Achilles Tendinopathy

Risk factors, imaging, and treatment

Aart Cornelis van der Vlist

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Colophon

ISBN: 978-94-6416-181-6

Cover-design: Arco van der Vlist

Lay-out and Printing: Ridderprint | www.ridderprint.nl.

Financial support for this thesis was provided by:

Erasmus MC University Medical Center, Rotterdam

Haaglanden Medical Center, the Hague

ReumaNederland, Amsterdam

Annafonds | NOREF, Leiden

ABN AMRO, Amsterdam

Chipsoft, Amsterdam

Golazo | RMSG Rotterdam Marathon Study Group, Rotterdam

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Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof. dr. F.A. van der Duijn Schouten

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op

woensdag 20 januari 2021 om 15.30 uur

door

Aart Cornelis van der Vlist
geboren te Gouda

Erasmus University Rotterdam

Promotiecommissie

Promotor:	Prof. dr. J.A.N. Verhaar
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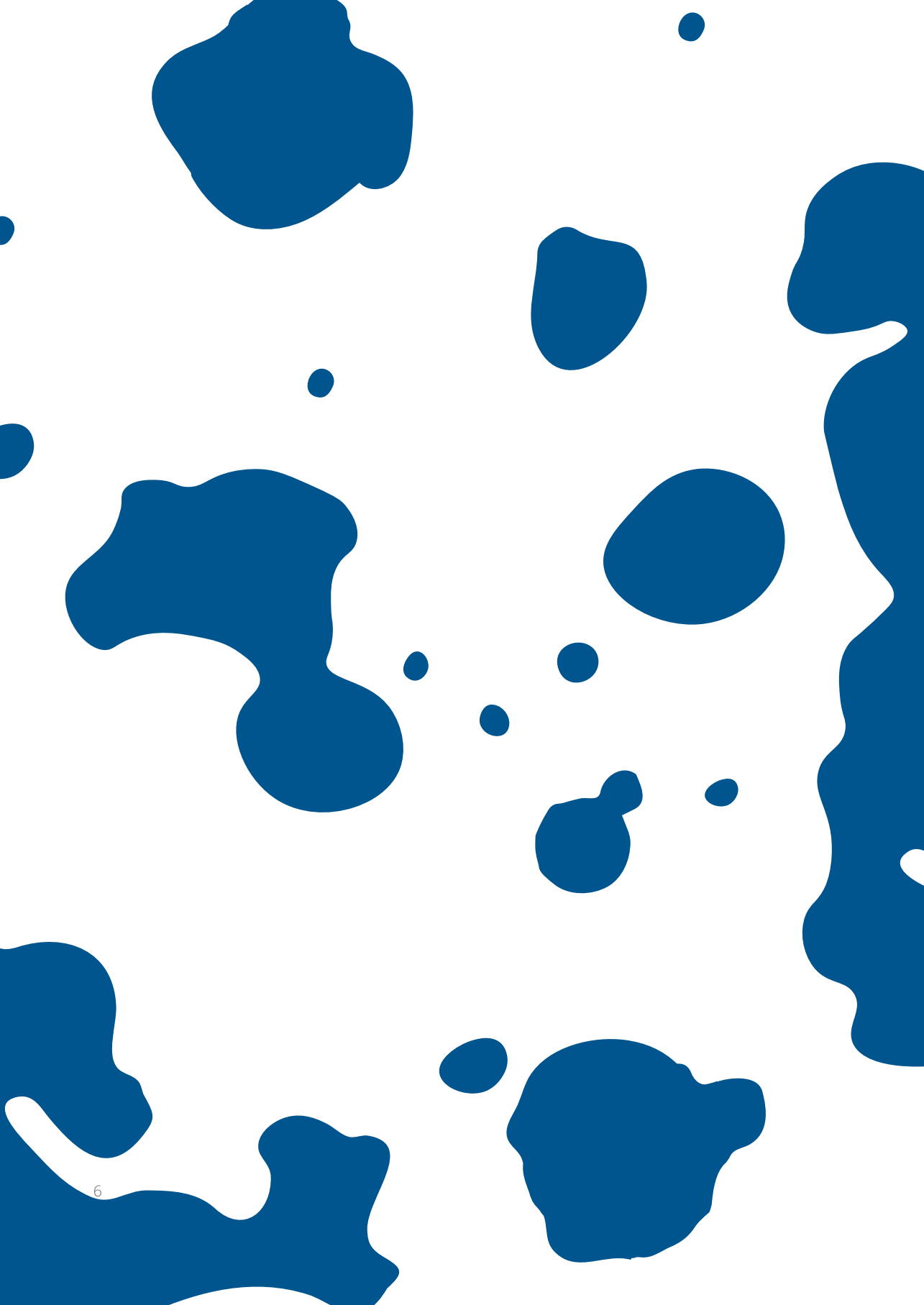
Content



Chapter 1

General introduction

Preface

The Achilles tendon is the largest and strongest tendon in the human body, as it is subjected to enormous tensile loads up to twelve times the body weight.[1] Hierarchically arranged tendon collagen bundles transfer these forces from the calcaneus to the calf muscles during ankle movement.[2] Despite its strength, the Achilles tendon is prone to overuse injuries also referred to as tendinopathy. Achilles tendinopathy is a common musculoskeletal condition with an annual incidence of 2-3 cases per 1000 patients in general medical practice.[3] Approximately two-third of these patients is physically active or participating in sports, compared to one-third who has a sedentary lifestyle.[4] The disorder is, however, most frequent in running sports with up to 52% of high-level running athletes suffering from Achilles tendinopathy at least once in their lifetime.[5]

The diagnosis tendinopathy is based on clinical findings, consisting of persistent localised tendon pain in relation to loading.[6] Pathology located at the distal insertion on the calcaneus (<2 cm from the insertion) and the midportion area of the tendon (2-7 cm from the insertion) are generally considered to be two different clinical entities. These are distinguished since these parts of the tendon show different loading profiles and anatomy, which should be taken into consideration during treatment.[7] In midportion Achilles tendinopathy, tensile loads are thought to be most prominent in the pathogenesis. In insertional Achilles tendinopathy, however, the Achilles tendon is also transversely compressed to the calcaneal bone which has been found to result in degenerative changes in tendon tissue due to compression forces.[8 9] Treatment of Achilles tendinopathy is often challenging, and patients frequently receive multiple, often unsuccessful treatment modalities. Symptoms persist in 60% of patients 5 years after start of treatment.[8 10]

Below an overview will be provided on several topics of Achilles tendinopathy. We will focus on risk factors, imaging, and treatment options.

Risk factors

Experts consider the aetiology to be multifactorial including both intrinsic factors (e.g. previous injury, plantar flexor strength, obesity) and extrinsic factors (e.g. change in load, environmental conditions, use of corticosteroids).[11] The strength of the evidence for these risk factors remains uncertain, as there is no adequately performed recent systematic review evaluating these risk factors for Achilles tendinopathy.

Imaging; a focus on neovascularisation and its role in pain sensation

The role of imaging in diagnosing Achilles tendinopathy is currently topic of debate. When imaging is considered, the first choice is ultrasonography as it is cheap and easily accessible.[12] Characteristic findings on ultrasonography include fusiform thickening of the Achilles tendon in anteroposterior direction and the presence of hypoechoic areas. Both findings are caused by disorganisation of the hierarchically arranged tendon collagen bundles, with the attraction of water in the extracellular matrix.[13] Additionally, increased blood supply is usually present. In a normal state, small blood vessels run from proximally and distally inside the Achilles tendon towards the midportion area of the tendon (2-7 cm from the insertion). As a result, the midportion area of the Achilles tendon forms a watershed area and as a consequence physiologically has the lowest blood supply.[14 15] An imaging technique to visualise blood flow is Doppler ultrasonography.[16] Doppler ultrasonography uses the Doppler effect to measure movement of tissues, most often blood in the human body. In a normal state, blood flow in asymptomatic tendons is too low to visualise with Doppler ultrasonography.[17] Therefore, the presence of Doppler flow usually represents an abnormal increase in blood flow. In tendon tissue, Doppler flow has been found to be present within and around the Achilles tendon in 50-100% of the symptomatic tendons, compared to 0-30% of the asymptomatic tendons.[18-22] This Doppler flow is considered to reflect the presence of newly formed blood vessels (neovascularisation) with an increased blood supply.[14 23] These newly formed blood vessels originate from the Kagers' fat pad anterior of the Achilles tendon and infiltrate the Achilles tendon diffusely with a tortuous course.[14] As a result, Doppler flow is initially most often present at the anterior aspect of the Achilles tendon in symptomatic tendons. When Doppler flow increases, it can also be visualised at the dorsal aspect of the Achilles tendon.[19] Most frequently these neovessels are thought to be secondary to the failed healing of tendinopathic tissue, but to date this is uncertain.

Treatment

Managing Achilles tendinopathy is often challenging for both patients and their healthcare providers. The main treatment modalities offered to patients with Achilles tendinopathy are wait-and-see, exercise therapy, injections, shockwave therapy, orthosis, medication, and surgery.[7] Most patients receive multiple treatments over time, resulting in increased healthcare consumption.[10] It is generally accepted in clinical care that exercise therapy and load management should be part of the initial treatment. As both short-term and long-term outcome of initial treatment are often unsatisfactory, numerous additional treatment options have been investigated.[24 25] To date, the comparative effectiveness of all these treatments has never been examined. Being faced with so many potentially effective treatments, it is challenging for healthcare providers to adequately treat patients using a shared decision making model.

To evaluate symptoms and activity levels in patients with Achilles tendinopathy the Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire is a valid and reliable tool and most often used in both a clinical and a research setting.[26] The VISA-A score ranges from 0 to 100; 100 indicates no pain with full activity level and the score decreases with increasing severity of symptoms. The questionnaire has been shown to be reliable, but to date the clinical relevance of the outcome is uncertain as the change that an individual patient would identify as important is unknown. This change is called the minimal clinically important difference (MCID) and this score is important to determine the effectiveness of a certain treatment.

Some novel interventions go off the beaten path of restoring tendon structure organisation, but primarily focus on the modulation of pain in tendinopathy. This shift has took place as tendon structure disorganisation is seen in symptomatic tendons, however, this disorganisation has not been found to be directly related to symptoms.[27] In other words, if there is more severe tendon structure disorganisation, this does not directly result in an increased symptom severity. Two mechanisms could play a role in persisting pain in Achilles tendinopathy. First, nerve structures accompanying the neovascularisation have been found in histopathological examination.[28] These nerve structures could play a significant role in the chronic aspect of the pain in Achilles tendinopathy.[14 29] Indeed, a large study showed an association between the degree of ultrasonographic Doppler flow and the severity of symptoms.[18] Second, altered central pain processing may play an important role in persisting symptoms, with pathophysiological pain (central sensitisation) as a result.[30 31] Due to these changes in central pain processing, the disorder could become resistant to tissue-based treatment options that are currently available.[32] Isometric exercises of several muscle groups have been found to result in an immediate analgesic effect, which suggests these exercises influence central pain processing.[33-36] As a consequence, isometric exercises are frequently being used as 'in-season pain management'.[37] One previous study specifically investigated the role of isometric exercises of the calf muscles in patients suffering from Achilles tendinopathy and found no difference after the performance of these exercises.[38] The power of these contradictory studies was, however, limited and a clinically relevant immediate effect could not be excluded as adequate control groups were lacking.

Another novel intervention focussing on the modulation of pain is a high-volume injection, in which a large amount of fluid is injected in the peritendinous area with the aim to obliterate the neovascularisation and the adjacent nerve structures.[29] Very promising short-term (6-12 weeks) results on the VISA-A score were found in several case series.[29 39 40] Consequently, this therapy is increasingly used in the clinical setting. The effectiveness has, however, not been tested in a large robustly designed study.

Aim and outline of this thesis

The general aim of this thesis is to evaluate risk factors, imaging, and treatment options in patients with Achilles tendinopathy.

We were at first interested to identify clinical risk factors for Achilles tendinopathy, as these could prove useful for prevention and treatment of Achilles tendinopathy. In **Chapter 2** we conducted a systematic review of the literature to identify these risk factors. This will provide the level of evidence for all clinical risk factors to inform future prevention and treatment strategies.

Neovascularisation, as usually seen during ultrasonography, is of increasing interest in the pathophysiology of Achilles tendinopathy. It is, therefore, important to adequately evaluate Doppler flow following treatment to further investigate the role of neovascularisation in tendinopathy. Most previous studies used the semi-quantitative modified Öhberg score to evaluate Doppler flow. As this outcome measure is observer-dependent and has a ceiling effect with higher degrees of neovascularisation, we investigated a quantitative method in which the amount of coloured pixels during power Doppler ultrasonography is measured. In **Chapter 3** we evaluated the inter-observer reliability of both the modified Öhberg score and a surface area quantification (SAQ) method in patients with chronic midportion Achilles tendinopathy.

In **Chapter 4** we determined the minimal clinically important difference (MCID) and patient acceptable symptom state (PASS) for the Victorian Institute of Sports Assessment-Achilles (VISA-A) score that is most often used in studies to evaluate symptom severity in Achilles tendinopathy. Both scores are currently not very well studied and are very important to determine the effectiveness of the available treatment options.

In **Chapter 5** we evaluated the comparative effectiveness of all available treatments for Achilles tendinopathy with a living systematic review with network-meta-analysis. This living systematic review will be updated regularly, which allows for a contemporary evidence synthesis for clinical practice.

The last decades the number of available treatments for Achilles tendinopathy increased rapidly, but scientific evidence for these treatments is often missing. Novel treatments for Achilles tendinopathy increasingly focus on the modulation of pain in tendinopathy. This shift seems to occur as severity of local tendon structure disorganisation has been found to be not directly related to the amount of symptoms. Isometric exercises for lower-limb tendinopathies have also been found to influence central pain processing. As a result, these exercises are often suggested as initial management for Achilles tendinopathy. Current evidence is, however, heterogeneous and sample sizes in previous studies were small. We performed a quasi-randomised

clinical trial in **Chapter 6** in which we investigated whether isometric exercises result in an immediate analgesic effect in patients with chronic midportion Achilles tendinopathy.

In **Chapter 7** we investigated the effectiveness of the high-volume injection, which is considered to be a very promising treatment option according to previous case series and a small randomised clinical trial. We performed a randomised clinical trial to study whether a high-volume injection improves clinical outcome in addition to usual care for patients with chronic midportion Achilles tendinopathy.

The mechanism of the high-volume injection is to date unclear. The hypothesised mechanism involved destruction of the neovascularisation and the adjacent nerve structures. The mechanical effect of a high-volume injection is explored in **Chapter 8**. We evaluated ultrasonographic Doppler flow to explore the effect of the high-volume injection on the neovascularisation during the injection procedure and at short- and intermediate term follow-up.

In **Chapter 9** a general discussion regarding the results of the different studies in this thesis is provided. Clinical relevance, implications for research and treatment and future research are discussed.

Chapter 10 comprises a summary of this thesis in English and Dutch (appendix).

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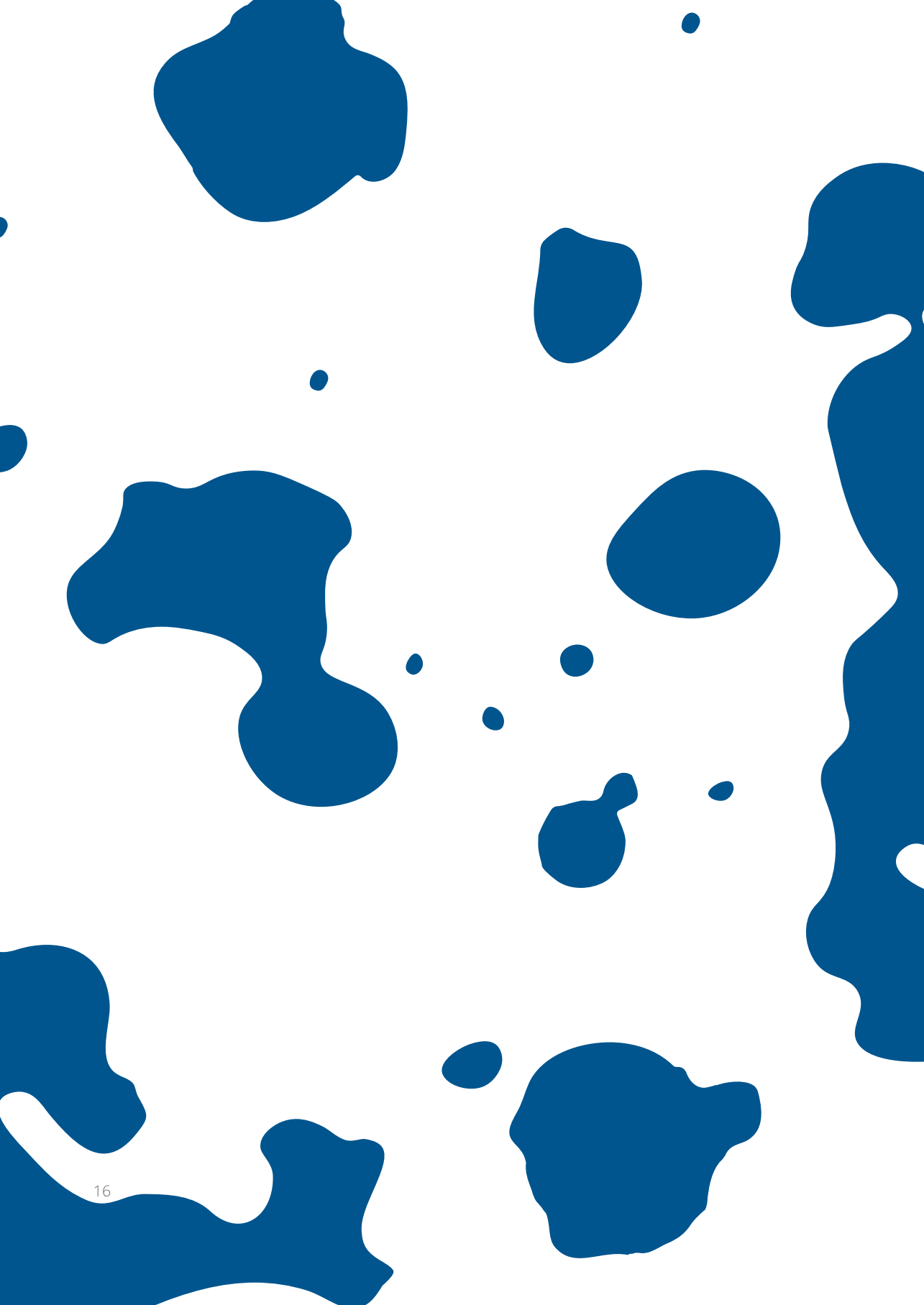

Chapter 2

Clinical risk factors for Achilles tendinopathy: a systematic review

Arco C van der Vlist, Stephan J Breda, Edwin HG Oei, Jan AN Verhaar, Robert-Jan de Vos

Br J Sports Med. 2019 Nov;53(21):1352-1361

Abstract

Background: Achilles tendinopathy is a common problem but its exact aetiology remains unclear.

Objective: To evaluate the association between potential clinical risk factors and Achilles tendinopathy.

Design: Systematic review.

Data sources: The databases Embase, MEDLINE Ovid, Web of Science, Cochrane Library and Google Scholar were searched up to February 2018.

Eligibility criteria: To answer our research question, cohort studies investigating risk factors for Achilles tendinopathy in humans were included. We restricted our search to potential clinical risk factors (imaging studies were excluded).

Results: We included 10 cohort studies, all with a high risk of bias, from 5111 publications identified. There is limited evidence for nine risk factors: (1) prior lower limb tendinopathy or fracture, (2) use of ofloxacin (quinolone) antibiotics, (3) an increased time between heart transplantation and initiation of quinolone treatment for infectious disease, (4) moderate alcohol use, (5) training during cold weather, (6) decreased isokinetic plantar flexor strength, (7) abnormal gait pattern with decreased forward progression of propulsion, (8) more lateral foot-roll over at the forefoot flat phase and (9) creatinine clearance of <60 mL/min in heart transplant patients. Twenty-six other putative risk factors were not associated with Achilles tendinopathy, including being overweight, static foot posture and physical activity level.

Conclusion: From an ocean of studies with high levels of bias, we extracted nine clinical risk factors that may increase a person's risk of Achilles tendinopathy. Clinicians may consider ofloxacin use, alcohol consumption and a reduced plantar flexor strength as modifiable risk factors when treating patients with Achilles tendinopathy.

PROSPERO registration number: CRD42017053258

Introduction

The Achilles tendon is the largest and strongest tendon in the human body, yet it is prone to injury such as tendinopathy. The presence of Achilles tendon pain, swelling and an impaired load-bearing capacity indicate Achilles tendinopathy (AT).[1-3] From a clinical perspective, insertional and midportion Achilles tendinopathy should be distinguished since these are two separate entities with different treatment approaches.[4] AT is most frequently seen in elite running athletes, with a lifetime risk of 52%.[5] It should, however, be noted that one-third of all AT patients have a sedentary lifestyle.[6] This emphasizes that there is probably a broad spectrum of potential risk factors for Achilles tendinopathy, yet the exact aetiology remains uncertain.[7]

Over the last decades, various determinants have been proposed as risk factors in the development of AT. A recent systematic review examined risk factors for AT with a primary focus on genetic aspects.[8] They found that certain genetic determinants may contribute to the development of AT, such as genetic contributors to collagen structure formation and tendon homeostasis. However, results were ambiguous due to the methodology in the publications included. These publications had mixed study designs and the number of non-genetic clinical risk factors was limited. Therefore, there is a need to evaluate clinical risk factors in the development of AT with an extensive literature search and robust methodological design.

In this study, we systematically review the literature regarding the potential clinical risk factors that have been investigated for AT. This provides the level of evidence for all known clinical risk factors to inform future prevention and treatment strategies.

Methods

Protocol and registration

The protocol for this systematic review was prospectively registered in the international PROSPERO database. Protocol details can be accessed via http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017053258. A protocol revision was performed in July 2017 from midportion AT as site of injury to AT in general (insertional and midportion AT combined). This was done as we observed during data extraction that a substantial number of publications did not specify the specific location.

Eligibility criteria

Publications were eligible for inclusion when there was (1) a potential risk factor investigated in relation to AT and (2) a diagnosis of AT based on clinical findings (local pain and impaired load-bearing capacity). We restricted our selection to prospective

and retrospective cohort studies written in English. A determinant was considered to be a potential clinical risk factor if no extensive examination (eg. biopsies) had been performed. Publications were excluded if there was: (A) no adequate control group (eg. contralateral Achilles tendon), (B) a preclinical study design or (C) an imaging study design (eg. potential risk factors derived from MRI or ultrasound examinations). Imaging studies were excluded, since these are regularly not directly available in the sports physician consultation room. For an overview of imaging, we refer to a recent systematic review.[9]

We also aimed to identify potential novel risk factors as secondary outcome measure by including cross-sectional studies. While the level of evidence from cross-sectional studies is lower than that from cohort studies, they might identify interesting factors to explore in future research.

Literature search strategy and information sources

We conducted a sensitive search strategy for multiple databases with the assistance of a medical librarian (WM Bramer). The following databases were searched up to 12 February 2018: Embase, MEDLINE Ovid, Web of Science, Cochrane Library and Google Scholar. The search strategy is shown in online supplementary appendix 1.

Study selection and data extraction

Titles and abstracts were screened by two independent reviewers (ACvdV and RJdV) to identify eligible publications. Disagreements were solved by consensus, with the involvement of a third review author (EHGO) if necessary. Data extraction was performed by one author (ACvdV) and a data check was performed by a second author (SJB) for 100% of the primary outcomes and for 20% of the other data. This has been shown to be a methodologically sound procedure.[10] The potential risk factors were extracted and grouped into patient characteristics (modifiable and non-modifiable), biomechanical factors, pre-existing diseases, medication and training factors. AT subgroup analysis results are presented in case subgroup analyses were performed in studies describing associations for multiple injuries. If multiple populations with AT were assessed in a single publication, only combined results are presented.

Risk of bias assessment

Two reviewers (ACvdV and SJB) independently assessed the methodological quality of all included prospective (level of evidence II) and retrospective cohort studies (level of evidence III). No risk of bias assessment was performed for cross-sectional studies (level of evidence IV), since these studies are considered to be of high risk of bias for the purpose of this review.

To assess risk of bias, we used a standardised set of criteria based on modified questions of existing quality assessment tools (table 1).[11-13] This tool has previously been used in a systematic review on risk factors for Achilles tendon rupture.[14] If a criterion was met, one point was given. No points were given if the criterion was not met or when it was unclear if the specific criterion was met. A maximum score of 10 points could be obtained. Publications were considered to be of low risk of bias if: (1) a total score of 6 points or more was given and (2) 1 point was given to criterion 6, 7, 8 and 10.[14]

Table 1. Risk of bias assessment tool

Criteria	Response	Yes	No/ not reported
A clearly stated aim	• Did they have a 'study question' or 'main aim' or 'objective'?	☐	☐
	• The question addressed should be precise and relevant in light of available literature	☐	☐
	• To be scored adequate the aim of the study should be coherent with the 'Introduction' of the paper	☐	☐
Inclusion of consecutive patients	• Did the authors say: 'consecutive patients' or 'all patients during period from … to….' or 'all patients fulfilling the inclusion criteria'?	☐	☐
A description of inclusion and exclusion criteria	• Did the authors report the inclusion and exclusion criteria?	☐	☐
Inclusion of patients	• Did the authors report how many eligible patients agreed to participate (i.e., gave consent)?	☐	☐
Prospective collection of data. Data were collected according to a protocol established before the beginning of the study	• Did they say 'prospective', 'retrospective' or 'follow-up'?	☐	☐
	• The study is **not** prospective when it is a chart review, database review, clinical guideline, or practical summaries	☐	☐
Outcome measures	• Did they report the association between the potential risk factors and manifestation of Achilles tendinopathy as outcome? The valid outcome measure for Achilles tendinopathy is clinical examination	☐	☐

Unbiased assessment of the study outcome and potential risk factors	• To be judged as adequate, the following two aspects had to be positive:
	  • Outcome and potential risk factors had to be measured independently
	  • The outcome and potential risk factors for both cases and controls had to be assessed in the same way
		☐	☐

Were the determinant measures used accurate (valid and reliable)?	• For studies where the determinant measures are shown to be valid and reliable, the question should be answered adequate. For studies that refer to other work that demonstrates the determinant measures are accurate, the question should be answered as adequate	☐	☐

Criteria	Response	Yes	No/ not reported
Loss to follow-up	• To be judged as adequate the following two aspects had to be positive: • Did they report the losses to follow-up? • Loss to follow-up was <20 %	☐	☐
Adequate statistical analyses	• To be judged as adequate the following two aspects had to be positive: • There must be a description of the relationship between the potential risk factors and Achilles tendinopathy (with information about the statistical significance) • Was there adjustment for possible confounders (age, sex, body mass index) by multivariate analysis?	☐	☐

For each methodological criterion that is met 1 point is given. If the criterion was not met zero points were given. Publications were considered to be of low risk of bias if (1) a total score of at least 6 points was given and (2) 1 point was given to questions 6, 7, 8 and 10 (marked with the grey columns).

Data synthesis

A subgroup analysis was initially planned for insertional and midportion AT; however, we revised the PROSPERO protocol (revision date 20 July 2017) because a substantial number of publications did not specify the AT location. Homogeneity of the data was evaluated, and if data could not be pooled because of heterogeneity, a best evidence synthesis based on the study of van Tulder et al. was carried out for each potential risk factor.[15]

- Strong evidence: ≥2 studies with high quality and generally consistent findings in all studies (≥75 % of the studies reported consistent findings).
- Moderate evidence: one high-quality study and ≥2 low-quality studies and generally consistent results (≥75 % of the studies reported consistent findings).
- Limited evidence: generally consistent findings in ≥1 low-quality study (≥75 % of the studies reported consistent findings).
- Conflicting evidence: <75 % of the studies reporting consistent findings.
- No evidence: no studies could be found

Results

Study selection

We identified 5,111 potentially relevant publications and after removing duplicates, 3225 remained. After screening title and abstract, we assessed 109 publications in full-text. Fifty-four publications were excluded for different reasons after full-text evaluation, as shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart (figure 1). We included the remaining 55 publications for analysis.

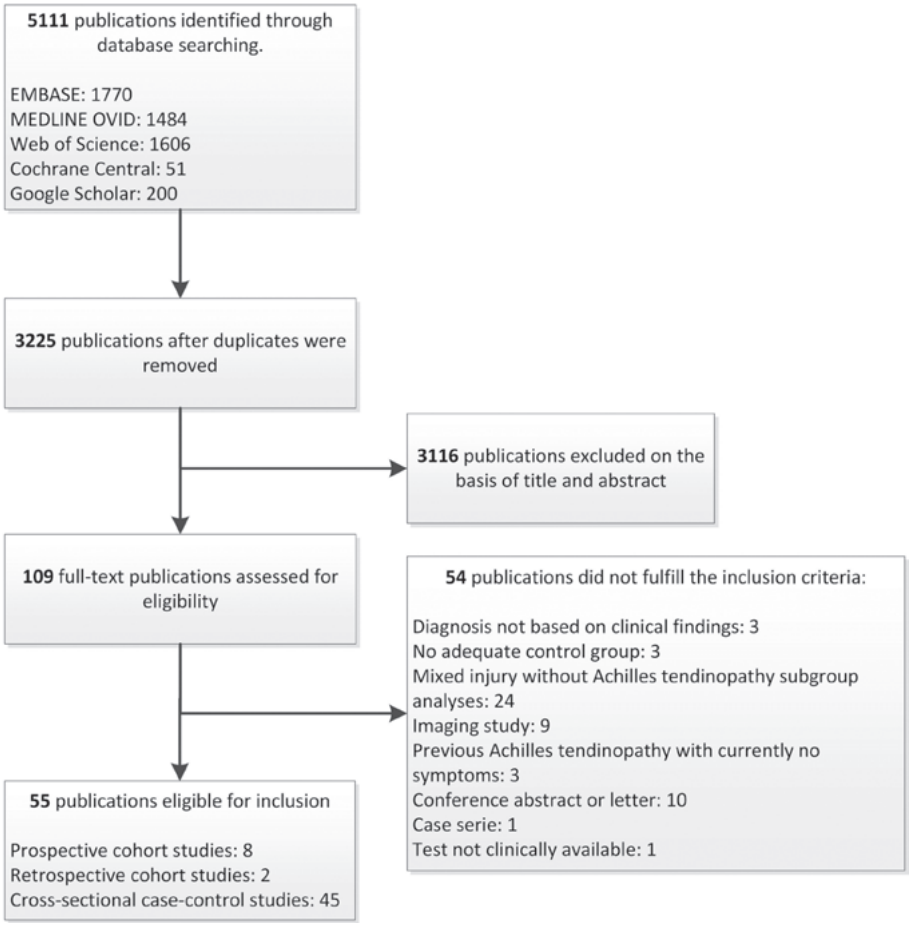

Figure 1. PRISMA 2009 flow diagram of study selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Characteristics of the included publications

We included eight prospective cohort studies[16-23] and two retrospective cohort studies.[24 25] Additionally, 45 cross-sectional studies were included.[5 26-69] The characteristics and main findings of the included studies are summarised in table 2 for the cohort studies and online supplementary appendix 2 for the cross-sectional studies.

Of the 10 cohort studies, five studies included only participants with midportion AT and five studies did not specify the AT location. Sample sizes of the included cohort studies ranged from 69 to 80,106 participants (median 285) with the number of AT cases ranging from 5 to 450 (median 18). Mean age ranged from 18 years old to 59 years old (median 21). This relatively young median age was caused by the profession of most of the populations investigated (military recruits in five studies, students in one study). There was a greater proportion of male participants in seven cohort studies, compared with two studies in which there was a greater proportion of female participants (median percentage males 78%). Data regarding the number of participants, mean age or sex was incomplete in two studies. The follow-up period for the prospective cohort studies ranged from 6 weeks to 2 years (median 39 weeks).

Of the 45 cross-sectional studies, 15 studies included only participants with midportion AT, one study included patients with insertional AT and 29 studies did not specify the AT location. Sample sizes ranged from 20 to 57,725 participants (median 201).

Table 2. Data extraction of the included prospective and retrospective cohort studies

Study	Study type	Duration of follow-up (weeks)	Participants (total group and cases of AT)	Sex (% male)	Age, mean ± SD (years)	Location injury
Barge-Caballero et al. (2008) [24]	RC	NR	149 (14); Heart transplant patients who were prescribed quinolones	77.9%	58.8 ± 10.6	Achilles tendinopathy (not specified midportion or insertional)
Hein et al. (2014) [20]	PC	52	269 (10); Recreational runners	NR	NR	Achilles tendinopathy (not specified midportion or insertional)
Kaufman et al. (1999) [21]	PC	104	449 (30); Navy Sea, Air and Land (SEAL) candidates	100%	22.5 ± 2.5	Achilles tendinopathy (not specified midportion or insertional)
Mahieu et al. (2006) [16]	PC	6	69 (10); Officer cadets	100.0%	18.4 ± 1.3	Midportion Achilles tendinopathy
Milgrom et al. (2003) [22]	PC	14	1405 (95); Infantry recruits	100.0%	18.7 ± 7	Midportion Achilles tendinopathy
Owens et al. (2013) [17]	PC	52	80 106 (450); Military service members	70.3%	NR	Achilles tendinopathy (not specified midportion or insertional)
Rabin et al. (2014) [18]	PC	26	70 (5); Military recruits	100.0%	19.6 ± 1.0	Midportion Achilles tendinopathy

	Risk factors (Risk ratio, odd's ratio, hazard ratio)	Quality score (points)
	• A creatinine clearance <60 ml/min was associated with AT compared to a creatinine clearance ≥ 60 ml/min (OR 6.14; 95% CI 1.23-30.64; p=0.03) • increased time (in years) between heart transplantation and initiation of quinolone treatment for infectious disease was associated with AT (OR 1.39; 95% CI 1.11-1.74; p=0.005) • No associations were found for age, sex, levofloxacin use and daily prednisone dose (mg)	5
	• No statistical analyses were performed	4
	• A tight ankle dorsiflexion with knee extended (<11.5°) was associated with AT compared to a normal dorsiflexion (11.5-15.0°) (RR 3.57; 95% CI 1.01-12.68; p<0.05) • No associations were found for hindfoot inversion, hindfoot eversion, static arch index of the foot, dynamic arch index of the foot, dorsiflexion of the ankle with the knee bent	5
	• Isokinetic plantar flexion strength at 30 degrees/s was decreased in patients who developed AT for both the right and the left leg and at 120 degrees/s for the right leg (p=0.042, p=0.036 and p=0.029 respectively). Plantar flexion strength was measured using the Cybex Norm dynamometer, which measures strength at constant velocity. • No associations were found for weight, BMI, length, physical activity level, Achilles tendon stiffness, isokinetic plantar flexion strength at 120 degrees/s for the left leg, explosive gastrocnemius-soleus muscle strength (standing broad jump test) and passive and active ankle joint range of motion outcomes.	4
	• An increase in AT was seen when training in the winter season compared to summer training (p=0.001) • No differences were found in height, weight, BMI, external rotation of the hip, tibial intercondylar distance, arch type, physical fitness performance (2-km run and maximum number of chin-ups and sit-ups done) and shoe type	4
	• Being overweight and obesity were associated with AT compared to underweight or normal weight (AOR 1.29, 95% CI 1.04-1.59 and AOR 1.59, 95% CI 1.16-2.17 respectively) • A prior lower limb tendinopathy or fracture was associated with AT (AOR 3.87, 95% CI 3.16-4.75) • Moderate alcohol use (7-13 units per week for men, 4-6 units per week for women) was associated with AT compared to no alcohol use (AOR 1.33, 95% CI 1.00-1.76) • A birth year of 1980 and later was associated with a decreased risk for AT compared to a birth year before 1960 (AOR 0.62, 95% CI 0.38-1.00) • No associations were found for sex, ethnicity, smoking status and heavy alcohol use (14+ units per week for men, 7+ units per week for women)	6
	• Every one-degree increase in ankle dorsiflexion with the knee bent was associated with a decreased risk for AT (OR 0.77; 95% CI 0.59-0.94) • No associations were found for BMI and lower extremity quality of movement	7

Study	Study type	Duration of follow-up (weeks)	Participants (total group and cases of AT)	Sex (% male)	Age, mean ± SD (years)	Location injury
Van Ginckel et al. (2008) [19]	PC	10	129 (10); Novice runners	14.7%	39 ± 10	Midportion Achilles tendinopathy
Van der Linden et al. (1999) [25]	RC	NR	10 800 (8); Patients using fluoroquinolones (index group) or amoxicillin, trimethoprim, cotrimoxazole or nitrofurantoin (reference group)	29.8%	46.3 (SD NR)	Achilles tendinopathy (not specified midportion or insertional)
Wezenbeek et al. (2018) [23]	PC	104	300 (27); first-year students	47%	18.0 ± 0.8	Midportion Achilles tendinopathy

AOR, Adjusted odds ratio; AT, Achilles tendinopathy; BMI, Body Mass Index; CI, Confidence interval; CON; Unaffected controls; HR, Hazard ratio; km, kilometer; NA, not applicable; OR, Odds ratio; PC, Prospective cohort study; RC, Retrospective cohort study; RR, Risk ratio; SD, Standard deviation.

