerd om de anale druk in rust en tijdens aanspannen en persen vast te stellen. De anorectale functietesten omvatten 3-Dimensional High Resolution Manometry (3D-HRAM), ballon expulsietest, transperineale echografie en oppervlakte-elektromyografie (s-EMG).

In totaal werden 50 patiënten geïncludeerd, waarvan 37 (74%) vrouwen, met een gemiddelde leeftijd van 51 jaar. Drieëntwintig (62%) vrouwen hadden in het verleden twee of meer vaginale bevallingen gehad. De meest voorkomende indicatie voor verwijzing naar de bekkenfysiotherapeut in deze populatie was fecale incontinentie (54%). De beoordeelde druk en de bekkenbodemfunctie, gemeten met digitaal rectaal onderzoek door de chirurg en de bekkenfysiotherapeut, tijdens rust, aanspannen en persen correleerden respectievelijk in 78%, 78% en 84% van de gevallen. De correlatie tussen digitaal rectaal onderzoek en 3D-HRAM of s-EMG was beter voor aanspannen dan in rust. De correlatie tussen s-EMG en 3D-HRAM was beter tijdens aanspannen dan in rust met een overeenkomst van respectievelijk 59% en 37%. Geconcludeerd werd dat digitaal rectaal onderzoek door een ervaren zorgverlener van voldoende waarde is voor de dagelijkse klinische praktijk om dyssynergie te diagnosticeren en de sfincterdruk te meten. Gangbare anorectale functietesten correleren matig met digitaal rectaal onderzoek. Deze testen kunnen echter wel enige duidelijkheid geven bij complexe patiënten met gecombineerde problematiek zoals incontinentie- en obstructieve defecatieklachten, patiënten die refractair zijn voor conservatieve behandelingen en bij patiënten waarbij meer invasieve procedures zoals botulinetoxine en/of chirurgie worden overwogen. Bovendien zijn deze testen waardevol bij de evaluatie van nieuwe (chirurgische) behandelingen.

Hoofdstuk 5

Bekkenfysiotherapie bij de behandeling van een chronische anale fissuur (PAF-studie); studieprotocol voor een gerandomiseerde studie

Bekkenfysiotherapie is een behandeloptie voor een verhoogde tonus van de bekkenbodem en/of dyssynergie die vaak gepaard gaat met een CAF.

De Pelvic Floor Anal Fissure (PAF)-studie heeft tot doel de effectiviteit van bekken-fysiotherapie aan te tonen op verbetering van de tonus en functie van de bekkenbodem, vermindering van pijn, genezing van de fissuur, verbetering op kwaliteit van leven en klachtvermindering bij patiënten met een CAF. Dit hoofdstuk beschrijft de grondgedachte, het ontwerp, de methodologie en het behandelprotocol van de PAF-studie.

De PAF-studie is een mono-center, tweearmige, gerandomiseerde gecontroleerde trial. Patiënten met een CAF en bekkenbodemdysfunctie komen in aanmerking voor deze studie. Uitgesloten van de studie zijn patiënten met een abces, fistel, ziekte van Crohn, colitis ulcerosa, anorectale maligniteit, eerdere rectale bestraling, en zwangerschap. In totaal worden

er 140 patiënten gerandomiseerd. De patiënten worden verdeeld in een groep die meteen start met bekkenfysiotherapie na inclusie en een groep die een uitgestelde behandeling met bekkenfysiotherapie krijgt. Bekkenfysiotherapie inclusief biofeedback bestaat uit een gestandaardiseerd protocol bestaande uit 5 consulten in een periode van 8 weken.
De primaire uitkomstmaat is tonus in rust tijdens elektromyografische registratie van de bekkenbodem voor- en na de gestandaardiseerde therapie. Secundaire uitkomstmaten bestaan uit genezing van de fissuur, verbetering van pijnscores, verbetering van de bekkenbodemfunctie, klachtenvermindering en verbetering op kwaliteit van leven. Primaire- en secundaire uitkomstmaten worden gemeten na 8- en 20 weken en na 1 jaar follow-up.

