Ministry of Defence

Improving clinical evaluation and decision-making in military personnel with mid-portion Achilles tendinopathy

Focusing on Ultrasound Tissue Characterization

Marc A. Paantjens

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Colophon

Improving clinical evaluation and decision-making in military personnel with mid-portion Achilles tendinopathy. *Focusing on Ultrasound Tissue Characterization*
Utrecht University, Utrecht, The Netherlands

ISBN 978-90-393-7636-2
DOI https://doi.org/10.33540/2161

I thankfully acknowledge the support for this thesis from the Ministry Of Defence.

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Verbeteren van klinische evaluatie en besluitvorming bij militairen met mid-portion Achilles tendinopathie
Focus op Ultrasound Tissue Characterization
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof. dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

dinsdag 2 april 2024 des ochtends te 10.15 uur

door

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geboren op 16 augustus 1976
te Sittard

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Beoordelingscommissie:
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Dit proefschrift werd (mede) mogelijk gemaakt met financiële steun van het Ministerie van Defensie.

Contents

Chapter 1.

General introduction

History

The Achilles tendon is named after Achilles, a famous hero of the Trojan war in Greek mythology. In order to make him physically invulnerable, his mother had dipped him in the River Styx when he was a baby. As she held him by one heel, this became his only point of weakness ('Achilles heel') that eventually killed him.

Achilles tendon disorders are common in physically active populations, such as athletes and military service members, and can have a profound impact on physical performance and military operational readiness.[1-3]

Anatomy

The Achilles tendon (Figure 1) is the strongest and thickest tendon in the human body.[4, 5] It is a conjoined tendon with contributions from soleus and gastrocnemius muscles, which act as main plantar flexors of the ankle joint.[4, 6] Mid-calf, the tendon is formed from the gastrocnemius muscle, and more distally the soleus muscle fibers insert into the anterior part of the Achilles tendon.[4, 6]

The Achilles tendon fibers are not strictly vertically oriented, as from proximal to distal, the subtendons of soleus, medial gastrocnemius and lateral gastrocnemius muscles intertwine and rotate internally before eventually attaching to the calcaneal bone. The Achilles tendon is surrounded by the paratenon, which is a peritendinous sheath that reduces friction during tendon motion.[4]
Healthy tendons have almost ideal mechanical properties for the transmission of force from muscles to bone, as they are stiff, resilient and with high tensile strength.[4] In case of the Achilles tendon, forces up to 12.5 times body weight have been reported during running.[4]

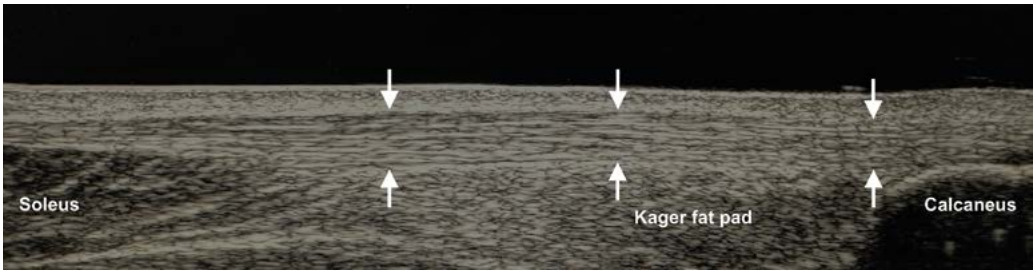

Figure 1. *Long-axis ultrasound image of a non-symptomatic Achilles tendon (left side: proximal; right side: distal). From the left, the distal soleus muscle fibers insert into the anterior aspect of the Achilles tendon, which is indicated by the white arrows. Distally, the Achilles tendon attaches to the calcaneal bone. Notice the echogenic and fibrillar echo pattern of the Achilles tendon, which is characteristic for healthy tendon tissue.*

Pathology

Achilles tendinopathy (AT) is defined as persistent Achilles tendon pain with loss of function related to mechanical loading.[7]
AT indicates an non-rupture injury of the Achilles tendon[8] that is generally attributed to ageing and overuse.[9,10] While recent studies have suggested a potential role of various pathophysiological mechanisms (e.g., plantaris tendon involvement,[11] neurogenic inflammation,[12] free Achilles tendon length[6, 13]), the exact pathophysiology and source of nociception remain unknown.[6, 10-12, 14-19]

Histologically, AT is associated with degenerative tendon changes that may progress as a result of tendon loading,[9, 10, 20] in rare occasions ultimately leading to a tendon rupture.[9] However, degenerative tendon pathology can also exist in the absence of symptoms.[18,21]

Two types of AT can be distinguished:[17]
1. mid-portion Achilles tendinopathy (mid-AT), with symptoms 2 to 7 cm proximal to the calcaneal insertion;
2. insertional Achilles tendinopathy (ins-AT), with symptoms located within the first 2 cm proximal to the calcaneal insertion.

Mid-AT and ins-AT are considered distinct clinical entities in the literature,[22] with an apparently different response to conservative treatment.[23, 24] Ins-AT may be accompanied by metabolic diseases,[25] and often includes pathology in adjacent bursae and bone,[17, 26] while mid-AT is regarded an isolated tendinopathy.[17]

Epidemiology

In the general population, AT has been reported to occur in a wide age range of 20-69 years, but is most common between 40 and 59 years.[9] Although sedentary as well as active individuals may be affected,[27-29] most cases are related to various sports,[27-29] of which runners seem to be the most frequently affected cohort.[27, 29] About one in 20 recreational runners can be expected to develop symptoms,[30] while the life-time prevalence in former top-level endurance runners ranges up to 52%.[28]

Following inception of treatment, pain and function in AT may already improve after 2 weeks, with results peaking at 12 weeks.[31] However, a significant number of patients experience long term symptoms,[17, 24, 32-34] and improvement of symptom severity beyond 1 year has shown to be limited[34] or even absent.[32, 33] A recent prospective cohort study concluded that one-fifth of patients still reported symptoms after 10 years of follow-up.[32] In this study, only one-third of all patients returned to their preferred sports activities at pre-injury level and without pain. Half of all patients were forced to adjust their sports activities.[32]

Clinical diagnosis of mid-AT and ins-AT

A diagnosis of mid-AT can be made upon the presence of all following clinical findings:[17]
1. symptoms localized 2 to 7 cm proximal to the calcaneal insertion;
2. painful Achilles tendon mid-portion upon (sports) loading;
3. local thickening of the Achilles tendon mid-portion, which may be absent in cases with short symptom duration;
4. pain on local palpation of the tendon mid-portion.

A diagnosis of ins-AT is made upon the presence of all following clinical findings:[17]
1. symptoms localized to the Achilles tendon insertional region (within 2 cm of the insertion of the Achilles tendon);
2. painful Achilles tendon insertional region upon (sports) loading;
3. local thickening of the Achilles tendon insertion (this may be absent in cases with short symptom duration);
4. pain on local palpation of the tendon insertion.

Outcome measures

Clinical guidelines recommend the Victorian Institute of Sport Assessment – Achilles (VISA-A) questionnaire as the primary patient-reported outcome measure for evaluation of the clinical course of AT.[17, 29] VISA-A is a validated, disease-specific questionnaire that assesses pain, function in daily living, and sporting activity.[35] Scores on VISA-A can range from 0 to 100, where 100 equals a perfect asymptomatic score.[35]
In the general population, the minimal important change (MIC) for VISA-A was recently estimated at 14 points after 12 weeks and 7 points after 24 weeks, post-baseline.[36] Additionally, the patient-acceptable symptom state (PASS) for VISA-A was estimated at 50 points (12 weeks) and 60 points (24 weeks), respectively.[36]

As secondary outcome measures, patient satisfaction and return to sports can be considered, but no predefined clinically important cut-off points have been established for these outcome measures.[17]

Although most research focuses on pain and physical impairments, several recent studies have indicated that psychosocial factors play a role in chronic AT.[19, 37, 38] Slagers et al.[37] suggested that clinicians should pay particular attention to individuals with lack of psychological readiness to return to sports, as well as patients with kinesiophobia or catastrophizing thoughts when experiencing pain.

The role of imaging in AT

Conventional ultrasonography and MRI are imaging modalities that can be used to support the diagnostic process in AT.[17, 29] Ultrasonography is the preferred modality,[17] as it is accurate, relatively cheap, easily accessible and patient-friendly.[17, 39] Clinical guidelines recommend imaging in suspected tendinopathy patients when history and physical examination do not provide a clear diagnosis.[17, 29] In these cases, imaging can be used to rule out alternative or coexisting pathology, such as a partial rupture, paratendonitis, or bursitis.[17, 29] Imaging may also be indicated in case of an unexpected course of symptoms or during a pre-operative work-up.[17, 29]

When using conventional ultrasonography in addition to clinical diagnosis, the following ultrasound parameters should be reported: increased anterior-posterior thickness of the Achilles tendon; altered tendon structure (altered echogenicity); and the presence of peritendinous or intratendinous vascularization.[17, 40]

Besides contributing to diagnosis, conventional ultrasonography is commonly used to evaluate Achilles tendon structure in response to treatment or tendon loading.[40-44] For the assessment of tendon structure, ultrasonography has several disadvantages, as it is limited in quantifying intra-tendinous structure, relies largely on the subjective interpretation of ultrasound images, and is operator dependent.[42, 45]

Ultrasound tissue characterization (UTC) is a specialized imaging modality that bypasses the disadvantages of conventional ultrasonography.[45] First, UTC is able to visualize three-dimensional Achilles tendon structure, therefore providing a better overview of tendon structure than conventional, two-dimensional ultrasonography. Second, UTC does not rely on the subjective interpretation of images, as it quantifies the Achilles tendon matrix integrity into four echo-types percentages discriminating aligned fibrillar structure (echo-types I + II) from disorganized tendon structure (echo-types III + IV). Third, compared to conventional ultrasonography UTC has limited operator dependency due to an automated scanning procedure.

Despite the fact that the majority of trials use imaging as a part of the diagnostic process for mid-AT,[17] it should be emphasized that imaging in tendinopathy is heavily debated.[7, 41, 46] This discussion mostly relates to the diagnostic value of imaging over clinical assessment, the costs of imaging, and the unclear relationship between imaging outcomes and symptoms.[7, 41, 46]

Treatment of AT

Clinical guidelines recommend active treatment, patient education, and loading advice as first line of treatment.[17, 29] A wait-and-see policy is no longer recommended for chronic AT, as all active treatments seem superior.[47] With regard to tendon loading, patients may be advised to:

temporarily cease pain provoking (sports) activities or replace them by non-provocative (sports) activities; increase the load of (sports) activities gradually; and use a pain scale to monitor the level of complaints related to (sports) activities, and adjust these activities based on the pain scale.[17] Progressive calf-muscle exercises should be performed for at least 12 weeks.[17] Eccentric exercises have long been regarded a superior exercise intervention, but recent systematic reviews have indicated that various tendon loading programs appear equally effective, regardless of contraction type.[47, 48] In case of insufficient effectiveness, additional extracorporeal shockwave therapy (ESWT) is recommended as a possible secondary treatment for refractory Achilles tendinopathies.[17]

Aims of the thesis

The military population is a unique population. Despite an increase in female military personnel in the last decade, the military is still a male-dominant organization, typically characterized by a culture of toughness and strict fitness requirements.[49] Military training and combat operations are physically demanding, regularly exposing military personnel to high- and low-volume physical activities in different environments (e.g., heat, cold, altitude) and under different circumstances (e.g., sleep deprivation, negative energy balance, psychological stress). These conditions place great strain on, amongst other things, the warfighter's musculoskeletal system. Musculoskeletal injuries are among the main causes of dropout from military training,[50] and are considered a significant cause of medical care in the military.[51]

AT is a musculoskeletal injury that can have a significant impact on physical activity levels and military operational readiness.[1, 2] Although incidence/prevalence rates of AT in military populations are largely unknown, it is a common and physically disabling overuse injury in service members.[1, 2] As mid-AT occurs more frequently than ins-AT, it is the primary focus of this thesis.[52]

The majority of patients consulting the department of Military Sports Medicine of the Royal Netherlands Army have shown low responsiveness to exercise interventions in primary care. Primary reasons for referral are: (1) finding an explanation for persisting symptoms, and/or (2) a request for additional ESWT.

According to the Dutch multidisciplinary guideline, at the department of Military Sports Medicine of the Royal Netherlands Army, AT treatment is guided by an individualized and gradual build-up of tendon loading activities over time, using a pain scale to adjust these activities.[17] Tendon degeneration is associated with AT, and can progress as a result of load.[10] More objective measuring instruments to guide treatment and determine prognosis may enhance the management of AT. Therefore, in physically highly active populations, such as military personnel, clinical evaluation using VISA-A combined with UTC as a specialized modality for monitoring of tendon structure may be warranted, to prevent progression of degeneration or even rupture of the Achilles tendon.[9]

UTC has previously shown to have excellent reliability,[45] while appearing to be negligibly associated with VISA-A.[43, 53] Although the collection of UTC scans is an automated procedure, the processing of these scans is performed manually, during which operators have to select an anatomical region of interest for quantification of tendon structure. Currently, there is a lot of variation across studies in selecting an anatomical region of interest in patients with mid-AT, ranging from 4 mm as measured at the thickest part of the tendon mid-portion, to analyzing the entire free Achilles tendon, including the insertional part.[45, 54]

As tendon architecture in mid-AT is known to be heterogeneous,[40, 45] selecting different anatomical regions of interest is most likely a source of quantitative variation, possibly contributing to different study outcomes when evaluating patients with UTC.
Uniformity in clinical terminology has been reported to facilitate the communication between clinicians and researchers.[20] Therefore, when using UTC, we have chosen to quantify mid-portion tendon structure according to the generally accepted clinical definition of mid-AT based on symptom location, which is 2 to 7 cm proximal to the calcaneal insertion.[17] Whether this method of analysis is reliable and valid for determining symptoms in a population of military service members is currently unknown.

We conducted two reliability studies. First, the inter-rater reliability of conventional ultrasonography for the assessment of mid-portion Achilles tendon structure was studied in a population of asymptomatic military personnel (**Chapter 2**). This study gains insight into asymptomatic tendon structure in our population, putting the ultrasonographic evaluation of military patients with mid-AT into perspective. Second, the intra-rater and inter-rater reliability of our protocol for processing UTC scans in military service members with mid-AT were investigated (**Chapter 3**).

Then, we wanted to determine the clinical effectiveness of ESWT for AT. Several systematic reviews have been performed on ESWT so far, but no review has synthesized the available literature including only experimental studies. Therefore, we conducted a systematic review of randomized controlled trials aiming to assess the effectiveness of ESWT for mid-AT and ins-AT separately (**Chapter 4**).

In clinical practice, we frequently observe that military service members with mid-AT report relatively high VISA-A scores, while showing only limited tendon degeneration on UTC, and vice versa. In the general population, it has been demonstrated that Achilles tendon structure is negligibly associated with VISA-A scoring.[43, 53] We aimed to clarify the association between self-reported symptoms (VISA-A) and mid-portion tendon structure (UTC) in military service members with mid-AT (**Chapter 5**).

The ability of VISA-A for detecting true changes in health status is both context-specific and population-specific.[55, 56] Such detecting values are currently lacking in military personnel, hampering the interpretation of VISA-A change scores. Therefore, we estimated thresholds for MIC and PASS for return to pre-symptom activity level in military service members with mid-AT (**Chapter 6**).

In active individuals, mid-AT recurrences rates have been reported to be as high as 27%.[3] Despite successful conservative treatment for mid-AT, we regularly encounter recurrent episodes in military service members. Therefore, we conducted a prospective cohort study to determine the prognostic value of UTC for a recurrence of mid-AT, in military service members reporting to be recovered following conservative care (**Chapter 7**).

The findings of this thesis are reflected in the general discussion (**Chapter 8**).

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Chapter 2.

The interrater reliability of ultrasonography for Achilles tendon structure

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Abstract

Aim of the study: Reliable assessment of Achilles tendon structure (architecture and morphology) may help prevent clinical symptoms or progression of Achilles tendinopathy. The objective of this study was to determine the interrater reliability of musculoskeletal ultrasonography for the assessment of the mid-portion Achilles tendon: (1) structure, (2) anteroposterior diameter and (3) neovascularization,in asymptomatic military personnel.

Materials and Methods: Two sonographers acquired B-mode images of the Achilles tendon mid-portion in 74 volunteers (148 tendons) in short-axis plane and long-axis plane, to assess structure and measure the maximum anteroposterior diameter. Power Doppler Ultrasound was performed to assess neovascularization. Tendon structure and neovascularization were graded using a modified four-graded Öhberg-score.

Results: Weighted kappa for assessing tendon structure showed almost perfect agreement (0.87; 95% CI: 0.79, 0.95). Spearman's rho showed a: very high positive interobserver correlation for tendon structure (0.92; 95% CI: 0.89, 0.94), very high positive interobserver correlation for the diameter measurement in short-axis plane (0.91; 95% CI: 0.87, 0.93) and high positive interobserver correlation in long-axis plane (0.87; 95% CI: 0.83, 0.91). The Wilcoxon signed-rank test showed no significant differences between observers during diameter measurements (*p* value > 0.05). Both sonographers reported absent neovascularization in all subjects, resulting in overall Öhberg-score of 0.

Conclusions: (1) Interrater reliability of ultrasonography for grading mid-portion Achilles tendon structure shows almost perfect agreement and (2) ultrasonography is highly reliable in measuring the anteroposterior diameter. (3) In a large group of asymptomatic service members neovascularization of the Achilles tendon is consistently absent.

Keywords: Military personnel, tendons, sports medicine, musculoskeletal system.

Introduction

Achilles tendinopathy is a condition that is clinically characterized by pain, swelling and impaired function, typically related to sports or exercise overuse[1,2]. The average age at first presentation is 43 years[3]. However, in highly active subjects, tendinopathy can occur at younger age[4]. Achilles tendon disorders are common in military personnel. Individuals who are overweight, report moderate alcohol use and those with a prior diagnosis of tendinopathy are at higher risk for developing pathology[5].

Although Achilles tendinopathy incorporates elements of the inflammatory response, it is generally considered to represent a degenerative condition[6,7]. Degenerative tendon abnormalities are common in asymptomatic individuals above the age of 35 years[8]. In sporting populations, they have been identified in up to 59% of asymptomatic athletes[7].

Such tendon changes are predictive of future symptomatic tendinopathy, with at least a sevenfold increased risk[7].

Musculoskeletal ultrasonography (MSU) is currently able to detect early changes in tendon structure (architecture and morphology) due to its excellent spatial resolution[9]. MSU-assessment of the Achilles tendon can help in making a diagnosis or defining treatment strategy. It may also identify individuals at-risk for developing Achilles tendinopathy, and allow preventative programs to be implemented[7]. The department of sports medicine of the Royal Netherlands Army is exploring all options to predict and reduce dropout from military training based on injuries. Therefore, we sought to determine the interrater reliability of MSU for assessing the mid-portion Achilles tendon: (1) structure (2) anteroposterior diameter and (3) neovascularization, in a cohort of asymptomatic service members.

Materials and Methods

This cross-sectional study was approved by the ethics committee METC Brabant, Tilburg, the Netherlands (number of approval NW2018-72) and by the Joint Health Care Division of the Ministry of Defence. All participants provided written informed consent before participation. Sample size calculation was performed according to recently published guidelines[11]. Based on a default α of 0.05 and statistical power (1-β) of 0.80 a sample size of 74 subjects was calculated. In January and February 2019, asymptomatic service members were recruited from an infantry unit in the Royal Netherlands Army. Men and women in the age range of 18-58 years were eligible for inclusion. The exclusion criteria were: (1) an episode of Achilles tendinopathy within the last 12 months, (2) prior Achilles tendon surgery, (3) rheumatoid arthritis, diabetes mellitus, psoriasis or spondyloarthropathy, (4) recent or current (at the time of recruitment to the study) use of statins, fluoroquinolones or corticosteroids[12].

Grayscale MSU and Power Doppler Ultrasound (PDU) examinations were performed (Philips CX50, Philips, Eindhoven, the Netherlands) and measurements were obtained with a L12-3 MHz broadband linear array transducer. The machine settings for MSU and PDU were standardized. A week before performing the measurements in the study participants, both sonographers (two physical therapists, MSc in MSU, with at least 5 years of experience) defined and agreed standardized consistent settings and practiced on a volunteer. All studies were performed independently by the two sonographers, blinded to each other's measurements to prevent review bias.

Short-axis views followed by long-axis views of the mid-portions of the Achilles tendons were acquired according to the "Musculoskeletal Ultrasound Technical Guidelines VI. Ankle", published online by the European Society of Musculoskeletal Radiology (ESSR)[13].

To minimize observer bias, both tendon structure and neovascularization were graded using the modified four-graded Öhberg-score (tab. 1)[10].

All investigations started with grading tendon structure while subjects lay prone on the examination table with the ankle joints in 90° of flexion. The transducer was placed as perpendicular as possible, with a uniform layer of gel to minimize anisotropy artifact and to standardize the scanning technique. The maximum anteroposterior Achilles tendon diameter was measured in the Achilles tendon mid-portion, located 2-6 centimeters proximal to the superior border of the calcaneus. At first the thickest part of the tendon was determined by means of short-axis views. Subsequently, this part of the tendon was scanned longitudinally, and the diameter was measured in this plane. After the dimensional measures were completed, the participants were asked to relax the foot for assessment of neovascularization. Transducer pressure was as minimal as possible for this assessment. For calculating percentages of structural abnormalities, a tendon was considered structurally abnormal if one of the two sonographers graded the Öhberg-score as 1-3.