	Risk factors (Risk ratio, odd's ratio, hazard ratio)	Quality score (points)
	• An increased total anterior displacement of the Y-component of the Center of Force was associated with a decreased risk for AT (OR 0.919; 95% CI 0.859-0.984; p=0.015) • A more medial directed force distribution underneath the forefoot at forefoot flat was associated with a decreased risk for AT (OR 0.000; 95% CI 0.000-0.158; p=0.016) • No associations were found for age, height, weight, BMI or physical activity score	6
	• The use of ofloxacin was associated with AT compared to the reference group (AOR 10.1; 95% CI 2.20-46.04) • No associations were found for fluoroquinolones as a group, ciprofloxacin use and norfloxacin use compared to the reference group.	3
	• Female sex was associated with AT (HR 2.82, 95% CI 1.16-6.87) • Height and body weight were increased in patients with AT (p=0.028 and p=0.015) • No association was found for a pronated foot posture • No differences were found for BMI, rating of perceived exertion, hours of sports participation and leg dominance	7

Risk of bias assessment

All 10 cohort studies were considered to be of high risk of bias according to the predefined criteria (tables 1 and 3). Seven cohort studies scored six points or higher; however, they were lacking clinical examination as valid outcome (two studies), a valid and reliable determinant measure (four studies), an unbiased assessment of the study outcome (one study) and/or adequate statistical analyses (three studies). As a result, at best, a limited evidence for the association between the potential risk factor and tendinopathy could be detected. Results of the best evidence synthesis are presented in table 4.

Table 3. Risk of bias assessment scores of the ten included cohort studies

Study	Criteria										Total score	Risk of bias
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**		
Barge-Caballero et al. (2008) [24]	1	1	1	0	0	0	0	1	0	1	5	High
Hein et al. (2014) [20]	1	0	1	1	1	0	0	0	0	0	4	High
Kaufman et al. (1999) [21]	1	1	0	1	1	1	1	0	0	0	5	High
Mahieu et al. (2006) [16]	0	1	0	1	1	1	1	0	0	1	6	High
Milgrom et al. (2003) [22]	0	0	0	1	1	1	0	0	0	0	3	High
Owens et al. (2013) [17]	1	1	0	1	1	0	1	1	0	0	6	High
Rabin et al. (2014) [18]	1	1	1	1	1	1	1	0	1	1	9	High
Van der Linden et al. (1999) [25]	1	1	1	0	1	0	1	1	0	0	6	High
Van Ginckel et al. (2008) [19]	1	0	1	1	1	1	1	0	0	1	7	High
Wezenbeek et al. (2018) [23]	1	1	1	0	1	1	0	1	0	1	7	High

Outcomes of the risk of bias assessment tool as presented in table 1. Publications were considered to be of low risk of bias if (1) a total score of at least 6 points was given and (2) 1 point was given to questions 6, 7, 8 and 10 (marked with the grey columns).

Table 4. Potential risk factors investigated in the ten cohort studies as potential risk factor for Achilles tendinopathy. Associations found in this systematic review are marked with the grey columns.

Potential risk factors	Study (first author and reference number)	Best evidence synthesis
Patient characteristics (non-modifiable)		
Age	Barge-Caballero = [24], Owens birth year >1980 ↓ [17], Van Ginckel = [19]	Conflicting evidence
Sex	Barge-Caballero = [24], Owens = [17], Wezenbeek female ↑ [23]	Conflicting evidence
Ethnicity	Owens = [17]	Limited evidence for no association
Height	Mahieu = [16], Milgrom = [22], Van Ginckel = [19], Wezenbeek ↑ [23]	Limited evidence for no association
Prior lower limb tendinopathy or fracture	Owens ↑ [17]	Limited evidence for positive association
Patient characteristics (modifiable)		
Body Mass Index	Owens BMI >25.0 ↑[17], Mahieu = [16], Milgrom = [22], Rabin = [18], Van Ginckel = [19], Wezenbeek = [23]	Limited evidence for no association
Body weight	Mahieu = (18), Milgrom = [22], Van Ginckel = (23), Wezenbeek ↑ [23]	Limited evidence for no association
Alcohol use	Owens 7-13 units per week for men, 4-6 units per week for women↑ [17], Owens 14+ units per week for men, 7+ units per week for women =[17]	Limited evidence for positive association (moderate alcohol use)
Smoking	Owens = [17]	Limited evidence for no association
Physical activity level and performance	Mahieu physical activity level = [16], Van Ginckel physical activity level= [19], Milgrom physical activity performance (2-km run and maximum number of chin-ups and sit-ups) = [22], Wezenbeek = [23]	Limited evidence for no association
Biomechanical factors		
Shoe type	Milgrom = [22]	Limited evidence for no association
Leg dominance	Wezenbeek = [23]	Limited evidence for no association
Limited non-weight-bearing ankle dorsiflexion with knee extended	Kaufman <11.5° ↑ [21], Mahieu = [16]	Conflicting evidence

Potential risk factors	Study (first author and reference number)	Best evidence synthesis
Increased non-weight-bearing ankle dorsiflexion with the knee bent	Mahieu = [16], Rabin ↓ [18], Kaufman = [21]	Conflicting evidence
Hindfoot inversion	Kaufman = [21]	Limited evidence for no association
Hindfoot eversion	Kaufman = [21]	Limited evidence for no association
Static arch index of the foot	Kaufman = [21], Milgrom = [22]	Limited evidence for no association
Dynamic arch index of the foot	Kaufman = [21]	Limited evidence for no association
Pronated foot posture	Wezenbeek = [23]	Limited evidence for no association
Increase in isokinetic plantar flexor strength at 30 degrees/s (low velocity)	Mahieu ↓ [16]	Limited evidence for protective association
Explosive gastrocnemius-soleus muscle strength	Mahieu = [16]	Limited evidence for no association
External rotation of the hip	Milgrom = [22]	Limited evidence for no association
Tibial intercondylar distance	Milgrom = [22]	Limited evidence for no association
lower extremity quality of movement test	Rabin = [18]	Limited evidence for no association
Increased total displacement of the Y-component of the Centre of Force	Van Ginckel ↓ [19]	Limited evidence for protective association
Increased medial directed force distribution	Van Ginckel ↓ [19]	Limited evidence for protective association
Pre-existing diseases		
Renal dysfunction (Creatinine clearance <60 ml/min)	Barge-Caballero ↑ [24]	Limited evidence for positive association
increased time between heart transplantation and initiation of quinolone treatment for infectious disease	Barge-Caballero ↑ [24]	Limited evidence for positive association

Potential risk factors	Study (first author and reference number)	Best evidence synthesis
Medication		
Fluoroquinolones as group	Van der Linden = [25]	Limited evidence for no association
Levofloxacin	Barge-Caballero = [24]	Limited evidence for no association
Ofloxacin	Van der Linden ↑ [25]	Limited evidence for positive association
Ciprofloxacin	Van der Linden = [25]	Limited evidence for no association
Norfloxacin	Van der Linden = [25]	Limited evidence for no association
Daily prednisone dose	Barge-Caballero = [24]	Limited evidence for no association
Training factors		
Training in the winter season	Milgrom ↑ [22]	Limited evidence for positive association

= no association; ↑ positive association; ↓protective association

Risk factors

Patient characteristics (non-modifiable)

Age There is conflicting evidence that age affects the risk for AT. One cohort study reported in 2013 that a birth year of 1980 or later is associated with a decreased risk for AT.[17] Two cohort studies showed no association.[19 24]

Sex There is conflicting evidence that sex affects the risk for AT. One cohort study reported that being female is associated with AT.[23] No association was demonstrated in two cohort studies.[17 24]

Ethnicity There is limited evidence that ethnicity does not affect the risk for AT. One cohort study reported no increased risk for white (non-Hispanic), black (non-Hispanic) or other ethnicity.[17]

Height There is limited evidence that height does not affect the risk for AT. No association was found in three cohort studies.[16 19 22] One cohort study reported an increased height in patients with AT.[23]

Prior lower limb tendinopathy or fracture There is limited evidence that a prior lower limb tendinopathy or fracture increases the risk for AT. One cohort study reported that a prior lower limb tendinopathy (plantar fascia, Achilles or patellar) or fracture (regardless side of injury) is associated with AT.[17]

Patient characteristics (modifiable)

Body Mass Index (BMI) and body weight There is limited evidence that BMI or body weight do not affect the risk for AT. No association was found in five cohort studies for BMI [16 18 19 22 23] and in three cohort studies for body weight.[16 19 22] One cohort study found that being overweight (BMI ≥25.0) and obesity (BMI ≥30.0) are associated with AT.[17] Another cohort study found that body weight is increased in people who develop AT.[23]

Alcohol use There is limited evidence that moderate alcohol use increases the risk for AT. Moderate alcohol use was defined as 7-13 units per week for men and 4-6 units per week for women. One cohort study reported that moderate alcohol use is associated with AT compared with no alcohol use. No association was found for light alcohol use or heavy alcohol use compared with no alcohol use. [17]

Smoking There is limited evidence that smoking is not associated with AT based on one cohort study.[17]

Physical activity level, physical activity performance and hours of sports participation There is limited evidence that physical activity level, physical activity performance or hours of sports participation do not affect the risk for AT. Two cohort studies found no association between the physical activity level measured with the Baecke questionnaire and AT.[16 19] One cohort study found no association between the physical activity performance (2-km run and maximum number of chin-ups and sit-ups) and AT.[22] Another cohort study found no differences in hours of sports participation between patients with AT and unaffected controls.[23]

Biomechanical factors

Shoe type There is limited evidence that the type of shoes is not associated with AT. One cohort study found no difference in AT incidence between modified basketball shoes and standard lightweight infantry boots.[22]

Leg dominance There is limited evidence that leg dominance is not associated with AT based on one cohort study.[23]

Static and dynamic properties of the foot There is limited evidence that hindfoot inversion, hindfoot eversion, the static arch index of the foot, the dynamic arch index of the foot and a pronated foot posture do not increase the risk for AT. One cohort study reported that hindfoot inversion, hindfoot eversion, the static arch index of the foot and the dynamic arch index of the foot are not associated with AT.[21] Another cohort study also found no association between the static arch index of the foot and AT.[22] The third cohort study found no association between a pronated foot posture and AT.[23]

Static and dynamic properties of the ankle There is conflicting evidence that a decreased non-weight-bearing ankle dorsiflexion is associated with AT. One cohort study found that a limited ankle dorsiflexion (<11.5°) with the knee extended is associated with AT compared with a normal ankle dorsiflexion (11-15°).[21] Another cohort study evaluating ankle dorsiflexion with the knee extended did not show an association.[16] One cohort study found that a one degree increase in ankle dorsiflexion with the knee bent is associated with a decreased risk for AT.[18] Two cohort studies evaluating ankle dorsiflexion with the knee bent demonstrated no association.[16 21]

Limited evidence was found that an increased isokinetic plantar flexor strength at 30°/s (low velocity) is associated with a decreased risk for AT. No association between explosive gastrocnemius-soleus muscle strength (measured with the standing broad jump test) and AT was found in this study.[16]

Static and dynamic properties of the knee There is limited evidence that the tibial intercondylar distance is not associated with AT based on one cohort study.[22]

Static and dynamic properties of the hip There is limited evidence that the amount of external rotation of the hip is not associated with AT based on one cohort study.[22]

Gait analysis There is limited evidence that an abnormal gait pattern with decreased forward progression of the propulsion and a more lateral foot-roll over at the forefoot flat phase are associated with AT. One cohort study reported a protective association per millimetre increase in total displacement of the Y-component of the centre of force. This cohort study also reported a decreased risk for AT if the mediolateral pressure distribution ratio underneath the forefoot at forefoot flat phase increased.[19] No associations were found in another cohort study for the lower extremity quality of movement test.[18]

Pre-existing diseases

Renal dysfunction There is limited evidence that a creatinine clearance <60 mL/min is associated with AT in heart transplant patients. One cohort study reported an increased risk to develop AT in this specific group compared with heart transplant patients with a creatinine clearance ≥60 mL/min.[24]

Heart diseases There is limited evidence that an increased time (in years) between heart transplantation and initiation of quinolone treatment for infectious disease is associated with AT. One cohort study described this association.[24] This outcome was solely investigated in heart transplant patients that all received quinolone treatment. Therefore, heart transplantation and quinolone treatment cannot be evaluated as individual risk factors in this cohort study.

Medication

Fluoroquinolones There is limited evidence that the use of ofloxacin is associated with AT. One cohort study found an increased risk to develop AT when using ofloxacin compared with other antibiotic drugs (without fluoroquinolones).[25] This cohort study found no associations for fluoroquinolones as a group, ciprofloxacin and norfloxacin. Another cohort study found no association between levofloxacin use and AT specifically in heart transplant patients compared with no use of levofloxacin.[24]

Corticosteroids There is limited evidence that daily oral prednisone dose is not associated with AT based on one cohort study.[24]

Training factors

Training season There is limited evidence that training during cold weather is associated with AT. One cohort study found that the incidence of AT increased during recruit winter training compared with summer training.[22]

Potential risk factors evaluated in cross-sectional studies

In the 45 cross-sectional studies 296 risk factors were investigated. 115 associations were found, mostly consisting of biomechanical factors (56 associations) or genetic factors (30 associations). All data are presented in online supplementary appendix 2.

Discussion

Summary of main findings

This is the first high-quality systematic review of clinical risk factors for Achilles tendinopathy. We identified 10 cohort studies, all of which had a high risk of bias and 45 cross-sectional studies.

There is limited evidence for the following nine risk factors: (1) prior lower limb tendinopathy or fracture, (2) use of ofloxacin antibiotics, (3) increased time between heart transplantation and initiation of quinolone treatment for infectious disease, (4) moderate alcohol use, (5) training during cold weather, (6) decreased isokinetic plantar flexor strength, (7) abnormal gait pattern with decreased forward progression of propulsion, (8) more lateral foot-roll over at the forefoot flat phase and (9) a creatinine clearance of <60 mL/min in heart transplant patients.[16 17 19 22 24 25]

Although other potential risk factors such as body weight or BMI, static foot posture measurements and physical activity level are often said to be risk factors in clinical practice, there is currently no scientific evidence that they are associated with AT.[16-19 21-24 70]

Clinical implications

Our systematic review indicates that for AT prevention and treatment the advice to patients might include: (1) to reduce the use of alcohol to less than 7 units per week for men and less than 4 for women, (2) to avoid the use of ofloxacin if alternatives are available and (3) to improve plantar flexor strength by performing strengthening exercises of the calf muscles.[16 17 25]

Whether these interventions will be effective is unknown. For example, calf muscle exercises seem a plausible preventive intervention as decreased plantar flexor strength is a risk factor. However, eccentric calf muscle exercises did not decrease AT incidence in soccer players in a randomised trial.[72] Further research is needed before we can state whether the logical interventions work or not.

Abnormal gait pattern with decreased forward progression of the propulsion and a more lateral foot-roll over at the forefoot flat phase were found to be risk factors for AT in novice runners. Van Ginckel et al. stated that more research is needed to confirm these findings, since this gait pattern with a decreased forward progression might be commonly used in well-trained athletes to improve gait economy.[73] Since the gait pattern was determined barefoot, it is also not known whether these findings can be extrapolated to the running population, as running shoes might alter running gait.[19] Biomechanical characteristics in AT are discussed in more detail in a recent systematic review.[74]

Previous research showed the relationship between BMI, body weight or waist circumference and tendon pathology.[75] The hypothesis of this relationship is primarily based on the fact that the absolute tendon load is increased and that increased cytokine levels (Prostaglandin E2, tumour necrosis factor- α and Leukotriene B4) cause low-grade inflammation in obese individuals.[76 77] In our systematic review, we were not able to find an association between being overweight and AT.[16-19 22 23] It should be noted that more than half of the cohort studies that investigated BMI as a risk factor were in adolescent populations, in which being overweight is less common.[78] Arnoczky and colleagues hypothesised based on an animal model that being underweight is associated with AT, as a consequence of a catabolic state causing a decreased collagen production.[79] This could lead to a U-shaped relationship for the BMI and AT, making it less likely that an association be found.[80] More cohort studies are needed in heterogeneous populations.

Another striking finding is the limited evidence for the absence of an association between physical activity level and AT. Inconclusive results regarding physical activity level were previously also demonstrated in patellar tendinopathy.[81] In the majority of the scientific literature, tendinopathy is described as 'overuse injury'. It could be that 'overuse' or 'physical activity level' is not measured accurately enough to detect

associations. It could also be hypothesised that a sudden change in load is more important than the absolute load that is currently being measured in studies. To date, there is, however, no convincing evidence that AT is a result of overuse.

Moderate alcohol use and increased time between heart transplantation and initiation of quinolone treatment for infectious disease were potential risk factors for AT.[17 24] It is hard to hypothesise why these determinants are risk factors for AT. They might be a confounding factor, with lifestyle factors that influence AT risk. Another reason might be that these findings have been detected by chance. When a high number of analyses are performed, the chance of statistical significance findings increases. Adequate statistical methods can prevent possible coincidental findings. Another potential risk factor that is lacking a clear explanation is training during cold weather.[22] The direct cause-relationship is not known, as the results might be influenced by temperature or type of surface. This particular study did not report information on the temperature or training surface during the training period. These results are therefore difficult to extrapolate.

Research implications

Our review showed that the majority of potential risk factors have only been investigated in cohort studies with a low number of cases (median 18 cases). Professor Roald Bahr and colleagues demonstrated that 20-50 cases are needed to detect moderate to strong associations and even 200 cases to detect small to moderate associations.[82] Therefore, most studies in this review are likely to be underpowered to detect associations. Sample sizes in future studies should therefore be considered carefully. Future studies should also distinguish insertional from midportion AT, since these are two separate entities. It has been suggested that compression forces due to the bony prominence of the calcaneus play a role in the development of insertional AT, while this does not occur in midportion AT.[4] Combining these entities, as occurred in most studies, is not ideal.

There are several interesting determinants found in the cross-sectional studies for future research. Use of oral contraceptives and hormone replacement therapy were more common in patients suffering from AT.[38] Only one research group investigated these factors; therefore, more research is needed to confirm these findings. Regarding lipid profile, Dr Jamie Gaida and colleagues reported that triglyceride level, triglyceride/high-density lipoprotein cholesterol ratio and apolipoprotein B were elevated in patients with AT.[34] Hypertension prevalence was found to be increased in females in the study by Holmes and Lin, suggesting a possible relationship between blood flow circulation to the Achilles tendon and AT.[38] However, all of these factors should be studied in a longitudinal study design since it is not clear whether there is a cause-effect relationship.

Genetic profiling is also a major topic in AT. Since 2002, 16 cross-sectional studies have evaluated the presence of genetic variations in AT.[26 29 33 37 39 44-49 51-55] These genetic variations are linked to collagen structure, tendon or matrix homeostasis, apoptosis or inflammation pathways.[8] This type of research provides more information regarding the biological pathways of the disorder. Future therapy strategies could focus on targeting these pathways.

Strengths and limitations

The strength of this systematic review is that we performed this structured analysis according to the PRISMA guidelines.[71] Consequently, we were able to include 10 cohort studies, whereas a different systematic review on this topic only included 1 cohort study.[8] That recent systematic review provided an excellent overview of all the literature considering genetic variants in AT, but important publications considering non-genetic risk factors in AT were missing. By including these cohort studies, our methods provide evidence that can be used directly in a clinical setting. We were also able to present an overview of topics on which future research should focus. Despite our robust research design, there are also methodological limitations. First, we only selected publications written in the English language. Second, we were not able to pool data because of the heterogeneity. The strength of the associations could therefore only be evaluated with a best evidence synthesis and not with meta-analysis. Third, we chose to use a standardised set of criteria based on modified questions of existing quality assessment tools. This was recommended by Hayden et al., since no validated tools are available for systematic reviews on risk factors.[83] Our tool used strict criteria, primarily considering clinical examination as valid outcome measure (criterion 6). Four cohort studies did not meet this criterion of which three of these studies used International Statistical Classification of Diseases and Related Health Problems (ICD) codes/search terms.[17 24 25] The fourth study examined only runners with serious symptoms.[20] These approaches to case-finding creates a bias. Furthermore, if this criterion would not be taken into account, the studies would still be considered to be of high risk of bias based on the other criteria. Fourth, the median age of the included cohort studies was 21 years due to the profession of most of the populations investigated. This is a relatively young age, since the mean age to develop AT is 30-60 years and AT is therefore expected to be less common in these studies.[69]

Conclusion

There is a lack of high-quality prospective studies investigating risk factors for AT. We found limited evidence for nine determinants as risk factor for Achilles tendinopathy: a history of lower limb injury, season of training, calf muscle strength, gait analysis parameters, moderate alcohol use, fluoroquinolone antibiotic treatment and

suboptimal renal function in a specific heart transplant population. Research funding agencies should prioritise research into modifiable determinants as these could prove useful for AT prevention and treatment. Quality studies will use valid clinical examination (focal Achilles tendon pain in relation to load with impaired load-bearing capacity) as outcomes, valid and reliable risk factor measurements and adequate statistical analysis in heterogeneous populations.

Footnotes

Acknowledgements: The authors would like to thank Wichor Bramer (Medical Library, Erasmus MC University Medical Centre Rotterdam, The Netherlands) for assistance with designing and performing the literature search.

Funding: This research is funded by the Dutch Arthritis Association and the Anna Foundation. Both are non-commercial organizations and were not involved in the content of this publication.

Competing interest: None declared

Link for online supplementary appendices: https://bjsm.bmj.com/content/53/21/1352

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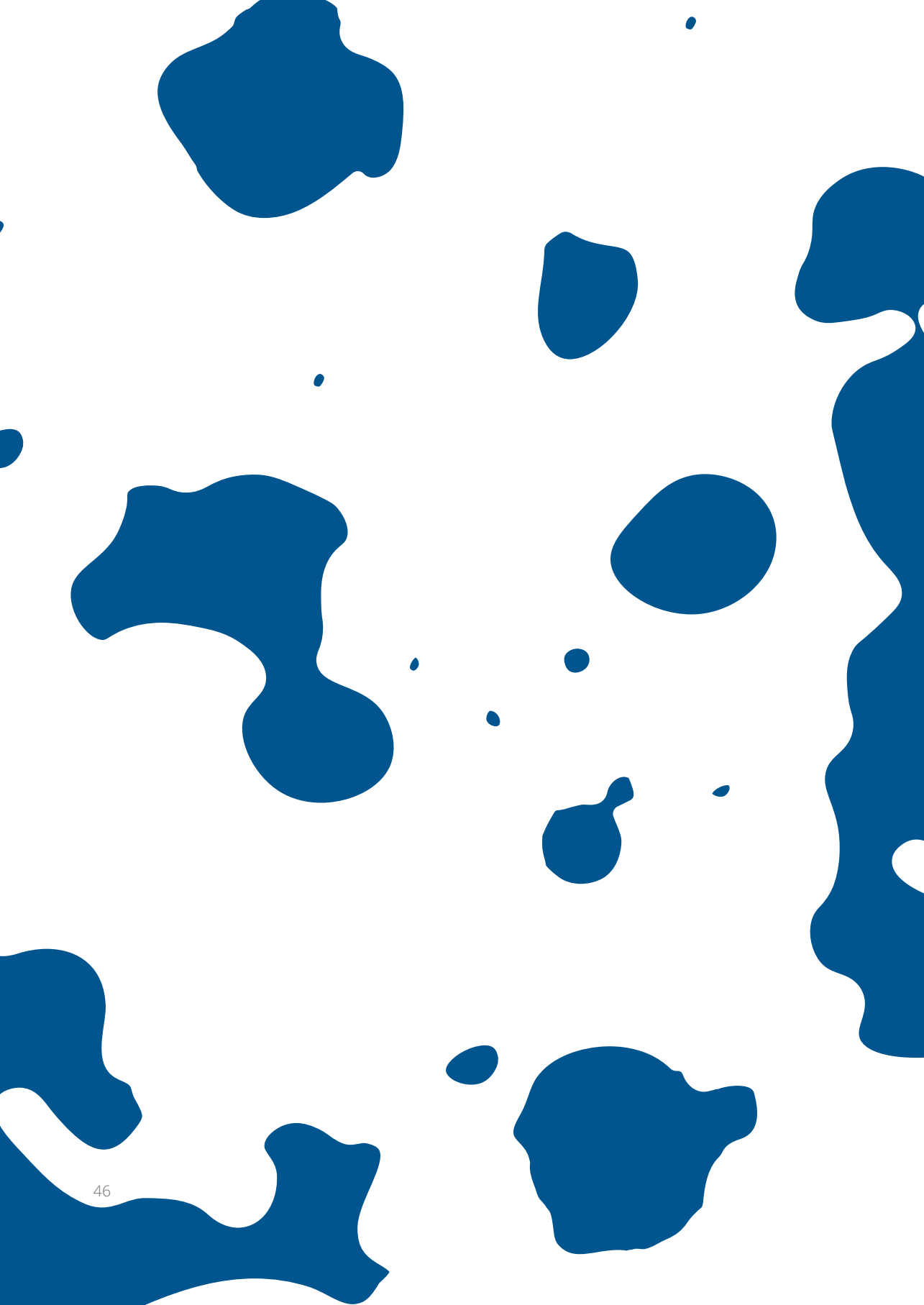

Chapter 3

Ultrasound Doppler flow in patients with chronic midportion Achilles tendinopathy:

is surface area quantification a reliable method?

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J Ultrasound Med. 2020 Apr;39(4):731-739

Abstract

Objectives: Ultrasound assessments of patients with chronic midportion Achilles tendinopathy include determining the degree of neovascularization using Doppler flow. A frequently used measure to quantify neovascularization is the modified Öhberg score. It is unknown whether the semiquantitative modified Öhberg score (0–4+) has higher reliability than a quantified measure of Doppler flow (0–100%). The purpose of this cross-sectional study was to evaluate the interobserver reliability of the modified Öhberg score and a surface area quantification (SAQ) method for Doppler flow in patients with chronic midportion Achilles tendinopathy.

Methods: Two observers examined the degree of Doppler flow independently using SAQ and the modified Öhberg score during a single consultation. The intraclass correlation coefficient, standard error of measurement, and minimal detectable difference were determined to evaluate the reliability and measurement properties of the SAQ method and the modified Öhberg score.

Results: In total, 28 consecutive patients with chronic midportion Achilles tendinopathy participated. The intraclass correlation coefficient for interobserver reliability of the SAQ method was 0.81 (95% confidence interval, 0.58–0.91), compared to 0.64 (95% confidence interval, 0.45–0.81) for the modified Öhberg score. The standard error of measurement and minimal detectable difference values for the SAQ method were 2.9% and 8.0%, respectively, and for the modified Öhberg score, they were 0.55 and 1.53 points.

Conclusions: The SAQ method shows good reliability to evaluate the degree of Doppler flow in patients with chronic midportion Achilles tendinopathy, and it overcomes the ceiling effect of the modified Öhberg score. Future research should focus on the relationship between the SAQ method and clinical outcomes and use this method to monitor treatment responses.

Introduction

Chronic midportion Achilles tendinopathy (AT) is a degenerative condition of the Achilles tendon that most often occurs in running sports.[1-3] Up to 52% of running athletes have AT at least once in their lifetimes.[1] The clinical diagnosis AT is based on a combination of local Achilles tendon pain, swelling of the Achilles tendon, and an impaired load-bearing capacity.[4 5]

Ultrasound (US) is frequently used to verify the diagnosis of AT. One of the features that have been reported in a substantial number of articles is the prevalence of US Doppler flow. Ultrasound Doppler flow indicates neovascularization, which is the formation of new small blood vessels within and around tendons.[6] This process is driven by the production of vascular endothelial growth factor, which also stimulates nerve growth alongside the neovascularization.[7 8] It is hypothesized that these newly formed nerve structures are a contributor or the cause of the pain in chronic tendinopathy.[6] Since these nerve structures cannot be visualized with US, US Doppler flow is being used as a marker for the amount of newly formed nerve structures.

Increased US Doppler flow can be determined by both colour Doppler ultrasound and power Doppler ultrasound (PDUS). Power Doppler ultrasound is the preferred method to use, since it is more sensitive to detect blood flow and is less operator dependent.[9] Increased Doppler flow is present in 47% to 100% of symptomatic Achilles tendons compared to 0% to 50% of asymptomatic tendons.[6 10-18] Most of the studies used the modified Öhberg score to quantify the amount of Doppler flow, which has shown higher reliability compared to the original Öhberg score.[19] The modified Öhberg score runs from 0 to 4+.[4 20] A higher score indicates more Doppler flow in the peritendinous and intratendinous tissues.

The interobserver reliability of the modified Öhberg score varies from moderate to perfect [10 12 19]. Some studies described other disadvantages of the modified Öhberg score. It is considered to have weak applicability to measure higher amounts of Doppler flow (called the ceiling effect), and the scoring system is operator dependent, since the assessment of the score is difficult.[11 20] To make the assessment less difficult, it has been suggested to reduce the modified Öhberg score to a 4 -point scale by combining the 3+ and 4+ categories.[10 12] This will, however, further increase the ceiling effect of this method. Therefore, reliable alternatives for the modified Öhberg score with a quantitative approach are warranted. The surface area quantification (SAQ) method was introduced by Boesen et al. to overcome these limitations and has been used by several other research groups.[21 22] This method aims to determine the percentage of colour pixels within the Achilles tendon, the peritendinous region, or both. This enables a more quantitative analysis and potentially increases the accuracy of the measurement in a research setting. As the analysis is directly accessible and easy to perform, implementation in the clinical setting would also be feasible if medical device

manufacturers were to implement this method as a real-time application on their US machines. Both previous studies that investigated the SAQ method standardized the colour Doppler settings for all examinations to increase reliability.[21 22] The reliability of such a standardized method is, however, currently unknown because previous studies did not assess reliability measures.

Our primary aim was to compare the reliability of the SAQ method with the modified Öhberg method in patients with AT by determining the intraclass correlation coefficient (ICC) between 2 observers. We hypothesized that the ICC of the SAQ method would be considerably higher compared to the semiquantitative modified Öhberg method. Secondary aims were (1) to evaluate the correlation between both methods to test whether the same feature (amount of Doppler flow) was being measured and (2) to evaluate the standard error of measurement (SEM) and minimal detectable differences (MDD) of these methods.

Methods

Study design

This cross-sectional study was conducted as a part of an ongoing double-blind, placebo-controlled randomized clinical trial (RCT). The aim of this RCT was to evaluate the effect of a high-volume injection in patients with chronic midportion AT (ClinicalTrials.gov identifier NCT02996409). Written informed consent was obtained before participation for all patients and also for the cross-sectional part of this study. The protocol of the study was approved by the regional Medical Ethical Committee (registration number 14-100).

Setting and participants

This cross-sectional study was performed at the Department of Sports Medicine in a large district general hospital (The Hague Medical Centre). The first 32 consecutive included patients who participated in the RCT were asked to take part in this cross-sectional study from April 2017 to November 2017. Inclusion criteria were: (1) the presence of a chronic midportion AT for at least 2 months, (2) the completion of an exercise training program for at least 6 weeks with an unsatisfactory outcome, (3) age between 18 and 70 years, and (4) the presence of Doppler flow on PDUS imaging. The diagnosis was established on the basis of a clinical examination (local tendon pain, swelling of the Achilles tendon 2–7 cm proximal to its calcaneal insertion, and an impaired load-bearing capacity) by a physician with experience in sports medicine (15–20 years). As AT is considered a clinical diagnosis in principle, grayscale US was not used to verify the diagnosis.[3] Main exclusion criteria were: (1) a clinical suspicion

of other musculoskeletal disorders (insertional AT, inflammatory systemic disorders, and quinolone-, corticosteroid- or statin-induced tendinopathy), (2) a previous Achilles tendon rupture or surgery, (3) the inability to perform an exercise program, and (4) a medical condition that would affect the safety of the injection (eg, peripheral vascular disease or the use of anticoagulant medication). Detailed information regarding all exclusion criteria is provided in the trial registration. In cases of bilateral symptoms, only the most affected tendon was included in the study.

Test methods

Demographic details

Demographic characteristics of the study population were collected at baseline. We collected the following characteristics: age, sex, body mass index (BMI), duration of symptoms, Victorian Institute of Sport Assessment – Achilles (VISA-A) score, primary sport, and activity level. The VISA-A questionnaire consists of 8 questions and covers 3 domains: pain, activity, and function. Scores vary from 0 to 100, where 100 indicates an asymptomatic person, and 0 is defined as maximum pain, no activity, and no function. The activity level was determined by the researcher as recreational (1 or 2 sports activities per week), competitive (≥3 sports activities per week), or professional (≥3 sports activities per week at a national level).

Ultrasound

Two observers analysed the Achilles tendons of the included patients independently during a single consultation. The PDUS was performed by 1 observer, while the other observer was not present in the room to maintain blinding. Both observers (1 PhD candidate [A.C.v.d.V.] and 1 research student (J.M.V.]) were trained to perform US measurements of the Achilles tendon with greater than 20 training hours and at least 10 patients before the start of the study. Ultrasound examinations for this study were performed during one of the follow-up visits after inclusion in the RCT. Before the US examination was performed, all patients climbed 2 stairs to reach the examination room. No specific instructions were provided about activities before the consultation (eg, sports activities the day before). The patient was placed in a prone position on the examination table, and the ankle was placed over the table in a relaxed position. A Pro Focus type 2202 US scanner (BK Medical, Herlev, Denmark) with a type 8811 5–12-MHz linear transducer was used to perform US measurements. Neovascularization was detected by PDUS with predefined settings: mechanical index, 1.28; thermal index, 1.2; pulse repetition frequency, 1.0 kHz; and gain, 50%. These settings were determined before the start of the study according to the optimization suggestions by Yang et al.[9] Depth was standardized for every patient at 3.0 cm, and the colour

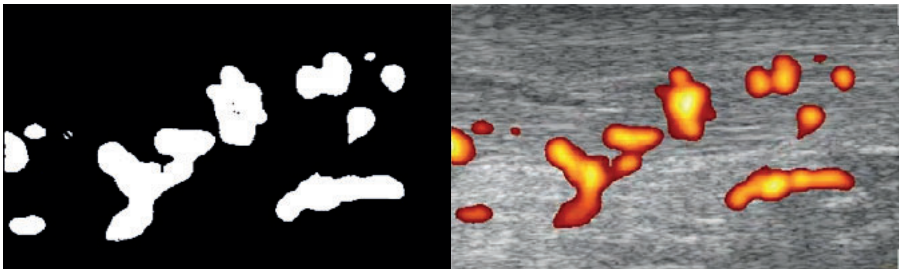
box size during the PDUS examination at 4.6 cm2 (depth, 1.7 cm; width, 2.7 cm). This colour box size was chosen to measure the maximum intratendinous Doppler flow and peritendinous flow in the Kagers' triangle. Peritendinous flow was included to assess the same regions of interest for both the modified Öhberg score and the SAQ method.

The transducer was placed perpendicular to obtain a sagittal view of the Achilles tendon at the most painful part on palpation. The upper limit of the colour box was placed on the dorsal side of the tendon. Pressure from the transducer was kept to a minimum to prevent occlusion of neovascularization.[16 23] Both observers screened the tendon for the area of maximum Doppler flow during the preparation phase for 1 minute. The transducer was gently moved to medial and lateral over the area where Doppler flow was present. When the location of maximum Doppler flow was identified, a 20-second video was recorded. The modified Öhberg score was determined dynamically during the US examination according to previous studies.[10 16 24] When the first observer completed the US examination, the second observer directly performed the examination to keep the time between the examinations to a minimum. The patient remained in the same prone position and was blinded to the outcome of the first observer to standardize for possible confounders.

Analysis using SAQ

We used Kinovea (Bordeaux, France) software to observe the PDUS video in steps of 0.04 seconds to obtain 3 frames with visually maximum Doppler flow. To measure the surface area of the Doppler flow, we used the program ImageJ version K 1.45 (National Institutes of Health, Bethesda, MD). The area directly around the colour box was selected, and the outer part was cleared. Predefined transformations were applied in this study to limit the noise close to 0: threshold colour, black and white; hue, 255; saturation, 165; and brightness, 250. After transformation, colour pixels of blood vessels were shown as white pixels with a value of 255, and noncolor pixels were shown as black pixels with a value of 0. The number of white pixels was subsequently determined by creating a pixel histogram. The number of white pixels was divided by the total number of pixels in the colour box (99,119 pixels) to measure the percentage of displayed blood vessels. This percentage was determined for the 3 frames, and the highest percentage was selected for the analysis. The transformation of the Doppler flow using the SAQ method is illustrated in Figure 1. Both observers analysed their own PDUS videos and remained blinded to the results from the other observer.

Figure 1. Left, Colour box during PDUS of a patient with chronic midportion AT in a sagittal view. Right, Same colour box after transformation of colour pixels to white pixels to make SAQ possible.