Hoofdstuk 6

Bekkenfysiotherapie bij de behandeling van een chronische anale fissuur; een gerandomiseerde trial

In dit hoofdstuk worden de resultaten beschreven van de PAF-studie bij 8- en bij 20 weken follow-up.
Tussen december 2018 en juli 2021 werden in de Proctos Kliniek patiënten met een CAF en bekkenbodemdysfunctie geïncludeerd in de PAF-studie. De onderzoekspopulatie bestond uit 140 patiënten, 68 mannen (48.6%) en 72 vrouwen (51.4%) met een gemiddelde leeftijd van 44.5 jaar (range 19-79). De primaire uitkomstmaat, de gemiddelde electromyografische waarden in rust van de bekkenbodem, in de interventiegroep verbeterden significant na de behandeling ten opzichte van baseline (p<0.001) en ten opzichte van de controlegroep (-1.88 µV; 95% CI, -2.49 tot -1.27; p<0.001) bij de eerste follow-up na 8 weken en bleven significant bij 20 weken follow-up (p<0.001). De interventiegroep liet in vergelijking met de controlegroep betere resultaten zien op alle secundaire uitkomstmaten, namelijk de genezing van de fissuur (55.7% van de patiënten versus 21.4% in de controlegroep), pijn (p<0.001), vermindering van dyssynergie (p<0.001) en afname van klachten (p<0.001) bij de eerste follow-up. De bevindingen van deze studie leveren overtuigend bewijs dat bekkenfysiotherapie effectief is bij patiënten met een CAF en bekkenbodemdysfunctie en ondersteunen de aanbeveling van bekkenfysiotherapie als adjuvante behandeling naast de reguliere conservatieve behandeling.

Hoofdstuk 7

Bekkenfysiotherapie bij de behandeling van een chronische anale fissuur (PAF-trial): invloed op kwaliteit van leven

Een CAF is geassocieerd met een verminderde kwaliteit van leven. Dit hoofdstuk beschrijft de resultaten van het effect van bekkenfysiotherapie op de kwaliteit van leven bij patiënten met een CAF die werden geïncludeerd in de PAF-trial met behulp van de Short-Form 36 Health Survey (RAND-36). Kwaliteit van leven en pijnscores (VAS) waren uitkomsten van het onderzoek en werden gemeten bij 8- en 20 weken follow-up. In totaal vulden 100 patiënten, 50 vrouwen en 50 mannen, met een gemiddelde leeftijd van 44.6 jaar (range 19-68), de RAND-36-vragenlijst en VAS-pijnscore in bij inclusie. De RAND-36 bevat 36 gesloten vragen onderverdeeld in negen schalen. De vragen worden per subschaal opgeteld en omgerekend met een algoritme. Een hogere score komt overeen met een betere gezondheidstoestand. In alle domeinen van de RAND-36 werd er een significante verbetering gezien bij 20 weken follow-up; fysiek functioneren, pijn, gezondheidsverandering (p<0.001); rolbeperkingen fysiek probleem, vitaliteit, sociaal functioneren, rolbeperkingen emotioneel probleem, mentale gezondheid en algemene gezondheidsbeleving (p<0.05). VAS-pijn verminderde significant na 8 weken follow-up (1.98; 95% CI. 1.55 tot 2.42, p<0.001) en bleef significant na 20 weken follow-up (p<0.001). Het verschil tussen de groepen voor verandering in de gemiddelde pijn scores op 8 weken was 2.48 (95% CI. -3.20 tot -1.75; p<0.001).

Vergeleken met de referentiewaarden van de Nederlandse bevolking, rapporteerden de patiënten uit onze studie een verminderde kwaliteit van leven in 8 van de 9 domeinen van de RAND-36. Na behandeling werden er significant lagere scores gevonden in 2 van de 9 domeinen.

De resultaten van deze studie leveren het bewijs dat behandeling met bekkenfysiotherapie de kwaliteit van leven verbetert en de pijn doet verminderen bij patiënten met een CAF en bekkenbodemdysfunctie.

Hoofdstuk 8

Bekkenfysiotherapie bij patiënten met chronische anale fissuur: lange termijn follow-up van een gerandomiseerde gecontroleerde studie

De optimale behandeling van een CAF is een uitdaging, met name vanwege de hoge kans op een recidief. In dit hoofdstuk worden de resultaten besproken na 1 jaar follow-up van de patiënten uit de PAF-studie die het traject van 2 maanden bekkenfysiotherapie hadden voltooid en in hoeverre er een recidief was opgetreden in deze groep.

