Title: Tendinopathy Education on the Achilles (TEAch)
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Description of the clinical study
This is a randomized double-blind, placebo-controlled trial with individuals who have chronic Achilles tendinopathy (AT). This study investigates the effects of education on outcomes (specified in hypotheses below) related to participation in an exercise program. Participants were randomized to one of two educational programs. All participants received the same exercise intervention. This study enrolled (consented and randomized) 66 participants to complete 2 evaluation sessions (baseline, 8-week follow-up), 6-7 treatment sessions with a physical therapist (between baseline and 8-week follow-up), and 1 survey-based evaluation sessions (12-week follow-up).

Specific Aims

Specific Aim 1. Determine if an educational intervention focusing on a biopsychosocial approach to pain mechanisms (i.e. Explain Pain) compared to education based primarily on a biomedical model geared at peripheral pain mechanisms (i.e. standard of care) is more effective at reducing pain and disability in a feasibility RCT exercise program for Achilles tendinopathy.

> We hypothesize that a biopsychosocial approach to education will decrease pain and disability more than the standard of care for patients with AT after an 8-week intervention and be maintained at 12-week follow-up.

Specific Aim 2. Determine which central pain mechanisms (nociplastic pain, pain psychology, motor dysfunction) are improved by an exercise program, regardless of education group.

> We hypothesize that exercise will improve all three central pain mechanisms.

Study Design

Interventional, 2-arm randomized, controlled trial with parallel assignment.

Study Methods

Evaluation sessions involved the following 4 types of testing a 0-weeks and 8-weeks.

1) Clinical exam (including ultrasound imaging)
2) Movement analysis and verbal pain rating
3) Sensory testing (Pain pressure threshold at the hamstring and Achilles bilaterally; Conditioned pain modulation at the Achilles)
4) Questionnaires (demographics, symptom description, and psychological)

In addition, participants completed questionnaires again at 12-weeks.

Participants attended 7 treatment sessions over 8 weeks that included:

1) Questionnaires (exercise adherence, educational quizzes, symptom description)
2) Exercise participation where participants were given exercises to do at home in between treatment sessions. Participants received instruction from a physical therapist prior to doing the exercise at home.
3) Education where participants were given homework and online quizzes to do at home in between treatment sessions. The physical therapist reviewed the educational material with the participant at each visit.

Additional description of the primary outcome measures are provided below.

a) Self-reported pain: The numeric pain rating scale (NPRS) was used to monitor pain with rest and activity throughout study participation, including single limb heel raises.[1]

b) Self-reported disability: Disability was assessed with the PROMIS physical function computer adaptive test, which has been used in orthopaedic and Achilles tendon populations.[2, 3]

c) Performance-based function: Plantarflexor endurance was quantified with the maximum number of single limb heel raises the participant could perform with good technique.

d) Psychosocial factors: The Tampa Scale of Kinesiophobia (TSK) rates current level of fear about movement causing pain and injury.[4]

e) Nociplastic pain: Conditioned pain modulation (CPM) was assessed utilizing:

- Test stimulus

    - Pressure pain thresholds (PPTs) are collected at the Achilles (centered around most painful region) with a pressure algometer (Somedic Algometer Type II, Horby Sweden, probe 1cm^2) at a rate of 50 kPa/sec. PPTs will be collected at the Achilles (painful side) during the conditioning stimulus.
    - ~~o~~ PPTs are the average of a series of 3 repeated pressures per site from posterior to anterior. The site for the Achilles on the painful side will be at the location reported to be most painful.
    - To minimize temporal summation the inter-stimulus interval will be $\geq$10 seconds
    - PPTs are collected with hand in room temperature water and during the conditioning stimulus starting at 20s. The order of collecting PPT during room temperature water vs during the conditioning stimulus was pseudo-randomized based on study id (even or odd).
    - Participants were instructed to press a trigger when the pressure first becomes painful (pain > 0/10)
- Conditioning stimulus
    - Participant's right hand was immersed up to the wrist in ice water (6$\pm$0.5°C) for a total of 2 minutes
    - The intensity of the conditioning stimulus was maintained by visually monitoring temperature throughout CPM testing and circulating the water with an aquarium air pump.

Sample size justification

Specific Aim 1: This analysis will compare the *between* group (biopsychosocial vs biomedical approach to education) changes in pain and disability scores from baseline to 8-weeks and to 12-weeks follow-up for participants with AT participating in an exercise program. Based on findings from Moseley et al.[5] for an RCT comparing a 4-week exercise program with education on central pain mechanisms to standard of care in 49 patients with chronic low back pain, we anticipate between group differences with Cohen's d ≥0.36 for pain (between group difference across 2 time points=0.75, SD of 1.05 on the NPRS, effect size of f=0.36, correlation between repeated measures=0.5) and disability (between group difference across 2 time points=1.95, SD of 2.33 on low back pain-specific measure, effect size of f=0.42, correlation between repeated measures=0.5).[5] Under these assumptions, a sample size of 30 patients per group would be needed to reach 80% power for the time averaged difference between two group means in a repeated measures design with α=0.025 (Bonferroni correction of 0.05/2 for 2 outcomes in Aim 1) to detect a between group effect size of 0.36.