Analysis using the modified Öhberg score

The modified Öhberg score is a 5-point grading scale to score neovascularization in various types of tendinopathy: 0 indicates the absence of Doppler flow; 1+ indicates 1 or 2 neovessels in the Kagers' fat pad; 2+ indicates 1 or 2 intratendinous neovessels; 3+ indicates 3 or 4 intratendinous neovessels; and 4+ indicates a network of neovascularization with more than 5 intratendinous neovessels.[10 16 24]

Statistical analyses

Both researchers imported data from the measurements they performed themselves. The normality of the data was checked visually with Q-Q plots and statistically with the Shapiro-Wilk test. The correlation between the degree of Doppler flow measured by the SAQ method and modified Öhberg score was analysed with the Spearman correlation coefficient. The Spearman correlation coefficient was interpreted as a scale from poor to almost perfect correlation (<0.00, poor; 0.00–0.20, slight; 0.21–0.40, fair; 0.41–0.60, moderate; 0.61–0.80, substantial; and 0.81–1.00, almost perfect).[25] The interobserver reliability of both methods was analysed first by determining the Spearman ρ correlation coefficient for non–normally distributed data and the Pearson ρ correlation coefficient for normally distributed data. Correlations were controlled visually by constructing a scatterplot. The ICC for interobserver reliability was determined by the 2-way random-effect model with absolute agreement. Interpretation of the ICC was as suggested by Portney and Watkins; values of less than 0.5 indicate poor reliability; scores between 0.5 and 0.75 indicate moderate reliability; and scores of greater than 0.75 indicate good reliability.[26] In addition, the SEM and MDD were determined for both methods by the following equations: [27 28]

$$SEM = \sqrt{(MSw)}$$

$$MDD = SEM * 1.96 * \sqrt{2}$$

Where MSw represents the within-subject mean square derived from the analysis of variance. We used SPSS Statistics version 24.0 software (IBM Corporation, Armonk, NY) to analyse data, and statistical significance was set at $\alpha = .05$ (2-tailed). Additionally, we determined the prevalence- and bias-adjusted κ for ordinal data (PABAK-OS) for the modified Öhberg score using a Web-based PABAK-OS calculator (http://www.singlecaseresearch.org/calculators/pabak-os). We performed this test to adjust for chance agreement of the ordinal modified Öhberg score, since the ICC is designed to be used for continuous outcomes. Using the PABAK-OS, we were able to determine whether it was justified to determine the ICC for the modified Öhberg score.[29]

Results

Patient characteristics

Of the first 32 consecutive patients who were included in the RCT, 4 patients did not participate in this cross-sectional study. Two patients were lost to follow-up in the RCT, and 2 patients declined to participate in this study part (lack of time). Consequently, 28 patients participated in this cross-sectional study, which was performed during follow-up of the RCT. The mean population age was 49.6 years (range, 35–59 years), and the median symptom duration was 56 weeks (range, 10–1040 weeks). The mean VISA-A score at baseline was 42.8 points (range, 9–73 points). Detailed baseline demographic characteristics are presented in Table 1.

Table 1: Demographic baseline characteristics of the study population (n=28)

Age, mean ± SD, years	49.6 ± 6.4
Sex, n (%)	
Male	16 (57.1%)
Female	12 (42.9%)
Body Mass Index, mean ± SD, kg/m^2	26.3 ± 5.0
Affected side, n (%)	
Left	10 (35.7%)
Right	11 (39.3%)
Bilateral	7 (25.0%)
Duration of symptoms, median (IQR), weeks	56.0 (10.0-104.0)
VISA-A score, mean ± SD	42.8 ± 15.0
Primary sport, n (%)	
Running	12 (42.9%)
Fitness	3 (10.7%)
Cycling	3 (10.7%)
Hockey/soccer	2 (7.1%)
Handball	1 (3.6%)
Volleyball	1 (3.6%)
Tai Bo	1 (3.6%)
Shooting archery	1 (3.6%)
Hiking	2 (7.1%)
No sports	2 (7.1%)
Activity level, n (%)	
Professional	0 (0%)
Competitive	5 (17.9%)
Recreational	23 (82.1%)

SD: standard deviation, IQR: interquartile range, VISA-A: Victorian Institute of Sport Assessment – Achilles (measured at baseline)

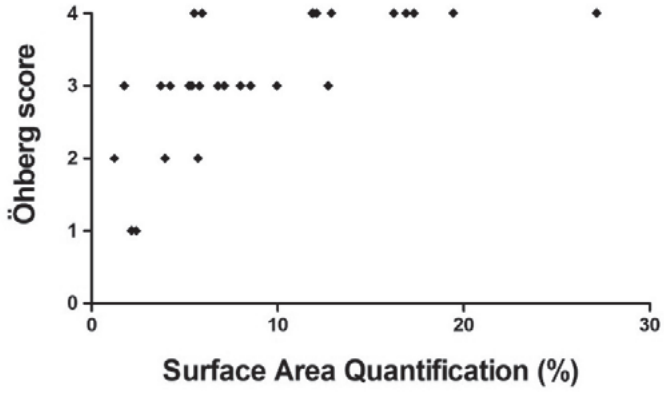
Ultrasound assessments

The mean colour fraction of the SAQ method ranged from 9.0% to 10.9% for both observers (mean ± SD: observer 1, 9.0% ± SD 6.6%; observer 2, 10.9% ± SD 6.8%). The lowest observed colour fraction was 0.4%, and the highest was 27.2%. The median of the modified Öhberg score (0–4+) ranged from 3.0 to 3.5 for both observers (observer 1, 3.0 [interquartile range, 1.0]; observer 2, 3.5 [interquartile range, 2.0]). The range was 1+ to 4+ for both observers.

Correlation between the SAQ method and modified Öhberg score

The Spearman correlation coefficient between the SAQ method and the modified Öhberg score showed a substantial correlation for both observers. The correlations were found to be 0.76 for observer 1 and 0.62 for observer 2. The SAQ outcomes for the modified Öhberg 4+ group ranged from 5.5% to 27.1% for observer 1 and from 5.2% to 27.2% for observer 2 (Figure 2).

Figure 2. Scatterplot showing the correlation between the modified Öhberg score and SAQ. Note the ceiling effect in the Öhberg 4+ group, in which the SAQ ranges between 5.2% and 27.2%.



Intraclass correlation coefficient for interobserver reliability

The ICC of the SAQ method was found to be 0.81 (95% confidence interval [CI], 0.58–0.91), whereas it was 0.64 (95% CI, 0.35–0.81) for the modified Öhberg score. The ICCs, SEMs, and MDDs are reported in Table 2. The PABAK-OS for the modified Öhberg score was found to be 0.33 (95% CI, 0.17–0.50).

Table 2: Intraclass correlation coefficients of the Surface Area Quantification (SAQ) method and modified Öhberg score

	Correlation (95% CI)	P-value	SEM	MDD	n
ICC SAQ method (0-100%)	0.81 (0.58-0.91)	<0.001	2.88%	7.99%	28
ICC modified Öhberg score (0-4 points)	0.64 (0.35-0.81)	<0.001	0.55 points	1.53 points	28

The correlation for an individual measurement method was significant below the .05 level (2 tailed). Note that the SAQ method ranges from 0% to 100%, and the modified Öhberg score ranges from 0 to 4+ points. The SEM and MDD are therefore presented as a percentage for the ICC of the SAQ method and as a number for the modified Öhberg score.

Discussion

To our knowledge, this was the first study to investigate the reliability of the SAQ method in midportion AT and to compare it with the most widely used quantification method (modified Öhberg score). We showed that the SAQ method is a reliable measurement tool in a research setting to evaluate the degree of US Doppler flow in patients with chronic midportion AT. According to our findings, the SAQ method is not superior to the modified Öhberg score for quantifying neovascularization. There are, however, advantages to the SAQ method, since it is a more quantitative method and overcomes the ceiling effect of the modified Öhberg score by differentiation between high amounts of Doppler flow.

Surface area quantification is a method to quantify the fraction of colour pixels during a PDUS examination. We found good interobserver reliability for the SAQ method (ICC, 0.81) compared to moderate interobserver reliability for the modified Öhberg score (ICC, 0.64).

Similar findings for the ICC of the modified Öhberg score were published by Risch et al, in which moderate absolute interobserver agreement (0.64–0.80) was also observed.[19] Sengkerij et al and Watson et al observed considerably higher ICCs for the modified Öhberg score (0.85 and 0.86, respectively).[10 12] In all studies, measurements were determined by experienced radiologists or sports and exercise medicine consultants. One major difference between the studies was that the modified Öhberg scores were determined on the basis of US recordings in the study performed by Risch et al, whereas the US examinations were performed by the observers themselves in the other 2 studies. This indicates that agreement between observers is not dependent solely on the experience of the observer performing the US examination but also on the observer interpreting the findings. Since the SAQ method selects multiple frames with visually maximum Doppler flow and provides an objective percentage for the colour fraction, interpretation of the US recordings that can cause interobserver variability will play a minor role.

We have demonstrated that there is a substantial correlation between the SAQ method and the modified Öhberg score (Figure 2). A perfect correlation was not expected, since the modified Öhberg score is limited to a maximum score of 4, whereas the SAQ method can detect any amount of Doppler flow. The modified Öhberg score is therefore less applicable when there is a high degree of Doppler flow present, as the modified Öhberg 4+ subgroup will represent a wide variation in the degree of Doppler flow. This is called the ceiling effect, in which an extra amount of Doppler flow no longer has an effect on the Öhberg score. This ceiling effect was shown in our study for the modified Öhberg 4+ group (range for the SAQ method, 5.2%–27.2%). This could also be an explanation of why the degree of Doppler flow is to date only weakly related to clinical severity, and future research should therefore focus on the correlation between the SAQ measurement and clinical severity.[13 15 18]

The ICC does not provide a measure of the precision: ie, the difference in individual patients. The precision of a measurement can be determined by calculating the SEM, which reflects the boundaries around the true score of the individual and is largely independent of the variance between patients.[28] The SEM for the SAQ method was 2.9% in this study. This indicates that when a colour fraction of 11.0% is be found, the true value of the observation would be between 8.1% and 13.9%. It is difficult to compare this SEM with the SEM of the modified Öhberg score, since this is an ordinal score ranging from 0 to 4+, whereas the SAQ method ranges from 0% to 100%. The SEM of the modified Öhberg score was 0.55. An observed Öhberg score of 2 would therefore have a true value between 1.45 and 2.55.

The MDD is calculated from the SEM and reflects the threshold for the change within a patient that can be considered a real change.[28] This is relevant to determine, since these kind of quantification methods will be primarily used during follow-up to monitor treatment responses. The MDD for the SAQ method was found to be 8.0%. This indicates that in the same patient with a colour fraction of 11.0%, a value of less than 3.0% or greater than 19.0% during follow-up would indicate a real decrease or increase in the colour fraction, respectively. The MDD of the modified Öhberg score was found to be 1.5. When an observed Öhberg score of 2 is found in a patient, a value of less than 0.5 or greater than 3.5 during follow-up would indicate a real change.

Limitations

This study had some methodological limitations. First, we chose a standardized size of the colour box to only detect intratendinous and peritendinous neovascularization in the Kagers' fat pad in most of the patients. In a case of a relatively small Achilles tendon, deeper structures such as the posterior tibial artery tibialis could be included in the colour box. The presence of this artery was not discussed in the standardized protocol. There was 1 patient in whom this artery was present, and a single observer measured the artery in contrast to the other observer. Determination of the modified Öhberg score was not affected by the presence of the artery in this case. The reliability of the SAQ could potentially be further improved if the posterior tibial artery is recognized and not included in the colour box during the US examination. We think that adding this to the SAQ protocol is most appropriate, since the posterior tibial artery is part of the normal vascular structure, and it is not a result of the process of neovascularization. Second, we have not determined intraobserver reliability. In patellar tendinopathy, it was previously demonstrated that day-to-day variability in Doppler flow is present; however, in midportion AT, it was shown that the intraobserver reliability of the modified Öhberg score was excellent.[19 30] Future research should investigate the intraobserver reliability of the SAQ method to verify the diagnostic value

of SAQ. Third, ideally a minimum of 3 observers would be involved in a reliability study, since a lack of variability would increase the ICC. We have, however, demonstrated that the SEM indicates fairly good precision. The SEM is, contrary to the ICC, largely independent of variation between patients. We therefore expect that the use of this method would be valid in future research projects. Fourth, US measurements were performed by relatively inexperienced sonographers (1 PhD candidate and 1 research student). Our results demonstrated that the SAQ method is less operator dependent and therefore can be performed well after some practice. Fifth, since the modified Öhberg score is an ordinal scale, the ICC (designed for continuous scales) is not the most appropriate measure for expressing reliability. Therefore, we determined the PABAK-OS to control for the fact that the chance of agreement is higher in an ordinal scale compared to a continuous scale. We have demonstrated that the PABAK-OS was indeed lower for the modified Öhberg score, indicating that the ICC does not overestimate the reliability of the modified Öhberg score. Sixth, we chose to refrain from a power analysis, since data for this novel measurement tool were not available when designing this study, and post hoc power analyses are discouraged.[31] Last, the SAQ method is currently not available as a measurement function on US machines, and computers and (free) software packages have to be used to determine the value of the SAQ. Since we used a relatively easy method to calculate the value of the SAQ, we expect that this function could be implemented easily on US machines via a real-time application once it has shown its clinical relevance in future studies through estimating the prognosis or personalized treatment based on SAQ scores.

Conclusion

To our knowledge, this was the first study to evaluate the diagnostic value and reliability of measuring the surface area of Doppler flow in patients with chronic midportion AT. This study demonstrates that SAQ has similarly good reliability as the modified Öhberg score. Surface area quantification, however, overcomes disadvantages of the modified Öhberg score, of which the ceiling effect in the modified Öhberg 4+ category is most important. These findings could inspire medical experts to use the SAQ method for research purposes to determine the degree of US Doppler flow quantitatively in patients with chronic midportion AT. Ultimately, treatment responses of interventions acting on neovascularization could be monitored quantitatively and with good reliability. More research is needed regarding the intraobserver reliability to evaluate the clinical applicability.

Footnotes

Acknowledgements: We would like to thank our biomedical statistician J.H. Waarsing for his statistical expertise during the data analysis and interpretation of the data.

Funding: This research is funded by the Dutch Arthritis Association and the Anna Foundation. Both are non-commercial organizations and were not involved in the content of this publication.

Competing interest: None declared.

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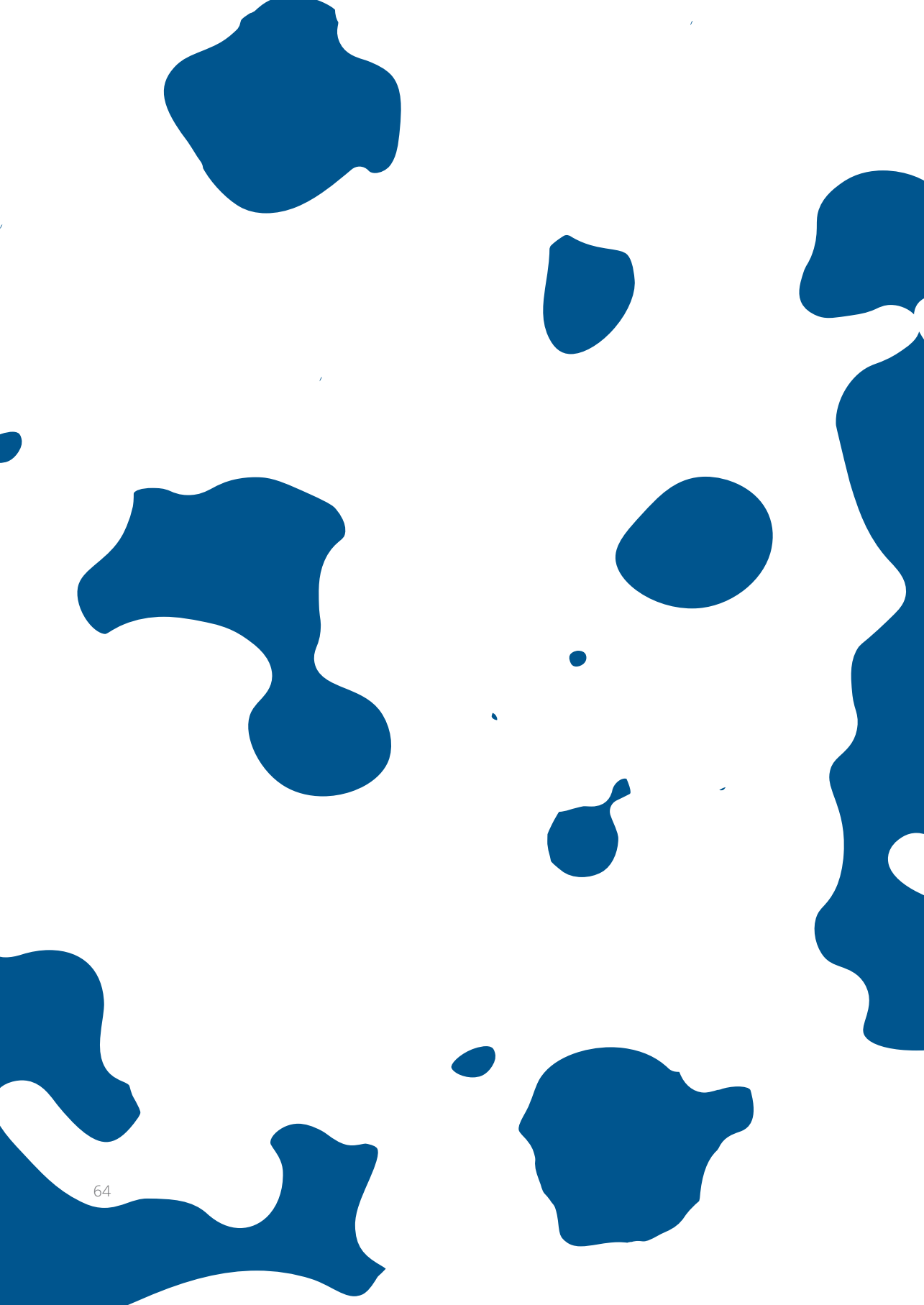

Chapter 4

Minimal clinically important difference of the validated patient-reported VISA-A questionnaire for Achilles tendinopathy:

a prospective cohort study

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Submitted for publication

Abstract

Objective: To determine the minimal clinically important difference (MCID) of the Victorian Institute of Sports Assessment-Achilles (VISA-A) score in patients with midportion Achilles tendinopathy (AT).

Design: Prospective cohort study.

Methods: In this study a cohort of physically active patients with midportion AT was included. The patients all underwent treatment with exercises and an injection. We measured the VISA-A score (0-100 points, where 100 points represent a healthy tendon), a 7-point Global Assessment Scale (GAS; ranging from 'worse than ever' to 'completely recovered') at baseline, after 12 and after 24 weeks. We dichotomised GAS to not improved ('worse than ever' to 'unchanged') or improved (moderately improved to completely recovered). The area under the curve (AUC) and Youden's index closest to 1 were determined for both MCID with corresponding sensitivity and specificity.

Results: A total of 64 active patients were included in this study and 61 patients (95%) completed the 24-week follow-up. The MCID was 14 points over a 12-week period, corresponding with a 57.1% sensitivity and 88.0% specificity, and 7 points over a 24-week period with 85.4% sensitivity and 61.5% specificity.

Conclusions: A change in VISA-A score of $\geq$14 points after 12 weeks or $\geq$7 points after 24 weeks of exercise therapy and an injection can be used as guidance for reflection of a meaningful change for physically active patients with midportion AT. This information can be used to better interpret meaningful treatment effects for patients with AT.

Trial registration number: Clinical Trials (Identifier: NCT02996409).

Introduction

Achilles tendinopathy (AT) is a common tendon overuse injury in sports, especially among runners.[1] The symptoms of AT cannot be expressed by pain alone, as AT influences physical (physical function, disability), psychosocial (sports participation, pain rating) and overall impact (quality of life).[2] Symptom evaluation in AT patients should be done within the 9 core domains which recently have been published as a result of cooperation between health care providers and patients.[2] These domains are: patient overall rating, participation, pain on activity/loading, disability, function, physical function capacity, quality of life, psychology and pain over a specified timeframe.[2] The impact of symptoms on an individual can be measured using patient-reported outcome measures (PROMs) within one of these 9 established core domains for tendinopathy.[3]

The Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire is a validated and disease-specific PROM within the core domain 'disability'.[2 4] The VISA-A score was developed as a standardised outcome measure to evaluate the treatment effect in physically active patients with AT.[4] It evaluates physical disability via questions about pain, functional status and sports activity, and ranges from 0-100 points with higher scores indicating less symptoms during activities.[4] Since its introduction in 2001, the VISA-A questionnaire has been validated and translated to seven other languages, and is widely used in AT studies.[5 6]

Responsiveness is an important characteristic of a PROM, indicating the ability of an instrument to measure clinically significant changes. The minimal clinically important difference (MCID) reflects the smallest change in a score that is meaningful for patients.[7] Previous literature suggests a MCID on the VISA-A score ranging from 6.5 to 20 points.[8-10] However, the studies are heterogeneous, as the study population ranges from insertional AT to midportion AT, number of inclusions ranges from 15 to 54 patients and the applied statistical methods are very different [8-10]. The most accepted method for determining a MCID is an anchor-based method where a numerical outcome, such as the VISA-A score, is 'anchored' to a categorical assessment, such as a Likert scale.[11] While the MCID reflects improvement (feeling better), the patient acceptable symptom state (PASS) reflects wellbeing or sufficient remission of symptoms (feeling good).[12] While a certain increase in VISA-A score could reflect a clinically relevant improvement, it is not self-evident that AT symptoms are acceptable. Calculation of the PASS is performed by using an anchor to identify cut-points in numerical PROMs. The PASS could thereby further improve the interpretation of a treatment effect by determining which portion of patients consider their symptoms acceptable.

While the VISA-A score has been used in most of the intervention studies for midportion AT patients, there is absence of an anchor-based MCID value and PASS threshold. This limits adequate interpretation of trial results which are relevant to patients. Therefore, we conducted this study with the aim to determine the anchor-based MCID and PASS of the VISA-A score in patients with midportion AT.

Methods

This study is a prospective cohort study, which is part of a randomised controlled trial, the High-volume image-guided injections in midportion Achilles Tendinopathy (HAT) study.[13] In this trial patients were randomised to either a high-volume injection (50 mL) or a low-volume injection (2 mL) and all patients performed strengthening exercises for the calf muscles. The injections consisted of a 0.9% NaCl solution with 1% lidocaine. We were able to consider the patients of the HAT study as a cohort as there was no between-group difference in VISA-A score.[13] For more details about the interventions used in the HAT study, we refer to the main article [13] The HAT study was approved by the Medical Research Ethics Committee of Southwest Holland, the Netherlands (MEC-14-100). Materials and methods were reported in the pre-registered study protocol at clinicaltrails.gov (identifier: NCT02996409).

Subjects

Patients were recruited at a large district general hospital (The Hague Medical Centre, Leidschendam, the Netherlands) between December 2016 and January 2019. A sports medicine physician evaluated patient suitability for inclusion. Inclusion criteria were (1) the presence of clinically established midportion AT for more than 2 months, (2) having completed an exercise training program for at least six weeks with unsatisfactory outcome, (3) an age between 18-70 years, and (4) the presence of Doppler flow on Power Doppler Ultrasonography (PDU). Midportion AT was defined as a painful swelling of the Achilles tendon, 2-7 cm proximal to the calcaneal insertion. Main exclusion criteria were (1) presence of other musculoskeletal disorders (such as insertional tendinopathy, tendon rupture, inflammatory internal disorders, or drug-induced tendinopathy), (2) pregnancy, and (3) the inability to perform an exercise program. Informed consent was obtained from all patients before inclusion and the rights of the patients were protected. As the VISA-A score is validated for active patients only, we also chose to exclude patients with an ankle activity score <4 for this specific study.[14] Other eligibility criteria are reported in the study protocol.

Outcome measures

We used the VISA-A questionnaire (0-100 points) to determine severity of symptoms in AT patients.[4] The VISA-A questionnaire is a disease-specific questionnaire and has been validated in Dutch language.[15] It evaluates the categories pain, functional status and sports activity and uses those categories to express the severity of AT symptoms on a scale of 0 to 100, where 100 represents a healthy tendon.[15] The VISA-A questionnaire was administered digitally at baseline and after 12 and 24 weeks follow-up. The 7-point Global Assessment Scale (GAS) was completed by the patients at 12 and 24 weeks. They had to rate their symptoms of the prior week compared to the week before baseline, with answers ranging from 'worse than ever' to 'completely recovered'. To calculate MCID, we dichotomised the 7-point global assessment scale to 'not improved' ('worse than ever' to 'unchanged') and 'improved' ('moderately improved' to 'completely recovered') (Table 1).[8] According to existing literature, the cut-off was set at 'moderately improved', as the MCID reflects the minimal positive effect that is meaningful for the patient, with the emphasis on 'minimal'.[7] PASS was calculated by using the perception of symptoms, which was inquired via one single question: 'If you had to live with your current symptoms for the rest of your life, would this be acceptable or unacceptable? Answer options were 'acceptable' or 'unacceptable'.

Table 1. Statements with corresponding points of the 7-point Global Assessment Scale.

Number	Statement
1	Worse than ever
2	Much deteriorated
3	Moderately deteriorated
4	Not changed
5	Moderately improved
6	Much improved
7	Completely recovered

Statistical analysis

We used SPSS software (V.24.0.0.1; SPSS, Chicago, Illinois, USA) for statistical analysis. As the sensitivity analysis reported less than 5% missing data in the primary study,[16] imputation was not needed.[13] We used a Shapiro-Wilk test for normality, where we assumed normal distribution if $p>0.05$. To calculate MCID, a Receiver Operating Characteristics (ROC) curve was created using the dichotomised GAS and the change in VISA-A score between baseline, 12, and 24 weeks. To determine the PASS, we

created a ROC curve using the VISA-A score at 12 and 24 weeks and the perception of symptoms (acceptable/unacceptable). The Area Under the Curve (AUC) represented improvement and was interpreted as fail (0.50-0.59), poor (0.60-0.69), fair (0.70-0.79), good (0.80-0.89) and excellent (0.90-1.0).[17] The Youden's index was calculated to maximise sensitivity and specificity with the following formula: . The MCID and PASS values were determined with a Youden's index nearest to 1. The positive predictive value (PPV) was calculated with the following formula: .

Results

A total of 64 patients were included in the study, of which 61 patients completed follow-up after 24 weeks (95%) (Table 2). Endpoint data of three patients were missing, of which 1 was unreachable and 2 did not complete all questions. The VISA-A score increased from a mean of 40 (standard deviation (SD), 15) points at baseline to 52 (20) points after 12 weeks and 60 (22) points after 24 weeks. The median ankle activity score (interquartile range, IQR) was 5 (5-6). Median score (interquartile range, IQR) of the 7-point GAS was 5 (4-6) after 12 weeks and 6 (5-6) after 24 weeks. The perception of symptoms was acceptable for 36% of patients after 12 weeks, which increased to 51% after 24 weeks.

Table 2. Baseline characteristics of patients

	Included patients, n (%)/mean (SD) / median (IQR)
N	64
Sex (male)	30 (47%)
Age (years)*	50.0 (44.3-54.0)
BMI (kg/m2)*	25.4 (24.0-31.4)
Duration of symptoms (weeks)*	77 (40-134)
VISA-A score	40 (15)

*Non-normal distribution, expressed in median (IQR).

Abbreviations: BMI, body mass index; IQR, interquartile range; SD, standard deviation; VISA-A, Victorian Institute of Sports Assessment-Achilles questionnaire

Minimal clinically important difference of the VISA-A score

After 12 weeks, 58% of the patients reported improvement of their symptoms (Table 3). The mean improvement (standard deviation, SD) of this subgroup on the VISA-A scale was 17 (16) points. The Area Under the Curve (AUC) of the ROC curve was

0.762, 95% confidence interval (CI) [0.640-0.884] (Figure 1A). The Youden's index closest to 1 was 0.451, which corresponded with an improvement of 14 points and a 57.1% sensitivity and 88.0% specificity. The PPV was 97.4%. After 24 weeks, 79% of the patients reported that their symptoms had improved (Table 3). The mean improvement (SD) of this subgroup on the VISA-A scale was 25 (17) points. The AUC was 0.806, [95% CI of 0.669-0.943] (Figure 1B). The Youden's index closest to 1 was 0.469, corresponding with 7 points improvement after 24 weeks. The sensitivity was 85.4% and specificity was 61.5%. The PPV was 89.3%.

Table 3. Global assessment score, perception of symptoms and VISA-A score at 12 and 24 weeks after baseline

	Week 12		Week 24	
	N	**n (%)/mean (SD) / median (IQR)**	**N**	**n (%)/mean (SD) / median (IQR)**
GAS*	60	5 (4-6)	61	6 (5-6)
Dichotomised GAS (improved)	60	35 (58%)	61	48 (79%)
Perception of symptoms (acceptable)	59	21 (36%)	61	31 (51%)
VISA-A score	61	52 (20)	63	60 (22)

*Non-normal distribution, expressed in median (IQR)

SD = standard deviation

IQR = interquartile range

GAS = Global Assessment Scale

VISA-A = Victorian Institute of Sports Assessment-Achilles questionnaire

Patient acceptable symptom state of the VISA-A score

After 12 weeks, 36% deemed their symptoms acceptable (Table 3). The AUC of the ROC curve was 0.852, [95% CI of 0.753-0.950] (Figure 2A). The Youden's index closest to 1 was 0.589 and corresponded with a VISA-A score of 50. The sensitivity was 90.5% and specificity was 68.4%. The PPV was 61.7%. After 24 weeks, 51% of patients reported that their symptoms were acceptable (Table 3). The AUC was 0.766, [95% CI of 0.648-0.883] (Figure 2B). A Youden's index of 0.444 was closest to 1 and corresponded with a VISA-A score of 60 points. The sensitivity was 67.7% and specificity was 76.7%. The PPV was 75.2%.

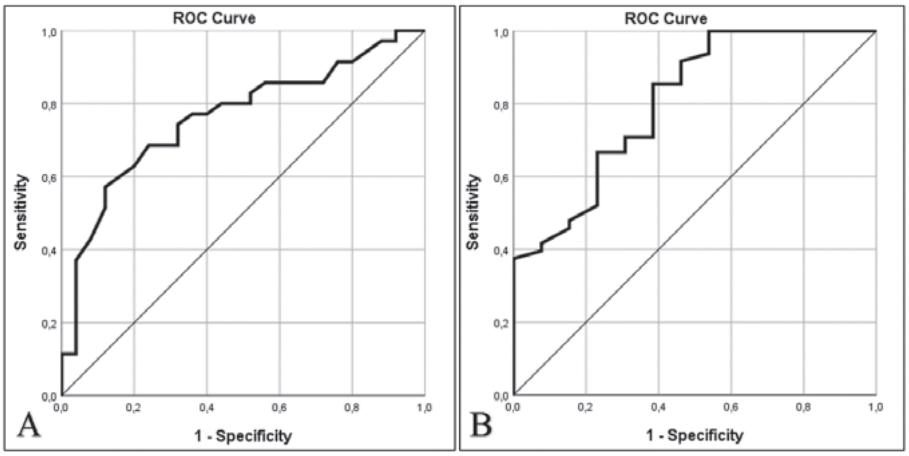

Figure 1. A. Receiver Operating Characteristic (ROC) curve for the Minimal Clinically Important Difference (MCID) per change in VISA-A score after 12 weeks. The ROC curve visualises the probability distribution that a certain change in Victorian Institute of Sports Assessment-Achilles questionnaire (VISA-A score) is deemed as 'improved' by the patient. The point closest to the upper left corner has the most optimal balance between sensitivity and specificity is calculated with the Youden's index. B. ROC curve for MCID per change in VISA-A score after 24 weeks.

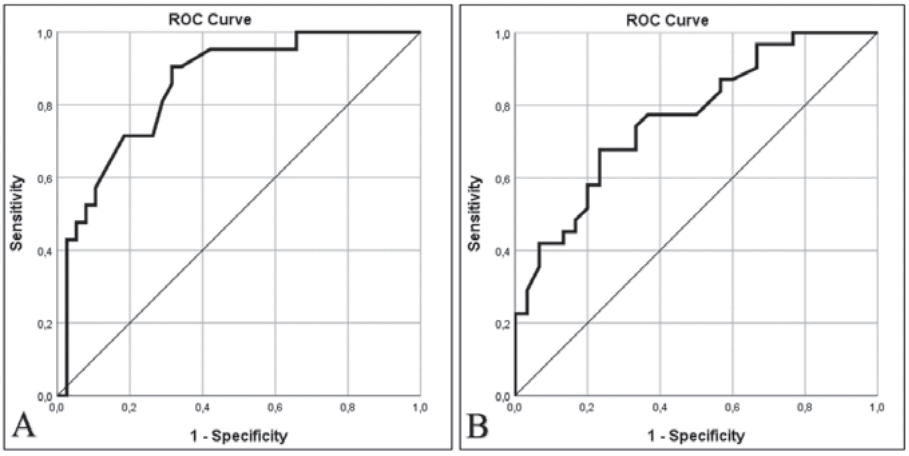

Figure 2. A. Receiver Operating Characteristic (ROC) curve for Patient Acceptable Symptom State (PASS) per Victorian Institute of Sports Assessment-Achilles questionnaire (VISA-A score) after 12 weeks. B. ROC curve for PASS per VISA-A score after 24 weeks.

Discussion

To our knowledge, this is the first study that investigated the responsiveness of the VISA-A scale in physically active patients with midportion AT, treated with exercise therapy and an injection. With an anchor-based approach, we defined that the MCID for the VISA-A score is a change greater than 14 points over a 12-week time period or a change greater than 7 points over a 24-week time period. Symptoms of AT were perceived as acceptable (PASS) if the VISA-A score was ≥50 points after 12 weeks or ≥60 points after 24 weeks. Patients with similar characteristics as the patients in this study are more likely to experience a meaningful change in their symptoms or perceive their symptoms acceptable if they meet these mentioned thresholds. These thresholds can be used by researchers as a guidance to estimate whether patients with midportion AT will notice improvement after exercise therapy and an injection or perceives their symptoms acceptable after a certain period of time.

While the VISA-A questionnaire is widely used to analyse treatment outcome and progression, anchor-based MCID and PASS had never been determined for VISA-A score in patients with midportion AT. This enables comparative effectiveness research with a patient-centred approach. These findings will also aid researchers as guidance in detecting clinically meaningful changes in PROMs, rather than focussing on statistically significant differences. However, as both MCID and PASS are subjected by the study population, applied treatment and follow-up time, the outcomes should be interpreted with caution.

Minimal clinically important difference of the VISA-A score

Previous studies suggested that the MCID for the VISA-A score ranges from 6.5 to 20 points.[8-10] McCormack et al.[8] calculated the MCID of the VISA-A score in a small population of 15 patients with insertional AT after 12 weeks. The primary study researched the effect of Astym® and eccentric exercises in the management of insertional AT and concluded that Astym® was beneficial.[18] It is not mentioned whether patients were active or sedentary. McCormack et al.[8] used a similar anchor-based method as our study, and defined a MCID of 6.5 points on the VISA-A scale after 12 weeks. This MCID value is similar as determined in our study after 24 weeks. Our study included a larger study population which further increased the likelihood that the MCID is around this value at 24 weeks. Additionally, an advantage of our study is that we were able to differentiate between several time points. De Vos et al.[9] researched the effect of a platelet-rich plasma injection compared to placebo injection on chronic midportion AT in 54 active and sedentary patients (mixed group), and concluded no difference between groups. They suggested a MCID of 12 points after 24 weeks, based on the assumption that a change of 10-15% on the scale is in

general clinically meaningful. Tumilty et al.[10] compared the effect of low-level laser therapy with eccentric exercises in 20 patients with AT, of which effectiveness could not be determined due to low statistical power. It is not mentioned whether patients were active or sedentary. They suggested a MCID of 20 points after 12 weeks on a distribution-based method, where MCID was based on 75% of patients achieving this change in VISA-A score or better. Similar to de Vos et al,[9] this distribution-based method lacks a connection with clinical relevance for the patient.[11] As insertional AT and midportion AT are different in both identified pathology and treatment response,[19] it is important to study these patient populations separately. Furthermore, the high PPV supports the evidence that if a patient has an increase of the MCID cut-off or higher, the patient really notices the improvement. Therefore, the reported MCID of our study probably best represents clinically meaningful improvement of patients with midportion AT.

There is a large difference in MCID over a 12-week period (14 points) compared to the 24-week period (7 points). As this is the first study to analyse the MCID over different time periods in the same study population, we cannot compare these findings with the existing literature. One explanation for this large difference in MCID could be recall bias; patients could be remembering their symptoms worse than they were, leading to patients reporting improvement. This emphasises that although MCID was calculated in a large, homogenous cohort, interpretation should be done with caution.

Patient acceptable symptom state of the VISA-A score

The thresholds for PASS of the VISA-A score is 50 points after a 12-week period and 60 points after a 24-week period. To our knowledge, the PASS has never been determined for the VISA-A score. It is interesting that the threshold for acceptable symptoms increases when analysing a longer time period. An explanation could be that patients interpret the question as if the symptoms are 'acceptable at this moment' and not 'acceptable for life', despite our efforts to emphasise the 'for life' part of the question. Furthermore, it is notable that both thresholds are relatively low: in order to reach a VISA-A score of 50 or 60 points, the patient is limited in multiple domains (pain in activities of daily living, function and sports activity). A possible explanation could be that patients accept living with negligible pain and a decreased sports activity level. We therefore emphasise that it is important to determine the goals of the patients in order to set the correct targets in both research and in a clinical setting.

Sensitivity and specificity

As there is currently no gold standard to calculate the MCID and the PASS, the anchor-based method is currently the most accepted method.[11] Sensitivity for MCID

represents the ability to correctly detect whether patients with midportion AT that noticed improvement of their symptoms are actually improved, while specificity represents the ability to correctly reject whether patients did not notice improvement of symptoms. To increase clarity, we will explain by using the MCID after 12 weeks of 14 points with a 57% sensitivity and 88% specificity. This means that if a patient increases 14 points, we are 57% sure that patients who notice improvement are actually improved, while we are 88% sure that we correctly reject patients who did not improve their symptoms. The Youden's index calculates the most optimal balance between sensitivity and specificity. However, it could be more valuable for a certain condition that patients noticed improvement than to identify patients who did not notice improvement. For instance, a randomised controlled trial that evaluates the efficacy of an existing conservative treatment for AT patients would probably benefit more from a high sensitivity – low specificity combination, which would correspond with a different MCID and PASS. The anchor-based method in combination with the Youden's index is currently most accepted to calculate MCID and PASS,[11] but researchers and clinicians should be aware that the given balance of sensitivity and specificity might not be optimal to answer their research question.

Strengths and limitations

The most important strength of this study is the relatively large number of included patients, in comparison to other studies.[8-10] Second, we used a Global Assessment Scale with 7 points, which offers balance between adequate discriminative ability, patient preference and reliability.[20] Last, the advantage of using an anchor-based method is the connection between the subjective assessment of the patient and a numerical score.[11] However, anchor-based methods are limited by the choice of the anchor, as it might be susceptible to recall bias.[11] To optimise interpretability and reliability, we explicitly mentioned the specific condition (AT) and time point, and used a 7-point scale with written descriptors.[20] By combining prospectively collected data with the anchor-based method, our reported MCID probably most accurately represents the true value of clinically relevant improvement on the VISA-A scale in patients with midportion AT.