Het behandelprotocol werd gevolgd door 133 patiënten. 97 patiënten (71%) voltooiden de 1 jaar follow-up, 48 vrouwen (49.5%) en 49 mannen (50.5%) met een gemiddelde leeftijd van 44.4 jaar (range 19-68). De gemiddelde electromyografische waarden van de bekkenbodem in rust verbeterden significant van baseline tot 1 jaar follow-up (2.20 μV; 95% CI, 1.79 tot 2.61; $p<0.001$). Bij 15 patiënten (15.5%) was er sprake van een recidief van de fissuur. VAS-pijn nam significant af van baseline tot follow-up (gemiddeld verschil 4.16; 95% CI, 3.75 tot 4.58; $p<0.001$). Dyssynergie werd gevonden bij 72.9% van de patiënten bij inclusie en nam af tot 14.4% na 1 jaar follow-up ($p<0.001$). Klachtenvermindering, gemeten met de Proctoprom, verbeterde significant van baseline tot 1 jaar follow-up ($p<0.001$). De kwaliteit van leven (RAND-36) verbeterde significant in 8 van de 9 domeinen bij 1-jaar follow-up. Er werd geen significante verbetering gevonden in het domein vitaliteit.
In de PAF-trial hebben wij aangetoond dat bekkenfysiotherapie een significant en klinisch positief effect heeft op de langere termijn.

Discussie en toekomstperspectieven

In dit proefschrift hebben we getracht een overzicht te geven van de huidige inzichten, de diagnostiek en (conservatieve) behandeling van een CAF met als doel een stap voorwaarts te zetten in de behandeling.
Samenvattend bestaat de eerste stap uit conservatieve behandeling door middel van het reguleren van de ontlasting, toilet- en leefstijladviezen, het op de juiste wijze inzetten van de lokale behandeling met zalf (diltiazem of isosorbinedinitraat) en bekkenfysiotherapie.
Wij streven naar een betere herkenning van een CAF om daarmee in een vroeg stadium een adequate behandeling te starten die kan leiden tot een sneller en beter resultaat voor de patiënt.
Digitaal rectaal onderzoek, inclusief onderzoek van de bekkenbodem, zou routinematig in de klinische praktijk toegepast moeten worden in de chronische fase om onderscheid te kunnen maken tussen de verschillende oorzaken van anorectale pijn. Hierdoor kunnen patiënten gerichter worden behandeld en worden doorverwezen naar een bekken-fysiotherapeut.
Om de juiste diagnose te stellen en om verschillende behandelopties te evalueren, is een lokaal en/of regionaal samenwerkingsverband tussen een huisarts (en collectief) en een bekkenfysiotherapeut een gewenst toekomstperspectief. De bekkenfysiotherapeut als praktijkondersteuner is dan een mogelijkheid. Maar ook een verdere ontwikkeling

van de 1,5 lijnszorg met de bekkenfysiotherapeut in een éénmalig consult in de rol van consulent-specialist zien wij als een reële optie om de zorg rondom deze anorectale aandoening te optimaliseren.

In dit proefschrift hebben wij het effect van bekkenfysiotherapie aangetoond bij patiënten met een CAF en bekkenbodemdysfunctie. Bekkenfysiotherapeuten zijn opgeleid om een breed scala aan diagnoses met betrekking tot bekkenbodemdysfuncties te diagnosticeren en te behandelen. Het persoonlijke contact en de vaardigheden van de bekkenfysiotherapeut zijn cruciaal voor het effect van conservatieve behandeling bij de invaliderende klachten van een CAF. Verder onderzoek naar implementatie binnen de 1,5 lijnszorg en binnen de huidige richtlijnen is noodzakelijk.

Voor een optimaal behandeleffect is het van belang actief naar de patiënt te luisteren om diens zorgen te identificeren, voorlichting te geven over een CAF, realistische doelen te stellen, en verwachtingen te managen. Het succes van bekkenfysiotherapie hangt af van een zorgvuldige diagnose, patiënten selectie en evaluatie van de motivatie en inzet van de patiënt voor de behandeling.

Het gebruik van biofeedback was effectief in onze studie, maar vermeld moet worden dat het een intensieve en invasieve behandeling is, dat de behandelprotocollen per centrum verschillen en biofeedback niet overal beschikbaar is. Therapietrouw en voltooiing van de behandeling zijn cruciaal voor het behoud van de effectiviteit. Na de bekkenfysiotherapie sessies zou een follow-up afspraak kunnen worden gemaakt om na te gaan of de oefeningen nog correct worden uitgevoerd en de adviezen worden gevolgd. Lange termijn studies zijn de volgende stap om het nut en de waarde van deze follow-up aan te tonen.