The statistical analysis was performed using MedCalc® statistics (version 18.11.3).
The Kolmogorov-Smirnov test was used to assess the normality of data[14]. Ordinal data (Öhberg-scores for tendon structure) and ratio data (anteroposterior Achilles tendon diameter) were not normally distributed. Therefore, non-parametric tests were chosen to assess the interrater reliability and differences between paired samples. The Spearman's rank correlation coefficient (Spearman`s rho: ρ) was used to calculate the correlation between raters in assessing Achilles tendon structure and measuring the anteroposterior tendon diameter[15]. Interrater reliability for evaluation of the Achilles tendon structure was calculated as weighted Kappa-coefficient (kw)[16]. The Wilcoxon signed-rank test was applied to evaluate quantitative differences between sonographers in measuring the tendon diameter. Bland-Altman plots were constructed to represent the interrater agreement[17].

Table 1. The modified four-graded Öhberg-score for Achilles tendon structure and neovascularization.[10]

	Öhberg-score for Achilles tendon structure	Öhberg-score for Neovascularization
0	Normal structure (homogeneous, echogenicity)	No neovascularization
1	Light structural changes (discrete hypoechogenic areas)	Mild neovascularization (a few solitary blood vessels)
2	Moderate structural changes (some well-defined hypoechogenic areas)	Moderate neovascularization (moderate quantity, mostly transversal blood vessels)
3	Severe structural changes (extended hypoechogenic areas)	Severe neovascularization (several, mostly horizontal blood vessels spread in the whole depth of the tendon)

Results

Seventy-four infantry soldiers (all men) were included in the study. Demographic data are presented in Table 2. In total 148 tendons (74 participants) were evaluated of which 28 tendons (18.9%) showed signs of degeneration, and were subsequently graded as abnormal (Öhberg-score 1 or more). In participants under the age of 35 years (47 participants, 94 tendons), 10 tendons (11%) were graded as abnormal. Most abnormalities were seen in asymptomatic service members of 35 years and older. In this age group (27 participants, 54 tendons), 18 Achilles tendons (33.3%) were considered abnormal. Bilateral Achilles abnormalities were present in 9 out of 74 participants (12%).

Both sonographers reported that none of the service members showed signs of Achilles tendon neovascularization on PDU, resulting in overall Öhberg-scores of 0. The distribution of the pattern of the Achilles tendon structure observed is presented in Table 3. Measurements of Achilles tendon anteroposterior diameter are shown in Table 4.

Weighted Kappa for assessing the Achilles tendon structure showed almost perfect agreement (kw 0.87; 95% CI: 0.79, 0.95). Spearman's rho showed a: (1) very high positive interobserver correlation for Achilles tendon structure (ρ 0.92; 95% CI: 0.89, 0.94), (2) very high positive interobserver correlation for the anteroposterior diameter measurement in short-axis plane (ρ 0.91; 95% CI: 0.87, 0.93) and (3) high positive correlation in long-axis plane (ρ 0.87; 95% CI: 0.83, 0.91). The Wilcoxon signed-rank test showed no significant differences (= *p*-value > 0.05) between the observers for both long-axis ($p = 0.073$) and short-axis ($p = 0.189$) measurements.

The Bland-Altman plot graphically visualizes the differences between observers 1 and 2 in measuring the short-axis Achilles tendon diameter (Fig. 1) and long-axis tendon diameter (Fig. 2). The paired differences are plotted against the mean difference for both observers. The mean difference between observers was -0.004 cm (95% CI: -0.009, 0.001) for measuring the short-axis tendon diameter and 0.003 cm (95% CI: -0.002, 0.008) for the long-axis tendon diameter.

Table 2. Demographics (n=74, 148 Achilles tendons).

	Mean*	Range
Age (years)	33 ± 11.7	18 - 59
Height (cm)	183 ± 6.2	164 - 199
Weight (kg)	85 ± 10.7	63 - 120
BMI	25.4 ± 2.3	21-31

Abbreviations: n, number of participants; cm, centimeter; kg, kilogram; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters).
* *Values are mean ± SD.*

Table 3. The distribution of the pattern of the Achilles tendon structure for two observers using the Öhberg-score (n=74, 148 Achilles tendons).

Öhberg-score	Observer 1		Observer 2	
	Tendons (n =)	*% of 148 tendons*	*Tendons (n =)*	*% of 148 tendons*
0	120	81.1	124	83.8
1	23	15.5	18	12.2
2	3	1.4	6	4.1
3	2	1.4	0	0.0
Total	**148**	**100**	**148**	**100**

Abbreviations: n, number of tendons.

Table 4. MSU-measurements of the Achilles tendon anteroposterior diameter (n=74, 148 Achilles tendons).

	Short-axis		Long-axis	
	*Thickness (mm) Mean**	*Range (mm) Min - Max*	*Thickness (mm) Mean**	*Range (mm) Min - Max*
Observer 1	5.0 (4.9, 5.2)	3.7 - 10.6	5.0 (4.8, 5.2)	3.5 - 11.4
Observer 2	5.1 (4.9, 5.2)	3.7 - 10.9	5.0 (4.8, 5.1)	3.2 - 11.1
Combined	**5.1 (4.9, 5.2)**	**3.7 - 10.9**	**5.0 (4.9, 5.1)**	**3.2 - 11.4**

Abbreviations: n, number of tendons; mm, millimter; min, minimum; max, maximum.
* *Values in parentheses are 95% confidence interval.*

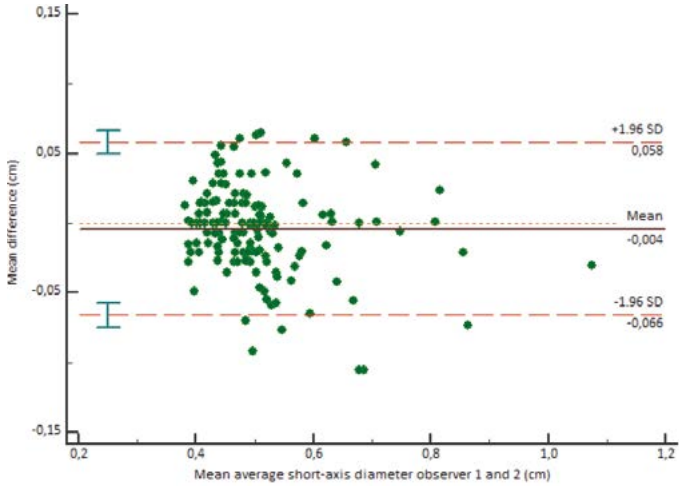

Figure 1. *The Bland-Altman plot graphically visualizes the differences between observers 1 and 2 in measuring the Achilles tendon short-axis diameter. The paired differences are plotted against the mean difference for both observers (solid horizontal black line). The two broken red lines represent the upper and lower 95% limit of agreement (LOA). The mean difference between observers was -0.004 cm (95% CI: -0.009, 0.001), the lower LOA was -0.066 cm (95% CI: -0.075, -0.057) and the upper LOA was 0.058 cm (95% CI: 0.049, 0.067).*
Abbreviations: SD, Standard deviation; LOA, limits of agreement; cm, centimeter; CI, confidence interval.

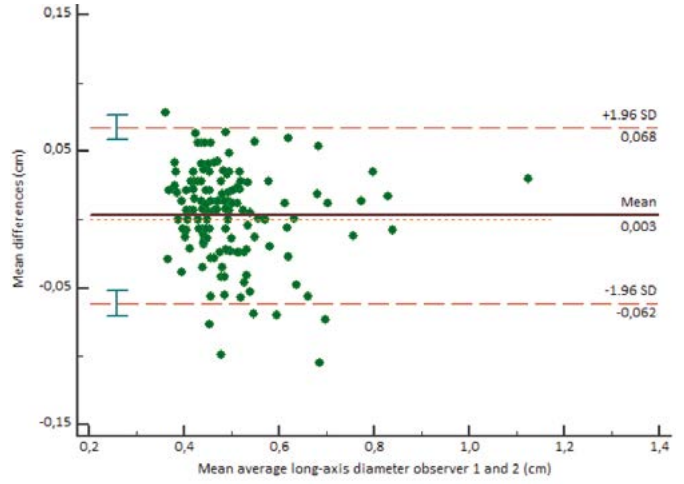

Figure 2. *The Bland-Altman plot graphically visualizes the differences between observers 1 and 2 in measuring the Achilles tendon long-axis diameter. The paired differences are plotted against the mean difference for both observers (solid horizontal black line). The two broken red lines represent the upper and lower 95% LOA.*
The mean difference between observers was 0.003 cm (95% CI: -0.002, 0.008), the lower LOA was -0.062 cm (95% CI: -0.07, -0.05) and the upper LOA was 0.068 cm (95% CI: 0.06, 0.08).
Abbreviations: SD, Standard deviation; LOA, limits of agreement; cm, centimeter; CI, confidence interval.

Discussion

Asymptomatic Achilles tendon abnormalities are predictive of future symptomatic tendinopathy[7]. MSU-assessment of tendon structure may help prevent clinical symptoms by identifying high-risk individuals, and allowing preventative interventions to be implemented[7]. Our results demonstrate that in asymptomatic service members, MSU shows almost perfect agreement and very high interobserver correlation in grading Achilles tendon structure using the Öhberg-score. These results differ from Sunding *et al*.[10], who reported a poor to moderate interobserver reliability and a weak to moderate interobserver correlation for grading Achilles tendon structure[10]. The different findings of these two studies may be attributed to different study populations. We evaluated a cohort of asymptomatic participants, while Sunding *et al*.[10] recruited symptomatic and asymptomatic individuals. A larger variation in tendon architecture among the symptomatic participants could have contributed to a lower interobserver agreement and interobserver correlation. Most Achilles tendons in our study were graded with Öhberg-scores 0 and 1 whilst Öhberg-scores 2 and 3 were found to be rare (Tab. 3).

Furthermore, in our study both sonographers were equally experienced, while Sunding *et al*.[10] used observers with different experience levels.

We also found a very high positive correlation for measuring Achilles tendon anteroposterior diameter in short-axis plane and a high positive correlation in long-axis plane. These findings are consistent with previous studies[10,18].

Almost 19% of all asymptomatic Achilles tendons examined in our study showed degenerative signs on MSU. In contrast, Nicol *et al*.[19] reported a much higher prevalence of degenerative Achilles tendon changes in asymptomatic service members of the British Armed Forces: 59% of all asymptomatic Achilles tendons exhibited ultrasonographic signs of degeneration. Different inclusion and exclusion criteria for service members to participate may explain the large difference in prevalence between both studies. In our study, individuals who experienced an episode of Achilles tendinopathy within the last 12 months were excluded, while in the British study, subjects with a recent episode of Achilles tendinopathy were included when free of symptoms for at least four weeks. Tendon degeneration on MSU appears to be more common in service members with a prior history of symptomatic Achilles tendinopathy[19], which most likely has contributed to a higher percentage of abnormal tendons in their study. Furthermore, Nicol *et al*.[19] did not mention excluding service members on the basis of various disorders or medication use that are known to cause tendon degeneration[12]. This can also account for a higher prevalence of abnormal Achilles tendons in their study.

Achilles tendinopathy is often associated with neovascularization, but its clinical significance is somewhat contested[20,21,22]. It is assumed that asymptomatic tendons show no signs of neovascularization on PDU, although some studies suggest the opposite[23,24]. In contrast, patients with symptomatic tendinopathy do not always exhibit signs of neovascularization on PDU[22]. In our current study, we did not observe neovascularization in any of the 148 asymptomatic Achilles tendons examined. From this we may conclude that this phenomenon is possibly limited to pathological tendons.

During the assessment of Achilles tendon diameter, we frequently observed that the thickest part of the Achilles tendon mid-portion was often the location where the plantaris tendon inserted on the Achilles tendon. The plantaris tendon is reported to be present in 92-94% of individuals[25]. In most cases it inserts into the medial border of the mid-portion Achilles tendon, while in 6-8% of individuals the tendon inserts into the flexor retinaculum[25]. In our study we observed subjects in which the plantaris tendon was not present or visible. We also evaluated subjects with visible plantaris tendons, in which it was sometimes difficult to distinguish the plantaris tendon from the tendon borders of the Achilles tendon. Therefore, when quantifying or comparing Achilles tendon diameter, sonographers should consider the locoregional anatomy including the presence or absence of the plantaris tendon.

This study has several limitations. First, the absolute size of the anteroposterior tendon measurements may be an overestimation, since the tendon borders of the plantaris tendon and Achilles tendon were not always discernable on MSU.

Second, our study results may be limited to the male gender because we weren't able to recruit any female volunteers. In the unit where we recruited participants, only 8 out of 440 service members were women. In de military, Owens *et al*.[5] found no evidence for gender as a risk factor for mid-portion Achilles tendinopathy, however, there's conflicting evidence regarding its significance in the general population.

Our high reliability scores may not be applicable for the assessment of moderate or severe Achilles tendon changes, as these changes were rare in our study population (tab. 3). Discriminating normal tendons (Fig. 3 and 4) from abnormal tendons may be easier than judging whether a specific Achilles tendon shows moderate or severe signs of degeneration (Fig. 5 and 6). Most tendon abnormalities occurred in service members of 35 years and older, as previously reported in the literature[8]. Increasing the minimum age for inclusion to 35 years could result in finding more moderate or severe Achilles tendon abnormalities.

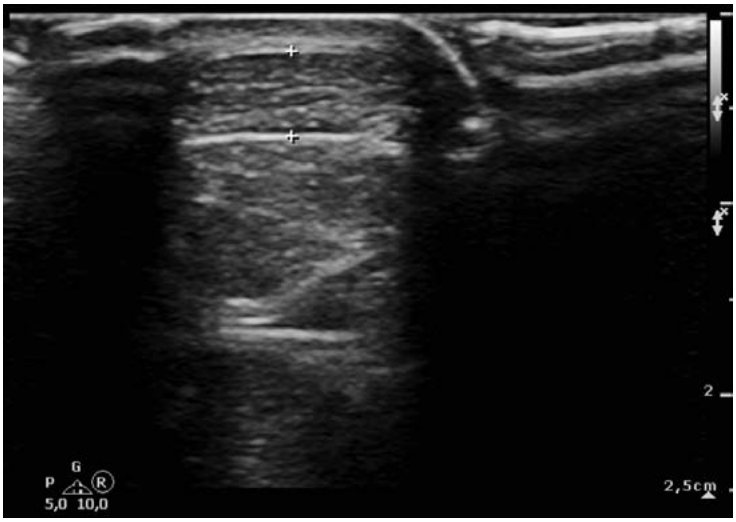

Figure 3. *MSU image of a volunteer with Öhberg-score 0, short-axis view (++ anterior and posterior border of the Achilles tendon). The tendon structure was graded normal with a homogeneous echogenicity.*

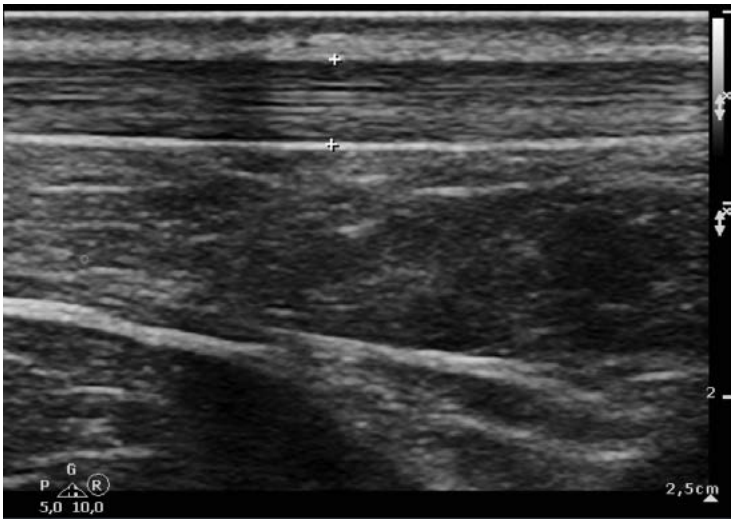

Figure 4. *MSU image of a volunteer with Öhberg-score 0, long-axis view (++ anterior and posterior border of the Achilles tendon). The tendon structure was graded normal with a homogeneous echogenicity.*

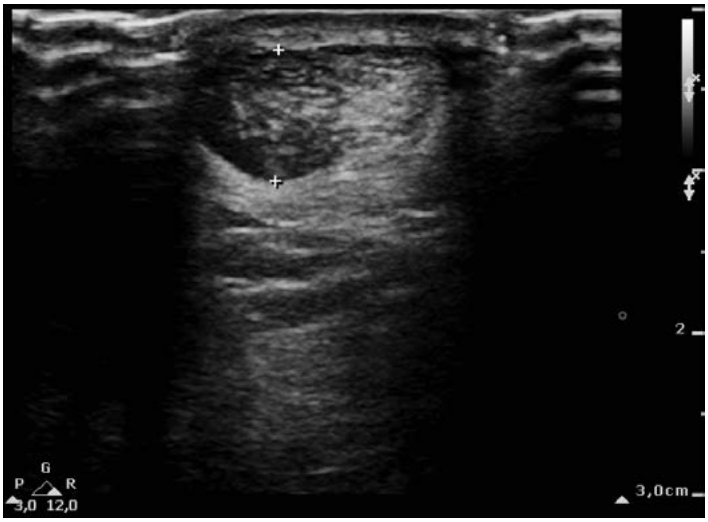

Figure 5. *Short-axis view of an MSU image in which observer 1 graded the Öhberg-score as 3, while observer 2 graded the Öhberg-score as 2 (++ anterior and posterior border of the Achilles tendon). Discriminating severe structural changes (extended hypoechogenic areas) from moderate structural changes (some well-defined hypoechogenic areas) turned out to be difficult in this subject.*

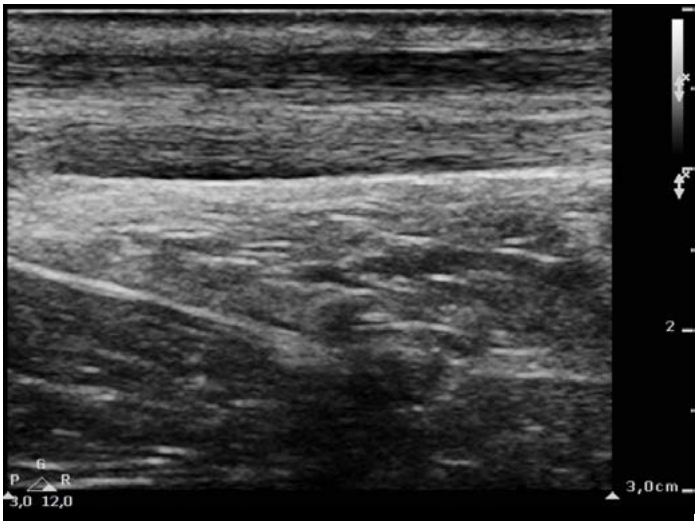

Figure 6. *Long-axis view of an MSU image in which observer 1 graded the Öhberg-score as 3, while observer 2 graded the Öhberg-score as 2. Discriminating severe structural changes (extended hypoechogenic areas) from moderate structural changes (some well-defined hypoechogenic areas) turned out to be difficult in this subject.*

Conclusion

In asymptomatic individuals, MSU is highly reliable for grading mid-portion Achilles tendon structure and measuring anteroposterior tendon diameter. The absence of neovascularization in our asymptomatic population suggests that this phenomenon may be limited to pathological Achilles tendons. Caution may be warranted when generalizing our reliability results to individuals with symptomatic or severe Achilles tendon changes, as these changes appear to be more difficult to grade.

Acknowledgement

We thank the staff and personnel of 44 mechanized infantry batallion Johan Willem Friso (Royal Netherlands Army) for participating in this study.

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Chapter 3.

Intra- and inter-rater reliability of processing ultrasound tissue characterization scans in mid-portion Achilles tendinopathy

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Abstract

Purpose: Ultrasound tissue characterization (UTC) is used to visualize and quantify the Achilles tendon structure. We investigated the intra-rater and inter-rater reliability of UTC for quantifying the mid-portion tendon structure, and the area of maximum degeneration (AoMD), in military personnel with mid-portion Achilles tendinopathy.

Method: UTC scans of 50 patients (16-60 years) were processed twice by rater 1 and once by rater 2. First the mid-portion tendon structure was quantified and subsequently the AoMD. The intraclass correlation coefficient (ICC) was calculated for echo-types I, II, III, IV, aligned fibrillar structure (echo-types I + II), and disorganized tendon structure (echo-types III + IV).

Results: For mid-portion tendon structure, all ICC values were excellent for intra-rater reliability (range 0.97 to 0.99), and inter-rater reliability (range 0.98 to 0.99).
Regarding the AoMD, intra-rater reliability showed excellent ICC values for all echo-types (range 0.94 to 0.98) except for echo-type II (0.85). Inter-rater reliability showed excellent ICC values for all echo-types (range 0.92 to 0.98).

Conclusion: Processing of UTC scans is highly reliable in quantifying the mid-portion Achilles tendon structure and the AoMD.

Keywords: Ultrasound tissue characterization, ultrasonography, imaging, Achilles tendon, tendinopathy, tendinosis, musculoskeletal.