A possible limitation is the cut-off we used to dichotomise the Global Assessment scale. Based on the article of McCormack et al.[8] we chose to divide the groups in 'not improved' ('worse than ever' to 'unchanged') and 'improved' ('moderately improved' to 'completely recovered'). When changing the cut-off, we would probably find a different MCID. However, as the MCID stands for minimal clinically important difference, we think our dichotomization is most accurate and should not be changed to 'stable' ('worse than ever' to 'moderately improved') and 'much improved' ('much improved' to 'completely recovered'). Another possible limitation is that the MCID of both 12 weeks

and 24 weeks lies within the standard deviation of the VISA-A score. A change within the standard deviation of a score makes interpretation difficult as the change could be either meaningful or due (lack of) precision of the score. This possible limitation applies to the individual patient, and does not apply to sample size calculations on group level or interpretation of change in VISA-A score between different groups. Last, the cohort was based on a RCT where the effect of an injection in addition to exercise therapy was researched. The improvement of 20 points in VISA-A score is comparable to other studies that researched the effect of exercise therapy in patients with midportion AT.[21 22]

Recommendations for future research

The results of this study can be used as guidance to calculate an adequate sample size when designing trials. The presented values of the MCID and PASS for the VISA-A score can aid in interpreting study results. However, due to the presented limitations, specifically the difference in specificity and sensitivity of the cut-offs, calculations and interpretation of the outcome should be done with caution.

Conclusion

The MCID for the VISA-A score (0-100) in active patients with midportion AT after exercise therapy and an injection is a change ≥ 14 points over a 12-week period and ≥ 7 points over a 24-week time period. AT symptoms are deemed acceptable (PASS) if the VISA-A score is ≥50 points at 12 weeks post-treatment and ≥60 points after 24 weeks. Researchers and clinicians can use these clinically meaningful thresholds as a guidance for treatment outcome of patients with midportion AT. The provision of MCID and PASS estimates will increase the interpretability of the VISA-A scale, but caution on their interpretation is needed due to the presented limitations.

Footnotes

Acknowledgements: Our thanks go out to the participants of the HAT trial.

Funding: This research is funded by the Dutch Arthritis Association and the Anna Foundation. Both are non-commercial organizations and were not involved in the content of this publication. The views expressed in the submitted article are our own and not an official position of the institution or funder.

Ethical approval: The HAT study was approved by the Medical Research Ethics Committee of Southwest Holland, the Netherlands (MEC-14-100). Trial registration number (The Netherlands Trial Register): ID number: NL4686, clinicaltrails.gov (identifier: NCT02996409)

Competing interest: None declared

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Chapter 5

Which treatment is most effective for patients with Achilles tendinopathy?

A living systematic review with network meta-analysis of 29 randomised controlled trials

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Br J Sports Med. 2020 Jun 10; bjsports-2019-101872.

Abstract

Objective: To provide a consistently updated overview of the comparative effectiveness of treatments for Achilles tendinopathy.

Design: Living systematic review and network meta-analysis.

Data sources: Multiple databases including grey literature sources were searched up to February 2019.

Study eligibility criteria: Randomised controlled trials examining the effectiveness of any treatment in patients with both insertional and/or midportion Achilles tendinopathy. We excluded trials with 10 or fewer participants per treatment arm or trials investigating tendon ruptures.

Data extraction and synthesis: Reviewers independently extracted data and assessed the risk of bias. We used the Grading of Recommendations Assessment, Development and Evaluation to appraise the certainty of evidence.

Primary outcome measure: The validated patient-reported Victorian Institute of Sport Assessment-Achilles questionnaire.

Results: 29 trials investigating 42 different treatments were included. 22 trials (76%) were at high risk of bias and 7 (24%) had some concerns. Most trials included patients with midportion tendinopathy (86%). Any treatment class seemed superior to wait-and-see for midportion Achilles tendinopathy at 3 months (very low to low certainty of evidence). At 12 months, exercise therapy, exercise+injection therapy and exercise+night splint therapy were all comparable with injection therapy for midportion tendinopathy (very low to low certainty). No network meta-analysis could be performed for insertional Achilles tendinopathy.

Conclusion: In our living network meta-analysis no trials were at low risk of bias and there was large uncertainty in the comparative estimates. For midportion Achilles tendinopathy, wait-and-see is not recommended as all active treatments seemed superior at 3-month follow-up. There seems to be no clinically relevant difference in effectiveness between different active treatments at either 3-month or 12-month follow-up. As exercise therapy is easy to prescribe, can be of low cost and has few harms, clinicians could consider starting treatment with a calf-muscle exercise programme.

Prospero registration number: CRD42018086467.

Introduction

The incidence of Achilles tendinopathy is 2–3 per 1000 patients in general medicine practice, and its lifetime cumulative incidence can even increase to more than 50% in specific active populations (eg, runners).[1 2] Achilles tendinopathy is an overload injury that is diagnosed clinically, and can affect the distal insertion or the midportion of the tendon.[3 4] Managing tendinopathy is challenging. Patients can expect their symptoms to improve between 3 and 12 months after commencing treatment, but not beyond 12 months.[5] Chronic symptoms persist in approximately a quarter of patients 10 years after treatment, and tendinopathy impairs both quality of life and physical activity.[5 6]

Wait-and-see, exercise therapy, injections, shockwave therapy, orthosis, medication, and surgery are the main treatment options offered to patients with Achilles tendinopathy.[7-14] Most patients receive multiple treatments over time, thereby impacting on healthcare consumption.[15] Trials and conventional meta-analysis do not directly assess the relative effectiveness of all available treatments – challenging patients and clinicians when they make treatment decisions. Network meta-analysis (NMA) allows the simultaneous comparison of the effectiveness of all treatments, and can rank treatments from most to least effective.[16 17] As no comprehensive NMA of all treatment options for Achilles tendinopathy exists, our aim was to evaluate the comparative effectiveness of all available treatments for Achilles tendinopathy in a regularly updated ('living') systematic review using NMA.

Methods

Protocol and registration

Our living systematic review with NMA was prospectively registered on PROSPERO (International Prospective Register of Systematic Reviews: CRD42018086467) and published in an open repository.[18] We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline, the Meta-Analysis of Observational Studies in Epidemiology guideline, and the PRISMA-NMA extension for reporting NMA.[19-21]

Administration and update of the living systematic review

This systematic review with NMA is part of the Dutch multidisciplinary guideline for Achilles tendinopathy. As we (1) plan to update the search and review process every 5 years as part of the guideline revision process, and (2) perform annual screening to identify new data that may alter the conclusions and recommendations,[18] we defined this as a 'living' systematic review with NMA. A living systematic review's main advantage is that it assumes that new knowledge will appear and allow improvements

in clinical decision-making. As we already have a structured protocol and database for this systematic review, we will be able to answer future research questions quickly and promote faster translation of new scientific evidence into clinical practice.

Patient involvement

To determine clinically relevant outcomes, we performed a pilot round of focus interviews with consecutive patients suffering from chronic midportion Achilles tendinopathy (n=9) who were participating in a randomised clinical trial (NCT02996409), and administered a survey to patients identified through the Dutch national patient federation (n=97).[18] The results are presented in online supplementary web appendix 1. We also considered recently defined core domains for tendinopathies from an international consensus involving patients and healthcare providers.[22] Based on these data, we decided to evaluate clinical outcome with the validated and disease-specific Victorian Institute of Sport Assessment-Achilles (VISA-A) score as the primary outcome.[18 23]

Outcome measures

The VISA-A score quantifies pain and activity level and can range from 0 to 100; a score of 100 indicates no pain with full activity level, while a score of 0 indicates severely limited activity levels and severe levels of pain. The minimal important difference (MID) for the VISA-A score is 14 points.[24] Return to sports activities was the secondary outcome. We assessed outcomes at 3, 6 and 12 months.

Eligibility criteria

Trials were eligible if they investigated the effectiveness of any treatment in adults (≥18 years) with Achilles tendinopathy, using the outcome measures VISA-A questionnaire and/or return to sports activities. Populations with midportion tendinopathy, insertional tendinopathy, or a combination of both were included. Achilles tendinopathy must have been diagnosed based on clinical findings (eg, local pain reproduced on clinical examination).[25] Imaging to confirm the diagnosis was not an inclusion criterion. Trials including athletes and/or inactive patients were eligible. There were no language restrictions.

Any treatment, control treatment, placebo, wait-and-see or no treatment group studied in a trial was eligible for inclusion. We predefined a number of treatment classes, based on the assumption that some treatments have a similar effect due to a comparable working mechanism.[18] Table 1 shows the treatments that are subdivided into treatment classes.

Table 1. Assignment of treatments to classes

Treatments	Studies	Classes
Placebo-injection + eccentric exercises (high-dose)	Bell 2013, Boesen 2017, De Jonge 2011	Exercise therapy + placebo injection
Autologous blood injection + eccentric exercises (high-dose)	Bell 2013, Pearson 2012	Exercise + injection therapy
High-volume injection + eccentric exercises (high-dose)	Boesen 2017	Exercise + injection therapy
Platelet-rich plasma (PRP) -injection + eccentric exercises (high-dose)	Boesen 2017, De Jonge 2011	Exercise + injection therapy
Eccentric exercises (high-dose)	Pearson 2012, Beyer 2015, De Jonge 2010, Silbernagel 2007, Yelland 2011, Rompe 2007, Rompe 2009, Zhang 2013, Balius 2016, Stevens 2014	Exercise therapy
Heavy slow resistance exercises	Beyer 2015	Exercise therapy
Night splint + eccentric exercises (high-dose)	De Jonge 2010	Exercise + night splint therapy
Continued sports activity + eccentric exercises (high-dose)	Silbernagel 2007	Exercise therapy
Prolotherapy injections	Yelland 2011	Injection therapy
Prolotherapy injections + Eccentric exercises (high-dose)	Yelland 2011	Exercise + injection therapy
Shockwave therapy	Rompe 2007	Shockwave therapy
Wait-and-see	Rompe 2007	Wait-and-see
Shockwave therapy + eccentric exercises (high-dose)	Rompe 2009	Exercise + shockwave therapy
Acupuncture treatment	Zhang 2013	Acupuncture therapy
Mucopolysaccharides supplement + eccentric exercises (high-dose)	Balius 2016	Exercise + mucopolysaccharides supplement therapy
Mucopolysaccharides supplement + passive stretching	Balius 2016	Exercise + mucopolysaccharides supplement therapy
Eccentric exercises as tolerated	Stevens 2014	Exercise therapy

We excluded trials with (1) 10 or fewer participants per study arm, (2) an inadequate control group (eg, the use of the contralateral Achilles tendon), (3) a population with full-thickness ruptures of the Achilles tendon, and (4) animal or in vitro studies.

Literature search strategy and information source

We developed a sensitive search strategy for multiple databases with the assistance of a medical librarian (online supplementary web appendix 2). The following databases were searched for published and unpublished trials up to 21 February 2019: Embase, MEDLINE Ovid, Web of Science, Cochrane CENTRAL, CINAHL EBSCOhost, SPORTDiscus EBSCOhost, AMED EBSCOhost, WHO ICTRP, ClinicalTrials.gov, WorldCat.org, OpenGrey and Google Scholar. We used the validated Cochrane search filter 'Embase search strategy for finding randomised clinical trials in Embase', and modified this for all conventional databases.[26] We screened the reference lists of all included publications for potentially eligible trials.

Study selection and data extraction

Titles and abstracts were screened by two independent reviewers (ACV and RJ-V) after duplicate removal. Disagreements were resolved by consensus. Two reviewers independently applied eligibility criteria to the full text reports. Disagreements were resolved by a third reviewer (AW). In case of unpublished records, authors were contacted for data availability. We uploaded all trials to Covidence (Veritas Health Innovation, Melbourne, Australia).

Data were extracted independently by two reviewers (ACV plus one of: AW, CLA or RJ-V) using standardised extraction forms adapted from the Cochrane Collaboration.[26] Disagreements were resolved by consensus, or a fifth reviewer (MW) in case of persistent disagreement. We extracted publication and trial details, population characteristics, eligibility criteria, treatment details, relevant outcome information, details of analysis, and study authors' key conclusions. If there were multiple time points available within a study, and these were equally close to the time point being synthesised across trials, we extracted the outcome of the latest follow-up for analysis.[18]

Risk of bias assessment

We used the Risk of Bias 2 tool to assess risk of bias for each trial outcome.[27] We assessed risk of bias on the basis of 'assignment to intervention' for all five domains: (1) randomisation process, (2) deviations from intended interventions, (3) missing outcome data, (4) outcome measurement and (5) selection of the reported result. An overall risk of bias judgement was made for each outcome and each time point as either 'low risk', 'some concerns' or 'high risk' of bias.[28 29]

The assessment was performed independently by two reviewers (ACV plus one of MW, CLA, AW or R-JV). The reviewers did not perform risk of bias assessment or data

extraction for publications in which they were involved as author. Disagreements were resolved via consensus or by a third reviewer (MW or AW) if necessary.

Data synthesis and statistical methods

We constructed network plots using Stata V.15 to visualise all head-to-head comparisons. Eccentric exercises were labelled as high-dose (daily) or low-dose (less than once a day). We planned a time course analysis for the VISA-A score; however, insufficient data precluded the analysis.[18] Instead, we modelled networks for the primary and secondary outcomes at 3 months, 6 months and 12 months, where possible. Four reviewers (ACV, MW, AW, and R-JV) labelled the treatments and assigned them to categories (classes) (see table 1). We assessed the assumption of exchangeability required for NMA before commencing the analyses. We appraised clinical homogeneity by tabulating study and population characteristics and inspecting them for differences in effect modifiers.

Treatment-level and class-level models were fitted in a Bayesian framework using Markov chain Monte Carlo simulations in WinBUGS (V.1.4; Medical Research Council, UK, and Imperial College of Science, Technology and Medicine, University of Cambridge, UK).[17 30] Continuous outcomes are presented as mean difference, with their 95% credible intervals. We reported the mean, median and 95% credible intervals for the ranking of each treatment or class to estimate the likelihood of individual treatments being superior to other treatments, and interpreted the primary outcome results in light of the MID.

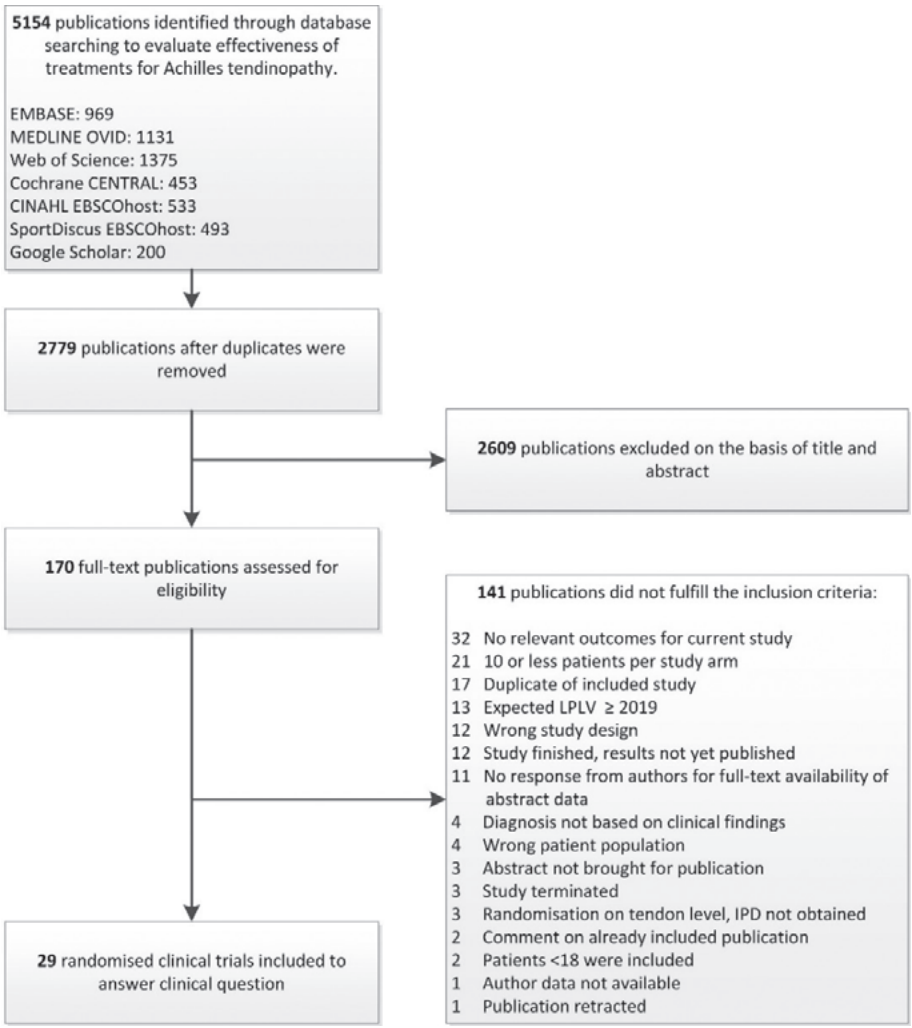
For both treatment-level and class-level models, we fitted fixed and random effects models, and compared model fit using the deviance information criterion and posterior mean residual deviance.[17] Lower deviances depict a better model fit. For the class-level models we attempted to fit a hierarchical model where treatment effects were assumed to be similar within class, but due to insufficient data we were only able to fit a fixed class effect model where all treatments were assumed to have the same effect within class.

We assessed statistical heterogeneity by inspecting the between-trial SD and comparing the fit of the fixed and random effects models.[17] We planned to explore sources of statistical heterogeneity if there were 10 or more trials available per comparison. In the presence of evidence from direct and indirect comparisons it is important to assess whether the direct and indirect evidence is consistent.[31] We assessed the consistency assumption for each network by comparing model fit between the NMA model and an unrelated mean effects model that relaxes the consistency assumption. We planned to assess small study bias using comparison-adjusted funnel plots if 10 or more trials were available for one comparison..[31]

Certainty of evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) for NMAs to appraise the certainty of evidence.[32] Evidence from each comparison was appraised for direct and indirect comparisons, and for the combined evidence, where applicable. Evidence could be of 'high certainty', 'moderate certainty', 'low certainty' or 'very low certainty'. All ratings started at the level of 'high certainty'. Two authors (ACV and MW) independently rated the evidence down on the basis of risk of bias, inconsistency, indirectness, imprecision and publication bias. Inconsistency in GRADE involves heterogeneity across trials and is not related to inconsistency in the network. We rated the overall body of evidence in the network to indicate the strength of the NMA recommendations.

Figure 1. PRISMA flow diagram of study selection process. IPD, individual patient data; LPLV, last patient last visit; PRISMA, preferred reporting items for systematic reviews and meta-analyses.



Results

We identified 5,154 potentially relevant publications, of which 170 articles were screened in the full-text analysis. Twenty-nine trials (n=1,640 patients) met our eligibility criteria and were included (figure 1).[33-61] Online supplementary web appendix 3 lists the 14 unpublished trials and the 3 trials awaiting classification.

Characteristics of the included trials

Forty-two treatments were investigated in 29 trials. Sixty-five treatment arms were included in the trials, and 40 of these included exercise therapies. There were 180 treatment comparisons in the NMAs. The majority of trials (86%) investigated midportion Achilles tendinopathy, one investigated insertional Achilles tendinopathy and three trials did not specify the location of Achilles tendinopathy. Twenty-five trials evaluated clinical outcome using the VISA-A score and six trials reported return to sports activities. Sample sizes ranged from 12 to 117 per treatment arm (median 20 patients, IQR 16–27). Follow-up duration ranged from 1 to 52 weeks (median 27 weeks, IQR 12–52).

The baseline characteristics of patients and all trial characteristics are shown in online supplementary web appendices 4 and 5. Study populations reflect clinical practice with equal sex distribution, participants in their 40s and slightly overweight. Three-quarters of the included participants were active individuals. Participants typically had symptoms for nearly 2 years prior to treatment; approximately 20% had bilateral symptoms. The severity of symptoms measured with the VISA-A score was usually between 40 and 60 points.

Risk of bias and certainty of evidence

Twenty-two trials (76%) were at high risk of bias (online supplementary web appendix 6). We had some concerns about bias in seven trials (24%). No trials were at low risk of bias. In studies that used both the VISA-A score and return to sport as outcome measures, there was no difference in risk of bias between the outcomes. In 48% of the trials, outcome measurement was a source of bias. All other sources of bias were also commonly judged as high risk: the randomisation procedure (21%), deviations from the intended intervention (28%), missing outcome data (28%) and selection of reported results (24%).

Certainty of evidence for all comparisons was low to very low, except for autologous blood+eccentric exercise therapy versus placebo injection+eccentric exercise therapy, for which there was moderate certainty of evidence (online supplementary web appendix 7). The main reasons to rate down the certainty of evidence were study

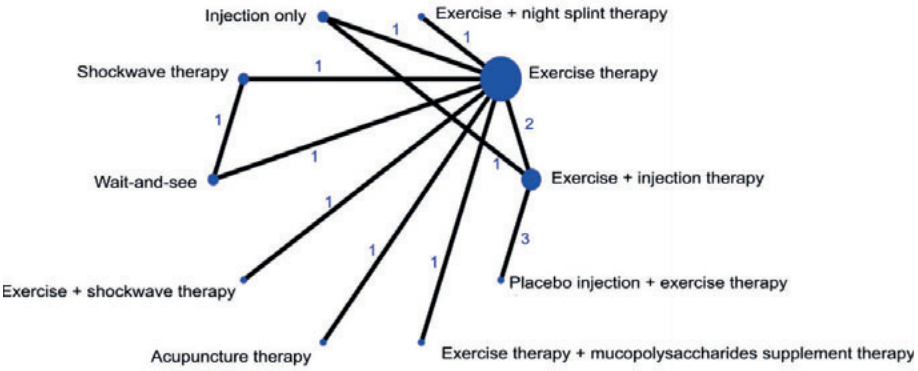
limitations (n=180, 100%) and imprecision (n=158, 88%). We did not rate down for inconsistency, indirectness, or publication bias. Only two treatment comparisons were studied in multiple (ie, 2) trials (ie, platelet-rich plasma injection+eccentric exercise therapy vs placebo injection+eccentric exercise therapy, and laser+eccentric exercise therapy vs placebo laser+eccentric exercise therapy). Where this was the case, estimates and credible intervals had substantial overlap. Populations, treatments, and outcome measures followed those used in clinical practice; hence, there was no indication of indirectness in the evidence. We did not assess publication bias because there were fewer than 10 trials available for each of the comparisons.

Network meta-analyses

Figure 2A, B shows direct treatment class comparisons in the field of midportion Achilles tendinopathy for VISA-A score. Model fit statistics are reported in online supplementary web appendix 8. Ten classes were included in the network analyses. None of the networks included evidence from both direct and indirect comparisons, so the consistency assumption for NMA could not be checked. Figure 3 shows the comparative treatment class effects on the VISA-A score at 3 months (figure 3A) and 12 months (figure 3B). Figures 4 and 5 show the treatment class rankings for 3 and 12 months. No class analyses could be performed for the VISA-A score at 6 months and return to sports activities at 6 months (only time point in NMA) due to insufficient evidence (online supplementary web appendix 8). Treatment effect NMAs for VISA-A and return to sports activities are presented in online supplementary web appendix 9. No NMA could be performed for insertional Achilles tendinopathy. Studies that could not be included in the NMA are presented in online supplementary web appendix 10.

Figure 2. Network plots for treatment classes on the VISA- A score at 3 and 12 months in patients with midportion Achilles tendinopathy. The size of the dots is proportional to the number of participants who received the treatment, respectively. Blue numbers indicate the number of trials the classes were compared in. Note that intraclass comparisons are not included in the plot (eg, eccentric exercises vs heavy slow resistance exercises); all treatment comparisons can be found in online supplementary appendix 9. (A) VISA- A score at 3 months. (B) VISA- A score at 12 months. VISA- A, Victorian Institute of Sport Assessment- Achilles.

A)



B)

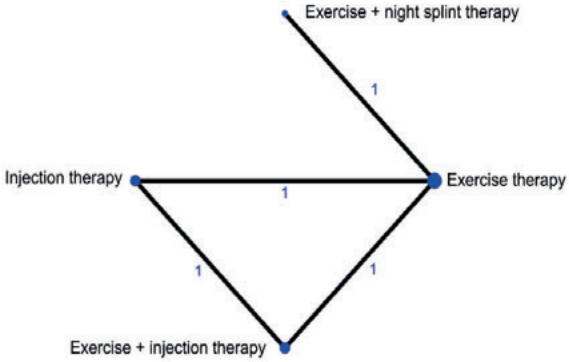


Figure 3. Comparative treatment class effects expressed with a mean difference for the VISA- A score at 3 months (A) and at 12 months (B) in patients with midportion Achilles tendinopathy. Mean differences on the VISA- A score with their 95% credible intervals from the network meta-analysis. For any cell, a negative mean difference favours the upper- left treatment, and a positive mean difference favours the lower- right treatment. Comparative treatment class effect differences are shown in bold. VISA- A, Victorian Institute of Sport Assessment- Achilles.

A)

Wait-and-see									
19 (-3 to 34)	**Exercise + placebo injection**								
23 **(8 to 38)**	4 (-11 to 19)	**Injection therapy**							
20 **(11 to 30)**	1 (-10 to 15)	-2 (-14 to 9)	**Exercise therapy**						
15 **(6 to 24)**	-4 (-19 to 13)	-8 (-23 to 8)	-5 (-15 to 5)	**Shockwave therapy**					
22 **(7 to 36)**	4 (-2 to 8)	0 (-13 to 14)	2 (-10 to 13)	7 (-8 to 22)	**Exercise + injection therapy**				
34 **(21 to 47)**	**15** **(1 to 31)**	11 (-4 to 26)	**14** **(5 to 23)**	**19** **(5 to 32)**	12 (-2 to 27)	**Exercise + shockwave therapy**			
21 **(4 to 39)**	2 (-18 to 21)	-2 (-21 to 17)	1 (-14 to 15)	6 (-12 to 23)	-1 (-20 to 17)	-13 (-30 to 4)	**Exercise + night splint therapy**		
35 **(25 to 45)**	**16** **(4 to 30)**	13 (0 to 25)	**15** **(11 to 19)**	**20** **(9 to 31)**	**13** **(2 to 25)**	1 (-9 to 11)	14 (-1 to 30)	**Acupuncture therapy**	
28 **(14 to 41)**	9 (-7 to 25)	5 (-11 to 20)	7 (-3 to 17)	13 (-2 to 26)	6 (-10 to 20)	-6 (-20 to 7)	7 (-11 to 24)	-7 (-19 to 3)	**Exercise + mucopolysaccharides supplement therapy**

B)

Injection therapy			
-5 (-19 to 9)	**Exercise therapy**		
2 (-10 to 13)	7 (-4 to 17)	**Exercise + injection therapy**	
3 (-16 to 22)	8 (-6 to 21)	1 (-16 to 18)	**Exercise + night splint therapy**

Figure 4. Treatment class rankings from the network meta- analysis for the VISA- A score at 3 months in patients with midportion Achilles tendinopathy. The asterix indicates that the 95% credible interval was rank 10 to 10 for wait- and- see therapy. MPS, mucopolysaccharides supplement; VISA- A, Victorian Institute of Sport Assessment- Achilles.

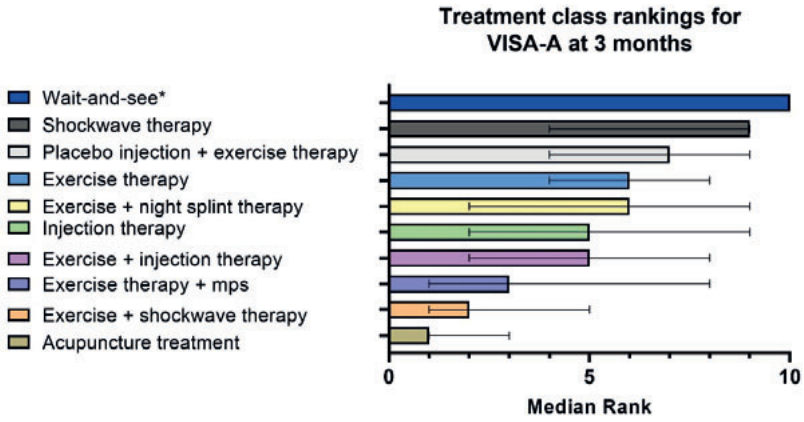
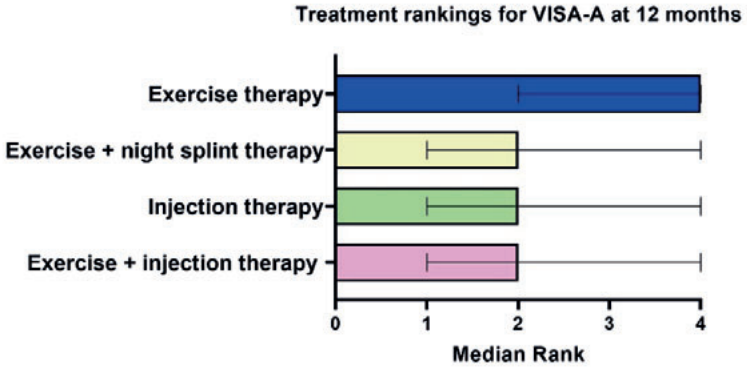


Figure 5. Treatment class rankings from the network meta- analysis for the VISA- A score at 12 months in patients with midportion Achilles tendinopathy. VISA- A, Victorian Institute of Sport Assessment- Achilles



Comparative treatment class effectiveness on the primary outcome (VISA-A score)

VISA-A score at 3 months

Seventeen treatments, studied in 13 randomised controlled trials (RCTs), were assigned to 10 classes. Any treatment seemed superior to wait-and-see: exercise+placebo injection therapy (mean difference 19 points, 95% CrI −3 to 34 points), injection therapy (23 points, 8 to 38 points), exercise therapy (20 points, 11 to 30 points), shockwave therapy (15 points, 6 to 24 points), exercise+injection therapy (22 points, 7 to 36 points), exercise+shockwave therapy (34 points, 21 to 47 points), exercise+night splint therapy (21 points, 4 to 39 points), acupuncture therapy (35 points, 25 to 45 points) and mucopolysaccharides supplement+exercise therapy (28 points, 14 to 41 points) (figure 3A).

Acupuncture therapy seemed superior to placebo injection therapy (16 points, 4 to 30 points), injection therapy (13 points, 0 to 25 points), exercise therapy (15 points, 11 to 19 points), shockwave therapy (20 points, 9 to 31 points), exercise+injection therapy (13 points, 2 to 25 points), exercise+night splint therapy (14 points, −1 to 30 points) and mucopolysaccharides supplement+exercise therapy (7 points, −3 to 19 points), but not to exercise+shockwave therapy (1 point, −9 to 11 points).

Exercise+shockwave therapy seemed superior to placebo injection therapy (15 points, 1 to 31 points), injection therapy (11 points, −4 to 26 points), exercise therapy (14 points, 5 to 23 points), shockwave therapy alone (19 points, 5 to 32 points), exercise+injection therapy (12 points, −2 to 27 points) and exercise+night splint therapy (13 points, −4 to 30 points), but not to acupuncture therapy (−1 point, −11 to 9 points) and mucopolysaccharides supplement+exercise therapy (6 points, −7 to 20 points).

VISA-A score at 12 months

At 12 months, six treatments, studied in four RCTs, were assigned to four treatment classes and compared in a network model. Exercise therapy (−5 points, −19 to 9 points), exercise+injection therapy (2 points, −10 to 13 points) and exercise+night splint therapy (3 points, −16 to 22 points) were all comparable with injection therapy (figure 3B).

Treatment class rankings

According to the NMA rankings, acupuncture therapy seemed the best treatment at 3 months (mean ranking 1.56, median ranking 1, median's 95% CrI 1 to 3), and

exercise+shockwave therapy seemed second best (mean ranking 1.98, median ranking 2, median's 95% CrI 1 to 5). At 12 months, injection therapy (mean ranking 2.47, median ranking 2, median's 95% CrI 1 to 4), exercise therapy (mean ranking 3.51, median ranking 4, median's 95% CrI 2 to 4), exercise+injection therapy (mean ranking 2.03, median ranking 2, median's 95% CrI 1 to 4) and exercise+night splint therapy (mean ranking 1.99, median ranking 2, median's 95% CrI 1 to 4) had similar rankings (figures 4 and 5).

Comparative treatment class effectiveness on the secondary outcome (return to sports activities)

No class analyses could be performed for return to sports activities at 6 months (only time point for NMA) due to insufficient evidence. The results of the treatment-level analyses for return to sports activities at 6 months are presented in online supplementary web appendix 9.

Discussion

In this living systematic review and NMA, none of the trials were at low risk of bias, and all evaluated treatments had large uncertainty in the estimates. From a myriad of treatments for midportion Achilles tendinopathy, active treatment classes seems to have clinically meaningful benefits (mean difference exceeded VISA-A MID of 14 points) at 3 months compared to wait-and-see.[24] For two classes (acupuncture therapy, and shockwave therapy combined with exercise therapy), the credible intervals exceeded the MID of 14 points. However, these results were based on two small trials (64 and 68 included patients, respectively) at high risk of bias. There were no estimates for effectiveness of wait-and-see at 12 months. The effectiveness of most active treatments in the long term is uncertain. At 12 months, there was no difference between exercise therapy, injection therapies and combined therapies.

Clinical implications

Based on the findings in this study, we advise against recommending wait-and-see therapy as a treatment strategy. Active treatments had overlapping comparative effects, leaving uncertainty about which treatment is best for Achilles tendinopathy. Shared decision-making plays an important role in managing Achilles tendinopathy. Safety profile, treatment availability and costs should be considered in this clinical decision-making process. Calf-muscle exercise therapy is easy to prescribe because it is easy to instruct, can be cheap, is available everywhere and has a low risk of harm.[14 62]

The preinjury activity level could play an important role in the response to treatments such as exercise therapy as this will possibly influence the load that can be applied to the tendon. There is currently no tool available to distinguish sedentary from athletic patients, and people define this differently. When a patient is considered to be sedentary, the VISA-A score could be less sensitive to changes as 40% of the score can be obtained from sporting activities.[23] Therefore, a novel modified version of the existing VISA-A questionnaire is currently being developed to evaluate treatment response in sedentary individuals.[63] In two trials, lower baseline VISA-A score was associated with a greater increase in VISA-A score.[38 49] This is most likely explained by regression to the mean (outliers will tend to move towards the mean score). Furthermore, physical activity level was not a prognostic factor for change in VISA-A score in the trials that attempted to measure physical activity.[34] More research is needed to determine whether athletic and sedentary patients should be considered separate patient groups.

Strengths and weaknesses in relation to other studies

The uncertainty around the effectiveness for specific treatments has previously been described in Achilles tendinopathy. Most recent meta-analyses on treatment effectiveness for Achilles tendinopathy did not find superiority of a single treatment.[8 10 64-66] All other systematic reviews included randomised clinical trials or quasi-randomised controlled clinical trials and made strong to weak recommendations in favour of exercise therapy [8], platelet-rich plasma [66] or against platelet-rich plasma [10] or splinting [8] single therapies. Our NMA results conflict with a recent systematic review with head-to-head meta-analysis where prolotherapy and sclerotherapy were superior to other treatments.[13] Differences in study selection criteria (case-series were also included vs only randomised clinical trials in our NMA) and outcome measure selection (eg, general Visual Analogue Scale vs a validated patient-reported outcome measure in our NMA) may explain the discrepancy.

Unanswered questions and future research

As uncertainty around treatment effectiveness remains, future trials should be adequately powered and designed. Universally agreed diagnostic criteria for both insertional and midportion Achilles tendinopathy are needed to prevent heterogeneity in included participants. More trials investigating treatment effects for insertional Achilles tendinopathy are warranted. New trials should include exercise therapy as a stand-alone comparator with long-term (≥12 months) follow-up. This would facilitate assessment of the comparative effectiveness of new treatments in the network. Based on our findings it is not ethical to perform new studies using wait-and-see as a treatment arm. The role of patient education has never been explored, but

should be further assessed. Trialists must include measures from the core outcome set for tendinopathy (patient overall rating, participation, pain on activity/loading, disability, function, physical function capacity, quality of life, psychology and pain over a specified timeframe).[22] We identified eight ongoing trials on the effectiveness of multiple treatments for Achilles tendinopathy. We aim to perform horizon scanning annually to screen for recently published trials. In case of relevant trials, we will update the analyses and publish the results when there are important changes that affect clinical care. We plan to update this 'living' systematic review and NMA at least every 5 years as part of the Dutch national guideline revision process.

Strengths and limitations

We compared treatments in an NMA despite some of these treatments having never been compared head-to-head in trials. Our living NMA will be updated at least every 5 years, which allows for a contemporary evidence synthesis for clinical practice.[67 68] The protocol was registered prospectively and patients were involved in selecting outcomes most relevant to them in the design phase.

The small sample sizes and bias in the included trials limit our conclusions.[69] Many of the investigated treatments were not connected to the network, which hampered assessing the comparative effectiveness of all available treatments. Sources of heterogeneity could not be investigated as there were less than the required 10 trials per comparison. None of the comparisons in the networks had both direct and indirect evidence and so we could not check the consistency.[17]

Treatment outcomes may be different on the basis of some patient characteristics and previous Achilles tendinopathy treatment. For example, a sedentary population may respond to exercise treatment differently compared with an athletic population. Other effect modifiers may be unilateral/bilateral symptoms, duration of symptoms and type/number of previous treatments. However, to the best of our knowledge, there is presently no evidence supporting any of these factors as treatment effect modifiers. The limited amount of study-level data precluded investigating effect modification. This may be possible in the future using pooled individual patient data.