Specific Aim 2: This analysis will compare the *within* group changes (baseline to 8-weeks) in central pain mechanisms (nociplastic pain, psychosocial factors, motor dysfunction*)* with an exercise intervention for participants with AT, regardless of educational group. The power analysis for this aim is based on data from 3 studies that have had a moderate to large (Cohen's d ≥0.47) treatment effects on central pain mechanisms. A double-blinded, cross-over study led by Dr. Sluka[6] found that Active-TENS improved CPM more than Placebo-TENS (Mean difference between treatments over time=18.8%, SD=33.4%, effect size= 0.56). A study by Tompra et al[7] reported a mean increase in PPT at the Achilles on the involved side during CPM testing in the AT population was 36.4± 68.1 kPa (14.4% increase, before= 253±80.5 kPa, during= 289.4±114.3 kPa). An 18.8% improvement with treatment over time would correspond to an 84kPa (33.2%) increase in PPT during CPM in the AT population. Cai et al.[8] found that a 4-week cognitive behavioral therapy program reduced fear of movement by 8.1 points with a SD of 5.44 (effect size= 1.5). Based on our preliminary data from the K99 phase, there was a mean improvement of 3.4 repetitions (SD of change= 6.7) in heel rise performance after an anesthetic injection for the AT group (effect size=0.51). Type I error rate of α=0.017 (Bonferroni correction of 0.05/3 for 3 outcomes in Aim 2) will be used for this aim to adjust for the multiple comparisons. The sample size of 60 patients calculated for Aim 1 would allow us to detect an effect size of d ≥0.43 with 80% power under these assumptions.

Allowing for a 40% ineligible rate after consent and 10% dropout rate after randomization, we will consent 110 participants, enroll/randomize 66 participants, and anticipate a final sample size with 60 completers. A final sample size of 60 is sufficient to detect estimated effect sizes for the primary outcome measures based on previously published differences or clinically meaningful (MCD/MCID) and standard deviation (SD) for the Achilles tendinopathy (AT) population (**Table 1**). For Aims 1 and 2, outcomes will be analyzed according to a modified intention-to-treat principle with only those who complete 8-week follow-up included in the analysis. We do not expect any cross-over between groups. This level of attrition is similar to that observed in prior studies conducted by Drs. Sluka and Rakel at the University of Iowa in intervention trials including exercise.[12, 13]

Table 1. Published differences or clinically meaningful (MCD/MCID) and standard deviation (SD) for the Achilles tendinopathy (AT) population were used to calculated estimated effect sizes of the primary outcomes for Aims 1 and 2.

Outcome	Published difference or MCD/MCID	Standard deviation	Estimated effect size
Specific Aim 1, powered to detect between group effect sizes of d ≥0.36			
Pain (NPRS)	1.0[9]	1.9[10]	0.53
Disability (PROMIS PF)	7.9[2]	9.0[3]	0.88
Specific Aim 2, powered to detect within group effect sizes of d ≥0.43			
Nociplastic pain (CPM)	84.0[6, 7]	68.1[7]	1.23
Pain psychology (TSK)	5.6[11]	6.2	0.90
Motor dysfunction (heel raises)	4.7	10.0	0.47

Statistical Analysis

The data analysis plan was developed in collaboration with Dr. Bayman, the study statistician. All analyses will be done by Dr. Bayman to ensure robust and reliable results. The normality of the continuous data will be tested by the Shapiro-Wilk test and by examining the quantile-quantile plot. Normally distributed Continuous variables will be presented as mean ± SD for normally distributed data and median with interquartile ranges for non-normally distributed data. When the normality assumption is not met, transformation, such as log, will be used to complete planned parametric analyses. Type I error rate will be maintained at 0.05 by using Bonferroni adjustment for multiple comparisons. First, potential differences between group demographics at baseline will be examined univariately using two independent samples t-tests and chi-square tests, as appropriate. If differences are observed, these variables will be used as covariates in the multivariable models.

A modified intention-to-treat principle will be followed, which will include outcome data on all participants, who complete 8-week follow-up, based on the group they were randomized. We will also compare patient characteristics of those who remained in the study to those who dropped out to determine if data at subsequent time points is consistent with missing at random.

For *Aim 1* we will assess the effect of the interventions on the primary outcomes for pain (NPRS) and disability (PROMIS physical function) from baseline to 8-weeks and to 12-weeks follow-up using linear mixed model for repeated measures. Similarly, for Aim 2 a linear mixed model for repeated measures will assess the effect of the interventions by group on the primary outcomes for central pain mechanisms (nociplastic pain: PPT, psychosocial factors: TSK, motor control: heel raises) from baseline to 8-weeks. For Aims 1 and 2, the factors in the linear mixed model will include group and time effects. In addition, the significance of the group*time interaction term, where the group*time interaction tests if the change over time differs between groups, will also be tested.

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