1. Introduction

Achilles tendinopathy (AT) is a painful overuse condition[1] that affects the tendon mid-portion more frequently (55-65%) than the insertion (20-25%),[2] specifically between the ages of 30-50 years.[3] In recreational running, about one in 20 runners develops AT,[4] and one in three runners experiences persisting symptoms 1 year after new-onset AT.[5] AT is also common in the military,[6] where musculoskeletal injuries may affect combat readiness,[7] and can result in discharge.[8]

Histologically, AT is considered a degenerative condition, in which the pathogenesis may be regarded as a continuum.[9, 10] As degeneration progresses, the tendon's ability to regain normal morphology and architecture is considered to decrease.[9, 10] Approximately 4% of all patients that were previously diagnosed with AT sustain an Achilles tendon rupture.[11] While spontaneous tendon rupturing is, almost without exception, preceded by degenerative changes,[12] the extent of degeneration in ruptured Achilles tendons appears more severe than in tendinopathic Achilles tendons.[13]

Ultrasound tissue characterization (UTC) is a non-invasive imaging modality that is reported to be able to visualize the Achilles tendon structure, and quantify the Achilles tendon matrix integrity.[14] In AT, UTC is used to evaluate non-surgical[15, 16] and surgical interventions[17, 18]

targeting the Achilles tendon structure. UTC can also be used to monitor the reaction of the tendon to load,[19, 20] as this is considered of importance in preventing progression of tendon degeneration in AT.[9, 10]

While the scanning procedure in UTC is relatively standardized and automated, the processing of UTC scans to quantify the Achilles tendon structure is highly operator dependent. Processing is performed manually, and depends on the assessor's ability to mark the anatomical borders of the Achilles tendon in the anatomical region of interest in consecutive, short-axis images. The processing of UTC scans has been tested for reliability in patellar tendons,[21] but not yet in Achilles tendons. Our objective was to determine the intra-rater and inter-rater reliability of processing UTC scans in a large cohort of military personnel suffering from mid-portion Achilles tendinopathy (mid-AT).

2. Materials and Methods

2.1 Study Setting and Participants

The study was conducted at the Department of Sports Medicine of the Royal Netherlands Army, in Utrecht, the Netherlands. The UTC scans had been collected as part of an observational study (https://www.toetsingonline.nl/to/ccmo_search.nsf/Searchform?OpenForm, Dossier number ToetsingOnline NL69527.028.19) aimed to evaluate shockwave therapy, load management, and return to running as standard care for mid-AT.

2.2 Enrollment

Consecutive patients consulting the Department of Sports Medicine between February 2019 and January 2021 were eligible if the following inclusion criteria were met: (1) military personnel in active duty (18-60 years); (2) patients with a clinically established diagnosis of mid-AT;[22] and (3) symptoms for two months or more. In the case of bilateral symptoms only the most severely affected side, defined as the side with the lowest Victorian Institute of Sports Assessment – Achilles questionnaire (VISA-A) score, was included in the analysis. Subjects were excluded if they reported: (1) concomitant insertional Achilles tendinopathy (ins-AT); and (2) factors that are known to adversely affect the Achilles tendon morphology and architecture, i.e., signs of a complete Achilles tendon rupture; prior surgery to the Achilles tendon; use of statins, fluoroquinolones, or corticosteroids;[23, 24] and a previous diagnosis of rheumatoid arthritis, diabetes mellitus, or psoriasis.[25] All participants were recruited by the main researcher (MP, physical therapist).

2.3 Ethical Considerations

The study protocol was reviewed by the ethics committee METC Brabant, Tilburg, the Netherlands (NW2021-69), and was judged not to be subjected to the Medical Research Involving Human Subjects Act. All participants provided written informed consent for anonymous use of their data.

2.4 Patient Characteristics

Patient characteristics and UTC scans were collected by the main researcher, who had 8 years of experience in UTC. The following characteristics were retrieved: age (years), height (cm), weight (kg), gender (male/female), Body Mass Index (BMI, in %), symptom duration (months), baseline VISA-A scores, baseline Numeric Rating Scale (NRS) scores for maximum Achilles tendon pain.

The VISA-A is considered the gold standard for assessing pain and function in AT, ranging from 0 to 100 points, where 100 equals a perfect asymptomatic score.[22, 26] While the validity and reliability of the NRS for pain (ranging from 0, no pain, to 10, worst conceivable pain) has not yet been formally established in AT, it is often used to evaluate progress in these patients.[26] The NRS has been proven valid in numerous musculoskeletal pain conditions.[26]

2.5 UTC Scanning

All UTC scans were performed (Figure 1) using a standardized scanning protocol,[18, 27] as well as standardized ultrasound parameters (12 MHz, depth 3 cm, focus 1.3 cm). Prior to scanning, all patients were asked to lay prone with their feet hanging freely over the examining table. The main researcher sat on a stool behind the treatment couch, and used his knee to fix the patients ipsilateral foot in maximum dorsiflexion. This way perpendicular scanning was secured over the length of the Achilles tendon. A UTC tracker (UTC imaging, 6171 GD Stein, The Netherlands, serial no. UTC-201-041) was placed over the Achilles tendon, and remained in a manually fixed position during the scanning procedure.

A 12-MHz linear-array transducer (Terason 12L5 Smartprobe, Vermon, France) using Terason software (t2000+ OEM) was embedded in the UTC tracker, ensuring a fixed angle of insonation. The transducer was mounted to move automatically over an acoustic standoff pad. Ultrasound transmission gel (Aquasonic 100, Hannover, Germany) was applied between the transducer and the acoustic standoff, and also on the Achilles tendon.

During UTC scanning, a motor drive automatically moved the tranducer 12 centimeter forth and back over the Achilles tendon, capturing a short-axis grey scale image (Figure 2) every 0.2 millimeter. The total time of the scanning procedure takes less than 45 seconds. The images were stored on a computer and a back-up was created.

Subsequently, the greyscale images were composed into a three-dimensional volume block of data, allowing tomographical visualization of the Achilles tendon in three planes: coronal, transverse, and sagittal. A validated algorithm analyzed three-dimensional stability of the grey scale echo patterns, quantifying the Achilles tendon structure in percentages of echo-type I (colored green), echo-type II (colored blue), echo-type III (colored red), and echo-type IV (colored black), respectively (Figures 3 and 4).[14] Research has shown that greyscale dynamics are strongly related to tendon architecture and histopathology.[28] Echo-type I is the most stable echo-pattern of consecutive short-axis images, while echo-type IV is the least stable echo-pattern. Together, echo-types I + II are considered to represent aligned fibrillar structure, whereas echo-types III + IV can be seen as disorganized Achilles tendon structure.

Aligned fibrillar structure and disorganized tendon structure can be used as outcome measures when evaluating patients with UTC.[14, 16-18, 21] Normative data for the Achilles tendon structure in asymptomatic individuals, with regard to age, race and gender, have recently been published.[29]

All participants were instructed not to engage in any sports activities involving running and jumping for at least 48-hours prior to UTC scanning, in order to exclude possible transient load-related changes in UTC echo pattern.[19]

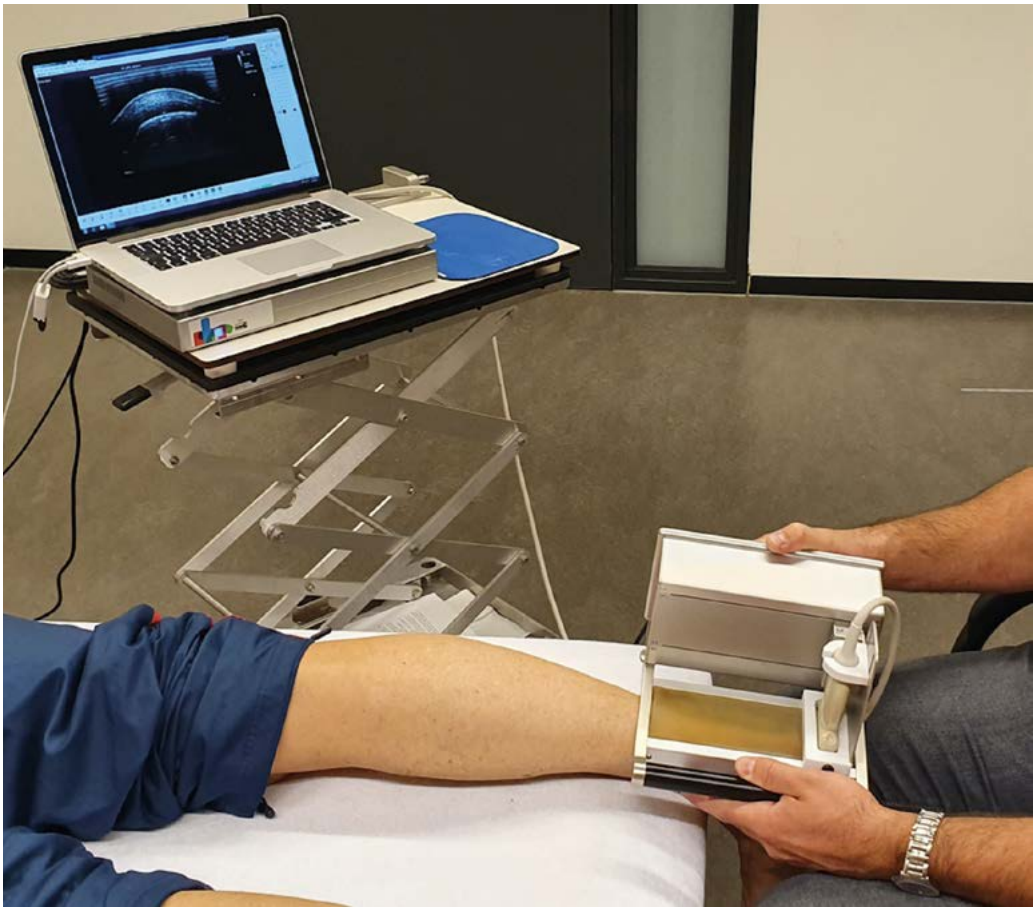

Figure 1. *UTC-scanning procedure.*

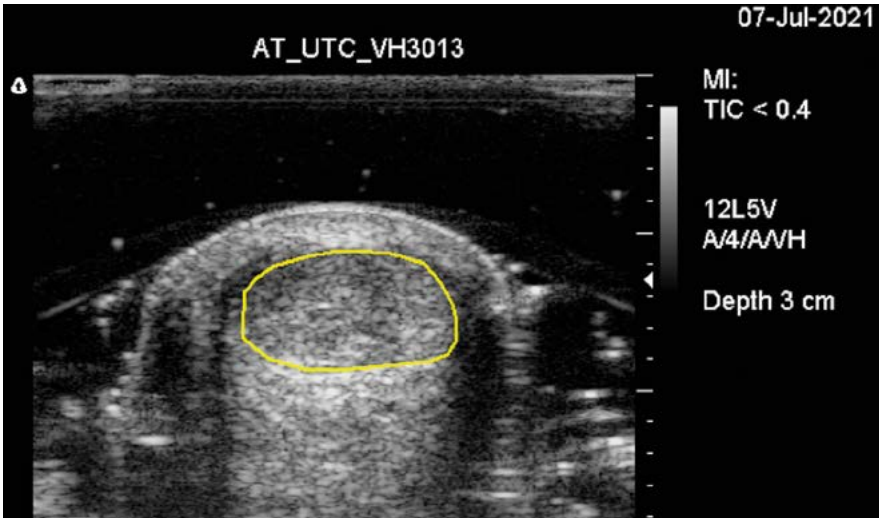

Figure 2. *Short-axis greyscale image of the mid-portion of the Achilles tendon.*
The yellow circle marks the anatomical borders of the Achilles tendon.

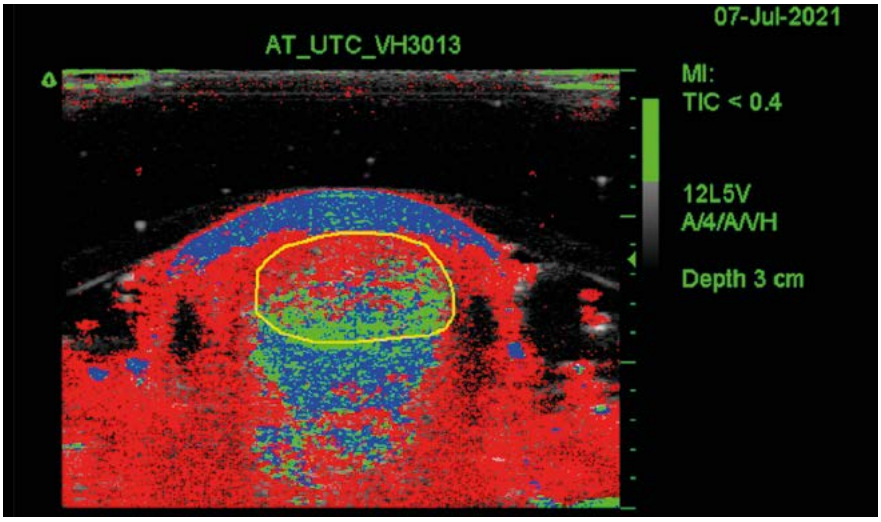

Figure 3. *Short-axis UTC-image of the mid-portion of the Achilles tendon.*
The yellow circle marks the anatomical borders of the Achilles tendon. Echo-type I = colored green, echo-type II = colored blue, echo-type III = colored red, and echo-type IV = colored black. Echo-types I + II represent aligned fibrillar structure, whereas echo-types III + IV can be seen as disorganized Achilles tendon structure.

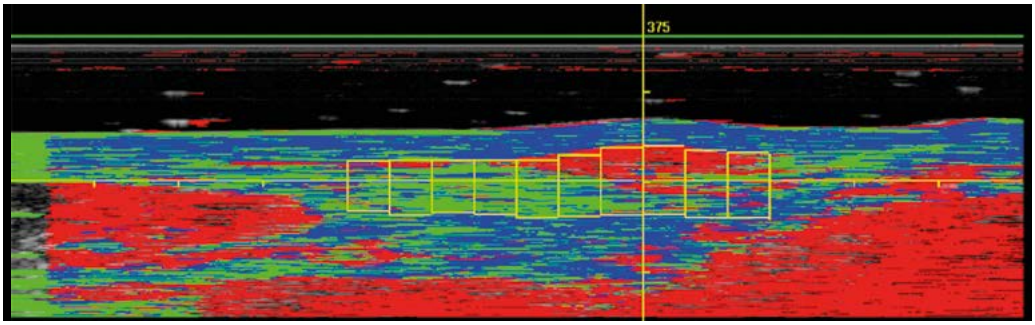

Figure 4. *Long-axis UTC-image of the Achilles tendon.*
Eleven consecutive contours (vertical yellow lines) capture the entire tendon mid-portion, starting 2 cm proximal to the calcaneus (most right sided contour), and continuing up to the myotendinous junction (most left sided contour). Echo-type I = colored green, echo-type II = colored blue, echo-type III = colored red, and echo-type IV = colored black. Echo-types I + II represent aligned fibrillar structure, whereas echo-types III + IV can be seen as disorganized Achilles tendon structure.

2.6 Intra-rater Reliability and Inter-rater Reliability

Two physical therapists (MSc), also musculoskeletal sonography teachers, performed all measurements for the study. Rater 1 (MM) had 9 years of experience in musculoskeletal sonography, rater 2 (JvD) 8 years of experience.

Prior to the study, both raters, who were unfamiliar with UTC, participated in a 3-day consensus procedure, consisting of instruction and practice, to standardize the processing of the UTC scans. During this procedure each rater processed 10 UTC scans.

All UTC scans were collected by the main researcher (MP), and were anonymized and processed independently by these two raters. Rater 1 processed each UTC scan twice, with at least four weeks in between, to determine the intra-rater reliability.

2.7 Processing of UTC scans

First, both raters quantified the structure of the Achilles tendon mid-portion, defined as the part of the Achilles tendon 2-7 cm proximal to the calcaneal insertion.[22] For this, each rater marked the contours of the Achilles tendon borders in consecutive short-axis images (Figures 2 and 3), using UTC software. The first contour was placed 2 centimeters (101 frames) proximal to the calcaneus, and continuing every 0.5 cm (25 frames) up to the myotendinous junction, or a length of 7 cm (maximum of 11 contours) (Figures 2-4). The contours were automatically interpolated and the tendon volume between the first and the last contour was expressed in percentages of echo-types I, II, III and IV (Figure 5). Both raters used the default setting of window size 25 (the stability of the greyscale echo pattern over 4.8 millimeter) for contour marking, and the default setting of window size 17 (the stability of the greyscale echo pattern over 3.2 millimeter) for the quantification of tendon structure. All contours were saved to the corresponding UTC images.

Following structural quantification of the Achilles tendon mid-portion, both raters identified the area of maximum degeneration (AoMD) within the tendon mid-portion (Figure 5). The AoMD was defined as the area (1 frame) in which intact and aligned tendon bundles (echo-type I) were lowest represented. The AoMD was identified by using a slider in the UTC graph while reading the values of echo-type I in real-time (Figure 5).

Data were extracted using a standardized Microsoft Excel extract form.

For this reliability study, we recruited a sample of 50 patients (50 symptomatic mid-portion Achilles tendons).[30]

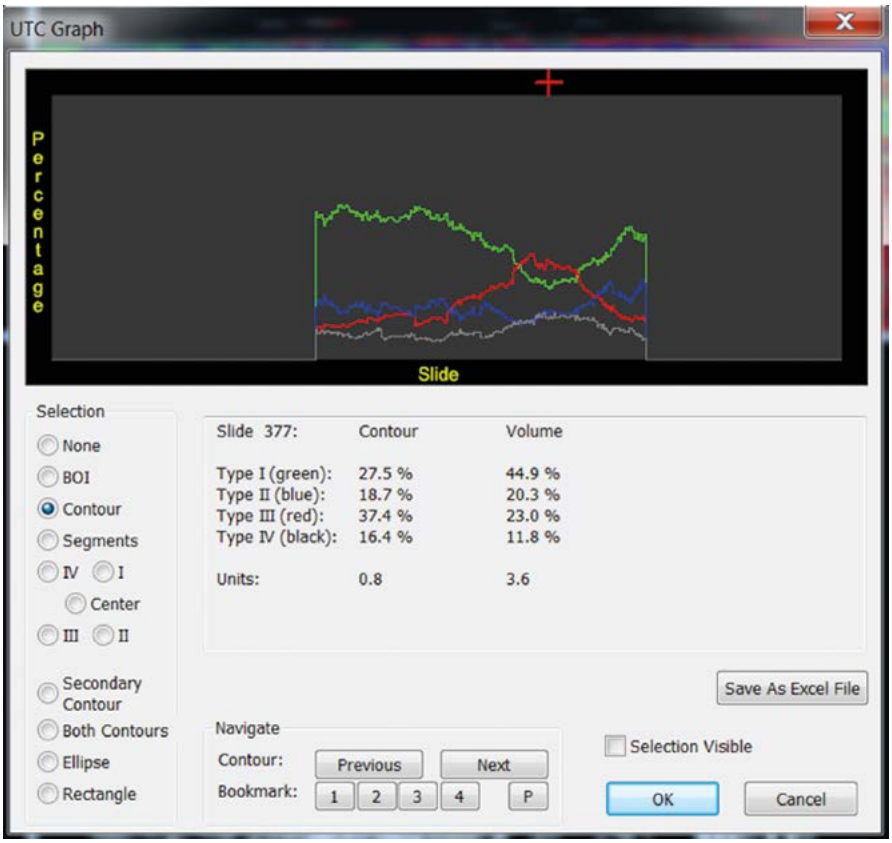

***Figure 5**. UTC-Graph of the mid-portion Achilles tendon structure.*
The red cross indicates from which short-axis image the figures under contour (=AoMD) come from. This position can be changed by sliding through the sagittal plane. A certain plane is identified by the number mention by slide. In this graph, the AoMD consists of 27.5% echo-type I, while the total volume of the Achilles tendon mid-portion (between the first and last contour) consists of 44.9% echo-type I.

2.8 Statistical Analysis

Baseline characteristics of our studied population were presented with appropriate measures of central tendency and dispersion. The intraclass correlation coefficient (ICC) was used to assess the intra-rater and the inter-rater reliability. The ICC was calculated (ICC 2.1, two-way random, single measurement, absolute agreement) for the echo-types I, II, III, IV, aligned fibrillar structure (echo-types I + II), and disorganized tendon structure (echo-types III + IV). For the interpretation of the ICC we adopted the guideline of Koo et al.[31] in which values were considered to represent poor (ICC < 0.5), moderate (ICC 0.5-0.75), good (ICC 0.75-0.90), and excellent (ICC > 0.90) reliability. We also calculated the Standard Error of Measurement (SEM = SD of population × √(1 − ICC)) and the Minimal Detectable Change (MDC = 1.96 × SEM × √2). MDC values can be used to distinguish true differences in Achilles tendon matrix integrity from random variation.
All analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 25.0, IBM Corp., Armonk, NY).

3. Results

From March to July 2021, all UTC scans were independently processed by the two raters to ensure blinding of the procedure. A total of 50 scans of service members with symptomatic mid-AT were included in the study. Both raters indicated that all UTC scans were of sufficient quality to perform the rating procedure. Bilateral symptoms were present in 14 out of 50 participants (28%). In these cases, we only included the side with the lowest VISA-A score in the analysis. Patient characteristics are presented in Table 1. The mean echo-type percentages of the study population are displayed in Table 2.

For quantification of the structure of the Achilles tendon mid-portion, the ICC showed overall excellent scores for intra-rater reliability, ranging from 0.97 (0.94-0.99) to 0.99 (0.97-0.99), as well as for inter-rater reliability, ranging from 0.98 (0.95-0.99) to 0.99 (0.99-1.00) (Table 3). MDC values for intra-rater and inter-rater reliability ranged from 1.9 % to 5.9% and 1.9% to 6.0%, respectively (Table 3).

Quantification of the AoMD also resulted in excellent ICC values for intra-rater reliability, ranging from 0.94 (0.90-0.97) to 0.98 (0.97-0.99), except for echo-type II 0.85 (0.75-0.91), which was considered good reliability (Table 4). ICC's for inter-rater reliability in assessing the AoMD were all excellent, ranging from 0.92 (0.86-0.95) to 0.98 (0.95-0.99).
MDC values for intra-rater reliability ranged from 4.6 % to 10.0 %, and for inter-rater reliability from 3.3 to 8.6% (Table 4).

Table 1. Patient characteristics.