We excluded many trials because they did not use commonly accepted and validated outcomes in the field of Achilles tendinopathy.[70] It is unclear whether our NMA results apply to all patients with Achilles tendinopathy because we only included one trial with patients with insertional Achilles tendinopathy. We planned a time course analysis for the VISA-A score, as outcomes within the first year are of equal importance. Due to a lack of data, we were not able to perform this analysis and, in accordance with our protocol, we modelled outcomes for 3 months, 6 months and 12 months instead.

We planned threshold analysis as a quantitative means to assess the robustness

of NMA recommendations to potential limitations in the evidence. We were unable to use this approach because of substantial overlap in credible intervals from the NMA. Due to overlap in the intervals, no recommendations could be made, which is a fundamental prerequisite to performing a valid threshold analysis. To comply with our protocol, we report threshold results in online supplementary web appendix 11, but chose to use GRADE to interpret the evidence. We were not able to evaluate small study bias due to too low number of trials. We found three completed trials in trial registers; two are under review, and the publication status of one trial is unknown. Therefore, it seems unlikely that, in an era of prospective trial registrations, significant publication bias is present in the field of Achilles tendinopathy.

Conclusion

Our living NMA of 29 RCTs on Achilles tendinopathy included 42 different treatments. No trials were at low risk of bias, most had only short follow-up, and there was large uncertainty in the comparative estimates. For midportion Achilles tendinopathy, active treatments seem superior to wait-and-see at 3-month follow-up. There was no evidence of a clinically relevant difference in effectiveness between different active treatments at 3-month and 12-month follow-up. Calf-muscle exercise therapy is easy to prescribe in practice, is widely available, and is regarded as safe and cheap. Consequently, clinicians should consider starting this as initial treatment.

Footnotes

Acknowledgements: We would like to extend our gratitude to W.M. Bramer, research librarian at Erasmus MC, for his help with developing a sensitive search strategy. The Dutch Patient Federation assisted in sending, receiving, and extracting surveys that were completed online by patients who suffered self-reported Achilles tendinopathy. We are grateful for their help and input in the design of the survey, thereby improving knowledge on important and relevant outcome domains for patients with Achilles tendinopathy. We thank Andreas Serner (Aspetar Orthopaedic & Sports Medicine Hospital) for screening the full texts of non-English publications. We thank Michael Skovdal Rathleff, Henrik Riel, and Mads Hilligsøe (Centre for General Practice at Aalborg University, Aalborg, Denmark) for their help in conducting data-extraction tables for publication. No financial compensation was provided to any of these individuals.

Funding: This research received a grant from the Dutch Association of Medical Specialists to develop a clinical guideline for the treatment of patients with Achilles tendinopathy. The Dutch Patient Federation is involved in this guideline development and assisted in sending out patient surveys. This non-commercial association is not involved in the planning, conduct or reporting of this study.

Ethical approval: Not required

Competing interests: NJW led a research project in collaboration with Pfizer plc (project ended 31/12/18). Pfizer part-funded a junior researcher. The project was purely methodological, using historical data on pharmacological treatments for pain relief. NJW has no other conflicts. All other authors report to have no conflicts of interest.

Link for online supplementary web appendices:

https://bjsm.bmj.com/content/early/2020/06/15/bjsports-2019-101872

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Chapter 6

Isometric exercises do not provide immediate pain relief in Achilles tendinopathy:

a quasi-randomised clinical trial

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Scand J Med Sci Sports. 2020 May; sms.13728. Online ahead of print.

Abstract

Background: Isometric exercises may provide an immediate analgesic effect in patients with lower-limb tendinopathy and have been proposed as initial treatment and for immediate pain relief. Current evidence is conflicting, and previous studies were small.

Objective: To study whether isometric exercises result in an immediate analgesic effect in patients with chronic midportion Achilles tendinopathy.

Methods: Patients with clinically diagnosed chronic midportion Achilles tendinopathy were quasi-randomised to one of four arms: isometric calf-muscle exercises (tiptoes), isometric calf-muscle exercises (dorsiflexed ankle position), isotonic calf muscle exercises, or rest. The primary outcome was pain measured on a visual analogue scale (VAS) score (0-100) during a functional task (10 unilateral hops) both before and after the intervention. Between-group differences were analysed using a generalized estimation equations model.

Results: We included 91 patients. There was no significant reduction in pain on the 10 hop test after performing any of the four interventions: isometric (tiptoes) group 0.2, 95%CI −11.2 to 11.5; isometric (dorsiflexed) group −1.9, 95%CI −13.6 to 9.7; isotonic group 1.4, 95%CI −8.3 to 11.1; and rest group 7.2, 95%CI −2.4 to 16.7. There were also no between-group differences after the interventions.

Conclusion: The isometric exercises investigated in this study did not result in immediate analgesic benefit in patients with chronic midportion Achilles tendinopathy. We do not recommend isometric exercises if the aim is providing immediate pain relief. Future research should focus on the use of isometric or isotonic exercise therapy as initial treatment as all exercise protocols used in this study were well-tolerated.

Introduction

Chronic tendon overuse injuries (tendinopathy) are common and account for 30-50% of all sports-related injuries.[1] Achilles tendinopathy (AT) is common in runners with up to 52% of athletes being affected during their lifetime.[2 3] AT is a clinical diagnosis based on a combination of local Achilles tendon pain, swelling of the Achilles tendon, and an impaired load-bearing capacity.[4 5] Treatment outcomes are often disappointing, with persisting symptoms in 35%-60% of the patients at 5-year follow-up.[6 7]

The underlying histopathology of tendinopathy is an increased tenocyte response and local disorganization of the tendon structure.[8 9] The severity of local tendon tissue disorganization is, however, not directly related to the degree of pain.[10 11] As a result, peripheral pain is not considered to be the only driver of pain sensation in tendinopathy. Recent evidence found that altered central pain processing might be an important factor in persisting Achilles tendon pain, with pathophysiological pain (central sensitization) as a result.[12-14] These alterations in central pain processing may explain why AT can be resistant to tissue-based treatment options.[15]

Isometric exercises of several muscle groups (eg, quadriceps muscles) have been found to influence central pain processing.[16 17] These changes resulted in a substantial immediate analgesic effect in patients with patellar tendinopathy.[18 19] As a consequence, it has been suggested that isometric exercises can be used to provide immediate pain relief for athletes as 'in-season management'.[20] To date only one research group has investigated the immediate analgesic effect of isometric exercises in AT. No reduction in pain was found in this study after the performance of isometric exercises of the calf muscles.[21] The power of all previous studies was limited, and a clinically relevant immediate effect of exercises cannot be excluded, as no control groups were included in which no exercises were performed.[18 19 21] As the current treatment advices of tendinopathy are being influenced by these heterogeneous findings,[22] it is important to clarify the role of isometric exercises in AT.

Our primary aim was to determine the immediate effect of isometric exercises on pain during a functional task in patients with chronic midportion AT. The secondary aim was to compare these results with the effect after the performance of isotonic exercises and rest.

Methods

Study design

This quasi-randomised clinical trial with four intervention arms was conducted as a part of a randomised clinical trial (RCT). The aim of this larger RCT was to evaluate the effect of a high-volume injection in patients with chronic midportion AT (ClinicalTrials.

gov Identifier: NCT02996409). The current study was performed before patients received any type of intervention, and the outcome of the current study did not affect participation in the larger RCT. All patients provided written informed consent prior to participation. The protocol of the study was approved by the regional Medical Ethical Committee (registration number 14-100). Study findings are reported following the CONSORT guideline, the Pain specific CONSORT supplement checklist, and the TIDieR guideline for reporting interventions. Originally, the aim was to compare three intervention arms: isometric exercises (tiptoes), isotonic exercises, and rest. During the course of the study, there was enhanced insight in this research field that the joint position could influence the analgesic effect as previous research demonstrated that tendon loading varies at different joint positions.[23] Therefore, we decided to add an intervention arm in which isometric exercises were performed with the ankle dorsiflexed.

Setting and subjects

This clinical trial was performed at the Sports Medicine department in a large district general hospital (Haaglanden Medical Centre, Leidschendam, the Netherlands) and a university medical centre (Erasmus MC University Medical Centre, Rotterdam, the Netherlands). All 80 patients who were included in the RCT participated also in the current study. Additionally, patients with AT who presented after inclusion of the larger RCT was completed were allowed to still participate when visiting one of these research centres. Inclusion was carried out by two sports medicine physicians. Inclusion criteria were as follows: (a) the presence of chronic midportion AT for at least 2 months, (b) no subjective symptomatic improvement after exercise therapy of at least 6 weeks, (c) aged between 18-70 years, and (d) the presence of Doppler flow on power Doppler ultrasonography. The diagnosis was established based on clinical examination (local tendon pain and swelling of the Achilles tendon 2-7 cm proximal to its calcaneal insertion, and impaired load-bearing capacity) by the sports medicine physician. The main exclusion criteria were as follows: (a) a clinical suspicion of other musculoskeletal disorders (insertional AT, inflammatory internal disorders, quinolone-, corticosteroid- or statin-induced tendinopathy), (b) a previous Achilles tendon rupture or surgery, (c) the inability to perform an exercise program, and (d) a medical condition that could affect the safety of the injection in the larger RCT (eg, peripheral vascular disease or use of anticoagulant medication). Detailed information regarding all eligibility criteria is provided in the trial registration. In case of bilateral symptoms, the patient selected the most symptomatic tendon for inclusion in this study.

Quasi-randomization

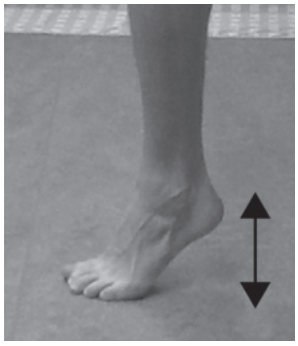
Patients were originally allocated to one of the three intervention arms based on the inclusion number in the larger RCT. Using this method of quasi-randomization,

all patients were equally distributed between the groups. The last 11 participants in the larger RCT and seven extra patients who visited the outpatient department for clinical care (18 in total) were allocated to the additional intervention arm performing isometric exercises with a dorsiflexed position of the ankle.

Interventions

The intervention arms consisted of a specific loading protocol or a period of rest. Patients were told that the loading exercises were performed to determine the maximum amount of weight that could be lifted to personalise the exercise program for the following weeks. Patients in the rest group were asked to sit on a chair while they received verbal instructions regarding the exercise program for the following weeks. The hypothesis of the current study was therefore unknown to all participants. Instructions were provided by a single non-blinded, trained PhD-candidate with 2 years of practical medical training who included patients at both research centres. The interventions were based on previous work in this research field.[18 21] Of a total of four intervention arms, three groups performed plantar flexor contractions both in seated and standing position and the control group rested. The different loading protocols are presented in Table 1. The duration of all programs was identical (13 minutes). Prior to the programs, patients completed a warming-up consisting of walking up and down four flights of stairs followed by 1 minute of non-loaded mobility exercises of the ankle. Patients were subsequently instructed that exercises should be performed at maximal intensity and may be painful. Patients were instructed to ignore pain unless it was unbearable. Patients started with an additional weight of 30 kg for the first set in seated position of the loading protocols. Standardised feedback was provided during the loading protocols (“come-on, half-way there”).

Table 1. Interventions used in the study. For the plantar flexor contraction groups, five sets of exercises were performed, of which two sessions were performed with the knee bent followed by three sessions with the knee extended. Exercises were performed barefoot under supervision of the researcher. All patients rested for two minutes between sets to allow sufficient recovery. A stopwatch was used to control for the prescribed contraction and rest times. Joint positions of the ankle are presented as positive numbers for plantarflexion, and as negative numbers for dorsiflexion.

	Joint position (degrees of flexion)	Sets /duration	Recovery (minutes)	Example of setup in standing position
Isometric (tiptoes)				
Seated	Hip 90° Knee 90° Ankle 20°	2x45s	2	
Standing	Hip 0° Knee 0° Ankle 20°	3x45 s	2	
Isometric (dorsiflexed)				
Seated	Hip 90° Knee 90° Ankle -10°	2x45 s	2	
Standing	Hip 0° Knee 0° Ankle -10°	3x45 s	2	
Isotonic				
Seated	Hip 90° Knee 90° Ankle 0-20°	2x15 rep (both concentric and eccentric phase 1-2s)	2	
Standing	Hip 0° Knee 0° Ankle 0-20°	3x15 rep (both concentric and eccentric phase 1-2s)	2	
Rest	-	-	13	

Abbreviations: rep, repetitions; s, seconds

The rate of perceived exertion (RPE) was recorded between sets. A score of 0 indicates rest and a score of 10 maximal effort. If exercises were relatively easy to perform (RPE < 7), additional weight was applied using weighted vests up to a maximum of 60 kg and adjustable per 1.5 kg (in seated position resting on the upper leg). To evaluate intensity of the loading protocols, an overall RPE score for the loading protocol was obtained after the performance of all sets of exercises. The weight was lowered in case of unbearable pain or when patients could not complete the contraction times.

Test methods

Demographic details

We recorded the following relevant baseline characteristics: age, sex, body mass index (BMI), activity (active or sedentary), sports participation (hours/wk), affected side, duration of symptoms, and Victorian Institute of Sport Assessment-Achilles (VISA-A) score.[24]

Outcome measures

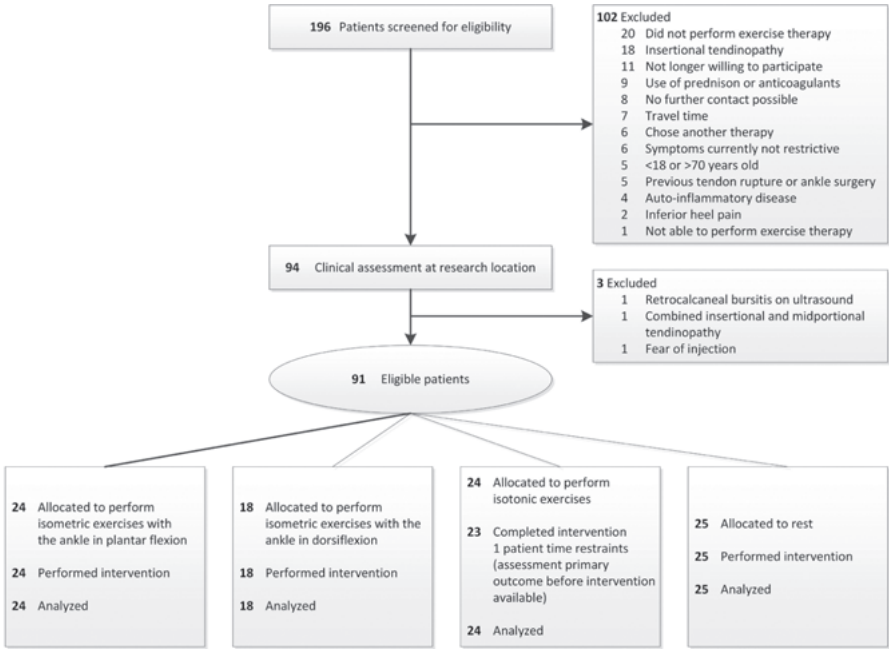
The primary outcome measure we used was the patient-reported pain after the performance of 10 unilateral hops.[25 26] We used this outcome measure to test the immediate effect primarily of isometric exercises, but also for isotonic exercises and rest as secondary outcome. According to a recent consensus meeting with patients and healthcare professionals, pain on loading was found to be one of the core domains for tendinopathy.[27] Patient-reported pain was measured using a visual analogue scale (VAS) ruler with slider, in which 0 represents no pain and 100 represents the worst pain imaginable. This outcome measure (10 hop VAS-score) was assessed at the start of and immediately after the intervention. To evaluate success of the procedure, we evaluated the mean added weight (in kg) during the loading protocol both in the seated and standing position. Additionally, we started to obtain the RPE scores (0-10) after the first 20 inclusions to determine whether exercises were performed with sufficient effort due to empirical knowledge.

Statistical analyses

Our sample size calculation showed that 16 patients in each group were required to detect a minimal clinically important difference of 20 points on the VAS-score (power 0.80, 2-sided significance level 0.05, SD 20).[21 28 29] Data were analysed using SPSS 25.0.0.1 (SPSS Inc.) according to a statistical analysis plan uploaded on clinicaltrials.gov before evaluating the last patient in the RCT. Within-group differences of the 10 hop VAS-scores were analysed using a Generalized Estimation Equations (GEE) model. To test whether changes in VAS-score before and after the program were

different between groups, we added the interaction term of intervention arm*pre/post testing. Adjustments were made for the following pre-defined baseline variables: age, sex, BMI, baseline VISA-A score, and duration of symptoms. Outcomes of the GEE-model are presented as estimated marginal means with their 95% confidence interval, unless otherwise stated. Between-group differences in the RPE score and the added weight during the loading protocol were analysed using a one-way ANOVA test. Differences of $P < .05$ were considered to be statistically significant. Missing data were not imputed, but we planned to perform sensitivity analyses if missing data would exceed 5% for a certain time point.[30]

Figure 1. CONSORT Flow Diagram demonstrating the Flow of Patients Through the Study.



Results

From December 2016 to August 2019, 196 patients were screened for eligibility and 91 patients were included and allocated to one of the four intervention arms (Figure 1). Only one patient in the isotonic group could not perform the complete loading protocol due to time restraints (assessment primary outcome before intervention available, but not post-intervention). There were no visual or statistical differences in the majority of the baseline characteristics between the four intervention arms (Table 2), except for the BMI which was higher in the rest group compared to the isometric (tiptoes) group and the VISA-A score that was lower in the isometric (dorsiflexed) group compared to both the isotonic group and the rest group. Both these characteristics were already included in the GEE-model.

Primary outcome measure – patient-reported pain

The within-group differences in estimated mean 10 hop VAS-score were not statistically significant in all the intervention groups as presented in Table 3. Ten hop VAS-scores are presented as raw individual patient data and mean scores in Figure 2. The interaction term intervention arm*pre/post -testing was not statistically significant (P = .26), meaning that the change in 10 hop VAS-score did not differ between the four groups. Between-group differences were thus all not statistically significant after the interventions (Table 3). The unadjusted analyses are reported in Web Appendix 1.

Success of procedures

The mean (SD) RPE (0-10) during the loading protocol was 7.0 (1.7) in the isometric (tiptoes) group (n = 17), 7.7 (1.2) in the isometric (dorsiflexed) group (n = 18), and 7.8 (1.5) in the isotonic group (n = 17). The mean (SD) added weight during the loading protocol in seated position was 28 kg (7) in the isometric (tiptoes) group, 31 kg (4) in the isometric (dorsiflexed) group, and 30 kg (4) in the isotonic group. In the standing position, the mean (SD) added weight was 25 kg (12) in the isometric (tiptoes) group, 16 kg (16) in the isometric (dorsiflexed) group, and 22 kg (12) in the isotonic group. Between-group differences were not statistically significant for the mean RPE (P = .22), the mean added weight in seated position (P = .28), and the mean added weight in standing position (P = .10).

Table 2. Baseline characteristics of the four intervention arms with between-group p-values

	Isometric (tiptoes) (n=24)	Isometric (dorsiflexed) (n=18)	Isotonic (n=24)	Rest (n=25)	P-value[3]
Age, y	47.3 (10.9)	47.6 (9.3)	48.7 (7.4)	49.7 (7.4)	0.775
Sex, male, n (%)	9 (38)	9 (50)	13 (54)	14 (56)	0.569
BMI	24.5 (4.5)	28.6 (5.4)	26.4 (5.4)	28.5 (5.5)	0.026[4]
Activity[1]					0.090
Active, n (%)	22 (92)	10 (56)	19 (79)	20 (80)	
Sedentary, n (%)	2 (8)	8 (44)	5 (21)	5 (20)	
Sports participation in desired sport (total hours per week), median (IQR)	4.0 (9.0)	4.3 (3.5)	3.5 (3.5)	3.0 (2.0)	0.242
Affected side					0.374
Unilateral, left/right, n (%)	5/10 (62)	3/6 (50)	11/7 (75)	8/7 (60)	
Bilateral, n (%)	9 (38)	9 (50)	6 (25)	10 (40)	
Duration of symptoms, wk, median (IQR)	62.0 (120)	104.0 (98)	88.0 (61)	59.0 (46)	0.223
VISA-A score[2]	42.8 (15.1)	32.7 (13.5)	46.0 (15.5)	45.2 (14.7)	0.023[5]

Data are presented as mean ± SD unless otherwise specified.

Abbreviations: BMI, body mass index; IQR, interquartile range; n, number of participants; SD, standard deviation; VISA-A, Victorian Institute of Sports Assessment-Achilles; wk, weeks; y, years.

[1] To determine whether participants were active or sedentary we used the ankle-activity score. If the score was ≥4 points the participant was considered to be active (starting from heavy physical work). If the score was ≤3 points the participant was considered to be sedentary (cycling, equestrian or less activity). Sports participation is only presented for the active group.31

[2] The VISA-A questionnaire consists of eight questions and covers three domains of Achilles tendon symptoms: pain, activity, and function. Scores vary from 0 to 100 where 100 indicate an asymptomatic person and 0 is defined as maximum pain, no activity, and no function.

[3] P-values for between-group differences in baseline characteristics were calculated using the one-way ANOVA for normally distributed continuous outcomes, the Kruskal Wallis test for non-normally distributed outcomes, and the chi-square test for categorical outcomes.

[4] Post hoc testing with Bonferroni correction showed there was a significant difference in BMI between the isometric (tiptoes) group and the rest group (p=0.05). There were no other significant between-group differences.

[5] Post hoc testing with Bonferroni correction showed there were significant differences in VISA-A score between the isometric (dorsiflexed) group and both the isotonic group and the rest group (p=0.031 and p=0.047). There were no other significant between-group differences.

Figure 2: Individual patient data and means per intervention arm (A-D) for the patient-reported pain (visual analogue scale (VAS) score) immediately after performing 10 unilateral hops. VAS-scores were assessed before (pre) and immediately after the intervention (post)**.** The grey lines represent the individual VAS-scores, the black line the raw mean VAS-scores of the intervention arm. No statistically significant differences between the four intervention arms were found. A clinical relevant immediate analgesic effect of 20 points was detected in six patients (25%) in the isometric (tiptoes) group, 3 patients (17%) in the isometric (dorsiflexed) group, four patients (17%) in the isotonic group, and 1 patient (4%) rest group.

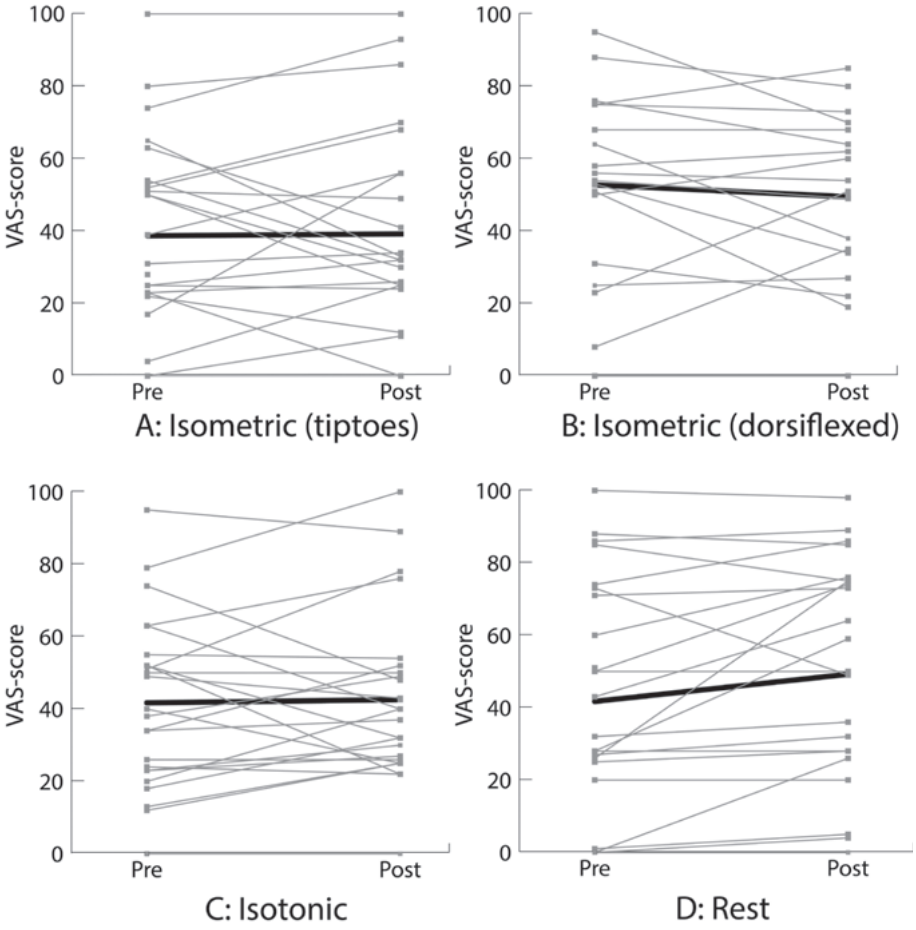


Table 3. Outcomes of the Generalized Estimation Equations (GEE) model used to evaluate whether any of the loading protocols/rest provided an immediate analgesic effect. Adjustments were made for the following pre-defined baseline variables: age, sex, BMI, baseline VISA-A score and duration of symptoms. Outcomes of the GEE-model are presented as estimated marginal means with their 95% confidence interval. A higher 10 hop VAS-score indicates more pain. Positive values for the between-group differences correspond to more improvement in 10 hop VAS-score compared to the other intervention group. Negative values correspond with less improvement in 10 hop VAS-score compared to the other intervention group.

Estimated mean 10 hop VAS-scores (0-100) before and after the performance of one of the interventions			
	Before	**After**	**Within-group difference**
Isometric (tiptoes)	39.7 (31.8 to 47.6)	39.9 (29.9 to 49.8)	0.2 (-11.2 to 11.5)
Isometric (dorsiflexed)	41.7 (29.0 to 54.4)	39.8 (28.2 to 51.3)	-1.9 (-13.6 to 9.7)
Isotonic	44.8 (37.7 to 51.8)	46.2 (37.9 to 54.5)	1.4 (-8.3 to 11.1)
Rest	44.7 (35.7 to 53.7)	51.9 (43.1 to 60.6)	7.2 (-2.4 to 16.7)

Between-group differences immediately after the performance of the loading protocol/rest				
	Isometric (tiptoes)	**Isometric (dorsiflexed)**	**Isotonic**	**Rest**
Isometric (tiptoes)		0.1 (-24.9 to 25.1)	-6.3 (-27.4 to 14.7)	-12.0 (-33.2 to 9.2)
Isometric (dorsiflexed)			-6.4 (-29.9 to 17.0)	-12.1 (-34.9 to 10.7)
Isotonic				-5.7 (-24.8 to 13.5)
Rest				

Abbreviations: VAS, visual analogue scale.

Discussion

Summary of main findings

Our trial compared the effects of two different isometric exercises, isotonic exercises, or resting on pain during a functional test in chronic midportion Achilles tendinopathy. Neither isometric nor isotonic exercises provided an immediate analgesic effect.

Clinical implications

Our findings are important and clinically relevant, since the performance of isometric

exercises has become increasingly popular as initial treatment and for immediate pain relief in several lower-limb tendinopathies. The popularity is based on a study that found a large and meaningful decrease in pain score of 6.8 (scale 0-10) following isometric exercises in patients with patellar tendinopathy, compared to a decrease of 2.6 points following isotonic exercises.[18] Despite the fact that this was a single study with a very small sample size (n=6), isometric exercises were implemented rapidly.[32] Results were quickly extrapolated to other lower-limb tendinopathies such as AT.[32]

To date, one other research group investigated the analgesic effect of isometric exercises in a relatively small group of patients (n = 16) with chronic midportion AT. Heterogeneous individual responses were found, with no overall meaningful change in pain scores during a functional task after performing isometric exercises.[21] A difference between that particular study and ours is that in the previous study patients performed exercises using a Wii platform. We performed the exercises in the way they are performed in the clinical setting during rehabilitation with the use of additional weight. Comparable results with no meaningful change were also found in patients with lateral elbow tendinopathy, plantar fasciopathy, and a recent second study in patellar tendinopathy.[19 29 33] We also demonstrated no meaningful change in pain score after the performance of isometric exercises with either a dorsiflexed or a plantar flexed position of the ankle.

In previous research, isotonic exercises provided immediate pain relief with small magnitude in patellar tendinopathy.[18] This is the first study to investigate the possible analgesic effect of isotonic exercises in AT. We also found no meaningful change in pain score after isotonic exercises. Our study was the first to include a rest group in which no exercises were performed. Results of the intervention arms performing a loading protocol did not differ from the rest group, indicating that both isometric and isotonic calf-muscle exercises have no immediate analgesic effect.

Research implications

The previous study in patients with chronic midportion AT demonstrated that the severity of symptoms could play a role in the analgesic effect of isometric exercises. Individuals with higher pain scores worsened in that study, compared to individuals with lower pain scores who improved after isometric exercises.[21] We did not replicate this finding with our study, as the individual responses to the intervention were very heterogeneous (Figure 2). More research would be needed to determine whether subgroups are present and if so, whether different treatment regimens should be provided. This would involve very large study numbers. We did not investigate the role of isometric or isotonic exercises as an actual treatment for AT, and more research regarding the efficacy of the different exercise programs on the intermediate and long-term effects is necessary.[34] Our study shows that both types of exercises also

do not aggravate immediate pain. Both exercises are well-tolerated and could represent a starting point for therapy, self-efficacy, and self-management. We also did not investigate the analgesic effect of isometric exercises in patients with a short symptom duration (reactive stage). It could be hypothesised that possible cortical reorganization depends on the chronicity of symptoms, making patients with chronic symptoms less sensitive to an analgesic effect of isometric exercises.

Strengths and limitations

This is the largest study to date investigating the immediate analgesic effect of both isometric (two groups with different ankle positions) and isotonic exercises in patients suffering from tendinopathy. This is also the first study to include a control group who rested to rule out an analgesic effect from activation of the musculotendinous unit.

Despite our robust research design, there are some methodological limitations. First, we estimated our sample size on a SD of 20 points. However, it transpired that the SD of the changes in the VAS scores was approximately 26 points and thus 28 patients per group would have been required to detect a meaningful change. Additionally, the secondary outcomes could also be slightly underpowered as multiple testing was performed. If we would adjust the alpha level using the Bonferroni method for a total of 6 comparisons, 41 patients per group would have been required. However, if we overlook the mean between-group differences and the very few responders, it is unlikely that this study does involve a type II error. Furthermore, the above-mentioned potential limitations do not influence our primary aim to determine whether isometric exercises provide an immediate analgesic effect. Second, the method of quasi-randomization was used to allocate patients to the intervention arms. Although this method is not preferable, it was most appropriate as patients were already being randomised to evaluate the effect of an injection treatment. We also adjusted for relevant pre-defined baseline variables in the GEE-model, making it unlikely that differences in baseline characteristics will have influenced results. Third, it was not feasible to blind the outcome assessor (patients) for the type of intervention. However, we did not mention the hypothesis of the study and in doing so avoided influencing patient beliefs regarding the immediate effect of exercise therapy. Fourth, patient beliefs regarding exercise therapy could already be influenced since absence of symptomatic improvement after exercise therapy at short term (at least 6 weeks) was an inclusion criterion. It is, therefore, questionable whether we could extrapolate these results to the broader population of patients with midportion Achilles tendinopathy. Fifth, we did not obtain the RPE scores from the first 20 inclusions. The RPE was still obtained in the majority of the patients (17/24) in both the isometric (tiptoes) group and the isotonic group and in all 18 patients within the isometric (dorsiflexed) group. Sixth, some patients (n = 9) had a 10 hop VAS-score of zero at the

start of the exercise therapy and could thus not show an immediate analgesic effect. Additional sensitivity analyses excluding those patients did not affect outcomes of this study. Future studies are advised to exclude these patients in their trial.

Perspective

Isometric and isotonic exercises do not result in immediate pain relief in patients with chronic midportion AT. After one small study investigating patients with patellar tendinopathy demonstrated that isometric exercises resulted in a large immediate pain relief, these exercises gained a lot of attention and were implemented rapidly. A recent smaller study in patients with AT was not able to replicate these findings. As a result, there was conflicting evidence for the analgesic effect of isometric exercises. Based on the findings in this study, we do not recommend the use of isometric exercises for immediate pain relief in patients with chronic midportion AT. Future research should focus on the intermediate and long-term efficacy of isometric and isotonic exercises as a treatment for AT and the analgesic effect of isometric exercises in the reactive stage of AT.

Footnotes

Acknowledgements: We would like to thank our biomedical statistician Erwin Waarsing for his help in the statistical process. We would like to thank all patients for their active participation and all healthcare providers for referring the patients to our study.

Funding: This research is funded by the Dutch Arthritis Association and the Anna Foundation. Both are non-commercial organizations and were not involved in the content of this publication.

Ethics approval: Regional Medical Ethical Committee, registration number 14-100

Competing interest: None declared

Link for online web appendix: https://onlinelibrary.wiley.com/doi/full/10.1111/sms.13728

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6

Chapter 7

Effectiveness of a high volume injection as treatment for chronic Achilles tendinopathy:

randomised controlled trial

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BMJ 2020 Sep;370:m3027

Abstract

Objective: To study whether a high-volume injection without corticosteroids improves clinical outcome in addition to usual care for adults with chronic midportion Achilles tendinopathy.

Design: Patient and assessor-blinded, placebo-controlled randomised clinical trial.

Setting: Sports medicine department of a large district general hospital, the Netherlands.

Participants: 80 adults aged 18-70 years with clinically diagnosed chronic midportion Achilles tendinopathy and neovascularisation on ultrasonography were eligible to participate. 39 were randomised to a high-volume injection without corticosteroids and 41 to placebo.

Interventions: Participants were instructed to perform an exercise programme for 24 weeks (usual care) combined with one 50 mL high-volume injection of saline and lidocaine (intervention group) or one 2 mL placebo injection of saline and lidocaine (placebo group) at baseline.

Main outcome measures: Primary outcome was pain and function assessed using the validated Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire at 24 weeks (analysed using a generalised estimation equations model). Secondary outcomes were patient satisfaction, return to sport, degree of ultrasonographic Doppler flow, visual analogue scale on 10-hop test, power and flexibility of the gastrocnemius and soleus muscles, pain detect questionnaire for neuropathic pain, and pain coping inventory. Participants were evaluated at baseline and at 2, 6, 12, and 24 weeks.

Results: Only one participant (1%) was lost to follow-up. The estimated mean VISA-A score improved significantly, from 40.4 (95% confidence interval 32.0 to 48.7) at baseline to 59.1 (50.4 to 67.8) at 24 weeks in the high-volume injection group and from 36.9 (27.1 to 46.8) to 58.5 (47.9 to 69.1) in the placebo group. The VISA-A score over time did not differ between the groups (adjusted between group difference at 24 weeks 0.5 points, 95% confidence interval −17.8 to 18.8). No significant between group differences were found for patient satisfaction (21/37 (57%) v 19/39 (49%) patients, P=0.50) and return to desired sport (15/29 (52%) v 19/31 (61%) patients active in sports, P=0.65) at 24 weeks. None of the other secondary outcomes differed between the two groups.

Conclusions: A high-volume injection without corticosteroids in addition to usual care is not effective for symptom reduction in patients with chronic midportion Achilles tendinopathy. On the basis of our findings, we cannot recommend the use of a high-volume injection in this patient group.

Trial registration: Clinicaltrials.gov Identifier: NCT02996409

Introduction

Chronic disorders of the Achilles tendon (tendinopathy) are a common overuse injury seen in general practice, with an incidence rate of 2-3 per 1,000 registered adult patients.[1] Most (74%) of these patients have midportion Achilles tendinopathy.[2] Runners are most at risk of developing symptoms, with a lifetime risk of 52%.[3] The initial treatment of Achilles tendinopathy is exercise combined with load management.[4] Despite initiation of treatments, two thirds of patients continue to have symptoms at one year follow-up.[5] At 10-years follow-up, about a quarter of patients still have symptoms.[5 6] About one third of these non-responders eventually require surgery.[4 7] Therefore, effective conservative treatment options are necessary to improve the outcome of patients with chronic Achilles tendinopathy who fail to respond to initial exercise treatment.

Formation of blood vessels (neovascularisation) around and within the tendon is one of the features of chronic Achilles tendinopathy. Neovascularisation can be identified in 50-100% of patients with tendon symptoms using Doppler ultrasonography, compared with 0-30% in asymptomatic patients.[8-12] The infiltration of nerve structures alongside this neovascularisation has been suggested to play a role in the chronicity of pain from Achilles tendinopathy.[13 14] A large study showed an association between the degree of ultrasonographic Doppler flow and patient-reported severity of symptoms.[8]

Consequently, treatments have been developed to target neovascularisation. A novel technique is high-volume injection, in which a large amount of fluid is injected into the area surrounding the tendon with the aim of obliterating peritendinous and intratendinous neovascularisation from high mechanical pressure.[14] Current debate is on the addition of corticosteroids to the injection mixture. Recent evidence shows that a high-volume injection with corticosteroids is associated with superior short-term improvement at 6-12 weeks compared with a high-volume injection without corticosteroids, but intermediate term effects are similar.[15] Several cohort studies and one small randomised controlled trial found that a high-volume injection (both with and without corticosteroids) resulted in decreased pain and improved function in the short-term (6-12 weeks).[14 16-19] As a consequence, this treatment is increasingly being used in the clinical setting although its effectiveness has not been tested in a large well designed study. In this study, we compared the effect of a high-volume injection without corticosteroids with a placebo injection (both combined with an exercise programme) on pain and functional outcome at 24 weeks in patients with chronic midportion Achilles tendinopathy.