Het is van belang te beseffen dat er een samenhang bestaat tussen een voorgeschiedenis van seksueel en/of fysiek misbruik en gastro-enterologische klachten. Een verhoogde tonus van de bekkenbodem kan ook geassocieerd zijn met seksueel misbruik. Een voorgeschiedenis van seksueel en/of fysiek misbruik kan een rol spelen bij de divergentie tussen de symptomen die de patiënt rapporteert en de objectieve bevindingen, en daarmee de aanbevelingen voor de behandeling beïnvloeden. Bovendien bestaat er een hoge comorbiditeit van psychologische stoornissen zoals angst en depressie bij patiënten met een CAF, die eveneens een negatieve invloed zouden kunnen hebben op de kwaliteit van leven en de seksuele functie. Er moet meer aandacht worden besteed aan seksuele gezondheid en andere geassocieerde psychologische factoren in de klinische praktijk door het implementeren van vragen over deze onderwerpen en bekkenbodemdysfuncties in de anamnese.

Verdere studies zijn nodig om het effect van de onderliggende psychologische mechanismen vast te stellen en het gebruik van aanvullende gedragsinterventies, waaronder psycho-educatie naast bekkenfysiotherapie te onderzoeken om zo nog doeltreffender te behandelen.

Hoewel wij geen evaluatie hebben uitgevoerd met betrekking tot de werkelijke kosten van elke behandeling, met inbegrip van bekkenfysiotherapie, moet hiermee wel rekening worden gehouden. De behandeling van een CAF is een evenwicht tussen effectiviteit, bijwerkingen, risico op recidief en kosten. Verbetering van het dagelijks functioneren en afname van het aantal recidieven heeft gevolgen voor de kosten en het is waarschijnlijk dat onze conservatieve behandeling kosteneffectiever is vanwege de afgenomen behoefte aan chirurgie. Een kosteneffectiviteitsanalyse is aangewezen, en zou naast de directe kosten voor bekkenfysiotherapie, ook de uitgespaarde kosten voor een operatief traject, een beter resultaat van een operatie in combinatie met bekkenfysiotherapie en een schatting van maatschappelijke kosten bij ziekteverzuim na operatieve ingreep moeten omvatten.

De bevindingen van onze studie benadrukken de haalbaarheid en doeltreffendheid van een multidisciplinaire behandeling en wijzen op het belang van de integratie van alle betrokken zorgverleners om de behandeling van patiënten met een CAF te verbeteren. De behandeling van een CAF moet afgestemd zijn op de gepresenteerde pathologie en de behoeften van de patiënt. Een holistische en multimodale aanpak is hierbij een vereiste. Verwijzing naar een gastro-intestinaal chirurg is essentieel wanneer een digitaal rectaal onderzoek niet mogelijk is, en/of wanneer patiënten niet reageren op conservatieve maatregelen, waaronder bekkenfysiotherapie. Deze aanpak wordt voorgesteld in het behandelingsalgoritme.

Hoewel meer studies nodig zijn om het effect van bekkenfysiotherapie bij patiënten met een CAF te bevestigen, zijn wij ervan overtuigd dat bekkenfysiotherapie de kloof kan dichten tussen de conservatieve behandeling en chirurgie en geïmplementeerd zou moeten worden in de huidige richtlijnen.

PART IV

APPENDICES

List of abbreviations

PAF	Pelvic floor anal fissure
CAF	Chronic anal fissure
IAS	Internal anal sphincter
EAS	External anal sphincter
s-EMG	Surface electromyography
DRE	Digital rectal examination
MAPLe	Multiple array probe
HRM	Anorectal high-resolution manometry
3D-HRAM	Three-dimensional high-definition manometry
IAPWG	International anorectal physiology working group
PTNS	Percutaneous tibial nerve stimulation
PFPT	Pelvic floor physical therapy
BT	Botulinum toxin
LIS	Lateral internal sphincterotomy
CHERRIES	Checklist for Reporting Results of Internet E-Surveys
ASCR	American Society of Colon and Rectal Surgeons
PFH	Pelvic floor hypertonicity
RCT	Randomized controlled trial
IUGA	International Urogynaecological Association
ICS	International Continence Society
MTrP	Myofascial trigger point
VAS	Visual analog scale
PRISMA	Preferred reporting Items for Systematic Reviews and Meta-Analyses
PVD	Provoked vestibulodynia
IC/PBS	Interstitial cystitis/painful bladder syndrome
CP/CPPS	Chronic prostatitis/chronic pelvic pain syndrome
PERFECT	P= power, E = endurance, R = repetitions, F = fast contractions, ECT= every contraction timed
NIH-CPSI	National Institutes of Health-Chronic Prostatitis Symptom Index
PPSS	Pelvic Pain Symptom Scale
FSFI	Female Sexual Function Index
SHIM	Sexual Health Inventory for Men
ICSI/ICPI	O'Leary-Sant IC Symptom/Problem Index
QoL	Quality of life