Measure	Total group (n=50) Mean ± SD
Age (years)	41.1 ± 9.9
Height (cm)	185 ± 6.8
Weight (kilograms)	93.1 ± 14.9
Body Mass Index (%)	27.2 ± 3.5
Gender (male/female)	48/2
Duration of symptoms (months)	15 ± 22.3
Baseline VISA-A (0-100)	59.8 ± 17
Numeric rating scale for maximum pain (0-10)	6.5 ± 1.6

Abbreviations: SD, standard deviation.

Table 2. Mean echo-types percentages of the participants Achilles tendons (reviewer 1 MM, rating 1).

Echo-type	Mid-portion Total group (n=50) Mean ± SD (min-max)	AoMD Total group (n=50) Mean ± SD (min-max)
Echo-type I %	47.6 ± 11.9 (24.7-75.2)	37.1 ± 12.2 (14.7-64.8)
Echo-type II %	20.3 ± 5.3 (10.5-35.8)	22.5 ± 7.6 (10.8-42.9)
Echo-type III %	19.4 ± 9.2 (2.6-43)	26.6 ± 12.2 (1.5-49.7)
Echo-type IV %	12.7 ± 6.7 (1.9-29.2)	13.5 ± 6.8 (0.4-28)
Total	**100%**	**100%**
Echo-type I + II %	67.9 ± 15 (40.4-95.3)	59.6 ± 17.6 (30-98.1)
Echo-type III + IV %	31.9 ± 15.3 (4.7-59.6)	40.1 ± 18 (1.9-70)
Total	**100%**	**100%**

Echo-types I, II, III, and IV are expressed as a percentage of the analyzed Achilles tendon volume. Combined, the echo-types I + II represent aligned fibrillar structure, and the echo-types III + IV disorganized tendon structure. Abbreviations: SD, standard deviation; min, minimum; max, maximum; AoMD, area of maximum degeneration (1 slide in the Achilles tendon mid-portion with the lowest representation of echo-type I).

Table 3. Intra-rater and inter-rater reliability for the processing of UTC scans in quantifying the structure of the Achilles tendon mid-portion (n=50).

	Intra-rater reliability			Inter-rater reliability		
Echo-type	***ICC (95% CI)***	***SEM***	***MDC***	***ICC (95% CI)***	***SEM***	***MDC***
Echo-type I %	0.98 (0.97-0.99)	1.7	4.7	0.99 (0.95-0.99)	1.2	3.3
Echo-type II %	0.97 (0.94-0.99)	0.9	2.5	0.98 (0.96-0.99)	0.7	2.1
Echo-type III %	0.98 (0.96-0.99)	1.3	3.6	0.99 (0.95-0.99)	0.9	2.6
Echo-type IV %	0.99 (0.97-0.99)	0.7	1.9	0.99 (0.99-1.00)	0.7	1.9
Echo-type I + II %	0.98 (0.96-0.99)	2.1	5.9	0.99 (0.97-1.00)	1.5	4.2
Echo-type III + IV %	0.99 (0.97-0.99)	1.5	4.2	0.98 (0.95-0.99)	2.2	6.0

Intra-rater and inter-rater reliability is calculated for echo-types I, II, III, and IV individually, and combined for aligned fibrillar structure (echo-types I + II), and disorganized tendon structure (echo-types III + IV). Abbreviations: CI, confidence interval; ICC, intraclass correlation coefficient; MDC, minimal detectable change (%); SEM, standard error of measurement (%).

Table 4. Intra-rater and inter-rater reliability for the processing of UTC scans in quantifying the AoMD (n=50).

	Intra-rater reliability			Inter-rater reliability		
Echo-type	***ICC (95% CI)***	***SEM***	***MDC***	***ICC (95% CI)***	***SEM***	***MDC***
Echo-type I %	0.98 (0.97-0.99)	1.7	4.8	0.97 (0.92-0.98)	2.1	5.9
Echo-type II %	0.85 (0.75-0.91)	2.9	8.2	0.92 (0.86-0.95)	2.1	5.9
Echo-type III %	0.96 (0.94-0.98)	2.4	6.8	0.96 (0.92-0.98)	2.4	6.8
Echo-type IV %	0.94 (0.90-0.97)	1.7	4.6	0.97 (0.95-0.99)	1.2	3.3
Echo-type I + II %	0.96 (0.93-0.98)	3.5	9.8	0.98 (0.95-0.99)	2.5	6.9
Echo-type III + IV %	0.96 (0.93-0.98)	3.6	10.0	0.97 (0.94-0.98)	3.1	8.6

Intra-rater and inter-rater reliability is calculated for echo-types I, II, III, and IV individually, and combined for aligned fibrillar structure (echo-types I + II), and disorganized tendon structure (echo-types III + IV). Abbreviations: CI, confidence interval; ICC, intraclass correlation coefficient; MDC, minimal detectable change (%); SEM, standard error of measurement (%); AoMD, area of maximum degeneration (1 slide in the Achilles tendon mid-portion with the lowest representation of echo-type I).

4. Discussion

This is the first study to investigate both the intra-rater and inter-rater reliability for the processing of UTC scans in patients suffering from mid-AT. Excellent ICC's were found for the processing of the mid-portion Achilles tendon structure, ranging from 0.97 to 0.99 (intra-rater reliability) and from 0.98 to 0.99 (inter-rater reliability) (Table 3). Also for the quantification of the AoMD we found excellent ICC's values for intra-rater and inter-rater reliability (ICC all ≥ 0.92), except for the intra-rater reliability for echo-type II (ICC 0.85), which was considered good reliability (Table 4). We cannot explain this outlier.

To our current knowledge, quantifying the AoMD has not been previously reported or tested for intra-rater and inter-rater reliability; therefore, we cannot compare these results to the literature.

Our results for processing the mid-portion Achilles tendon structure are comparable to those reported for patellar tendon structure, as Van Ark et al.[21] reported similar ICC's for intra-rater reliability (ICC 0.97 to 0.99), and slightly lower ICC's for inter-rater reliability (ICC 0.84 to 0.94). The lower ICC's for inter-rater reliability found in their study may be attributed to either artifacts caused by the near presence of the apex patella, or to the fact that the optimal knee angle to perform a UTC scan can vary, which makes standardization difficult, in contrast to the ankle joint.[21]

The inter-rater reliability of UTC for the mid-portion Achilles tendon structure was previously investigated in a study[14] where two raters individually collected and processed UTC scans. In this study, Van Schie et al.[14] reported slightly lower ICC's compared to our study, ranging from 0.92 to 0.95. The fact that these raters analyzed different UTC scans, along with the use of a not yet automated scanning procedure, may have accounted for their somewhat lower inter-rater reliability scores. Moreover, UTC equipment has advanced in the last decade, incorporating a higher frequency transducer, most likely resulting in superior imaging quality, thus, making it easier for raters to distinguish the Achilles tendon borders from the peritendinous structures. Additional methodological differences between the two studies may hamper a direct comparison between the reported ICC's: Van Schie et al.[14] quantified a relatively small region of interest in the Achilles tendon mid-portion (4 mm, 3 contours), in a mixed cohort of symptomatic and asymptomatic individuals, whereas in our study the full anatomical mid-portion of the Achilles tendon (up to 5 cm or a maximum of 11 contours) was analyzed, including only symptomatic participants. Despite all these differences, outcomes were quite comparable between the two studies. In other words, including a non-automated scanning procedure with a lower frequency transducer into the reliability analysis, analyzing different regions of interest, and targeting either symptomatic or asymptomatic cohorts, all appear to have little influence on the high inter-rater reliability of UTC.

The intra-rater reliability of UTC for Achilles tendon structure was previously tested in a smaller cohort (n=10), also reporting excellent reliability.[32]

Regarding the mean distribution of echo-types in our symptomatic population, we found 47.6% echo-type I, 20.3% echo-type II, 19.4% echo-type III, 12.7% echo-type IV, 67.9% echo-types I + II (aligned fibrillar structure), and 31.9% echo-types III + IV (disorganized structure) (Table 2). Elgart et al.[29] recently published normative data for Achilles tendon structure in asymptomatic individuals, stratified by age, race, and gender. They found no statistically significant differences between their age groups. For males they reported a distribution of 68.0% echo-type I, 29.5% echo-type II, 1.8% echo-type III, and 0.7% echo-type IV. Comparing these values to our findings, aligned fibrillar structure appears to be lower in our symptomatic population (67.9%) in contrast to asymptomatic peers (97.5%), while the amount of disorganized tendon structure was much higher in our study (32.1%) than reported in asymptomatic tendons (2.5%).[29]

The tendon structure of our population is quite comparable to the symptomatic population of De Jonge et al.[16], who evaluated the mid-portion Achilles tendon structure in nonoperatively treated mid-AT. The echo-type distribution in their study was: 48.6% echo-type I, 26.0% echo-type II, 14.3% echo-type III, 11.1% echo-type IV, 74.6% echo-types I + II, and 25.4% echo-types III + IV. If we compare the aligned fibrillar structure of our study to the population of De Jonge et al.[16], the values for echo-types I were 47.6% and 48.6%, and for echo-type II 20.3% and 26.0%, respectively. While echo-type I appears to be equally distributed between both symptomatic populations, echo-type II was lower in our study. This may be due to a very low representation of female participants in our population (Table 1), as it has been shown that asymptomatic female Achilles tendons contain more echo-type II in both the insertion and the mid-portion, compared to male tendons.[32]

We tried to avoid several sources of bias that could have distorted the results of our study. To prevent review bias, all UTC scans were anonymized and independently processed by the two raters. The first rater (MM) processed each UTC scan twice to determine the intra-rater reliability. These ratings were performed with at least 4 weeks in between, in order to prevent recall bias. In general, the most recommended interval between tests during test-retest reliability assessment is 2 weeks.[33] As the construct of a UTC scan does not change over time, with an additional 2 weeks we were on the safe side. Furthermore, we aimed to prevent observer bias[34] due to variation in experience level of the raters by selecting two equally experienced musculoskeletal sonographers to rate the UTC scans. In retrospect we do not believe that observer bias plays a major role; processing UTC scans appeared to be relatively easy to learn after following a user course from the manufacturer.

Our study has several limitations.
First, variation in the outcomes between the two raters in quantifying the mid-portion Achilles tendon structure is attributed to marking different tendon boundaries, while variation in the AoMD was due to selecting a different slide considered to have the lowest representation of echo-type I. We did not explore the nature and extent of these variations, as our primary interest was to determine the intra-rater and inter-rater reliability of the quantitative analyses for Achilles tendon structure. Scanning tendon cross-sectional area (CSA) using ultrasonography has shown to be less accurate than MRI, both in the Achilles tendon and patellar tendon.[35] Therefore, contour marking is a major influencer, especially when one expresses the different echo-types as percentages.

Second, with respect to the processing of scans, we have chosen to standardize the Achilles tendon mid-portion based on symptom location (2-7 cm proximal to the calcaneus), analogous to the generally accepted definition of mid-AT in clinical practice and scientific research.[22] This choice was made as uniformity in clinical terminology may contribute to accurate diagnostics, effective treatment, and targeted research. While processing the UTC scans in our study, we have noticed that resting Achilles tendon lengths can vary largely between subjects. Despite these anatomical variations, our mid-portion standardization has been applicable to the processing of all scans in our study. However, it is possible that our standardization is not applicable to all individuals, especially to those with a free tendon shorter than 2 centimeters. For this reason, future studies may consider analyzing a region of interest that defines the Achilles tendon mid-portion, as previously conducted in UTC research.[14, 16]

Third, our ICC's may be generalized to diagnosing patients suffering from mid-AT, or to the evaluation of interventions targeting the Achilles tendon structure in these individuals. However, it should be acknowledged that our results are based on a single UTC scan. In clinical practice, physical data acquisition over time, combined with short-term variations in tendon architecture, may introduce additional unexplained variability. Moreover, our ICC's may be of limited generalizability to the assessment of asymptomatic Achilles tendons, as UTC is used to evaluate load,[19, 20] or sometimes to predict injury[36] in asymptomatic subjects. Finally, our results may also be of limited generalizability to the female population, since only 2 out of 50 service members were female.

5. Perspective

UTC is an imaging modality that can visualize the Achilles tendon structure and quantify the Achilles tendon matrix integrity.[14] Normative data for tendon structure have been recently published.[29, 32]

In asymptomatic individuals, UTC is used to monitor load[19, 20] and predict injury,[36, 37] while in clinical practice it can be used to establish a diagnosis of AT, or to evaluate interventions targeting Achilles tendon structure.[15-18]

The intra-rater and inter-rater reliability of the processing of UTC scans for Achilles tendon structure have not previously been investigated in a large cohort of subjects with mid-AT.[21] Although our ICC's show overall excellent reliability, it should be emphasized that the corresponding MDC's have to be taken into account when evaluating tendon structure in mid-AT. In general, our MDC's for mid-portion tendon structure are relatively low, while in the AoMD they range up to 10%.

Growing evidence indicates that UTC of Achilles tendon structure should not be used as a biomarker for explaining the presence or severity of current and future symptoms,[16, 37] however, there's conflicting evidence on this topic.[14, 36] In a future study, we aim to determine if, and to what extent, our mid-portion structural assessment and the AoMD are associated with self-perceived pain and function by means of the VISA-A questionnaire.[38]

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Chapter 4.

Extracorporeal shockwave therapy for mid-portion and insertional Achilles tendinopathy: a systematic review of randomized controlled trials

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Abstract

Background
Extracorporeal shockwave therapy (ESWT) is used commonly to treat pain and function in Achilles tendinopathy (AT). The aim of this study was to synthesize the evidence from (non-) randomized controlled trials, to determine the clinical effectiveness of ESWT for mid-portion Achilles tendinopathy (mid-AT) and insertional Achilles tendinopathy (ins-AT) separately.

Methods
We searched PubMed/Medline, Embase (Ovid), and Cochrane Central, up to January 2021. Unpublished studies and grey literature were searched in trial registers (ACTRN, ChiCTR, ChiCtr, CTRI, DRKS, EUCTR, IRCT, ISRCTN, JPRN UMIN, ClinicalTrials.gov, NTR, TCTR) and databases (OpenGrey.eu, NARCIS.nl, DART-Europe.org, OATD.org). Randomized controlled trials (RCT's) and non-randomized controlled clinical trials (CCT's) were eligible when investigating the clinical effectiveness of ESWT for chronic mid-AT or chronic ins-AT. We excluded studies that focused on treating individuals with systemic conditions, and studies investigating mixed cohorts of mid-AT and ins-AT, when it was not possible to perform a subgroup analysis for both clinical entities separately. Two reviewers independently performed the study selection, quality assessment, data extraction, and grading of the evidence levels. Discrepancies were resolved through discussion or by consulting a third reviewer when necessary.

Results
We included three RCT's on mid-AT and four RCT's on ins-AT. For mid-AT, moderate quality of evidence was found for the overall effectiveness of ESWT compared to standard care, with a pooled mean difference (MD) on the VISA-A of 9.08 points (95% CI 6.35 to 11.81). Subgroup analysis on the effects of ESWT additional to standard care for mid-AT resulted in a pooled MD on the VISA-A of 10.28 points (95% CI 7.43 to 13.12). For ins-AT we found very low quality of evidence, indicating that, overall, ESWT has no additional value over standard care, with a standardized mean difference (SMD) of -0.02 (95% CI -0.27 to 0.23). Subgroup analysis to determine the effect of ESWT additional to standard care for ins-AT showed a negative effect (SMD -0.29; 95% CI -0.56 to -0.01) compared to standard care alone.

Conclusions
There is moderate evidence supporting the effectiveness of ESWT additional to a tendon loading program in mid-AT. Evidence supporting the effectiveness of ESWT for ins-AT is lacking.

Registration
PROSPERO Database; number CRD42021236107

Key points
- Adding extracorporeal shockwave therapy to a tendon loading program for midportion Achilles tendinopathy results in a clinical important improvement on the VISA-A questionnaire.

- Extracorporeal shockwave therapy seems to be ineffective for the treatment of insertional Achilles tendinopathy.

Keywords
Achilles tendinopathy, Midportion Achilles tendinopathy, Insertional Achilles tendinopathy, Extra corporeal shockwave therapy, Sports medicine.

Background

Chronic Achilles tendinopathy (AT) is a clinical condition characterized by pain, swelling, and decreased performance [1]. AT can be divided in mid-portion Achilles tendinopathy (mid-AT) and insertional Achilles tendinopathy (ins-AT). Mid-AT is more common (55-65%) than ins-AT (20-25%) [2]. AT occurs most frequently between the ages of 40-59 years [3], and is particularly prevalent in athletes, especially in runners [4].

Mechanical loading regimes are currently the standard of care for subjects with AT [4, 5]. Eccentric exercises have been considered a superior intervention, but recent studies conclude that various loading programs seem equally effective, regardless of contraction type [5-7]. Following inception of a loading program, pain and function may already improve after 2 weeks with results peaking at 12 weeks [8]. At 5-year follow-up, however, a significant portion of patients has not responded adequately to a loading strategy [9, 10], and up to half of all patients seek alternative treatment [9].

Extracorporeal shockwave therapy (ESWT) is used as a secondary conservative treatment for refractory tendinopathies [11-13]. It is thought that ESWT can influence the pathophysiological processes in various musculoskeletal conditions [14], and, by this, decrease pain and improve function in AT [4, 15]. ESWT can be used as a monotherapy [16], but is usually part of a multi-modal treatment strategy [11], and is considered to improve long-term outcomes when combined with eccentric exercises [17]. ESWT is reported to be safe [18, 19] and (cost)effective for patients with persistent AT who have low responsiveness to standard care [11, 19], but the evidence is conflicting [11, 12, 20, 21].

To our current knowledge, no systematic reviews so far have included only experimental studies to review the effectiveness of ESWT for mid-AT and ins-AT separately. Therefore, we aimed to synthesize the evidence from (randomized) controlled studies to determine the clinical effectiveness of ESWT, either as a monotherapy or as an additional intervention for both chronic mid-AT and ins-AT.

Methods

Protocol and registration

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22] and the Cochrane Handbook for Systematic Reviews of Interventions [23]. To enhance validity and reduce unintentional

duplication of effort, the study protocol was registrated in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number: CRD42021236107 (https://www.crd.york.ac.uk/prospero/).

Eligibility criteria

Types of studies

Designs eligible for inclusion were: (1) randomized controlled clinical trials (RCT's), and (2) non-randomized controlled clinical trials (CCT's).

Types of participants

Studies were eligible if ESWT was used to treat patients of 18 years and older, with a clinical or radiological confirmed diagnosis of either mid-AT or ins-AT, and whose symptoms were present for at least three months. We excluded studies that focused on treating individuals with systemic conditions (e.g., rheumatoid arthritis and diabetes mellitus). Studies investigating the clinical effectiveness of ESWT in mixed cohorts of mid-AT and ins-AT were also excluded when results were not presented separately for both conditions and were also not available after contacting the authors, preventing subgroup analysis for mid-AT and ins-AT separately.

Types of interventions

Two types of ESWT are common in musculoskeletal practice: focused extracorporeal shockwave therapy (F-ESWT) and radial extracorporeal shockwave therapy (R-ESWT). Both treatments are commonly applied for treating tendinopathies [11, 19]. We included studies that either used F-ESWT or R-ESWT, as a monotherapy or as an additional intervention, regardless of energy level or numbers of shockwave-treatments administered.

Types of comparisons

Studies investigating the efficacy of shockwave compared to different surgical and conservative interventions were eligible (e.g., tendon loading programs, surgical techniques, injections or dry needling, oral medication, placebo interventions, different shockwave modalities, or other commonly used non-surgical interventions for AT).

Types of outcome measures

Studies that used validated and reliable outcome measures to assess the clinical effectiveness of ESWT in multiple domains representing functional improvement, pain reduction, and self-perceived recovery were eligible for inclusion, such as the Victorian Institute of Sports Assessment – Achilles (VISA-A) questionnaire, the Numeric Rating Scale for pain (NRS) or Visual Analogue Scale for pain (VAS), and the Global Perceived Effect.

All steps in this review were independently performed by two reviewers (MP, PH). Differences were resolved by discussion. When disagreement persisted, the opinion of a third reviewer (EWP) was decisive.

Search strategy

Electronic databases and reference lists

With the assistance of a medical librarian of the Amsterdam University Medical Center (UMC), we developed an extensive search strategy. The following databases were searched from inception up to 21th January 2021: Medline, Embase, and Cochrane. The search strategy is reported in Appendix I.

Hand searching

Reference lists of the included articles were manually checked for additional eligible studies. If the information provided by full-texts articles led to uncertainty regarding possible inclusion, the original authors were contacted for clarification.

Unpublished data and grey literature

We also searched for unpublished studies and grey literature [24] in trial registers (ACTRN, ChiCTR, ChiCtr, CTRI, DRKS, EUCTR, IRCT, ISRCTN, JPRN UMIN, ClinicalTrials.gov, NTR, TCTR), and databases (OpenGrey.eu, NARCIS.nl, DART-Europe.org, OATD.org). No language restrictions were applied. Both published and unpublished studies were eligible.

Study selection

First, the search strategy was applied and all hits were screened on the basis of title and abstract. Eligible studies were then imported into EndNoteX9 and duplicates were removed. Subsequently, full-text studies were obtained and eligibility criteria applied to select studies meeting our research question. The selection process was recorded in a PRISMA flow diagram (Fig. 1).

Data collection process

The following data were extracted from the included studies using a standardized extraction form: (1) authors, (2) year of publication, (3) study design, (4) study population and setting, (5) AT-type (ins-AT and/or mid-AT), (6) duration of symptoms, (7) type of shockwave therapy (F-ESWT or R-ESWT), (8) number of shocks applied, (9) dose of ESWT, (10) number of treatment sessions, (11) treatment duration and frequency, (12) comparisons (e.g., oral medication, injections, surgical or other conservative interventions), (13) outcome measures, (14) length of follow-up, (15) results/conclusions, and (16) industry funding (y/n). For all outcome measures in each study the following data were extracted to facilitate meta-analysis: (a) point estimates of effect: mean differences, risk ratios or odds ratios; (b) estimates of variability: 95% confidence intervals, standard deviations or standard errors; (c) the number of participants, and (d) P-values. In case of missing data the original authors were contacted for further information.

