THE ROLE OF PATIENT ADVICE, RESISTANCE TRAINING, AND CORTICOSTEROID INJECTION IN THE MANAGEMENT OF PLANTAR FASCIOPATHY

PHD THESIS

by

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Henrik Riel completed his B.Sc. in physiotherapy at University College of Northern Denmark in 2011 and obtained a M.Sc. in Clinical Science and Technology at Aalborg University in 2016. After completion of the M.Sc. programme, he received a PhD stipend at the Center for General Practice at Aalborg University and was enrolled in May 2017 under supervision by Prof. Michael Skovdal Rathleff and co-supervision by Prof. Martin Bach Jensen, Prof. Jens Lykkegaard Olesen, and Prof. Bill Vicenzino. Henrik's research has concerned musculoskeletal disorders and treatment through strengthening exercises with a special focus on plantar fasciopathy in the PhD.

ENGLISH SUMMARY

Plantar fasciopathy is a common musculoskeletal condition with a yearly prevalence of 2.4 to 6.5 per 1000 registered patients in general practice and affects approximately 8 to 31% of runners. The aetiology of the condition is unknown, but factors such as a high body mass index or tissue overload due to extended periods of weightbearing have been proposed. Patients experience pain under the plantar heel that is usually worst on the first step when getting out of bed in the morning or after periods of prolonged sitting. Despite many different treatments have been explored and used over the course of time, none appear to be consistently favourable for individuals suffering from plantar fasciopathy. A new approach that showed preliminary superiority to stretching was heavy-slow resistance training. Heavy-slow resistance training has been frequently used to manage tendinopathies but before this PhD, resistance training had only been used in a single study of individuals with plantar fasciopathy. Due to its novelty, further exploration and development of its use in the management of plantar fasciopathy was required before implementation into practice. Hereof, if a combination of heavy-slow resistance training and an ultrasound-guided corticosteroid injection renowned for its short-term pain reduction could lead to improved recovery among patients.

The PhD consisted of four studies. The first study, which was a randomised crossover study with 20 participants, aimed at investigating the acute analgesic effect of isometric resistance exercise, isotonic resistance exercise, and walking. The results showed that contrary to the hypothesis, isometric exercise was not associated with a larger acute pain reduction compared to either isotonic exercise or walking. Furthermore, only 3/20 participants experienced clinically relevant pain reductions during the resistance exercises and only 2/20 did so during walking. In the second study, the superiority of using a self-dosed exercise programme compared to a predetermined programme was investigated among 70 participants randomised to either of the approaches. The self-dosed programme was not superior to the predetermined programme and despite participants of both groups improved over the 12 weeks the intervention lasted, only 4 participants across the groups achieved improvement to a point where they did not feel further treatment was needed. The third study was a feasibility study of 20 participants who received an ultrasound-guided corticosteroid injection and were asked to start performing heavy-slow resistance training as soon as possible 24 hours after the injection. Feasibility was based on a set of pre-registered criteria concerning participant acceptability and exercise compliance. Participants found the combined treatments acceptable, however, loss of training diaries made firm conclusions regarding exercise compliance difficult. Based on the training diaries that were retrieved, exercise compliance was adequate, but special attention would need to be made in the future trial. This trial was the fourth and final study of the PhD. It was a three-armed randomised superiority trial with 180 participants comparing patient advice and a heel

cup (PA) versus fundamental patient advice and a heel cup plus heavy-slow resistance training (PAX) versus a combination of fundamental patient advice and a heel cup plus heavy-slow resistance training and an ultrasound-guided corticosteroid injection (PAXI). After the 12-week follow-up, PAXI was significantly superior to PA, but no other between-group differences of the primary outcome were found. Despite the statistical superiority, the difference between PAXI and PA did not reach the minimal important difference and the clinical significance of this difference is questionable.

The results of this PhD indicate that heavy-slow resistance training should not be recommended for an acute pain reduction and a self-dosed programme is associated with similar improvement as a predetermined programme. In spite of similar improvement, few individuals with plantar fasciopathy will achieve an acceptable symptom state within 12 weeks, and heavy-slow resistance training with patient advice and a silicone heel cup is not superior to patient advice and a heel cup alone. Only combined with an ultrasound-guided corticosteroid injection, heavy-slow resistance training shows superiority, yet this superiority is only statistically significant, and it cannot be inferred that it is a meaningful difference to patients. These findings are in line with other recent research within individuals with plantar fasciopathy that indicates no treatment is superior and should be tailored to the individual. Whether stratified care based on prognostic factors to aid clinicians when deciding on treatment together with patients may lead to improved management could be an area worth of further exploration.

DANSK RESUME

Plantar fasciopati er en hyppig muskelskeletlidelse med en årlig prævalens på 2.4 til 6.5 per 1000 registrerede patienter i almen praksis og rammer ca. 8 til 31% af løbere. Ætiologien er fortsat ukendt, men faktorer såsom et højt BMI og overbelastning af fascia plantaris grundet lange perioder med vægtbæring er blevet foreslået som årsager til lidelsen. Patienter oplever smerte under den plantare hæl, der oftest er værst i forbindelse med de første skridt om morgenen, efter de er stået op, eller når de rejser sig igen efter at have siddet ned i længere tid. Til trods for at mange forskellige behandlingsmuligheder har været undersøgt og anvendt gennem tiderne, så er der ingen behandling, der konsekvent har vist sig at være favorabel. En ny behandlingstilgang, der foreløbigt havde vist sig at være bedre end udstrækning, var tung og langsom styrketræning. Denne træningsform er hyppigt blevet anvendt som behandling af tendinopatier, men før denne ph.d. var den kun blevet anvendt i et enkelt studie af personer med plantar fasciopati. Da dette var en ny tilgang til behandlingen af denne patientgruppe, var der behov for yderligere studier af dens effekt og muligheder, inden man kunne anbefale bred implementering i praksis. Herunder om kombinationen af tung og langsom styrketræning o gen ultralydsvejledt injektion med binyrebarkhormon, som er kendt for at have en god kortsigtet smertereducerende effekt, kunne føre til bedre behandling af patienter.

Denne ph.d. bestod af fire studier. Det første studie, hvilket var et randomiseret crossover studie med 20 deltagere, havde til formål at undersøge den akutte smertereducerede effekt af isometrisk styrketræning, isotonisk styrketræning og gang. Resultaterne viste i modsætning til hypotesen, at isometrisk styrketræning ikke var associeret til en større akut smertereduktion end isotonisk styrketræning eller gang. Kun 3/20 deltagere oplevede en klinisk relevant smertereduktion som følge af styrketræningen og kun 2/20 deltagere oplevede en klinisk relevant smertereduktion efter gang. I det andet studie blev det undersøgt, om en selvdoseret træningsprotokol var bedre end en fastsat træningsprotokol blandt 70 deltagere, der blev randomiserede til én af disse træningstilgange. Den selvdoserede træningsprotokol var ikke bedre end den fastsatte træningsprotokol og til trods for at deltagerne i begge grupper oplevede forbedring over de 12 uger, som studiet varede, så oplevede kun 4 deltagere på tværs af grupperne, at de nåede til et punkt, hvor de ikke længere følte et behov for yderligere behandling af lidelsen. Det tredje studie var et feasibility-studie med 20 deltagere, der modtog en ultralydsvejledt injektion med binyrebarkhormon og blev herefter opfordret til at starte med at udføre tung og langsom styrketræning snarest muligt 24 timer efter injektionen. Feasibility blev vurderet på baggrund af en række forudregistrerede kriterier, der omhandlede deltagernes acceptabilitet af kombinationen af behandlingerne og træningscompliance. Deltagerne vurderede kombinationen af behandlingerne acceptable, men på baggrund af at flere træningsdagbøger ikke blev afleveret, blev det udfordrende at drage endelige konklusioner vedrørende træningscompliance. Baseret på de træningsdagbøger der

dog blev indleveret, var træningscompliance tilstrækkelig, men der skulle rettes et særligt fokus på compliance i det følgende studie. Dette studie var således det fjerde og sidste studie i ph.d.'en. Det var et trearmet randomiseret studie med 180 deltagere, der havde til formål at sammenligne patient information og en silikone hælkop (PA) med patient information og en silikone hælkop og tung og langsom styrketræning (PAX) med patient information og en silikone hælkop og tung og langsom styrketræning og en ultralydsvejledt injektion med binyrebarkhormon (PAXI). Efter 12-ugersopfølgningen var PAXI signifikant bedre end PA, men der var ikke andre signifikante forskelle mellem grupperne på baggrund af det primære effektmål. Skønt forskellen mellem PAXI og PA var statistisk signifikant, var den mindre end den mindste relevante forskel og den kliniske relevans er derfor tvivlsom.

Resultaterne af denne ph.d. antyder, at tung og langsom styrketræning ikke kan anbefales som et middel til akut smertereduktion og en selvdoseret træningsprotokol medførte sammenlignelig forbedring af symptomerne som en fastsat træningsprotokol. Til trods for at deltagerne i begge grupper oplevede færre symptomer, så er det forventeligt at kun få patienter med plantar fasciopati vil opnå et punkt hvor de ikke længere føler behov for behandling inden for 12 uger, og tilføjelsen af tung og langsom styrketræning til blot patientinformation og et silikoneindlæg medfører ikke større forbedring. Kun når styrketræningen bliver kombineret med en ultralydsvejledt injektion med binyrebarkhormon, ser man, at den er bedre end patientinformation og en hælkop, men denne overlegenhed er kun statistisk signifikant og det kan ikke udledes, at denne forskel vil være klinisk relevant forskel for patienter. Disse fund er i tråd med anden nylig forskning inden for patienter med plantar fasciopati, der indikerer, at der ikke findes en behandling, der er andre overlegen, og behandlingen af patienter bør skræddersys til den enkelte. Om stratificeret behandling på baggrund af prognostiske faktorer vil kunne hjælpe klinikere med at planlægge behandling med patienten og i sidste ende medføre bedre behandling af lidelsen, kan være et fokuspunkt i fremtidig forskning.

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CHAPTER 1. INTRODUCTION

1.1. MUSCULOSKELETAL DISORDERS

According to the Global Burden of Disease study, musculoskeletal disorders are the second most common reason for years lived with disability. Hereof, low back pain is the most prevalent condition followed by neck pain and osteoarthritis.[1] Musculoskeletal disorders are the leading cause of lost work productivity across the EU and through both direct and indirect costs the total cost has been estimated to be 2% of the gross domestic product.[2] Despite their high prevalence and societal costs, they are often devalued by national healthcare systems and policymakers compared to cancer or cardiovascular diseases because of their low death rate and chronic nature.[3,4] Musculoskeletal disorders are known for affecting the health-related quality of life of patients negatively in both short and long term which emphasises the impact they may have on patients' lives.[5,6] Taking the consequences on both a societal and personal level into account and the fact that the prevalence of musculoskeletal disorders has increased by 7% in Europe from 2000 to 2015, there is an increasing need for better treatment of individuals with musculoskeletal disorders.[3]

General practitioners are important in the management of musculoskeletal disorders as up to one third of consultations regard individuals with musculoskeletal conditions.[7] Tendinopathies, defined as consistent pain and loss of function in a tendon, account for a large proportion of these consultations.[8] The prevalence of lower-extremity tendinopathies in a general practice population has been investigated in both the Netherlands and in Denmark with an annual prevalence of 11.8/1000 patients versus 16.6/1000 patients, respectively.[9,10] The incidence rate in Denmark was 7.9/1000 patients, which is comparable to that of osteoarthritis in the UK.[10,11] The most common lower-extremity tendinopathy in the Danish general practice was plantar fasciopathy with a prevalence of 6.5/1000 patients.

1.2. PLANTAR FASCIOPATHY

In the US, the direct costs of treatment were estimated to be between $192 and $376 million in 2007.[12] These estimates do not take indirect costs such as work absenteeism and loss of productivity into account which means that the true cost of plantar fasciopathy is much greater. In a study from the US, 6 of 105 individuals with plantar fasciopathy had taken up to 3 months off work due to the condition and two more recent studies from Denmark found that 20 to 23% patients had been absent from work for up to 1.5 years.[13–15] Consequently, plantar fasciopathy is associated with substantial societal costs.

Compared to sex and age-matched controls, individuals with plantar fasciopathy exhibit higher levels of depression, anxiety, and stress, and the psychosocial variables are associated with the severity of the condition.[16–19] Moreover, they may experience kinesiophobia and be less physically active compared to controls which puts them at a higher risk of developing cardiovascular disease.[18,20,21] This emphasises the grave consequences that plantar fasciopathy may lead to on a personal level.

Individuals with plantar fasciopathy often refer to the pain as a feeling of walking on pins and needles or pieces of shattered glass. The pain pattern is characterised by first-step pain, i.e. pain is worse during the first steps when getting out of bed in the morning or after prolonged periods of non-weightbearing, however, pain improves with ambulation.[22] Traditionally, the pain has been thought to be localised at the plantar fascia insertion on the calcaneus but recently a study investigated the magnitude of the painful area using digital pain drawings and found a pain that spread beyond the plantar heel.[23,24]

The pathology of plantar fasciopathy has been discussed over the years which may be reason why the terminology has changed as well. Plantar fasciopathy was previously referred to as 'heel spur syndrome' or 'plantar fasciitis', yet, more recently it has been suggested to use 'plantar heel pain' as the preferred term when diagnosis is based on patient history and clinical examination, and 'plantar fasciopathy' when diagnosed using diagnostic imaging that shows an increased plantar fascia thickness.[25] Inflammation was historically thought to be the origin of the pain but in 2003, Lemont et al. found no evidence of inflammation in painful plantar fasciae that had been surgically removed. What they did see evidence for, however, was fragmentation and degeneration of the plantar fascia.[26] This shift from referring to tendinopathies as inflammatory conditions to degenerative conditions might be questionable as recent data suggest the presence of inflammation in chronic tendinopathies.[27,28] Whether this is also true for plantar fasciopathy is currently unknown.

The plantar fascia may not be the sole contributor to pain under the plantar heel. Imaging findings include heel spurs, bone marrow oedema, and perifascial oedema which indicate an involvement of other structures.[29–31] Yet, individuals with plantar fasciopathy are 105 times more likely to have a plantar fascia thickness equal to or above 4 mm compared to matched controls. Moreover, only two in three individuals with plantar fasciopathy have a heel spur and heel spurs are common findings in non-painful heel as well.[29] So despite other structures may be involved, an increased plantar fascia thickness is the commonest finding and the fascia may well be the structure treatment should be targeted at. Because a plantar fascia thickness of at least 4 mm was used as an inclusion criterion in the studies of this PhD, the condition was referred to as plantar fasciopathy. To improve readability, the condition is also referred to as plantar fasciopathy when referring to other studies despite they may have used other terminology and diagnostic criteria. The aetiology of plantar fasciopathy is unknown, but several risk factors have been suggested.[32] These include

being overweight, prolonged weightbearing, reduced dorsiflexion of the ankle and first metatarsophalangeal joint, and among runners; varus knee alignment, cavus arch posture, and a greater weekly running volume.[33,34] The pitfall when interpreting data on potential risk factors is that they are based on either case-control or cross-sectional studies and have only been performed prospectively among runners.[34] Therefore, it is not possible to conclude if the factors were present before the individual had pain or something that has come after.

The condition was considered to be partially self-limiting for years and 80% of patients are expected to be pain free within 12 months.[32,35] However, a study conducted a long-term follow-up of patients who had received treatment at a specialised orthopaedic clinic. They found that approximately half of the patients still had symptoms up to 15 years after having attended the clinic.[36] This was, of course, a sub-group of the general patient population as these patients had been referred to a specialised clinic, but even the more common individuals may experience plantar fasciopathy for a long time. In a randomised trial that compared different techniques of stretching, a follow-up 2 years after treatment start was conducted. At that point, 40% still had symptoms.[37] There are a few factors that may be associated with prognosis. If patients are female, have had symptoms >7 months, are below 40 years of age, and have bilateral pain, they will have a poorer prognosis.[36,38]

The care pathway is designed in such a way that the general practitioner is usually the first point of contact for individuals with plantar fasciopathy. The general practitioner acts as a gatekeeper and controls referrals to either hospital care, medical specialist clinics or to a physiotherapy clinic but the aim is to be able to treat patients at the lowest effective care level and not to refer.[39] Therefore, it is important to have effective treatment options that fit into general practice. Not all patients will seek help from their general practitioner. This means that some patients either self-treat the condition, seek care from other healthcare practitioners directly or do not receive treatment at all. There are a number of different treatment options for plantar fasciopathy and some are viable options in the primary healthcare sector whereas others are only possible in secondary or tertiary sectors. Foot orthoses are a common choice of treatment, however, the evidence of their effectiveness is conflicting.[40–43] Over-the-counter insoles may be an inexpensive option for some individuals with plantar fasciopathy and could be part of their self-treatment. Recommendation of insoles could also fit into a general practice consultation as well as simple stretching or resistance training exercises. Fascia-specific stretching was found to be superior to Achilles tendon stretching but this very stretching protocol was compared to heavy-slow resistance training in a randomised trial where heavy-slow resistance training was found to be superior after 3 months of performing exercises.[37,44] A systematic review and network meta-analysis investigated the effectiveness of different commonly used treatments for plantar fasciopathy and concluded that no treatment is superior but corticosteroid injection and shockwave is most likely to be effective. This review did not include heavy-slow resistance training.[45] Despite several treatments

are superior to placebo or sham, a vast proportion of patients do not recover and weak or limited evidence for treatments is a general theme in the plantar fasciopathy literature.[32,37,45] Corticosteroid injection is another option that fits into general practice as opposed to shockwave due to the lack of equipment available. The evidence of the effect of corticosteroid injection to treat tendinopathies in general is conflicting and has previously been associated with a high risk of a plantar fascia rupture when used to treat plantar fasciopathy.[46,47] Nevertheless, a Cochrane review and two large placebo-controlled trials concluded that it was a safe and effective short-term treatment that, unfortunately, is no better than placebo on longer terms.[48–50] It may be difficult to generalise the findings from one tendinopathy to them all as it appears that corticosteroid injection is much more effective in plantar fasciopathy than in other tendinopathies.[51,52] In severe cases where pain does not resolve, surgery may be an option but this is based on weak evidence.[32] Molund et al. compared proximal medial gastrocnemius recession and stretching with stretching only and concluded that surgery was superior.[53] Endoscopic fasciotomy was also recently found to be superior to a combination of different exercises and corticosteroid injection after one year but failed to show superiority after two years.[54] To this date, no randomised placebo-controlled trials have been performed to establish the effect of surgery.

In summary, despite evidence for the effects of a variety of different treatments, a large proportion of individuals with plantar fasciopathy will continue to have symptoms for years and there is a need for more effective treatment modalities. The condition may have serious personal and societal consequences and patients want their pain to go away as quickly as possible. Optimal management of plantar fasciopathy would be something that would fit into general practice as this is the first point of care and it would give patients an almost instant resolution of pain that continues with no relapses. Therefore, the overarching aim of this PhD was to further explore the role of resistance training in plantar fasciopathy management and if a combination of resistance training and corticosteroid injection would provide individuals with plantar fasciopathy with an effective treatment modality on both short and long term. Both treatments have shown to be effective separately and are treatments that a general practitioner would be able to use in their everyday practice.

1.3. AIMS

The PhD includes four studies that are presented in Table 1. The first study aimed at exploring if resistance training could provide individuals with plantar fasciopathy with an acute analgesic effect and compared isometric exercise to isotonic exercise, and walking. The aim of the second study was to investigate if a 12-week self-dosed heavy-slow resistance training program was more beneficial than a 12-week pre-determined heavy-slow resistance training program. The third study had the aim of exploring the feasibility of combining an ultrasound-guided corticosteroid injection

with heavy-slow resistance training. And lastly, the aim of the fourth study was to test if adding heavy-slow resistance training to fundamental patient advice and an insole improved outcome and if a corticosteroid injection added even further to that effect.

1.4. HYPOTHESES

Based on the aims listed above, we hypothesised that (1) an isometric exercise would be superior to both an isotonic exercise and walking on acute pain reduction, (2) a self-dosed heavy-slow resistance training program would be superior to a pre-determined heavy-slow resistance training program, (3) combining an ultrasound-guided corticosteroid injection with heavy-slow resistance training would be feasible, and (4) the combination of an ultrasound-guided corticosteroid injection, heavy-slow resistance training, patient advice and an insole would be superior to heavy-slow resistance , patient advice and an insole, and heavy-slow resistance training, patient advice and an insole would be superior to just patient advice and an insole.

1.5. PAPERS ASSOCIATED WITH THE DISSERTATION

TABLE 1: OVERVIEW OF STUDIES INCLUDED IN THE PHD

	Title	Study design	Aim
Study 1[15]	The effect of isometric exercise on pain in individuals with plantar fasciopathy: A randomized crossover trial	Randomised crossover trial	To compare the acute analgesic effect of isometric resistance exercise, isotonic resistance exercise, and walking, in participants with plantar fasciopathy.
Study 2[14]	Self-dosed and pre-determined progressive heavy-slow resistance training have similar effects in people with plantar fasciopathy: a randomised trial	Randomised clinical trial	To investigate whether a self-dosed heavy-slow resistance training programme was more effective than a pre-determined heavy-slow resistance training programme in improving the Foot Health Status Questionnaire pain domain score in individuals with plantar fasciopathy after a 12-week intervention.
Study 3[55]	Heavy-slow resistance training in addition to an ultrasound-guided corticosteroid injection for individuals with plantar fasciopathy: a feasibility study	Feasibility study	To evaluate the feasibility of combining heavy-slow resistance training with a corticosteroid injection for individuals with plantar fasciopathy before investigating the efficacy in a clinical trial.
Study 4 (Riel et al. *in preparation*)	Corticosteroid injection plus exercise versus exercise, beyond advice and a heel cup for patients with plantar fasciopathy: a randomised clinical superiority trial (the FIX-Heel trial)	Randomised clinical trial	To investigate the efficacy of fundamental patient advice and a heel cup versus fundamental patient advice and a heel cup plus heavy-slow resistance training versus a combination of fundamental patient advice and a heel cup plus heavy-slow resistance training and an ultrasound-guided corticosteroid injection in improving the Foot Health Status Questionnaire pain domain score after 12 weeks in individuals with plantar fasciopathy.

1.6. COMMON METHODS

All studies were prospectively registered on clinicaltrials.gov before enrolment commenced (Study 1: NCT03264729; Study 2: NCT03304353; Study 3: NCT03535896; Study 4: NCT03804008). The SPIRIT protocol of Study 2 was uploaded on clinicaltrials.gov whereas the protocol of Study 4 was published open access.[56,57] All studies but Study 3 were approved by the Ethics Committee of the North Denmark Region. According to the committee, an approval of Study 3 was not needed as this was considered a study with the purpose of quality assurance. The studies were conducted in accordance with the Declaration of Helsinki III and participants consented to participating by signing a consent form.[58]

CHAPTER 2. STUDY 1

2.1. ISOMETRIC EXERCISE FOR EXERCISE-INDUCED HYPOALGESIA

Patients with musculoskeletal conditions are mostly concerned about the pain they experience and the consequences this is associated with such as loss of function and participation. From their perspective, there is a need for treatments that may reduce pain as soon as possible. Though resistance training exercises are recognised for long-terms effects in the management in tendinopathies and in musculoskeletal conditions in general, less is known about the acute pain reducing effects of resistance training in patients.[44,59–64] The exact mechanisms behind the positive effects of long-term rehabilitation using resistance training are unknown, however, mechanisms such as local effects on tendon and muscle structure, or central pain mechanisms have been proposed.[65,66] Exercise in general may provide an immediate reduction in pain sensitivity to a painful stimulus. This is referred to as exercise-induced hypoalgesia.[67] These analgesic effects have commonly been investigated in healthy individuals and may not necessarily be transferable to patients suffering from chronic pain as altered pain processing may be a feature of tendinopathies.[67–70] The analgesic effects of exercise may also be less in patients compared to healthy individuals, but the potential for an effective method for acute pain reduction merits the investigation of exercise-induced hypoalgesia in patients.

Rio et al. investigated the immediate pain reduction following a bout of isometric and isotonic exercise in individuals suffering from patellar tendinopathy.[71] They found that an isometric exercise reduced pain during an aggravating task significantly more than an isometric exercise. These effects were even sustained 45 minutes after the exercises were performed. Therefore, it appears that performing an isometric exercise has great potential for being the tool that patients ask for; an effective way of reducing pain immediately. Such a tool could be used in a variety of ways in the rehabilitation of individuals with tendinopathies in general and among individuals with plantar fasciopathy. E.g., patients may be more likely to adhere to exercises if they experience a pain reduction and the pain reduction could be utilised for making resistance exercises with the purpose of long-term rehabilitation possible. However, the reason for why an isometric exercise proved to be superior to an isotonic exercise is unclear. In order for tendons to adapt to load applied through resistance training it is important that the forces exceed those that are transferred during activities of daily living.[72] Force is mass*acceleration which means that higher acceleration should lead to larger forces being applied, thus, the tendon load should be greater during isotonic exercises. Therefore, other mechanisms may help explain why isometric exercises appear superior to isotonic exercises for an acute reduction in pain.

Despite the findings by Rio et al. could not be replicated in individuals with Achilles tendinopathy, the promising potential of isometric exercise was worthwhile investigation in other tendinopathies such as plantar fasciopathy as it could prove to be an invaluable tool in plantar fasciopathy management.[73] On that basis, Study 1 of this PhD compared the acute analgesic effect of isometric resistance exercise, isotonic resistance exercise, and walking, in participants with plantar fasciopathy.[15] Contrary to other studies comparing only isometric and isotonic exercise, walking was added as a third comparator. The reason for this was that individuals with plantar fasciopathy often describe that pain improves with ambulation.[22,32] Therefore, we wanted to investigate how walking would fare compared to resistance exercises in terms of an acute pain reduction.

2.2. METHODS

2.2.1. PARTICIPANTS

Individuals with plantar fasciopathy were recruited through paid advertisement on Facebook. A Facebook page called *"Behandling af smerter under foden"* was created and through this page recruitment posts were made possible. We asked people 18 years or older with pain under the plantar heel for more than 3 months to contact the primary investigator if they were interested in participating in a study that investigated the pain reducing effects of different types of activities. Additional inclusion criteria were: pain on palpation of the medial calcaneal tubercle or the proximal plantar fascia; thickness of the plantar fascia of 4.0 mm or greater measured using ultrasonography; pain during at least one of three pain-aggravating activities; and mean heel pain of ≥20 mm on a 100-mm Visual Analogue Scale (VAS; 0 mm=no pain, 100 mm=worst heel pain imaginable) during the past week. The exclusion criteria were: history of inflammatory systemic diseases; pain or stiffness in the 1st metatarsophalangeal joint to an extent where the exercises could not be performed; prior heel surgery; pregnancy; pain medication; and corticosteroid injection for plantar fasciopathy within the past 6 months.[15] In order to be able to replicate the primary outcome in the study by Rio et al., a pain-aggravating activity was needed.[71] In a study by Saban and Masharawy they found that 88% of patients with plantar fasciopathy experienced pain during either of the following three single-legged activities: static stance, dynamic half squat, or dynamic heel raise.[74] So to use a similar primary outcome, participants were required to experience pain during at least one of these activities.

2.2.2. INTERVENTIONS

Within 14 days, participants were required to attend three sessions where they performed either an isometric exercise, an isotonic exercise, or walking in a randomised order with at least 48 hours between sessions. To prevent any influence of time-of-day variation in symptoms, all sessions had to be performed within ±1 hour each time. Both resistance training exercises consisted of a heel raise standing with

the forefoot on a step bench.[15] The exercise descriptors are presented in Table 2 and the exercise is depicted in Figure 1. Different loading progressions were used to arrive at an adequate load. The lowest possible load was standing with both feet on the step bench were as the highest load was standing single-legged with a backpack containing a kettlebell. Walking was performed barefoot at participants' own chosen pace. They were asked to walk with a pace similar to how they would be walking around indoors at home. They walked for 4 minutes as this duration was comparable to the total contraction times during the isometric or isotonic exercises. Participants were not allowed to receive treatment or to participate in unusual intense physical activities during their participation in the study.[15]

TABLE 2: EXERCISE DESCRIPTORS[75]

	ISOTONIC HEEL RAISE	ISOMETRIC HEEL RAISE
1. Load magnitude	8 RM	As heavy as possible for 1 minute
2. Number of repetitions	8	1
3. Number of sets	4	5
4. Rest in between sets	2 min	2 min
5. Number of exercise interventions (per (day) or week)	1/day	1/day
6. Duration of the experimental period ((day) or weeks)	1 day	1 day
7. Fractional and temporal distribution of the contraction modes per repetition and duration (s) of one repetition	3s concentric 2s isometric 3s eccentric	0s concentric 45s isometric 0s eccentric
8. Rest in-between repetitions ((s) or (min))	No	No
9. TUT ((s) or (min))	8s/repetition 64s/set	45s/repetition 45s/set

	256s/total intervention	225s/total intervention
10. Volitional muscular failure	Yes	Yes
11. Range of motion	65° from 20° dorsi flexion to 45° plantar flexion	Static (0°)
12. Recovery time in-between exercise sessions ((h) or (d))	N/A	N/A
13. Anatomical definition of the exercise (exercise form)	The participant is standing with the forefoot on a step. The toes are maximally dorsi flexed by placing a towel underneath them. The participant is instructed to perform a heel raise to maximal plantar flexion in the ankle joint and afterwards to lower the heel to maximal dorsi flexion. Supporting oneself for balance by placing the hands on a wall or a rail is allowed.	The participant is standing with the forefoot on a step. The participant is instructed to stand still with the ankle joint in neutral and hold this position. Supporting oneself for balance by placing the hands on a wall or a rail is allowed.

