STATISTICAL ANALYSIS PLAN

Modified exercise therapy as a treatment of Achilles tendon enthesopathy supplemented by injection of corticosteroid or local anesthetic.

Trial Registration

Clinicaltrials.gov Trial registration identifier: NCT04232358

Ethical Committee of the Capital Region: H-190413740270,

Protocol Version and Date

This document has been written based on information contained in the study protocol version 4, December 2019 approved by the Ethical Committee.

Statistical Analysis Plan Version and Date

Version 1

29th September, 2022

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1 SIGNATURES

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2 INTRODUCTION

Achilles tendinopathy (AT) is a frequent and often long-lasting disease especially in athletes. The cumulative incidence in former elite athletes is 50% compared to 5.9% in inactive individuals (Kujala, 2005). In particular, athletes involved in running and jumping activities are at risk (Kvist 1991). In the case of running, the incidence is 9%. In approximately 20% of cases the injury is localized to the tendon enthesis (Lysholm 1987).

In mid-substance AT (in the tendon proximal to tendon attachment), the primary treatment is eccentric exercises that have a positive effect on 60% to 90% of patients (Silbernagel2001, Maffuli, 2008, 2010, Ohberg). Other studies have shown positive effects of stretching exercises (Porter 2002) and in a randomized study, no difference in outcome could be seen when treating with eccentric exercises compared to stretching exercises (Nørregård 2007). In a recent study at our institute, heavy slow strength training has been shown to be equally effective compared to eccentric training (Beyer 2015). However, patients with AT most distally in the tendon attachment to the bone, called enthesopathy, is often excluded from these studies. Eccentric training in maximum dorsiflexion has been shown to have a poor effect on enthesopathies (Fahlstöm 2003). In a non-controlled pilot study, a good effect of eccentric exercises avoiding dorsiflexion has been documented in patients with Achilles enthesopathy (Jonsson 2008). In another study, we found that patients with mid-substance AT and patients with Achilles tendon enthesopathy responded equally well to a cautious progressive exercise program (Wetke 2015).

Injection with Cortikosteroid (CS) is often used in the clinic, but since there is usually an absence of inflammatory cells in AT, the rationale behind the treatment is controversial (Khan 2002). However, a randomized clinical controlled trial (RCT) has shown good efficacy of CS injections given ultrasound-guided in chronic AT (Fredberg 2004). A significant short-term positive effect on symptoms and a reduction in the thickness of the tendons were seen, but relapse of tendinopathy after 6 months, possibly due to an aggressive rehabilitation course. In exercise efficacy studies that include patients with mid-substance AT, 60 to 90% of patients will typically have a positive effect of treatment (Silbernagel 2001, Fahlström 2003, Maffuli 2008). However, the effectiveness of exercise therapy was significantly lower in a mixed cohort that included all consecutive patients with achilles tendinopathy, as well as enthesopathy, where only 26% had a satisfactory effect from

exercise alone (Wetke 2014). Likewise, only 10% of a mixed cohort had satisfactory effect of a program consisting of eccentric exercises for home training (Ram 2013). Overall, exercise most often has a beneficial effect in patients with tendinopathy proximal for attachment, whereas the beneficial effect of training in patients with tendinopathy at the attachment – enthesopathy – is more questionable. In the study by Wetke (2015), it was documented that the exercise therapy by need supplemented with injection of CS mixed with local anesthetics in both mid-substance AT and enthesopathy, but whether this effect was due to a pain-reducing effect of local anesthesia or an anti-inflammatory effect of CS is not known. So far, no RCT study has been conducted assessing the combined effect of exercise and injections in patients with enthesopathy. Our hypothesis is that exercise therapy combined with CS will have a better effect than exercise therapy combined with injection of local anesthetics

The existing standard treatment of AT, without differentiation between tendinopathy in mid-substance or enthesopathy, is, according to clinical guidelines in the Danish Sports Medicine Society (DIMS) and in the Danish Rheumatological Society (DRS), primarily load reduction supplemented by exercise therapy with strengthening exercises. If necessary, this can be supplemented by injection of CS, usually mixed with local anesthetics.

The purpose of our study is to investigate whether the existing standard treatment with load reduction by reduced running and jumping activities and slowly progressed controlled exercises in combination with injection of CS reduces pain and improves function more than treatment consisting of the same load reduction and exercise program combined with placebo injection in patients with enthesopathy.