Risk of bias assessment in individual studies

We used the Risk of Bias in Randomized Trials (RoB 2) tool to determine the risk of bias in the primary studies [25]. The RoB 2 assesses risk of bias in 5 distinct domains: (1) bias arising from

the randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcomes, and (5) bias in selection of the reported results. After formulating a risk of bias judgement for each domain, an overall risk of bias judgement was formulated for the outcomes being assessed, and defined as either: 'low risk', 'some concerns', or 'high risk' of bias.

Methodological and clinical heterogeneity

A priori we defined subgroups to address methodological and clinical heterogeneity between studies. With regard to the study design we distinguished RCT's from CCT's, since results of the latter are known to be more susceptible to various kinds of bias [26]. Furthermore, clinical heterogeneity is expected to be introduced by including participants with both AT-types in our study. Because mid-AT and ins-AT are considered different clinical entities in the literature [27, 28], we divided them into subgroups.

Data syntheses

Collected data were entered in Review Manager (RevMan) 5.4 [29]. If data were clinically and statistically sufficiently homogeneous, we summarized them in a meta-analysis using Random Effects Models (REM) under the assumption that different studies were estimating different, yet related intervention effects (e.g., ESWT-types applied or treatment protocols) [23]. In case fewer than 5 studies were included per AT-type (ins-AT or mid-AT), analyses were performed using Fixed Effect Models (FEM). Continuous outcomes were calculated and expressed as mean difference (MD) or as standardized mean difference (SMD), depending on the similarity of the used scales. Dichotomous data were expressed as relative risk (RR).

In case different scales were used in the reported outcomes (i.e. continuous, categorical, or dichotomous scales), we dichotomized the continuous and categorical scales for our data synthesis. For this, we used the minimal clinically important difference (MCID) as a cutoff point to measure clinically relevant treatment effects. With regard to the VISA-A questionnaire, we considered a decrease of 6.5 points as the MCID [30]. For pain we incorporated the results of Salaffi et al. [31], in which one point (scale 0-10) or 15% reduction of pain on a NRS represents the MCID for a patient.

We assessed statistical heterogeneity by visually inspecting forest plots for: (1) adequate or poor overlap of 95% confidence intervals (CI's), as poor overlap may be indicative of statistical heterogeneity; and (2) the magnitude and direction of effects. Subsequently, the presence of heterogeneity was statistically determined using the I^2 statistic and classified. We considered a value of less than 40% as an indication of low heterogeneity and a value of 75% or more as an indication of high heterogeneity [23]. In case of heterogeneity, we planned a subgroup analysis and meta-regression analysis to explore possible differences in AT-type, type of ESWT applied, duration of follow-up, or methodological features respectively. Results were presented in a descriptive summary of findings table. We categorized follow-up into short-term (≤ 3 months), mid-term (3 to 12 months), and long-term (≥ 12 months) as previously reported [11].

A priori we planned sensitivity analyses to test the robustness of our results for the impact of removing results from: (1) CCT's, (2) studies with high or unclear risk of bias, and (3) studies that received industry funding.

In case ten or more studies were included in the meta-analysis, we generated a funnel plot for every outcome to assess publication bias [23].

Grading the evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to rank the body of evidence [32]. Quality of evidence can be defined as either: 'high quality', 'moderate quality', 'low quality', or 'very low quality'. Using the GRADE approach, RCT's start with a 'high quality' rating and can be downgraded to 'moderate quality', 'low quality' or 'very low quality', depending on the presence of five factors: (1) risk of bias, (2) inconsistency of results, (3) indirectness of evidence, (4) imprecision, and (5) publication bias. Usually a quality rating will fall down by one level for each factor that is present, up to a maximum of three levels for all factors. In case of major concerns regarding the presence of a factor, the evidence level may fall down by two levels due to that factor alone. Despite the fact that CCT's start with a 'low quality' rating, grading upwards to 'moderate quality' in case of large treatment effects, or even to 'high quality' in case of very large treatment effects, may be warranted if no obvious bias explains these large effects [23].

Results

Search results

Our database search yielded 1533 hits (Fig. 1). After removal of duplicates, the 962 remaining articles were screened for potential inclusion on the basis of title and abstract. We identified 14 studies for full-text review. Among these was one trial protocol [33] that we later included because it was published [34] before submitting this systematic review. Following full-text screening, seven studies were excluded for not meeting our eligibility criteria: in four studies ESWT was investigated in a mixed cohort from which subgroup analysis for mid-AT and ins-AT separately was not possible [20, 35-37], one study did not meet the required symptom duration prior to inclusion [38], one study was not a (randomized) controlled clinical trial [39], and one study was excluded due to use of local anesthesia in the experimental group [40]. The search resulted in the inclusion of 7 RCT's. Despite the fact that we performed an extensive search for grey literature (Fig. 1), we were not able to retrieve any additional studies. No deduplication was performed for our grey literature search.

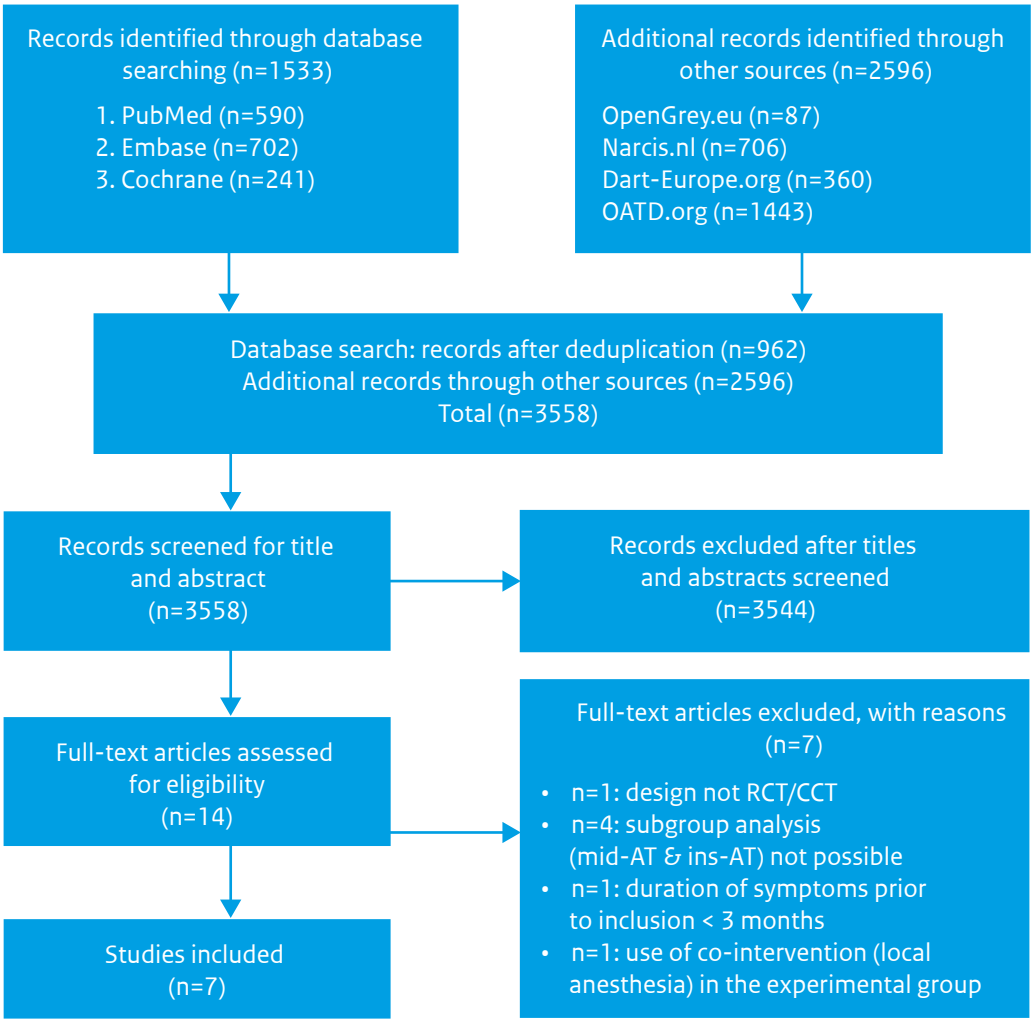

Figure 1. *Search strategy.*

Included studies

Midportion Achilles tendinopathy

We included 3 RCT's meeting our eligibility criteria for mid-AT [21, 41, 42]. Study characteristics, results of primary outcomes and conclusions are summarized in Table 1.

Rompe et al. [21] randomized participants in three groups, comparing ESWT to eccentric loading, and to a wait-and-see strategy. Eligible secondary outcomes were the NRS for

load-induced pain and a Likert scale to evaluate self-perceived recovery. While there were no baseline differences between the groups, patients in the ESWT group and the eccentric loading group achieved significant better results than patients in the wait-and-see group.

In a second RCT, Rompe et al. [41] compared eccentric loading with additional ESWT to eccentric loading alone. Secondary outcomes were identical to their previous study [21]. There were no baseline differences between the groups. Although both groups improved over time, the ESWT group achieved significant better results than the eccentric loading group.

In a double-blind RCT by Abdelkader et al. [42], eccentric loading exercises and stretching were performed in the experimental group and the control group. While the experimental group received additional ESWT, sham-ESWT was administrated in the control group. The VAS for pain was the secondary outcome. Although both groups were comparable at baseline and improved over time, the ESWT group achieved better than the sham-ESWT group.

Insertional Achilles tendinopathy

We included 4 RCT's that investigated the effectiveness of ESWT for ins-AT [34, 43-45]. Study characteristics, results of primary outcomes and conclusions are summarized in Table 1.

Rompe et al. [45] compared ESWT alone to an eccentric loading program [21]. Eligible secondary outcomes were the NRS for load-induced pain and a Likert scale. There were no baseline differences between the groups. While both groups improved, eccentric loading showed inferior results to ESWT.

In a double-blind RCT, Pinitkwamdee et al. [44] compared standard care and ESWT to standard care and sham-ESWT. The secondary outcome was the Visual Analogue Scale Foot and Ankle (VAS-FA), to evaluate pain and function. The VAS-FA showed no significant difference in outcome between the two groups.

Notarnicola et al. [43] compared standard care with ESWT to standard care and Cold air and High Energy Laser Therapy (CHELT). Secondary outcomes were the Ankle-Hindfoot scale to evaluate pain and function, and the Roles and Maudsley Score for self-perceived recovery. There were no baseline differences between both groups. While the Ankle-Hindfoot scale showed significant improvement in both groups, CHELT achieved better than ESWT. Self-perceived recovery only improved significantly in the CHELT group and not in the ESWT group.

Mansur et al. [34] performed a double-blind RCT comparing eccentric exercises and ESWT to eccentric exercises and sham-ESWT. Eligible secondary outcomes were the VAS for pain, the Foot and Ankle Outcome Score (FAOS) to evaluate pain and function, and the 12-item Short Form Health Survey to assess health-related quality of life. Both groups showed significant improvements from baseline in all secondary outcomes with no differences between the groups.

Risk of bias assessment in included studies

Risk of bias was assessed using the RoB2; results are presented in Fig. 2. There were no

disagreements between both reviewers.

Risk of bias arising from the randomization process
All three studies on mid-AT [21, 41, 42], and three of the four studies on ins-AT [34, 44, 45] reported using computer-generated numbers in sealed opaque envelops to draw up an allocation schedule. Allocation was concealed until participants were assigned to an intervention. In the fourth ins-AT study by Notarnicola et al. [43], a stratified randomization procedure was used, aimed at distributing important prognostic variables evenly across both intervention groups. Despite the fact that all studies performed correct randomization procedures, Mansur et al. [34] performed a second randomization procedure due to unforeseen loss to follow-up at week 12. This decision raises concerns as information concerning the procedures followed is lacking, and baseline characteristics are not presented separately for the primary and secondary randomized group. Due to an inappropriate randomization procedure, the risk of bias arising from the randomization process was considered high for this study [34], and low for the other studies [21, 41-45] included.

Risk of bias due to deviations from the intended interventions
In two studies on mid-AT [21, 41] and two studies on ins-AT [43, 45] blinding participants was not possible due to the obvious nature of the treatments (e.g., eccentric loading, ESWT, or laser therapy). One study on mid-AT [42] and two studies on ins-AT [34, 44] used sham-ESWT in the control groups. It is questionable if performing sham-ESWT always results in complete unawareness of the assigned intervention. For individuals who are familiar with ESWT, the absence of pain or observable shockwaves during treatment may provide some indication of allocation. All studies reported that all randomized participants received the allocated interventions. This has resulted in low risk of bias judgements due to deviations from the intended interventions for all seven studies included.

Missing outcome data
Two studies on ins-AT [43, 44] and one study on mid-AT [42] reported no loss to follow-up. The remaining two studies on mid-AT [21, 41], and one study on ins-AT [45] reported limited loss to follow-up in the experimental groups, ranging from 4% to 8%. In these studies baseline values were imputed. Mansur et al. [34] reported a high loss to follow-up, as 13 out of 58 randomized participants (22,4%) in the experimental group discontinued the study. Since the authors did not report the reasons for leaving the study, we cannot exclude the possibility that loss to follow-up was related to participants health statuses. A best case - worst case scenario was performed for missing data [34]. For this, missing values were imputed for five scenario's, assigning: 0, 25, 50, 75, or 100 points for all missing VISA-A scores. In all cases the effect was not statistically significant. Due to high loss to follow-up, the risk of bias for missing outcome data was judged to have some concerns for this study [34], and was considered low for the other six studies [21, 41-45] included.

Risk of bias in measurement of the outcome
In all three studies on mid-AT [21, 41, 42], and in two studies on ins-AT [34, 45], the VISA-A [46] was used as the primary outcome. The remaining two studies on ins-AT [43, 44] adopted the

VAS for pain. Although both instruments are used commonly to evaluate progress in AT [27], the VISA-A questionnaire currently represents the gold standard for the assessment of pain and function [4, 13, 27]. All studies evaluated the experimental and control groups at comparable time points, using the same outcome measures. Six studies [21, 41-45] reported using observer-blinded outcome assessors. Despite the fact that Mansur et al. [34] provided no information on who performed the outcome assessments, blinding was sufficiently executed in their study because a self-completing VISA-A questionnaire was used as primary outcome. Therefore, it is unlikely that this outcome was influenced by knowledge of the intervention received. We considered the risk of bias in measurement of the outcome to be low for all studies [21, 34, 41-45] included.

Risk of bias in selection of the reported result

In all studies, eligible reported results for the outcome domains corresponded to all intended outcome measurements. In six studies [21, 41-45] data were analyzed in accordance with either a trial protocol or a pre-specified statistical analysis plan.
Mansur et al. [34] performed a secondary randomization procedure due to unforeseen loss to follow up at 12 weeks, which they did not state in their trial protocol [33]. This decision may have influenced the outcome as selection bias can occur due to selective loss to follow-up [47]. Moreover, both randomized groups may not be comparable because time period effects may have influenced outcomes [48]. Therefore, the risk of bias in selection of the reported result was judged to have some concerns in this study [34], while in the remaining studies [21, 41-45] this risk was considered to be low.

Overall risk of bias judgements in individual studies

The overall risk of bias was judged to be low in six studies [21, 41-45] and high in one study [34] (Fig. 2).

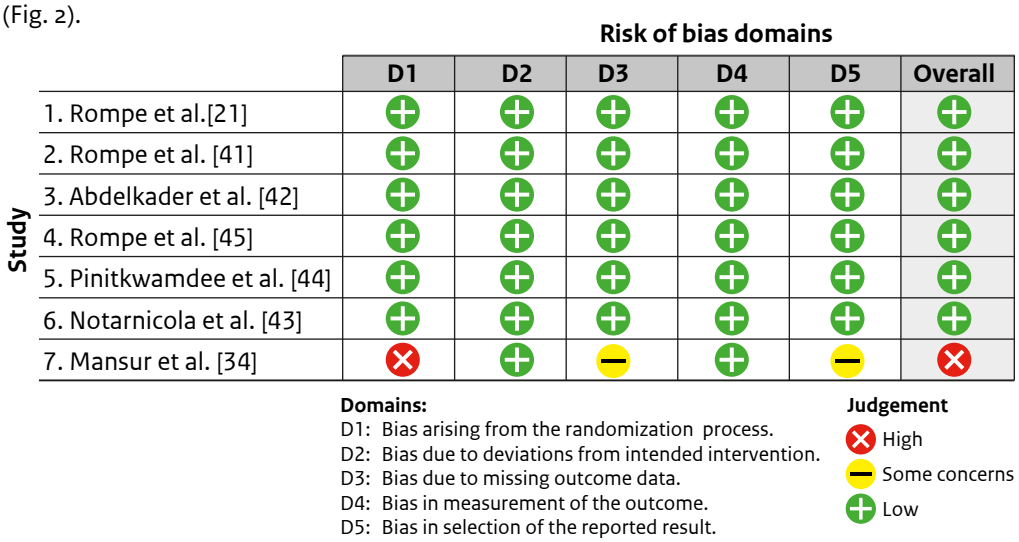

Figure 2. *The risk of bias in randomized trials (RoB 2 tool).*

Synthesis of results

We compared ESWT, either as a monotherapy or as an additional intervention to standard care, to standard care alone. For the purpose of meta-analysis, standard care was defined as conservative care in which at least tendon loading exercises or load-management was included. We did not compare ESWT to a wait-and-see strategy, since current literature indicates that all active treatments perform superior [5]. Differences in primary outcome measures from baseline to follow-up were defined as treatment effects. For synthesis of results, the study end was used for studies that reported multiple follow-ups [34, 42-44]. With regard to primary outcomes, all studies on mid-AT [21, 41, 42] used the VISA-A questionnaire. Results are therefore presented as MD. Included studies on ins-AT used either the VISA-A [34, 45] or the VAS for pain [43, 44], hence results are reported as SMD. For interpretation of the SMD we applied Cohens d [49]: (1) small effect size: SMD 0.2-<0.3, (2) moderate effect size: SMD 0.3-< 0.8, and a (3) large effect size: SMD ≥ 0.8. Since less than 10 studies were included in the meta-analysis, we did not generate a funnel plot to assess publication bias.

ESWT for mid-AT

Results are presented in Fig. 3; the intervention characteristics are defined in Table 1. In the first study, Rompe et al. [21] used ESWT as a monotherapy, reporting a small and non-significant effect in favor of standard care (MD VISA-A -4.90, 95% CI -14.62 to 4.82).
The second study of Rompe et al. [41] showed that combining ESWT and standard care was more effective than standard care alone (MD VISA-A 13.90, 95% CI 5.55 to 22.25).
In the third study, Abdelkader et al. [42] concluded that ESWT additional to standard care performed superior to sham-ESWT and standard care (MD VISA-A 9.80, 95% CI 6.78 to 12.82).
Meta-analysis was performed using FEM and resulted in a pooled MD on the VISA-A of 9.08 points (95% CI 6.35 to 11.81) in favor of ESWT (Fig. 3).

An I^2 statistic of 79% was indicative of high (≥ 75%) statistical heterogeneity. Visual inspection of the forest plot (Fig. 3) showed opposite directions of effects and a poor overlap of the 95% CI's, when comparing the first study of Rompe et al [21] with the second study of Rompe et al. [41] and the study of Abdelkader et al. [42]. In the latter two studies [41, 42], ESWT was used as an additional intervention to standard care, achieving higher VISA-A scores than the first study [21], in which ESWT was administrated as a monotherapy. In order to explore clinically relevant heterogeneity we created two subsets in R studio [50] (version R-3.6.3), using the packages Meta, Metafor and Readr: (1) ESWT versus standard care, and (2) ESWT additional to standard care versus standard care (Fig. 3). Due to apparent differences in outcomes and treatment programs, plural-FEM were used for subgroup analysis. The test for subgroup differences (meta-analytical method: Inverse variance method) indicated a significant (p = 0.0033) between-group difference between ESWT versus standard care and ESWT additional to standard care versus standard care. Subgroup analysis of ESWT additional to standard care [41, 42] resulted in a pooled MD on the VISA-A of 10.28 points (95% CI 7.43 to 13.12). In this subgroup, the I^2 statistic was 0% whereas the 95% CI showed excellent overlap.

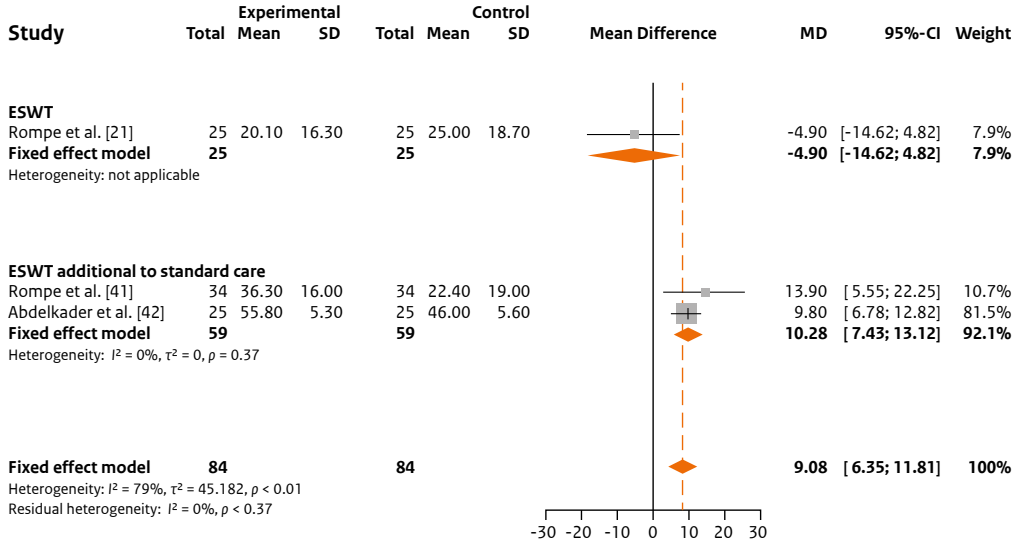

Figure 3. *Forest plot of ESWT versus standard care for mid-AT, with a subset of ESWT additional to standard care versus standard care alone. MD > 0 in favor of experimental intervention.*

ESWT for ins-AT

Results are presented in Fig. 4; the intervention characteristics are defined in Table 1. Rompe et al. [45] reported a positive effect (SMD 1.36, 95% CI 0.74 to 1.98) for ESWT (MD VISA-A 26.20) compared to standard care (MD VISA-A 10.70). This was the only study that evaluated ESWT as a monotherapy. In contrast, Notarnicola et al. [43] reported a significant negative effect (SMD -0.86, 95% CI -1.39 to -0.33) for ESWT additional to standard care (MD VAS 3.70) compared to standard care alone (MD VISA-A 5.30). It should be acknowledged that CHELT was part of the standard care program in their control group.