Figure 1: Photograph of the heel raise exercise [57]

2.2.3. OUTCOMES

The primary outcome was pain during the most pain-aggravating activity during screening for eligibility measured on a 0 to 100 mm VAS. The pain-aggravating activity was performed on each day of testing before and after exercises were performed. To investigate other potential effects of the exercises secondary outcomes included plantar fascia thickness measured in mm in the sagittal plane with the participant lying in prone, and pressure pain threshold under the most painful spot under the heel measured in kPa with a handheld pressure algometer. Three measurements of both plantar fascia thickness and pressure pain threshold were performed and an average of the three was used for analyses. Measurements of the plantar fascia thickness were primarily included to investigate if pain reductions were associated with a decrease in plantar fascia thickness as an increased thickness is associated with plantar fasciopathy. Therefore, a decrease could potentially help explain a pain reduction. A final secondary outcome was pain while the exercises were performed measured on a 0 to 100 mm VAS.[15]

2.2.4. STATISTICS

Sample size was based on the ability to detect a greater reduction in pain during the aggravating activity after the isometric exercise compared to the isotonic exercise of 19 mm VAS which is similar to the minimal important difference in VAS in individuals with plantar fasciopathy.[76] The standard deviation found in the study by Rio et al. (19 mm VAS), a two-sided 5% significance level and a power of 80% were used which meant a sample size of 16 participants was needed.[71] However, to account for greater variability among a more heterogenous population of patients with plantar fasciopathy, 20 participants were included. No conclusions favouring either of the exercises would be drawn unless the mean difference was at least equal to the minimal important difference in pain. If a participant would drop out of the study, their data would be excluded from the analyses.[15]

The primary analysis tested the presence of a difference in pain between isotonic and isometric exercise and walking and a 3 X 2 repeated measures ANOVA was used. Independent factors were exercise type (isometric vs. isotonic vs. walking) and time (before vs. after) with pain as the dependent variable. The same model was applied to investigate differences in plantar fascia thickness and pressure pain threshold whereas a one-way repeated measures ANOVA, with exercise (isometric, isotonic, or walking) as the independent factor, and pain as the dependent variable was used to investigate a difference of pain during exercises. A potential association between plantar fascia thickness and pain from before to after the exercises was investigated using Pearson's correlation coefficient.[15]

2.3. RESULTS

Participants were recruited between August and September 2017, with the final follow-up conducted in October 2017. Twenty-eight people contacted the primary investigator after having seen the advertisement. After a telephone screening, 26 were eligible for the clinical examination and hereof 20 participants who met all eligibility criteria were included. One participant withdrew due to illness.[15]

There was no significant difference in pain during the pain-aggravating activity ($F(1,95)=0.28$, P=0.753). The isometric and isotonic exercises led to pain reductions in three participants while the walking sessions led to pain reductions in two participants that were larger than the minimal important difference (Figure 2). There were no significant differences in pain during exercises ($F(2,38)=1.45$, P=0.248), in pressure pain threshold ($F(1,95)=0.18$, P=0.837) or in plantar fascia thickness ($F(1,95)=0.33$, P=0.718). Furthermore, there was no association between plantar fascia thickness and change in pain during the aggravating activity ($r = 0.15$, P = 0.266).[15]

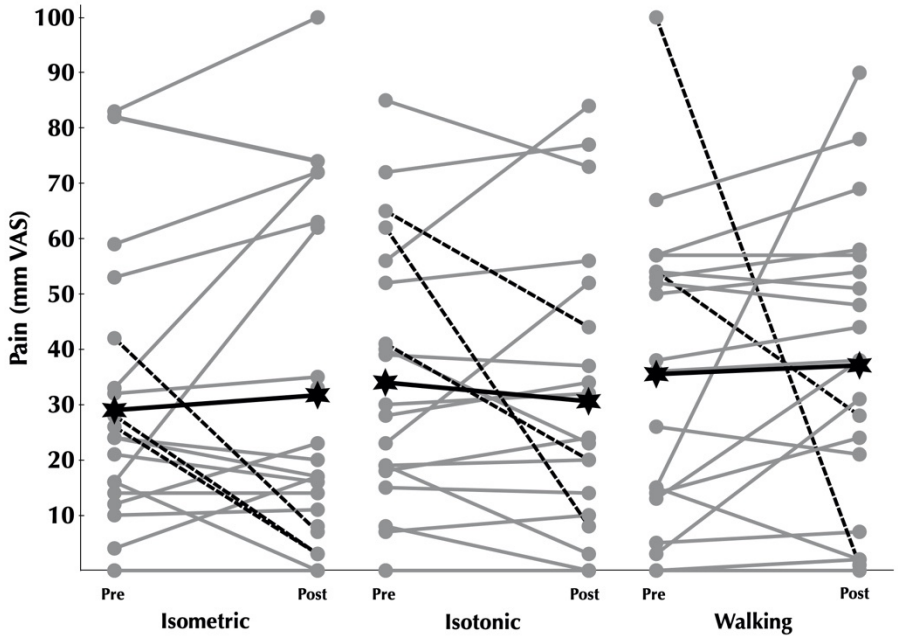

Figure 2: Individual participant data on pain during the aggravating activity before and after the exercises. The stars depict mean pain. Dotted lines show clinically relevant pain reductions according to VAS. Adopted from Riel et al. 2018[15]

2.4. CONCLUSIONS DRAWN FROM STUDY 1

Isometric exercise was no better than isotonic exercise or walking in reducing pain during a pain-aggravating activity in individuals with plantar fasciopathy. Neither of the exercises or walking had an acute analgesic effect and were not associated with changes in plantar fascia thickness or pressure pain threshold. These findings suggest that isometric or isotonic exercises should not be prescribed for acute pain management in this patient population.

CHAPTER 3. STUDY 2

3.1. SELF-EFFICACY AND SELF-DOSING

In 2015, Rathleff et al. introduced a new and effective method for plantar fasciopathy management. They compared heavy-slow resistance training consisting of a heel raise standing with the forefoot on a step with the toes maximally dorsiflexed by a towel and compared this to plantar fascia stretching. After 3 months, participants randomised to heavy-slow resistance training experienced a 29-point lower Foot Function Index corresponding to a medium effect size.[44] At that point in time, using heavy resistance training to treat tendinopathies had already been used for more than 20 years, but it was new to individuals with plantar fasciopathy.[77] The rationale for why it might show comparable effectiveness in plantar fasciopathy as with other tendinopathies was that the plantar fascia consists of collagen type 1 fibres similar to tendons and shows the same pathological changes as tendons with a tendinopathy.[26,78] Based on both anatomical studies and modelling, the Achilles tendon should be loaded and the toes dorsiflexed to generate the largest possible tensile forces within the fascia which is the reason for using the rolled-up towel.[79–81] Another benefit of using the towel is that it may be more comfortable to be standing with the forefoot on a towel rather than a hard step or book which is commonly used.

Despite the fact that heavy-slow resistance exercise is frequently used during rehabilitation of tendinopathies, optimal mode and dosages in reducing pain are unknown.[44,59–62] The exercise dose used in the study by Rathleff et al. was smaller than the exercise doses that have been used in the successful treatment of other tendinopathies.[44,52,62,65,82,83] As stated in Chapter 2, a high load is important to cause adaptation in a tendon but so is the exercise volume.[72,84] Therefore, a larger dose could potentially lead to a faster recovery, however, exercises only have an effect if they are being performed and exercise compliance is a large challenge to overcome. Compliance with exercise prescribed by a physiotherapist has been found to as low as 35% which is even lower than the 50% adherence to medication among individuals suffering from chronic diseases.[85,86] A plethora of different factors may play a role as either facilitators or barriers such as pain during exercise, the severity of the condition, the patient-therapist relationship, or a history of low physical activity.[87–91] Low self-efficacy is seen as yet another reason for poor compliance. [90] Self-efficacy is defined as "*an individual's belief in his or her capabilities to organize and execute the courses of action required to produce given attainments".*[92] Thus, using self-management strategies may increase self-efficacy if successful. Theoretically, allowing patients to self-dose exercises to a higher degree than when using fixed exercise protocols as is the norm could improve their belief in their own abilities to do what is necessary to recover. Thereby, using self-dosed exercise regimens could increase self-efficacy and exercise compliance. Self-management strategies for exercises among individuals with tendinopathies have been explored before. Littlewood et al. investigated an

exercise programme in which patients with rotator cuff tendinopathy were asked to use pain during exercise to guide the progression of the programme.[82] This approach was not found to be superior to usual physiotherapy. Nevertheless, other approaches to self-managing exercises could yield more beneficial outcomes. In Study 2, self-dosing was achieved by asking participants to perform as many sets as they possibly could with a load as high as possible but no heavier than an 8RM.[14] The purpose of this approach was to increase both self-efficacy and thereby exercise compliance and ultimately improve outcomes.

3.2. METHODS

3.2.1. PARTICIPANTS

Individuals with plantar fasciopathy were recruited by referral from their general practitioner or via advertisement on Facebook. Please refer to Chapter 2.2.1 for details on Facebook advertisement and eligibility criteria with the exception of the criterion of pain during an aggravating activity which was not used in Study 2.[14]

3.2.2. RANDOMISATION AND BLINDING

Participants were randomised 1:1 in blocks of 2 to 6 to either a self-dosed or a predetermined exercise programme. The randomisation was stratified by sex as sex has been found to be predictor of response to treatment and based on the experience from Study 1, females may be more likely to be recruited as 18 of the 20 participants included were female.[36] Participants were blinded by informing them that the study was investigating different ways of performing exercises to treat the condition and, thus, they did not know the contents of the intervention of the group they were not randomised to.[14]

3.2.3. INTERVENTIONS

Both groups received patient advice regarding plantar fasciopathy. They were informed about what was known about the condition in terms of risk factors and aetiology, the pathology, activity modification (i.e. being less physically for a period of time if the activities aggravate symptoms and then slowly increase their physical activity level), and the rationale for why their specific exercise programme (self-dosed or predetermined) could lead to recovery. The participants of the predetermined group were told that this specific exercise and exercise programme had been found to be superior to stretching but it was important to follow the exercise protocol as closely as possible. The participants of the self-dosed group were informed that this specific exercise had been found to be superior to stretching but based on previous research of other tendinopathies we believed that doing the exercise as heavy as possible but not heavier than 8RM and with as many sets as possible would increase the odds of recovery. Both groups were told that complying with their protocol was very

important and that compliance to the exercises was associated with their recovery. They were also informed about other types of evidence-based treatments; however, they were asked to refrain from seeking other treatments during the course of the study. A silicone heel cup was given to all participants. This was also used in the study by Rathleff et al.[44] If the participant already used an insole or any other type of foot orthosis they were allowed to continue wearing this if they did not want to use the heel cup. They were asked to wear the heel cup whenever they wore shoes.[14]

Both groups performed heel raises every other day over the course of 12 weeks. They were informed that pain during the exercise was common and expected and that there was no upper limit of pain they were allowed to experience when they performed the exercise as long as they found it to be tolerable. Pain during exercise is generally debated but due to a lack of evidence to support that it should be avoided, participants were not asked to consider pain during exercise.[93,94] The exercise form used by both groups was the same form used in Study 1 when participants performed the isotonic exercise (Table 2) and similar to Rathleff et al. and participants in the predetermined group performed the exercise according to the progressive protocol that was found to be superior to stretching.[44] The load is progressed from 12RM to 8RM from week 1 to week 5 and continues with that load during the remainder of the intervention. Contrary to this, participants in the self-dosed group were asked to perform the exercise with a load as heavy as possible but no heavier than they would be able to perform 8 repetitions (i.e. 8RM) and do as many sets as possible. This meant that in situations where they did not feel that it was possible to perform the exercise with a load corresponding to an 8RM, they could perform the exercise with a lighter load however, they should always aim for a load corresponding to an 8RM.[14]

3.2.4. OUTCOMES

The primary outcome was change in the pain domain of the Foot Health Status Questionnaire from baseline to 12 weeks.[14] The Foot Health Status Questionnaire consists of four domains that cover pain, function, footwear and general foot health and has 13 items.[95] Each domain provides a score from 0 to 100 with the latter being the best possible score. A Danish validated version of the questionnaire that had been adapted to Danish individuals with plantar fasciopathy was used.[96] It is recommended for individuals with plantar fasciopathy, it has been found to have a high reliability, and has been used in several previous randomised trials in this patient population.[49,95,97–101]

Secondary outcomes were the other domains of the Foot Health Status Questionnaire, a 7-point Global Rating of Change after 12 weeks ranging from “Much worse” to “Much improved”, plantar fascia thickness measured by ultrasonography, number of training sessions performed estimated by training diaries, Patient Acceptable Symptom State as a measure of when participants felt no further treatment was needed, the Danish Pain Self-Efficacy Questionnaire to measure potential

improvements in self-efficacy related to pain [102], and the short version of the International Physical Activity Questionnaire which was used to estimate time spent performing vigorous and moderate activities, and time spent walking measured in metabolic equivalent of task (MET)-minutes.[103,104] Participants filled out the questionnaires during baseline, after 4 weeks, and after 12 weeks with the exception of the Global Rating of Change which was only used during the 12-week follow-up. Participants were asked to contact the primary investigator as soon as they achieved their Patient Acceptable Symptom State. If they had not contacted the primary investigator, they were asked about their symptom state during follow-ups to ensure they had not forgotten to contact the primary investigator.[14]

3.2.5. STATISTICS

Sample size was aimed to detect a larger increase of the Foot Health Status Questionnaire pain domain of 14.1 points in the self-dosed group versus the predetermined group corresponding to the minimal important difference of this domain.[105] Based on a standard deviation of 20 points, which was comparable to the overall standard deviations found in previous studies of this patient population [49,98,100,106], a two-sided 5 % significance level and a power of 80 %, a sample size of 33 participants in each group was necessary. Taking into consideration possible dropouts, 70 participants would be recruited.[14]

The primary intention-to-treat analysis tested the between-group difference in the Foot Health Status Questionnaire pain domain using a repeated measures ANCOVA with the outcome as the dependent variable, time (baseline, 4 weeks and 12 weeks) as the within-subjects factor, group allocation as the between-subjects factor and the baseline value as the covariate. This model was also used to test differences in the other Foot Health Status Questionnaire domains, Pain Self-Efficacy Questionnaire, and plantar fascia thickness. Because a repeated measures ANCOVA uses listwise deletion if there is missing outcome data, multiple imputation was used and estimates from 10 data sets were combined using Rubin's Rules.[107] A complete case sensitivity analysis was performed and results were compared to those of the analyses performed with imputed data. Results from the International Physical Activity Questionnaire were not normally distributed, and differences were therefore explored using Mann-Whitney U tests. The responses to the Global Rating of Change were dichotomised as "Improved" if participants had rated their current status as "better" or "much better" (category 6-7) compared to baseline or "Not improved" if they rated their current status from "much worse" to "slightly better" (category 1-5). Using this dichotomisation, the relative risk of being improved was calculated and the relative risk of having achieved a satisfactory result within 12 weeks was also calculated according to the Patient Acceptable Symptom State. To investigate a potential between-group difference in exercise compliance, the number of training sessions performed were compared between groups using an independent *t*-test. The association between plantar fascia thickness and the Foot Health Status Questionnaire

pain domain, and the association between compliance and the Foot Health Status Questionnaire pain domain were investigated using Pearson's correlation coefficient.[14]

3.3. RESULTS

A total of 91 individuals either contacted the primary investigator or were referred from their general practitioner. Seventy participants were included in the study from October 2017 to February 2018 and the final 12-week follow-up was conducted in May 2018.[14]

There was no statistically significant or clinically relevant between-group difference in the improvement of the Foot Health Status Questionnaire pain domain after 12 weeks (adjusted mean difference: -6.9 points, 95%CI: -15.5 to 1.7, P=0.115) (Figure 3) and the complete case sensitivity analysis supported this finding (mean difference: -6.7 points, 95%CI: -16.2 to 2.7, P=0.160). Furthermore, there were no between-group differences at any follow-up in Foot Health Status Questionnaire function domain, Foot Health Status Questionnaire general foot health domain, plantar fascia thickness, Pain Self-Efficacy Questionnaire, 12-week International Physical Activity Questionnaire or 4-week Foot Health Status Questionnaire footwear domain (P>0.05). At the 4-week follow-up, participants of the self-dosed group were walking significantly less than those of the predetermined group (P=0.013) and at the 12-week follow-up participants of the self-dosed group had a significantly larger improvement than participants of the predetermined group in Foot Health Status Questionnaire footwear domain (adjusted mean difference: -5.8 points, 95%CI: -11.4 to -0.2, P=0.042). According to the Global Rating of Change, 24/33 (73%) in the self-dosed group and 20/32 (63%) in the predetermined group were improved (RR=1.16). 3/35 in the self-dosed group and 1/35 in the predetermined group achieved Patient Acceptable Symptom State (RR=3.0). The self-dosed group completed 36 (±8) training sessions and the pre-determined group completed 34 (±12) training sessions (mean difference: -2 sessions, 95%CI: -8 to 3, P=0.412). The self-dosed group performed an average of 5.0 (±2.8) sets per training session whereas 4.5 sets per training session were prescribed over 12 weeks when following the programme used by the predetermined group. There were no associations between change in Foot Health Status Questionnaire pain and change in plantar fascia thickness (r=-0.234, P=0.084), or change in Foot Health Status Questionnaire pain and number of training sessions performed (r=-0.082, P=0.570).[14]

The multiply imputed analysis and the complete case analysis found conflicting results in only two cases: 1) a significant between-group difference in Foot Health Status Questionnaire footwear domain at 12 weeks was found to be non-significant in the complete case analysis (P=0.057), and 2) a non-significant between-group difference in Pain Self-Efficacy Questionnaire at 4 weeks was found to be significant

(P=0.039); the difference did not reach the minimal important change of this questionnaire.[108]

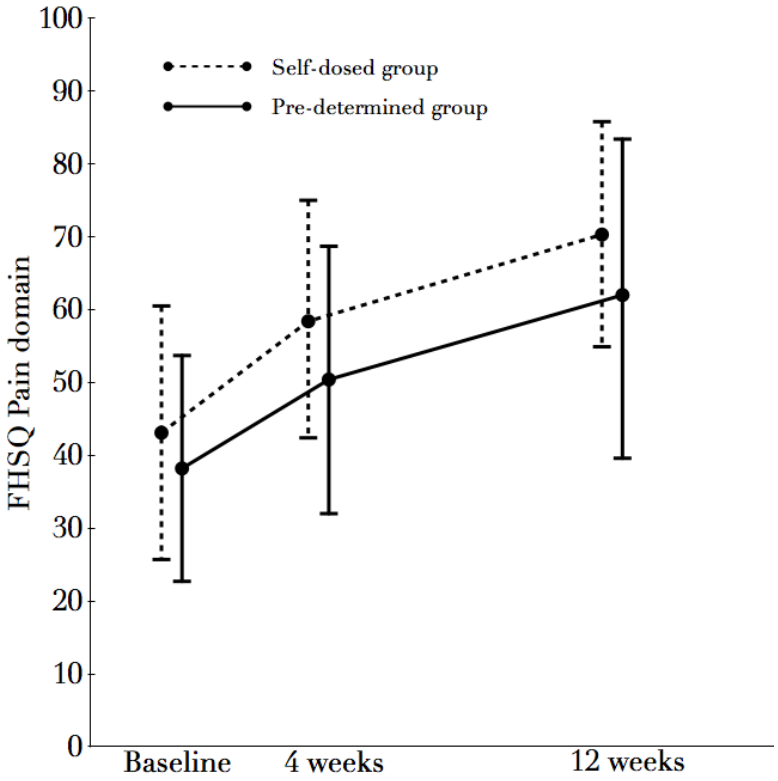

Figure 3: Pain domain of the Foot Health Status Questionnaire (FHSQ) by time. Error bars depict standard deviations. Adopted from Riel et al. 2019.[14]

3.4. CONCLUSIONS DRAWN FROM STUDY 2

A self-dosed heavy-slow resistance training programme was not superior to a standardised predetermined programme in improving the Foot Health Status Questionnaire pain domain score after 12 weeks. Both programmes lead to similar clinically important improvements and exercise compliance over 12 weeks. Despite patients improved, only 3 patients in the self-dosed group and 1 patient in the predetermined group achieved an acceptable symptom state and there was no association between Foot Health Status Questionnaire pain and exercise compliance which means that no dose-response relationship was found. Self-dosing could be an alternative to using predetermined programmes, however, due to the negligible proportion of patients achieving an acceptable symptom state within 12 weeks, there is a continued need for improved treatment.

CHAPTER 4. STUDY 3

4.1. COMBINING AN ULTRASOUND-GUIDED CORTICOSTEROID INJECTION WITH HEAVY-SLOW RESISTANCE TRAINING

A systematic review of randomised trials from 2010 aimed at establishing the efficacy of corticosteroid injection for tendinopathies.[52] The authors found that despite corticosteroid reduced pain in the short term when compared to other interventions, the effect was reversed at medium or long term. The effect also seemed to vary between different tendinopathies. For example, the evidence was unclear for rotator cuff tendinopathy whereas corticosteroid had a large short-term effect on pain among individuals with lateral epicondylalgia. Two high-quality randomised trials investigating the effects of corticosteroid injection for lateral epicondylalgia and lateral hip pain both concluded that exercise without corticosteroid was superior to exercise combined with corticosteroid.[51,52] One of the main concerns about the use of corticosteroid injection to treat tendinopathies is that corticosteroid has negative effects on tendon cells and the mechanical properties of the tendon are reduced.[109] Nevertheless, corticosteroid injection has been found to be efficacious in plantar fasciopathy and although it has been criticised for increasing the risk of plantar fascia ruptures, a Cochrane review of the literature concluded that it was safe.[47,50] The earlier reports of plantar fascia ruptures associated with corticosteroid injections may be due to methods applied as injections were performed palpation-guided rather than ultrasound-guided which is the more popular choice now. Two randomised trials that found corticosteroid injection to be superior to placebo in patients with plantar fasciopathy reported no adverse events.[48,49] Ultrasound-guided injections have even been found to be superior to palpation-guided injections albeit one of the studies concluding this used an assistive device during ultrasound.[110,111] Whether to use ultrasound-guided or palpation-guided injections is not the only consideration to make when deciding on the technique applied as the placement of the injection may also be associated with the outcome of the treatment. A randomised trial compared ultrasound-guided injections either superficial or deep to the plantar fascia and found that the deep placement resulted in larger improvements in pain, disability, plantar fascia thickness, and foot-related quality of life.[112]

Similar to the reports of only short-term superiority of corticosteroid injection in the treatment of other tendinopathies, it appears that this is also the case for corticosteroid injection to treat plantar fasciopathy.[50] Recently Whittaker et al. compared a prefabricated foot orthosis with a single corticosteroid injection and found that corticosteroid injection was superior to the orthosis after 4 weeks, however, after 12 weeks the orthosis was more effective.[99] Therefore, there is a rationale for combining corticosteroid injection with another treatment that may have a better long-term outcome such as heavy-slow resistance training. Johannsen et al. investigated the

efficacy of repeated corticosteroid injections versus different foot and calf strengthening exercises and stretching versus a combination of the two and concluded that the combination was superior to the other treatments alone.[113] Yet, the question still remains if a single injection combined with heavy-slow resistance training is feasible. This could fit into general practice as a somewhat time-efficient treatment option that does not require repeated consultations for continuous treatment. Taking into consideration the novelty of this combination of treatments and the *in vitro* and *in vivo* reports of negative effects on the mechanical properties of tendons that corticosteroid might have, a feasibility study was needed before investigating the effects of the combined treatments in a trial.

4.2. METHODS

4.2.1. PARTICIPANTS

Individuals with plantar fasciopathy were recruited via advertisement on Facebook or by referral from a single general practice. Please refer to Chapter 2.2.1 for details on Facebook advertisement and eligibility criteria, however, due to the use of a corticosteroid injection additional criteria were included. These were: breastfeeding, known hypersensitivity to corticosteroids or local anaesthetics or; skin or soft tissue infection near the injection site. To better reflect clinical practice with regards to who would be offered an injection, the level of average pain intensity that had to be experienced during the previous was increased to 30 mm VAS as opposed to 20 mm VAS in Study 1 and Study 2.[55]

4.2.2. INTERVENTIONS

Participants received the same intervention as participants in the self-dosed group in Study 2 (i.e. patient advice, a silicone heel cup, and self-dosed heavy-slow resistance training) with the addition of an ultrasound-guided corticosteroid injection and performed heavy-slow resistance training for 8 weeks. Before participants started to perform exercises, they received the injection. They were asked to start performing exercises as soon as possible hereafter and to wait no more than 24 hours upon receiving the injection. The only restriction regarding the exercise was that they were asked not to make a load progression during the first two weeks. If their own bodyweight was enough to achieve an 8RM at baseline, then they should not add a backpack with additional weight until the third week of the intervention. They were, however, allowed to increase the exercise volume (i.e., perform more repetitions per set or more sets).[55]

Participants received an ultrasound-guided corticosteroid injection between 5 and 8 days after baseline. A 21-gauge, 40 mm needle was connected to a 2.5 cm^3 syringe filled with 1 ml Triamcinolonhexacetonid (Lederspan, Meda) + 1 ml Lidocain 10 mg/ml (Xylocain, AstraZeneca). The needle is inserted with a medial approach under

ultrasound-guidance aligned to the long axis of the ultrasound transducer. The injection was distributed deep and superficially on the plantar fascia surface anterior to the plantar fascia insertion on the calcaneal bone in the region of maximal plantar fascia thickness. If participants were not improved according to the dichotomised Global Rating of Change (please see 3.2.5 for an elaboration of the Global Rating of Change), they were offered a second injection and would be followed for an additional 8 weeks.[55]

4.2.3. OUTCOMES

The outcomes were divided into feasibility outcomes based on which the conclusion would be drawn and explorative outcomes. Feasibility outcomes were: 1) acceptability of the combined interventions measured by a participant acceptability questionnaire that included a 7-point rank scale ranging from "Very unacceptable" to "Very acceptable". The questionnaire was filled out at the 8-week follow-up. This was not an evaluation of whether the participant's symptoms had improved but if treatment matched their expectations and whether they found it acceptable to perform heavy-slow resistance exercises shortly after receiving an injection. This was clearly stated on the questionnaire and was further emphasised by the primary investigator. The combined interventions would be categorised as "Unacceptable" if participants rated it as "Very unacceptable" or "Unacceptable" (category 1-2) and categorised as "Acceptable" if it was rated from "Slightly unacceptable" to "Very acceptable" (category 3-7). Participants were asked to elaborate their response in a free-text field. The rationale for using the categorisation "Acceptable" despite including "Slightly unacceptable" is that slight unacceptability may be acceptable if the treatment is effective. As the treatment effect was yet to be established, treatment effect could not be used as an argument as to why participants should accept and comply with the intervention. However, if the intervention was too unacceptable (category 1-2) it would not be feasible to investigate the effect in a future trial. 2) Recruitment rate as measured by the mean number of participants recruited per week throughout the recruitment period. 3) Compliance to the exercises as measured by the mean number of training sessions performed per week throughout the intervention measured by a training diary that each participant is handed out at baseline. As the future trial aimed at investigating the efficacy of the treatments combined, participants were required to perform exercises. The injection was known for an immediate analgesic effect and the sudden pain reduction could potentially influence compliance. Symptom severity has been suggested to affect exercise compliance which is why participants could be less likely to comply with the exercises if their heel pain was decreased.[114] 4) Mean days until the participant started to perform exercises from after the injection based on training diary data. Participants were asked to start performing the exercise as soon as possible 24 hours after the injection. The rationale was that if participants did not have confidence in the strength of the plantar fascia after the injection, they may have waited an undesirably long time before they started to perform the exercise. This had the potential to affect their recovery negatively.[55]

The explorative outcomes used were the Foot Health Status Questionnaire, the Pain Self-Efficacy Questionnaire, the International Physical Activity Questionnaire, and the Global Rating of Change which are all described in Chapter 3.2.4. Participants filled out these questionnaires at baseline, after 4 weeks and after 8 weeks with the exception of the Global Rating of Change which was only filled out during the 8-week follow-up. To explore the popular belief of an almost immediate effect of the injection change in mean daily heel pain measured on an 11-point Numerical Rating Scale (NRS) (ranging from 0=no pain to 10=worst heel pain imaginable) from the days before the injection to one week after the injection was recorded. Participants received a daily SMS asking them to rate their mean heel pain during the past 24 hours from the day after baseline to one week after the injection. The SMS was sent automatically using an app on a smartphone. The SMS was scheduled to be sent at the same time every day.[55]

4.2.4. STATISTICS

No sample size calculation was performed as this was a feasibility study.[115,116] Twenty participants were included as this was considered enough to evaluate the feasibility of the interventions.[55]

As no hypothesis testing was performed, descriptive statistics were used and mean or median changes over time and 95% confidence intervals are reported. The following criteria had to be met to conclude feasibility and were decided before recruitment start: 1) ≥10/20 had to rate the intervention as “Acceptable”. If any participant would drop out after the injection their missing response would be dichotomised as "Unacceptable". 2) ≥15/20 participants needed to have performed ≥20/28 possible training sessions; and 3) ≥15/20 participants needed to have started performing the exercise ≤7 days after the injection.[55]

4.3. RESULTS

Participants were recruited between June and August 2018 and the final follow-up was conducted in October 2018. One participant was lost to follow-up and five training diaries could not retrieved.[55]

The responses by 18/20 participants were categorised as “Acceptable”, 10/15 participants performed ≥20 training sessions and 15/15 started exercising ≤7 days after injection. The commonest reason (n=3) for evaluating the treatment as acceptable was that pain was reduced before exercise start. When recruitment was active, 3.3 participants were recruited per week.[55]

Mean daily heel pain during the days before the injection was 5.5 (±1.8) NRS and 4.3 (±2.1) NRS during the week after. 6/19 participants were categorised as being improved according to the dichotomised Global Rating of Change during the 8-week

follow-up. Therefore, 13 participants were offered a second injecvtion. Hereof, four agreed to this and were followed for an additional 8 weeks. Two were lost to follow-up and one was improved at the follow-up and the other was still not. Results of the other explorative outcomes are presented in Table 3.[55]

TABLE 3: RESULTS OF EXPLORATIVE OUTCOMES[55]

		MEAN CHANGE (95%CI)		
	MEAN (SD)	Baseline vs 4 weeks	Baseline vs 8 weeks	4 weeks vs 8 weeks
FHSQ PAIN (0-100)				
Baseline	41.1 (12.7)			
4 weeks	56.5 (26.6)	15.8 (3.0 to 28.6)	13.5 (-0.3 to 27.2)	-2.3 (-12.2 to 7.6)
8 weeks	54.8 (28.2)			
FHSQ FUNCTION (0-100)				
Baseline	61.9 (19.3)			
4 weeks	71.9 (24.8)	11.8 (-0.1 to 23.7)	12.9 (-1.4 to 27.1)	1.0 (-9.8 to 11.9)
8 weeks	74.3 (26.0)			
FHSQ FOOTWEAR (0-100)				
Baseline	35.8 (21.8)			
4 weeks	45.8 (29.0)	8.8 (-5.0 to 22.6)	12.0 (-0.4 to 24.5)	3.2 (-2.6 to 9.1)
8 weeks	48.3 (27.6)			
FHSQ GENERAL FOOT HEALTH (0-100)				
Baseline	44.5 (21.0)			
4 weeks	35.1 (27.5)	-6.3 (-21.3 to 8.8)	9.0 (-0.2 to 18.3)	15.3 (2.4 to 28.2)
8 weeks	50.9 (26.6)			
PSEQ (0-60)				
Baseline	42.1 (8.9)			
4 weeks	47.0 (12.2)	5.2 (0.5 to 10.0)	5.8 (0.2 to 11.3)	0.6 (-4.4 to 5.5)
8 weeks	48.2 (10.6)			
PLANTAR FASCIA THICKNESS (MM)				
Baseline	5.6 (0.9)		0.3	
8 weeks	5.3 (1.2)		(-0.1 to 0.7)	
		MEDIAN CHANGE (95%CI)		
	MEDIAN (IQR)	Baseline vs 4 weeks	Baseline vs 8 weeks	4 weeks vs 8 weeks
IPAQ WALK (MET)				
Baseline	1155 (330-1732.5)			
4 weeks	1386 (198-2079)	-132 (-251 to 231)	-99 (-921 to 317)	-1155 (-1598 to -330)
8 weeks	495 (297-1386)			
		IPAQ MODERATE (MET)		
Baseline	540 (300-2220)			
4 weeks	720 (40-2880)	0 (-1254 to 600)	0 (-480 to 480)	600 (-2104 to -360)
8 weeks	480 (240-960)			
		IPAQ VIGOROUS (MET)		
Baseline	440 (0-1520)			
4 weeks	240 (0-1440)	0 (-480 to 480)	0 (-73 to 313)	-400 (-1107 to 0)
8 weeks	240 (0-960)			
		IPAQ TOTAL (MET)		
Baseline	2475.5 (1391-4614)			
4 weeks	1935 (1200-6906)	242 (-922 to 2681)	-171 (-1592 to 864)	423 (-712 to 2084)
8 weeks	2217 (1059-2772)			

FHSQ, Foot Health Status Questionnaire. PSEQ, Pain Self-Efficacy Questionnaire. IPAQ, International Physical Activity Questionnaire. MET, metabolic equivalent.

4.4. CONCLUSIONS DRAWN FROM STUDY 3

Both the number of participants who evaluated the combination of an ultrasound-guided corticosteroid injection and heavy-slow resistance training acceptable and the time to exercise start reached and surpassed the criteria for feasibility. Five training diaries could not be retrieved which meant that it was not possible to evaluate exercise compliance based on the a priori criteria as all training diaries were needed. However, 10/15 of participants had performed at least 20 training sessions and combined with acceptability and time to exercise start, the combined treatments were evaluated as feasible.

CHAPTER 5. STUDY 4

5.1. RESULTS FROM STUDIES 1-3 LEADING TO STUDY 4

The overarching aim of this PhD was to build on preliminary evidence suggesting heavy-slow resistance training for individuals with plantar fasciopathy and further explore the role of resistance training in plantar fasciopathy management and if a combination of resistance training and corticosteroid injection would provide individuals with plantar fasciopathy with an effective treatment modality on both short and long term. The first three studies were used to inform the final randomised trial.