The study is based on the following hypothesis:

Treatment of Achilles tendon enthesopathy with controlled exercises and reduced running and jumping activities combined with corticosteroid injection (current standard treatment) provides better pain reduction and increase in function than treatment consisting of the same load reduction and exercises combined with placebo injections.

3 MATERIAL AND METHODS

Patients with suspected Achilles tendinopathy are usually referred to the Department of Sports Medicine at Bispebjerg Hospital or specialist practice in rheumatology.

Inclusion criteria

1. Ultrasound diagnosed Achilles entesopati.
2. In ultrasound scanning, the affected Achilles tendon must be trumpet-shaped thickened in the attachment (enthesis) and with increased flow in the tendon itself.
3. Duration of pain should be a minimum of 3 months
4. Participants are from 18 years to 65 years.
5. Participant may provide relevant and adequate informed consent.

Exclusion criteria.

1. Previous lower limb surgery. Arthroscopy of the knee excepted.
2. No known medical conditions, including insulin-dependent diabetes mellitus or rheumatic diseases.
3. Infection of the foot or lower leg.
4. Mental state that does not allow participation.
5. Assessed not able to partcipate in the exercise therapy.
6. Lack of presence in the region during the project period.
7. Daily use of pain medications, including NSAIDs.
8. Cannot read or understand Danish*.
9. Steroid injection to treat Achilles enthesopathy/tendinopathy within the last 6 months.
10. Previous allergic reaction to treatment with corticosteroid (Depomedrol®) or local anesthetics.
11. Pregnancy/breastfeeding or planning of pregnancy during the intervention period.

*Due to the cost of an interpreter, the subject has to read and understand Danish.

4 STUDY METHODS

Triple blinded Randomized Controlled Trial.

Randomization method

Randomization must be preceded by informed consent and power of attorney. The randomization of patients is done by an independent project secretary who is not involved in the patient treatment. This is done by a computer randomization program. Patients will be divided equally into 2 groups. The independent project secretary is then in charge of filling out randomization sheets and mixing injection for the investigator. The project secretary must prepare the 2 injections according to the description below, and must keep the randomization sheet for patients secretly and securely locked until the end of the trial, which is defined as 12 months of follow-up of patient number 50. The project secretary will also be responsible for accounting for used medicine. The project secretary has no treatment contact with the patients.

Blinding

Randomization is performed by an independent office employee not involved in patient care (Charlotte Bilde) using a computer generated randomization schedule (MINIMPY, Maghaei 2010) using permuted block sizes (four to six). The employee is blinded to the block sizes. The allocation of each patient is stored in a computer drive with exclusive access only for the responsible office employee (Charlotte).

All patients are given consecutive research numbers.

Patients are blinded to treatment: The syringe are blinded with tape only showing the patients research number. The content is visually identical and with similar viscosity by mixing intralipid to the placebo injection. There is a risk that blinding will be affected by the known side effects of injection with corticosteroids (flare-up and flushing). Therefore, at the first check-up after the injection, patients are asked which of the two groups they think they have been in.

Doctors performing the injections are blinded (JR, CB): The syringe are blinded with tape only showing the patients research number. The content is visually identical and with similar viscosity by mixing intralipid to the placebo injection.

Data entry investigator are blinded (JR). All data is transferred from Redcap / CRF to Xcel sheet without knowledge of treatment group allocation. After all data is transferred, the patients are divided into two groups "A" and "B" but still blinded to actual treatment groups, by information from the independent office employe.

Statistician is blinded (PSM): After data entry and the patients are divided in two groups: group A and group B still blinded to the actual treatment group, all statistics are performed until agreement of the results. Thereafter the blinding is broken.

The 2 treatment arms are:

GROUP 1 Exercise + placebo injection: Treatment with controlled training controlled via the training app "Injurymap" (CE approved by the Danish Medicines Agency as a medical device) and reduced running and jumping activities combined with injection of local anesthetics. This consists of lidocaine as well as intralipid. Lidocaine is a mild pain reliever and the intralipid is added so that the mixture is not visibly distinguishable from the corticosteroid.

GROUP 2: Exercise + corticosteroid injection. Treatment with controlled training controlled via the training app "Injurymap" and reduced running and jumping activities combined with corticosteroid injection. This injection consists of Depo-medrol® (methylprednisolone acetate) 1ml and lidocaine 10mg/ml 1ml.

Description of load reduction

For the first 3 months, the patient must refrain from jumping and running activities (impact training). They are allowed to do non-impact training such as cycling, swimming, rowing and strength training. Shoes that do not press into the back of the heel are recommended. After 3 months, they must slowly return to their previous sports activity with jumping and running, without provoking further pain or morning stiffness.