SF-12	12-item Short Form survey
RAND-36	Short-Form 36 Health Survey
GRA	Global Response Assessment
BET	Balloon expulsion test
TPUS	Transperineal ultrasound
MRP	Mean resting pressure
MSP	Mean squeeze pressure
PI	Principal investigator
AE	Adverse event
SUSAR	Suspected unexpected serious adverse reactions
MERC	Medical Ethics Review Committee
ANCOVA	Analysis of covariance
ANOVA	Repeated measure analysis of variance

List of publications

1. *Pelvic Floor Physical Therapy for Pelvic Floor Hypertonicity: A Systematic Review of Treatment Efficacy*
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Voor mijn lieve kinderen,
Josephine, door jouw sterren is de wereld nog mooier,
Emma, jouw inspirerende brein zal veel zielen helen,
Pepijn, jouw krachten zullen de aarde veroveren,
Olivier, jouw lieve lach maakt iedereen blij,
Sebastiaan, je bent een engel die verbindt.

Curriculum Vitae

Daniëlle Adriëtte van Reijn was born on the 25th of June 1968 in Zwolle, the Netherlands.

After graduating high school at Carolus Clusius College in Zwolle, she studied physiotherapy in Utrecht. She graduated in 1991 and obtained a bachelor's degree in Human Movement Sciences at the University of Amsterdam in the year after. In 1994 she graduated with a master's degree in Pedagogical sciences (Sport, exercise and health) at the University of Social Sciences in Utrecht.

She worked as a physiotherapist in the Isala Klinieken in Zwolle from 1994 until 2008 and during this period she became interested in urology and gynaecology and worked in a multidisciplinary team for pelvic floor disorders.

She started a master in Pelvic Floor Physical Therapy in 2003 at the Erasmus University in Rotterdam and was rewarded with the "Eefje" from the Dutch Association for Pelvic Physical Therapy (NVFB) in 2006 when completing this study.

Since 2008, Danielle is running her private practice in pelvic floor physical therapy in Baarn. She also works in a multidisciplinary team, specialized in coloproctology at the Proctos Kliniek in Bilthoven and as an education teacher at SOMT University of Physiotherapy in Amersfoort.

Danielle gained a broad experience in all kinds of pelvic floor disorders and is specialized in gastroenterology and coloproctology. She became a member in committees for guidelines and is a representative for the NVFB in the scientific committee.

Because of her interest in scientific research, she started her external PhD at Leiden University, department of Urology in cooperation with the Proctos Kliniek in 2018.

Her affiliation with anorectal complaints is now integrated with this research and the results of the studies were presented at national and international congresses.

Danielle's dedication to pelvic floor disorders will hopefully continue in future research with other pelvic floor physical therapists and healthcare practioners in this field.

Achtergrondinformatie cover

Het kunstwerk afgebeeld op de cover is van de bekende Nederlandse kunstenares Corry Ammerlaan-van Niekerk. Dit beeld is in 2006 voor het eerst uitgegeven door de NVFB en wordt ‘het Eefje’genoemd, verwijzend naar Eef Versprille-Visscher, grondlegger van de bekkenfysiotherapie in Nederland.
Het beeld heeft als titel ‘Op de voorste golf’ met als betekenis; een ieder levert zijn eigen specifieke bijdrage aan het geheel met vooruitgang als resultaat.
Het beeld is een nominatie voor net afgestudeerde bekkenfysiotherapeuten en staat voor innovatie, wetenschappelijke onderbouwing en inzet voor de bekkenfysiotherapie.
Daniëlle heeft als eerste het beeldje in 2006 mogen ontvangen.