The results of Study 1 did not suggest that isometric exercise could be used as a way of inducing an acute pain reduction that could be used before exercises with the purpose of long-term rehabilitation were to be performed.[15] Nor did isotonic exercise or walking. Therefore, it was decided not to include isometric exercise in the Study 4 intervention. Study 2 compared two different approaches to prescribing exercise programmes. The self-dosed programme was not superior to the predetermined programme, however, small but non-significant effects were observed in the majority of outcomes favouring the self-dosed programme and this approach might be simpler for general practitioners to prescribe which is why self-dosing would be used in both Study 3 and 4.[14,55] Based on the small number of participants achieving an acceptable symptom state in both groups of Study 2 (4/70), the question of the efficacy of heavy-slow resistance training in this patient population arose. Thus, there was a growing rationale for including a group in Study 4 that did not perform exercises to compare this to a group that did perform exercises. Combining an ultrasound-guided injection with heavy-slow resistance training was feasible according to Study 3.[55] However, firm conclusions could not be drawn regarding exercise compliance which is why special attention should be paid to compliance during Study 4.

5.2. METHODS

5.2.1. PROTOCOL DEVIATIONS

The analyses regarding exercise compliance were not originally planned in the protocol, but they were described in the Statistical Analysis Plan which was published on Aalborg University's research portal prior to the last 12-week follow-up.[117] As participants were allowed to stop performing exercises 4 weeks after achieving the Patient Acceptable Symptom State, achieving this state could be associated with a low number of training sessions performed. Therefore, to perform meaningful comparisons of exercise compliance between PAX and PAXI and to explore an association between the number of training sessions performed and change in Foot Health Status Questionnaire pain, participants who had achieved the Patient

Acceptable Symptom State were excluded from these analyses. Results regarding physical activity and the health economic evaluation were not finalised before the submission of the PhD and, thus, are not included.

5.2.2. PARTICIPANTS

Individuals with plantar fasciopathy were recruited either by referral from their general practitioner or via advertisement on Facebook. Please refer to Chapter 2.2.1 for details on Facebook advertisement and eligibility criteria. Similar to Study 3, the additional criteria were included due to the injection (see Chapter 4.2.1).[55] To include a washout period of any previous treatment for plantar fasciopathy, these exclusion criteria were also used: 1) having received treatment by a healthcare professional for plantar fasciopathy within 12 weeks before baseline, 2) made any substantial changes to usual self-care of the condition in the last 4 weeks (e.g., started using insoles, started performing stretching, made a substantial decrease in physical activity level).[57]

5.2.3. RANDOMISATION AND BLINDING

Participants were randomised 1:1:1 in blocks of 3 to 12 to either PA (patient advice and an insole), PAX (patient advice, an insole, and heavy-slow resistance training), or PAXI ((patient advice, an insole, heavy-slow resistance training, and an ultrasound-guided corticosteroid injection). Similar to Study 2, the randomisation was stratified by sex.[57]

To blind the primary investigator who was responsible for data treatment and statistical analyses, the randomisation was coded so that the primary investigator did not know which group (1, 2, or 3) received which intervention. The primary investigator and the group of authors remained blinded until after the analyses had been made and the conclusions had been decided upon.[57] The analyses were made on December 22nd, 2020, and an agreement on the conclusion was made on January 11th, 2021, by all authors. (Riel et al. *in preparation)*

5.2.4. INTERVENTIONS

Regardless of group allocation, all participants received patient advice about plantar fasciopathy. It consisted of the same information that was delivered as patient advice in Study 2 and 3, but instead of just delivering the advice orally, all participants were provided with a leaflet containing the information and were encouraged to read it at home. All participants also received a silicone heel cup and were asked to use the heel cup as much as possible when wearing footwear. Participants in PAX and PAXI groups performed heavy-slow resistance training using the self-dosed programme which was tested in Study 2 and 3. They were told to continue performing exercises until they reached the Patient Acceptable Symptom State and then an additional 4

weeks. Participants in the PAXI group also received an ultrasound-guided corticosteroid injection similar to participants in Study 3.[55,57]

5.2.5. OUTCOMES

Similar to Study 2, the primary outcome was the Foot Health Status Questionnaire pain domain and secondary outcomes were the other domains of the Foot Health Status Questionnaire, a 7-point Global Rating of Change after 12 weeks ranging from "Much worse" to "Much improved", number of training sessions performed estimated by training diaries, Patient Acceptable Symptom State as a measure of when participants felt no further treatment was needed, the Danish Pain Self-Efficacy Questionnaire to measure potential improvements in self-efficacy related to pain.[102] The difference between Study 2 and 4 in terms of outcomes was that plantar fascia thickness was not included in Study 4 due to lack of an association with symptoms as found in Study 2, and the International Physical Activity Questionnaire was not included in Study 4 either. Physical activity was measured objectively using accelerometry instead of self-reports. Weekly physical activity level expressed as Metabolic Equivalents (METs) was collected by a wrist-worn ActiGraph wGT3X-BT (ActiGraph LLC, Pensacola, FL, USA). Participants wore the ActiGraph twice; three weeks after baseline and three weeks after the 12-week follow-up. To be able to conduct a future health economic evaluation, participants also filled out the EQ-5D-5L instrument and were asked about days of sick leave, level of productivity, and participants' co-payments and other condition-related expenses during all follow-ups using a self-developed questionnaire.[57,118]

5.2.6. STATISTICS

Sample size was aimed to detect a between-group difference of the Foot Health Status Questionnaire of 14.1 points. This corresponds to the more conservative minimal important difference of the domain.[76,105] Based on a standard deviation of 22 points similar to standard deviations found in previous studies [49,98,100,106], a two-sided 5% significance level and a power of 90%, a sample size of 53 participants in each group would be necessary. Taking into consideration possible dropouts, 60 participants in each group were included.[57]

Analyses were performed in accordance with a Statistical Analysis Plan that was published online before the last 12-week follow-up was conducted. The primary analysis was a linear mixed effects model with the participant as random effect. The baseline value, time (4, and 12 weeks), group allocation (PA or PAX or PAXI) and term for interaction between time and group were treated as fixed-effect variables. The same model was applied to investigate between-group differences in the other domains of the Foot Health Status Questionnaire and the Pain Self-Efficacy Questionnaire.[57]

Using the dichotomisation of the Global Rating of Change, the relative risk of being improved was calculated and the relative risk of having achieved a satisfactory result within 12 weeks was calculated according to the Patient Acceptable Symptom State and the number needed to treat (NNT) was calculated as 1/risk difference. Potential differences in number of training sessions performed between PAX and PAXI were explored using an unpaired t-test and Pearson's correlation coefficient was used to explore an association between the number of training sessions performed and change in Foot Health Status Questionnaire pain.[57]

5.3. RESULTS

A total of 369 individuals either responded to the Facebook advertisement or were referred from their general practitioner. The 180 participants were included from February 2019 to September 2020 and the final 12-week follow-up was conducted in December 2020. Nine participants in PA, 13 participants in PAX, and 10 participants in PAXI dropped out of the study before the 12-week follow-up. (Riel et al. *in preparation)*

The primary analysis revealed a statistically significant difference in the Foot Health Status Questionnaire pain domain between PAXI and PA (adjusted mean difference: -9.5 (95%CI: -15.3 to -3.6, p=0.002)), but no difference between PAXI and PAX (adjusted mean difference -5.5 (95%CI: -11.5 to 0.4, p=0.069)) or between PA and PAX (adjusted mean difference 3.9 (95%CI: -2.0 to 10.0, p=0.190)) (Figure 4). The difference between PAXI and PA did not exceed the minimal important difference of 14.1 points. PAXI was also superior to PA in the Foot Health Status Questionnaire function domain (adjusted mean difference: -7.5 (95%CI: -2.0 to -13.2, p=0.009)), but no other statistically significant differences were found in the Foot Health Status Questionnaire or Pain Self-Efficacy Questionnaire (Table 4). According to the Global Rating of Change, 25/53 improved in PA, 25/46 improved in PAX, and 31/49 improved in PAXI. The relative risk between PAX and PA was 1.2 (p=0.475, NNT=13.9), the relative risk between PAXI and PA was 1.3 (p=0.106, NNT=6.2), and the relative risk between PAXI and PAX was 1.2 (p=0.381, NNT=11.2). The Patient Acceptable Symptom State was achieved no later than at the 12-week follow-up by 11 in PA, 8 in PAX, and 21 participants in PAXI. The relative risk between PA and PAX was 1.3 (p=0.530, NNT=23.9), the relative risk between PAXI and PA was 2.0 (p=0.032, NNT=5.6), and the relative risk between PAXI and PAX was 2.5 (p=0.010, NNT=4.5). Participants in PAX performed 30.9 (±12.4) training sessions (74% of prescribed sessions) and participants in PAXI performed 29.9 (±10.4) training sessions (71% of prescribed sessions). There was no difference between groups (mean difference: 1.0 sessions, 95%CI: -5.9 to 7.8, p=0.779), and there was no association between the number of training sessions performed and change in FHSQ pain (r=-0.044, p=0.770). (Riel et al. *in preparation)*

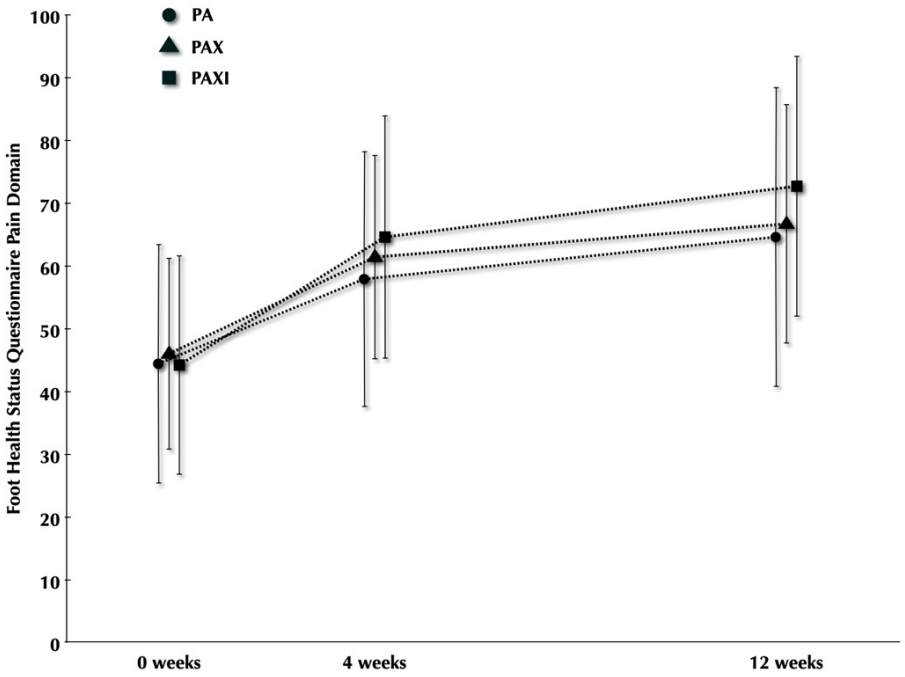

Figure 4: Pain domain of the Foot Health Status Questionnaire by time. Error bars depict standard deviations.

TABLE 4: RESULTS OF CONTINUOUS OUTCOMES

	Mean (SD)			Adjusted mean difference (95%CI)		
	PA	**PAX**	**PAXI**	**PA vs PAX**	**PA vs PAXI**	**PAX vs PAXI**
FHSQ Pain						
Baseline	44.4 (19.0)	46.0 (15.2)	44.2 (17.4)	-5.5 (-11.5 to 0.4, p=0.069)	-9.5 (-15.3 to -3.6, p=0.002)	-3.9 (-10.0 to 2.0, p=0.190)
4 weeks	57.9 (20.3)	61.4 (16.2)	64.6 (19.3)			
12 weeks	64.6 (23.8)	66.7 (19.0)	72.7 (20.7)			
FHSQ Function						
Baseline	60.3 (19.4)	60.0 (18.0)	56.9 (23.6)	-4.5 (-10.0 to 1.3, p=0.126)	-7.5 (-13.1 to -2.0, p=0.009)	-3.2 (-8.9 to 2.6, p=0.277)
4 weeks	68.9 (20.0)	71.6 (17.5)	70.4 (20.7)			
12 weeks	75.4 (19.5)	79.6 (18.0)	82.9 (20.5)			
FHSQ Footwear						
Baseline	39.9 (19.6)	39.1 (20.0)	37.4 (23.1)	3.3 (-5.6 to 12.2, p=0.463)	3.4 (-5.3 to 12.2, p=0.443)	0.1 (-8.9 to 9.1, p=0.981)
4 weeks	47.7 (23.8)	46.3 (24.2)	42.4 (26.9)			
12 weeks	51.7 (26.2)	51.1 (25.3)	49.8 (28.8)			
FHSQ GFH						
Baseline	49.0 (26.4)	45.0 (28.8)	46.4 (26.8)	2.0 (-7.0 to 10.9, p=0.666)	-2.0 (-10.8 to 6.9, p=0.661)	-3.9 (-13.0 to 5.1, p=0.392)
4 weeks	50.4 (28.3)	46.3 (24.9)	50.9 (25.6)			
12 weeks	55.5 (26.6)	56.1 (27.0)	59.2 (27.5)			
PSEQ						
Baseline	41.1 (11.0)	39.3 (12.1)	39.2 (11.2)	-2.8 (-6.9 to 1.3, p=0.175)	-2.3 (-6.3 to 1.8, p=0.267)	0.5 (-3.6 to 4.7, p=0.798)
4 weeks	44.9 (13.3)	45.8 (10.4)	44.5 (11.8)			
12 weeks	46.6 (12.7)	49.1 (10.4)	49.9 (11.7)			

FHSQ, Foot Health Status Questionnaire. GFH, General Foot Health. PSEQ, Pain Self-Efficacy Questionnaire.

5.4. CONCLUSIONS DRAWN FROM STUDY 4

All three groups had statistically significant and clinically meaningful improvements in Foot Health Status Questionnaire pain during the 12-weeks of follow-up. PAXI was significantly superior to PA, but not significantly superior to PAX after 12 weeks. No superiority was found between PAX and PA. Despite a statistically superior result by PAXI versus PA, the mean difference did not reach the pre-defined minimal clinically important difference of 14.1 points. Hence, the choice of treatment is expected to depend much on preferences by patient and clinician.

CHAPTER 6. DISCUSSION

6.1. MAIN FINDINGS

Overall, the findings of this PhD have made a significant contribution to the management of plantar fasciopathy. The results from Study 1 showed that exercises whether they are performed isometrically or isotonically do not induce an acute pain reduction in individuals with plantar fasciopathy and, thus, should not be incorporated in rehabilitation for that purpose.[15] In Study 2, two different exercise programmes were compared and were associated with similar improvements over time.[14] The self-dosed programme may provide clinicians a simpler method for prescribing heavy-slow resistance training in this patient population. This programme was combined with an ultrasound-guided corticosteroid injection in Study 3 that had the purpose of investigating the feasibility of this combination.[55] Results showed that it was feasible to perform heavy-slow resistance training after having received an injection and that participants were complying with the exercises adequately. In the final trial, Study 4 (Riel et al. *in preparation*), no exercises were compared with exercises and exercises and an ultrasound-guided corticosteroid injection. The group that had received the injection and performed exercises was superior to the group that did not perform exercises but not to the group that performed exercises only. There was no difference between the groups that either did not perform exercises or performed exercises without an injection. Despite the statistically significant superiority between the group that received an injection and performed exercises compared with the group that did not perform exercises, the difference did not reach the minimal important difference. Therefore, all three different approaches may be viable options and the choice should rely and both patient and clinician preferences.

6.2. INTERPRETATION OF RESULTS

The overarching aim of this PhD was to further explore and develop the role of resistance training in the management of individuals with plantar fasciopathy after preceding preliminary evidence indicated that this treatment had great potential. Nevertheless, the combined results of the studies suggest that the future role of resistance training should be lessened. Exercises were no better than walking to induce an acute pain reduction in Study 1[15], only 4/70 participants achieved an acceptable symptom state over the course of 12 weeks in Study 2[14], and in Study 4 (Riel et al. *in preparation*), no superiority was found between PAX and PA. Several factors may help explain why exercises did not prove to be superior. One of the physiological explanations relates to the load applied not being sufficient to achieve an adaptation in the plantar fascia.[72] The fascia is subjected to forces two times greater than the person's bodyweight during walking and four times greater during running.[119] Pain during exercise is a limiting factor that makes patients perform the heel raise with a

load that is lighter than their muscular strength allows them to. To counteract this limitation, participants of studies 2-4 were told that pain was expected, and no upper threshold of allowed pain was used.[14,55,57] Exercises performed with pain have been found to have similar effects as exercises performed with no pain allowed across various musculoskeletal conditions including plantar fasciopathy, but pain may inhibit maximal voluntary contraction force and, thus, may limit the load during exercises.[94,120] It is likely that participants who performed the heel raise standing on both feet had sufficient muscular strength to perform it with single-leg stance, but pain during single-leg stance was intolerable. Therefore, the strain applied to the plantar fascia was not above the threshold that would trigger an adaptation.[72] However, sufficient loading is only important if tendinous changes associated with strength training are the reason for why resistance training is considered a key element in the rehabilitation of tendinopathies. The design of the heel raise has been focussed on maximising the strain e.g. by including dorsi-flexion of the toes.[44,79] Yet, another argument for using exercise therapy is to increase self-efficacy through the self-management of this approach to rehabilitation. In Study 4 (Riel et al. *in preparation*), the Pain Self-Efficacy Questionnaire was used as a secondary outcome but performing exercises versus not performing exercises did not result in larger increases in self-efficacy.

Another consideration regarding heavy-slow resistance training and individuals with plantar fasciopathy is that the condition is considered the result of an imbalance between the load the plantar fascia is subjected to and the capacity it has to counteract this load. This load cumulates from both exercise and activities of daily living. If the patient does not successfully decrease the activities that aggravate the condition, exercises are yet another activity that adds to the overall daily load which can hinder recovery. In athletic populations, decreasing activities that aggravate pain may be easier than among non-athletic populations where everyday activities are considered the cause of plantar fasciopathy. Even if 8/59 participants in PAX achieved the Patient Acceptable Symptom State in Study 4, PAX was not superior to PA in any outcome. When heavy-slow resistance training was introduced in 2015 by Rathleff et al. and found to be superior to stretching, heavy-slow resistance training was a completely new approach in this patient population.[44] Subsequently, it received a great deal of attention among practitioners and several participants of the studies included in the PhD would have tried the exercise unsuccessfully. This may have hampered the odds of a successful outcome and greater improvements might be experienced in clinical practice among patients with a more recent onset of symptoms. Participants of the PhD were required to have had symptoms for at least 3 months.[14,15,55] Earlier loading of type I collagen tissue may lead to improved outcomes, which is why loading programmes may still serve a purpose in plantar fasciopathy management.[121] There may also be some who simply respond well to exercises whilst others do not. In Study 1, two in three responders to exercise experienced acute pain reduction when they performed both the isometric and isotonic exercise which indicated that they were responders regardless of the method applied.[15] However, this study only investigated

the acute effects of exercise and if acute responses could be transferred to long-term rehabilitation outcomes, remains unknown.

Pain experienced during the exercise could be a factor to consider before applying heavy-slow resistance training. This was explored in Study 1 and participants experienced a pain intensity of 42.3 (±29.5) mm VAS.[15] This should be taken into account together with the uncertainty of a successful outcome and the time requirements as part of the shared decision-making between clinicians and patients when planning rehabilitation.

Heavy-slow resistance exercise is frequently used during rehabilitation of tendinopathies and is considered a key factor in recovery.[44,59–62] Despite the similarities between tendinopathies and plantar fasciopathy such as the content of collagen type 1 fibres in the plantar fascia similar to tendons and how plantar fasciopathy shows the same pathological changes as tendons with a tendinopathy, there are anatomical differences as well.[26,78] The plantar fascia is an aponeurosis that originates and inserts on bone and does not attach a muscle to bone such as the patellar or Achilles tendons. Therefore, it remains questionable if plantar fasciopathy is indeed a tendinopathy and, thus, should be treated as such.

The most commonly used treatment approach to managing plantar fasciopathy in general practice is a wait-and-see approach.[122] The PA group in Study 4 cannot be considered wait-and-see approach as it included both patient advice and silicone heel cups.[57] A wait-and-see group was not included due to ethical considerations and because it was considered a barrier to recruitment and retainment in the study. The efficacy of foot orthoses to treat plantar fasciopathy is debatable with conflicting findings in systematic reviews and meta-analyses.[40,41] A recent randomised clinical trial compared foot orthoses with an ultrasound-guided corticosteroid injection found that foot orthoses were significantly superior after 12 weeks, however, the between-group difference did not reach the minimal important difference of Foot Health Status Questionnaire pain.[43] The improvement seen in the PA group in Study 4 could be the result of a combination of regression to the mean and the placebo effect from entering the study.[123] Therefore, the importance of foot orthoses and patient advice cannot be concluded based on this PhD and the lack of superiority of PAX compared to PA could be derived from an insufficiency of exercises rather than the effect of the intervention used in PA. Yet, this type of treatment approach is minimally invasive, inexpensive, and could easily fit into a general practice setting.

Despite PAXI was superior to PA, PAXI was not superior to PAX in Study 4 (Riel et al. *in preparation*). When patients are aware of receiving an additional treatment, part of the effect of that treatment will be a placebo effect when they believe the treatment might be to their benefit.[123] The placebo effect of believing that patients received an effective treatment among patients with plantar fasciopathy was investigated in a randomised trial that compared two groups that both received a sham shockwave

intervention.[124] One group was informed that the treatment was effective while the other group was told that the treatment was a sham. After 6 weeks, the participants who believed in the efficacy of the treatment experienced a significantly larger pain reduction. Not only did the participants of PAXI receive an extra treatment compared to PAX; they also had an additional consultation with an experienced rheumatologist at a private clinic which could have introduced a larger placebo effect. However, corticosteroid injection has been found to be superior to a placebo injection and serves a purpose in plantar fasciopathy management. When used in isolation, the short-term effects are well-documented.[43,48–50] The difference between the improvement trajectory of the participants in Study 4 and those of previous studies investigating the effects of corticosteroid is that participants of PAXI experienced a constant improvement over time whereas studies that use an injection with no heavy-slow resistance training find a large short-term improvement but after this, the curve flattens or patients even experience a slight deterioration.[43,48,49] This indicates an interaction between the injection and the heavy-slow resistance training. Several participants in Study 3 reported that the exercise became less painful to perform after having received the injection.[55] Nevertheless, PAXI was not superior to PAX. An important consideration before injecting a patient with corticosteroid is that patients often ask for an immediate pain reduction. Yet, daily monitoring of heel pain in Study 3 did not support a pain reduction within the first week after the injection and Study 4 did not find a clinically relevant superiority of PAXI versus PA.[55] (Riel et al. *in preparation*) Therefore, it should be carefully considered and discussed with the patient whether a painful injection is worthwhile.

Study 4 was the first ever study to investigate the effect of heavy-slow resistance training compared to heavy-slow resistance training and an ultrasound-guided corticosteroid injection, yet, the effect of a combination of strength training and stretching has been compared against either a corticosteroid injection alone or a corticosteroid injection and strength training and stretching before.[113] That study found that the combination of an injection and strength training with stretching was superior to the other two groups. There are several differences between Johannsen et al. and Study 4. They used six resistance training and stretching exercises that participants were instructed in performing on four different occasions by a physiotherapist. In Study 4, participants received a single exercise instruction to perform a single exercise. Furthermore, a single injection was used in Study 4 whereas up to three repeated injections were used in the aforementioned study.[57] Repeated injections may increase the risk of plantar fascia rupture as corticosteroid affects the and mechanical properties of collagen tissue.[47,109] Johannsen et al. did not record any severe adverse events or plantar fascia ruptures and a Cochrane-review concluded that an ultrasound-guided corticosteroid injection was a safe treatment in this patient population, thus, repeated corticosteroid injections may be an area worth of further exploration.[50,113] In Study 3, participants were offered an additional injection if they were not satisfied after 8 weeks, however, only 4 out of 13 participants who were

eligible for this agreed to the second injection.[55] Therefore, it may only be feasible for some.

The long-term effects of corticosteroid injection should be monitored closely. Despite the significant superiority after 12 weeks of PAXI compared to PA, there might be a risk of larger recurrence rates when among patients who have received an injection. (Riel et al. *in preparation*) In a randomised trial of patients with lateral epicondylalgia, the group that had received a corticosteroid injection had a significantly larger 1-year recurrence compared to the group that received a placebo injection.[52] Albeit, recurrences among patients with plantar fasciopathy who have received a corticosteroid injection appear less frequent and at the 1-year follow-up in the study by Johannsen et al., the group that received both exercises and a corticosteroid injection was still superior compared to the other two groups.[50,113] Still, the 6-month and 12-month follow-ups of Study 4 will shed additional light on the long-terms effects of corticosteroid injection and heavy-slow resistance training.

In addition to evaluating results based on statistical significance, the minimal important difference of FHSQ pain was used as another factor to form the basis of conclusions in Study 2 and Study 4.[14] (Riel et al. *in preparation*) The minimal important difference of 14.1 points was calculated by Landorf and Radford based on the results of FHSQ pain and Global Rating of Change from 175 participants from two randomised trials that had investigated the effects of conservative treatments.[105] An important point that must be considered is that the minimal important difference was calculated in a different setting and among Australians who had received conservative treatments. Danish individuals with plantar fasciopathy who have received more invasive treatments may need either a larger or smaller improvement for it to be considered an important improvement. If the minimal important difference is calculated based on the data from Study 4 using the same methods applied by Landorf et al., the minimal important difference of Foot Health Status Questionnaire pain is 9.9 (95%CI: 0.4 to 19.4) points (data not presented in chapter 5.3). This difference is smaller than the minimal important difference found by Landorf et al., albeit still larger than the between-group difference of PAXI and PA. (Riel et al. *in preparation*) Another limitation of using minimal important differences is that there is a discrepancy between using a Global Rating of Change that asks participants to rate improvement compared to the start of the treatment and the Foot Health Status Questionnaire that asks participants about their current symptoms. The use of a Global Rating of Change has been criticised for introducing recall bias, however, there is no consensus on how to best calculate a minimal important difference.[125] It is, however, important to consider if statistically significant between-group differences are of importance for patients as statistical significance may be reached by simply increasing sample size and only informs about the confidence that the results were not found by chance.[126] Involving participants into the interpretation of the results may add an important aspect regarding how the results should be perceived and if small differences in improvement make the extra effort worthwhile for patients.

In recent years, there has been a trend towards large high-quality randomised trials investigating treatments for musculoskeletal conditions finding no clinically relevant superiority of one treatment over the other. This has been the case for studies of individuals with plantar fasciopathy, patellofemoral pain, Achilles tendinopathy, patellar tendinopathy, and rotator cuff tendinopathy.[42,43,127–130] Study 4 is yet another trial that cannot draw firm conclusions to support the future use of one treatment approach over another. (Riel et al. *in preparation*) This is in line with systematic reviews and network meta-analyses that aimed to establish which treatment was the most effective for plantar fasciopathy and Achilles tendinopathy, respectively.[45,131] Both reviews concluded that any treatment was better than placebo or wait-and-see, but there was no superiority between the other treatments included in the reviews. It appears that the better researchers are becoming at conducting trials using rigorous and transparent methods, the smaller the differences between treatment groups become. This may potentially lead to making clinical guidelines more difficult; however, it reflects clinical practice. Tailoring treatment to the individual patient is considered an important part of clinical practice and evidence-based medicine consists of both research, clinical expertise and patient values.[132] Patients are more than a diagnosis and many bio-psycho-social factors come into play that makes any given treatment more or less successful when applied to a specific patient. This is potentially what the recent trials are reflecting when they find that no treatment is superior as there are large differences in how individuals respond to those treatments. It is critical that clinicians are aware of these nonuniform treatment responses as they may emphasise the importance of tailoring treatment. One way to support clinical decision-making could be to explore if certain characteristics of patients are predictive to the outcome of a given treatment. McClinton et al. identified symptom duration as a predictor of a successful outcome of a physical therapy intervention where participants with a symptom duration <7.2 months were more likely to respond to treatment compared to those with a longer symptom duration. They did not find that age or BMI were predictive of treatment outcome.[38] Further exploration of how different patient characteristics may be associated with prognosis could lead to the development of prognostic tools that can aid the clinical decision-making. Such tools have been developed for low back pain and for pediatric pain, and is currently being developed for adolescent knee pain, but not for individuals with plantar fasciopathy.[133–135] Stratified care could lead to improved outcomes and hinder expensive and time-consuming treatments are applied to patients who are likely to benefit from a minimally invasive intervention such as advice on load management and a silicone heel cup.

Exercises and an injection with corticosteroid share the same focus on targeting structural changes. In the case of plantar fasciopathy, these treatments aim to remodel the plantar fascia. However, a shift away from focussing on structures among individuals with non-traumatic musculoskeletal pain has been proposed recently.[136] Rather than trying to normalise structural changes through interventions designed to do so, it might be better to adopt the same approach to management such as what is

currently being used in other chronic health conditions (e.g. advice on sleep, physical activity, nutrition, and stress). In Study 2, there was no association between change according to FHSQ pain and change in plantar fascia thickness, and in Hansen et al. 2018 participants who had been pain free for years remained to have an increased plantar fascia thickness compared to the average thickness among people with no history of plantar fasciopathy.[14,29,36] This indicates that focus should not be placed on structures but on the patient as a whole. Considering the current inability to find treatments for musculoskeletal conditions that show superiority, the exploration of an alternative management might be merited.

CHAPTER 7. CONCLUSIONS AND FUTURE PERSPECTIVES

The overarching aim of this PhD was to further explore and develop the role of heavy-slow resistance training in the management of individuals with plantar fasciopathy. Despite preliminary evidence to support superiority of heavy-slow resistance training over stretching, the findings of this PhD do not support widespread implementation of heavy-slow resistance training for acute or medium-term pain relief. Only when combined with an ultrasound-guided corticosteroid injection heavy-slow resistance training was superior to not performing exercises. Yet, this difference was only statistically significant and did not reach the minimal important difference of the Foot Health Status Questionnaire pain domain and clinician experiences and patient preferences should be a strong factor in deciding on treatment. These findings are in line with recent findings within plantar fasciopathy research as well as research conducted on patients with other chronic musculoskeletal conditions that do not support the use of one treatment over another. It remains unknown if stratified care using prognostic tools or reframing current care for patients with plantar fasciopathy could help improve outcomes, but this is an area worth further exploration.

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APPENDICES

Appendix A: Riel H, Vicenzino B, Jensen MB, Olesen JL, Holden S, Rathleff MS. The effect of isometric exercise on pain in individuals with plantar fasciopathy: A randomized crossover trial. *Scand J Med Sci Sport*. 2018;28(12):2643-2650. doi:10.1111/sms.13296

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Appendix D: Riel H, Vicenzino B, Olesen JL, Jensen MB, Ehlers LH, Rathleff MS. Corticosteroid injection plus exercise versus exercise, beyond advice and a heel cup for patients with plantar fasciopathy: Protocol for a randomised clinical superiority trial (the FIX-Heel trial). *Trials*. 2020;21(1):5. doi:10.1186/s13063-019-3977-0

Appendix E: Riel H, Vicenzino B, Olesen JL, Jensen MB, Ehlers LH, Rathleff MS Corticosteroid Injection plus Exercise versus Exercise, beyond Advice and a Heel Cup for Patients with Plantar Fasciopathy: a Randomised Clinical Superiority Trial (The FIX-Heel Trial). (*in preparation)*

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ORIGINAL ARTICLE

WILEY

The effect of isometric exercise on pain in individuals with plantar fasciopathy: A randomized crossover trial

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Isometric exercise is commonly recommended for immediate pain relief in individuals suffering from lower limb tendinopathies, despite the limited evidence supporting its analgesic effect. Due to the similarities between plantar fasciopathy and tendinopathies, the aim of this trial was to investigate the acute effect of isometric exercise on pain, compared to isotonic exercise, or walking, in individuals with plantar fasciopathy. We recruited 20 individuals with plantar fasciopathy for this prospectively-registered, participant-blinded, randomized, superiority crossover trial (ClinicalTrials.gov: NCT03264729). Participants attended three exercise sessions (isometric, isotonic, or walking) in a randomized order, within a 2-week period. Both isometric and isotonic exercises were performed standing with the forefoot on a step bench, while walking was performed barefoot. The primary outcome was pain (measured on a 0-100-mm VAS) during a pain-aggravating activity. Secondary outcomes included pressure pain threshold (PPT) under the heel, and plantar fascia thickness (PFT). All outcomes were measured before and after each exercise session. There were no significant differences between the three exercises on pain ($P = 0.753$), PPTs ($P = 0.837$), or PFT ($P = 0.718$). Further, there was no change in pain from before to after any of the exercises (isometric exercise 2.7 mm [95% CI: −12.2; 6.8], isotonic exercise −3.4 mm [95% CI: −5.0; 11.8], or walking 1.6 mm [95% CI: −16.1; 12.9]). Contrary to expectations, isometric exercise was no better than isotonic exercise or walking at reducing pain in individuals with plantar fasciopathy. None of the exercises induced any systematic analgesic effect.