The remaining two studies [34, 44] presented comparable results. Both Pinitkwamdee et al. [44] and Mansur et al. [34] compared ESWT to sham-ESWT as additional interventions to standard care. Pinitkwamdee et al. [44] found no significant difference (SMD 0.00, 95% CI -0.70 to 0.70) between the ESWT group (MD VAS 3.20) and the sham-ESWT group (MD VAS 3.20). Mansur et al. [34] also reported no significant difference (SMD -0.10, 95% CI -0.46- to 0.26) in comparing ESWT (MD VISA-A 19.30) to sham-ESWT (MD VISA-A 21.70).

Meta-analysis was performed using FEM and resulted in a pooled SMD of -0.02 (95% CI -0.27 to 0.23), indicating a not statistically significant negative effect for ESWT (Fig. 4).

An I^2 statistic of 90% was indicative of high (≥ 75%) statistical heterogeneity. Visual inspection of the forest plot showed (Fig. 4) no overlap of the 95% CI's between the study of Rompe et al. [45] and the remaining three studies [34, 43, 44] that used ESWT as an additional intervention to standard care. In order to explore clinically relevant heterogeneity we created two subsets in R studio [50]: (1) ESWT versus standard care, and (2) ESWT additional to standard care versus standard care (Fig. 4). The test for subgroup differences (fixed effect model) indicated a significant ($p < 0.0001$) between-group difference between ESWT versus standard care and ESWT additional to standard care versus standard care (meta-analytical method: Inverse variance method). Quantitative synthesis of the three studies [34, 43, 44] that used ESWT as an additional intervention to standard care resulted in a pooled SMD of -0.29 (95% CI -0.56 to -0.01), indicating a small but statistically significant negative effect of ESWT additional to standard care compared to standard care alone. In this subgroup analysis there was still substantial heterogeneity, as the I^2 statistic was reduced to 68%. In the subgroup, the forest plot showed excellent overlap of the 95% CI's between the studies of Mansur et al. [34] and Pinitkwamdee et al. [44], and to a lesser extent when comparing these studies to the study of Notarnicola et. al. [43].

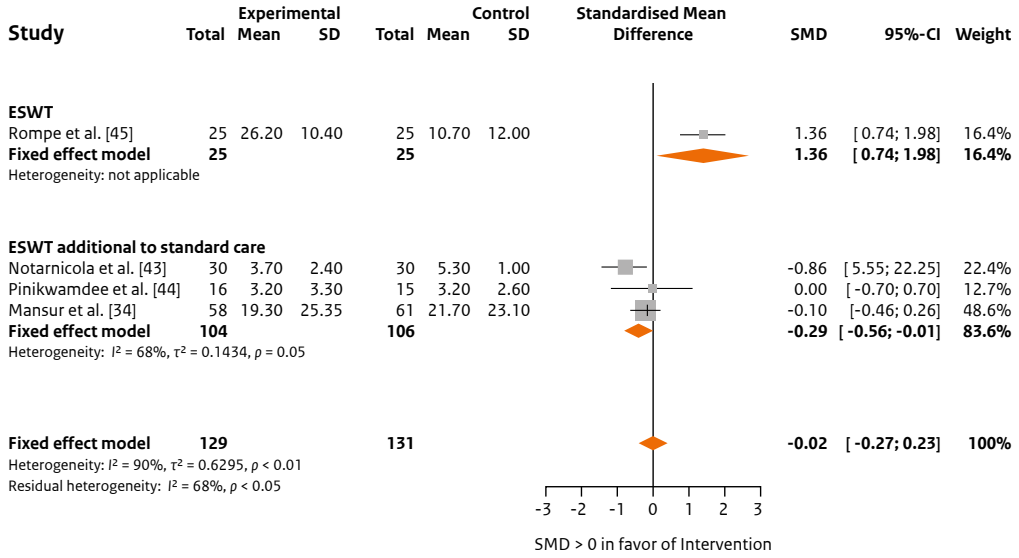

Figure 4. *Forest plot of ESWT versus standard care for ins-AT, with a subset of ESWT additional to standard care versus standard care alone.*

Table 1. Individual study characteristics of the included studies.

Author/ year	Population and setting, inclusion- & exclusion criteria	Experimental group	Control group(s)	Follow-up	Primary outcome, results & conclusions	Industry funding
Rompe et al. 2007 [21]	*Population and setting:* Primary care setting in Gruenstadt, Germany *Inclusion criteria:* • 18-70 years • mid-AT symptoms ≥ 6 months • failure of non-operative management *Exclusion criteria:* • peritendinous injection within the last 4 weeks • bilateral mid-AT • symptoms ≤ 6 months • concomitant painful ankle conditions • congenital or acquired deformities of ankle or knee • prior surgery to the ankle or the Achilles tendon	*R-ESWT (n=25):* 2000 pulses, 8 pulses/sec, 3 bar pressure, equals an energy flux density (EFD) of 0.1mJ/mm^2, 3 sessions, weekly intervals	*Eccentric loading (n=25):* Progressive build-up from 1 set of 10 repetitions to 3 sets of 15 repetitions (1 minute rest between sets), twice a day, 7 days a week, for 12 weeks (mild-moderate pain was allowed), starting with body weight and continuing painfree training with 5 kg rucksack *Wait-and-see (n=25):* 1 visit to their orthopedic physician for load management, stretching- and ergonomic advice.	4 months	VISA-A (range 0-100, mean ± SD) *ESWT:* Baseline: 50.3 ±11.7 • 4 months: 70.4 ± 16.3 *Eccentric loading:* Baseline: 50.6 ± 11.5 • 4 months: 75.6 ± 18.7 *Wait & see:* • Baseline: 48.2 ± 9.0 • 4 months: 55.0 ± 12.9 *Results:* No baseline differences between all groups ESWT & eccentric loading improved over time; no differences between treatments The ESWT & eccentric loading groups achieved better VISA-A scores than wait-and-see group	No potential conflict of interest declared

Author/ year	Population and setting, inclusion- & exclusion criteria	Experimental group	Control group(s)	Follow-up	Primary outcome, results & conclusions	Industry funding
	• prior Achilles tendon rupture • prior dislocations or fractures in the area in the preceding 12 months		Pain medication was prescribed if necessary		*Conclusions:* ESWT & eccentric loading showed comparable results at 4 month follow-up. The wait-and-see strategy was ineffective	
Rompe et al. 2009 [41]	*Population and setting:* Primary care setting in Gruenstadt, Germany. Enrollment via orthopedic physician *Inclusion criteria:* • 18-70 years • mid-AT symptoms ≥ 6 months • failure of non-operative management *Exclusion criteria:* • professional athletes • peritendinous injection within the last 4 weeks • bilateral mid-AT	*Eccentric loading + R-ESWT (n=34):* Loading consisted of progressive build-up from 1 set of 10 repetitions to 3 sets of 15 repetitions (1 minute rest between sets), twice a day, 7 days a week, for 12 weeks (mild-moderate pain was allowed), starting with body weight and continuing pain-free training with 5 kg rucksack	*Eccentric loading (n=34):* Progressive build-up from 1 set of 10 repetitions to 3 sets of 15 repetitions (1 minute rest between sets), twice a day, 7 days a week, for 12 weeks (mild-moderate pain was allowed), starting with body weight and continuing painfree training with 5 kg rucksack	4 months	VISA-A (range 0-100, mean ± SD) *Eccentric loading + ESWT:* • Baseline: 50.2 ± 11.1 • 4 months: 86,5 ± 16.0 *Eccentric loading:* • Baseline: 50.6 ± 10.3 • 4 months: 73.0 ± 19.0 *Results:* • No baseline differences between groups • Both groups improved over time • Eccentric loading + ESWT achieved better VISA-A scores than eccentric loading alone	No potential conflict of interest declared

Author/ year	Population and setting, inclusion- & exclusion criteria	Experimental group	Control group(s)	Follow-up	Primary outcome, results & conclusions	Industry funding
	• symptoms ≤ 6 months • concomitant painful ankle conditions • congenital or acquired deformities of ankle or knee • prior surgery to the ankle or Achilles tendon • prior Achilles tendon rupture • prior dislocations or fractures in the area in the preceding 12 months	R-ESWT consisted of 2000 pulses, 8 pulses/sec, 3 bar pressure (equals EFD 0.1mJ/mm^2), 3 sessions for each participant, weekly intervals after 4 weeks of eccentric training			*Conclusions:* At 4 month follow-up, eccentric loading alone was less effective than eccentric loading combined with shockwave treatment	

Author/ year	Population and setting, inclusion- & exclusion criteria	Experimental group	Control group(s)	Follow-up	Primary outcome, results & conclusions	Industry funding
Abdelkader et al. 2021 [42]	*Population and setting:* Faculty of Physical Therapy in Cairo, Egypt. Referral by the orthopedic department physician *Inclusion criteria:* • unilateral mid-AT symptoms for ≥ 6 months • failure of conservative treatment for at least 3 months *Exclusion criteria:* • physical therapy or peritendinous injection within the previous 4 weeks • use of NSAID's in the previous week • bilateral AT • concomitant painful ankle conditions • previous injury or surgical treatment to the ankle	*Eccentric loading + stretching + R-ESWT (n=25):* Loading consisted of 3 sets of 15 repetitions (1 minute rest between sets), twice a day, seven days a week, for 4 weeks Gastrocnemius and soleus stretches were performed twice a day, 3 repetitions (30 sec stretch, 30 sec rest) R-ESWT consisted of 2000 pulses, 8 pulses/second, 3 bar pressure (equals EFD 0.1mJ/mm^2), 4 sessions, weekly intervals	*Eccentric loading + stretching + sham R-ESWT (n=25):* Loading consisted of 3 sets of 15 repetitions (1 minute rest between sets), twice a day, seven days a week, for 4 weeks Gastrocnemius and soleus stretches were performed twice a day, 3 repetitions (30 sec stretch, 30 sec rest) Sham-ESWT was administrated in the same way as ESWT.	1 month and 16 months	VISA-A (range 0-100, mean ± SD) *Eccentric loading, stretching & ESWT:* • Baseline: 24.2 ± 6.5 • 1 month: 85 ± 6.2 • 16 months: 80 ± 5.3 *Eccentric loading, stretching & Sham-ESWT:* • Baseline: 21.0 ± 5.2 • 1 months: 53.4 ± 7.7 • 16 months: 67 ± 5.6 *Results:* • Both groups were comparable at baseline • Both groups improved over time • The experimental group achieved better VISA-A scores than the control group	No funding

Author/ year	Population and setting, inclusion- & exclusion criteria	Experimental group	Control group(s)	Follow-up	Primary outcome, results & conclusions	Industry funding
			Machine settings were adjusted to generate zero energy, while producing the same sound effect		*Conclusion:* Adding ESWT to an eccentric loading and stretching program resulted in greater improvements in both the short and long term	
Rompe et al. 2008 [45]	*Population and setting:* Primary care setting in Gruenstadt, Germany. Enrollment via orthopedic physician *Inclusion criteria:* • 18-70 years • ins-AT ≥ 6 months • failure of non-operative management *Exclusion criteria:* • (imaging) signs of mid-AT, retrocalcaneal bursitis, and Haglund deformity • peritendinous injection within the last 4 weeks	*R-ESWT (n=25):* 2000 pulses, 8 pulses/sec, 2.5 bar pressure (equals EFD 0.12 mJ/mm^2), 3 sessions, weekly intervals	*Eccentric loading (n=25):* Progressive build-up from 1 set of 10 repetitions to 3 sets of 15 repetitions (1 minute rest between sets), twice a day, 7 days a week, for 12 weeks (mild to moderate pain was allowed), starting with own body weight and continuing pain-free training with 5 kg rucksack	4 months	VISA-A (range 0-100, mean ± SD) *ESWT:* • Baseline: 53.2 ± 5.8 • 4 months: 79.4 ± 10.4 *Eccentric loading:* • Baseline: 52.7 ± 8.4 • 4 months: 63.4 ± 12.0 *Results:* • No baseline differences between groups • Both groups improved over time • The ESWT group achieved better VISA-A scores than the eccentric loading group	No funding

Author/ year	Population and setting, inclusion- & exclusion criteria	Experimental group	Control group(s)	Follow-up	Primary outcome, results & conclusions	Industry funding
	• bilateral mid-AT • symptoms ≤ 6 months • concomitant painful ankle conditions • congenital or acquired deformities of ankle or knee • prior surgery to the ankle or Achilles tendon • prior Achilles tendon rupture • prior dislocations or fractures in the area in the preceding 12 months				*Conclusion:* Eccentric loading showed inferior results to ESWT	

Author/ year	Population and setting, inclusion- & exclusion criteria	Experimental group	Control group(s)	Follow-up	Primary outcome, results & conclusions	Industry funding
Pinitkwamdee et al. 2020 [44]	*Population and setting:* Orthopedic outdoor clinic in Bangkok, Thailand *Inclusion criteria:* • 18-70 years • clinical or radio-graphical diagnosis of ins-AT • symptoms > 6 months • failed other standard conservative care for 3 months (e.g. rest, medication, activity modification, stretching exercise, and heel lift orthosis) *Exclusion criteria:* • injection to the insertion within the previous 4 weeks • mid-AT symptoms • neurological deficit • history of foot and ankle infection or trauma	*R-ESWT + standard care (n=16):* R-ESWT consisted of 2000 pulses, 8 to 12 Hz, 2.5-3.5 bar pressure (equals EFD 0.12-.16 mJ/mm^2), 4 sessions, weekly intervals Standard care consisted of rest, medication, activity modification, stretching, and heel lift orthosis	*Sham-ESWT + standard care (n=15):* Sham-ESWT was administered by disconnecting the treatment probe while connecting a second probe that generated the shockwave sound (without patient contact) Standard care consisted of rest, medication, activity modification, stretching, and heel lift orthosis	2,3,4,6, 12, and 24 weeks	VAS (range 0-10, mean ± SD) *ESWT + standard care:* • Baseline: 6.0 ± 2.6 • 2 weeks: 4.6 ± 3.1 • 3 weeks: 3.7 ± 3.0 • 4 weeks: 2.9 ± 2.2 • 6 weeks: 3.0 ± 2.3 • 12 weeks: 2.3 ± 2.5 • 24 weeks: 2.8 ± 3.3 *Sham-ESWT + standard care:* • Baseline: 5.2 ± 2.2 • 2 weeks: 2.9 ± 1.9 • 3 weeks: 3.1 ± 2.3 • 4 weeks: 2.6 ± 2.2 • 6 weeks: 3.7 ± 2.9 • 12 weeks: 2.3 ± 2.6 • 24 weeks: 2.0 ± 2.6 *Results:* • No baseline differences between groups	No funding

Author/ year	Population and setting, inclusion- & exclusion criteria	Experimental group	Control group(s)	Follow-up	Primary outcome, results & conclusions	Industry funding
	• foot or ankle deformity • history of foot or ankle surgery • contraindications for ESWT (hemophilia, coagulopathy, or foot and ankle malignancy)				• ESWT showed significant improvements at weeks 4, 6, and 12 • Sham-ESWT showed significant improvements at weeks 12 and 24 • No differences between groups at 24 weeks *Conclusion:* There was no difference at 24 weeks with the use of ESWT for chronic insertional Achilles tendinopathy, especially in elderly patients. However, it may provide a short period of therapeutic effects as early as weeks 4 to 12	

Author/ year	Population and setting, inclusion- & exclusion criteria	Experimental group	Control group(s)	Follow-up	Primary outcome, results & conclusions	Industry funding
Notarnicola et al. 2014 [43]	*Population and setting:* Hospital in Bari, Italy. Patients were recruited from an orthopedic hospital unit *Inclusion criteria:* • 18-80 years • ins-AT symptoms ≥ 6 months • functional VAS score > 4 *Exclusion criteria:* • (imaging) signs of mid-AT, partial rupture, calcaneal spurs or calcifications	*F-ESWT + eccentric loading + stretching (n=30):* F-ESWT consisted of 1600 pulses, EFD 0.05-0.07 mJ/mm^2, 3 sessions, at 3 to 4 day intervals Eccentric loading consisted of 3 sets of 10 repetitions using a TheraBand (i.e. a thin ribbon of stretchy material that enables resistance during movement exercises), 2-3 weekly sessions for 2 months Calf and Achilles stretching consisted of 4 sets of 15-20 seconds, 2-3 weekly sessions for 2 months	*Cold air and high energy laser therapy (CHELT) + eccentric loading + stretching (n=30):* CHELT consisted of simultaneous wavelengths (1,064, 810 and 980 nm; total dosage 1,200 J) together with a flow of cold air (- 30 degrees C), 10 daily sessions Eccentric loading consisted of 3 sets of 10 repetitions using a TheraBand, 2-3 weekly sessions for 2 months	10-15 days (end of complete session of treat-ment), 2 months, and 6 months	VAS (range 0-10, mean ± SD) *ESWT +standard care:* • Baseline: 7 ± 1.2 • 10th-15th days: 4.9 ± 0.9 • 2 months: 5.4 ± 2.7 • 6 months: 3.3 ± 2.4 *CHELT + standard care:* • Baseline: 7 ± 1.0 • 10th-15th days: 2.3 ± 1.1 • 2 months: 2.4 ± 1.6 • 6 months: 1.7 ± 1.0 *Results:* • No baseline differences between groups • Both groups improved over time • CHELT achieved better than ESWT	Not reported

Author/ year	Population and setting, inclusion- & exclusion criteria	Experimental group	Control group(s)	Follow-up	Primary outcome, results & conclusions	Industry funding
	• contraindications to laser therapy or ESWT (neoplasia, current or previous infections of the affected area, history of epilepsy, coagulopathies, cardiac pacemaker, pregnancy, intolerance to cold) • previous Achilles tendon surgery • peritendinous injection within the previous 4 weeks • ESWT or laser therapy within the previous 2 months • congenital or acquired deformities of the lower limb		Calf and Achilles stretching consisted of 4 sets of 15-20 seconds, 2-3 weekly sessions for 2 months		*Conclusion:* CHELT gave quicker and better pain relief. It also gave the patient a full functional recovery and greater satisfaction	

Author/ year	Population and setting, inclusion- & exclusion criteria	Experimental group	Control group(s)	Follow-up	Primary outcome, results & conclusions	Industry funding
Mansur et al. 2021 [34]	*Population and setting:* Tertiary teaching hospital in São Paulo, Brazil. *Inclusion criteria:* • 18-75 years • pain at the calcaneal tendon insertion for ≥ 3 months • diagnosis of ins-AT *Exclusion criteria:* • bilateral tendinopathy • previous surgery • autoimmune conditions • neuropathy • inflammatory diseases • noninsertional or mixed tendinopathy • previous infiltration • pregnancy • use of a pacemaker • coagulopathies • local infection	*R-ESWT + Eccentric loading (n=58):* R-ESWT consisted of 2000-3000 pulses, 7-10 Hz, and 1,5-2,5 bars of pressure, 3 sessions: at baseline, after two weeks, and after 4 weeks Loading consisted of 3 sets of 15 repetitions with a stretched knee, and 3 sets of 15 repetitions with a 20 degree flexed knee were performed twice a day, 7 days per week, for 3 consecutive months.	*Sham R-ESWT + Eccentric loading (n=61):* Sham-ESWT was administered in the same way as in the experimental group, except that the firing transmission piece was removed from the therapeutic pistol head prior to initiation of ESWT Loading consisted of 3 sets of 15 repetitions with a stretched knee, and 3 sets of 15 repetitions with a 20 degree flexed knee were performed twice a day, 7 days per	2,4,6, 12, and 24 weeks	VISA-A (range 0-100, mean ± SD) *ESWT + eccentric loading:* Baseline: 43.9 ± 23.2 2 weeks: 43.8 ± 21.3 4 weeks: 50.2 ± 19.6 6 weeks: 49.3 ± 21.2 12 weeks: 53.7 ± 22.0 24 weeks: 63.2 ± 27.5 *Sham-ESWT + eccentric loading:* Baseline: 40.6 ± 21.1 2 weeks: 47.6 ± 19.8 4 weeks: 52.9 ± 20.6 6 weeks: 54.8 ± 19.4 12 weeks: 61.8 ± 23.2 24 weeks: 62.3 ± 25.1 *Results:* No baseline differences between groups Both groups improved significantly from baseline	No funding

Author/ year	Population and setting, inclusion- & exclusion criteria	Experimental group	Control group(s)	Follow-up	Primary outcome, results & conclusions	Industry funding
			week, for 3 consecutive months.		No differences between the groups at any time point in the study *Conclusion:* ESWT does not potentiate the effects of eccentric strengthening in the management of insertional Achilles tendinopathy	

Sensitivity analysis

In our protocol, we planned sensitivity analyses to test the robustness of our results for the impact of removing results from: (1) CCT's; (2) studies with high or unclear risk of bias, and (3) studies that received industry funding. We did not perform a sensitivity analysis for study design since all studies included were randomized controlled trials. Due to a lack of studies, we also did not perform sensitivity analyses for risk of bias and industrial funding, as only one study [34] showed a deviating risk of bias judgement (Fig. 2), and only one study [43] did not declare no conflicts of interest (Table 1).