Description of training with CE approved training app: Injurymap.

The strength training will consist of a gently progressive training program with daily training. The training program starts with gentle exercises without dorsal flexion and is slowly progressed after feedback from the patient. If the patient register pain of 5 or above on a 0-10 scale, the program will choose a lighter exercise and not until 2 weeks later offer the same exercise again. The program consists of both movement exercises, stretching exercises, balance exercises and strength exercises similar to the exercise program we have used and found effective in a previous study (Wetke 2015)

For bilateral symptoms, both sides must be trained, but only one side is included in the evaluation of outcome parameters.

Description of injection of corticosteroid

The corticosteroid injection consists of the mixture of 1 ml of Depomedrol (40 mg/ml) and 1 ml of lidocaine 1% (10mg/ml). The mixtrure will be prepared before injection with the syringe covered with non transparent tape marked with the study number of the patient and stored in a fridge. Under ultrasound guidance, the 2 ml mixture will be injected underneath the tendon close to the enthesis. The preparation of the mixtures will be performed by an assistant not involved in the treatment and without contact to the patients, thereby maintaining the blinding of both the patient and the medical practitioner. Regardless of whether the symptoms are bilateral or unilateral, only one side is injected. As long as there is morning pain above 20 (VAS 0-100) or exercise pain above 20 (VAS 0-100) or overall assessment less than +3 on (Lickert scale from -5 to +5, where "0" is the status at entry and +5 is completely cured), injection is given at inclusion and 1 and 2 months after inclusion, but not more than 3 times.

Description of injection of local anesthetics

Local anaesthetic treatment (placebo) will contain a mixture of 1 ml lidocaine 1% (10 mg/ml) and 1 ml 20% Intralipid. Intralipid will be added to give the mixture similar appearance as the corticosteroid injection. The mixture will be prepared before injection with the syringe covered with non transparent tape marked with the study number of the patient and stored in a fridge. The injection technique is the same as for steroid injection. The preparation of the mixtures will be performed by an assistant not involved in the treatment and without contact to the patients, thereby

maintaining the blinding of both the patient and the medical practitioner. The indication for supplementary injection is similar to injection with corticosteroid.

Trial Design

Triple-blinded parallel group randomized superiority controlled trial with follow-up at 1,2, 3, 6 and 12 months. 25 patients are included in each of the 2 groups. If people are included and receive treatment from the doctor, but do not show up for the first follow-up after 1 month, they will be replaced. Patients leaving the trial after 1 month of follow-up will not be replaced.

5 OUTCOME MEASURES

Primary outcome measures:

The primary endpoint: VISA-A (total and pain subscales) at 6 months. Collected by blinded evaluator via "Redcap".

All patients are thoroughly instructed in visa-A score, on all visits, as it can be difficult to understand. However, it is important that they fill out the score at home directly in the assessment-app: "Redcap" without interference of any involved investigators. Intention to treat analysis is performed by using mixed effect analysis.

Secondary outcome measures

Lickert scale at 1, 2, 3, 6, 9 and 12 months: 11 point box scale from -5 to +5, where 0 is the status at **entry,** +5 is cured, and -5 is much worse.

VISA-A scores (total and pain subscales) at 1, 2, 3, 9 and 12 months.

Thickness of the Achilles tendon measured by ultrasound scan, cross-sectionel image on the thickest of the tendon at 1, 2, 3, 6, 9 and 12 months. The thickness of the "healthy" tendon is also measured for comparison.

Ultrasound Scanning Doppler Activity assessed with Color Doppler at 1, 2, 3, 6, 9 and 12 months.

After 6, 9 and 12 months, it is also assessed how many percentage of previous activity level (from before the injury) they have recovered. The patient himself states this as a percentage.

6 SAMPLE SIZE AND POWER

The risk of finding a difference between groups, even if there really is none, is set at 5% (risk of type I error), while the risk of overlooking a difference between the groups that is actually present is set at 20% (type II error). Individual changes from baseline over time will be calculated and all outcome parameters analyzed using mixed effect analysis. Q-Q plots will be visually examined prior to analysis to ensure that the assumption of normal distribution is not violated. Significance level is set to 0.05.

The minimum relevant difference in VISA-A is set at 15. Based on other studies on pain intensity, we expect a baseline mean of 50. Standard deviation is estimated to be 16 on VISA-A. Power of 80% provides a sample size of 20 participants in each group. We will include 25 patients in each group in case of data loss and no-shows, thereby including a total of 50 patients.