KEYWORDS
exercise, pain, plantar fasciopathy, tendinopathy

1 | INTRODUCTION

Patients with plantar fasciopathy (PF), a condition affecting one in 10,[1-4] often report a sharp heel pain. The pain is usually intense during the first steps in the morning or after periods of inactivity, and improves with ambulation but can worsen during the day.[5]

Resistance exercise is commonly prescribed for patients with musculoskeletal pain[6] and is effective in long-term pain reduction in patients with tendon pain.[7] As such, there is strong evidence (systematic reviews) supporting loaded exercise programs as treatment for both Achilles and patellar tendinopathy.[8,9] Preliminary evidence suggests that PF also responds favorably to a loading program.[10]

Rio et al[11] found that isometric exercise reduced pain during an aggravating task, compared to isotonic (or dynamic) resistance exercise, in six male volleyball players with patellar tendinopathy. This is the only available published

study evaluating the acute analgesic effect of different resistance exercises in patients with lower limb tendinopathy. Despite the limited evidence, isometric exercise is now recommended for lower limb tendinopathies.[12] The immediate effect of similar exercises on pain has not been examined in PF. As they require minimal equipment or time, these simple exercises could be valuable to help patients manage their pain, if effective.

The aim of this trial was to compare the acute analgesic effect of isometric resistance exercise, isotonic resistance exercise, and walking, in participants with plantar fasciopathy. We hypothesized that isometric exercise would induce more analgesia than isotonic exercise or walking.

2 | MATERIALS AND METHODS

2.1 | Study design

This trial was a randomized crossover, participant-blinded, superiority trial, prospectively registered on clinicaltrials.gov (ID: NCT03264729), conducted in Aalborg, Denmark. Participants were blinded to the hypotheses and, thus, did not know which exercise was hypothesized to reduce pain the most. Reporting of this trial follows CONSORT guidelines for reporting non-pharmacologic treatments[13] and TIDieR for intervention description.[14,15] The trial was approved by the Ethics Committee of the North Denmark Region (Project ID: N-20170021) prior to recruitment.

2.2 | Participants

Participants were recruited through advertisement on Facebook. Potentially eligible participants were screened by telephone and subsequently invited to a clinical examination to ensure they met the inclusion criteria (outlined below). The assessor, who was responsible for inclusion, exercise instructions, and data collection, was a registered physiotherapist with 6 years of experience in treating patients with musculoskeletal disorders. Written informed consent was obtained prior to the physical examination. The inclusion and exclusion criteria were applied as follows (in line with previously published criteria in plantar fasciopathy)[16]: history of inferior heel pain for at least 3 months before enrollment; pain on palpation of the medial calcaneal tubercle or the proximal plantar fascia; thickness of the plantar fascia of 4.0 mm or greater; pain during at least one of three pain-aggravating activities (static stance, half squat, and heel raise); and mean heel pain of ≥20 mm on a 100-mm Visual Analogue Scale (VAS; 0 mm = no pain, 100 mm = worst pain imaginable) during the past week. The exclusion criteria were: below 18 years of age; history of inflammatory systemic diseases; pain or stiffness in the 1st metatarsophalangeal joint to an extent where the exercises cannot be performed; prior heel surgery; pregnancy; pain medication; and corticosteroid injection for PF within the past 6 months. The procedure for the three single-leg pain-aggravating activities is described in detail below.

- The static stance was performed for 30 seconds. Participants were allowed to stabilize themselves by placing a hand on the wall.
- The half squat was performed with the participant flexing the knee of the stance leg to 45-degree knee flexion. The test was performed for 10 repetitions with a 1-second eccentric phase and a 1-second concentric phase.
- The heel raise was performed with participants performing a maximal plantar flexion of the ankle joint with the knee in full extension. The test included 10 repetitions with a 1-second eccentric phase and a 1-second concentric phase. Based on a previous study[17], we expected that 88% of participants would experience pain aggravation from at least one of these tests.

Participants provided a pain rating by marking a 100-mm line anchored left with "No pain" and right with "Worst pain imaginable" immediately after termination of each of the tests. In cases where bilateral pain was present, the most affected side was used for investigation.

2.3 | Intervention

Participants attended three sessions (isometric, isotonic, and walking) over the course of 2 weeks. The order of the exercises was randomized for all participants, using a Williams Design, with six different potential exercise sequences (eg, A-B-C, B-C-A, C-A-B).[18] The allocation sequence was generated using a random number generator on www.random.org by an independent researcher not involved in the study, who placed them into sequentially numbered opaque sealed envelopes. The assessor was blinded to the allocation sequence and assigned each participant to the next envelope upon inclusion. There was a minimum 48-hour interval between sessions, with all three being completed within a 2-week period. Participants performed the sessions at approximately the same time (within ±1 hour) to account for any variations according to time of day.

Participants were instructed in the first of the three exercises after being diagnosed, randomized, having baseline outcomes assessed, and having performed the aggravating activity. The isometric and isotonic exercises were a heel raise, performed standing with the forefoot on a step (full details are outlined in Table 1).[19] The load used for either the isometric or isotonic session was determined on the same day as the respective type of exercise was performed. The load for the isometric exercise was determined by instructing participants to find a load they would be able to

TABLE 1 Exercise descriptors

	Isotonic heel raise	Isometric heel raise
1. Load magnitude	8 RM	As heavy as possible for 1 min
2. Number of repetitions	8	1
3. Number of sets	4	5
4. Rest in-between sets	2 min	2 min
5. Number of exercise interventions	1/d	1/d
6. Duration of the experimental period	1 d	1 d
7. Fractional and temporal distribution of the contraction	3 s concentric	0 s concentric
	2 s isometric	45 s isometric
	3 s eccentric	0 s eccentric
8. Rest in-between repetitions	No	No
9. Time under tension	8 s/repetition	45 s/repetition
	64 s/set	45 s/set
	256 s/total intervention	225 s/total intervention
10. Volitional muscular failure	Yes	No
11. Range of motion	65° from 20° dorsiflexion to 45° plantar flexion	Static (0°)
12. Recovery time in-between exercise sessions	≥48 h	≥48 h
13. Anatomical definition of the exercise (exercise form)	Participant was standing with the forefoot on a step. The toes were maximally dorsiflexed by placing a towel underneath them. The participant was instructed to perform a heel raise to maximal plantar flexion in the ankle joint and afterward to lower the heel to maximal dorsiflexion. Supporting oneself for balance by placing the hands on a wall or a rail was allowed. The contraction time was guided by a metronome	Participant was standing with the forefoot on a step. The participant was instructed to stand still with the ankle joint in neutral and hold this position. Supporting oneself for balance by placing the hands on a wall or a rail was allowed

endure for no more than 1 minute. Participants were able to try different exercise variations such as standing on one leg or by adding a backpack. They were allowed to use the different exercise variations for a self-selected period of time, until they felt confident that the correct load was found. The load for the isotonic exercise was 8-repetition maximum (RM), determined by instructing participants to find a load with which they would only be able to perform 8 repetitions (ie, 8-RM). If the participant's bodyweight was inadequate to reach sufficient loading, the participant was fitted with a backpack with books or weights. The walking session was performed barefoot, participants were instructed in walking at a pace they would use when walking at home. The duration was 4 minutes, to match the contraction time of the exercises.

To promote retention, participants were offered to be instructed in performing exercises with the purpose of long-term recovery after they had completed the trial.[10] If a participant would withdraw from the trial prematurely (eg, if they were unable to perform the activities or withdrew consent) they would be excluded from the data analysis.

All intense activities that were unusual to the participant in duration and load were prohibited for the 48 hours prior to each session. Participants were not allowed to receive treatment for PF during the course of participation in the trial.

2.4 | Outcomes

The primary outcome was pain experienced during the most pain-aggravating activity found during screening, measured on a 100-mm VAS (0 mm = no pain, 100 mm = worst pain imaginable).

Secondary outcomes included (a) thickness of the plantar fascia measured by ultrasound; (b) pressure pain threshold (PPT) on the most painful spot under the heel; and (c) pain

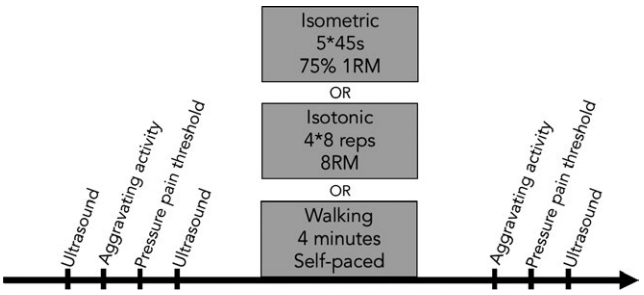

FIGURE 1 Flow chart of measurements

TABLE 2 Baseline participant characteristics

Women (%)	18 (90)
Age (y)	48.9 (12.3)
Height (cm)	169.7 (8.0)
Weight (kg)	90.1 (14.3)
BMI (kg/m^2)	31.3 (4.8)
Weekly sports participation (min)[a]	255.0 (90-360)
Symptom duration (mo)[a]	8.5 (6-19.5)
Pain during past week/100 mm	64 (18.2)
Bilateral pain (%)	7 (35)
Plantar fascia thickness (mm)	5.9 (1.1)

Data are presented as mean (SD) or count.
[a]Indicates median (inter-quartile range).

(measured on a 100-mm VAS) during the exercise sessions (isometric, isotonic and walking sessions). After completion of each session, participants rated their average pain experienced during the session.

Outcomes were evaluated in the same order before and after each session, as shown in Figure 1.

First, the plantar fascia thickness was measured using ultrasound (SonoSite M-Turbo® [FUJIFILM SonoSite, Inc, Washington, DC, USA]), with a 6-13 MHz transducer frequency (see web-Figure S1 for a sample image of the ultrasound measurement). The participant was lying in prone, with the toes dorsiflexed against the examination table while a longitudinal scan was performed. The average of three consecutive measurements was used for analysis. This method has established reliability (ICC = 0.67-0.77).[20] This was chosen as an outcome to investigate if there were changes in plantar fascia thickness in response to the exercises. To investigate if the aggravating activity and PPT measurement influenced plantar fascia thickness, an ultrasound measurement was performed both before and after aggravating activity and PPTs (Figure 1).

Pressure pain thresholds were measured using a hand-held mechanical pressure algometer (Somedic, Hörby, Sweden) with a 1-cm^2 probe on the most painful spot under the heel (found by palpation). This was conducted with the participant lying in prone on the examination table, with the feet hanging freely over the end of the table. The probe was placed perpendicular to the skin, and pressure was increased gradually at a rate of 30 kPa/s. Participants were instructed to press a hand-held switch when the sensation changed from pressure, to the first onset of pain. This was repeated three times, with a 30-second break between tests, and the average being used for the analysis. This was chosen as an outcome to provide a reliable measure of pain sensitivity.[21] Pressure pain threshold testing under the heel in patients with PF has been found to have a good intrarater reliability (ICC = 0.75-0.92).[22]

2.5 | Sample size estimation

We expected a 19-mm greater reduction on VAS in the isometric exercise compared to the isotonic exercise (with 19 mm being considered the the minimally important difference in this patient population).[23] Based on a standard deviation of 19 mm (similar to the overall standard deviation found in the study by Rio et al[11]), a two-sided 5% significance level and a power of 80%, a sample size of 16 participants would be necessary. Despite an effect size of 4.64 in the study by Rio et al, we aimed to include 20 participants to account for a potentially greater variability due to a more heterogeneous patient population compared to Rio et al.

2.6 | Statistical analyses

All statistical analyses were pre-specified. We assessed normality using Q-Q plots. The assumption of negligible carryover effects was investigated with preliminary unpaired *t* tests.[24] The primary analysis (investigating the effect of isometric vs isotonic exercise vs walking on pain during aggravating activity) was undertaken with a 3×2 repeated measures ANOVA. Independent factors were exercise type (isometric vs isotonic vs walking) and time (pre vs post). Dependent variable was pain.

Additionally, the proportion of participants achieving a clinically relevant pain reduction was calculated for each exercise. It was defined a priori that no conclusions would be made favoring any of the exercises, unless pain was reduced more than the clinically important difference (19-mm VAS).[23]

Analysis of secondary outcomes (plantar fascia thickness, and PPTs) was done using 3×2 repeated measures ANOVA (factors as above). Pain during exercises was examined using a one-way repeated measures ANOVA, with exercise (isometric, isotonic, or walking) as the independent factor, and pain (VAS) as the dependent variable.

As plantar fascia thickness was measured after the other measurements, paired t-tests of plantar fascia thickness measurements were used to determine if the aggravating activity and PPT impacted plantar fascia thickness. Pearson's correlation coefficient was used to test the association between change in plantar fascia thickness and the pain reduction during exercise. All statistical analyses were performed according to a pre-established analysis plan (clinicaltrials.gov: NCT03264729) using STATA ver. 14 (StataCorp LLC, College Station, TX, USA).

3 | RESULTS

Participants were recruited between August and September 2017, with the final follow-up conducted in October 2017.

TABLE 3 Outcomes measured before, during and after the exercises and comparisons between exercises

	Before	During	After	Mean change from before to after
Isometric				
Pain (0-100-mm VAS)	29.0 (24.1)	32.4 (26.1)	31.7 (30.7)	2.7 (20.4)
Pressure pain threshold (kPa)	384.5 (207.2)	N/A	383.7 (229.7)	−0.9 (111.6)
Plantar fascia thickness (mm)	5.7 (1.1)	N/A	5.7 (1.2)	−0.1 (0.3)
Isotonic				
Pain (0-100 mm VAS)	34.0 (24.8)	42.3 (29.5)	30.6 (26.4)	−3.4 (17.9)
Pressure pain threshold (kPa)	389.2 (205.0)	N/A	388.4 (230.0)	−0.9 (145.9)
Plantar fascia thickness (mm)	5.9 (1.1)	N/A	5.8 (1.1)	−0.1 (0.3)
Walking				
Pain (0-100-mm VAS)	35.5 (27.1)	33.5 (21.9)	37.1 (26.7)	1.6 (30.9)
Pressure pain threshold (kPa)	435.6 (249.9)	N/A	413.0 (252.7)	−22.6 (88.1)
Plantar fascia thickness (mm)	5.9 (1.3)	N/A	5.7 (1.2)	−0.2 (0.4)
Exercise comparisons				
Mean differences (95% CI)				
	Change in pain	**Pain during exercise**	**Pressure pain threshold**	**Plantar fascia thickness**
Isometric vs isotonic	6.1 (−3.9 to 16.1)	−9.9 (−23.0 to 3.2)	0.0 (−77.1 to 77.0)	0.1 (−0.2 to 0.3)
Isometric vs walking	1.1 (−14.6 to 16.8)	−1.1 (−15.5 to 13.3)	21.7 (−32.7 to 76.1)	0.1 (−0.1 to 0.4)
Isotonic vs walking	−5.0 (−21.7 to 11.7)	8.8 (−3.7 to 21.3)	21.7 (−43.8 to 87.3)	0.1 (−0.1 to 0.2)

Data are presented as mean (SD) unless otherwise stated

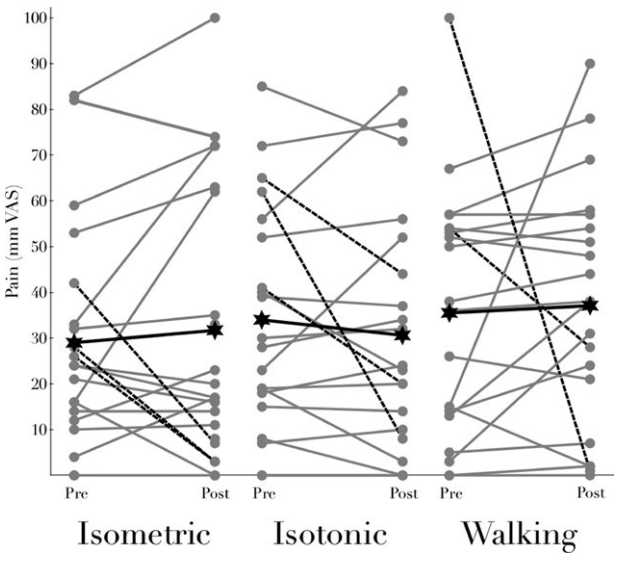

FIGURE 2 Individual participant data on pain during the aggravating activity before and after the exercises. The stars depict mean pain. Dotted lines show clinically relevant pain reductions

Twenty-eight potential participants responded to the advertisement, with 26 eligible for clinical examination. Of these, two declined, one had no pain during any of the aggravating activities, one had a mean heel pain during the past week <20mm VAS, and one had a plantar fascia thickness <4.0 mm. One participant was withdrawn after inclusion due to illness. Baseline characteristics of the included 20 participants are presented in Table 2.

Fifteen participants had sought medical care for their pain, all of whom had been in contact with their general practitioner. Ten participants had been treated by a physiotherapist, which was the second most common healthcare personnel that had been contacted. Other treatment providers were medical specialists (n = 3), acupuncturists (n = 3), chiropractors (n = 2), craniosacral therapist (n = 1), massage therapist (n = 1), and reflexologist (n = 1). Three of the 15 participants who were in the work force had taken time (5-548 days) off work because of heel pain. For the aggravating activity, 15 participants felt most pain during heel raise, three during half squat, and two during static stance.

3.1 | Primary analysis

There was no significant exercise type × time interaction for pain during the pain-aggravating activity ($F(1,95) = 0.28$, $P = 0.753$; Figure 2). Despite all participants reporting pain during at least one of the aggravating activities during eligibility screening, two participants felt

no pain during the aggravating activity before either of the exercises. In three participants the isometric and isotonic exercises led to clinically relevant pain reductions (reduction ≥19 mm) while the walking sessions led to clinically relevant pain reductions in two participants. Two participants experienced clinically relevant pain reductions after both the isometric and isotonic exercises. To test the robustness of our findings, we also used a nonparametric statistical analysis which supported our pre-determined primary analyses (full nonparametric analyses can be seen in web-Appendix S1).

3.2 | Secondary analyses

There were no significant interactions for pain during exercises ($F(2,38) = 1.45$, $P = 0.248$), for PPT ($F(1,95) = 0.18$, $P = 0.837$) or for plantar fascia thickness ($F(1,95) = 0.33$, $P = 0.718$; Table 3). There was no association between change in pain and change in plantar fascia thickness ($r = 0.15$, $P = 0.266$). Performing the aggravating activity and the PPT test had no effect on the plantar fascia thickness during either session (mean difference = 0.1 mm, 95% CI: −0.1 to 0.2, $P = 0.482$; mean difference = 0.0 mm, 95% CI: −0.2 to 0.2, $P = 0.763$; and mean difference = −0.1 mm, 95% CI: −0.3 to 0.0, $P = 0.124$).

4 | DISCUSSION

This was the first trial comparing the acute analgesic effect of different types of resistance exercise and walking, in participants with PF. Contrary to expectations, isometric exercise was not better than isotonic exercise or walking at reducing pain with none of the exercises inducing any systematic analgesic effect.

4.1 | The role of isometric exercise in PF

Participants had a varied response to isometric exercise. As only three of 20 participants had a clinically relevant pain reduction, isometric exercises can only be recommended on a trial and error basis. Similar results were seen in the isotonic exercise. The effect of walking was similar to that of the resistance exercises, but less time consuming as there were no rest periods.

This trial investigated the acute pain-relieving effect of exercises and walking. Loading programs are often an important part of long-term management of tendinopathies.[7-10] The acute effect may be different to long-term treatment effects, and we still lack data on loaded exercises in PF. The type of loading may be less important than the load itself as no difference between heavy slow resistance training and eccentric training was found in patients with Achilles tendinopathy and no difference between an isometric and an isotonic program was found in patients with patellar tendinopathy.[7,25] Isotonic exercise has been found to be superior to stretching in PF[10] and other types of loading could be tested to provide clinicians with an alternative potentially based on patient preferences as there was no difference in pain during the exercises of our present trial. The effects of other types of loading need to be investigated in PF before they can be recommended in clinical practice.

4.2 | Comparison with previous studies

Rio et al[11] found a superior analgesic effect of isometric exercise. Their study included six male young athletic volleyball players, whereas the 20 participants in the current study were older and primarily female. This may partially explain differences in results between the studies. Younger people have greater exercise-induced hypoalgesia than older people, and males generally respond better to isometric exercise than females.[26,27] Additionally, participants of the current study had a median symptom duration of 8.5 (IQR: 6-19.5) months. This indicates a chronic state, although symptom duration was not reported in the study by Rio et al.[11] Patients with chronic pain often demonstrate lesser response to exercise than healthy individuals.[28,29] Participants responded variably to the isometric exercise similar to what has been demonstrated in patients with lateral epicondyalgia.[30] This highlights the need for research to determine which patient groups will benefit from isometric exercise, as findings in one type of tendinopathy may not necessarily be generalizable to others.

4.3 | Strengths and limitations

This trial was prospectively registered on clinicaltrials.gov. The number of repetitions, sets, and contraction time of the isometric exercise matched those used by Rio et al[11], to replicate their methods. Nonetheless, the load magnitude could have been different as Rio et al used isokinetic dynamometry to determine the target load while we used a more pragmatic method to achieve a load of 70%-75% 1-RM. This method was chosen to make the protocol more clinically applicable. Additionally, two participants did not feel pain during the aggravating activity after inclusion. This made a pain reduction impossible and could have lead to a slight underestimation of analgesic effect. Even though the aggravating activities did not cause pain before exercise on every occasion, the lack of change in PPTs supports the conclusion that neither of the exercises had an acute analgesic effect. Load determination was performed on the same day as testing which introduced a slight variation in overall training volume between participants.

5 | PERSPECTIVE

Contrary to what was hypothesized based on previous research in patellar tendinopathy[11], isometric exercise was no better than isotonic exercise or walking in reducing pain in individuals with plantar fasciopathy. Neither of the exercises or walking had a consistent acute analgesic effect, or change in pain sensitivity. This suggests that findings in one type of tendinopathy may not necessarily be generalizable to others and isometric exercise should not be prescribed for immediate pain relief in individuals with plantar fasciopathy. As previous research of other lower limb tendinopathies has not found superiority of one resistance type over the other,[7,25] isometric exercise could play a role in the long-term management of PF. However, the long-term effects of different loading programs in PF remain to be investigated.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Research

Self-dosed and pre-determined progressive heavy-slow resistance training have similar effects in people with plantar fasciopathy: a randomised trial

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KEY WORDS

Tendinopathy
Plantar fasciopathy
Exercise
Rehabilitation
Strengthening

ABSTRACT

Question: For people with plantar fasciopathy, is a 12-week self-dosed heavy-slow resistance training program more beneficial than a 12-week pre-determined heavy-slow resistance training program? **Design**: A randomised trial with concealed allocation, partial blinding, and intention-to-treat analysis. **Participants**: Seventy people with plantar fasciopathy confirmed on ultrasonography. **Intervention**: Both groups performed a repeated heel raise exercise in standing for 12 weeks. Participants in the experimental group were self-dosed (ie, they performed as many sets as possible with as heavy a load as possible, but no heavier than 8 repetition maximum). The exercise regimen for the control group was pre-determined (ie, it followed a standardised progressive protocol). **Outcome measures**: The primary outcome was the Foot Health Status Questionnaire pain domain. Secondary outcomes included: a 7-point Likert scale of Global Rating of Change dichotomised to 'improved' or 'not improved'; Patient Acceptable Symptom State defined as when participants felt no further need for treatment; and number of training sessions performed. **Results**: There was no significant between-group difference in the improvement of Foot Health Status Questionnaire pain after 12 weeks (adjusted MD −6.9 points, 95% CI −15.5 to 1.7). According to the Global Rating of Change, 24 of 33 in the experimental group and 20 of 32 in the control group were improved (RR = 1.16, 95% CI 0.83 to 1.64). Only four participants achieved Patient Acceptable Symptom State: three of 35 in the experimental group and one of 35 in the control group. No significant between-group difference was found in the number of training sessions that were performed (MD −2 sessions, 95% CI −8 to 3). **Conclusion**: Self-dosed and pre-determined heavy-slow resistance exercise programs are associated with similar effects on plantar fasciopathy pain and other outcomes over 12 weeks. Advising people with plantar fasciopathy to self-dose their slow-heavy resistance training regimen did not substantially increase the achieved dose compared with a pre-determined regimen. These regimens are not sufficient to achieve acceptable symptom state in the majority of people with plantar fasciopathy. **Registration**: ClinicalTrials.gov NCT03304353. **[Riel H, Jensen MB, Olesen JL, Vicenzino B, Rathleff MS (2019) Self-dosed and pre-determined progressive heavy-slow resistance training have similar effects in people with plantar fasciopathy: a randomised trial. *Journal of Physiotherapy* ■:■–■]**

Introduction

Plantar fasciopathy is one of the most prevalent musculoskeletal conditions and will affect one in every ten people during their lifetime.[1] The condition was formerly labelled as 'plantar fasciitis' but due to histological findings similar to those of tendinopathies, long-standing plantar fasciopathy is now considered a tendinopathy.[2–4] The condition is characterised by severe and well-localised pain that often persists for several months or even years.[5] People with plantar fasciopathy report pain during the first steps in the morning or after inactivity, which improves with ambulation and worsens during the day.[6] Runners and 40 to 60-year-old people with low activity levels and high body mass index are the most prone to plantar fasciopathy.[7,8] The condition also affects mental health and as many as one in five people will have several days of sick leave due to their pain.[9–11]

A recent systematic review and network meta-analysis evaluated the comparative effectiveness of commonly used treatments for plantar fasciopathy and none was superior to any other.[12] A new approach not included in that review is heavy-slow resistance training, which involves repeated slow contractions through concentric, isometric and eccentric phases against a heavy load. Heavy-slow resistance training is often used for other tendinopathies, despite uncertainty about the optimal regimen.[13–17] Preliminary

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Table 1
Mechanobiological descriptors of the exercise interventions.

Descriptor	Exercise programs	
	Experimental	Control
Load magnitude	As heavy as possible, but no heavier than a weight that can be lifted at least 8 times (8RM)	Week 1+2: 12RM Week 3+4: 10RM Week 5+: 8RM
Number of repetitions	≥ 8 depending on the load	Week 1+2: 12 Week 3+4: 10 Week 5+: 8
Number of sets	As many as possible	Week 1+2: 3 Week 3+4: 4 Week 5+: 5
Rest between sets	2 min	
Session frequency	3.5/week	
Duration of program	12 weeks	
Contraction modes within one repetition	3 s concentric, 2 s isometric, 3 s eccentric	
Rest between repetitions	Nil	
Time under tension	8 s/repetition, ≥ 64 s/set, ≥ 64 s/training session Total over 12 weeks: varies between participants depending on number of sets performed	Week 1+2: 8 s/repetition, 96 s/set, 288 s/training session Week 3+4: 8 s/repetition, 80 s/set, 320 s/training session Week 5+: 8 s/repetition, 64 s/set, 320 s/training session Total over 12 weeks: 13 216 s
Volitional muscular failure	Yes	
Range of motion	Full range of motion	
Recovery between sessions	48 hours	
Anatomical definition of the exercise (exercise form)	The participant stood with the forefoot on a step. A towel was placed underneath the toes to dorsiflex them throughout the exercise. With a fully extended knee, the participant performed a heel raise to maximal plantarflexion in the ankle joint and afterwards lowered the heel to maximal dorsiflexion. Support for balance by placing the hands on a wall or a rail was allowed.	

RM = repetition maximum.

evidence found heavy-slow resistance training to be superior to stretching in plantar fasciopathy,[18] but the exercise dose was far lower than that prescribed in trials of other tendinopathies.[15,17,19–22] Increasing exercise dose could lead to greater improvement in outcomes through a greater mechanobiological stimulus.[23] One way to increase dose is to prescribe a larger exercise dose, but compliance is often compromised by low self-efficacy.[24,25] An alternative approach is to encourage patients to be in charge of their own rehabilitation and thereby increase exercise dose through increased self-efficacy.

Therefore, the research question for this randomised trial was:

For people with plantar fasciopathy, is a 12-week self-dosed heavy-slow resistance training program more beneficial than a 12-week pre-determined heavy-slow resistance training program?

Method

Study design

A randomised trial was conducted with concealed allocation, partial blinding and intention-to-treat analysis. Two 12-week heavy-slow resistance training regimens – one self-dosed and one pre-determined – were compared in people with plantar fasciopathy. Prior to recruitment the trial protocol, template informed consent forms and participant information were approved by the Ethics Committee of the North Denmark Region in accordance with the Declaration of Helsinki.[26] People provided written informed consent before enrolment. Reporting followed CONSORT and TIDieR guidelines.[27–29] The trial planning was performed in accordance with the PREPARE Trial guide.[30] Before inclusion of the first participant, the trial was registered on clinicaltrials.gov, where the trial protocol was made publicly available.

Participants, therapist, centre

People with plantar fasciopathy were recruited through Facebook advertisement or by referral from their general practitioner. Telephone screening was performed and individuals who fulfilled the criteria were invited to a clinical examination at the Research Unit for General Practice in Aalborg, Denmark. The primary investigator – who was responsible for inclusion, exercise instructions and data collection – was a registered physiotherapist with 6 years of experience in treating patients with musculoskeletal disorders. Inclusion criteria were: history of inferior heel pain for at least 3 months before enrolment; pain on palpation of the medial calcaneal tubercle or the proximal plantar fascia; thickness of the plantar fascia of ≥ 4.0 mm; and mean heel pain ≥ 20 mm on a 100-mm visual analogue scale during the previous week.[31] Exclusion criteria were: age < 18 years; diabetes; inflammatory systemic diseases;[31] pregnancy; prior heel surgery; or corticosteroid injection for plantar fasciopathy within the previous 6 months.

Randomisation

After eligibility had been confirmed, participants were stratified by gender and block randomised (block sizes of two to six) at 1:1 to the experimental group or the control group. A researcher not involved in the trial generated the allocation sequence using a random number generator on www.sealedenvelope.com and was the only person who knew the block sizes. After enrolment, the primary

investigator opened a sequentially numbered, opaque, sealed envelope in which the participant's group allocation was found.

Interventions

Both groups received standardised patient education, a silicone heel cup, and performed either a self-dosed or a pre-determined non-supervised exercise program.

Participants were told that the trial was about exercise for treating plantar fasciopathy and that there would be two groups that performed exercises in different ways. They were blinded to which of the outcomes was the primary outcome and to the differences between the heavy-slow resistance training programs.

Both groups were informed about plantar fasciopathy in terms of risk factors, aetiology, pathology, and were informed that heavy-slow resistance training was superior to stretching in plantar fasciopathy. Participants in the pre-determined group were informed that it was important to follow the program as closely as possible, whereas participants in the self-dosed group were told that (based on research on other tendinopathies) it was believed that performing the exercise as heavily as possible, but no heavier than 8 repetition maximum (RM), and with as many sets as possible would increase the likelihood of recovery. Both groups were told that compliance with their program was very important and associated with recovery. Participants were told that pain during exercise was not associated with tissue damage and that there was no upper limit of pain during exercise, as long as it was tolerable. The aim of this was to reduce any potential fear of exercise-related pain. Participants were advised to decrease their physical activity level and slowly rebuild it depending on their symptoms. They were also advised that it was acceptable to participate in physical activities that did not exacerbate symptoms that outlasted the activity. If participants already used a foot orthosis, they were allowed to continue wearing this if they did not want to use the heel cup. No concomitant treatments were allowed. Participants were contacted either by telephone or by e-mail 2 weeks after inclusion to ask if they had experienced difficulties with the exercise and to encourage them to continue the intervention.

