Study protocol and statistical analysis plan

Evaluation of the course and effectiveness of conservative therapy in patients with Achilles tendinopathy

NCT number: NCT05702918

Date: March 28, 2022

(Date of approval of the project by the ethics committee)

Study design and description

This work is designed as a randomized clinical trial, in which the effects of a protocol of 12-week resistance training loading the Achilles tendon and low-energy focused extracorporeal shock wave therapy (ESWT) in patients with Achilles tendinopathy (AT) will be monitored. It is estimated that at least 40 patients will participate, randomly divided into two groups. Group A will be instructed to perform a training protocol in combination with ESWT according to selected parameters. Group B only completes the same training protocol.

The research within one patient will last a total of 26 weeks from the initial to the final examination and will include several control measurements: at 6, 12, and 26 week from the beginning of therapy. Potential participants will be selected based on the recommendation of a specialist doctor and their suitability will be assessed according to the inclusion criteria. They will then be invited to an initial examination. This will include an objective examination by a physiotherapist, a subjective assessment by the patient and an ultrasonographic (USG) examination followed by a micromorphological analysis using special software. At the end of the initial examination, the participant will be randomly assigned to group A or B. Group A will follow resistance training protocol and receive ESWT. Group B will follow resistance training only. The study program for a specific participant will depend on the assigned group.

Patient selection

Inclusion criteria: age 18–50 years; localized Achilles tendon pain limiting daily or sports activity; clinical manifestation of AT confirmed by a clinician; and unilateral symptoms.

Exclusion criteria: professional or high-volume recreational sports (>4 sessions/week, >1h each); contraindications to ESWT according to International Society for Medical Shockwave Treatment (ISMST) guidelines at https://shockwavetherapy.org; previous symptomatic mechanical tendon injury (partial/complete rupture); history of contralateral AT; neurological, metabolic, oncologic, or systemic disease (e.g., diabetes, neuropathy, lupus, spondyloarthritis, rheumatoid arthritis); AT-specific treatment within the past 6 months; or use of anticoagulants or statins.

Initial and final examination

During the initial and final examinations, the several tasks to the patient will be performed. Firstly the anamnestic data will be collected, then the area of greatest pain will be localized by palpation.

Secondly, the patient will be asked to complete a validated Victorian Institute of Sports Assessment - Achilles (VISA-A) questionnaire, which assesses the subjectively perceived severity of the disease and partly its impact on the quality of normal daily or sports activities.

The patient's maximal pain will be assessed using a standardized numerical rating scale (NRS) of pain. The patient will be asked about the morning and maximum pain that could be caused by various factors.

Lastly, the ultrasonographic (US) examination and subsequent software analysis using Spatial Frequency Analysis (SFA) of patient's AT in both legs will be performed. This examination is described in the following chapter.

Both, inital and final examinations in each patient will be performed by only one person (the investigator of the study).

Ultrasonographic examination

Ultrasound imaging will be performed by the same experienced examiner using a linear probe (L12-3E, 12 MHz) on a Mindray DC-70 system in MSK preset (B-mode). The participant will placed in the prone position with the knee in an extended position and the ankle passively maintained in neutral position. The midportion of the Achilles tendon will be evaluated from the

myotendinous junction to the upper border of calcaneus. The probe will be placed as parallel to the tendon fibers as possible, and the image capture will be always carefully performed to ensure optimal image quality and minimize movement artifacts.

The values of anteroposterior tendon width at the anteroposterior widest point will be collected using the measuring instruments included in USG machine.

After that, the preset will be changed to the specific setting, and three pictures will be saved in long axis for subsequent micromorphological analysis using SFA. SFA is a non-invasive, specialized method which analyzes the US image in vivo. In particular, it analyzes the anisotropic B-mode speckle pattern arising from within a tissue type in the spatial frequency domain and is capable of detecting and comparing collagen fascicles organization, spacing, and density across various parameters. Mean of those three values will be used for statistical analysis.

ESWT application

The low-energy focused ESWT will be applied using the BTL-6000 FSWT machine with piezoelectric generator and a coupling pad which modulates penetration depth to 0-35 mm. The setting is chosen based on ISMST guidelines (https://shockwavetherapy.org): Energy Flux Density (EFD) between 0.10-0.15 mJ/mm2 due to patient tolerance, frequency at 5 Hz. A total of 2000 shocks will be applied semi-statically to the most US defined pathological tendon area using a contact gel. The set parameters will not change during the study and will remain the same for each patient.

Data analysis

The normality of the data distribution will be determined by calculating the Shapiro-Wilk p value. Independent t-tests (or Mann Whitney U tests for non-parametric) will be performed for each parameter to compare baseline values between groups. In addition, paired t-tests (or Wilcoxon tests) will be performed for each parameter, evaluated in each group separately between baseline and final values. To reach effect size, Cohen's d will be calculated for paired t-tests and biserial rank correlation for non-parametric Wilcoxon test.

Intergroup statistical significance between baseline and follow-up values of morphological parameters will be evaluated using two-way ANOVA with repeated measures or non-parametric Friedman test. Statistical significance is set to $p < .05$.