The primary analysis will be blinded and follow the intention-to-treat principle with baseline values as covariates. but we will also perform a per-protocol analysis only including patients performing at least 75% of the training programs and receive the per-protocol injections. No interim analyses will be made.

Data processing:

Entry data is registered in Redcap, where all information from each individual subject is collected.

Each patient is assigned an anonymous unidentifiable project number: AE2019-n.

Project numbers are listed on all CRF and patient diaries.

Folders, CRF and patient diaries are stored blinded only with study numbers in the departments computers. After 12 months follow-up of the last patient, a blinded statistician will make the statistical calculations. After data entry, the patients are divided in two groups: group A and group B by help from independent office employee. The primary investigator will group the patients in the two groups still blinded to the treatment group. All statistics are performed until agreement of the results. Thereafter the blinding is broken.

Analysis of data will take place in consultation with the statistician.

7 Adverse events

The adverse effects committee is chaired by JR. All adverse events, defined as any negative or unwanted reactions to the interventions will be recorded. A patient diary will be given to patients at baseline where patients are asked for any adverse events during the first three months. This will capture additional ill effects not reported at the time of their occurrence.

4 STATISTICAL ANALYSES

4.1 General

we will perform an intention to treat analysis using mixed effect analysis.

4.2 Statistical Analysis Plan

Statistical analysis will be undertaken using PRISM version 9.3.1. All analyses will be conducted on an intention-to-treat principle using all randomised participants in the groups they were originally randomised to. A blinded statistician will perform the data analysis. In the per-protocol analysis only patients complying with the treatment protocol are included in the statistics, this means that the patient has received all per-protocol injections and performed at least 75% of the training program.

A blinded statistician will perform the data analysis.

Demographic and anthropometric characteristics (gender, age, mass, height, body mass index, sporting activities and pain duration) will be determined at the baseline visit for each treatment group.

Statistical analyses will be conducted on 1, 2, 3, 6, 9 and 12 months on all outcome measures. However, the primary end-point will be total score and subscores of the VISA-A questionnaire at 6 months.

Between-group comparisons of treatment effect for all primary and secondary outcomes, will be performed with a mixed effect analysis. To assess for superiority, mean between-group differences in changes from baseline and two-sided 95% confidence intervals will be calculated.

The ordinal scaled data of patients overall assessment of the treatment effect (Lickert score -5 to +5) will be analyzed with mixed effect analysis, if the data is found normally distributed.

The ordinal scaled data of grading the flow within the tendon into 4 categories will be calculated using non parametric statistics: Mann-Whitney U-tests.

Return to sport in percent of earlier sports activity will be compared using unpaired t-test if the data is normally distributed, otherwise non parametric analysis (Mann-Whitney) is performed.

A two-sided P value of less than 0.05 will be considered to indicate statistical significance.

4.3 Interim analysis and early stopping rules

Anecdotally, an increased risk of tendon rupture have been reported. To account for this, we have introduced an early stopping rule if the rate of Achilles tendon ruptures exceeds 2 ruptures.

4.4 Timing of analyses

When this statistical analysis plan was signed, recruitment to the trial had started, but analysis had not been initiated.

	Enrolment	Allocation						
TIMEPOINT**	**June 2021 – end June 2023**	**June 2021 – end June 2023**	***Month 1***	***Month 2***	***Month 3***	***Month 6***	***Month 9 March 2022 end 2024***	**Month 12 *June 2022 end 2024***
ENROLMENT:								
Eligibility screen	X	X						
Informed consent		X						
Allocation		X						
INTERVENTIONS:								
Intervention group			←	—	→			
Control group			←	—	→			
ASSESSMENTS:								
Diagnosis		X						
VISA-A		X	X	X	X	X	X	X
Morning pain [VAS]		X	X	X	X	X	X	X
Pain after activity [VAS]		X	X	X	X	X	X	X
Return to usual sports participation						X	X	X
Satisfaction with result of treatment			X	X	X	X	X	X
Patient diary for reporting compliance and adverse events			←	—	→			
Ultrasound examinations		X	X	X	X	X	X	X
Demographics		X						

Table 1: SPIRIT figure. Schedule of enrolment, interventions and assessments

5 DEVIATIONS FROM THE PROTOCOL

The following details in this SAP represents deviations from protocol version 3

Header in protocol	Change	Reason