Methods

Study design and participants

This study was conducted as a stratified, patient and assessor-blinded, placebo-controlled, randomised clinical trial with 1:1 allocation ratio at the sports medicine department of a large district general hospital (Haaglanden Medical Centre, The Hague, Netherlands). The study was announced through letters to healthcare professionals, presentations at national conferences, and information on a national sports medicine platform. Potentially eligible participants were identified from referrals by healthcare providers and self-referrals, thereby comprising a mix of patients with and without primary care from healthcare providers. The coordinating researcher (AvdV) provided participants with detailed information on the study. Participants were screened for eligibility by telephone and online (using a pain map). A sports medicine physician (RvO) evaluated potentially eligible participants for inclusion at a booked appointment. Participants provided written informed consent before inclusion.

We included patients if they were aged 18-70 years, had a painful swelling of the Achilles tendon 2-7 cm proximal to the insertion on the calcaneus, had had symptoms for at least two months, had an unsatisfactory outcome after a six week exercise programme, and had detectable Doppler flow. When symptoms were bilateral, participants selected the most severely affected tendon for treatment. All the participants performed a minimum of six weeks of exercise treatment before inclusion.

Patients were excluded if they had a history of an Achilles tendon rupture or surgery; were unable to perform the exercise programme, were engaged in concomitant treatment programmes, had sural nerve disease, had recent drug use (within two years) with putative effect on symptoms and tendon healing (quinolone antibiotics, corticosteroids), were suspected of having other musculoskeletal disorders clinically (insertional Achilles tendinopathy, plantar flexor tenosynovitis, peroneal subluxation, inflammatory internal disorders, or quinolone, corticosteroid, or statin induced tendinopathy), had a medical condition that would affect the safety of the participant when using the injection (eg, peripheral vascular disease, use of anticoagulant drugs, allergy for lidocaine), or were pregnant.

Procedures

One researcher (AvdV) prepared five 10-mL syringes (total volume 50 mL) for each patient. These syringes contained a mixture of 8 mL 0.9% sodium chloride solution (saline) and 2 mL 1% lidocaine (B Braun; Melsungen, Germany). Before and directly after injection, we used a Pro Focus Type 2202 (BK Medical; Herlev, Denmark) with a 5-12 MHz linear probe type 8811 to perform ultrasonography. The area of maximum

Doppler flow was detected using power Doppler ultrasonography with predefined settings determined before the start of the study (mechanical index 1.28, thermal index 1.2, pulse repetition frequency 1.0 kHz and gain 50%).[20] We recorded the presence of intratendinous and peritendinous Doppler flow immediately after the injection. A blinded observer evaluated the presence of Doppler flow on these records to verify the success of the procedure after the trial has ended. These results had no consequences on the injection procedure - that is no second injection was performed if Doppler flow was still present after the high-volume injection. Complications and co-interventions were registered at each visit. All participants received daily compliance logs to complete for evaluation of adherence to the exercise programme. The participants were asked to upload these logs digitally every week. Reminders were sent to non-responders after five days.

Randomisation and masking

We used stratification for pre-injury activity level, since this could be a confounder for the primary outcome of pain and functional activity using the Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire.[21] Stratification was conducted using the ankle activity score, which quantifies ankle-related activity based on type and level of activities.[22] Participants with an ankle activity score of 4 points or more were considered to be active those with a score of 3 points or less were considered to be sedentary.[23] Participants were randomised using a computer-generated randomisation list (Microsoft Access; Redmond, WA). To ensure a balance between the number of participants in each treatment group, we performed block randomisation with a variable block size of 4-10). To ensure blinding of the outcome assessor (AV), a secretary performed the randomisation who was independent of the researchers responsible for enrolment or the assessment of outcome measures. After randomisation, an unblinded sports medicine physician (RvO) who was not involved in the assessment of outcome measures carried out the allocated injection treatment. The participants were blinded to their assigned treatment, as they could not see the injection procedure. All the participants completed a short questionnaire immediately after the injection to check whether the blinding procedure was successful (which type of injection do you think you have received (high-volume injection or placebo)?) and to assess the amount of pain (visual analogue scale 0-100, using a 100 mm line) during the procedure.

Interventions

High-Volume Injection

The participants were placed in the prone position on the examination table with the

affected ankle hanging over the edge of the table. To ensure blinding, participants were asked not to turn their head during the injection procedure. The sports medicine physician inserted a 21-gauge and 40 mm long needle from the medial side of the ankle between the anterior aspect of the Achilles tendon and the anteriorly located Kager's fat pad. The needle was attached to a connecting tube of 30 cm with Luer taper (Argon MC; Frisco, TX) to attach the syringes on the other side. The first syringe with the saline and lidocaine mixture (10 mL) was injected at the area of maximum Doppler flow. The following four syringes (10 mL each) were injected 1-2 cm proximal, distal, medial, and lateral, with coverage of the whole width of the tendon under real-time ultrasonography. The injection technique was identical to that described previously.[14] Materials were stored in an opaque box to ensure blinding of the participants after the injection. The participants remained prone on the examination table for 5-7 minutes after the procedure.

Placebo Injection

The placebo injection was performed using a similar technique, mixture, and duration as for the high-volume injection. The only difference was the amount of injected fluid. Except for the third syringe, only 0.5 mL of each of the five syringes was injected at the different injection locations in the placebo group. The third syringe was attached to the connecting tube and the needle was localised at the injection site, but no fluid was injected. Therefore, 2 mL of the saline and lidocaine mixture was injected in total. To ensure blinding, the participants were unaware of the amount of injected fluid and type of procedure used for either treatment group. The participants were advised to refrain from strenuous walks and sports activities during the first 24 hours after the injection.

Exercise programme

The blinded outcome assessor (AV) instructed all participants to perform a daily calf muscle exercise programme using detailed written information and videos. The exercise programme was based on an existing protocol, consisting of three consecutive phases: isometric exercises, concentric exercises, and eccentric exercises.[24 25] The participants were asked to start the next phase if exercises could be performed for one week with acceptable symptoms (visual analogue scale score of ≤3/10 in activities and in daily life). If eccentric exercises could be performed without problems for at least one week, the participants continued with the return to sports module. This module consisted of four phases: simple plyometric exercises, fast plyometric exercises, a gradual increase in running, and interval training (if necessary for the type of sports). Web appendix 1 provides detailed information on the exercise programme and return to sport module.

All the participants were advised to refrain from weightbearing sporting activities for at least five weeks. The exercises and activities should be performed with only mild pain (maximum score of 3 on a scale from 0 to 10, with 0 indicating no pain and 10 maximum pain) and the participants were advised to decrease the activity level when the pain increased to more than 3 points during or after the activity or when morning stiffness increased one day after the activity compared with the previous days.[24] The participants were then instructed to decrease their activity until symptoms had returned to an acceptable level. They were discouraged from using other treatments for their Achilles tendinopathy.

Outcome measures

The primary outcome measure was the Dutch version of the VISA-A questionnaire.[26] This validated and disease-specific questionnaire quantifies pain and activity levels, with scores ranging from 0 to 100: 100 indicates no pain with full activity level, with the score decreasing with increasing severity of symptoms.[27].

Secondary outcomes were patient satisfaction, return to sport, degree of ultrasonographic Doppler flow, visual analogue scale on 10-hop test, power and flexibility of the gastrocnemius and soleus muscles, pain detect questionnaire, and pain coping inventory. Patient satisfaction was scored as moderate or poor or as excellent or good. Return to sport was scored as "no return to the desired sport" or "return to the desired sport" (regardless of reaching pre-injury level). All outcome measures were assessed at baseline (before intervention) and at 2, 6, 12, and 24 weeks.

Statistical analysis

Our sample size calculation showed that 40 participants were required in each group to detect a difference of 12 points on the VISA-A score (power 0.80, two sided significance level of 0.05, SD 18, and accounting for a 10% loss to follow-up).[23 28 29] A researcher (AvdV) performed the statistical analyses under the supervision of a biomedical statistician (JW); both were blinded to the allocated treatment. Data were analysed on an intention-to-treat basis using SPSS 25.0.0.1 (SPSS, Chicago, IL). Normality of the data was checked visually with Q-Q plots and statistically using the Shapiro-Wilk test. Between-group differences for the primary outcome were analysed using a generalised estimation equations model. To test whether the time course of the VISA-A score was different between groups we added the interaction term of treatment group x time point. Adjustments were made for the four predefined baseline variables of age, sex, body mass index, and duration of symptoms. Additionally, we adjusted for the stratification factor (ankle activity score).[30] Outcomes of the generalised estimation equations model are presented as estimated means,

unless otherwise stated. The same method was used to evaluate most of the secondary outcomes (see web appendix 2). A Fisher's exact test was used to evaluate only patient satisfaction, return to sport, and the patient acceptable symptom scale. The outcomes to evaluate the success of the procedures were analysed using a Fisher's exact test or χ^2 test (categorical outcomes) or unpaired t-test or Mann-Whitney U-test (continuous outcomes). We considered differences of $P<0.05$ to be statistically significant. Missing data were not imputed, but we would have carried out sensitivity analyses if missing data exceeded 5%.

Patient and public involvement

Patients were not involved in defining the research question. Two patients participated in a pilot test round to evaluate the impact of the placebo and high-volume injection procedure. Patients were not involved in other aspects of the study design. After completion of the trial, all trial participants were contacted to evaluate relevant outcome measures and the burden of participation to improve future trials. Five patients took part in a patient meeting to discuss these items. Study results will be disseminated to the trial participants by email or letter.

Results

From December 2016 to January 2019, 185 patients with posterior ankle pain were screened for eligibility. After exclusions 80 participants were included in the study and randomised to either a high-volume injection without corticosteroids or a saline injection (placebo group). At the 24 week endpoint, only one participant was lost to follow-up (1%). Figure 1 shows the flow of participants through the trial. No differences in baseline characteristics were found between the groups, except for the presence of bilateral symptoms (table 1). A higher proportion of participants in the high-volume injection group had bilateral symptoms (17/39 (44%) v 11/41 (27%)). An additional analysis using a generalised estimation equations model was done to correct for the variable unilateral or bilateral symptoms.

Figure 1. Flow of patients through study.

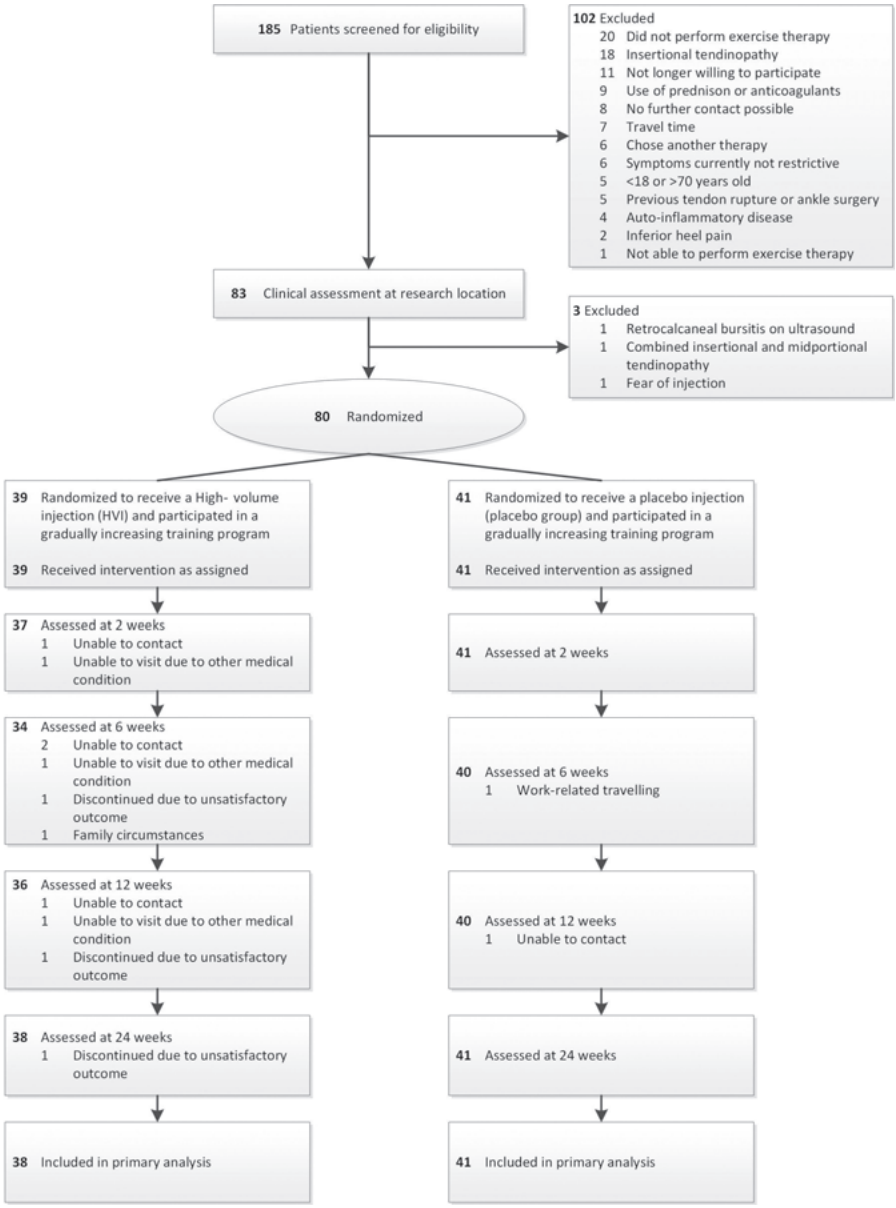

Table 1. Baseline characteristics of adults with chronic midportion Achilles tendinopathy assigned to a high-volume injection without corticosteroid or placebo injection. Values are numbers (percentages) unless stated otherwise

	High-volume injection group (n= 39)	**Placebo injection group (n= 41)**
Mean (SD) age (years)	46.9 (8.1)	48.9 (9.9)
Men	17 (44)	22 (54)
Mean (SD) body mass index	26.8 (5.7)	27.6 (5.1)
Activity level[1]		
Active in sports	31 (79)	33 (80)
Sedentary	8 (21)	8 (20)
Participation in desired sport (total hours per week)	3.9 (2.0)	4.9 (3.6)
Affected side		
Unilateral, left/right	11/11 (56)	15/15 (73)
Bilateral	17 (44)	11 (27)
Median (interquartile range) duration of symptoms (weeks)	64 (17-112)	60 (14-107)
Mean (SD) VISA-A score	44.4 (15.5)	41.0 (16.0)
Interventions at study start		
None	24 (62)	19 (46)
Night splint	1 (3)	0 (0)
Foot orthoses	10 (26)	18 (44)
Pain killers	1 (3)	4 (10)
Others	3 (8)	1 (2)
Doppler flow		
Intratendinous	33 (85)	37 (90)
Peritendinous	6 (15)	4 (10)

VISA-A, Victorian Institute of Sports Assessment-Achilles

[1] Determined using the ankle activity score. Participants who scored ≥4 points were considered to be active in sports (starting from physical work). Participants who scored ≤3 points were considered to be sedentary (cycling, equestrian, or less activity). Level of sport and sports participation is only presented for the active group.

Outcome measures

VISA-A score: In the high-volume injection group the estimated mean VISA-A score improved from 40.4 (95% confidence interval 32.0 to 48.7) at baseline to 59.1 (50.4 to 67.8) at 24 weeks and in the placebo group from 36.9 (27.1 to 46.8) to 58.5 (47.9 to 69.1). The interaction term treatment group×time point was not statistically significant (P=0.42), meaning that the VISA-A score did not differ over time between the groups.

The adjusted between group difference in VISA-A score at 24 weeks was 0.5 (95% confidence interval −17.8 to 18.8) in favour of the high-volume injection group (table 2). Improvement in VISA-A score was not significant at two weeks for either group. VISA-A scores improved significantly in both groups at six weeks (P=0.05) and at 12 and 24 weeks (P<0.01). Figure 2 presents the raw VISA-A scores. In the sensitivity analysis using the additional generalised estimation equations model to correct for unilateral or bilateral symptoms, the results for the primary outcome (interaction term treatment group×time point, P=0.44) remained unchanged.

Figure 2. Between group differences in Victorian Institute of Sports Assessment-Achilles (VISA-A) score from baseline in participants treated with a high-volume injection without corticosteroids or a placebo injection at 2, 6, 12, and 24 weeks. Whiskers represent 95% confidence intervals

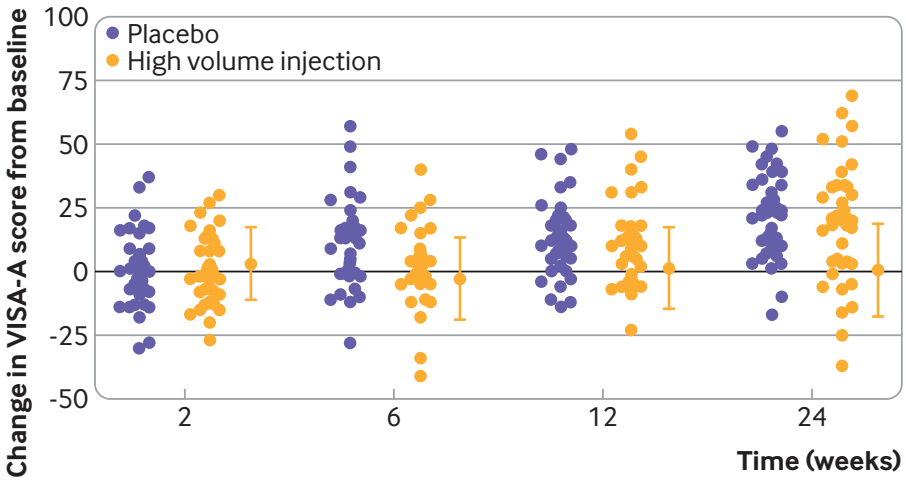

Table 2. Primary and secondary outcome measures in adults with chronic midportion Achilles tendinopathy assigned to a high-volume injection without corticosteroid or placebo. Values are numbers (percentages) unless stated otherwise

Outcome measures	High-volume injection group (n=39)	Placebo injection group (n=41)	Adjusted between group difference
	Primary outcome measure		
Estimated mean (95% CI) VISA-A score at follow-up (weeks)[1]			
2 weeks	41.4 (33.7 to 49.1)	38.2 (28.3 to 48.1)	3.2 (-11.2 to 17.5)
6 weeks	43.3 (34.6 to 52.0)	46.1 (35.7 to 56.6)	-2.8 (-18.9 to 13.3)
12 weeks	50.9 (42.3 to 59.5)	49.6 (39.3 to 60.0)	1.3 (-14.7 to 17.3)
24 weeks	59.1 (50.4 to 67.8)	58.5 (47.9 to 69.1)	0.5 (-17.8 to 18.8)
	Secondary outcome measures		
Patient satisfaction[2]			
Moderate or poor	16 (43)	20 (51)	
Excellent or good	21 (57)	19 (49)	
	HVI group (n=29)	**Placebo group (n=31)**	
Return to sport[3]			
No return to sport	9 (31)	7 (23)	
Returned to sports, but not to desired type	5 (17)	5 (16)	
Returned to the desired sport, but not at pre-injury level	11 (38)	14 (45)	
Returned in the desired sport at pre-injury level	4 (14)	5 (16)	

VISA-A, Victorian Institute of Sports Assessment-Achilles.

[1]Scores and adjusted between group differences were calculated using a generalised estimation equations model with adjustments for predefined baseline variables: age, sex, body mass index, duration of symptoms, and ankle activity score. Positive values favour the high-volume injection group. No statistically significant differences were found between the treatment groups at any time point.

[2]For analysis purposes, good or excellent patient satisfaction was dichotomised as "satisfied," and a poor or moderate satisfaction as "dissatisfied." Two patients in each group did not return the questionnaire in which patient satisfaction was assessed. No statistically significant differences were found between the treatment groups at 24 weeks (P=0.50).

[3] Number represents the proportion of participants who were active in sports before the study start (n=31 in the high-volume injection group and n=33 in the placebo injection group). Two patients in each group did not return the questionnaire in which return to sport was assessed. Return to sport was dichotomised as "no return to desired sport" (no return to sport or return to sport, but not in the desired sport) or "return to desired sport" (regardless reaching pre-injury level). No statistically significant differences were found between both treatment groups at 24 weeks (P=0.65).

Patient satisfaction: No significant difference was found in patient satisfaction between the treatment groups at 24 weeks (P=0.50). In the high-volume injection group, 21/37 patients (57%) reported an excellent or good outcome compared with 19/39 (49%) in the placebo group.

Return to sport: No significant difference was found for return to the desired sport at 24 weeks (P=0.65). In the high-volume injection group, 15/29 (52%) patients returned to their desired sport compared with 19/31 (61%) in the placebo group. Of these participants, only 4/29 (14%) returned to their pre-injury level in the high-volume injection group and 5/31 (16%) in the placebo group.

Web appendix 2 shows the results of the other secondary outcome measures. No significant between group differences were found for any of these outcome measures.

Success of procedures

*Success of the injection procedure on Doppler flow***:** In participants with intratendinous Doppler flow before the injection procedure (n=33 in the high-volume injection group and n=37 in the control group; table 1), Doppler flow was no longer detectable inside the Achilles tendon in 26/33 patients (79%) in the high-volume injection group compared with 11/37 patients (30%) in the control group (P<0.001). The disappearance of Doppler flow after the high-volume injection did not appear to influence the course of the VISA-A score over time compared with the presence of Doppler flow after the high-volume injection (P=0.99), as explained in detail in web appendix 4.

Success of patient blinding: In the high-volume injection group, 25/39 patients (64%) correctly thought they had received the high-volume injection. In the placebo group, 22/41 patients (54%) correctly thought they had received the placebo injection (P=0.36).

Complications/pain during injection procedure: No complications (infections, haematomas, or tendon ruptures) were reported during the study period. The median pain score (visual analogue scale score 0-10) during the injection procedure was 6.0 (interquartile range 5.0-8.0) for the high-volume injection group and 5.0 (2.0-7.0) for the placebo group (P=0.10).

Adherence: 80% of participants (1536 out of 1920 questionnaires) completed the weekly online questionnaires to evaluate adherence to exercise treatment. The median percentage of performed exercises (compared with the amount of prescribed exercises) was 76% (interquartile range 46-100%) in the high-volume injection group and 72% (43-100%) in the placebo group (P=0.17).

Co-interventions: The use of 12 co-interventions (eg, foot orthoses, manual treatment, and sports massage) was reported in 12 patients (31%) in the high-volume intervention group compared with nine co-interventions in six patients (15%) in the placebo group (P=0.30).

Discussion

In our patient and assessor-blinded, placebo-controlled randomised clinical trial we found that a high-volume injection without corticosteroids has no added value to an exercise programme in patients with chronic midportion Achilles tendinopathy. We found no differences in patient-reported outcomes between the high-volume injection and a placebo injection. Also, no between-group differences were found in any of the secondary outcome measures, indicating that a high-volume injection does not have mechanistic effects.

Clinical implications

These findings are important and clinically relevant, as high-volume injections have become increasingly popular after several non-blinded case-series and one cohort study showed an improvement in pain during activities at intermediate-term follow-up (30-52 weeks).[14 18 31] These findings exceeded the improvement known from eccentric exercises.[24 32-34] As previous high-volume injection studies were only performed in non-responders to eccentric training, this treatment gained even more attention. Surprisingly, large improvements (38 points on the VISA-A score) after a high-volume injection were already seen in the short-term (three weeks).[17] This indicates a rapid decrease in symptoms of Achilles tendinopathy when a high-volume injection is given. A recent blinded randomised controlled trial with a small sample size (n=19 in each treatment group) confirmed these findings, in which patient-reported outcomes improved significantly more in the high-volume injection group at the six week follow-up compared with the placebo group. This improvement had slightly decreased at the 24 week follow-up. Improvement in VISA-A score was lower than expected in the placebo group at 24 weeks, thereby raising the possibility of unsuccessful blinding of the participants.[16 23 35 36] In our large study, we did not find any beneficial effect of the high-volume injection in either the short-term (2 or 6 weeks)

or the intermediate-term (12 or 24 weeks). An important difference between our study and previous studies investigating high-volume injections, is that we did not use corticosteroids in the injection mixture. The hypothesis is that the saline solution in the injection mechanically damages the neovascularisation and its adjacent nerves.[14] Corticosteroids are discouraged as treatment for tendinopathies owing to detrimental long-term effects and the risk of ruptures of the Achilles tendon.[37-39] Therefore, we decided not to include corticosteroids in the injection mixture. This could explain the difference in outcomes between our study and previous studies. We hypothesise that a high-volume injection does not have a mechanical pain-reducing effect, but that the short-term improvement as seen in previous studies might have been related to the corticosteroids. The previous randomised controlled trial evaluating the high-volume injection supports this hypothesis, since short-term outcome exceeded the long-term outcome. This is a typical course after treatment with a corticosteroid injection.[40] In studies that did not use corticosteroids in the injection mixture, comparable results to ours were seen at 12-24 weeks.[15 19 31] The clinical improvement in symptoms of Achilles tendinopathy for both treatment arms in our study is similar to that reported in a recent meta-analysis evaluating the effectiveness of treatment using heavy-load eccentric calf muscle exercise therapy and in a comparable population included at our research centre in which standalone exercise was provided.[28 41] The difference in the form of exercise programmes is not likely to have influenced the results, because no evidence suggests that one form of exercise training is superior to another.[42] Improvement could additionally be explained by the placebo effect, patient education, load management, and the clinical course of the disorder. Our findings indicate that an exercise programme, patient education and load management are still beneficial in patients with no previous improvement during calf muscle exercise training. We would therefore advice all patients to continue an exercise programme as the basis of their treatment.

Strengths and limitations of this study

The strength of our study is that we performed this randomised clinical trial according to the current consolidated standards of reporting trials (CONSORT) guideline. The patients, outcome assessor, and statistician were all blinded to the intervention, and only one participant was lost to follow-up. Despite our robust research design, our study also has some methodological limitations. Firstly, it was not feasible to blind the doctor who performed the injection procedure at baseline. As this doctor was not involved in the treatment allocation (randomisation), follow-up of participants, or data analysis, this probably did not influence study outcomes. Secondly, the lack of a group that only performed an exercise programme (without injection) might be regarded as limitation. We do not know whether the improvement of symptoms

over time in both groups is a consequence of the exercise programme, a promoted healing response after the injection procedure, a placebo effect from the injection procedure, or represents the clinical course of Achilles tendinopathy. Thirdly, a high-volume injection is a technically demanding and specific procedure. A single sports medicine doctor with extensive experience in injection procedures performed the interventions. Test sessions were carried out before the start of the study according to instructions provided by experts in high-volume injections.[14] Intratendinous Doppler flow disappeared in 79% of the patients in the high-volume injection group compared to 30% in the placebo group, indicating success with the high-volume injection.

Conclusion

In patients with a chronic midportion Achilles tendinopathy, a high-volume injection without corticosteroids did not result in a beneficial effect in addition to an exercise programme. On the basis of these findings, we cannot recommend the use of a high-volume injection in this patient group.

Footnotes

Acknowledgements: The authors would like to thank Eline van Es (Department of Orthopaedic Surgery, Erasmus MC University Medical Centre, Rotterdam, the Netherlands) for the design and evaluation of the allocation sequence; and Willemien Rebel-Wolterbeek and Monique de Kroes-Groeneveld (Department of Sports Medicine, Haaglanden Medical Centre, The Hague, The Netherlands) for their logistic help. These individuals were not compensated for their efforts. We would like to thank all patients for their active participation and all healthcare providers for referring the patients to our study.

Funding: This research is funded by the Dutch Arthritis Association and the Anna Foundation. Both are non-commercial organisations and were not involved in the design, analysis, and content of this publication.

Ethical approval: Medical Ethics Committee of Southwest Holland, the Netherlands (MEC 14-100).

Competing interest: All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Link for online web appendices: https://www.bmj.com/content/bmj/suppl/2020/09/09/bmj.m3027.DC1/vlia054573.ww.pdf

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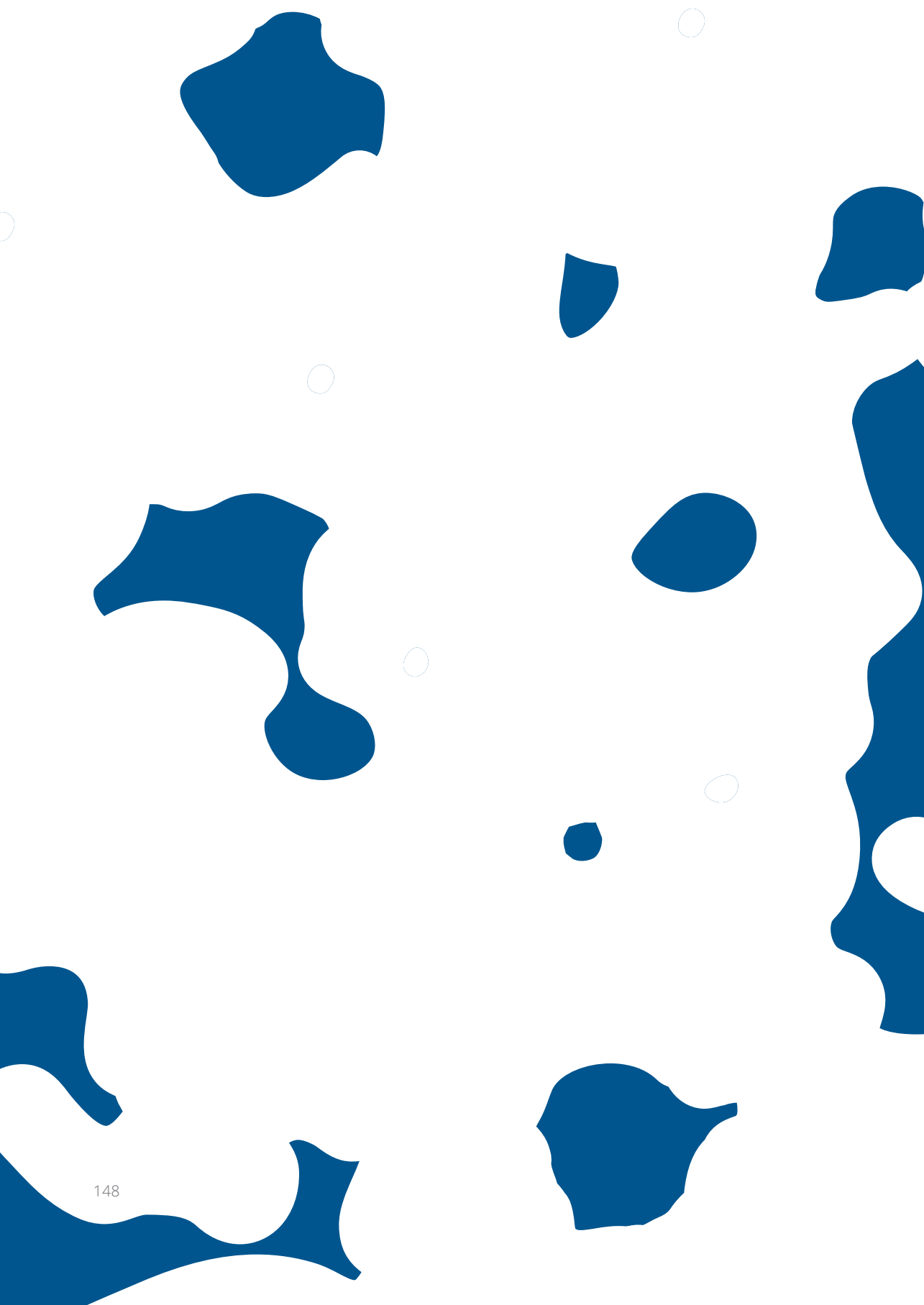

Chapter 8

Do high-volume injections affect the ultrasonographic neovascularisation in chronic Achilles tendinopathy?

A randomised placebo-controlled clinical trial

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Submitted for publication

Abstract

Background: Neovascularisation and accompanying nerve structures are considered to play a role in the symptoms of patients with chronic midportion Achilles tendinopathy (AT). High-volume injections (HVIs) are a novel treatment option, which specifically target this neovascularisation.

Objective: To evaluate whether a HVI decreases ultrasonographic Doppler flow in patients with chronic midportion AT.

Methods: A double-blind, randomised, placebo-controlled clinical trial. We included patients with clinically diagnosed chronic midportion AT and ultrasonographic Doppler flow. Patients received either a HVI (50 mL) or a placebo injection (2 mL), and performed a 24-week exercise program. Primary outcome was the surface area quantification (SAQ) score (%) of the Doppler flow during a 24-week follow-up period. Secondary outcome was the association between SAQ scores and symptoms (Victorian Institute of Sports Assessment–Achilles [VISA-A]). Outcomes were measured before, directly after, and one hour after the injection and at 2, 6, 12, and 24 weeks.

Results: We included 62 patients, 30 were randomised to the HVI-group and 32 to the placebo-group. There was no significant between-group difference in the course of the SAQ score. SAQ scores did not differ between groups directly post-injection (-2.0%, 95%CI -5.6 to 1.2). Change in SAQ score was not correlated with the change in VISA-A score (p=0.93).

Conclusion: A HVI does not affect Doppler flow in patients with chronic midportion AT. This finding challenges the theoretical basis of a HVI.

Trial registration: NCT02996409

Introduction

Achilles tendinopathy (AT) is common in the general population,[1] with the highest incidence in runners.[2] AT is diagnosed clinically and characterised by a triad of local pain, swelling, and an impaired load-bearing capacity.[3] Ultrasonographic features of chronic AT are presence of focal tendon thickening, hypoechoic areas, and Doppler flow in the peritendinous and/or intratendinous area.[4] Doppler flow indicates the formation of new blood vessels (neovascularisation) and is observed in 55-100% of the patients with AT.[5-9] Histopathological research demonstrated it is accompanied by redundant sympathetic and sensory nerves.[10] These nerves are hypothesised to be responsible for pain in AT patients.[9]

High-volume injections (HVIs) are a novel treatment option for patients with AT, which aims to obliterate the neovascularisation and sensory nerves. This is done by mechanically stripping the Achilles tendon from the fat pad.[11] Previous studies (3 case-series and one randomised clinical trial (RCT)) on effectiveness of HVI showed promising results 3-52 weeks follow-up.[11-14] Our recently performed large RCT, however, showed no effect on patient-reported outcomes at 24-weeks follow-up. The effectiveness of a HVI is currently topic of debate.[15] Since the effect of a HVI on Doppler flow is largely unknown, we further explored the mechanistic effect of a HVI as part of our RCT.

Our primary aim was to determine the effect of a HVI on the degree of ultrasonographic Doppler flow during 24 weeks in patients with chronic midportion Achilles tendinopathy. Secondary aims were to evaluate (1) the correlation between the baseline quantified Doppler flow and the change in symptoms and (2) the association between the change in quantified Doppler flow and the change in symptoms during follow-up.

Methods

Study design

This study was part of a double-blind, randomised, placebo-controlled clinical trial which investigates the effectiveness of a high-volume injection in patients with chronic midportion Achilles tendinopathy (ClinicalTrials.gov Identifier: NCT02996409). The protocol of the study was approved by the regional medical ethical committee (registration number 14-100). All patients provided written informed consent before inclusion.

Setting and patients

Study announcement took place via letters, social media, presentations, and a study website. When patients were potentially eligible for inclusion, they received

detailed information about the study and were screened by the researcher (AV). If patients were presumed to be eligible, a sports medicine physician (RO) at a large district general hospital (Haaglanden Medical Centre, the Netherlands) evaluated the eligibility criteria. Main inclusion criteria were 1) clinical diagnosis of chronic midportion Achilles tendinopathy for at least 2 months (localised Achilles tendon pain on palpation and swelling 2-7 cm proximal to its calcaneal insertion), 2) non-response to a calf-muscle exercise program for at least 6 weeks, 3) aged 18-70, and 4) presence of peritendinous/intratendinous Doppler flow on Power Doppler Ultrasonography (PDUS) examination. Main exclusion criteria were 1) suspicion of other musculoskeletal disorders, 2) previous Achilles tendon rupture or surgery, and 3) inability to complete an exercise program. All inclusion and exclusion criteria are presented in the trial register. In patients with bilateral symptoms, only the most symptomatic tendon was included in the study.

Procedures

A researcher (AV) prepared five syringes of 10 mL (total 50 mL). Each syringe consisted of 8 mL sodium chloride solution (saline) and 2 mL 1% lidocaine (B. Braun, Melsungen, Germany). Ultrasonography was performed before and directly after the injection, using a Pro Focus Type 2202 (BK Medical, Herlev, Denmark) with a 5-12 MHz linear probe (Type 8811).

Randomisation

As the activity level of patients could affect the primary outcome of the HAT-study (Victorian Institute of Sport Assessment – Achilles (VISA-A)), patients were stratified based on the ankle-activity score (AAS).[16] Patients with an AAS ≤3 were labelled as sedentary and patients with an AAS ≥4 were labelled as active.[17]

Patients were randomised with a 1:1 allocation ratio, using a computer-generated randomisation list with block randomisation with variable block size (4-10).

Intervention

High-Volume Injection (HVI; intervention group)

Patients were placed in prone position on the examination table and were not able to see which injection they received. A sports medicine physician (RO) determined the area with maximum Doppler flow using PDUS. The needle (21-gauge and 40mm long) was fixed to a 30cm connecting tube. The other side of the connecting tube was attached to the syringe using Luer taper (Argon MC, Frisco, USA). The needle was placed under ultrasound guidance in the area between the Achilles tendon and the

Kagers' fat pad, at the most thickened part of the tendon. A total of 50 mL solution was injected medial, lateral, proximal, and distal from this part. This procedure is corresponding to the description in previous literature.[11]

After the injection, patients were requested to rest on the examination table for 5-7 minutes. The syringes were collected in an opaque box to ensure blinding of the patient. Patients were recommended to avoid sport activities for 24 hours after the injection.