Grading the body of evidence

GRADE [32] was used to rank the body of evidence for the pooled VISA-A scores of mid-AT and ins-AT. There were no disagreements between both reviewers.

Regarding *risk for bias*, six out of the seven studies included in this systematic review were judged to be at low risk for bias, while in one study on ins-AT [34] the risk was considered high (Fig. 2). Since this study was not likely to seriously alter our results for ins-AT, the evidence levels for both mid-AT and ins-AT were not downgraded for *risk for bias*.

For *inconsistency*, no downgrading was performed for mid-AT since high heterogeneity (I^2 of 79%) [21, 41, 42] was reduced to low heterogeneity (I^2 of 0%) following subgroup analysis of the studies that used ESWT as an additional intervention to standard care [41, 42] (Fig. 3). In contrast, included studies on ins-AT showed varying directions of effect, poor overlap of the 95% CI's, and high heterogeneity (I^2 of 90%) that was still substantial (I^2 of 68%) following subgroup analysis [34, 43, 44] (Fig. 4). Therefore, we downgraded the evidence level for ins-AT to moderate quality of evidence.

Regarding *indirectness*, all studies on mid-AT made direct comparisons of ESWT to standard care, using the VISA-A score to assess pain and function. Moreover eligibility criteria, ESWT interventions and controls for mid-AT were also not indicative of downgrading of the evidence level for mid-AT. Contrastingly, one study on ins-AT [43] did not make a direct comparison between ESWT and standard care, as CHELT was part of the standard care program in the control group. This was the only study to report a statistically significant negative effect for ESWT. We downgraded the evidence level for ins-AT to low quality of evidence on behalf of *indirectness*.

With regard to *imprecision*, we downgraded the evidence for ins-AT to very low quality of evidence as applying the lower and upper boundary of the 95% CI around the pooled estimate would influence the clinical decision-making process. While the lower boundary indicates a negative effect for ESWT (SMD -0.27), the upper boundary favors ESWT (SMD 0.23) over standard care. Furthermore we included a relatively small total pooled sample for mid-AT (n=168) and ins-AT (n=260), not meeting the optimal information size of 400 patients (200 per group) for achieving sufficient power in a meta-analysis when pooling continuous data [51]. Therefore, we downgraded the evidence level for mid-AT to moderate quality of evidence, and for ins-AT to very low quality of evidence.

Publication bias was not assessed due to a small number of included studies.

In summary, we found moderate quality of evidence to support the effectiveness of ESWT for mid-AT, and very low quality of evidence indicating that ESWT has no additional value over standard care for ins-AT.

Discussion

To our current knowledge, this is the first meta-analysis that synthesizes evidence from RCT's only to assess the effectiveness of ESWT for mid-AT and ins-AT separately. For mid-AT we found moderate quality of evidence for the overall effectiveness of ESWT compared to standard care (pooled MD VISA-A 9.08, 95% CI 6.35 to 11.81) [21, 41, 42]. This effect is mainly attributed to the inclusion of two studies [41, 42] that used ESWT as an additional intervention to standard care, as the remaining study [21] showed a negative, though non-significant, effect for ESWT compared to standard care as monotherapies (Fig. 3).
Subgroup analysis to determine the effect of ESWT additional to standard care for mid-AT resulted in a pooled MD on the VISA-A of 10.28 points (95% CI 7.43 to 13.12) (Fig. 3). These findings are consistent with previous studies [16, 17] and clinical guidelines [4, 13], suggesting that combining ESWT and eccentric exercises may result in superior effectiveness for mid-AT. For ins-AT the evidence was more conflicting, as we included two studies [34, 44] that found no significant effect for ESWT over standard care, while the remaining two studies reported a large positive effect [45] and a small negative effect [43] for ESWT, respectively (Fig. 4). Overall, we found very low quality of evidence (SMD -0.02, 95% CI -0.27 to 0.23), indicating that ESWT has no added value to standard care for ins-AT (Fig. 4). Subgroup analysis for ESWT additional to standard care for ins-AT even indicated a negative effect (SMD -0.29, 95% CI -0.56 to -0.01) when compared to standard care alone (Fig. 4).

Our results for ins-AT are not supported by two recently published systematic reviews [52, 53], which indicate that adding ESWT to an eccentric loading program increases outcomes for ins-AT. As these two reviews included primary studies with predominantly lower evidence levels such as retrospective and prospective cohort studies, case series, case control studies and pilot studies, this may have contributed to different outcomes compared to our review. Two out of three RCT's [34, 44] in our subgroup analysis on ESWT additional standard care for ins-AT used sham-ESWT in their control groups (Table 1). Double-blinded placebo-controlled studies are more likely to approximate the true effect of ESWT than studies with an observational design. Both trials [34, 44] were double-blind, reporting no significant effect for ESWT over standard care (Fig. 4). In this light, we cannot explain the results of the third trial of the subgroup analysis [45] (Fig. 4), as this was the only study to report a positive effect for ESWT, using a comparable treatment program (Table 1).

Our subgroup analysis on ESWT additional to standard care for ins-AT indicates that adding ESWT to an eccentric loading program results in inferior outcomes (SMD -0.29, 95% CI -0.56 to -0.01) compared to standard care alone (Fig. 4). Caution is warranted when interpreting this pooled estimate, as it is unlikely that ESWT nullifies the effect of a standard care program. Both R-ESWT and F-ESWT have been reported to be safe interventions, with adverse effects such as post-therapy transient skin reddening or discomfort, typically being minor or occurring rarely [18, 19, 54]. Our negative pooled estimate is most likely the consequence of including the study of Notarnicola et al. [43] in our synthesis, being the only study showing a statistically significant negative effect of ESWT for ins-AT (Fig. 4). Notarnicola et al. [43] made no direct comparison between ESWT and standard care (e.g., loading exercises or load management) as high-intensity laser therapy was part of the standard care program in the control group (Table 1). From this study it is possible to deduce that either high-intensity laser therapy is a superior intervention, or that their ESWT program lacked effectiveness. We cannot substantiate which scenario is most likely applicable. Although laser therapy is widely used to reduce pain and promote tissue healing in multiple healthcare domains, experimental evidence regarding its effectiveness in AT is currently lacking [55, 56]. Randomized controlled studies comparing laser therapy and ESWT have indicated comparable effectiveness in bone healing [57], plantar fasciitis [58], tennis elbow [59], and subacromial pain [60], while reporting a significant advantage for ESWT in treating myofascial pain [61]. Moreover, the ESWT program in the study of Notarnicola et al. [43] differed from all other studies included in this systematic review, as participants received 3 sessions of F-ESWT at 3 to 4 day intervals, while all other studies included used R-ESWT at either 3 or 4 weekly intervals. To our current knowledge there is no evidence for superior effectiveness of either R-ESWT or F-ESWT for treating mid-AT or ins-AT. Both modalities are commonly indicated for treating various tendinopathies [11, 19]. Randomized controlled studies have shown that F-ESWT is superior to R-ESWT in treating non-calcific rotator cuff tendinopathies [62] and plantar fasciitis [63], while there appears to be no difference in effectiveness for treating patellar tendinopathy [64] and tennis elbow [65].

Despite the fact that various physiological effects have been attributed to ESWT (e.g., tissue and nerve regeneration, neovascularization, anti-inflammation, anti-apoptosis and a chondroprotective effect), the mechanism of action remains unknown [19]. This makes it particularly difficult to explain why our results indicate that ESWT appears to be effective for treating mid-AT, but not for ins-AT, although similar results have been reported for eccentric loading exercises [66]. Mid-AT appears to involve isolated tendon pathology, in contrast to ins-AT [13, 67]. It is possible that ESWT is less effective in treating certain non-tendinous tissues, as ins-AT may be accompanied by metabolic diseases [52], and often includes pathology in adjacent bursae and bone tissue, making the source of pain difficult to diagnose [13, 68, 69]. Especially intratendinous bone formation in ins-AT is considered difficult to treat [68].

We adopted a MCID of 6.5 points on the VISA-A in order to determine the clinical relevance of outcomes. To date, this score has only been formally established for ins-AT [30]. Most clinical trials investigating the effect of loading exercises in mid-AT use MCIDs ranging up to 20 points,

with a change score of 10 points being the most commonly adopted MCID [27]. Included primary studies in this systematic review reported mean improvements in VISA-A scores ranging from 20.1 to 55.8 points for mid-AT (Fig. 3), and 19.30 to 26.20 points for ins-AT (Fig. 4), while mean improvements for VAS scores for ins-AT ranged from 3.20 to 3.70 points. This should be kept in mind when interpreting our pooled estimates, as we compared ESWT to the standard of care, the latter being defined as a treatment program in which at least tendon loading exercises or load management was included. Since all active treatments for AT are reported to perform superior to a wait-and-see policy [5], we chose not to compare ESWT to such a policy, as this would artificially enhance the contrast between treatment arms, most likely resulting in more favorable effects for ESWT.

Regarding primary outcome measures, Pinitkwamdee et al. [44] and Notarnicola et al. [43] used the VAS for pain, while all remaining studies included [21, 34, 41, 42, 45] adopted the VISA-A questionnaire (Table 1). Although the latter is considered to represent the gold standard for evaluating the clinical course of AT [4, 13, 27], the VAS and NRS for pain are also commonly used to evaluate progress in these patients [27]. Murphy et al. [27] suggested that pain during a functional task may even be a beter measure of immediate treatment effect than the VISA-A questionnaire. The VAS and NRS have been found valid, reliable, and responsive in multiple musculoskeletal pain conditions [31, 70-74]. For these reasons, during risk of bias assessment, we did not consider the use of the VAS as primary outcome measure [43, 44] to be inappropriate. Using pain as a primary outcome measure for AT may be debatable, as the VAS and NRS both have not yet been validated in AT [27]. Moreover, apart from associated pain, AT is also known to affect function [1]. Despite the fact that most patients recover from AT, 23 to 37% experience long-term symptoms, lasting up to 10 years [9, 13]. It is possible that in these cases function will improve over time, without significant changes in pain levels. It should be acknowledged that if we had considered the use of the VAS to be inappropriate, this would have resulted in high overall risk of bias judgements for the studies of Pinitkwamdee et al. [44] and Notarnicola et al. [43] (Fig. 2). However, it is unlikely that using the VAS has contributed to inconsistent study outcomes for ins-AT, as Pinitkwamdee et al. [44] and Mansur et al. [34] reported similar results, using the VAS and VISA-A questionnaire as primary outcomes, respectively.

Our pooled estimate for mid-AT was graded *moderate* quality of evidence, while the evidence level for ins-AT was graded *very low* quality of evidence. Because less than 10 studies were included in the meta-analysis, we did not assess publication bias [23]. We decided not to downgrade the evidence level for lack of this assessment, as we performed an extensive search for grey literature, and were unable to find any (ongoing) trials. It is quite possible that only a few controlled studies have been conducted, since ESWT does not represent the state-of-the-art treatment for AT [4, 13].

Limitations

Our study has several limitations. First, our pooled estimates are most likely not generalizable to individuals unwilling or unable to perform a tendon loading program, as they may represent an underestimation of the true effect of ESWT in contrast to a wait-and-see strategy. This should be taken into account when considering ESWT as a monotherapy for these patients.

We found evidence from one high-quality study [21] for mid-AT, and one high-quality study for ins-AT [45], indicating that ESWT is effective as a monotherapy (Table 1). Caution is warranted when generalizing these results, since these were the only studies that evaluated ESWT as a monotherapy.

Second, our results may not be adequately generalizable to individuals suffering from combinations of mid-AT and ins-AT, as we aimed to establish the effectiveness of ESWT for mid-AT and ins-AT separately. We excluded studies evaluating the effectiveness of ESWT in mixed cohorts of mid-AT and ins-AT if it was not possible to perform a subgroup analysis. Although both tendinopathies are considered to be different clinical entities in the literature, they can coexist [27, 28].

Conclusion

The findings of this systematic review indicate that adding ESWT to a tendon loading program in mid-AT results in a clinically important improvement on the VISA-A. Our findings cannot support the use of ESWT for ins-AT, with two double-blind RCT's [34, 44] indicating that this treatment is ineffective. Although we were able to include several recently published studies, the availability of controlled studies, eligible to answer our review question, appears limited to the present day. It should be emphasized that the number of RCT's included in this systematic review was limited, and the pooled sample of mid-AT and ins-AT patients was relatively small. Future high quality RCT's are needed to support our findings.

List of abbreviations

AT:	Achilles tendinopathy
ESWT:	extracorporeal shockwave therapy
Mid-AT:	mid-portion Achilles tendinopathy
Ins-AT:	insertional Achilles tendinopathy
RCT's:	randomized controlled trials
CCT's:	controlled clinical trials
F-ESWT:	focused extracorporeal shockwave therapy
R-ESWT:	radial extracorporeal shockwave therapy
MD:	mean difference
SMD:	standardized mean difference
PRISMA:	preferred reporting items for systematic reviews and meta-analyses guidelines
PROSPERO:	international prospective register of systematic reviews
VISA-A:	Victorian Institute of Sports Assessment - Achilles questionnaire
NRS:	numeric rating scale for pain
VAS:	visual analogue scale for pain
UMC:	University Medical Center
RoB 2:	Risk of Bias in Randomized Trials
REM:	random effects models
FEM:	fixed effect models
MCID:	minimal clinically important difference
RR:	relative risk
CI's:	confidence intervals
GRADE:	grading of recommendations assessment, development and evaluation
VAS-FA:	visual analogue scale foot and ankle
CHELT:	cold air and high energy laser therapy
FAOS:	foot and ankle outcome score
EFD:	energy flux density
SD:	standard deviation

Appendix I

Searches: Faridi van Etten, Amsterdam UMC, Medical Library AMC. 21-1-2021:

Databases:		
PubMed/Medline, Embase (Ovid), Cochrane Central	Before deduplication	After deduplication
Total	**1533**	**962**

PubMed

590 hits: ("Achilles Tendon"[Mesh] OR "Tendinopathy"[Mesh] OR "Tendon Injuries"[Mesh] OR "Tendons"[Mesh] OR achilles[tiab] OR tendoachilles[tiab] OR calcaneal[tiab] OR tendinopath[tiab] OR tendon patholog*[tiab] OR tendon injur*[tiab] OR tendinos*[tiab] OR tendinitis[tiab]) AND ("Extracorporeal Shockwave Therapy"[Mesh] OR shockwave*[tiab] OR shock wave*[tiab] OR extra corporeal pulse-activ*[tiab] OR EPAT[tiab])*

EMBASE (OVID)

Database(s): Issue: Embase Classic+Embase 1947 to 2021 January 20

Search Strategy:

#	Searches	Results
1	achilles tendon/	11120
2	exp tendinitis/	18932
3	exp tendon injury/	24755
4	exp tendon/	49312
5	(achilles or tendoachilles or calcaneal or tendinopath* or tendinos* or tendinitis).ti,ab,kw.	30806
6	(tendon* adj3 (patholog* or injur*)).ti,ab,kw.	6900
7	1 or 2 or 3 or 4 or 5 or 6	94903
8	shock wave therapy/	1531
9	(shockwave* or shock wave* or extracorporeal pulse activ* or EPAT).ti,ab,kw.	15979
10	8 or 9	16242
11	7 and 10	702

Abbreviations: exp, "explodes" controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary's hierarchy).

Cochrane Central Register of Controlled Trials
Issue 1 of 12, January 2021:

ID	Search	Hits
#1	(achilles or tendoachilles or calcaneal or tendinopath* or tendinos* or tendinitis):ti,ab,kw	2730
#2	(tendon* near/3 (patholog* or injur*)):ti,ab,kw	659
#3	#1 or #2	3085
#4	(shockwave* or shock wave* or extracorporeal pulse activ* or EPAT):ti,ab,kw	2593
#5	#3 and #4 in Trials	241

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Chapter 5.

Poor association between tendon structure and self-reported symptoms following conservative management in active soldiers with mid-portion Achilles tendinopathy

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Abstract

Introduction

Mid-portion Achilles tendinopathy (mid-AT) is currently the preferred term for persistent Achilles tendon pain, defined as located 2 to 7 cm proximal to the calcaneus, and with loss of function related to mechanical loading. Histologically, mid-AT is considered to represent a degenerative condition. Therefore, monitoring of tendon structure additional to pain and function may be warranted, to prevent progression of degeneration or even tendon rupture. The aim of this study was to determine the association between pain and function, relative to the Achilles tendon structure, in soldiers treated with a conservative programme for mid-AT.

Methods

A total of 40 soldiers (40 unilateral symptomatic tendons) were included in this study. Pain and function were evaluated with the Victorian Institute of Sports Assessment – Achilles (VISA-A) questionnaire. Tendon structure was quantified using ultrasound tissue characterisation (UTC). We quantified both the Achilles tendon mid-portion (2-7 cm) and the area of maximum degeneration (AoMD) within the tendon mid-portion. VISA-A and UTC measurements were taken at baseline and after 26 weeks of follow-up. Spearman's rho was used to determine the correlation between VISA-A and UTC. Correlations were calculated for baseline, follow-up, and change score values.

Results

Negligible correlations were found for all analyses, ranging from -0.173 to 0.166 between mid-portion tendon structure and VISA-A, and from -0.137 to 0.150 between AoMD and VISA-A. While VISA-A scores improved, on average, from 59.4 points at baseline to 93.5 points at follow-up, no detectable improvement in aligned fibrillar structure was observed in our population.

Conclusion

Pain and function are poorly associated with Achilles tendon structure in soldiers treated with a conservative programme for mid-AT. Therefore, we advise clinicians to use great caution in communicating relationships between both clinical entities.
Trial registration number NL69527.028.19.

What is already known on this topic

- Achilles tendon structure appears poorly associated with disease severity and prognosis in non-military populations treated with eccentric loading exercises for mid-AT.

What this study adds

- Both the Achilles tendon mid-portion (2-7cm), and the area of maximum degeneration (AoMD) within the tendon mid-portion, are poorly associated with pain and function in soldiers treated with extra corporeal shockwave therapy (ESWT) and load management for mid-AT.

- In our population, a combined treatment of ESWT and exercise did neither improve aligned fibrillar structure in the Achilles tendon mid-portion nor in the area of maximum degeneration within a 26-week period.

How this study might affect military practice or policy

- In soldiers with mid-AT, great caution is advised in communicating (causal) relationships between tendon structure on the one hand and pain and function on the other hand.

Introduction

Achilles tendinopathy (AT) is currently the preferred term for persistent Achilles tendon pain and loss of function related to mechanical loading.[1] The treatment is initially conservative.[2] AT has been reported to occur in a wide age range of 20-69 years, with peaks between 40-59 years.[3] Active individuals are most frequently affected, particularly runners, with life-time prevalences ranging up to 52%.[2] AT is also common in soldiers, significantly impacting activity levels and military operational readiness.[4]

AT can be divided into mid-portion Achilles tendinopathy (mid-AT) and insertional Achilles tendinopathy.[2] Mid-AT, defined as located 2 to 7 cm proximal to the calcaneus, is an isolated tendinopathy, generally considered to represent a degenerative condition.[3, 5, 6] In tendinopathy, tendon loading may cause progressive degeneration,[6] in rare occasions (4%) ultimately leading to a tendon rupture.[3] However, tendon loading can also be an anabolic stimulus to improve tendon structure.[6]

Clinicians should primarily assess the domains of pain and function when evaluating patients with mid-AT, using the Victorian Institute of Sports Assessment – Achilles (VISA-A) questionnaire as the preferred patient reported outcome measure.[2, 7] Additional monitoring of a tendon's structural response to biomechanical loading may also be of importance, especially in physically demanding professions, such as soldiers, for whom the rare event of an Achilles tendon rupture can have serious consequences.

Ultrasound tissue characterisation (UTC) is an imaging technique to visualise and quantify the mid-portion Achilles tendon structure.[8] UTC discriminates 4 echo-types (I to IV) within the Achilles tendon matrix. Combined echo-types I + II represent aligned fibrillar structure, whereas echo-types III + IV can be seen as disorganised tendon structure. UTC can be used to monitor load[9, 10] or to evaluate treatment.[11, 12]

While growing evidence indicates that tendon structure should not be used to explain the presence or severity of current and future symptoms in AT, the evidence is still conflicting.[8, 10-13] With regard to the clinical applicability of UTC, we aimed to determine the association between pain and function, relative to the mid-portion Achilles tendon structure, in soldiers treated with a conservative treatment programme for mid-AT.

Methods

Study setting

The study was conducted at the Sports Medicine Centre of the Department of Training Medicine and Training Physiology of the Royal Netherlands Army, Utrecht, the Netherlands. This centre is a secondary care facility for soldiers that predominantly focuses on researching and treating persistent musculoskeletal health problems.

Eligibility criteria

Consecutive patients, referred to the Sports Medicine Centre for AT between July 2019 and January 2021, were potentially eligible for inclusion based upon the following criteria: (1) military personnel in active duty (18-60 years); (2) a clinically established diagnosis of mid-AT;[2] and (3) symptoms for two months or more. In case of bilateral symptoms, only the side with the lowest VISA-A score was included into the analysis.

Participants were excluded if they reported concomitant insertional Achilles tendinopathy; or on the presence of factors that may have adversely affected tendon structure: (1) signs of a complete Achilles tendon rupture; (2) prior surgery to the Achilles tendon; (3) use of statins, fluoroquinolones, or corticosteroids;[14] and (4) a previous diagnosis of rheumatoid arthritis, diabetes mellitus, or psoriasis.[14] All participants were recruited by the main researcher (MP, physical therapist). Prior to inclusion, each participant provided written informed consent for anonymous use of their data.