Heavy-slow resistance training

Both groups performed standing heel raises. Participants in the experimental group were instructed to perform the exercise with the load as heavy as possible but no heavier than 8RM and for as many sets as possible. Participants in the control group were instructed to perform the exercise according to a rigid protocol progressing from 12RM to 8RM. This progressive protocol was similar to the protocol used by Rathleff et al,[18] where heavy-slow resistance training was found to be superior to plantar fascia stretching. Both groups performed exercises every second day during the 12-week intervention. The exercise descriptors are displayed in Table 1.[32] If participants felt they could perform more repetitions than their load corresponded to (eg, 10 repetitions when the load was supposed to be 8RM), a backpack with books to add weight was used.

Outcome measures

The primary outcome was change in the Foot Health Status Questionnaire (FHSQ) pain domain from Week 0 to Week 12. The FHSQ is a self-report questionnaire ranging from 0 (poor foot health) to 100 (optimum foot health) that assesses multiple dimensions of foot health and function across four domains with a total of 13 items and has a high reliability (ICC = 0.74 to 0.92).[33] Responses were entered into the FHSQ software, which calculated scores for each domain. A validated Danish translation of the FHSQ was used.[34]

Secondary outcomes included: the function, footwear and general foot health domains of the FHSQ; Global Rating of Change; plantar fascia thickness measured in millimetres; exercise compliance; Pain Self-Efficacy Questionnaire; Patient Acceptable Symptom State; and physical activity level measured by the International Physical Activity Questionnaire short version. All questionnaires were completed at Weeks 0, 4 and 12. The Global Rating of Change was collected at Week 12 and was used to measure participants' self-reported improvement on a 7-point Likert scale ranging from 'much improved' to 'much worse'. Participants were categorised as improved if they rated themselves as 'much improved' or 'improved' (categories 6 or 7) and categorised as not improved if they rated themselves from 'slightly improved' to 'much worse' (categories 1 to 5). Plantar fascia thickness was measured using ultrasonography at Weeks 0, 4 and 12. The participant lay prone with the toes maximally dorsiflexed on the examination table and a longitudinal scan was performed. An average of three measurements was used. This method has been found to be reliable in a previous study (ICC = 0.67 to 0.77).[35] Compliance was estimated based on the number of training sessions performed throughout the intervention, according to a training diary that participants were given at baseline. Patient Acceptable Symptom State was defined as when participants achieved a self-evaluated satisfactory result and felt that no further treatment was needed; hence, it was not necessarily a measure of complete recovery.[36–38] The Pain Self-Efficacy Questionnaire was used to measure change in self-efficacy; it ranges from 0 to 60, with lower scores indicating lower self-efficacy.[39] A reliable Danish validated translation of the questionnaire was used (ICC = 0.89).[40] The International Physical Activity Questionnaire short version was used to estimate time spent performing vigorous and moderate activities, and time spent walking during the past week measured in metabolic equivalent of task (MET)-minutes.[41,42]

Data analysis

Sample size was based on the ability to detect a minimum clinically important between-group difference at the 12-week follow-up of 14.1 points in FHSQ pain.[43] Based on a standard deviation of 20 points (comparable with standard deviations found in previous studies of this population),[31,44,45] a two-sided 5% significance level and a power of 80%, a sample size of 33 participants in each group was required. Taking into consideration that drop-outs may occur, 70 participants were included.

Statistical analyses were performed according to a pre-established analysis plan in consultation with a statistician and using commercial software.[a] Q-Q plots were used to assess data distribution. The primary intention-to-treat analysis tested between-group difference in FHSQ pain at the 12-week follow-up using a repeated measures ANCOVA with the outcome as the dependent variable, time (4 weeks and 12 weeks) as the within-subjects factor, group allocation as the between-subjects factor, and the baseline value as the covariate.[46] The same model was used to perform between-group comparisons of the other FHSQ domains, Pain Self-Efficacy Questionnaire, and plantar fascia thickness, with the respective outcome as the dependent variable. Due to non-normal distribution of the data, the between-group difference in the International Physical Activity Questionnaire short version was investigated using Mann-Whitney U test. The between-group difference in the number of training sessions performed was tested using independent *t*-tests. The relative risk (RR) was calculated for the dichotomised Global Rating of Change and the dichotomised Patient Acceptable Symptom State. Associations between Pain Self-Efficacy Questionnaire score and compliance, FHSQ pain score and plantar fascia thickness, and the association between compliance and FHSQ pain score were investigated using Pearson's correlation coefficient. In an intention-to-treat analysis, multiple imputation was used to handle missing outcome data and estimates from 10 imputed data sets were combined using Rubin's Rules.[47] A complete case analysis only including cases with no missing outcome data was performed as a sensitivity analysis.

Results

Compliance with the study protocol

All participants received the intervention (ie, prescription of their heavy-slow resistance training regimen) as randomly allocated. All

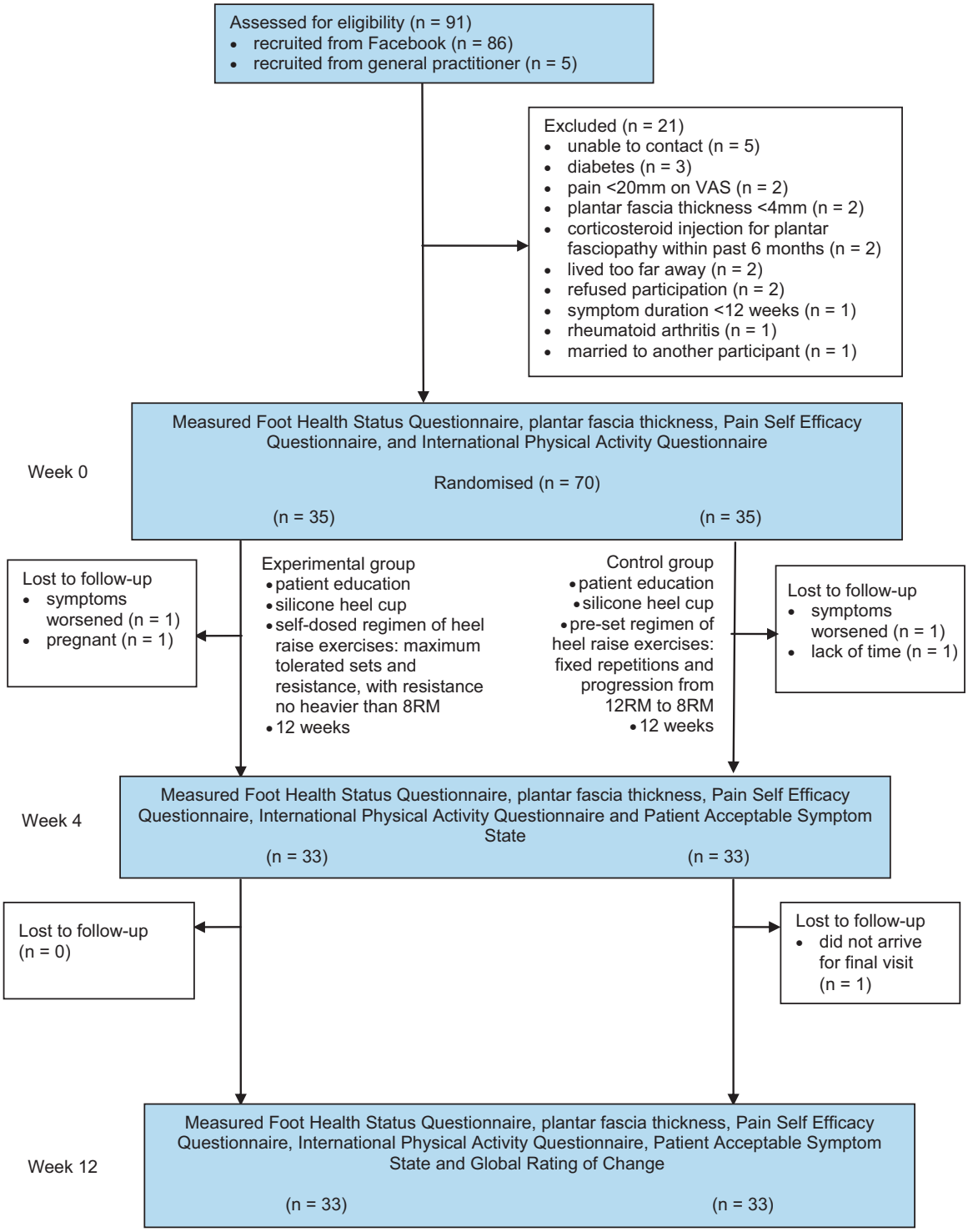

Figure 1. Design and flow of participants through the trial.
RM = repetition maximum, VAS = visual analogue scale.

registered outcomes were measured. However, 20 of 70 training diaries could not be retrieved.

Flow of participants through the study

A total of 91 individuals were interested in participation (Figure 1). Seventy participants were enrolled from October 2017 to February 2018, and the last 12-week follow-up was conducted in May 2018. Clinical and demographic baseline characteristics of the two groups were similar (Table 2). Fourteen participants (23% of those participants who had previously been in the workforce) reported that they had taken between one and 200 days off work due to plantar fasciopathy (median 30 days). Participants had consulted their general practitioner in 48 cases (69%) and 28 participants (40%) had consulted a physiotherapist. Foot orthoses were the most common treatment that participants had tried before enrolment (37 participants, 53%), with strengthening exercises including heel raises being the second most common treatment (36 participants, 51%). A full table of treatments and healthcare practitioners consulted is in Appendix 1 on the eAddenda.

Primary outcome

There was no significant between-group difference in the improvement of FHSQ pain after 12 weeks (adjusted MD −7 points, 95% CI −16 to 2), as presented in Table 3 and Figure 2. The upper limit of the confidence interval (ie, the estimate that most favours self-

Table 2
Baseline characteristics of all participants.

Characteristic	Randomised (n = 70)	
	Exp (n = 35)	Con (n = 35)
Age *(yr)*, mean (SD)	50 (10)	49 (12)
Gender, n female (%)	29 (83)	29 (83)
Height *(cm)*, mean (SD)	169 (10)	170 (8)
Mass *(kg)*, mean (SD)	85 (16)	90 (19)
Body mass index *(kg/m^2)*, mean (SD)	29.9 (6.3)	30.7 (5.5)
Symptom duration *(month)*, median (IQR)	9 (6 to 30)	8 (5 to 22)
Pain severity *(0 to 100)*, mean (SD) [a]	62 (24)	63 (19)
Bilateral pain, n (%)	12 (34)	19 (54)
Plantar fasciopathy episodes *(n)*, median (IQR)	1 (1 to 2)	1 (1 to 2)
Additional pain sites *(n)*, median (IQR) [b]	3 (1 to 6)	3 (1 to 5)

[a] Average during previous week.
[b] Includes the entire body and head, and are derived from a pain manikin that participants used during baseline assessment.[59]

directed dosing but remains consistent with the data collected) was 2, which was below the minimum clinically important difference in the prospective sample size calculation.

Secondary outcomes

Almost all between-group differences were non-significant at either assessment time point for the other three domains of the FHSQ (ie, function, footwear, and general foot health), as presented in Table 3. One result did reach statistical significance (footwear domain at Week 12). This result favoured the control group (adjusted MD −6 points). The confidence interval retained effects that were very close to no effect (0.2, rounded to 0 in Table 3). Again, none of the confidence intervals contained an effect that exceeded the same clinically worthwhile threshold in favour of the experimental group. Plantar fascia thickness and the Pain Self-Efficacy Questionnaire were also not significantly different between the groups (Table 3).

Data for the four measures derived from the International Physical Activity Questionnaire short version (ie, walking, moderate activity, vigorous activity and total activity) were not normally distributed, with most participants achieving low activity and a few achieving high activity. Most of the non-parametric comparisons showed statistically non-significant median differences between the groups (Table 4). The result for walking at Week 4 was significantly different in favour of the control group, with an unadjusted difference in medians of 759 MET (p = 0.013). However, the difference was no longer statistically significant at Week 12. Individual participant data used in the analyses in Tables 3 and 4, as well as for all the remaining outcomes, are presented in Table 5 on the eAddenda.

When participants provided a Global Rating of Change, 24 of 33 in the experimental group and 20 of 32 in the control group were categorised as 'improved'. This was a non-significant difference between the groups, with a relative risk of 1.16 (95% CI 0.83 to 1.64).

Only four participants improved enough to meet the Patient Acceptable Symptom State definition: three of 35 in the experimental group and one of 35 in the control group. Although the relative risk indicated that the experimental group were 3.0 times more likely to achieve Patient Acceptable Symptom State, this was not statistically significant (95% CI 0.33 to 27).

The self-dosed group completed 36 training sessions (SD 8) and the pre-determined group completed 34 training sessions (SD 12), with a mean difference of −2 sessions (95% CI −8 to 3). The lowest number of training sessions performed was three and the second lowest was 13. Both participants were randomised to the pre-determined group. The self-dosed group performed an average of 5.0 sets per training session (SD 2.8) whereas 4.5 sets per training session were prescribed in the pre-determined program.

There was no significant association observed between: baseline Pain Self-Efficacy Questionnaire and number of training sessions performed (r = −0.030, p = 0.837); change in FHSQ pain and change in plantar fascia thickness (r = −0.234, p = 0.084); or change in FHSQ pain and number of training sessions performed (r = −0.082, p = 0.570).

Four participants reported adverse events, but none related to performing the exercise. All were non-serious musculoskeletal injuries of the lower extremities.

Complete case sensitivity analysis

The sensitivity analysis, which included only cases with no missing 12-week FHSQ pain data, had similar results as the primary analysis (MD −7 points, 95% CI −16 to 3). The multiply imputed analysis and the complete case analysis found conflicting results in two analyses. A significant between-group difference in FHSQ footwear at Week 12 was found to be non-significant in the complete case analysis (p = 0.057). A non-significant between-group difference in the Pain Self-Efficacy Questionnaire at Week 4 was found to be significant (p = 0.039); however, the difference was less than the minimum clinically important change.[48]

Discussion

This was the first trial comparing the efficacy between a self-dosed and a pre-determined heavy-slow resistance training program. A 12-week self-dosed heavy-slow resistance training program did not reduce pain more than a pre-determined heavy-slow resistance training program that has previously been shown to be effective.[18] The self-dosed program was not associated with larger improvements in self-efficacy or larger exercise dose during the trial.

Table 3
Mean (SD) of groups and adjusted mean (95% CI) between-group differences for Foot Health Status Questionnaire, plantar fascia thickness and the Pain Self-Efficacy Questionnaire.

Outcome	Groups						Adjusted mean between-group difference (95% CI)	
	Week 0		Week 4		Week 12		Week 4 minus Week 0	Week 12 minus Week 0
	Exp (n = 35)	Con (n = 35)	Exp (n = 35)	Con (n = 35)	Exp (n = 35)	Con (n = 35)	Exp minus Con	Exp minus Con
FHSQ pain *(0 to 100)*	43 (17)	38 (16)	58 (16)	50 (18)	70 (16)	62 (21)	−7 (−15 to 1)	−7 (−16 to 2)
FHSQ function *(0 to 100)*	61 (23)	58 (21)	78 (23)	75 (19)	89 (12)	84 (19)	−1 (−8 to 6)	−4 (−11 to 3)
FHSQ footwear *(0 to 100)*	48 (16)	48 (15)	50 (16)	48 (16)	52 (16)	46 (16)	−2 (−9 to 4)	−6 (−11 to 0)
FHSQ general foot health *(0 to 100)*	51 (16)	55 (18)	53 (14)	50 (15)	49 (16)	54 (14)	−4 (−11 to 2)	5 (−2 to 12)
Plantar fascia thickness *(mm)*	6.1 (1.2)	5.9 (1.2)	5.9 (1.3)	5.9 (1.3)	5.7 (1.3)	5.6 (1.3)	0.2 (−0.3 to 0.7)	0.1 (−0.4 to 0.6)
PSEQ *(0 to 60)*	44 (12)	45 (12)	50 (9)	47 (12)	54 (6)	51 (12)	−3 (−7 to 0)	−3 (−7 to 1)

Con = control group = pre-determined regimen, Exp = experimental group = self-dosed regimen, FHSQ = Foot Health Status Questionnaire, PSEQ = Pain Self-Efficacy Questionnaire.
Shaded row = primary outcome.

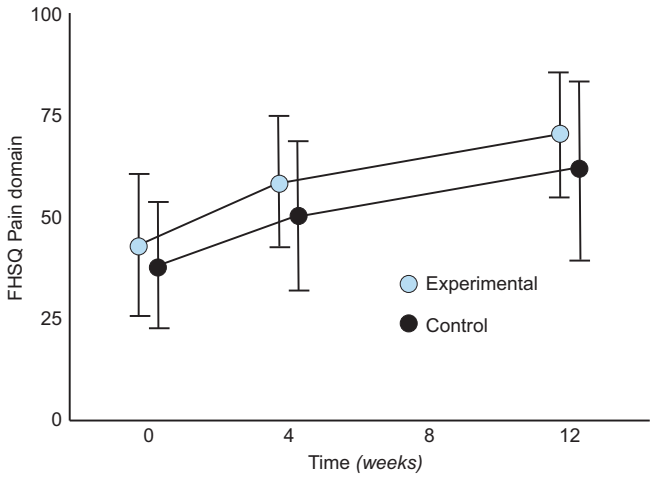

Figure 2. Pain domain of the Foot Health Status Questionnaire (FHSQ) by time. The experimental group was allocated self-dosed heavy-slow resistance training and the control group was allocated a pre-determined heavy-slow resistance training regimen. Symbols show means and error bars show standard deviations. Lines join group means at baseline and at Weeks 4 and 12. Experimental and control group data have been offset slightly for clarity.

Both groups had improvements in FHSQ pain larger than the minimum clinically important difference, but only three of 35 in the self-dosed group and one of 35 in the pre-determined group achieved Patient Acceptable Symptom State, indicating continued need for improved treatments for this long-term pain complaint.

The differences between the two exercise programs were mostly not statistically significant and the confidence intervals largely excluded effects that would be considered clinically worthwhile.[43] The few statistically significant results could well have been Type-I errors (ie, chance findings). This aligns with the findings from a study in rotator cuff tendinopathy where a self-dosed single-exercise program had effects that were equivalent to those of usual physiotherapy, which mostly consisted of resistance exercises.[20] Although the self-dosed approach was used with the intention of increasing self-efficacy and exercise dose, participants in the experimental group did not perform more training sessions or sets per training session (5.0 versus 4.5 sets) compared with the control group who undertook the pre-determined regimen. Both groups demonstrated high exercise compliance (on average two sessions per week).[25,49] The experimental and control programs appear to be two different ways of achieving the same exercise dose and clinical results. Although previous studies have indicated an association between exercise dose and recovery,[50,51] this association was not observed in the present trial; however, it should be noted that the analyses of correlations may not have been reliable due to the present trial's sample size.

The results of the present trial raise the question of whether there is a role for heavy-slow resistance training in plantar fasciopathy management. The magnitude, frequency, and duration of cyclic strains are all important for the response and adaptation of both muscle and connective tissue such as the plantar fascia.[32] It is possible that the load some participants used was inadequate to lead to an adaptation. If pain during exercise set an upper limit of load rather than muscular strength, adaptation could have been hampered. Pain during this specific exercise has previously been reported to be 42 mm on a 100-mm visual analogue scale and kinesiophobia is a recognised feature in individuals with plantar fasciopathy.[11,52] It remains unknown if using a higher load would lead to better recovery in plantar fasciopathy.

Even though both groups improved more than the nominated minimum clinically important difference on the FHSQ pain domain and the majority were improved according to the Global Rating of Change, few achieved Patient Acceptable Symptom State. When compared with other studies using FHSQ pain as an outcome, the level of improvement is comparable to that of foot orthoses, taping, corticosteroid injections, and even sham orthoses and placebo

Table 4
Median (IQR) of groups, unadjusted difference in medians, and statistical significance of the between-group difference in medians for four measures derived from the International Physical Activity Questionnaire.

IPAQ activity measure (*MET-minutes/week*)	Groups						Median difference [a]		Statistical significance of the difference (*p*)	
	Week 0		Week 4		Week 12		Exp minus Con			
	Exp (n = 35)	Con (n = 35)	Exp (n = 35)	Con (n = 35)	Exp (n = 35)	Con (n = 35)	Week 4	Week 12	Week 4	Week 12
Walk	693 (264 to 1386)	792 (198 to 2079)	693 (198 to 1782)	1452 (594 to 2772)	990 (396 to 1739)	1155 (462 to 2079)	−759	−165	0.013	0.576
Moderate	360 (0 to 840)	0 (0 to 800)	200 (0 to 720)	480 (0 to 720)	240 (0 to 1071)	720 (480 to 1440)	−280	−480	0.643	0.096
Vigorous	480 (0 to 1680)	240 (0 to 1920)	0 (0 to 1022)	320 (0 to 1001)	720 (0 to 1500)	800 (0 to 1920)	−320	−80	0.667	0.644
Total	2678 (1344 to 5226)	2106 (792 to 6079)	2412 (1386 to 3495)	3492 (1452 to 5118)	2556 (1188 to 4212)	3582 (1215 to 5439)	−1080	−1026	0.071	0.293

Con = control group, Exp = experimental group, IPAQ = International Physical Activity Questionnaire, MET = metabolic equivalent.
[a] Unadjusted for baseline difference in medians.

injections.[31,44,45] Therefore, the improvement seen in the present trial could have derived from regression to the mean or the silicone heel cups or patient education that participants received.[53]

Loading programs for other tendinopathies are usually predetermined, but our findings suggest there is no need for a standardised program if patients are advised to maximise their repetitions and load (up to 8RM) because such a self-dosed program led to similar results.[13,15,18,21,22] Physiotherapists might discuss the two forms of exercise program prescription (self-dosed or predetermined) to determine whether one appeals to the individual patient as being more motivating or acceptable. Heavy-slow resistance training provides clinicians with an alternative to other conservative treatments in plantar fasciopathy but the effects compared to wait-and-see and less time-consuming treatments need to be established.

Change in plantar fascia thickness and change in FHSQ pain were not associated, which is similar to previous findings of the lack of an association between pain, function, and plantar fascia thickness.[54] Furthermore, plantar fascia thickness is not associated with prognosis.[5] This indicates that repeated ultrasonography adds very little value to the patient and clinician alike and ultrasonography should only be used for diagnosing.[55]

The conduct of the trial involved many procedures to ensure that it generated robust results, such as randomisation, sample size calculation, concealed allocation, intention-to-treat analysis, and prospective registration. Also, by blinding participants to how the exercise program was prescribed to the opposite randomised group, the trial should have minimised any pressure on participants to exaggerate their improvement by knowing that they had been randomised to a group that the investigators hoped or anticipated would do better. The trial also had some limitations that ought to be considered. The validity of the training diaries from which compliance was estimated may be questionable, because patients tend to overestimate their physical activity level and exercise compliance.[56,57] In addition, patients may also have difficulties with replicating the exercise with an exactly correct technique when performing exercises at home.[58] Conceivably, these issues would have applied equally to both groups and would therefore be unlikely to strongly bias the inferences made from the data. Another limitation was that the treating therapist was not blinded to group allocation, which could have introduced bias when participants were instructed. To account for this, the patient education and instructions were standardised. Finally, musculoskeletal pain conditions involve a complexity of biopsychosocial aspects; hence, there may be some aspects of plantar fasciopathy that this trial did not embrace.

In conclusion, advising people with plantar fasciopathy to self-dose their slow-heavy resistance training regimen does not substantially increase the dose achieved. Self-dosed and pre-determined heavy-slow resistance exercise programs are associated with similar effects on plantar fasciopathy pain and other outcomes over 12 weeks. These regimens are not sufficient to achieve acceptable symptom state in the majority of people with plantar fasciopathy.

What was already known on this topic: Heavy-slow resistance training involves repeated slow contractions through concentric, isometric and eccentric phases against a heavy load. Heavy-slow resistance training is often used for tendinopathies. Prelminary evidence suggests that heavy-slow resistance training may be more effective than stretching in plantar fasciopathy, but the dose tested was lower than that typically used for other tendinopathies.

What this study adds: Advising people with plantar fasciopathy to self-dose their slow-heavy resistance training regimen does not substantially increase the achieved dose compared with prescribing a pre-determined regimen. Self-dosed and pre-determined heavy-slow resistance exercise programs are associated with similar effects on plantar fasciopathy pain and other outcomes over 12 weeks.

Footnotes: [a] SPSS Statistics for Windows, Version 25, IBM, Armonk, USA.

eAddenda: Table 5 and Appendix 1 can be found online at: https://doi.org/10.1016/j.jphys.2019.05.011.

Ethics approval: The Ethics Committee of the North Denmark Region approved this study. All participants gave written informed consent before data collection began.

Competing interests: Nil.

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Provenance: Not invited. Peer reviewed.

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Pilot and Feasibility Studies

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Heavy-slow resistance training in addition to an ultrasound-guided corticosteroid injection for individuals with plantar fasciopathy: a feasibility study

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Abstract

Introduction: Plantar fasciopathy, characterised by plantar heel pain, affects one in ten in a lifetime. Heavy-slow resistance training (HSR) is an emerging treatment, but it often takes considerable time before the effect starts to manifest. Combining HSR with a corticosteroid injection (known for its short-term pain relief) could potentially improve outcomes in both short and long term. As this combination is yet to be investigated, we aimed to evaluate the feasibility of combining HSR with a corticosteroid injection for individuals with plantar fasciopathy before investigating the efficacy in a clinical trial.

Materials and methods: We recruited 20 participants with plantar fasciopathy for this prospectively registered feasibility study (ClinicalTrials.gov: NCT03535896). Participants received an ultrasound-guided injection and performed heel raises on a step every second day for 8 weeks. To assess participant acceptability of the combined interventions and exercise compliance, we used a 7-point Likert scale dichotomised to "unacceptable" (categories 1–2) or "acceptable" (categories 3–7) and training diaries. Greater than or equal to 10/20 had to rate the combination "acceptable", ≥ 15/20 had to perform ≥ 20 training sessions, and ≥ 15/20 had to start exercising ≤ 7 days after injection to confirm feasibility.

Results: Eighteen out of 20 rated the combination acceptable. Five training diaries could not be retrieved. Ten out of 15 participants performed ≥ 20 training sessions, and 15/15 started exercising ≤ 7 days after injection.

Conclusions: Based on participant acceptability and time to exercise start, combining HSR with corticosteroid injection is feasible and the efficacy should be investigated in a future trial. Due to loss of 5/20 training diaries, firm conclusions regarding exercise compliance could not be drawn.

Trial registration: ClinicalTrials.gov, NCT03535896

Keywords: Plantar fasciopathy, Corticosteroid injection, Heavy-slow resistance training, Acceptability, Compliance

Background

Plantar fasciopathy is a common musculoskeletal condition and affects one in ten in a lifetime [1]. Pain is often exacerbated during the first steps in the morning and after prolonged periods of non-weight bearing [2]. Approximately half of patients referred to specialised clinics may still experience pain 10 years after treatment start [3]. Forty percent of patients still have symptoms after 2 years despite having performed plantar fascia-specific stretching and wearing insoles [4]. Patients with plantar fasciopathy have been found to show greater levels of depression, stress, anxiety, and kinesiophobia and have limitations in both mobility and health-related quality of life compared with sex- and age-matched healthy controls [5–7]. Plantar fasciopathy is also associated with several days of sick leave, and thus, plantar fasciopathy can have consequences for both patient and society [8, 9].

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A recent systematic review and network meta-analysis compared the effect of several treatment options for plantar fasciopathy. It concluded that no single treatment was superior to others and that different treatments may take different time to work [10]. A corticosteroid injection has been found to be a safe option for plantar fasciopathy and has a good short-term effect compared with placebo, but there is no added benefit after 1 month [11–13]. One treatment option not included in the review was heavy-slow resistance training (HSR). HSR is a frequently used treatment option in the rehabilitation of both upper and lower limb tendinopathies and has also been found to be superior to stretching in plantar fasciopathy, but its effects usually take several weeks to manifest [14–17].

An injection and HSR could potentially supplement each other and provide the patient with both the immediate pain reduction associated with the injection and the long-term pain reduction from performing HSR. Repeated corticosteroid injections and a combination of stretching and strengthening exercises have been investigated before, but the combination of HSR and a single corticosteroid injection is yet to be investigated [18]. Due to the novelty of combining these two treatments, the feasibility should be investigated before investigating the treatment effect in a larger-scale trial.

The purpose of this study is to investigate the feasibility of combining HSR with an ultrasound-guided corticosteroid injection to reduce pain in individuals with plantar fasciopathy. Feasibility is evaluated using the acceptability of the combined treatments and exercise compliance.

Methods

A cohort study design was implemented to follow patients with plantar fasciopathy over an 8-week period in order to determine feasibility of combining an ultrasound-guided corticosteroid injection with an HSR programme.

Study design and setting

This study was designed as an interventional feasibility study. Reporting follows the items of the CONSORT 2010 statement: *extension to randomised pilot and feasibility trials* that are applicable to a non-randomised design [19]. Before the inclusion of the first participant, the study was registered on ClinicalTrials.gov (NCT03535896). All examinations were conducted at the Research Unit for General Practice in Aalborg, Denmark, by an experienced physiotherapist. Injections were performed at a private rheumatology clinic in Aalborg, Denmark, by a rheumatologist with more than 15 years of experience with ultrasound-guided injections. Data were collected using REDCap (Vanderbilt University, Nashville, TN, USA). Baseline and the 8-week follow-up were conducted at the study site whereas a link to the questionnaires used was sent by REDCap to participants' e-mail address for the 4-week follow-up.

Recruitment and eligibility criteria

Participants were recruited through social media (Facebook) or from a local general practice. The primary investigator performed telephone screenings of potentially eligible participants, and those who were not excluded based on this screening were invited to a clinical examination where final eligibility was determined. Inclusion criteria were as follows: (i) history of inferior heel pain for at least 3 months before enrolment, (ii) pain on palpation of the medial calcaneal tubercle or the proximal plantar fascia, (iii) thickness of the plantar fascia of 4.0 mm or greater measured by ultrasound [20], and (iv) mean heel pain ≥ 30 mm on a 100-mm VAS during the previous week. Exclusion criteria were as follows: (i) below 18 years of age, (ii) diabetes, (iii) history of inflammatory systemic diseases, (iv) prior heel surgery, (v) pregnancy or breastfeeding, (vi) corticosteroid injection for plantar fasciopathy within the previous 6 months, (vii) pain or stiffness in the first metatarsophalangeal joint to an extent where the exercises could not be performed, (viii) known hypersensitivity to corticosteroids or local anaesthetics, or (ix) skin or soft tissue infection near the injection site. These criteria were in line with those of similar studies in this patient population and had to be met by all participants [8, 11, 21].

Intervention

Patient advice

After eligibility was confirmed, participants received information regarding what is known about the condition in terms of risk factors and aetiology, the pathology, and the rationale for why the combination of HSR and an ultrasound-guided corticosteroid injection could lead to recovery. They were advised to decrease activities which they felt caused symptom flare ups and slowly progress their activity level guided by symptoms. They were also informed about other types of evidence-based treatments; however, they were asked to refrain from seeking other treatments during the course of the study. Two weeks after inclusion, the primary investigator contacted participants to ask them if they had any questions regarding the condition or in relation to performing the exercise.

Heavy-slow resistance training and heel cup

Participants were instructed in performing a heel raise exercise standing with the forefoot on a step or a book as per Rathleff et al. [17]. The toes should be maximally

extended by placing a rolled towel underneath them. Supporting themselves for balance by touching the hands on a wall or a rail was allowed. Participants were instructed to perform the exercise with a load as heavy as possible, but no heavier than they would be able to perform eight repetitions per set (i.e. eight repetition maximum (RM)) and for as many sets as possible. This self-dosed approach was found to be equal to the predetermined programme used by Rathleff et al. [21]. Further information about the exercise is displayed in Table 1. If participants felt they were able to perform more repetitions than their load corresponded to (e.g. 10 repetitions when the load was supposed to be 8RM), an external load consisting of a backpack with books or water bottles to add weight was used. We told participants that pain during the exercise was expected and that there was no upper limit of pain they were allowed to experience as long as they felt it was tolerable. Participants were asked to start performing the exercise as soon as they felt ready but not before 24 h after the injection. During the first 2 weeks after the injection, they were asked not to progress the method used to achieve 8RM. If standing on both feet was sufficient to achieve 8RM at baseline, participants should not perform the exercise single-legged until the third week after the injection regardless of any pain reduction afforded by the injection. They were, however, still asked to perform as many sets as possible. Participants were told that complying with the exercise programme was very important and that exercise compliance was associated with their recovery. To support the exercise execution, participants received a training diary which included the exercise instruction and a link to a video in which the primary investigator showed the exercise instruction.