Placebo Injection (placebo-group)

The procedure of the placebo injection was similar to the HVI. The needle was placed in the same areas, the syringes were switched four times and this procedure had the same duration to ensure blinding of the patients. The only dissimilarity between both procedures was that patients in the placebo-group received an injection with a total volume of only 2 mL.

Exercise program

All patients performed a 24-week gradually progressive exercise program consisting of calf muscle exercises and gradual return to sport based on an existing protocol.[18,19] This daily exercise program consisted of different phases: isometric exercises, isotonic exercises, and eccentric exercises. Patients who were active in sports subsequently performed plyometric exercises and return to sport exercises. If patients were able to perform the exercises with only limited symptoms for one week, they were advised to go to the next phase. The researcher instructed the exercises to the patients at baseline and written information and videos were provided.[15]

Power Doppler Ultrasonography (PDUS)

PDUS of the Achilles tendon was performed before and directly after the injection procedure, and at 2, 6, 12, and 24 weeks follow-up. A subgroup of 20 patients additionally underwent PDUS examination one hour after the injection procedure, to investigate the direct effect of a HVI. A blinded researcher (AV) performed PDUS examinations before the injection and after 2, 6, 12, and 24 weeks. The sports medicine physician (RO) performed the PDUS post-injection and a blinded research student (JV) performed the PDUS one hour after the injection. All were extensively trained (> 20 training hours). Prior to every PDUS examination, patients had to climb two stairs to arrive at the examination room followed by 10 minutes of rest to complete their questionnaires. No other instructions about activity prior to the appointments were

provided. Patients were scanned in prone position on the examination table with loose hanging, slightly passively dorsiflexed feet over the edge of the table to ensure a neutral ankle angle. The most painful part of the Achilles tendon was scanned. Pressure of the probe was minimalised to prevent occlusion of blood vessels.[6] We used the following pre-defined settings for PDUS: mechanical index 1.28, thermal index 1.2, pulse repetition frequency 1.0 kHz and gain 50.[20] The size of the colour box was standardised for every patient at 4.6 cm^2 (depth 1.7 cm; width 2.7 cm). The upper bound of the colour box was put on the dorsal side of the Achilles tendon. The sonographer determined the location of maximum Doppler flow in a perpendicular view and recorded 20 seconds.

Outcome measures

Primary Outcome

The Surface area quantification (SAQ) of the Doppler flow was the primary outcome of this study. The SAQ has a good inter-observer reliability.[20] To determine the SAQ score, recorded PDUS were evaluated in steps of 0.04 seconds using Kinovea (Bordeaux, France) to select three frames with visually the maximum degree of Doppler flow. A researcher (AV) evaluated the quality of the recorded PDUS. If the noise on the recorded PDUS was more than half of the maximum Doppler flow in the colour box, the SAQ score was not representative and the researcher excluded the recorded PDUS for further analysis. We used ImageJ version K 1.45 (National Institutes of Health, Bethesda, MD) for analysis. First, the area outside the colour box was cleared. Subsequently, the colour threshold was used to transform the colour pixels of the Doppler flow into white pixels (hue: 255, saturation: 165, brightness: 250). We determined the SAQ score by dividing the number of white pixels by the total number of pixels in the colour box. We selected the frame with maximum Doppler flow for analysis.

Secondary Outcome

Our secondary outcomes were the validated VISA-A questionnaire (0-100) [21] and the visual analogue scale (VAS (0-100)) during a provocation test (VAS 10-hop-score). These were assessed at baseline and at 2, 6, 12, and 24 weeks. Patients completed the VISA-A questionnaire prior to their PDUS measurement and the VAS 10-hop-score afterwards (but prior to communicating the results of the PDUS). Patients performed ten hops on their affected limb and subsequently their VAS score was noted using a VAS ruler with slider.

Statistical Analysis

All analyses were performed on an intention-to-treat basis using SPSS version 25.0 (IBM Corporation, Armonk, NY) by a blinded researcher (CO). The sample size was based on the primary outcome (VISA-A score) of our RCT (n=40 per intervention arm). As the ultrasound machine was not available for the entire duration of the study, we were not able to include the last 18 of the 80 patients for this part of the study. We refrained from post-hoc power analysis as this is discouraged.[22] Between-group differences for the primary outcome were evaluated using a generalized estimating equations (GEE) model. To test whether the time course of the SAQ score was different between both groups we added the interaction term 'treatment group*time point'. We adjusted the model for several pre-defined baseline variables (age, gender, BMI, ASS, baseline VISA-A, and duration of symptoms). We performed a generalized linear model and a multivariate regression analysis to investigate the association between the change in symptoms and the baseline Doppler flow or the change in Doppler flow. Adjustments were made for variables influencing the outcome with a P-value <0.10. Results with a P-value <0.05 were considered statistically significant.

Results

After screening 185 potentially eligible patients between December 2016 and January 2019, we included 62 consecutive patients for this part of the study (Figure 1). Of these, 30 patients received the HVI (intervention group) and 32 patients received the placebo injection (placebo-group). Twenty-five PDUS measurements (6%) could not be performed during the 24-week follow-up period for varying reasons (Figure 1). We excluded 18 of the 62 (29%) PDUS measurements directly post-injection when analysing the data, because of extensive noise during those measurements (HVI-group: 7 and placebo-group: 11). Table 1 shows the baseline patient characteristics.

Figure 1. Flowchart demonstrating the Flow of Patients Through the Study.

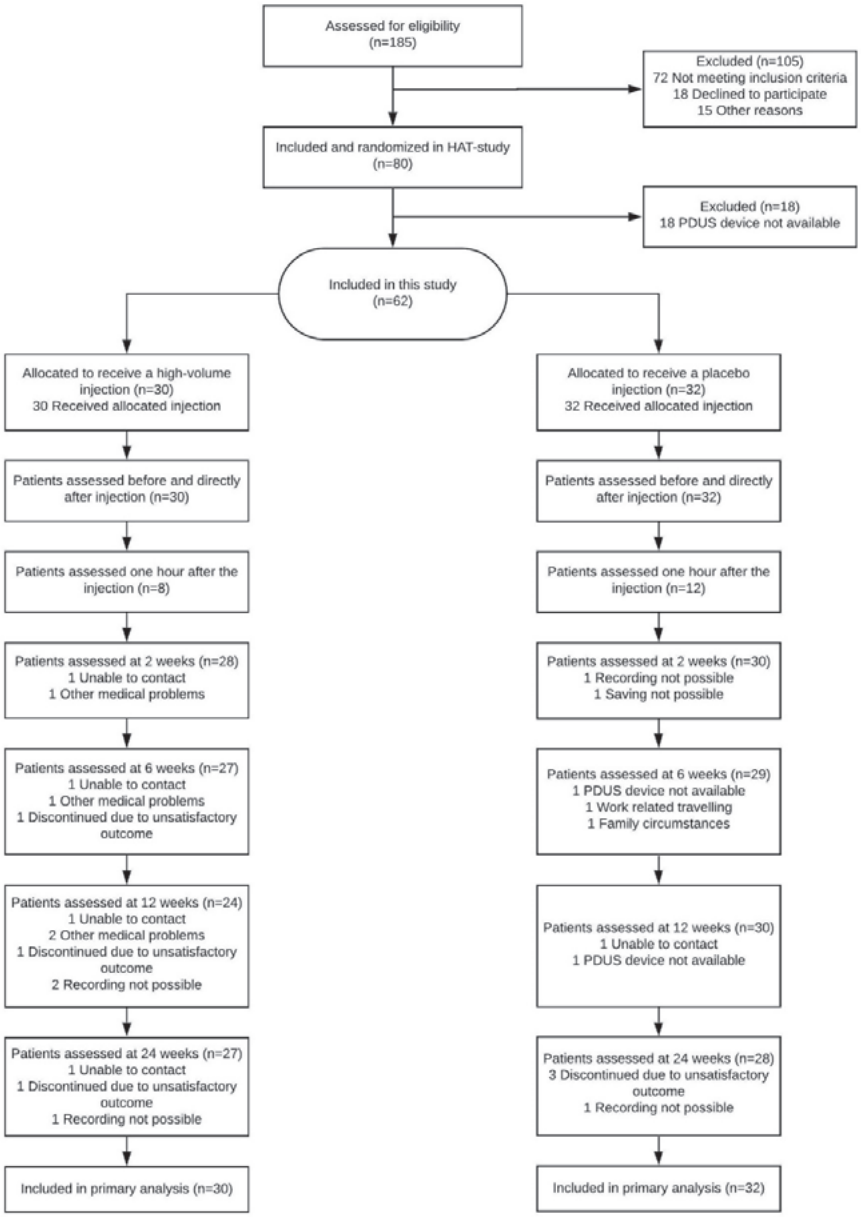


Table 1. Baseline characteristics of the study population.

Characteristics	HVI-group (n=30)	Placebo-group (n=32)
Age, median (IQR), y	50 (44-52)	50 (45-56)
Sex, male, n (%)	12 (40.0)	17 (53.1)
Duration of symptoms, median (IQR), wk	60 (34-99)	70 (43-150)
Affected side, n (%)		
Left	10 (33.3)	13 (40.6)
Right	9 (30)	10 (31.3)
Bilateral	11 (36.7)	9 (28.1)
Activity [†], n (%)		
Active in sports	24 (80)	27 (84)
Sedentary	6 (20)	5 (16)
BMI, median (IQR), kg/m^2	25.3 (22.7-29.8)	26.0 (24.3-29.9)
Baseline VISA-A score, mean (SD)	44.9 (15.2)	43.8 (15.5)
Baseline SAQ score (%), median (IQR)	3.5 (1.8-6.6)	4.1 (2.2-8.0)

Presented data was the raw data, before calculation of the estimated means.

Abbreviations: HVI, high-volume injection; IQR, interquartile range; BMI, body mass index; VISA-A, Victorian Institute of Sports Assessment-Achilles; SD, standard deviation; SAQ score, surface area quantification score; y, years; wk, weeks.

[†] Patients were labelled as 'sports' if their ankle-activity score (AAS) was ≥4, patients with an AAS ≤3 were labelled as 'sedentary'.

Primary outcome

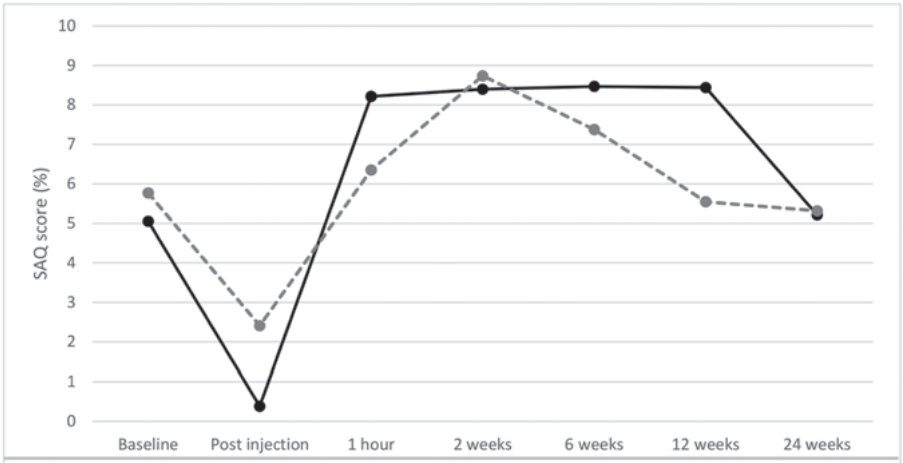
The estimated mean SAQ score decreased significantly directly post-injection in both groups (Figure 2). One hour after the injection procedure, estimated means in both groups increased to values exceeding baseline values. Over the following 24 weeks of follow-up, values return to the baseline values. During the follow-up period of 24 weeks, there were no significant differences at all time points.

Secondary outcomes

Baseline Doppler flow and patient reported outcome

The estimated mean VISA-A scores improved from 44.3 to 64.8 (p<0.01) and the estimated mean VAS 10-hop-scores improved from 41.5 to 15.7 (p<0.01) over the 24-week follow-up period. After adjustment for relevant predictors (age, p=0.09), there was no association between baseline Doppler flow and the course of the VISA-A score (β=-0.22, [95% CI: -0.08 to 0.04], p=0.45) or the course of the VAS 10-hop-score during the study (β=0.01, [95% CI: -0.05 to 0.06], p=0.76).

Figure 2. The courses of the estimated mean SAQ score.



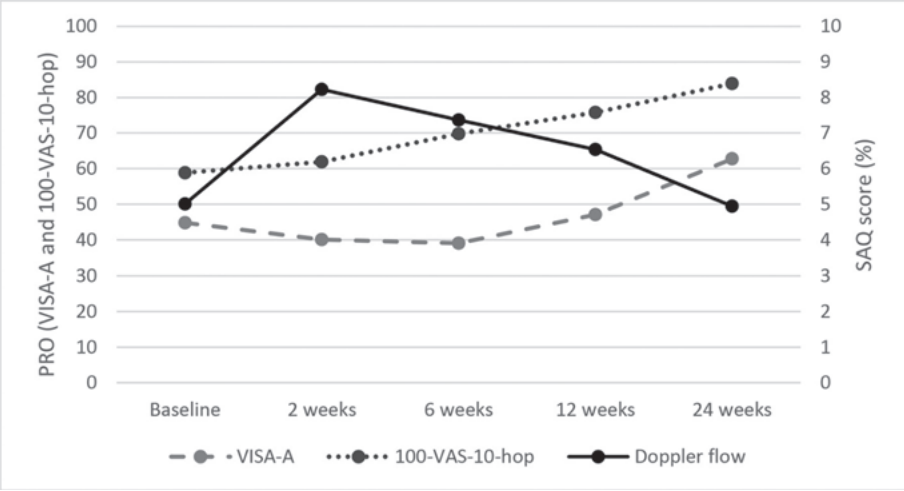
	Baseline	Post injection	1 hour	2 weeks	6 weeks	12 weeks	24 weeks
HVI-group (95% CI)	5.1 (2.6 to 7.5)	0.4 (-1.4 to 2.2)	8.2 (4.7 to 11.7)	8.4 (5.0 to 11.8)	8.5 (5.0 to 12.0)	8.4 (4.8 to 12.1)	5.2 (2.5 to 7.9)
Placebo-group (95% CI)	5.8 (3.4 to 8.1)	2.4 (0.2 to 4.6)	6.3 (2.9 to 9.8)	8.7 (5.7 to 11.8)	7.4 (4.7 to 10.0)	5.5 (3.4 to 7.7)	5.3 (3.3 to 7.3)
Adjusted difference (95% CI)	-0.7 (-5.1 to 3.7)	-2.0 (-5.6 to 1.2)	1.9 (-5.9 to 9.7)	-0.3 (-7.4 to 6.7)	1.1 (-5.7 to 7.9)	2.9 (-3.6 to 9.4)	-0.1 (-4.9 to 4.7)

Abbreviations: HVI, high-volume injection; SAQ score, surface area quantification score; CI, confidence interval.

Change in Doppler flow and patient reported outcome

There was no correlation between the change in Doppler flow and the change in VISA-A score (β=0.07, [95% CI: -1.43 to 1.56], p=0.93) and the change in VAS 10-hop-score (β=-0.76, [95% CI: -2.34 to 0.82], p=0.34) as demonstrated in Figure 3.

Figure 3. The courses of the estimated mean VISA-A scores, VAS 10-hop-scores, and SAQ score.



Abbreviations: VISA-A, Victorian Institute of Sports Assessment-Achilles; VAS, visual analogue pain scale; SAQ score, surface area quantification score; PRO, patient reported outcome.

The VISA-A score ranges from 0 to 100 in which a lower score indicates a higher symptom severity. The VAS-score ranges from 0 to 100, with 0 indicating no pain and 100 maximum pain. For a better interpretation of this figure, the VAS 10-hop-scores are presented as: 100 – VAS 10-hop-score. An increase in VISA-A score or 100-VAS 10-hop-score can be interpreted as a symptom improvement.

The change in VISA-A score from baseline to 24 weeks was not influenced by age (p=0.30), sex (p=0.15), BMI (p=0.12), duration of symptoms (p=0.28), or baseline VISA-A score (p=0.16). The change in VAS 10-hop-score from baseline to 24 weeks follow-up was influenced by age (p=0.05) and baseline VISA-A score (p=0.08). Sex (p=0.31), BMI (p=0.88), and duration of symptoms (p=0.22) did not affect the change in VAS 10-hop-score.

Discussion

We demonstrated in our double-blind, randomised, placebo-controlled clinical trial that a high-volume injection does not reduce Doppler flow in patients with chronic midportion Achilles tendinopathy. Also, the amount of Doppler flow at baseline is not associated with the course of patient-reported outcomes and there is no correlation between the change in Doppler flow and the change in patient-reported outcomes.

These findings are clinically relevant, as high-volume injections (HVIs) are a novel treatment option in patients with chronic AT that do not respond to usual care.[11] After publishing the clinical results of our recently conducted RCT[15], there is conflicting evidence for the effectiveness of HVIs on patient-reported outcomes.[14 23 24] Therefore, it is important to better understand the mechanistic effects of HVIs, which could help explaining these discrepancies from clinical studies.

In our RCT, we did not detect a change in improvement of clinical outcomes and amount of Doppler flow. One hypothesis might be that the injection procedure failed. However, we noticed a significant short-term reducing effect of the HVI on Doppler flow, which proves that the injection procedure was technically successful. This was not different to placebo, which implicates that a small volume already can have local effects on neovascularisation or disappearance is a result of inactivity. In the other RCT, corticosteroids were added to the injection mixture. The addition of corticosteroids could explain the promising short-term clinical effects and raises the question whether corticosteroids affect the neovascularisation. In a case-series corticosteroids were added to the HVI mixture and a significant decrease of 1.1 point in neovascularisation grade between baseline and 3-week follow-up using the modified semiquantitative Öhberg score (0-4) was described.[12] One RCT also reported a decrease in modified Öhberg score of approximately 2 points in the HVI-group (including corticosteroids) and 0.5 points in the placebo-group after 6 to 24 weeks follow-up.[14] The reduction in Doppler flow was larger in the HVI-group compared to placebo, but no statistical analysis were performed.[14] So adding corticosteroids to the HVI mixture might decrease Doppler flow. Although the difference between our study and the previous studies is that we assessed Doppler flow with an observer who was blinded to the allocated intervention and clinical status of participants. Another important difference between these studies is that we used the reliable quantitative surface area quantification (SAQ) method instead of the modified Öhberg score, which overcomes limitations of this semiquantitative scoring systems.[20]

We are the first to investigate the correlation between the baseline Doppler flow, the change in Doppler flow using a quantitative measurement and the change in patient reported outcome. We did not detect any correlation between baseline Doppler flow or change in Doppler flow and both the VISA-A questionnaire and the VAS 10-hop-score. The VISA-A score reflects symptom changes over the preceding week, while a VAS 10-hop-score reflects the actual irritability of the tendon at a specific moment. Our findings are in line with four previous studies, using the semiquantitative modified Öhberg score.[5-7 25] Therefore, we do not recommend the use of Doppler flow measurements with the aim to predict the symptom course or as a measure for recovery for patients with chronic midportion AT.

Strengths and limitations

This is currently the largest RCT investigating the effect of a HVI on Doppler flow in patients with AT. We used a reliable quantitative SAQ method to determine the degree of neovascularisation instead of a semiquantitative grading system.[20] Despite our robust design, there were some limitations. First, we could not include 18 of the PDUS measurements directly post-injection as there was a lot of noise present which

limited analyses. This was in contrast to the semiquantitative results of Doppler flow in our RCT, which showed a significant difference in Doppler flow between both groups, using the modified Öhberg score.[15] Since this discrepancy in results and the need to exclude PDUS measurements, we query whether SAQ is the best method to evaluate the amount of Doppler flow directly post-injection. Second, the sports medicine physician who performed the PDUS directly after the injection was not blinded for the allocated intervention. As he was not involved in the follow-up measurements and data analyses, it is unlikely that this influenced our results.

Conclusion

It is hypothesised that a HVI mechanically destructs the neovascularisation, but the absence of a significant lower Doppler flow at any follow-up point in our study indicates this is not the case. As we also previously demonstrated that there is no additional effect on patient-reported outcome following a HVI compared to a placebo injection, we highly question the use of HVI in patients with chronic midportion AT.

Footnotes

Acknowledgements: We would like to thank all patients for their active participation and all healthcare providers for referring the patients to our study.

Funding: This research is funded by the Dutch Arthritis Association and the Anna Foundation. Both are non-commercial organisations and were not involved in the content of this publication.

Ethics approval: Regional Medical Ethical Committee, registration number 14-100

Competing interest: None declared

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Chapter 9
General discussion

Since the year 2000 there is an exponential increase in publications regarding Achilles tendinopathy; currently more than a hundred studies each year are being published. Knowledge is increasing rapidly, however, literature is often inconclusive, and many questions remain unanswered. The general aim of this thesis was to evaluate risk factors, to study imaging with a focus on Doppler flow, and analyse treatment options in patients with Achilles tendinopathy.

Risk factors

The identification of risk factors for Achilles tendinopathy is of great importance, as basis for future primary prevention and treatment strategies. We identified the following nine risk factors for Achilles tendinopathy in our systematic review: a history of a lower limb injury, season of training, calf muscle strength, gait analysis parameters, moderate alcohol use, fluoroquinolone antibiotic treatment and suboptimal renal function in a specific heart transplant population.[1-6] High-quality prospective cohort studies investigating risk factors were unfortunately missing and most studies investigated a non-representative young population (median age 21 years), thereby resulting only in limited evidence for all risk factors.

An important risk factor for Achilles tendinopathy seemed to be a history of a lower limb injury, with an odds ratio of 4 in a single study.[3] In this study, 146 participants (2.1%) developed Achilles tendinopathy during a one year follow-up period in a population of 7,113 participants with a history of lower limb injury. In the 70,790 participants with no history of lower limb tendinopathy, only 304 participants (0.4%) developed symptoms. The relationship between the time that one has been asymptomatic, and the risk of developing Achilles tendinopathy has not been reported in this study for the group with a history of lower-limb injury. Most likely the risk for recurrent symptoms will be highest in patients that recently became asymptomatic. Unfortunately, this risk factor is not modifiable and cannot serve in future primary preventive strategies. Based on our results, we would advise patients that are at risk to develop Achilles tendinopathy to: (1) reduce the use of alcohol to a maximum of 7 units per week for men and 4 units for women, (2) avoid the use of ofloxacin if alternatives are available, and (3) improve plantar flexor strength by performing strengthening exercises of the calf muscles.[1 3 6]

Whether these preventive interventions are effective for Achilles tendinopathy is uncertain. Of our advices, only strengthening exercises of the calf muscles as preventive strategy have been investigated.[7] There was no preventive effect when performing these exercises in a group of professional soccer players. The discrepancy between the risk factor and the preventive effect could be explained by the low compliance (only 2 sessions per week were performed) and that no additional weights were used during the performance of the exercises.[8] Exercises were also performed in-season,

whereas it could be hypothesised that strengthening exercises are more effective when performed in the pre-season to gradually increase musculoskeletal load.

We demonstrated in our systematic review that there is currently no evidence for an association between physical activity level and Achilles tendinopathy. However, previous risk factor studies measured the absolute load and sudden changes in load could be more important. Recent studies in team sports and endurance sports showed that the overall injury rate is increased when there are rapid increases in training load.[9 10] This has been analysed using the acute:chronic workload ratio. In this ratio, the 'acute' training load is the load of a certain week (e.g. kilometres per week in runners), which is divided by the 'chronic' load (e.g. average kilometres per week in the previous four weeks). When the training load is almost equal every week, the ratio is approximately 1. An acute:chronic workload ratio of ≥1.5 increases the injury risk in the following week.[9 10] We recommend future risk factor research in this field to focus on changes in load, rather than the absolute load at one moment in time. Besides, physical activity level could have been measured not accurately enough to detect associations, as previous studies investigated hours of training or training distance as risk factor. The recent introduction of wearables in sports and tracking apps could prove useful in future studies. Parameters such as speed, cadence, step length, number of accelerations, and number of high-intensity sprints should be included when analysing change in physical activity level.

Training season and gait analysis parameters have both only been investigated in one relatively small cohort study.[2 4] Also, in both studies several important confounders could have been present. In the study analysing gait parameters the gait pattern was determined barefoot, whereas running shoes are likely to influence the gait pattern. Furthermore, two studies investigating the preventive effect of shoe orthoses did not demonstrate a risk reduction for developing Achilles tendinopathy.[11 12] It should, however, be noted that the number of cases (resp. 2 and 12 cases) in these studies were too low as 20-50 cases are necessary to detect moderate to strong associations.[13] In the study investigating training season as risk factor, temperature and type of surface when training could have been important confounders for this risk factor. As a result, both risk factors do not result in clinical implications.

Overweight is generally defined by clinical experts as important risk factor for Achilles tendinopathy. The hypothesis for the relationship between body weight and Achilles tendinopathy is primarily based on an increase in absolute tendon load, but also on increased cytokine levels (Prostaglandin E2, tumour necrosis factor-alfa and Leukotriene B4) that have been demonstrated to cause a low-grade inflammation.[14 15] Interestingly, we did not find evidence that overweight is associated with Achilles tendinopathy.[1-4 16 17] We cannot exclude a relationship, as the majority of the studies investigated an adolescent population in which overweight is less common.

Therefore, cohort studies are warranted in more heterogeneous populations. These studies should include the fat percentage as outcome measure. BMI that is most often investigated could be considered inaccurate in athletes, as an increased muscle mass could also lead to an increased BMI.[18]

Imaging; a focus on neovascularisation and its role in pain sensation

Doppler flow (neovascularisation) around and within the tendon is a characteristic feature in patients with longstanding symptoms of Achilles tendinopathy.[19-23] Nerve structures present alongside the neovascularisation suggest that the tendon tissue will be more susceptible for stimuli such as nociceptive pain. The amount of Doppler flow have been determined in previous studies using the modified Öhberg score, which exceeded the reliability of the original Öhberg score.[24] This modified Öhberg score is a semi-quantitative scoring system, which runs from 0-4+ (higher scores indicate more evident Doppler flow).[20 25 26] Inter-observer reliability varies from moderate to almost perfect, however, important disadvantages have been described as the scoring system in not able to distinguish higher amounts of Doppler flow (ceiling effect) and is less sensitive to detect changes.[24 26-29] As a result, novel quantitative scoring systems were warranted.

We investigated whether the quantification of coloured pixels of the Doppler flow is reliable. In this method, the percentage of colour pixels is determined within the Achilles tendon and/or the peritendinous region. This is called the surface area quantification (SAQ) method, which was first introduced by Boesen et al.[30 31] The reliability had, however, not been tested before commencement of our study. We demonstrated that the SAQ method is a reliable measurement tool in a patient group with longstanding symptoms of midportion Achilles tendinopathy (ICC 0.81). Reliability is as good as that of the modified Öhberg score, but it clearly overcomes the ceiling effect of the modified Öhberg score by differentiation between high amounts of Doppler flow. This is a prerequisite for its application in future research.[24 26 29]

Treatment modalities

A myriad of treatment modalities for Achilles tendinopathy have been investigated the last decades, including wait-and-see, exercise therapy, injections, shockwave therapy, orthosis, medication, and surgery. To compare the effectiveness of different treatment modalities, it is important to have knowledge of the minimal clinically important difference (MCID) of an outcome measure. In our randomised clinical trial, we used the generally accepted Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire to assess the effectiveness of the treatment.[32 33] Previous research in patients with midportion Achilles tendinopathy showed a very wide

range of 6.5 to 25 points for the MCID of the VISA-A.[34-37] These studies used a purely statistical approach to determine the MCID, thereby lacking a link with the difference that is clinical meaningful according to patients.

We determined the MCID in the population of the randomised clinical trial, in which patients were asked to rate the improvement/worsening of their symptoms using a global assessment scale.[35] Using this scale, we were able to determine the MCID using an anchor-based approach. This approach connects the subjective assessment of the patient to a numerical score such as the VISA-A score.[38] Previous studies most often used a distribution-based approach to determine the MCID, which lacks a clinical relevance for the patient as subjective assessments such as the global assessment scale are not included in this approach. We demonstrated that the MCID for the VISA-A score was 14 points in patients with longstanding symptoms of midportion Achilles tendinopathy after three months of conservative treatment or 7 points after six months of conservative treatment. Our sample size to determine the MCID for the VISA-A score was the largest to date, and we were the first study to differentiate between different timepoints. There was, however, a large difference of the MCID for the VISA-A score at 3 and 6 months (14 points at 3 months, 7 points at 6 months). This could be explained by recall bias; patients could have remembered symptoms to be worse than they actually were with subjective improvement as a consequence. Interpretation of data using the MCID should, therefore, always be done with caution.

Almost all studies included in our systematic review and network meta-analysis investigated a population with midportion Achilles tendinopathy; there is a lack of studies investigating a population with insertional Achilles tendinopathy. The most striking finding was that none of the current randomised clinical trials was at low risk of bias, and the effectiveness of the treatments showed large uncertainties in their estimates. The main finding was that active treatments seemed to have patient-important benefits at 3-month follow-up compared to a wait-and-see policy. All treatment modalities showed superiority to wait- and-see treatment, with most studies exceeding the MCID of 14 points. In other words, it is better to do something than do nothing. It should be noted that wait-and-see treatment has only been investigated in a single trial and data is, therefore, not robust. Also, the wait-and-see approach is questionable as an appointment with an orthopaedic surgeon was made with discussion of training modifications, implementation of stretching exercises, and ergonomic advices.[39] We feel, however, that based on current evidence it would not be ethical to include a pure wait-and-see approach as treatment arm in future trials.

But what is the most effective treatment if healthcare professionals want to actively treat Achilles tendinopathy? Two classes showed superiority in our network meta-analysis: Acupuncture therapy and shockwave therapy combined with exercise therapy.[40 41] These results were, however, based on two small trials (64 and 68 included

patients respectively) that were both at high risk of bias. We feel that there is too much uncertainty to explicitly support these as treatments of first choice. As all active treatments had overlapping comparative effects, we concluded that there was no evidence of a clinically relevant difference in effectiveness between the different active treatments at 3-month and 12-month follow-up. Shared decision making should play an important role when managing a patient with Achilles tendinopathy, considering the safety profile, treatment availability, and costs. In the absence of convincing evidence to support a specific treatment modality, we favour calf-muscle exercise therapy as treatment of first choice. Exercise therapy is suggested to be cheap, is available everywhere and has a low risk of harm.[42 43] Exercise therapy in general is recommended, as no specific type of exercise therapy has shown superiority over one another in the available trials.[44]The effectiveness of most active treatments in the long term (beyond 6 months) is uncertain. At 12 months, we did not find a difference between exercise therapy, injection therapies, and combined therapies. Also, our recommendations focus on patients with longstanding (>3 months) symptoms of midportion Achilles tendinopathy, as literature in patients with short living symptoms (<6 weeks) and insertional tendinopathy is extremely limited.[45]

Most available treatments in the network meta-analysis, such as injection therapies, exercise therapy, and surgery, are focusing on restoring the structure of the Achilles tendon. It has, however, been demonstrated that improvements in pain and function were not associated with improvements in tendon structure.[46] As a result, novel treatment modalities have been introduced with the aim to intervene on other aspects of the pathophysiological model in Achilles tendinopathy. An example of such a treatment option in midportion Achilles tendinopathy is the high-volume injection. As stated earlier, the aim of this injection technique is to obliterate the peri- and intratendinous neovascularisation and adjacent nerve structures that are present in Achilles tendinopathy through a high mechanical pressure.[47 48] This is expected to affect local pain processing. The technique has become increasingly popular after several case-series demonstrated a clinically relevant improvement in symptoms at both short-term and intermediate-term follow-up period.[47 49 50] A recent blinded RCT with small sample size (N=19 per intervention group) confirmed these findings, but robust evidence was still missing.[51] Contrary to previous findings, we demonstrated in our patient and assessor-blinded, placebo-controlled randomised clinical trial that a high-volume injection is not effective for symptom reduction in addition to usual care for patients with chronic midportion Achilles tendinopathy.

A crucial difference between our trial and previous studies is that we did not use corticosteroids in our injection mixture. We excluded corticosteroids as these do theoretically not affect the mechanical effect of the high-volume injection. Also, there is an increased risk of Achilles tendon ruptures following a corticosteroid injection

and corticosteroids are known to have detrimental long-term effects.[52-54] Most likely previous studies did not demonstrate the effectiveness of the high-volume injection procedure, but instead they demonstrated a pain-reducing short-term effect caused by the corticosteroids in the injection mixture. In the previous randomised clinical trial short-term outcome exceeded the intermediate-term outcome, which is a typical course following a corticosteroid injection.[51 52] Also, our ultrasonographic findings demonstrated that the degree of neovascularisation already returned to pre-injection levels only one hour after the injection procedure. This makes a mechanical effect of the high-volume injection itself unlikely.

Patients in both the high-volume injection group and the placebo group of the randomised clinical trial demonstrated significant improvements in pain and function over a 24-week follow-up period. The improvement in VISA-A score was approximately 20 points at 24 weeks follow-up, which is comparable with previous results in heavy-load eccentric calf muscle exercise therapy as standalone treatment.[42] Therefore, we advise all patients to continue exercise therapy as basis of their treatment. Patient education and load management could additionally play an important role in the improvement of symptoms over time, as these are usually incorporated in all investigated treatment options. This has also been the case in our study. To date, patient education and load management has not been studied as standalone treatment and should, therefore, be considered an addition to the exercise therapy.

We also used the SAQ method to explore the mechanical effect of a high-volume injection. The aim of this injection technique is to obliterate the peri- and intratendinous neovascularisation and adjacent nerve structures that are present in Achilles tendinopathy through a high mechanical pressure.[47] Directly following both injection procedures in our study, Doppler flow decreased from 4.8% to 0.1% in patients receiving a high-volume injection and from 5.4% to 2.0% in the placebo group with no significant difference between both study groups (between-group difference 1.9%, 95% CI -1.2 to 4.9%). Interestingly, one hour after the injection procedure the amount of Doppler flow returned to pre-injection levels in both study groups. This strongly suggests an absence of mechanical destruction of neovascularisation as a result of a high-volume injection. The decrease in Doppler flow directly after the intervention is more likely explained by inactivity during the injection procedure, as activity has been found to influence Doppler flow.[31] From 2 to 24 weeks follow-up, there was no significant change in Doppler flow in both study group. This is in line with two previous studies in which no clinically relevant difference was present during a 3 to 24 week follow-up period following a high-volume injection.[51 55] Both studies used the modified Öhberg score as outcome measure.

The association between Doppler flow and patient reported outcomes (e.g. VISA-A score) was of interest in the last decade. Previous studies measuring Doppler flow using

the modified Öhberg score demonstrated that a decrease in Doppler flow was not associated with an improvement in the patient reported VISA-A score.[19 25] Despite our surface area quantification overcoming limitations of the modified Öhberg score, an association between Doppler flow and patient reported outcome was still absent. We also demonstrated that quantified Doppler flow is no prognostic indicator of recovery, which is in line with two previous studies applying semiquantitative measures.[20 23] This further questions the clinical importance of neovascularisation in tendinopathy.

Pain processing is of increasing interest in tendinopathy. As stated earlier, the severity of tendon disorganisation is not directly related to the degree of pain.[56 57] Peripheral pain due to local tissue damage of the Achilles tendon is, therefore, considered not to be the only driver of pain sensation. Central pain processing has been found to be altered in patients with Achilles tendinopathy, causing pathophysiological pain (central sensitisation).[58-60] This could explain why some patients with Achilles tendinopathy do not respond to most treatments that are tissue-based. Isometric exercises of several muscle groups (e.g., quadriceps muscles) have been found to influence central pain processing.[61 62] Since 2015, isometric exercises gained a lot of attention after one study demonstrated a large and meaningful decrease in pain score following isometric exercises of the quadriceps femoris in patients with patellar tendinopathy.[63] Despite this being the only study and the very small sample size of only 6 participants, isometric exercises were implemented rapidly for immediate pain relief. Subsequently, results were quickly extrapolated to other tendinopathies such as Achilles tendinopathy. We demonstrated that neither isometric exercises nor isotonic exercises provided immediate pain relief in patients with chronic midportion Achilles tendinopathy. Recent studies in patients with lateral elbow tendinopathy, plantar fasciopathy, and patellar tendinopathy also reported no meaningful change in pain scores after the performance of isometric exercise.[63-65] Thereby, there seems to be no longer any ground to assume that isometric exercises provide immediate pain relief. Both isometric and isotonic exercises were well tolerated in our study and could still be considered a starting point for exercise therapy.

Future perspectives

Several aspects in the field of Achilles tendinopathy have been extensively discussed in this thesis, yet some questions remain unanswered and new questions arose. We feel that future research should focus on the following topics:

General perspectives

One of the main problems in the field of Achilles tendinopathy is the lack of consensus regarding core outcome measures. There is currently an international consensus to agree on these outcome measures. These results will, hopefully, improve

comparability of future trials. Furthermore, several subtypes of Achilles tendinopathy based on location of the symptoms (insertional/midportion Achilles tendinopathy) and duration of symptoms (reactive/chronic Achilles tendinopathy) are often not taken into account when designed trials. Future trials should specify their population to include a homogeneous population.

Risk factors

More adequately powered and designed prospective cohort studies are needed to investigate risk factors for Achilles tendinopathy. We would specifically recommend investigating changes in training load (e.g. acute:chronic workload ratio), plantar flexor strength, and fat percentage as potential risk factors for Achilles tendinopathy. These potential risk factors should be investigated in a heterogeneous population in which Achilles tendinopathy is most common (mean age 40-60 years old). These future risk factors could be used for designing preventive strategies.