A silicone heel cup was given to all participants, and they were advised to use the heel cup as much as possible. If participants already used an insole or any other type of foot orthosis, they were allowed to continue wearing this if they preferred it over the heel cup that we provided.

Ultrasound-guided corticosteroid injection

Participants received an ultrasound-guided corticosteroid injection between 5 and 8 days after baseline. A 21-gauge, 40-mm needle was connected to a 2.5-cm^3 syringe filled with 1 ml triamcinolonhexacetonid (Lederspan, Meda A/S, Allerød, Denmark) + 1 ml lidocain 10 mg/ml (Xylocain, AstraZeneca A/S, Copenhagen, Denmark). The skin was cleansed with chlorhexidine alcohol 0.5% (Medic, Meda A/S, Allerød, Denmark). The needle was inserted with a medial approach under ultrasound guidance aligned to the long axis of the ultrasound transducer. The injection was placed anterior to the plantar fascia insertion on the calcaneal bone in the region of maximal fascia thickness.

Table 1 Mechano-biological descriptors

1. Load magnitude	As heavy as possible, but no heavier than a weight that can be lifted at least 8 times (8RM)
2. Number of repetitions	≥ 8 depending on the load
3. Number of sets	As many as possible
4. Rest in between sets	2 min
5. Number of exercise interventions	Performed every other day
6. Duration of the experimental period	8 weeks
7. Fractional and temporal distribution of the contraction modes per repetition and duration (s) of one repetition	3 s concentric 2 s isometric 3 s eccentric
8. Rest in-between repetitions	No
9. Time under tension	8 s/repetition ≥ 64 s/set ≥ 64 s/training session
10. Volitional muscular failure	Yes
11. Range of motion	Full range of motion
12. Recovery time in-between exercise sessions	48 h
13. Anatomical definition of the exercise (exercise form)	The participant stands with the forefoot on a step. The toes are maximally dorsal flexed by placing a towel underneath them. The participant performs a heel raise to maximal plantar flexion in the ankle joint and afterwards lowers the heel to maximal dorsal flexion. Supporting oneself for balance by placing the hands on a wall or a rail is allowed.

Outcomes

Feasibility outcomes

Before embarking upon a large randomised controlled trial investigating the treatment effects, it is recommended to investigate the feasibility including participant acceptability [22]. We chose three feasibility outcomes: (i) Acceptability of the combined treatments measured by a participant acceptability questionnaire that included a 7-point Likert scale ranging from "very unacceptable" to "very acceptable". This was not a measure of whether participants' symptoms had improved or not, but if the treatment matched their expectations to the content of the intervention and acceptability of performing exercises after receiving an injection. This was clearly stated in the questionnaire to emphasise that changes in symptoms were not to be considered. The combined treatments were categorised as "unacceptable" if they were rated as "very unacceptable" or "unacceptable" (category 1–2) and categorised as "acceptable" if they were rated from "slightly unacceptable" to "very acceptable" (category 3–7). We encouraged participants to elaborate their response in a free-text field. The questionnaire was filled out during the 8-week follow-up. (ii) Compliance to the exercises as measured by the mean number of training sessions performed throughout the intervention measured by a training diary that each participant is handed out at baseline. The participants were instructed in filling out the number of repetitions and sets performed and the day on which they performed the exercise. (iii) Mean days until participants started to perform the exercise measured from after the injection.

Explorative outcomes

In addition to the feasibility outcomes, we collected the following explorative outcomes to inform sample size estimations for a future trial: (i) change in the domains of the Danish version of the Foot Health Status Questionnaire (FHSQ) from baseline to the 4-week and 8-week follow-ups [23]. The FHSQ is a self-report questionnaire ranging from 0 (poor foot health) to 100 (optimum foot health) that assesses multiple dimensions of foot health and function and has a high reliability (ICC = 0.74–0.92) [24]. The minimal important differences of the domains are 14.1 points for pain, 7.4 points for function, and 9.2 points for general foot health [25]. (ii) Change in mean daily heel pain measured on an 11-point Numerical Rating Scale (NRS) (ranging from 0 which is no pain to 10 which is worst pain imaginable) from before the injection to 1 week after. This was chosen as an outcome to explore the short-term effects of the injection. The minimal important difference of an 11-point NRS is 2 [26, 27]. Participants received an SMS at the same timepoint every day in which they were asked to rate their mean heel pain during the past 24 h. The first SMS was sent the day after baseline, and SMSs were sent until 1 week after the injection. The SMS was sent using a smartphone (Huawei Y5, Huawei Technologies, Shenzhen, China) and the application Do It Later (Go Vap Dst, Ho Chi Minh City, Vietnam). (iii) Self-reported improvement measured on a 7-point Likert scale ranging from "much improved" to "much worse" (the Global Rating of Change (GROC)) at the 8-week follow-up. Participants were categorised as improved if they rated themselves as "much improved" or "improved" (category 6–7) and categorised as not improved if they rated themselves from "slightly improved" to "much worse" (category 1–5) [28]. (iv) Change in plantar fascia thickness from baseline to the 8-week follow-up measured in millimetres by ultrasonography. Measurements were performed using a longitudinal scan with participants lying prone with the toes placed maximally extended on the examination table. An average of three measurements was used (ICC = 0.67–0.77) [20]. (v) Change in self-efficacy as measured by the Pain Self-Efficacy Questionnaire (PSEQ). The PSEQ ranges from 0 (not at all confident) to 60 (completely confident) with lower scores indicating lower self-efficacy [29]. A validated Danish translation was used (ICC = 0.89) [30]. (vi) Change in physical activity level as measured by the International Physical Activity Questionnaire short version (IPAQ). The IPAQ estimates time spent performing vigorous and moderate activities, and time spent walking during the past week measured in MET-minutes [31, 32]. (vii) Recruitment rate defined as the mean number of participants recruited per week throughout the recruitment period.

The FHSQ, PSEQ, and IPAQ were filled out during baseline and at the 4-week and 8-week follow-ups whereas the GROC was filled out during the 8-week follow-up only. If participants were not categorised as improved based on the GROC, they were offered a second injection. If they accepted, they would receive the GROC again after an additional 8 weeks of performing exercises.

Sample size

Due to the nature of a feasibility study, a formal sample size calculation was not performed [33, 34]. We aimed to include 20 participants as we considered this an adequate number to assess the feasibility of the combined treatments.

Analyses

Feasibility

To conclude that the combined treatments were feasible, we a priori decided during a consensus meeting that the following three criteria would have to be met: (i) ≥ 10/20

rated the combined treatments as "acceptable". If any participant dropped out after the injection, they would be dichotomised as "unacceptable". (ii) Based on the self-reported training diaries, ≥ 15/20 participants would need to have performed ≥ 20/28 possible training sessions, and (iii) ≥ 15/20 participants would need to have started performing the exercise ≤ 7 days after the injection.

Explorative

We used histograms and Q-Q plots to assess data normality. Due to the nature of a pilot study, no hypothesis testing was performed and we report mean or median changes over time and 95% confidence intervals or frequency [19].

Results

Recruitment was started on May 31, 2018. Between June 8 and August 10, 2018, we included 20 participants. The final day of data collection was October 11. Thirty-two potential participants were either referred from general practice or contacted the primary investigator directly. Of these, 24 were eligible for the clinical examination. Four were excluded; two individuals had a mean heel pain during the past week < 30/100 mm VAS, one individual was breastfeeding, and one individual had a plantar fascia thickness < 4 mm. After the final participant had been included, an additional 12 potential participants contacted the primary investigator to be included. One participant was lost to follow-up, and five training diaries could not be retrieved. None of these participants appeared dissimilar at baseline to those who handed in the training diary. Characteristics of the 20 included participants are shown in Table 2. One participant experienced an adverse event as she experienced pain in other areas of the foot than the heel during HSR. Participants' previous care-seeking behaviour is found in Additional file 1.

Feasibility results

The combined treatments were considered acceptable by 18/20 participants. According to the training diaries, 10/15 participants performed ≥ 20 training sessions (mean performed training sessions 20.8 (± 9.2)) and all started performing the exercise ≤ 7 days after injection (mean days 2.1 (± 1.1)).

Fifteen participants provided a reason for their response to the question of acceptability. The most common theme that emerged was reduced pain afforded by the injection when starting to perform the exercise (n = 3). Two participants thought that it was a good idea to combine several treatments to hopefully increase the odds of recovery. The one participant who evaluated the combined treatments as not acceptable reasoned this with increased pain in other parts of the foot than the heel when performing the exercise. All comments are found in Table 3.

Table 2 Clinical and demographic baseline characteristics

Women (%)	16 (80)
Age (years)	51.7 (± 12.5)
Height (cm)	169.7 (± 8.9)
Mass (kg)	87.3 (± 16.3)
BMI (kg/m^2)	30.3 (± 5.4)
Symptom duration (months)*	8 (6 to 11)
Pain during past week (/100 mm)	65.3 (± 13.3)
Bilateral pain (%)	6 (30)
Number of plantar fasciopathy episodes*	1 (1 to 3)

Data are presented as mean (SD) or count
*median (interquartile range)

Explorative results

Participants improved from baseline to 4 weeks in FHSQ pain (mean change 15.8, 95% CI 3.0 to 28.6) and to the 8-week follow-up (mean change 13.5, 95% CI − 0.3 to 27.2). In the function domain of the FHSQ, participants improved the scores more than the minimally important difference of 7.4 points from both baseline to the 4-week follow-up and to the 8-week follow-up (Table 4). Mean daily heel pain decreased 1.2 NRS (95% CI 0.7 to 1.7) from the days before (mean pain 5.5 (± 1.8) NRS) to 1 week after the injection (mean pain 4.3 (± 2.1) NRS) (Fig. 1). According to GROC, 6/19 participants were improved after the intervention. Four participants of those who were not improved according to GROC agreed to receive a second injection. One was dichotomised as improved after the additional 8-week follow-up, and one still had not improved. The remaining two were lost to follow-up. We were actively recruiting participants for a total of 6 weeks which led to a weekly recruitment rate of 3.3 participants per week. The mean number of sets performed per training session was 4.2 (± 2.4).

Discussion

Key results

This was the first study that included both HSR and an ultrasound-guided corticosteroid injection in the treatment of plantar fasciopathy. We found that 18/20 participants rated the combined treatments acceptable, and according to the 15 training diaries retrieved, they were adequately complying with the exercise programme.

Interpretation of feasibility

Despite the efforts made to ensure that participants disregarded any changes of their symptoms in the evaluation of acceptability, several of the comments (6/15) concerned the treatment effect and differentiating between treatment effect and acceptability of the content of treatments appeared to be difficult. Even if only 6/19 participants

Table 3 Participants' reasons for their acceptability response. Translations were made as true to the original statement as possible

Original quote	English translation
Det har været super fint at være smertefri i startet, hvor jeg skulle påbegynde træning.	It has been super nice to be pain-free from the start when I had to start the training.
Grunden til jeg er meget enig er fordi, den første tid mærkede jeg ikke noget til smerterne pga. Injektionen hvilket gjorde det nemmere at gennemføre øvelserne og opgaverne i dagligdagen.	The reason why I very much agree is that from the beginning I did not experience pain because of the injection which made it easier to perform the exercises and everyday tasks.
Hvis det har en effekt og injektionen sker sjældent så finder jeg det acceptabelt og en god måde at komme videre på. Det er ikke just behageligt at få den, så vil selfølgelig helst undgå det. Men som sagt finder jeg det acceptabelt når man tænker på for og imod.	If it has an effect and the injection happens rarely then I find it acceptable and a good way of moving on. It is not necessarily comfortable to get it so I would, of course, rather avoid it. But, as I said, I find it acceptable when you consider the pros and cons.
Stadig smerter og kraftløshed	Still pain and debilitation
Virkningen af injektionen er udeblevet	The effect of the injection failed to happen
Ukompliceret og nem behandling.	Uncomplicated and easy treatment.
ikke mærket den store forskel, efter de 2 første uge	Not felt any big change after the first 2 weeks
Kombinationen gav mening. Der er enkelte gange gået mere end to dage mellem træningen.	The combination made sense. A few times it has been more than two days between the training.
Det værste var smerten i forbindelse med injektionen	The worst was the pain in connection with the injection
Meget fint med blot træning hver 2. dag, således ikke så tidskrævende.	Very nice with training just every two days so not that time consuming.
Øvelserne har givet voldsomme smerter andre steder i foden	The exercises have led to severe pains in other parts of the foot
Træningen blev langt nemmere og meget midre smertefyldt efter injektionen med binyrebarkhomon	The training became much easier and less painful after the injection with corticosteroid
Det kan siges acceptabel hvis der er nogen effekt af indsprøjtningen	It can be called acceptable if there is any effect of the injection
Om binyren har nogen effekt ved jeg ikke, med det at man HAR fået en sprøjte giver en vis "effekt" mentalt.	I do not know if the corticosteroid has any effect but the fact that you HAVE received an injection has somewhat of an "effect" mentally.
Godt med flere muligheder for behandling på en gang. Så større chance for at det virker.	Nice with more treatment options at once. So bigger chance for it to work.

improved according to GROC, nearly all participants evaluated the combination of treatments as acceptable according to dichotomisation which emphasises the acceptability of combining both HSR and an injection.

Due to loss of training diaries, it is difficult to draw firm conclusions regarding exercise compliance in our study. Exercise compliance is considered a large challenge in the rehabilitation of musculoskeletal conditions, and strategies to increase compliance should be considered whenever exercises are prescribed [35, 36]. Participants performed approximately 75% of the training sessions prescribed which may be interpreted as a high compliance [37]. To increase compliance, we used training diaries and told patients that complying with the exercises was associated with the odds of recovery, but additional strategies such as phone calls or SMS reminders may be needed to increase compliance even further in future trials [35].

Interpretation of explorative outcomes

This study was not powered to detect changes over time in the explorative outcomes, and the results should be interpreted cautiously; however, several outcome measures pointed in the same direction. Participants improved in FHSQ pain, function, and footwear and in PSEQ from baseline to the 4-week follow-up, but there was only a negligible change from the 4-week to the 8-week follow-up. This is similar to what was observed by both McMillan et al. and Ball et al. following an ultrasound-guided corticosteroid injection [11, 12]. Individuals with plantar fasciopathy who perform HSR will usually experience a steady improvement whereas those who are treated with a corticosteroid injection will experience a fast improvement with no further benefit hereafter [11, 12, 17, 21]. While we did not compare the combination to either of the individual interventions, the trajectory of improvement in our study looks similar to what

Table 4 Results of explorative outcomes

	Mean (SD)	Mean change (95% CI)		
		Baseline vs 4 weeks	Baseline vs 8 weeks	4 weeks vs 8 weeks
FHSQ pain (0–100)				
Baseline	41.1 (12.7)	15.8 (3.0 to 28.6)	13.5 (– 0.3 to 27.2)	– 2.3 (– 12.2 to 7.6)
4 weeks	56.5 (26.6)			
8 weeks	54.8 (28.2)			
FHSQ function (0–100)				
Baseline	61.9 (19.3)	11.8 (– 0.1 to 23.7)	12.9 (– 1.4 to 27.1)	1.0 (– 9.8 to 11.9)
4 weeks	71.9 (24.8)			
8 weeks	74.3 (26.0)			
FHSQ footwear (0–100)				
Baseline	35.8 (21.8)	8.8 (– 5.0 to 22.6)	12.0 (– 0.4 to 24.5)	3.2 (– 2.6 to 9.1)
4 weeks	45.8 (29.0)			
8 weeks	48.3 (27.6)			
FHSQ general foot health (0–100)				
Baseline	44.5 (21.0)	– 6.3 (– 21.3 to 8.8)	9.0 (– 0.2 to 18.3)	15.3 (2.4 to 28.2)
4 weeks	35.1 (27.5)			
8 weeks	50.9 (26.6)			
PSEQ (0–60)				
Baseline	42.1 (8.9)	5.2 (0.5 to 10.0)	5.8 (0.2 to 11.3)	0.6 (– 4.4 to 5.5)
4 weeks	47.0 (12.2)			
8 weeks	48.2 (10.6)			
Plantar fascia thickness (mm)				
Baseline	5.6 (0.9)		0.3 (– 0.1 to 0.7)	
8 weeks	5.3 (1.2)			
	Median (IQR)	Median change (95% CI)		
		Baseline vs 4 weeks	Baseline vs 8 weeks	4 weeks vs 8 weeks
IPAQ walk (MET)				
Baseline	1155 (330–1732.5)	– 132 (– 251 to 231)	– 99 (– 921 to 317)	– 1155 (– 1598 to – 330)
4 weeks	1386 (198–2079)			
8 weeks	495 (297–1386)			
IPAQ moderate (MET)				
Baseline	540 (300–2220)	0 (– 1254 to 600)	0 (– 480 to 480)	600 (– 2104 to – 360)
4 weeks	720 (40–2880)			
8 weeks	480 (240–960)			
IPAQ vigorous (MET)				
Baseline	440 (0–1520)	0 (– 480 to 480)	0 (– 73 to 313)	– 400 (– 1107 to 0)
4 weeks	240 (0–1440)			
8 weeks	240 (0–960)			
IPAQ total (MET)				
Baseline	2475.5 (1391–4614)	242 (– 922 to 2681)	– 171 (– 1592 to 864)	423 (– 712 to 2084)
4 weeks	1935 (1200–6906)			
8 weeks	2217 (1059–2772)			

FHSQ Foot Health Status Questionnaire, *PSEQ* Pain Self-Efficacy Questionnaire, *IPAQ* International Physical Activity Questionnaire, *MET* metabolic equivalents

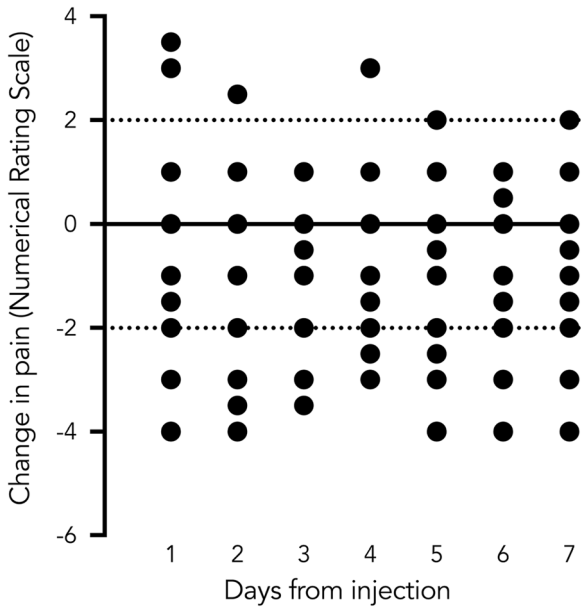

Fig. 1 Individual changes in pain during the days after the injection relative to the median of pain each individual experienced during the days prior to the injection. Dashed lines show the threshold for a minimally important change on a 0 to 10 Numerical Rating Scale. Positive values are an increase in pain, and negative values are a decrease in pain

has been observed in both lateral elbow tendinopathy and gluteal tendinopathy where an injection may hamper the effect of exercises [15, 38]. We only followed participants for 8 weeks as this was sufficient to allow for an evaluation of acceptability, and thus, we cannot make any statement on the long-term outcomes of combing HSR with a corticosteroid injection. Johannsen et al. [18] found a combination of repeated injections and different exercises to be superior to either exercises or injections alone. That study did not include follow-ups between baseline and the 3-month follow-up, so it is not possible to compare our findings with theirs.

To our knowledge, this was the first study that investigated the pain reduction following an ultrasound-guided corticosteroid injection by collecting daily pain data from the days before and after the injection was performed. Contrary to common expectation, the injection did not lead to a large pain reduction within a few days as the reduction of 1.2 NRS is approximately only half of the minimally important difference of NRS in chronic musculoskeletal pain conditions [26, 27]. Clinicians who use injections with corticosteroid for patients with plantar fasciopathy may want to inform patients that they may not experience a pain reduction within the first week.

Limitations

We believe our study has two limitations. Firstly, we were not able to retrieve five training diaries and two of our feasibility criteria were dependent on data from the diaries. As a result, we cannot draw firm conclusions regarding exercise compliance. In a future trial, additional emphasis should be put on the importance of returning the training diaries when they are handed to participants or other methods for collecting exercise compliance such as SMSs or mobile applications may be used. Secondly, we did not want the exercises to interfere with the measures of daily pain before the injection, so we did not allow participants to start performing the exercise until after the injection. Therefore, some participants did not start the exercise until 10 days after they received the exercise instruction. To counteract this limitation, participants received a written exercise instruction and a link to a video in which the primary investigator showed the instruction.

Conclusions

Based on participant acceptability and time from participants received the injection to exercise start, combining HSR with an ultrasound-guided corticosteroid injection is feasible and the efficacy compared to other conservative treatments may be investigated in a randomised trial. Due to loss of 5/20 training diaries, firm conclusions regarding exercise compliance could not be drawn.

Additional file

Additional file 1: Online supplementary table of previous care-seeking behaviour. (DOCX 16 kb)

Abbreviations

ANOVA: Analysis of variance; FHSQ: Foot Health Status Questionnaire; GROC: Global Rating of Change; HSR: Heavy-slow resistance training; IPAQ: International Physical Activity Questionnaire; MET: Metabolic equivalent; NRS: Numerical Rating Scale; PSEQ: Pain Self-Efficacy Questionnaire; RM: Repetition maximum; VAS: Visual analogue scale

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Authors' contributions

All authors were involved in writing the manuscript and HR led the process. All authors read and approved the final manuscript. HR, JLO, MBJ, BV, and MSR contributed to the study conception and design. HR, JLO, MBJ, BV, and MSR contributed to the analysis and interpretation of data. HR contributed to the data collection.

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Availability of data and materials

Data is available upon request.

Ethics approval and consent to participate

All participants signed an informed consent form prior to the examination. The Ethics Committee of the North Denmark Region was notified about the study before recruitment start, but an approval was not needed as they considered a feasibility study combining two commonly used treatments quality assurance.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Trials

STUDY PROTOCOL Open Access

Corticosteroid injection plus exercise versus exercise, beyond advice and a heel cup for patients with plantar fasciopathy: protocol for a randomised clinical superiority trial (the FIX-Heel trial)

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Abstract

Background: Plantar fasciopathy has a lifetime prevalence of 10%. Patients experience sharp pain under the heel, often for several months or years. Multiple treatments are available, but no single treatment appears superior to the others. A corticosteroid injection offers short-term pain relief but is no better than placebo in the longer term (> 8 weeks). Heavy-slow resistance training has shown potentially positive effects on long-term outcomes (> 3 months), and combining exercises with an injection may prove to be superior to exercises alone. However, the effect of heavy-slow resistance training compared with a simpler approach of patient advice (e.g., load management) and insoles is currently unknown. This trial compares the efficacy of patient advice with patient advice plus heavy-slow resistance training and with patient advice plus heavy-slow resistance training plus a corticosteroid injection in improving the Foot Health Status Questionnaire pain score after 12 weeks in patients with plantar fasciopathy.

Methods: In this randomised superiority trial, we will recruit 180 patients with ultrasound-confirmed plantar fasciopathy and randomly allocate them to one of three groups: (1) patient advice and an insole ($n = 60$); (2) patient advice, an insole, and self-dosed heavy-slow resistance training consisting of heel raises ($n = 60$); or (3) patient advice, an insole, heavy-slow resistance training, and an ultrasound-guided corticosteroid injection ($n = 60$). All participants will be followed for 1 year, with the 12-week follow-up considered the primary endpoint. The primary outcome is the Foot Health Status questionnaire pain domain score. Secondary outcomes include the remaining three domains of the Foot Health Status Questionnaire, a 7-point Global Rating of Change, the Pain Self-Efficacy Questionnaire, physical activity level, health-related quality of life measured by the EQ-5D-5L, and Patient Acceptable Symptom State, which is the point at which participants feel no further need for treatment. Additionally, a health economic evaluation of the treatments will be carried out.

Discussion: This trial will test if adding heavy-slow resistance training to fundamental patient advice and an insole improves outcomes and if a corticosteroid injection adds even further to that effect in patients with plantar fasciopathy.

Trial registration: ClinicalTrials.gov, NCT03804008. Prospectively registered on January 15, 2019.

Keywords: Plantar fasciopathy, Heavy-slow resistance training, Corticosteroid injection, Foot orthoses, Patient advice

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Background

One in ten persons will develop plantar fasciopathy (PF) [1, 2]. The condition accounts for 8% of all running-related injuries but is also common in the general population [3–5]. A high running volume is associated with a higher risk of developing PF, and despite a lack of prospective studies to identify risk factors among non-runners, a high body mass index is thought to be a risk factor [6]. Pain is often worse during the first steps after getting out of bed or during the first steps after periods of non-weight-bearing [7].

PF was formerly known as 'plantar fasciitis' or 'heel spur syndrome' and has historically been considered a self-limiting condition in which 80% are expected to achieve symptom-free status within 12 months. This view of a self-limiting condition has been challenged by research [1, 8–11]. Approximately half of patients referred to a specialised secondary care clinic still experienced pain 10 years after treatment [9], and 40% of patients in a randomised controlled trial still had symptoms 2 years after plantar fascia-specific stretching and wearing insoles [8]. Patients with PF show greater levels of depression, stress, anxiety and kinesiophobia and experience limitations in both mobility and health-related quality of life compared with pain-free individuals [12–14]. Moreover, PF may be associated with several days of sick leave. Davis et al. found that 6 of 105 patients had taken as much as 3 months off work [15], and we recently found that 23% of patients in the workforce had taken a median of 30 days off work due to their heel pain in one study [16] and 20% had taken between 5 and 548 days off work in another [17]. Thus, the consequences for both patients and society are marked.

A systematic review and network meta-analysis compared several commonly used treatment options for PF [18]. Overall, they concluded that none of the investigated treatments were superior to the others, but different treatments may have different temporal profiles. Some are efficacious in the short term (< 4 weeks), such as an injection with corticosteroid, whereas others (e.g., exercises or orthoses are more efficacious in the longer term [> 12 weeks]) [18–22]. Heavy-slow resistance training (HSR) was not included in the review, but it is generally known for a long-term efficacy in the rehabilitation of both upper- and lower-limb tendinopathies [23–25]. In PF, HSR has been found to be superior to plantar fascia-specific stretching, but only 6% achieve an acceptable symptom state within 12 weeks [16, 26]. This emphasises the need for additional improvements to current care of these patients.

Combining HSR with a corticosteroid injection may provide both short- and long-term pain relief for individuals with PF. We recently conducted a feasibility study of the combination of these two treatments, which supports running an efficacy trial. Patients' rating of acceptability, time to commencement of exercise after the injection, compliance with exercise, recruitment rate, and changes in foot-related health and function over time supported this current proposed trial [27]. In theory, combined treatments could supplement each other and give both an immediate and long-term pain reduction.

Repeated corticosteroid injections and a combination of stretching and foot-strengthening exercises have been investigated before, but the combination of HSR and a single corticosteroid injection is yet to be studied [28]. Previous studies in other tendinopathies only compared the combined treatments with one of the treatments and reported no differences [24, 29]. The limitation of these studies is that it remains unknown if any of the treatments have had some effect or no effect overall on the condition, because the trials did not include a control arm [24, 29]. We propose that a trial of combined interventions versus one of the interventions requires a control arm. A minimal intervention (control arm) consisting of patient advice, which reflects current general practitioner (GP) practice (unpublished data), will enable a meaningful comparison with more time-consuming and expensive treatments, such as exercises and injections. If we do not fill this knowledge gap, we might use costly and time-consuming treatments without knowing the effect compared with simpler treatment. To our knowledge, there is no literature available on the cost-effectiveness of alternative treatments of PF [30]. Despite treatment costs for PF possibly seeming relatively small compared with other more expensive health technologies, the productivity costs to society may be substantial in PF due to patients' sick leave.

The present trial is the product of a series of preceding studies conducted by our group in this patient population in general practice. Interviews with GPs about the management of PF showed a high heterogeneity wherein some would give a steroid injection at first consultation, some would prescribe exercises, and some would refer to a physiotherapist (unpublished data). However, commonalities were to give patients advice on what they could do to self-manage and an uncertainty about the effectiveness of the many treatments available for PF. To investigate if we could improve outcomes associated with HSR, we compared a traditional pre-determined HSR programme with a self-dosed programme to target self-efficacy and increase the exercise dose received. We found that both programmes were associated with similar improvements [16]. Following that randomised trial, we investigated the feasibility of combining HSR with an ultrasound-guided corticosteroid injection in the feasibility study described above as a final step before initiating the present trial [27].

Objectives

The purpose of this trial is to investigate the efficacy of fundamental patient advice and a heel cup (PA) versus

fundamental patient advice and a heel cup plus heavy-slow resistance training (PAX) versus a combination of fundamental patient advice and a heel cup plus heavy-slow resistance training and an ultrasound-guided corticosteroid injection (PAXI) in improving the Foot Health Status Questionnaire pain domain score after 12 weeks in individuals with PF.

Hypotheses

Hypothesis 1: The group receiving PAXI will be superior to the group receiving PAX.

Hypothesis 2: The group receiving PAXI will be superior to the group receiving PA only.

Hypothesis 3: The group receiving PAX will be superior to the group receiving PA only.

Methods

Design and setting

The FIX-Heel Trial is designed as a randomised superiority trial with a three-group parallel design. Reporting of the protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement (checklist uploaded as Additional file 1), TiDieR (Template for Intervention Description and Replication checklist and guide) and the Consensus on Exercise Reporting Template for intervention description [31–33]. The preparation of the trial, including publishing this trial protocol, was done in accordance with the PREPARE trial guide [34]. Before the inclusion of the first participant, the trial was registered with ClinicalTrials.gov (NCT03804008). Patients will be recruited from general practice and via social media (see below). However, for pragmatic reasons, the information and training instructions will be given at the physiotherapy department at Aalborg University Hospital, and injections will be given at a private rheumatology clinic (ReumaNord) situated in Aalborg, Denmark. Participants will attend the baseline and 12-week follow-up appointments at the hospital, whereas a link to the questionnaires used will be sent via REDCap (Vanderbilt University, Nashville, TN, USA) to participants' e-mail addresses for the 4-week, 26-week and 52-week follow-ups.

Roles and responsibilities

The project manager is a physiotherapist with 8 years of experience in treating patients with musculoskeletal conditions. He will be responsible for recruitment and analysing data whilst blinded to group allocation. Two physiotherapists working at the Aalborg University Hospital with 5 and 6 years of experience, respectively, were recruited and will be responsible for eligibility screening, delivering interventions and being in contact with participants throughout the trial. Before the inclusion of the first participant, the physiotherapists had received 10 and 19 h of training, respectively, in the procedures of the trial by the project manager. This includes putting four pilot study participants through all aspects of the trial processes. The ultrasound-guided injection will be performed by a rheumatologist who has more than 15 years of experience with performing ultrasound-guided injections.

The adaptive recruitment strategy

Participants will primarily be recruited from general practice, but to ensure that the trial timeline is maintained, we will include participants through social media (Facebook). Initially, we aim to recruit from ten general practices in the North Denmark Region. We will reach out to the practices using an open invitation in which we ask for practices interested in being part of trial recruitment through the Facebook page of the Center for General Practice at Aalborg University and through our network of GPs in the North Denmark Region. If this is not sufficient, the project manager will contact general practices directly. The GPs are offered a 30-min presentation about PF and the trial at their own practice. If recruitment from general practice is inadequate, we may employ one of the practices' secretaries, who examines the GPs' daily plans for potential trial participants. The secretary will then remind the GP of informing the patient about the trial if the patient is potentially eligible for inclusion.

General practices will receive an honorarium per patient they refer to the project manager. It is a standard honorarium stipulated by the Danish Committee of Multipractice Studies in General Practice (approximately €18). Before they agree to participate in recruitment, they will be informed that they are expected to refer a minimum of two patients per month. On the basis of the number of referrals we receive, we will categorise general practices into three symbolic zones: green, yellow and red. Practices in the green zone will have referred a minimum of two patients during the past month; practices in the yellow zone will only have referred one patient during the past month; and practices categorised in the red zone will have failed to refer any patients during the past month or they will have been in the yellow zone for two consecutive months. Practices in the red zone will be contacted by the project manager to discuss whether other strategies are needed to increase referrals or if the reason for the lack of referrals is a lack of potentially eligible participants presenting at the practice. If half of the clinics are categorised in the red zone or if less than half of the referred patients are not eligible during a 2-month period, we will recruit additional general practices.

Recruitment through Facebook will be used if fewer than ten participants have been included during any given month following referrals from general practices.

We will post information about the trial on a Facebook page called 'Treatment of pains under the foot' and use the sponsoring function. We target the sponsoring towards both males and females aged 18 years or older who are living within an 80-km radius of Aalborg, Denmark. Each sponsorship will last for 1 week. If this is not sufficient to achieve at least ten included participants per month, including those referred from general practices, we will increase the amount of money per sponsorship first and increase the radius second. Both strategies will increase the reach of the sponsorship. We are able to calculate the cost of each included participant recruited via Facebook by dividing the cost of 1 week of sponsoring by the number of participants included following that week. We have done this before in two studies to compare the cost of participants from general practice with participants from Facebook, and participants recruited from Facebook cost approximately half that of those from general practice [16, 27].

GPs will invite patients to be included in the trial during their normal consultations with patients with pain under the heel. The general practices will send the contact information of patients to the project manager, whereas potential participants recruited through Facebook will contact the project manager directly. The project manager will then inform the physiotherapists about the potential participant, whom they will contact to perform an eligibility telephone screening. The project manager will have no contact with participants after he has forwarded the contact details to the physiotherapists.

Eligibility criteria

The inclusion criteria are as follows: history of inferior heel pain for at least 3 months before enrolment, pain on palpation of the medial calcaneal tubercle or the proximal plantar fascia, thickness of the plantar fascia ≥ 4.0 mm, and mean heel pain of ≥ 30 mm on a 100-mm visual analogue scale (VAS) during the previous week. The exclusion criteria are as follows: younger than 18 years of age; diabetes; history of inflammatory systemic diseases (e.g., rheumatoid arthritis or spondyloarthritis) [19]; prior heel surgery; pregnancy or breastfeeding; corticosteroid injection specifically for PF within the previous 6 months; pain or stiffness in the first metatarsophalangeal joint to an extent that the exercises cannot be performed; known hypersensitivity to corticosteroids or local anaesthetics; skin or soft tissue infection near the injection site; receipt of any treatment by a healthcare professional for PF within the previous 12 weeks; or made any substantial changes to usual self-care of the condition in the last 4 weeks (e.g., started using insoles, started performing stretching, made a substantial decrease in physical activity level). These criteria are in line with those of similar studies in this patient population [16, 17, 19]. These criteria lead to a representative sample of patients with PF because previous studies include the majority of potentially eligible participants [16, 17, 19].

Randomisation and blinding

Participants will be stratified by sex and block-randomised in random concealed block sizes of 3 to 12 (1:1:1) in three parallel groups. A researcher not involved in the trial generated the allocation sequence using a random number generator on www.sealedenvelope.com and is the only person who knows the block sizes. The researcher was trained by the project manager in generating allocation sequences, and the process was piloted.

The randomisation is coded so that the project manager does not know which intervention is linked to which group number (group 1, 2 or 3). The envelopes will be kept in a locked room at Aalborg University Hospital where only the two physiotherapists involved in baseline testing have access. The randomisation schedule was prepared at the Center for General Practice at Aalborg University by a person not involved in the actual trial. The notes in the envelopes state both group number and intervention, and the physiotherapists responsible for assessing participants and delivering the interventions will not be aware of the coding before they open the first envelopes. In practice, after a participant has been enrolled, has filled out questionnaires, and has received initial patient advice and information regarding the practicalities of participation, the physiotherapist will take an envelope and assign the participant to the allocated treatment on the basis of randomisation.

The project manager will be responsible for performing the statistical analyses and will remain blinded to the coding until after the analyses have been performed. The analyses will be performed after the examination that includes the primary endpoint (the 12-week follow-up) of the last participant.

Interventions

Patient advice and heel cup

Participants in all three groups will receive the same initial fundamental patient advice and leaflet about their condition before randomisation. They receive brief information about pathology, risk factors and advice on how to decrease activities that lead to symptom flares and slowly progress back to former activity levels guided by symptoms. To ensure that all participants receive the exact same information, the physiotherapists read a written information out loud; however, they will ask control questions to clarify if the participants understand the information and allow participants to pose questions about the information and participation in general. The leaflet includes the same information that the physiotherapists deliver orally after inclusion in the trial.

Participants will be asked to refrain from seeking other treatments during the course of the trial. They will be allowed to self-treat their PF for pain relief (e.g., with ice or heat packs, rolling a tennis ball under the heel, or massaging the plantar fascia) if they have been doing this for at least 4 weeks prior to inclusion, but they will not be encouraged to do so. Participants will be handed a project diary in which they are asked to record any treatment that they may have received during the course of the trial, including any type of self-treatment and use of analgesic or anti-inflammatory substances. We will inform participants that follow-up on outcomes is critical, regardless of whether they comply with their allocated treatment. Two weeks after inclusion, the physiotherapist who included the participant will contact the participant to ask if they have any questions regarding the condition, the practicalities of participation, or in relation to performing the exercise depending on randomisation. If participants have not achieved a self-evaluated satisfactory result after 12 weeks, they may discuss other evidence-based treatments (e.g., plantar fascia stretching) with the physiotherapist, but they will be encouraged to continue to comply with their allocated treatment.

We will give all participants a silicone heel cup (Medi-Dyne Healthcare Products, Colleyville, TX, USA) for each shoe, and they are advised to use the heel cups whenever they are wearing shoes. If participants already use an insole or another type of foot orthosis, they are allowed to continue wearing this if they prefer this over the heel cups.

Heavy-slow resistance training

Participants of the PAX and PAXI groups will be instructed in performing a heel-raise exercise standing with the forefoot on a step or a book as per Rathleff et al. [26]. Unlike the pre-determined programme used in that trial, we will use a self-dosed programme that we recently found to be associated with the same level of improvement as the pre-determined programme [16]. Participants will be told that it is important that the exercise be performed with an adequately heavy load, and they will be instructed in performing the heel raise with a load corresponding to an 8 repetition maximum (RM) (i.e., a weight that can only be lifted eight times). They may only use a lower relative load if they feel they are unable to perform the exercise with 8 RM. They shall perform the exercise for as many sets as possible. The exercise descriptors are elaborated in Table 1. If participants feel they are able to perform more than eight repetitions with only their body mass (8 RM), an external load consisting of a backpack with books, weights or water bottles to add weight must be used. We will tell participants that pain during the exercise is expected and that there is no upper limit of pain they are allowed to experience, as long as they feel it is tolerable. Participants randomised to also receive the injection will be asked not to perform the exercise within 24 h from the injection and not to progress the method used to achieve 8 RM until 2 weeks after the injection. If heel raise without a backpack is sufficient to achieve 8 RM before the injection, participants should not perform

Table 1 Exercise descriptors

1. Load magnitude	8 repetition maximum
2. Number of repetitions	≥ 8 depending on the load
3. Number of sets	As many as possible
4. Rest between sets	2 min
5. Number of exercise interventions	Every other day
6. Duration of the experimental period	8 weeks
7. Fractional and temporal distribution of the contraction modes per repetition and duration (in s) of one repetition	3 s concentric 2 s isometric 3 s eccentric
8. Rest between repetitions	No
9. Time under tension	8 s/repetition ≥ 64 s/set ≥ 64 s/training session
10. Volitional muscular failure	Yes
11. Range of motion	Full range of motion
12. Recovery time between exercise sessions	48 h
13. Anatomical definition of the exercise (exercise form)	The participant stands with the forefoot on a step. The toes are maximally dorsally flexed by placing a towel underneath them. The participant performs a heel raise to maximal plantar flexion in the ankle joint and afterwards lowers the heel to maximal dorsal flexion. Supporting oneself for balance by placing the hands on a wall or a rail is allowed.

the exercise with a backpack until the third week after the injection, regardless of any pain reduction following the injection. They will be told to perform the exercise until they achieve their Patient Acceptable Symptom State (PASS) (please see 'Secondary outcomes' section for elaboration) and an additional 4 weeks. To support the exercise execution, participants receive a written exercise instruction that also includes pictures of the exercise (Fig. 1).

Ultrasound-guided corticosteroid injection

Participants randomised to PAXI will receive an ultrasound-guided corticosteroid injection, preferably within 8 days from baseline but no later than 14 days after baseline. A 21-gauge, 40-mm needle is connected to a 2.5-cm^3 syringe filled with 1 ml of triamcinolone acetonide 20 mg/ml (Trica; Evolan Pharma, Danderyd, Sweden) + 1 ml of lidocaine 10 mg/ml (Xylocaine; AstraZeneca, Wilmington, DE, USA). The skin is cleansed with chlorhexidine alcohol 0.5% (Medic, Jacksonville, FL, USA). The needle is inserted with a medial approach under ultrasound guidance aligned with the long axis of the ultrasound transducer. The injection is distributed deep and superficially on the plantar fascia surface anterior to the insertion on the calcaneal bone in the region of maximal fascia thickness (see Fig. 2).

Compliance

We will emphasise to participants that we do not know which of the three groups will be superior and that it is very important to comply with the group to which they are allocated for the future results to be meaningful. Participants in the PAX and PAXI groups will be told that complying with the exercise programme is very important and that exercise compliance is associated with the odds of their recovery. Complying with the exercise programme includes performing the exercise with the prescribed form, contraction time, and sufficient load and frequency. All participants will be asked to record their use of the heel cup and any other foot orthoses in a foot orthoses diary as an estimated percentage of the time they have worn shoes. In addition, participants performing exercise will receive a training diary in which they record the number of repetitions and sets and the date on which the exercise was performed.

Variables

Descriptive

The assessment schedule is found in the SPIRIT figure (Fig. 3). During the telephone screening and the clinical examination, we will collect the following data: age, height, body mass index, location and duration of heel pain, average heel pain intensity during the past week (0 to 100-mm VAS, where 0 is no pain and 100 is worst heel pain imaginable), plantar fascia thickness measured by ultrasonography perpendicular to the calcaneal insertion, presence of palpable pain under the plantar heel, comorbidity, treatment history, previous care-seeking behaviour, if females are pregnant or breastfeeding, number of PF episodes, education level, and work status.

Primary outcome

The primary outcome is the mean pain domain score of the FHSQ at the 12-week follow-up. The FHSQ is a questionnaire ranging from 0 (worst possible score) to 100 (best possible score) with high reliability (ICC, 0.74–0.92) that assesses multiple dimensions of foot-related health and function and is recommended in this patient population [35, 36]. The minimal clinically important difference of the pain domain is 14.1 points [37]. We will use a Danish validated translation of the original questionnaire [38].

Secondary outcomes

Secondary outcomes include (1) the other domains of the FHSQ (function, footwear and general foot health domains), (2) Global Rating of Change (GROC), (3) PASS, (4) Pain

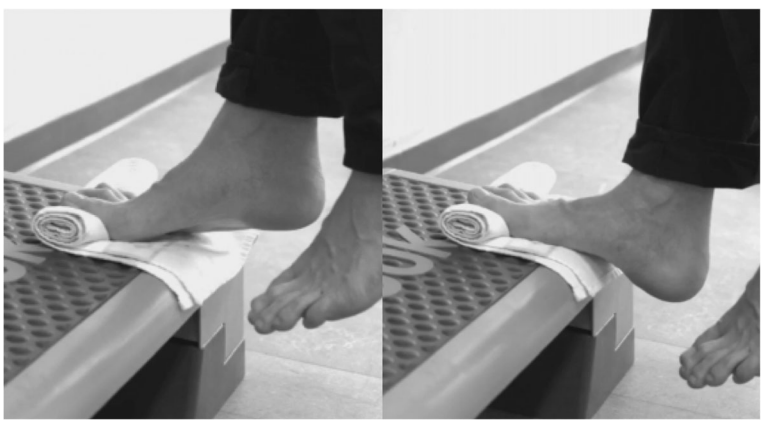

Fig. 1 Pictures of the exercise participants receive embedded in the written exercise instruction

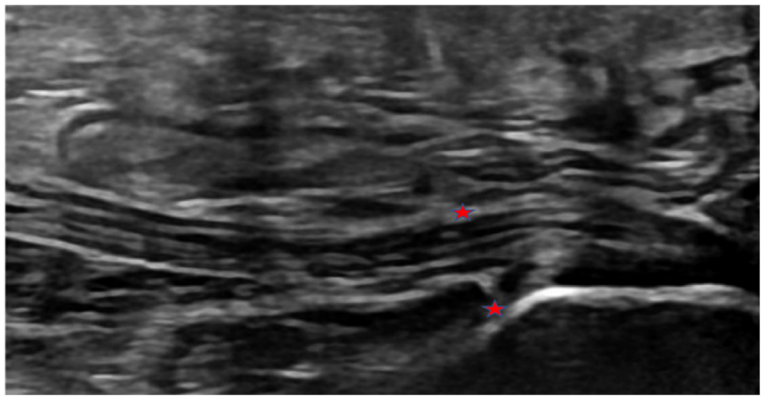

Fig. 2 Ultrasound image of the calcaneus and the plantar fascia. The stars depict the placement of the injection

Self-Efficacy Questionnaire (PSEQ), and (5) weekly light, moderate and vigorous physical activity levels.

We will use the GROC to measure participants' self-reported improvement on a 7-point Likert scale ranging from 'much improved' to 'much worse'. Participants are dichotomised as improved if they rate themselves as 'much improved' or 'improved' (categories 6 and 7) and categorised as not improved if they rate themselves from 'slightly improved' to 'much worse' (categories 1 to 5). PASS (yes/no) will be used as a measure of when participants achieve a self-evaluated satisfactory result and feel no need for further treatment. Therefore, this is not necessarily a measure of complete recovery, because some may be satisfied despite still experiencing symptoms. PASS has been used to evaluate clinically relevant states in PF and in other musculoskeletal disorders and post-operative pain [16, 39–41]. Participants will be asked to report to the physiotherapists as soon as they experience PASS, and the date will be noted. Furthermore, participants will be asked about their PASS status during follow-up. After the participant reports a PASS, they will be instructed to continue performing the exercise as prescribed for at least 4 weeks. The PSEQ measures pain self-efficacy and provides a score ranging from 0 (not at all confident) to 60 (completely confident), with lower scores indicating lower self-efficacy [42]. The Danish version of the PSEQ has been validated in a Danish chronic pain population and has high reliability (ICC, 0.89) [43]. To estimate weekly physical activity level expressed as metabolic equivalents (METs), we will use 3D accelerometry. Participants will be given a wrist-worn accelerometer (ActiGraph wGT3X-BT; ActiGraph LLC, Pensacola, FL, USA) during baseline and will be asked to wear this during the first 3 weeks after baseline and then return the accelerometer in a postmarked envelope. During the 12-week follow-up, participants receive the accelerometer again and will be wearing it for an additional 3 weeks before returning it. Participants will be instructed to wear the accelerometer at all times. We will use data from the first valid week recorded during the first and second rounds of wearing the accelerometer (i.e., 1 week during weeks 1 to 3 and 1 week during weeks 13 to 15). A valid week is defined as ≥ 4 days of ≥ 10 h of wear time [44]. Data will be extracted from the accelerometers using the ActiLife software.

Cost-effectiveness outcomes

A health economic evaluation will be conducted according to international guidelines [45, 46]. All clinical and cost data will be collected alongside the trial. A health sector perspective will be applied to estimate cost utility using the EuroQol Health Outcome EQ-5D-5L instrument and the Danish quality-adjusted life-year (QALY) weights to calculate gained QALYs within a 1-year horizon [47, 48]. For the estimation of patient-specific costs, we will apply the unique Danish civil registration number for each participant to combine registrations of all healthcare consumption from 1 year before enrolment to 1-year follow-up. Data will be taken from the National Patient Register, the National Health Insurance Register, and the Danish National Prescription Registry. Productivity costs will be estimated in a separate analysis measured by a self-developed questionnaire with questions regarding days of sick leave and level of productivity. Patients' co-payments and other condition-related expenses will also be estimated by using questionnaires during all follow-ups.

Adverse events

Participants will be asked to report any adverse events to the physiotherapists immediately after they occur by either telephone, text message or e-mail. Expected adverse events due to the injection are plantar fascia rupture, signs of infection (e.g., fever and local swelling and redness), and local pain in the area of injection lasting more than 48 h after injection. Adverse events after the

SPIRIT figure. Schedule of enrolment, interventions an assessments.		Study period				
	Enrolment	Allocation	Post-allocation			Close-out
TIMEPOINT**	January 21st 2019 – July 21st 2020	January 21st 2019 – July 21st 2020	4 weeks	12 weeks	26 weeks	January 21st 2020 – July 21st 2021 (52-week follow-up)
			52-week Intervention			
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
PAXI			←	—	→	
PAX			←	—	→	
PA			←	—	→	
ASSESSMENTS:						
Diagnosis	X					
Foot Health Status Questionnaire		X	X	X	X	X
Global Rating of Change				X	X	X
Pain Self-Efficacy Questionnaire		X	X	X	X	X
Physical activity level		←	—	→		
Compliance (only in PAX and PAXI)			←	—	→	
Patient Acceptable Symptom State			←	—	→	
EQ-5D-5L		X	X	X	X	X
Sick leave		X	X	X	X	X
Condition-related expenses		X	X	X	X	X
Anthropometric data	X					
Age	X					
Educational level and work situation	X					
Pain localisation	X					
Plantar fascia thickness	X					

Fig. 3 SPIRIT figure. Schedule of enrolment, interventions and assessments

palpation-guided injection are rare, and two trials that used ultrasound-guided injections reported that no adverse events occurred [19–21]. No stopping rules are planned. Expected adverse events due to the exercise are injuries to the musculoskeletal system, such as muscle tears, muscle strains, a sprained joint, injury from falling or exacerbation of symptoms related to PF, delayed-onset muscle soreness equal to or greater than 20 mm on a 0 to 100-mm VAS that lasts for more than 48 h after performing the exercises, or exacerbation of PF.

Adverse events will be graded 1 to 5 according to the Common Terminology Criteria for Adverse Events v4.03 [49]. A medical doctor specialised in either rheumatology or general medicine will assess and grade the adverse event and ultimately make the decision whether the participant should be withdrawn from the trial due to the adverse event. If the adverse event is a grade 1 (mild), the participant may be allowed to skip one or two training sessions without any assessment. If the adverse event recurs after having skipped the exercise, the participant will have to be assessed by the medical doctor before participation in the trial is continued. If a participant experiences an adverse event and requests withdrawal from the study, data until the last exercise activity before the adverse event occurred will be included in the analyses. The physiotherapists will report any incidents to the sponsor as quickly as possible and no later than 15 days after the participant reported the event. The sponsor will report any severe adverse events (grade 3–5) to the Ethics Committee of North Denmark Region no later than 7 days after being informed. All adverse events will be reported in the future reporting of the trial. Any participants who experience harm from trial participation will receive compensation by the Patient Compensation Association.

Concurrent observational cohort

Potential participants who are excluded during the physical examination and eligible participants who decide to withdraw before randomisation will be asked to be part of a concurrent observational cohort inspired by the Spine Patient Outcomes Research Trial [50]. This cohort will be used to describe how excluded participants fare and which treatment they seek. If they agree to be in the cohort, they will receive the same questionnaires as the participants of the FIX-Heel Trial with the addition of a questionnaire about care-seeking behaviour and treatments received during the time between the last follow-up and the current follow-up. We will use the same follow-up times (4, 12, 26 and 52 weeks) as in the FIX-Heel Trial; however, all follow-ups will be conducted through e-mail.

Patient and end-user involvement

To involve both patients and end users in designing the intervention, the participant leaflet was developed on the basis of semi-structured interviews with five patients with PF and five GPs. Patients were asked to describe their heel pain, how it had affected them and which topics they felt would be important to include in a leaflet and in advice to a patient in general. GPs were asked about their experience with the patient group, which treatments they would consider and which topics they felt would be important to include in a leaflet and in advice to the patient in general. The leaflet and fundamental patient advice that the physiotherapists will deliver orally to patients are a triangulation of the results of the interviews with both patients and GPs and recommendations from clinical guidelines and a systematic review [1, 6, 51].

We will invite representative participants from each group to be part of the future interpretation of the results. Their interpretation will be part of the dissemination of the results in the trial report and during conferences. In practice, we will invite two randomly selected participants of each group after the primary outcome has been collected. If a participant declines, we will randomly select a new participant from the same group.

Sample size

The minimal clinically important difference of the FHSQ pain domain has been found to be either 12.5 or 14.1 points in this patient population [37, 52]. We have chosen the most conservative option (i.e., 14.1 points) to form the basis of the sample size calculation. Based on a standard deviation of 22 points, which is comparable to the overall standard deviations found in previous studies of this patient population [19, 53, 54], a two-sided 5% significance level, and a power of 90%, a sample size of 53 participants in each group will be necessary. Taking into consideration possible drop-outs, we will include 60 participants in each group, and thus the total sample size will be 180 participants.

Statistical analyses

All statistical analyses will be performed by a blinded data analyst according to a pre-established analysis plan using the intention-to-treat principle. This plan is written in consultation with a statistician and will be published on the Aalborg University website before the inclusion of the last participant. SPSS software (IBM Corporation, Armonk, NY, USA) will be used as statistical software. We will use Q-Q plots and histograms to assess data normality. Missing outcome data will be imputed using multiple imputations based on the values from previous follow-ups, sex, age, and group allocation.

Primary analysis

The primary analysis will investigate the between-group difference in FHSQ pain. We will use a linear mixed effects model with the participant as a random effect, and time (4, 12, 26 and 52 weeks), group allocation (PA or PAX or PAXI) and baseline value as fixed effects. Conclusions will only be drawn on the basis of the primary endpoint (12 weeks).

Secondary analyses

We will also analyse the mean values of the secondary continuous outcomes (other domains of FHSQ,

PSEQ and physical activity level) using linear mixed models. The risk difference ($= \frac{Positive\ outcomes\ in\ one\ group}{Number\ of\ participants\ in\ group} - \frac{Positive\ outcomes\ in\ another\ group}{Number\ of\ participants\ in\ group}$) will be calculated for the dichotomised GROC to determine the probability of being improved, for the PASS (yes/no) to determine the probability of achieving a self-evaluated satisfactory result within the 12, 26 and 52 weeks of intervention. We will also calculate risk differences to determine the probability of experiencing a deterioration of PF, defined as a decrease in FHSQ pain ≥ 14.1 points from one follow-up to another or changing one's status from having achieved PASS to no longer having achieved PASS. We will calculate the number needed to treat for the primary outcome at the primary endpoint as 1/risk difference. We will use a Kaplan-Meier survival analysis and compare survival curves using log-rank tests to investigate between-group differences in time to achieving PASS [55, 56]. If a participant changes PASS multiple times (e.g., achieving PASS before 12 weeks, reporting not to have achieved PASS at 26 weeks and then having achieved PASS again at the 52-week follow-up), only time to the first PASS achieved is used in the analysis.

Cost-effectiveness analysis

The reporting of the economic evaluation will follow the Consolidated Health Economic Evaluation Reporting Standards checklist for a more transparent and complete reporting of methods and findings [57]. For each intervention, mean values (and standard errors of the mean) will be reported for the main categories of estimated costs and QALYs, as well as mean differences between the comparator groups. Probabilistic sensitivity analyses will be used to estimate the decision uncertainty and calculate incremental cost-effectiveness ratios.

Data monitoring and quality assurance

All data will be stored electronically and are handled according to the General Data Protection Regulation. Data safety may be overseen unannounced by the Danish Data Protection Agency. Participant data will be stored in REDCap, whereas data processor agreements, collaboration agreements between the project group and general practices and protocols will be stored on a secure server at Aalborg University. To prevent data entry errors, data collection instruments have been developed in REDCap so that required data must be included or an error will be displayed, and validation of each field has been chosen (e.g., if the format of the data does not appear to be a date in the field 'Date', an error is displayed). Data are checked once per week by the project manager to ensure there are no missing data. All data will be kept for 10 years after completion of the trial in accordance with the European Code of Conduct for Research Integrity.

Discussion

Future implications

PF is a condition with a wide variety of different treatment options available, with no single treatment showing superiority [18, 51]. HSR is increasingly being used for rehabilitation of PF, despite its effects having only been compared with stretching in a single study [26]. Our recent research with HSR for PF shows within-group improvements in pain similar to those of studies investigating foot orthoses, corticosteroid injections and even placebo injections [16]. By comparing HSR with no HSR and a heel cup and patient advice only, we will be able to answer if performing exercises is worth the extra time and effort required from the patient.

Corticosteroid injection may reduce heel pain for up to 1 month, and adverse events are generally rare and have been reported not to occur when the injection was performed under ultrasound guidance [19–21]. After 1 month, the improvement in symptoms is similar to that of placebo. In contrast, the effects of HSR are known for taking some time to manifest, and performing HSR is usually painful [16, 17, 26]. Patients ask for both short-term and long-term pain reduction, and the combination of these two treatments may potentially offer this. Moreover, in the qualitative data from our feasibility study, we found that several participants felt that pain during exercise was reduced due to the pain relief associated with the injection [27]. This may improve exercise compliance and overall improvement. Despite our hypothesis of superiority of combining the injection with HSR, an injection with corticosteroid may potentially reduce the effect of HSR. This would be similar to how corticosteroids reduced the effect of physiotherapy in a former trial in patients with lateral elbow tendinopathy. In that trial, corticosteroid injections and physiotherapy led to a lower rate of successful outcomes than placebo injections and physiotherapy after 1 year [24]. This indicates that corticosteroids decreased the effect of physiotherapy. Furthermore, the combination of exercise and an injection was not superior to an injection alone in patients with subacromial pain syndrome [29]. One concern is that the pain reduction following the injection will hamper exercise compliance and affect long-term outcomes negatively.

The implementation of our findings will be aided by the inclusion of a cost-effectiveness analysis. There are obvious differences between treatments in how much time and materials are required. The treatment offered in the PA group requires the least, whereas the PAXI group requires the most. However, this difference may be equalised by the potential savings on a societal level in terms of sick leave or on a personal level in terms of QALYs, condition-related improvement and personal expenses. Any future implementation will also be dependent on the patients' experiences and expectations, which is

why patients are involved in the interpretation of the trial findings.

Recruiting patients for trials in primary care is a large challenge, and less than one-third of trials recruit patients within the original recruitment time frame [58]. We use an adaptive recruitment strategy in which we focus primarily on recruitment from general practices, but we will use Facebook recruitment to ensure that the timeline is kept. We may increase the number of recruiting practices or the area and the money used for sponsoring Facebook posts, depending on recruitment rate. This may help inform effective ways of recruiting a large number of participants from general practice in studies requiring large numbers of patients.

Strengths

First, the involvement of patients and GPs in developing the patient advice intervention enables a high level of acceptability for users. Second, all of the interventions are within scope, knowledge and skill levels of primary care clinicians and practices, so they will have a high feasibility of being implemented, regardless of trial findings. Third, all potential outcomes of the trial may influence future clinical practice. If no superiority of one intervention is found over the others, the minimally invasive or the most cost-effective should be implemented, depending on patient preferences. Fourth, to minimise bias, the data analysis will occur blind to group allocation and will be performed according to a pre-established and publicly accessible analysis plan.

Limitations

First, despite the trial being rooted in general practice, the treatments are delivered at the hospital and at a private rheumatology clinic for logistical reasons by physiotherapists and a rheumatologist. Second, if the PAXI group is superior to the others, we cannot disregard that some of that superiority will derive from the placebo effect of receiving an injection. However, we evaluated how the relevance of adding a placebo injection to the PAX group had lessened in light of research concluding the superiority of corticosteroid injections compared with placebo [19–21]. Third, we recruit from both general practice and from Facebook, and we do not know if these recruitment sources yield the same type of patient; still, based on our previous study where we recruited patients solely via Facebook, three in four will have seen their GP due to their PF [17]. This may increase the generalisability of the patients recruited from Facebook to those seen in general practice.

Trial status

Recruitment was started on January 21, 2019, and the first participant was included on February 7, 2019. No amendments have been made to the protocol (version 2.0 January 14, 2019) since it was pre-registered with ClinicalTrials.gov. When this protocol was submitted for publication (October 5, 2019), a total of 96 participants had been included in the trial. We expect recruitment to be completed in July 2020.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13063-019-3977-0.

Additional file 1. SPIRIT 2013 checklist: recommended items to address in a clinical trial protocol and related documents.

Abbreviations

FHSQ: Foot Health Status Questionnaire; GP: General practitioner; GROC: Global Rating of Change; HSR: Heavy-slow resistance training; MET: Metabolic equivalent; PA: Patient advice and heel cup; PASS: Patient Acceptable Symptom State; PAX: Patient advice, heel cup and heavy-slow resistance training; PAXI: Patient advice, heel cup, heavy-slow resistance training and corticosteroid injection; PF: Plantar fasciopathy; PSEQ: Pain Self-Efficacy Questionnaire; QALY: Quality-adjusted life-year; RM: Repetition maximum; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; TiDieR: Template for Intervention Description and Replication checklist and guide; VAS: Visual analogue scale

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Authors' contributions

HR, BV, JLO, MBJ and MSR conceived the trial and developed the protocol. HR, BV, JLO, MBJ and MSR form the steering committee with HR as chair of the committee. HR is the project manager, handles recruitment and will perform the data analyses. LHE conceived the aspects of the cost-effectiveness analysis and will perform this portion of the study. All authors read and approved the final version of this manuscript and will interpret the future results. The definition of an author is based on the four criteria set forth by the International Committee of Medical Journal Editors: (1) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; (2) drafting the work or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. We do not plan on using professional writers for the future trial report.

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Availability of data and materials

Data will be made available upon reasonable request.

Ethics approval and consent to participate

The trial is being conducted according to the Declaration of Helsinki III, and the protocol, template informed consent forms, and participant information were approved by the Ethics Committee of North Denmark Region (N-20180066) prior to the inclusion of participants. All participants provide informed consent before enrolment. When participants sign the consent form, they agree that they have been adequately informed about the purpose, methods, advantages, and disadvantages of participation; they know that participation is voluntary; and they can withdraw from the trial without losing their current or future rights to receive treatment.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Publisher's Note

Corticosteroid Injection plus Exercise versus Exercise, beyond Advice and a Heel Cup for Patients with Plantar Fasciopathy: a Randomised Clinical Superiority Trial (The FIX-Heel Trial)

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Abstract

Objective

To compare the efficacy of patient advice versus patient advice plus heavy-slow resistance training versus patient advice plus heavy-slow resistance training plus a corticosteroid injection in improving the Foot Health Status Questionnaire pain score after 12 weeks in patients with plantar fasciopathy.

Design

A three-armed randomised single-blinded superiority trial.

Setting

Primary care with injections performed at a tertiary care clinic.

Participants

180 adults with plantar fasciopathy confirmed by ultrasound with a duration of a minimum of 12 weeks and pain intensity of at least 30 mm on a 0 to 100 mm Visual Analog Scale were recruited for the study by referral from general practices and Facebook advertisement.

Interventions

Patient advice and an insole (PA) (n=62), or patient advice, an insole, and self-dosed heavy-slow resistance training consisting of heel raises (PAX) (n=59), or patient advice, an insole, heavy-slow resistance training, and an ultrasound-guided corticosteroid injection (1 ml Triamcinolonhexacetonid 20 mg/ml) (PAXI) (n=59). Participants were asked to perform the heavy-slow resistance training until they reached an acceptable symptom state and then an additional 4 weeks.

Primary outcome measure

The primary outcome was change in the pain domain of the Foot Health Status Questionnaire (ranging from 0 “worst” to 100 “best”) from baseline to the 12-week follow-up.