Imaging; a focus on neovascularisation and its role in pain sensation

We feel that the surface area quantification method is adequate and reliable to detect Doppler flow in Achilles tendinopathy. We advise future trials to use this method to evaluate Doppler flow in Achilles tendinopathy, especially when treatment options target neovascularisation in Achilles tendinopathy.

Treatment modalities

First, there remains uncertainty in the treatment modality that should be advised as first line therapy in patients with Achilles tendinopathy. Most clinicians feel the urge to actively treat the disorder, however patient education and load management have never been examined as sole treatments. Also, research in insertional Achilles tendinopathy and patients with recent symptoms (<6 weeks) of Achilles tendinopathy is extremely limited. Especially research in patients with recent symptoms is warranted, as this could potentially contribute to prevent chronic symptoms in patients with Achilles tendinopathy. Future studies should be adequately powered and designed, using outcome measures from the current consensus procedure as described in the general future perspectives. As our systematic review and network meta-analyses has a 'living' design, we will update the analyses and publish the results when there are important changes that affect clinical care. Future research could provide insights to individualise treatment in patients with Achilles tendinopathy. Therefore, large studies are necessary to investigate factors that influence treatment effectiveness.

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Chapter 10

Summary

The general aim of this thesis was to evaluate risk factors, imaging, and treatment options in patients with Achilles tendinopathy. In **Chapter 1** an overview of the current literature has been given including risk factors to develop Achilles tendinopathy, imaging with a focus on ultrasonographic Doppler flow, and the available treatment options for Achilles tendinopathy.

Risk factors

In **Chapter 2** we performed a systematic literature review to identify risk factors for Achilles tendinopathy. Unfortunately, there appeared to be a lack of high-quality prospective studies that identified these potential risk factors. We found limited evidence for nine risk factors for Achilles tendinopathy: a history of lower limb injury, season of training, calf muscle strength, gait analysis parameters, moderate alcohol use, fluoroquinolone antibiotic treatment, and suboptimal renal function in a specific heart transplant population. As a result, we feel healthcare providers could advice all patients to: (1) reduce the use of alcohol to less than 7 units per week for men and less than 4 units for women, (2) avoid the use of ofloxacin if alternatives are available and (3) improve plantar flexor strength by performing strengthening exercises of the calf muscles. More high-quality research in this field is warranted, as modifiable determinants could prove useful for prevention and treatment of Achilles tendinopathy.

Imaging; a focus on neovascularisation and its role in pain sensation

Neovascularisation, one of the features during ultrasonography in patients with Achilles tendinopathy, is of increasing interest in this patient group. Most often the neovascularisation is evaluated using the modified Öhberg score, however, this score has several limitations in a research setting. In **Chapter 3** we evaluated the inter-observer reliability of a relatively novel surface area quantification method. Two observers examined the degree of Doppler flow independently during a single consultation. Both the most frequently used modified Öhberg score (a semi-quantitative score) and the surface area quantification method (a quantitative score) were determined. We included 28 consecutive patients with chronic midportion Achilles tendinopathy. We demonstrated that our surface area quantification method has a good reliability to evaluate the degree of Doppler flow in this patient group. When compared to the modified Öhberg score, the surface area quantification method is a fully quantitative score, at least as reliable as the modified Öhberg score and it overcomes the ceiling effect of the modified Öhberg score by differentiating

high amounts of Doppler flow. We advise using this quantitative measurement for research purposes to determine the degree of Doppler flow in patients with chronic midportion Achilles tendinopathy.

Treatment

Treatment effectiveness for patients with Achilles tendinopathy is currently most often evaluated using the validated and disease-specific Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire. The VISA-A questionnaire evaluates Achilles tendon pain, function, and activity level. There was, however, much uncertainty regarding the change in VISA-A score that is clinically meaningful for patients and at what VISA-A score patients consider symptoms to be acceptable. In **Chapter 4** we determined the minimal clinically important difference (MCID) and patient acceptable symptom state (PASS) of the VISA-A score in patients with chronic midportion Achilles tendinopathy. This study was part of the randomised clinical trial in which the effectiveness of a high-volume injection was evaluated. We demonstrated that a change in VISA-A score of 14 points reflects a meaningful change after 12 weeks of conservative treatment. Patients consider symptoms to be acceptable from a VISA-A score of 60 points and above. This is important information for designing future studies in this field.

In **Chapter 5** we evaluated the comparative effectiveness of all available treatments for Achilles tendinopathy in a living systematic review with network-meta-analysis. We included 29 randomised clinical trials, in which 42 different treatments were investigated. None of the trials was of low risk of bias, most had a short follow-up period of less than 6 months and there was large uncertainty in the comparative estimates. Active treatments seemed to be superior to a wait-and-see policy in patients with midportion Achilles tendinopathy at 3 months follow-up. There was no minimal clinically important difference between the different active treatments at 3- and 12-months follow-up. We advise clinicians to start with calf-muscle exercise therapy as initial treatment, as this is easy to prescribe in clinical practice, is widely available, and is regarded as safe and cheap. Evidence for treatment effectiveness in insertional Achilles tendinopathy is very limited, thereby limiting conclusions for this subgroup. We will update this living systematic review regularly, which allows for a contemporary evidence synthesis for clinical practice.

Novel treatments for Achilles tendinopathy are being introduced continuously, but often scientific evidence for these treatments is missing. In **Chapter 6**, 91 patients were quasi-randomised to perform either isometric exercises (plantarflexed or dorsiflexed ankle position), isotonic exercises, or rest with the aim to evaluate the immediate analgesic effect of isometric exercises. We demonstrated that neither

isometric exercises nor isotonic exercises result in an immediate analgesic effect in these population of patients with chronic midportion Achilles tendinopathy. As a result, we do not recommend the performance of isometric exercises with the aim to provide immediate pain relief.

Another very promising treatment seemed to be the novel high-volume injection, which aims to obliterate the neovascularisation that is frequently observed in Achilles tendinopathy. In **Chapter 7** we investigated whether a high-volume injection improves clinical outcome in addition to usual care. We performed a stratified, patient and assessor-blinded, placebo-controlled randomised clinical trial, in which we included 80 patients with chronic midportion Achilles tendinopathy. All patients performed a calf-muscle exercise program for 24 weeks (usual care) and were randomised to receive either a 50 ml high-volume injection or a 2 ml placebo injection. The injection mixture consisted of saline and lidocaine for both injections. We demonstrated that a high-volume injection does not provide a beneficial effect in addition to usual care in patients with chronic midportion Achilles tendinopathy, as no between-group differences were present. Based on this RCT, we do not recommend a high-volume as treatment in patients with chronic midportion Achilles tendinopathy.

The surface area quantification method was subsequently used to explore the mechanism of a high-volume injection. In **Chapter 8** we evaluated the ultrasonographic outcome measures of the randomised clinical trial in which the effectiveness of the high-volume injection was evaluated in patients with chronic midportion Achilles tendinopathy. We demonstrated that Doppler flow was not reduced at short or intermediate term follow-up following a high-volume injection, when compared to a placebo injection. A significant decrease was present directly after the high-volume injection procedure; however, this is most likely explained by inactivity as a similar decrease was seen following a placebo injection. Furthermore, Doppler flow returned to pre-injection levels one hour after the high-volume injection procedure. These findings challenge a mechanical effect of a high-volume injection. Additionally, we demonstrated that (1) baseline Doppler flow is not a prognostic indicator for patient reported outcome and that (2) changes in Doppler flow do not predict the course of symptoms over time.

In **Chapter 9** the main results of this thesis are described in relation to each other and the current scientific literature. Recommendation for future research are presented to further improve knowledge of Achilles tendinopathy.

10

Appendices

Nederlandse samenvatting

Dankwoord

Curriculum Vitae

PhD portfolio summary

List of publications

Nederlandse samenvatting

De achillespees is de grootste en sterkste pees van het menselijk lichaam, desondanks is een overbelasting blessure van de achillespees (achilles tendinopathie) een veelvoorkomende blessure. Het komt met name voor bij sporten waarbij er sprake is van hardloopbelasting, zoals hardlopen en voetbal. Bij recreatieve hardlopers heeft ongeveer 1 op de 12 hardlopers klachten van een achilles tendinopathie. Naarmate de sportbelasting verhoogd wordt neemt het risico verder toe; bij professionele hardlopers ontwikkelt zelfs de helft van de hardlopers achilles tendinopathie gedurende hun carrière. Ongeveer 1/3^{e} van de patiënten is echter niet sportief actief, hierbij spelen waarschijnlijk andere factoren zoals genetisch profiel en lichaamssamenstelling een rol.

Klachten bestaan voornamelijk uit pijn die optreedt bij belasting in het gebied van de achillespees. Daarnaast kan er sprake zijn van stijfheid van de achillespees in de ochtend, pijn bij aanraking van de achillespees en een zwelling van de achillespees. Klachten kunnen voorkomen in het middengedeelte van de achillespees (midportion achilles tendinopathie) of aan de aanhechting van de achillespees op het hielbeen (insertie achilles tendinopathie). Herstel duurt in veel gevallen lang en is hierdoor vaak frustrerend voor zowel de patiënt als de zorgverlener. Dit wordt mede veroorzaakt doordat onbekend is welke behandeling het beste werkt, waardoor vaak meerdere behandelingen achter elkaar uitgevoerd worden door patiënten.

Het doel van dit proefschrift is om een bijdrage te leveren aan de kennis op het gebied van risicofactoren op het ontwikkelen van achilles tendinopathie, beeldvorming en behandelopties bij patiënten met achilles tendinopathie.

In **hoofdstuk 1** is een overzicht gegeven van de huidige literatuur op het gebied van achilles tendinopathie met de focus op risicofactoren, beeldvorming met de focus op echografie en behandelopties.

Risicofactoren

In **hoofdstuk 2** is een systematisch literatuuronderzoek uitgevoerd voor het identificeren van risicofactoren voor het ontstaan van een achilles tendinopathie. Op dit gebied was er sprake van afwezigheid van studies van hoge kwaliteit. We vonden beperkt bewijs voor negen risicofactoren voor het ontstaan van achilles tendinopathie: 1) Een eerder doorgemaakte tendinopathie van de onderste extremiteit, 2) trainen in de winterperiode, 3) een verminderde spierkracht van de kuitspieren, 4) een meer laterale voetafwikkeling, 5) een afgenomen voorwaartse progressie tijdens de propulsie fase bij een loopanalyse, 6) alcoholgebruik, 7) het gebruik van fluoroquinolonen-antibiotica, 8) het aantal weken dat dit gebruikt wordt en 9) een verminderde nierfunctie specifiek bij patiënten die een harttransplantatie hebben ondergaan. Op basis van deze bevindingen raden wij aan dat zorgverleners

patiënten dienen te adviseren om: 1) het gebruik van alcohol te reduceren tot minder dan 7 eenheden per week voor mannen en minder dan 4 eenheden voor vrouwen, 2) het gebruik van ofloxacine (fluoroquinolone-antibioticum) te vermijden indien alternatieven beschikbaar zijn en 3) de spierkracht van de kuitspieren te verbeteren door krachtoefeningen uit te voeren. Aanvullend hoogkwalitatief onderzoek naar risicofactoren is zeer gewenst, omdat beïnvloedbare risicofactoren een bijdrage kunnen leveren aan het voorkomen van en de behandeling van achilles tendinopathie.

Beeldvorming; een focus op neovascularisatie en de rol in pijnbeleving

Vaatnieuwvorming, in medische taal neovascularisatie genoemd, is één van de bevindingen tijdens echografisch onderzoek bij patiënten met achilles tendinopathie. De mate van neovascularisatie wordt van oudsher uitgedrukt in categorieën van de locatie en ernst van de neovascularisatie. Dit wordt gedaan middels de zogenaamde gemodificeerde Öhberg score. In **hoofdstuk 3** hebben wij eerst de betrouwbaarheid van de relatief nieuwe oppervlakte kwantificatie methode beoordeeld die gebruikt kan worden om een score te hangen aan deze stromingen. Twee onderzoekers hebben voor deze studie de mate van Doppler flow onafhankelijk beoordeeld tijdens eenzelfde afspraak van een patiënt. Zowel de gemodificeerde Öhberg score (een semi-kwantitatieve schaal) die meestal gebruikt wordt in wetenschappelijk onderzoek om Doppler flow te beoordelen en de oppervlakte kwantificatie methode (kwantitatieve schaal) zijn verkregen. Er werden 28 patiënten met langdurige klachten van midportion achilles tendinopathie geïncludeerd. Wij hebben aangetoond dat de oppervlakte kwantificatie methode een goede betrouwbaarheid heeft om de mate van Doppler flow te evalueren in deze patiëntengroep. Wanneer deze methode vergeleken wordt met de gemodificeerde Öhberg score die tot op heden meestal gebruikt werd, is deze methode minstens zo betrouwbaar en beter in staat te differentiëren bij aanwezigheid van hoge waardes van Doppler flow. Wij adviseren om de oppervlakte kwantificatie methode te gebruiken bij toekomstig wetenschappelijk onderzoek waarin de mate van Doppler flow bepaald moet worden bij patiënten met langdurige klachten van midportion achilles tendinopathie.

Behandeling

Effectiviteit van behandelingen voor patiënten met achilles tendinopathie wordt in de meeste gevallen beoordeeld middels de gevalideerde en ziekte-specifieke Victorian Institute of Sports Assessment-Achilles (VISA-A) vragenlijst. Deze VISA-A vragenlijst evalueert pijnklachten van de achillespees, functie van de achillespees en activiteitenniveau. Hieruit volgt een score, waarbij een score van 100 een volledig gezonde sporter reflecteert met een afname van de score bij toenemende klachten. Er was echter veel onzekerheid welke verandering in VISA-A score klinisch relevant is voor patiënten en bij welke VISA-A score patiënten hun symptomen acceptabel vinden. In **hoofdstuk 4** hebben we het minimaal klinisch relevant verschil en het

niveau waarop patiënten hun symptomen acceptabel vinden bepaald bij patiënten met langdurige klachten van midportion achilles tendinopathie. Dit onderzoek was onderdeel van een gerandomiseerde klinische studie waarin de effectiviteit van een hoog-volume injectie is beoordeeld. We hebben aangetoond dat een verandering in VISA-A score van 14 punten klinisch relevant is na 12 weken conservatieve behandeling. Klachten zijn acceptabel voor patiënten vanaf een VISA-A score van 60 punten. Dit is belangrijke informatie voor het opzetten van toekomstig onderzoek bij patiënten met achilles tendinopathie.

In **hoofdstuk 5** is een grote internationale studie beschreven waarin de effectiviteit van alle behandelopties voor achilles tendinopathie vergeleken zijn. Dit is gedaan middels een systematisch literatuuronderzoek en een zogenaamde netwerk meta-analyse. In dit onderzoek zijn 29 gerandomiseerde klinische studies geïncludeerd, waarin in totaal 42 verschillende behandelopties onderzocht zijn. Geen van de studies had een laag risico op bias (vooringenomenheid), de meeste studies volgden patiënten voor een korte duur op (minder dan 6 maanden) en er was veel onzekerheid in de puntschattingen in de netwerk meta-analyse. Na 3 maanden leken actieve behandelopties effectiever te zijn dan een overwegend afwachtend beleid bij patiënten met midportion achilles tendinopathie. Er was geen sprake van een klinisch relevant verschil tussen de verschillende actieve behandelopties na respectievelijk 3 en 6 maanden behandeling. Wij adviseren zorgverleners daarom om te starten met oefentherapie van de kuitspieren als initiële behandeling, omdat dit gemakkelijk voor te schrijven is in de kliniek, breed beschikbaar is en veilig en goedkoop wordt geacht. Wetenschappelijk bewijs voor de effectiviteit van behandelopties voor insertie achilles tendinopathie is uiterst beperkt, waardoor er geen conclusies kunnen worden gedaan voor deze groep patiënten. Dit onderzoek zal regelmatig een update krijgen bij het verschijnen van nieuwe relevante literatuur, om daarmee te zorgen voor handvaten voor zorgverleners.

Nieuwe behandelopties worden regelmatig geïntroduceerd en toegepast, echter veelal ontbreekt wetenschappelijk bewijs voor het toepassen van deze behandelopties. In **hoofdstuk 6** zijn 91 patiënten willekeurig verdeeld in 4 groepen: (1) isometrische oefentherapie met de voet in plantairflexie ofwel strekken van de enkel, (2) isometrische oefentherapie met de voet in dorsiflexie ofwel naar boven buigen van de enkel, (3) isotonische oefentherapie en (4) rust. Het doel van dit onderzoek was of de verschillende vormen van spieractivatie een direct pijn reducerend effect hebben bij patiënten met langdurige klachten van een midportion achilles tendinopathie. In deze studie hebben wij aangetoond dat zowel isometrische alsook isotonische oefeningen niet zorgen voor een direct pijn reducerend effect in deze populatie. Daarop ontraden wij de uitvoering van isometrische oefeningen met het doel om pijnklachten direct te doen verminderen, bijv. voorafgaand aan een training.

Een andere veelbelovende nieuwe behandeloptie leek een hoog-volume injectie te zijn. Het doel van deze injectietechniek is het wegdrukken van de vaatnieuwvorming dat veelal gezien wordt bij patiënten met achilles tendinopathie. Het idee is dat de nieuwgevormde zenuwtakken die zich vormen naast de nieuwe bloedvaten een belangrijke rol spelen bij het langdurig aanwezig blijven van pijnklachten bij patiënten met achilles tendinopathie. In **hoofdstuk 7** is onderzocht of het toepassen van een hoog-volume injectie naast de standaard behandeling zorgt voor een verbetering van de klachten. De gedachte van een hoog-volume injectie is dus dat het vaatnieuwvorming en nieuwgevormde zenuwtakken rondom de achillespees wegdrukt. Het exacte mechanisme wat er rondom een hoog-volume kan worden waargenomen was echter nog niet eerder onderzocht. Dit kan gedaan worden door middels echografie te kijken naar zogenaamde Doppler flow, waarbij stromingen (bijv. van bloed) kunnen worden gevisualiseerd middels kleuren. Wij hebben een dubbelblinde, placebo-gecontroleerde gerandomiseerde klinische studie uitgevoerd, waarin 80 patiënten met langdurige klachten van midportion achilles tendinopathie geïncludeerd zijn. Alle patiënten voerden gedurende 24 weken opbouwende krachtoefeningen van de kuitspieren uit (standaard behandeling) en werden geloot om ofwel een hoog-volume injectie (50 ml) te ontvangen ofwel een placebo injectie (2 ml). Bij de placebo injectie werd verwacht dat dit niet zou zorgen voor het wegdrukken van de bloedvaten en daarmee geen toegevoegde waarde zou hebben. De injectievloeistof bestond uit een zoutoplossing en een pijnstiller voor beide injecties. In dit onderzoek hebben wij aangetoond dat een hoog-volume injectie geen toegevoegde waarde heeft naast de standaard behandeling bij patiënten met langdurige klachten van een midportion achilles tendinopathie. Op basis van deze resultaten raden wij het gebruik van de hoog-volume injectie af als behandeling voor patiënten met midportion achilles tendinopathie.

Vervolgens is de oppervlakte kwantificatie methode gebruikt om het mechanisme van de hoog-volume injectie verder te onderzoeken. In **hoofdstuk 8** zijn de echografische uitkomstmaten gepresenteerd van de gerandomiseerde klinische studie waarin de effectiviteit van een hoog-volume injectie bij patiënten met langdurige klachten van een midportion achilles tendinopathie is onderzocht. Wij hebben aangetoond dat Doppler flow niet afnam rondom de hoog-volume injectie en bij controle afspraken na 2-24 weken in vergelijking met de placebo behandeling. Er was sprake van een significante afname van de Doppler flow direct na de hoog-volume injectie, echter eenzelfde afname werd gezien in de placebo groep. Hierdoor wordt deze afname meest waarschijnlijk verklaard door inactiviteit en niet door de hoog-volume injectie zelf. Daarnaast was de hoeveelheid Doppler flow één uur na de injectie alweer terug op het niveau van voor de injectie. De bevindingen in deze studie maken een mechanisch effect van de hoog-volume injectie onwaarschijnlijk. Daarnaast hebben wij in deze studie aangetoond (1) dat de Doppler flow bij aanvang van de studie niet

de prognose van de patiënt-gerapporteerde uitkomstmaat beïnvloed en (2) dat de mate van verandering in Doppler flow het beloop van klachten niet beïnvloed.

In **hoofdstuk 9** worden de resultaten uit het proefschrift beschreven in relatie tot elkaar en de huidige wetenschappelijke literatuur. Er worden daarnaast aanbevelingen gedaan voor toekomstig onderzoek om de kennis over achilles tendinopathie verder te vergroten.

Dankwoord

Graag wil ik alle mensen bedanken die betrokken zijn geweest bij de totstandkoming van dit proefschrift. Ik heb van heel veel mensen ontzettend veel geleerd, steun gekregen, inspiratie gekregen en bovenal heb ik heel veel plezier gehad.

Allereerst wil **alle patiënten** bedanken die hebben deelgenomen aan de verschillende studies binnen het proefschrift. Jullie bereidheid voor het vooruitbrengen van de wetenschap is bewonderingswaardig en ik hoop dat dit ook positief heeft uitgepakt voor jullie peesklachten.

Robert-Jan, als copromotor hebben wij natuurlijk het meeste contact gehad over alles wat betreft de inhoud van dit proefschrift. Door jou is de term 'tendofiel' in het leven geroepen, want als promovendi kennen wij niemand die zo verzot is op pezen. Meestal kon je de laptop nog niet dicht klappen na het versturen van een e-mail of jouw reactie verscheen al in beeld en dat werkt erg motiverend. Bedankt ook voor alles waarin je mij betrokken hebt naast het promotietraject, van Excelsior tot de richtlijnontwikkeling van achilles tendinopathie.

Geachte promotor, **Prof. dr. Verhaar**, bedankt dat u het vertrouwen in mij hebt getoond om te promoveren bij de vakgroep Orthopedie. Bedankt ook uw oprechte interesse in mijn onderzoeken en voor alle wijze adviezen. Ook voor u zullen er nieuwe stappen aankomen de komende jaren en ik wens u daar alle geluk mee.

Geachte **Prof. Dr. Ribbers, Prof. Dr. Bindels en Prof. Dr. Zwerver**, bedankt dat jullie zitting wilden nemen in de kleine leescommissie. Ik hoop in de toekomst dat we regelmatig mogen discussiëren over achilles tendinopathie en de raakvlakken met jullie vakgebieden.

Het team van de afdeling Sportgeneeskunde in het Haaglanden MC. **Robert en Peter**, bedankt voor alle hulp en moeite die jullie in het onderzoek hebben gestoken en de fijne samenwerking. Ik heb ontzettend veel van jullie geleerd en ik hoop in de toekomst weer met jullie samen te mogen werken. **Belle en Linda** bedankt voor de eerste stappen binnen het wetenschappelijk onderzoek en de nuchtere blik op alles. **Christiaan**, aan enthousiasme geen gebrek en dat was fantastisch om mee samen te werken. **Cora, Willemien en Monique** bedankt voor de gezelligheid en dat jullie zonder probleem alle afspraken regelden binnen de studie.

Max, Eline en Erwin, jullie zijn de stabiele factoren van de klinische onderzoeksgroep van de Orthopedie. Het is ontzettend fijn om mensen om je heen hebben je alles van het reilen en zeilen van het doen van onderzoek afweten. Ik hoop dat het enthousiasme er altijd zal blijven en wat mij betreft volgt er in de toekomst nog een fietstocht, inclusief een koffiestop voor Max.

Annika, Lichelle, Pim, Iris, Michiel, Abi en Ellen, de kamergenoten van Nc-424.

Allemaal heel erg bedankt voor de gezellige tijd en ik ga onze koffiepauzes stipt om 10.00 en 15.00 erg missen. Heel veel succes met de trials en ik ben er graag bij als jullie in de toekomst jullie mooie proefschriften zullen gaan verdedigen. Ik wil ook graag **Susanne, Mark en Joost** bedanken die als oude garde mij hebben opgevangen in Hs-104.

Simone en Annet, ik waardeer het ontzettend dat jullie altijd klaar staan om ons (de promovendi) met allerlei uiteenlopende vragen te helpen of gewoon gezellig te praten. Het is fijn om te weten dat als je iets niet weet, je dit altijd nog aan één van jullie kan vragen.

Stephan en Iris, als mede 'tendofielen' is het altijd fijn om te sparren over alle frustrerende zaken die soms om de hoek kwamen kijken of juist om mooie publicaties/ prestaties te vieren. Ik hoop dat er nog mooie congressen voor ons zullen volgen om deze prestaties ook in de toekomst te blijven vieren!

Marinus, Adam en Clare, jullie enthousiasme voor de wetenschap is geweldig en dat wekt ontzettend veel motivatie op. Bedankt daarnaast voor de lessen in het kort en bondig schrijven; ik wist niet dat je halve manuscripten kon schrappen. Beste **Sita, Edwin, Nicky en Debbie,** bedankt voor al jullie hulp en expertise bij het tot stand komen van de verschillende manuscripten in dit proefschrift.

Jasper en Claire, tijdens het promotietraject heb ik jullie mogen begeleiden voor jullie wetenschapsstage. Jullie hebben dit fantastisch opgepakt en heeft geleid tot mooie publicaties. Heel veel succes met de volgende stappen van jullie carrière!

John, Patrick, Robert-Jan en Kevin, bedankt dat jullie mij betrokken hebben bij de jeugdafdeling van Excelsior. Jullie hebben een mooie structuur neergezet binnen de medische tak waar je makkelijk en met veel plezier in kan stromen. Jullie werken allemaal ontzettend hard en ik hoop dat dat snel weer leidt tot terugkeer naar de Eredivisie.

Steven, John, Theo, Eric, Jelmer, Amber, Patrick, Kim, Ankie, Edwin, Janny en alle andere vrijwilligers van Like2run, bedankt allemaal voor de mogelijkheid om klinisch actief te kunnen blijven tijdens mijn promotie traject. Ik heb elk evenement veel geleerd, maar bovenal ontzettend veel plezier gehad. Ik hoop nog lang mijn steentje bij te mogen dragen aan deze fantastische groep vrijwilligers.

Chris, in 2019 was je al de getuige op mijn bruiloft en ik vind het fantastisch dat je nu ook als paranimf bijstaat. Want als iemand je rustig kan houden op momenten dat het nodig is, dan ben jij het wel! **Pim**, je kwam nadat ik begonnen was met promoveren, was alweer weg toen ik nog bezig was en staat desondanks gewoon ook in 2021 met je proefschrift in je handen. Zo'n dr. gun je iedereen wel aan zijn zijde als paranimf en ik ben blij dat jij dat bij mij zal zijn.

Natuurlijk wil ik ook mijn familie bedanken. **Pap en mam**, heel erg bedankt voor alle steun die jullie mij altijd gegeven hebben. Jullie hebben ervoor gezorgd dat ik altijd zorgeloos door het leven heb kunnen gaan. Mijn zussen en zwagers, **Lianne, Cyril**, **Marco en Wessel,** jullie zijn geweldig. Jullie werken allemaal ontzettend hard om al jullie doelen te bereiken en ik hoop dat die allemaal zullen uitkomen. **Opa en oma**, jullie genieten nog elke dag met elkaar en dat maakt jullie een voorbeeld voor iedereen. Al bijna 60 jaar getrouwd en ik hoop dat er nog vele mooie jaren mogen volgen! Mijn schoonfamilie, **Ilsa, Marcel en Jonel,** bedankt dat jullie Milea en mij altijd zo hebben gesteund en interesse hebben getoond in onze werkzaamheden.

Lieve Milea, elke dag ben ik weer blij om met jou te zijn! Promoveren noemen ze ook wel eens een mentale marathon en wij besloten die dan maar samen te voltooien. Ik had me geen fijnere supporter kunnen wensen, want ik denk dat werkelijk alle lichtpuntjes gevierd zijn. Samen zullen we nog heel veel uitdagingen aangaan, maar ik weet zeker dat we er ons moeiteloos doorheen zullen slaan.

Curriculum vitae

Aart Cornelis (Arco) van der Vlist werd geboren op 8 april 1992 te Schoonhoven. Tussen 2005 en 2008 doorliep hij het Gymnasium aan het Coornhert te Gouda, om vervolgens dichter bij huis het VWO af te ronden aan het Schoonhovens College te Schoonhoven. Hierna startte hij aan de studie Geneeskunde aan de Universiteit van Rotterdam, waar hij in 2013 zijn Bachelor diploma behaalde. In het kader van Master Geneeskunde werd er gedurende 12 maanden bij afdeling Sportgeneeskunde van het Haaglanden MC te Leidschendam gewerkt aan een afstudeeronderzoek en het oudste coschap Sportgeneeskunde. In september 2016 werd de master Geneeskunde behaald.

In september 2016 werd hij door dr. Robert-Jan de Vos, drs. Peter van Veldhoven en prof. Dr. Jan Verhaar aangesteld als promovendus bij de afdeling Orthopedie en Sportgeneeskunde van het Erasmus MC. Dit promotietraject bestond primair uit de uitvoering van een gerandomiseerde studie waarin de effectiviteit van een hoog-volume injectie als behandeling voor patiënten met een langdurige achillespees blessure werd onderzocht. De studie is praktisch uitgevoerd bij de afdeling Sportgeneeskunde van het Haaglanden MC, waardoor een intensieve samenwerking op wetenschappelijk gebied tussen het Erasmus MC en het Haaglanden MC is blijven bestaan. Samen met voorzitter dr. Robert-Jan de Vos heeft hij als deelnemer en coördinator opgetreden in de werkgroep voor de multidisciplinaire richtlijn Achilles tendinopathie.

Arco van der Vlist is sinds 2013 samen met Milea Janne Mea Timbergen, waarmee hij sinds 2015 samenwoont in Rotterdam. Zij zijn in oktober 2019 getrouwd. Momenteel is hij werkzaam als arts-assistent spoedeisende hulp In het Albert Schweitzer ziekenhuis te Dordrecht. Aansluitend zal gesolliciteerd worden voor de opleiding Huisartsgeneeskunde.

PhD portfolio summary

Summary of PhD training and teaching

Personal details	
Name	Arco C van der Vlist
Department	Dept. Of Orthopedic Surgery and Sports Medicine
PhD period	2016 - 2021
Promotor	Prof. J.A.N. Verhaar
Supervisor	Dr. R.J. de Vos

Courses: General	Year	ECTS*
Endnote (Medical Library, Erasmus MC)	2016	0.25
Systematic Literature search strategies I, II, and III (Medical Library, Erasmus MC)	2016	0.75
Basiscursus Regelgeving en Organisatie van Klinische Trials (Examenbureau Medisch-Wetenschappelijk Onderzoeker, Amersfoort)	2016	1.5
Biomedical English writing (Medical Library, Erasmus MC)	2017	1.5
Research integrity (Erasmus MC)	2018	0.3
Evidence based richtlijnontwikkeling (Kennisinstituut, Utrecht)	2018	0.5

Courses: Statistics (NIHES, Erasmus MC)	Year	ECTS*
Topics in Meta-analysis	2018	0.7
CCO2 Biostatistical Methods I: Basic Principles	2018	5

Courses: Teaching skills	Year	ECTS*
Course 'Coaching Medical Students' (Erasmus MC)	2017	0.2
Course 'Individuele begeleiding' (Erasmus MC)	2017	0.2
Course 'Teach the teacher I' (Erasmus MC)		0.6

(Inter)national podium presentations	Year	ECTS*
The effectiveness of a high-volume injection as treatment for patients with chronic midportion Achilles tendinopathy: A Randomised Clinical Trial *Haaglanden MC science day, The Hague, The Netherlands*	2016	1
The effectiveness of a high-volume injection as treatment for patients with chronic midportion Achilles tendinopathy: A Randomised Clinical Trial *Erasmus MC science day, Rotterdam, The Netherlands*	2017	1
Risk factors for Achilles tendinopathy: A systematic review *Nederlandse Vereniging voor Sportgeneeskunde (NVS) Annual meeting, Ermelo, The Netherlands*	2017	1
Is a surface area quantification method more reliable to determine neovascularization in Achilles tendinopathy? *Nederlandse Vereniging voor Sportgeneeskunde (NVS) Annual meeting, Ermelo, The Netherlands*	2017	1
Neovascularization in patients with Achilles tendinopathy: Is surface area quantification a reliable method? *International Scientific Tendinopathy Symposium, Groningen, The Netherlands*	2018	1
Do isometric exercises provides an immediate analgesic effect in patient with midportion Achilles tendinopathy? *Nederlandse Vereniging voor Sportgeneeskunde (NVS) Annual meeting, Ermelo, The Netherlands*	2018	1
The influence of neuropathic pain on the effectiveness of conservative treatment in patients with chronic midportion Achilles tendinopathy *Nederlandse Vereniging voor Sportgeneeskunde (NVS) Annual meeting, Ermelo, The Netherlands*	2018	1
High-volume injections in Achilles tendinopathy: An overview *Nederlandse Vereniging voor Sportgeneeskunde (NVS) Annual meeting, Ermelo, The Netherlands* Award for best oral presentation	2019	1
Is a high-volume injection effective as treatment for patients with chronic midportion Achilles tendinopathy? A Randomised Clinical Trial *Haaglanden MC science day, The Hague, The Netherlands* Incentive award for best oral presentation	2019	1
Isometric exercises do not provide immediate pain relief in Achilles tendinopathy: A quasi-randomised clinical trial *Scandinavian Sports Medicine Congress, Copenhagen, Denmark*	2020	1

Is a high-volume injection effective as treatment for patients with chronic midportion Achilles tendinopathy? A Randomised Clinical Trial *Scandinavian Sports Medicine Congress, Copenhagen, Denmark*	2020	1

Teaching activities and student supervision	**Year**	**ECTS***
Supervising medical bachelor students – Risk factors in Achilles tendinopathy: A systematic review	2016-2017	1
Supervising master-student Jasper Veen - Ultrasound Doppler flow in patients with chronic midportion Achilles tendinopathy: Is surface area quantification a reliable method?	2017	3
Teaching assistant 'microscopic bone pathology' for first year medical students (annually)	2017-2018	0.5
Teaching 'study design' and 'writing tips' for minor students (annually)	2017-2018	0.5
Teaching minor students 'the role of ultrasonography in tendinopathy' and 'musculoskeletal disorders' (annually)	2017-2018	1
Coaching medical bachelor students (7 students)	2017-2019	3
Supervising master-student Claire van Oosten - Do high-volume injections affect the ultrasonographic neovascularisation in chronic Achilles tendinopathy? A randomised placebo-controlled clinical trial	2019	3
Supervising resident Sports Medicine Christiaan Schwellengrebel - Do runners with Achilles tendinopathy have different physical test results compared to asymptomatic runners?	2020	3
Total workload in ECTS*		**37.5**

Awards	**Year**
Award for best oral presentation *High-volume injections in Achilles tendinopathy: An overview* *Nederlandse Vereniging voor Sportgeneeskunde (NVS) Annual meeting, Ermelo, The Netherlands*	2019
Incentive award for best oral presentation *Is a high-volume injection effective as treatment for patients with chronic midportion Achilles tendinopathy? A Randomised Clinical Trial* *Haaglanden MC science day, The Hague, The Netherlands*	2019

Organizing activities	Year
Co-organizing Sportrefereeravond Dept. of Orthopedic Surgery and Sports Medicine, Erasmus MC (annually)	2017-2018
Co-organizing Academic Centre of Excellence (ACE) meetings ACE Bone and Joint in Motion, Erasmus MC (monthly)	2017-2019
Co-organizing Science day Dept. of Orthopedic Surgery and Sports Medicine, Erasmus MC	2019
Co-organizing Tour de Rotterdam (first aid in cycling) Rotterdam, The Netherlands	2019 - Now

Other scientific activities	Year
Member and coordinator in the working group for the development of the guideline Achilles tendinopathy (Federatie Medisch Specialisten, Utrecht)	2018 - Now
Reviewer for British Journal of Sports Medicine	2018 - Now
Reviewer for Sport en Geneeskunde	2019 - Now
Reviewer for Journal of Ultrasound in Medicine	2019 - Now
Journal of Sport and Health Science	2020 - Now

* ECTS (European Credit Transfer and Accumulation System) credits: a standardized measure for workload in higher education across the European Union. One ECTS comprises 28 hours.

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Eur Radiol. 2020 Jun; s00330-020-06952-0. Online ahead of print.

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BMJ. 2020 Sep;370:m3027

De Vos RJ, **van der Vlist AC,** Winters M, van der Giesen F, Weir A.

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Minimal clinically important difference of the validated patient-reported VISA-A questionnaire for Achilles tendinopathy
Submitted for publication

Lagas IF, **van der Vlist AC,** van Oosterom RF, van Veldhoven PLJ, Waarsing JH, Bierma-Zeinstra SMA, Verhaar JAN, de Vos RJ.

Are pain coping strategies and neuropathic pain associated with a worse outcome after conservative treatment for Achilles tendinopathy? A prospective cohort study
Submitted for publication

van Oosten CCM, **van der Vlist AC**, van Veldhoven PLJ, van Oosterom RF, Verhaar JAN, de Vos RJ
Do high-volume injections affect the ultrasonographic neovascularisation in chronic Achilles tendinopathy? A randomised placebo-controlled clinical trial
Submitted for publication

Sleeswijk Visser TSO, **van der Vlist AC,** van Oosterom RF, van Veldhoven PLJ, Verhaar JAN, de Vos RJ.

Impact of chronic Achilles tendinopathy on health-related quality of life, work performance, healthcare utilization, and costs
Submitted for publication

Swellengrebel HJC, **van der Vlist AC,** van Veldhoven PLJ, van Oosterom RF, de Vos RJ.

Do runners with Achilles tendinopathy have different physical test results compared to asymptomatic runners?
Submitted for publication