Results

The primary analysis revealed a statistically significant difference in the Foot Health Status Questionnaire pain domain between PA and PAXI (adjusted mean difference: -9.5 (95%CI: -15.3 to -3.6, p=0.002)), but no difference between PAX and PAXI (adjusted mean difference -5.5 (95%CI: -11.5 to 0.4, p=0.069)) or between PA and PAX (adjusted mean difference -3.9 (95%CI: -10.0 to 2.0, p=0.190)).

Conclusions

All three groups had statistically significant and clinically meaningful improvements in Foot Health Status Questionnaire pain during the 12-weeks of follow-up. PAXI was significantly superior to PA, but not significantly superior to PAX after 12 weeks. No superiority was found between PAX and PA. Despite a statistically superior result by PAXI versus PA, the mean difference did not reach the pre-defined minimal clinically important difference. Hence, the choice of treatment is expected to depend on patient and clinician preferences.

Trial registration

The trial was prospectively registered on January 15th, 2019 on ClinicalTrials.gov (NCT03804008).

Introduction

Plantar fasciopathy is a common musculoskeletal disorder in general practice with a yearly prevalence of 2.4 to 6.5 per 1000 patients.(1,2) Individuals with plantar fasciopathy often experience a pain pattern characterised by first-step pain, i.e. pain is worse during the first steps when getting out of bed in the morning or after prolonged periods of non-weightbearing, however, pain improves with ambulation.(3) Historically, the condition was considered to be partially self-limiting for years.(4,5) However, a study in which a long-term follow-up of patients who had attended a specialised clinic was conducted and approximately half of the patients still had symptoms up to 15 years after having attended the clinic.(6) Moreover, a randomised trial that compared different techniques of stretching, concluded that 40% of their participants still had symptoms at the 2-year follow-up.(7) This emphasises the need for improved treatment of these patients.

A systematic review and network meta-analysis investigated the effectiveness of different commonly used treatments for plantar fasciopathy and concluded that no treatment was superior, but corticosteroid injection and shockwave were most likely to be effective on short term.(8) One treatment not included in the review was heavy-slow resistance training (HSR). Preliminary evidence of HSR indicated superiority to plantar fascia specific stretching, but only 6% achieve an acceptable symptom state within 12 weeks.(9,10) Combining an ultrasound-guided corticosteroid injection with HSR could potentially provide patients with superior pain reduction on both short and long term. We recently investigated the feasibility of this combination and concluded that patients accepted this line of treatment. As the current evidence for HSR in this patient population is based on a single randomised trial that used a non-resistance training comparator, there is a need for additional studies to guide future recommendations to use HSR in clinical practice. Therefore, a group not performing exercises but otherwise receiving the exact same treatment was included in the present trial and, thus, the aim of the trial was to compare the efficacy of patient advice (PA) versus patient advice plus HSR (PAX) versus patient advice plus HSR plus a corticosteroid injection (PAXI) in improving the Foot Health Status Questionnaire pain score after 12 weeks in patients with plantar fasciopathy. We hypothesise that PAXI will be superior to both PA and PAX, and that PAX will be superior to PA.

Methods

Protocol deviations

The analyses regarding exercise compliance were not originally planned in the protocol, but they were described in the Statistical Analysis Plan which was published on Aalborg University's research portal prior to the last 12-week follow-up.(11) As participants were allowed to stop performing exercises 4 weeks after achieving the Patient Acceptable Symptom State, achieving this state could be associated with a low number of training sessions performed. Therefore, to perform meaningful comparisons of exercise compliance between PAX and PAXI and to explore an association between the number of training sessions performed and change in Foot Health Status Questionnaire pain, participants who had achieved the Patient Acceptable Symptom State were excluded from these analyses. Due to the COVID-19 restrictions, no inclusions were made, and 12-week follow-ups were conducted electronically between March 11th 2020 and April 24th 2020.

Design

This randomised, single-blinded superiority trial with a 3-group parallel design was prospectively registered on clinicaltrials.gov (NCT03804008) and the trial protocol was published before the inclusion of the final participant.(12) The trial was conducted according to the Declaration of Helsinki III and the protocol, template informed consent forms and participant information were approved by the Ethics Committee of the North Denmark Region (N-20180066) prior to recruitment. All participants provide informed consent before inclusion. The reporting of the trial follows the CONSORT guidelines for reporting randomised parallel-group trials.(13)

Participants

Individuals with plantar fasciopathy were recruited via referral from general practices of the North Denmark Region or via paid advertisement on Facebook. Participants were not informed about the hypotheses of the trial, but they were informed they the trial sought to find the best possible treatment among three commonly used treatment approaches. The inclusion criteria were: history of inferior heel pain for at least three months; pain on palpation of the medial calcaneal tubercle or the proximal plantar fascia; thickness of the plantar fascia ≥4.0 mm and; mean heel pain of ≥30 mm on a 100 mm VAS during the previous week. Major exclusion criteria were: below 18 years of age; diabetes; history of inflammatory systemic diseases (14); prior heel surgery; pregnancy or breastfeeding; known hypersensitivity to corticosteroids or local anaesthetics; skin or soft tissue infection near the injection site; received any treatment by a healthcare professional for PF within

the previous 12 weeks; or made any substantial changes to usual self-care of the condition in the last 4 weeks.(12)

Randomisation

Potential participants that were either referred by their general practitioner or contacted the primary investigator after seeing the Facebook advertisement underwent telephone screening and a clinical examination by one of three project physiotherapists. After baseline assessment, they were randomised stratified by sex in random concealed block sizes of 3 to 12 (1:1:1) into three parallel to receive either 1) patient advice and an insole (PA), or 2) patient advice, an insole and HSR (PAX), or 3) patient advice, an insole, HSR and an ultrasound-guided corticosteroid injection (PAXI). The randomisation schedule was prepared at the Center for General Practice at Aalborg University by an independent person not involved in the trial who generated the allocation sequence using a random number generator on www.sealedenvelope.com.

Interventions

The patient advice participants across all three groups received consisted of both oral information given by the physiotherapists and a leaflet that was handed out afterwards containing the same information. Patient advice consisted of brief information about pathology, risk factors and advice on how to decrease activities that lead to symptom flares and slowly progress back into former activity levels guided by symptoms. Participants asked not to seek other treatments during the course of the trial, however, they were allowed to self-manage their plantar fasciopathy for pain relief (e.g. with ice or heat packs, rolling a tennis ball under the heel, or massaging the plantar fascia) if they have been doing this for at least four weeks prior to inclusion, but they were not encouraged to do so. If participants chose to continue any type of self-treatment, they were asked to record this in a project diary that was given to them.

The insole used was a silicone heel cup (Medi-Dyne Healthcare Products, Colleyville, TX, USA) that participants were advised to use at all times when wearing shoes. If participants already used a type of foot orthosis that they preferred to wear after having tried out the heel cup, they are allowed to continue wearing this.

The HSR that was performed by participants in both PAX and PAXI was a heel raise exercise standing with the forefoot on a step or a book with a rolled-up towel underneath the toes as per Rathleff et al. 2015.(9) Participants were asked to perform the exercise every other day with a load

as heavy as possible but no heavier than a load corresponding to 8RM and with as many sets as possible separated by 2 minutes of rest. The concentric and eccentric phases should last for 3 seconds each and the isometric phase during maximal dorsi-flexion should last for 2 seconds. Pain during exercise was expected and no upper limit of pain allowed was used as long as participants evaluated pain to be tolerable. In both groups, participants were asked to perform the exercise until they reached a self-evaluated satisfactory result and then an additional 4 weeks. In PAXI, participants were not allowed to progress the method used to achieve an 8RM (e.g. progressing from performing the exercise on both feet to single-legged) until the third week after receiving the injection.

Participants in PAXI received an ultrasound-guided corticosteroid injection by an experienced rheumatologist preferably within eight days but no later than 14 days after baseline. The injection consisted of 1 ml Triamcinolonhexacetonid 20 mg/ml (Trica, Evolan Pharma) + 1 ml Lidocain 10 mg/ml (Xylocain, AstraZeneca). The needle was inserted with a medial approach and the injection was distributed deep and superficial on the plantar fascia surface anterior to the insertion on the calcaneal bone in the region of maximal fascia thickness.

All interventions are described in detail in the protocol.(12)

Outcome measures

Outcomes were assessed during baseline, after 4 weeks and after 12 weeks (primary endpoint). Participants attended baseline and the 12-week follow-up at the hospital whereas an e-mail with a link to questionnaires was sent by REDCap (Vanderbilt University, Nashville, TN, USA) to participants for the 4-week follow-up and for the 12-week follow-up in cases where attending the follow-up at the hospital was not possible.

Primary outcome

The primary outcome was the pain domain of the Foot Health Status Questionnaire (FHSQ) ranging from 0 (worst possible score) to 100 (best possible score).(15,16) The minimal important difference of the pain domain is 14.1 points.(17) We used a Danish validated version of the questionnaire.(18)

Secondary outcomes

Secondary outcomes were: 1) the other domains of the FHSQ (function, footwear and general foot health domains), 2) a dichotomised Global Rating of Change (GROC) to measure participants' self-

reported improvement from baseline to the 12-week follow-up on a 7-point Likert scale ranging from “much improved” to “much worse”. Participants are dichotomised as improved if they rate themselves as “much improved” or “improved” (categories 6 and 7) and categorised as not improved if they rate themselves from “slightly improved” to “much worse” (categories 1 to 5), 3) a dichotomised Patient Acceptable Symptom State (PASS) (Yes/No) used as a measure of when participants achieved a self-evaluated satisfactory result and felt no need for further treatment, 4) the Pain Self-Efficacy Questionnaire (PSEQ) as a measure of pain self-efficacy ranging from 0 (not at all confident) to 60 (completely confident) with lower scores indicating lower self-efficacy(19), and 5) number of training sessions performed by PAX and PAXI as an estimation of exercise compliance. The secondary outcomes and other outcomes to estimate physical activity level and cost-effectiveness of the interventions that were not included in the trial report are described in the protocol.(12)

Statistical analyses

The primary investigator who was blinded to group allocation performed the statistical analyses according to a statistical analysis plan that was developed in collaboration with a statistician and a biostatistician. The primary investigator and the group of authors remained blinded until after the analyses had been made and the conclusions had been decided upon. The analyses were made on December 22nd, 2020, and an agreement on the conclusion was made on January 11th, 2021, by all authors.

Sample size was based on the ability to detect the minimally important difference in FHSQ pain (14.1 points). Based on a standard deviation of 22 points (14,20–22), a two-sided 5% significance level and a power of 90%, a sample size of 53 participants in each group will be necessary. Taking into consideration possible dropouts, we included 60 participants in each group.

Statistical analyses were performed on an intention to treat basis using SPSS (IBM Corporation, New York, United States) as statistical software. Q-Q plots and histograms were used to assess data normality. The primary analysis was a linear mixed effects model to test between-group differences in FHSQ pain with the participant as random effect. The baseline value, time (4, and 12 weeks), group allocation (PA or PAX or PAXI) and term for interaction between time and group were treated as fixed-effect variables. Conclusions would only be drawn based on differences or the lack hereof at the primary endpoint (12 weeks). The same model was applied to investigate between-group differences in the other domains of the FHSQ and the PSEQ. Using the dichotomisation of

the GROC, the relative risk of being improved was calculated and the relative risk of having achieved a satisfactory result within 12 weeks was calculated according to the PASS and the number needed to treat (NNT) was calculated as 1/risk difference. Potential differences in number of training sessions performed between PAX and PAXI were explored using an unpaired t-test and Pearson's correlation coefficient was used to explore an association between the number of training sessions performed and change in FHSQ pain.

Patient and end-user involvement

The leaflet and patient advice which the physiotherapists delivered to participants were a triangulation of the results of semi-structured interviews with both patients and general practitioners about what was important to include in patient advice and recommendations from clinical guidelines and a systematic review.(4,23,24)

Results

Enrolment and follow-up

A total of 369 individuals were either referred from their general practitioner or responded to the Facebook advertisement. The 180 participants were included in the study from February 2019 to September 2020 and the final 12-week follow-up was conducted in December 2020. Baseline characteristics of the included participants are displayed in Table 1. The 4-week follow-up was completed by 54 (87%) of 62 participants in PA, by 52 (88%) of 59 in PAX, and by 54 (92%) of 59 in PAXI. The 12-week follow-up was completed by 53 (86%) of 62 participants in PA, by 46 (78%) of 59 in PAX, and by 50 (85%) in PAXI.(Figure 1) One participant in PAX reported an adverse event, but this was not related to performing the exercise.

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Table 1

	PA (n=62)	PAX (n=59)	PAXI (n=59)
Age (yr), mean (SD)	50.4 (10.2)	48.8 (11.3)	46.2 (11.6)
Sex, n (female%)	44 (71.0)	42 (71.2)	42 (71.2)
Height (cm), mean (SD)	171.9 (8.5)	172.6 (8.3)	173.2 (8.5)
Mass (kg), mean (SD)	89.8 (16.0)	88.1 (18.3)	87.8 (19.9)
Body mass index (kg/m2), mean (SD)	30.4 (5.2)	29.4 (5.2)	29.2 (6.0)
Symptom duration (month), median (IQR)	7 (5-18)	7 (5-12)	6 (5-14)
Pain during past week (0 to 100), mean (SD)	65.6 (17.2)	61.7 (18.4)	68.1 (17.3)
Bilateral pain, n (%)	20 (32)	14 (24)	17 (29)
Plantar fascia thickness (mm), mean (SD)	5.5 (1.2)	5.6 (1.1)	5.5 (1.2)
Comorbidities, n (%)	15 (24)	13 (22)	23 (39)
Educational level, n (%)			
-No vocational education	1 (1.6)	4 (6.8)	10 (17.0)
-One or more courses	1 (1.6)	2 (3.4)	3 (5.1)
-Vocational education (<1 year)	2 (3.2)	0 (0.0)	0 (0.0)
-Vocational education (>1 year)	33 (53.2)	34 (57.6)	28 (47.5)
-Short further education (2-3 years)	6 (9.7)	1 (1.7)	2 (3.4)
-Medium length further education (3-4 years)	13 (21.0)	18 (30.5)	11 (18.6)
-Long further education (>4 years)	6 (9.7)	0 (0.0)	5 (8.5)
In the workforce, n (%)	47 (75.8)	53 (89.8)	49 (83.1)
Care-seeking behaviour, n (%)			
-General practitioner	43 (69.4)	37 (62.7)	43 (72.9)
-Physiotherapist	11 (17.7)	4 (6.8)	7 (11.9)
-Medical specialist	10 (16.1)	6 (10.2)	5 (8.5)
-Other	5 (8.1)	6 (10.2)	11 (18.6)
-None	15 (24.2)	21 (35.6)	14 (23.7)
No previous treatment, n (%)	28 (45.2)	27 (45.8)	32 (54.2)

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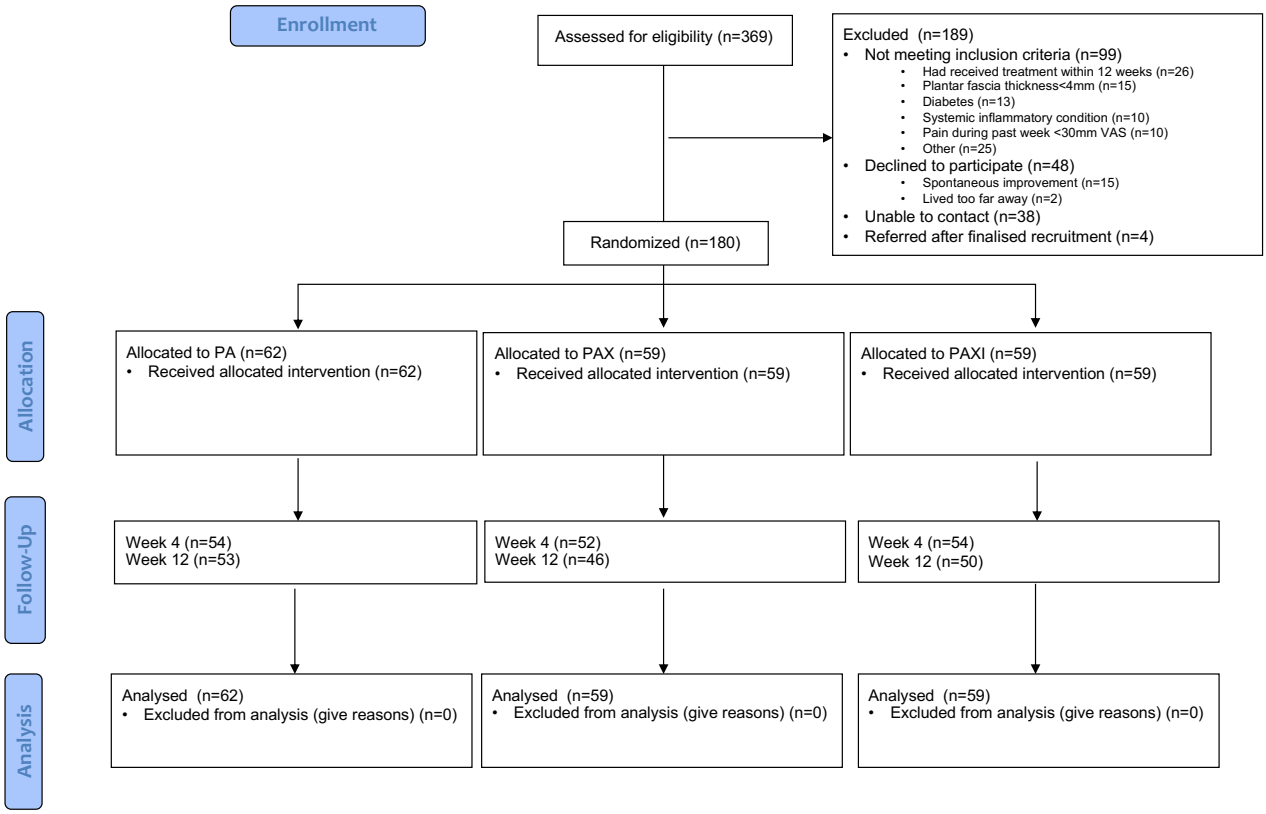
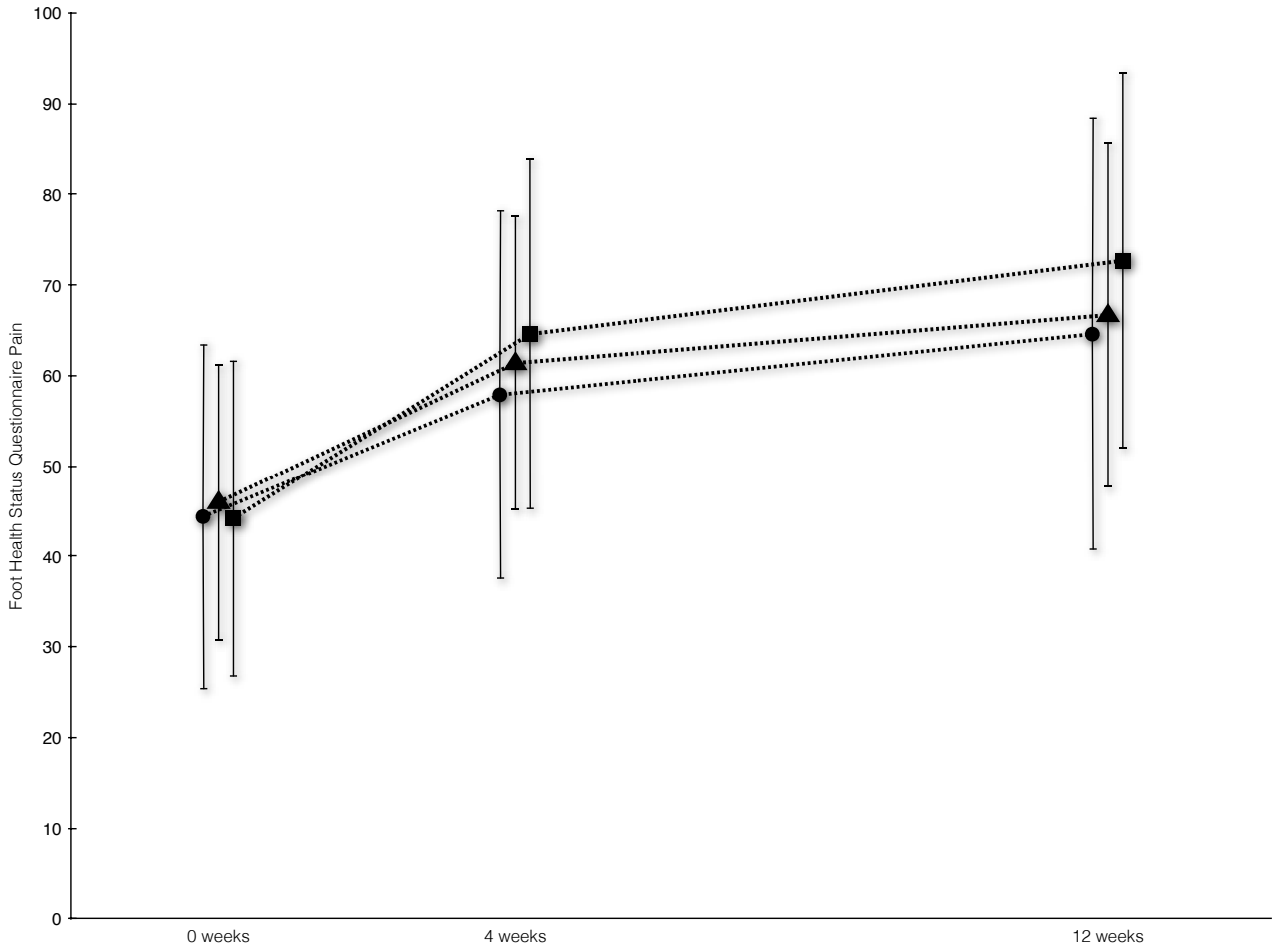


Primary outcome

The primary analysis revealed a statistically significant difference in FHSQ pain between PA and PAXI (adjusted mean difference: -9.5 (95%CI: -15.3 to -3.6, p=0.002)), but no difference between PAX and PAXI (adjusted mean difference -5.5 (95%CI: -11.5 to 0.4, p=0.069)) or between PAX and PA (adjusted mean difference 3.9 (95%CI: -2.0 to 10.0, p=0.190)) (Figure 2). The difference between PAXI and PA did not exceed the minimally important difference of 14.1 points.



Secondary outcomes

PAXI was statistically significantly superior to PA in FHSQ function domain (adjusted mean difference: 7.5 (95%CI: 2.0 to 13.2, p=0.009)), but no other statistically significant differences were found in the FHSQ or the PSEQ (Table 2). Results of the dichotomised GROC showed that 25/53 improved in PA, 25/46 improved in PAX, and 31/49 improved in PAXI. The relative risk between PAX and PA was 1.2 (p=0.475, NNT=13.9), the relative risk between PAXI and PA was 1.3 (p=0.106, NNT=6.2), and the relative risk between PAXI and PAX was 1.2 (p=0.381, NNT=11.2). PASS was achieved before the 12-week follow-up by 11 in PA, 8 in PAX, and 21 participants in PAXI. The relative risk between PA and PAX was 1.3 (p=0.530, NNT=23.9), the relative risk between PAXI and PA was 2.0 (p=0.032, NNT=5.6), and the relative risk between PAXI and PAX was 2.5 (p=0.010, NNT=4.5). Participants in PAX performed 30.9 (±12.4) training sessions (74% of prescribed sessions) and participants in PAXI performed 29.9 (±10.4) training sessions (71% of prescribed sessions). There was no difference between groups (mean difference: 1.0 sessions,

95%CI: -5.9 to 7.8, p=0.779), and there was no association between the number of training sessions performed and change in FHSQ pain (*r*=-0.044, p=0.770).

Table 2

	PA	PAX	PAXI	PA vs PAX	PA vs PAXI	PAX vs PAXI
FHSQ Pain						
Baseline	44.4 (19.0)	46.0 (15.2)	44.2 (17.4)	-5.5 (-11.5 to 0.4, p=0.069)	-9.5 (-15.3 to -3.6, p=0.002)	-3.9 (-10.0 to 2.0, p=0.190)
4 weeks	57.9 (20.3)	61.4 (16.2)	64.6 (19.3)			
12 weeks	64.6 (23.8)	66.7 (19.0)	72.7 (20.7)			
FHSQ Function						
Baseline	60.3 (19.4)	60.0 (18.0)	56.9 (23.6)	-4.5 (-10.0 to 1.3, p=0.126)	-7.5 (-13.1 to -2.0, p=0.009)	-3.2 (-8.9 to 2.6, p=0.277)
4 weeks	68.9 (20.0)	71.6 (17.5)	70.4 (20.7)			
12 weeks	75.4 (19.5)	79.6 (18.0)	82.9 (20.5)			
FHSQ Footwear						
Baseline	39.9 (19.6)	39.1 (20.0)	37.4 (23.1)	3.3 (-5.6 to 12.2, p=0.463)	3.4 (-5.3 to 12.2, p=0.443)	0.1 (-8.9 to 9.1, p=0.981)
4 weeks	47.7 (23.8)	46.3 (24.2)	42.4 (26.9)			
12 weeks	51.7 (26.2)	51.1 (25.3)	49.8 (28.8)			
FHSQ General Foot Health						
Baseline	49.0 (26.4)	45.0 (28.8)	46.4 (26.8)	2.0 (-7.0 to 10.9, p=0.666)	-2.0 (-10.8 to 6.9, p=0.661)	-3.9 (-13.0 to 5.1, p=0.392)
4 weeks	50.4 (28.3)	46.3 (24.9)	50.9 (25.6)			
12 weeks	55.5 (26.6)	56.1 (27.0)	59.2 (27.5)			
PSEQ						
Baseline	41.1 (11.0)	39.3 (12.1)	39.2 (11.2)	-2.8 (-6.9 to 1.3, p=0.175)	-2.3 (-6.3 to 1.8, p=0.267)	0.5 (-3.6 to 4.7, p=0.798)
4 weeks	44.9 (13.3)	45.8 (10.4)	44.5 (11.8)			
12 weeks	46.6 (12.7)	49.1 (10.4)	49.9 (11.7)			

Discussion

Principal findings

We hypothesised that PAXI would be superior to both PA and PAX, and that PAX would be superior to PA. As hypothesised, PAXI was superior to PA in FHSQ pain, however, the between-group difference was 4.6 points short of reaching the minimally important difference which questions the clinical relevance of the difference. No other hypothesis could be confirmed which means that performing HSR was no better than not performing HSR. Nor was it better to receive an ultrasound-guided corticosteroid injection and then perform HSR compared to just performing HSR.

Strengths and limitations

The trial had both several strengths and limitations to be considered. Due to the nature of the interventions, blinding of participants was not possible. Despite they were told that we expected an effect in all groups, it is very likely that participants knew that those receiving more treatment (i.e., PAX and PAXI) were considered more likely to recover. Not only could participants' expectations influence the results, but participants of PAXI also attended a tertiary clinic and the added attention and time from simply having seen an additional clinician could affect outcomes. In a general

practice setting where the general practitioner provides all treatments themselves, this would not be an issue.

The majority of participants had already sought care for their condition and had had a median symptom duration of 7 months at baseline. Therefore, it cannot be ruled out that we included several non-responders to treatment despite having used a 3-month washout period between having received treatment from healthcare personnel and participating in the study. However, the inclusion of non-responders would have affected all three groups and should not influence the conclusions of the trial. Moreover, having sought care cannot be mistaken for having received treatment as the most commonly applied treatment in a general practice setting is wait-and-see.(25) This is further corroborated by the fact that approximately half of all participants included had never received any treatment for plantar fasciopathy.

Comparison with other studies

This was the first trial that investigated the effect of HSR compared to no HSR and HSR to HSR and an ultrasound-guided corticosteroid injection, yet, the effect of a combination of strength training and stretching has been compared against either a corticosteroid injection alone or a corticosteroid injection and strength training and stretching before.(26) The authors of that study concluded that the combination of corticosteroid injection and strength training with stretching was superior to the other two groups. Their conclusions were based on their primary endpoint, which was 6 months, but already after 3 months, they found that combining exercises with an injection was significantly better than exercises alone. We did not find a similar superiority between PAX and PAXI, however, we used a single injection whereas Johannsen et al. continued to perform injections every month until the plantar fascia thickness was less than 4 mm or until participants had received three injections. Not only may the repeated administration of corticosteroid add to the effect of the treatment but every additional injection will also give an additional placebo effect.(27) Repeated injections may increase the risk of plantar fascia rupture as corticosteroid affects the and mechanical properties of collagen tissue.(28,29) Johannsen et al. did not record any adverse events and a Cochrane-review concluded that an ultrasound-guided corticosteroid injection was a safe treatment in this patient population, thus, repeated corticosteroid injections may be an area of further exploration as we did not find a single corticosteroid injection combined with HSR to be superior to HSR alone.(26,30)

The PA group received a combination of patient advice and a heel cup and should not be considered a wait-and-see approach but to a higher degree a minimally invasive approach. This approach is comparable to interventions in studies that have investigated the efficacy of foot orthoses compared to other treatments. A recent large randomised clinical trial compared foot orthoses with a single ultrasound-guided corticosteroid injection in 103 participants with plantar heel pain.(31) The study found that a corticosteroid injection was superior after 4 weeks whereas foot orthoses were superior after 12 weeks. The trajectory of improvement seen in the foot orthoses group was comparable to that of the PA group in our trial, but the trajectory of the injection group was more comparable to that of other studies using just an injection and not an injection in combination with HSR which the PAXI group of our trial received. Studies that use an injection in isolation find a large short-term improvement but after this, the curve flattens or patients even experience a slight deterioration.(14,31,32) In contrast, participants of PAXI experienced a constant improvement over time which suggests that adding HSR to an injection might be a preferred treatment approach compared to an injection alone.

Explanation of results and implications for clinicians and policy makers

Only PAXI was superior to PA and not PAX meaning that adding HSR to patient advice and a heel cup does not lead to superior outcomes. Despite the preliminary findings of HSR in patients with plantar fasciopathy suggested that HSR could be associated with improved management in this patient group, the results of the present trial find that this is not true.(9) Our previous trial in which we compared different HSR programmes found that only 4/70 participants achieved PASS within 12 weeks.(10) Even though 8/59 participants in PAX achieved PASS in the present trial, the role of HSR in plantar fasciopathy remains questionable as it was not superior to PA. However, as HSR was a completely new approach when it was compared to stretching by Rathleff et al. 2015 and subsequently received a great deal of attention among practitioners, several participants of the following studies would have tried the exercise unsuccessfully which may have hampered the odds of a successful outcome. Furthermore, participants of the present trial were required to have had symptoms for at least 3 months. Earlier loading of type I collagen tissue may lead to improved outcomes, which is why loading programmes may still serve a purpose in plantar fasciopathy management.(33)

Despite PAXI was superior to PA, PAXI was not superior to PAX. When patients are aware of receiving an additional treatment, part of the effect of that treatment will be a placebo effect when

they believe the treatment might be to their benefit.(27) Therefore, it cannot be ruled out that the superiority was the result of the combined placebo effects of HSR and the injection. Even though PAXI was statistically superior to PA, the difference did not exceed the minimally important difference of 14.1 points.(17) A less conservative minimally important difference of FHSQ pain was calculated to be 12.5 points, yet, this was still more than the between-group difference of 9.5 points which we found.(34) One thing to consider is that the minimally important difference was calculated in a different setting and among Australians using GROC that asks participants to rate improvement compared to the start of the treatment coupled with the FHSQ that asks participants about their current symptoms. The use of GROC has been criticised for introducing recall bias, however, there is no consensus on how to best calculate a minimally important difference.(35) Despite the difference between PAXI and PA was not important according to the minimally important difference, participants of PAXI were twice as likely to achieve PASS than participants of PA within 12 weeks.

In conclusion, all three groups had statistically significant and clinically meaningful improvements in FHSQ pain. PAXI was significantly superior to PA, but not significantly superior to PAX after 12 weeks. No superiority was found between PAX and PA. Despite a statistically superior result by PAXI versus PA, the mean difference did not reach the pre-defined minimal important difference. Hence, the recommended treatment approach is expected to depend on future health-economic evaluations and patient and clinician preferences.

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