Patient evaluation

Patient characteristics

At baseline, the following patient characteristics were retrieved: age (years), height (cm), weight (kg), Body Mass Index (BMI, %), gender (male/female), and symptom duration (months).

Baseline and follow-up measurements

Measurements were performed at baseline and during follow-up at week 26, and consisted of a written VISA-A questionnaire[7] and a UTC scan (Figure 1).[8]

VISA-A is a validated, disease-specific instrument to assess pain, function in daily living, and sporting activity.[7] The sum score on the VISA-A can range from 0 to 100 points, where 100 represents a perfect asymptomatic score. All participants independently completed the VISA-A questionnaire prior to the UTC investigation, in order to avoid the imaging outcome to influence the VISA-A scoring.

UTC scans were collected and processed according to a standardised protocol, that has shown excellent intra-rater and inter-rater reliability in the same patient group used for this study.[15] A single experienced examiner in UTC (MP) collected the UTC scans. Images were acquired with a 12-MHz linear ultrasound transducer (Terason 12L5 Smartprobe, Vermon, France), using Terason software (t2000+ OEM). This transducer was embedded in a motorized tracking device (UTC tracker, UTC imaging, 6171GD Stein, The Netherlands, serial no. UTC-201-041).

An independent researcher (MM, physical therapist), blinded to the VISA-A scoring, processed the UTC scans, aiming to quantify: (1) the mid-portion Achilles tendon structure (2-7cm), and subsequently (2) the area of maximum degeneration (AoMD) within the tendon mid-portion.[15]

Figure 1. *Ultrasound tissue characterisation scanning of the Achilles tendon with the patient in a prone position.*

Rehabilitation programme

The rehabilitation programme of 26 weeks (Figure 2) consisted of patient education,[2] extracorporeal shockwave therapy (ESWT), exercise on a cross-trainer or stair climber, and a return to running programme (supplemental file 1).[16]

Sample size calculation

Based on prior research,[8, 10, 11] for sample size calculation we assumed a low correlation of 0.45 between UTC and VISA-A scores.[17] With a default alpha of 0.05 and a statistical power of 0.80, a sample size of 36 participants was calculated. Taking into account a 10% loss to follow-up, we included a total of 40 active soldiers for this study.

Statistics

Baseline characteristics of our study population were presented with appropriate measures of central tendency and dispersion. For tendon structure, aligned fibrillar structure (echo-types I + II) and disorganised tendon structure (echo-types III + IV) were used as the two outcomes.[8]

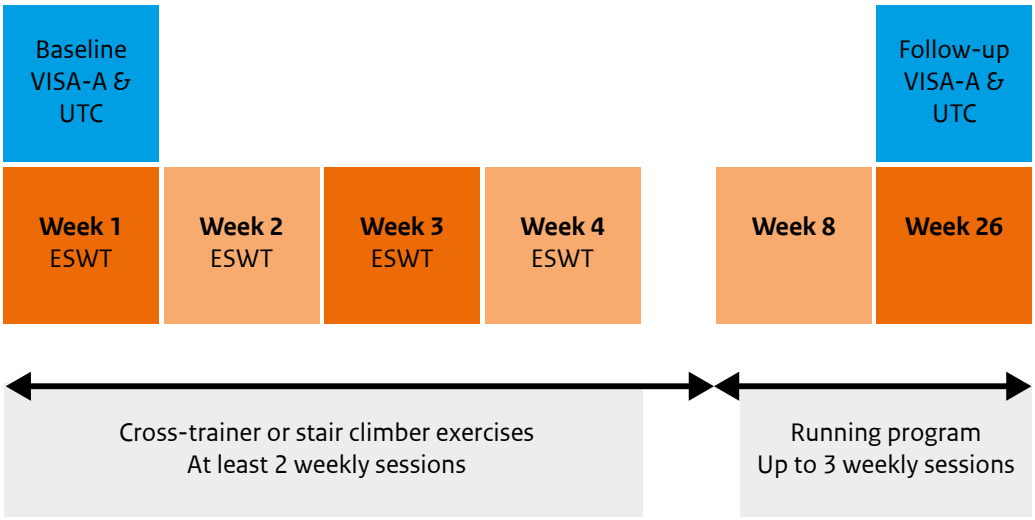

Figure 2. *The rehabilitation programme of soldiers with mid-portion Achilles tendinopathy. In the first 4 weeks, all soldiers received weekly sessions of extracorporeal shockwave therapy. During the first 8 weeks, all soldiers performed an individualised exercise programme on a stair climber or cross-trainer, followed by a return to running programme from week 8 to 26.*

Both echo-type combinations were expressed as a percentage of the total Achilles volume analyzed with UTC.

Pearson's correlation coefficients were chosen to determine the strength and direction of the association between UTC and VISA-A scores.[17] When data were not normally distributed, Spearman's rank correlation coefficients were used.[17] Correlation coefficients were interpreted either as: negligible (0.00 to 0.30), low (0.30 to 0.50), moderate (0.50 to 0.70), high (0.70 to 0.90), and very high (0.90 to 1.00).[17]

Correlations between VISA-A scores and UTC were calculated at baseline and follow-up, as well as for pre-post change scores, in order to evaluate the responsiveness of UTC.

All analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 25.0. Armonk, New York, USA).

Ethical considerations

The data were collected as part of an observational study (https://www.toetsingonline.nl/to/ccmo_search.nsf/Searchform?OpenForm, file number ToetsingOnline NL69527.028.19), aiming to evaluate ESWT and load management in service members suffering from mid-AT. The study was conducted according to the principles of good clinical practice, and was approved by the ethics committee METC Brabant, Tilburg, the Netherlands (number of approval 1921).

Results

A total of 40 patients were included in this study, of which 12 reported bilateral symptoms. No participants were lost to follow-up. Patient characteristics are presented in Table 1.

The mean VISA-A score improved from baseline (59.4 ± SD 17.3, range 15-86) to follow-up at 26 weeks (93.5 ± SD 9.8, range 48-100).

The mean UTC echo-types for the Achilles tendon mid-portion and the AoMD are displayed in Table 2. Echo-type change scores were calculated from baseline to follow-up. We determined their clinical relevance by comparing the values to the minimal detectable changes (MDC) calculated for this particular cohort.[15]

In the mid-portion, aligned fibrillar structure (echo-type I + II) showed a 4.6% improvement, which was below the MDC of 5.9%. Disorganised tendon structure (echo-type III + IV) in the mid-portion decreased with 4.6%, exceeding the MDC of 4.2%.
In the AoMD, aligned fibrillar structure improved with 4.1%, not exceeding the MDC of 9.8%. Disorganised tendon structure in the AoMD decreased with 4.2%, also not exceeding the MDC of 10.0%.

Regarding the changes of individual mid-portion echo-types, echo-type IV decreased with 2.3%. This was the only individual echo-type that showed a change score above the MDC (1.9%). All other change scores were below this threshold: echo-type I 3.1% (MDC 4.7%), echo-type II 1.6% (MDC 2.5%), and echo-type III 2.4% (MDC 3.6%).
No AoMD change scores of individual echo-types exceeded the MDC: echo-type I 3.6% (MDC 4.8%), echo-type II 0.4% (MDC 8.2%), echo-type III 2.9% (MDC 6.8%), and echo-type IV 1.4% (MDC 4.6%).

Baseline, follow-up and change score correlations between VISA-A and UTC are reported in Table 3.

Table 1. Patient characteristics of active soldiers with mid-AT.

Characteristics	Total group (n=40) Mean ± SD
Age (years)	40.1 ± 9.4
Height (cm)	185.1 ± 5.9
Weight (kilograms)	93.8 ± 13.2
Body Mass Index (%)	27.4 ± 3.3
Gender (male/female)	38/2
Duration of symptoms (months)	13.0 ± 16.5

n, number; SD, standard deviation.

Table 2. Mean UTC echo-types of the participants Achilles tendon mid-portion and the AoMD at baseline, and during follow-up at 26 weeks.

Echo-type	Mid-portion *Total group (n=40)* *Mean ± SD (min-max)*		AoMD *Total group (n=40)* *Mean ± SD (min-max)*	
	Baseline	*Follow-up*	*Baseline*	*Follow-up*
I (%)	48.3 ± 11.9 (27.3-75.2)	51.4 ± 11.3 (28.8-75.6)	37.1 ± 11.9 (14.7-64.8)	40.7 ± 11.8 (17.0-65.1)
II (%)	19.4 ± 4.6 (10.5-32.9)	21,0 ± 4.5 (10.5-32.1)	22.2 ± 7.4 (12.2-42.9)	22.6 ± 7.1 (9.8-39.9)
III (%)	19.1 ± 8.7 (2.6-35.5)	16.7 ± 8.7 (1.9-37.8)	26.6 ± 11.9 (1.5-49.7)	23.7 ± 11.5 (2.8-49.5)
IV (%)	13.1 ± 6.6 (1.9-29.2)	10.8 ± 5.3 (1.4-25.6)	13.8 ± 6.7 (0.4-24.3)	12.4 ± 5.9 (0.8-27.3)
Total	**100%**	**100%**	**100%**	**100%**
I+II (%)	67.8 ± 14.4 (40.8-95.3)	72.4 ± 13.2 (42.5-96.6)	59.2 ± 17.0 (30.0-98.1)	63.3 ± 16.4 (27.4-96.5)
III + IV (%)	32.2 ± 14.4 (4.7-59.3)	27.6 ± 13.2 (3.3-57.5)	40.4 ± 17.5 (1.9-70.0)	36.2 ± 16.4 (3.6-72.5)
Total	**100%**	**100%**	**100%**	**100%**

Echo-types I, II, III, and IV are expressed as a percentage of the analysed Achilles tendon volume. Combined, the echo-types I + II represent aligned fibrillar structure, and the echo-types III + IV disorganised tendon structure.
AoMD, area of maximum degeneration (1 slide in the Achilles tendon mid-portion with the lowest representation of echo-type I); max, maximum; min, minimum; n, number; SD, standard deviation; UTC, ultrasound tissue characterisation.

Table 3. Correlations between the VISA-A scores and UTC-typing at baseline, during follow-up after 26 weeks, and with regard to the change scores.

	VISA-A baseline	VISA-A follow-up	VISA-A Difference
MID-PORTION baseline ET1+2	ρ= 0.166, sig. (2-tailed) 0.306		
MID-PORTION follow-up ET1+2		ρ= 0.046, sig. (2-tailed) 0.778	
MID-PORTION Difference ET1+2			ρ= -0.013, sig. (2-tailed) 0.935
MID-PORTION baseline ET3+4	ρ= -0.173, sig. (2-tailed) 0.287		
MID-PORTION follow-up ET3+4		ρ= -0.048, sig. (2-tailed) 0.769	
MID-PORTION Difference ET3+4			ρ= 0.018, sig. (2-tailed) 0.912
AoMD baseline ET1+2	ρ= 0.131, sig. (2-tailed) 0.422		
AoMD follow-up ET1+2		ρ= 0.150, sig. (2-tailed) 0.354	
AoMD Difference ET1+2			ρ= 0.024, sig. (2-tailed) 0.882
AoMD baseline ET3+4	ρ= -0.126 sig. (2-tailed) 0.422		
AoMD follow-up ET3+4		ρ= -0.137, sig. (2-tailed) 0.398	
AoMD Difference ET3+4			ρ= -0.024, sig. (2-tailed) 0.885

AoMD, area of maximum degeneration (one slide in the Achilles tendon mid-portion with the lowest representation of ET I); ET, echo-type; sig., significance; UTC, ultrasound tissue characterisation; VISA-A, Victorian Institute of Sports Assessment – Achilles questionnaire; ρ, Spearman's rho.

Discussion

Association between the VISA-A and tendon structure

The primary objective of this study was to investigate the association between pain and function, relative to tendon structure, in soldiers treated with a conservative programme for mid-AT. In tendinopathy, improvements in pain and function generally precede the much slower restoration of tendon structure.[18] Therefore we hypothesised that the AoMD would show a stronger association with VISA-A than the tendon mid-portion, since relative changes in tendon structure can be expected to be larger than in the mid-portion analysis. This turned out not to be the case as we found negligible correlations for all analyses, indicating that tendon structure is poorly associated with pain and function in soldiers with mid-AT.

Our findings are supported by two non-military studies evaluating the association between pain and function versus tendon structure in mid-AT patients.[11, 12] In the first study, de Vos et al.[12] evaluated subjects who followed an eccentric loading programme, reporting negligible correlations between changes scores on VISA-A and echo-types I + II from baseline to follow-up at 24 weeks.[12] Baseline echo-types I + II also showed negligible correlations with VISA-A scores after 24 weeks.[12] In the second study, de Jonge et al.[11] evaluated eccentric loading combined with either a platelet-rich plasma injection or a saline injection,[11] also reporting no associations between VISA and UTC.[11] Both studies concluded that tendon structure was not related to disease severity or prognosis in mid-AT.[11, 12]

In tendinopathy, the exact pathophysiology and the source of nociception are currently unknown.[2, 6, 19] The fact that recovery of tendon structure and improvement in pain and function do not follow the same pace may partly explain the poor associations.[18] Positive changes in the pain system following tendinopathy treatment can already occur in 2 weeks, with results peaking at 12 weeks,[20] while full restoration of tendon structure takes considerably longer, from 24 weeks[11] up to several years.[18]

Mean improvement on the VISA-A

The VISA-A score improved, on average, from 59.4 points at baseline to 93.5 points at follow-up. Although scores can range from 0 to 100 points, a score of 90 points is reported to represent full recovery from mid-AT.[21] A recent meta-analysis concluded that VISA-A scores may be expected to improve by approximately 21 points, following exercise interventions for mid-AT.[20] We have found a considerably higher mean VISA-A improvement of 34.1 points.

Several factors may explain the large improvements found in our study. One possible explanation is that we used a combination of ESWT and exercise in our rehabilitation programme, as this combination is suggested to achieve higher VISA-A scores than exercise alone.[22] It is also possible that an above average treatment compliance of our study group, consisting of generally sports-minded, instruction-compliant soldiers, may have positively influenced the results. Finally, we cannot rule out the potential influence of additional ultrasonography in our programme. When subjects were in doubt whether continued or progressive exercise adversely affected their tendon structure, a grey scale ultrasound was

performed to rule out any tendon abnormalities. Grey scale ultrasound did not reveal any adverse tendon changes in the vast majority of the cases. It is possible that visual confirmation of unchanged or uncompromised tendon structure, along with patient education, may have positively influenced illness perceptions, contributing to higher VISA-A scores. Illness perceptions are reported to have a cross-sectional relationship with musculoskeletal pain.[23]

Mean changes of Achilles tendon structure

We have only observed detectable changes in the mid-portion analysis, with both disorganised tendon structure and echo-type IV barely exceeding the MDC by 0.4%. Despite an above-average increase in the mean VISA-A score, no improvement in aligned fibrillar tendon structure was observed after 26 weeks.

Our findings contradict the results of an in vivo study[24] and an in vitro study[25] that suggest ESWT-induced tendon structure improvements, but are in line with a study by de Vos et. al.,[12] who reported no increase of aligned fibrillar structure following an eccentric loading programme after 24 weeks. Contrastingly, de Jonge et. al.[11] reported a mean improvement in aligned fibrillar structure of 11% following an eccentric loading programme. It should be acknowledged that in the latter study, patients additionally received either a platelet-rich plasma injection or a saline injection.

Rehabilitation programme

A total of 9 out of 40 participants included in this study had not undergone previous treatment. The other 31 patients were referred for ESWT due to unsatisfactory results in primary care, where they received various interventions, i.e., NSAID's, ankle mobilisation, calf stretching exercises, massage, and gait retraining. Tendon loading exercises had been a part of the previous treatment in 28 participants. Although these exercises currently represent the standard of care for mid-AT,[2] a large number of patients does not seem to respond adequately, and up to half of all patients seeking alternative treatment.[26]

Clinical applicability

As tendon structure appears poorly associated with pain and function in mid-AT, we recommend assessing both clinical entities separately. We strongly advise clinicians to use great caution in communicating (causal) relationships between tendon structure and pain and function in soldiers suffering from mid-AT, as our results cannot support this in any way. It is our belief that in physically highly active populations, like soldiers, assessment of Achilles tendon structure should be used to evaluate load, or to evaluate interventions targeting tendon structure, and also to prevent potential structural damage to Achilles tendons.[3]

Limitations

A number of potential limitations may have influenced the results of this study.

First, both the UTC scans and VISA-A scores were collected by the same researcher. It is unlikely that this has influenced the outcomes, as the VISA-A is a self-completing questionnaire,[21] and the UTC scanning procedure is highly standardised.[15]

Second, for reasons of standardisation, but also due to positive clinical experiences over the years, we have chosen to replace traditional tendon loading exercises[2] by a stair climber or cross-trainer in our study. This appears to have had no major negative effects on pain and function, as the mean VISA-A score at follow-up (93,5 points) indicates complete recovery from mid-AT.[21] We did not observe detectable improvements in aligned fibrillar structure after 26 weeks. Whether this would have been the case if we had incorporated traditional tendon loading exercises into our rehabilitation programme is questionable, as there is currently limited and conflicting evidence regarding this topic.[11, 12] Possibly, our follow-up of 26 weeks was too short to observe improvement of aligned fibrillar structure.[18]

Third, while tendon loading exercises had been part of a previous treatment programme in 28 participants included in our study, it should be acknowledged that 13 of those 28 participants had not completed a full 12-week programme as recommended by the clinical guideline.[2] Because improvements in pain and function are reported to peak at 12 weeks following inception of such a programme,[20] it is quite possible that for some of these 13 participants tendon loading would have been more effective if they had completed the full 12 weeks.

Possible future studies could compare traditional tendon loading exercises with exercise on a stair climber or cross-trainer in mid-AT, or explore the relationship between the use of ultrasound, illness perceptions, and patient-reported outcomes evaluating pain and function in mid-AT.

Supplemental File 1. The rehabilitation programme of soldiers with mid-portion Achilles tendinopathy.

Patient education

First patient education was provided, emphasising the importance of an active treatment strategy, the nature of the pathological condition, pain education, psychosocial factors, load-management, the (long-term) prognosis, and return to full (sports) activities.

Focused extracorporeal shockwave therapy (F-ESWT)

All participants received weekly sessions of ESWT in the first 4 weeks. ESWT was administrated by MP, while subjects lay prone, with their feet hanging freely over the examining table. This allowed the ipsilateral foot to be fixed in maximum dorsiflexion, to make the tendon easily accessible for the shockwave applicator. Each ESWT session consisted of 2000 shocks, distributed evenly over the painful mid-portion area, with a frequency of 8 shocks per second. Immediately after initiating the ESWT treatment, the therapist rapidly increased the intensity to the level the subject considered tolerable for the treatment duration of approximately 4 minutes (up to a total energy density of 0.82mJ/mm^2).

Exercise interventions

Following a one on one instruction, the exercise interventions were carried out individually. Exercise related pain was allowed up to a threshold of 5 points on a numeric pain rating scale (range 0-10). Because running is known to be provocative of mid-AT symptoms in the majority of cases in our population, it was temporarily replaced with an individualised and gradual build-up programme on a stair climber or cross-trainer from week 1 to 8 of the rehabilitation programme (Figure 2). In our experience this is generally able to be conducted within the advised pain threshold. Exercise on a stair climber or cross-trainer was performed at least 2 times a week, up to one hour per session, during which the participants were instructed to actively lift their heels in order to facilitate plantar flexor activity.

From week 8 to 26, the running program from the Dutch Heart Foundation was performed, up to a maximum of 3 weekly sessions.

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Chapter 6.

Victorian Institute of Sport Assessment – Achilles thresholds for minimal important change and return to presymptom activity level in active soldiers with mid-portion Achilles tendinopathy

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Abstract

Introduction

Mid-portion Achilles tendinopathy (mid-AT) is common in soldiers, significantly impacting activity levels and operational readiness. Currently, Victorian Institute of Sport Assessment – Achilles (VISA-A) represents the gold standard to evaluate pain and function in mid-AT. Our objective was to estimate VISA-A thresholds for minimal important change (MIC) and patient-acceptable symptom state for return to the presymptom activity level (PASS-RTA), in soldiers treated with a conservative programme for mid-AT.

Methods

A total of 40 soldiers (40 unilateral symptomatic Achilles tendons) were included in this prospective cohort study. Pain and function were evaluated using VISA-A. Self-perceived recovery was assessed with the Global Perceived Effect scale. The predictive modeling method (MIC-predict) was used to estimate MIC VISA-A post-treatment (after 26 weeks) and after 1 year of follow-up. The post-treatment PASS-RTA VISA-A was estimated using receiver operating characteristic statistics. The PASS-RTA was determined by calculating Youden's index value closest to 1.

Results

The adjusted MIC-predict was 6.97 points (95% CI: 4.18 to 9.76) after 26 weeks and 7.37 points (95% CI: 4.58 to 10.2) after 1 year of follow-up post-treatment. The post-treatment PASS-RTA was 95.5 points (95% CI: 92.2 to 97.8).

Conclusions

A VISA-A change score of 7 points, post-treatment and at 1 year of follow-up, can be considered a minimal within-person change over time, above which soldiers with mid-AT perceive themselves importantly changed. Soldiers consider their symptoms to be acceptable for return to their presymptom activity level at a post-treatment VISA-A score of 96 points or higher.
Trial registration number NL69527.028.19.

What is already known on this topic

- The ability of Victorian Institute of Sport Assessment – Achilles (VISA-A) to detect true changes in health status is population-specific and context-specific. VISA-A thresholds for minimal important change (MIC) and patient-acceptable symptom state for return to presymptom activity level (PASS-RTA), regarding active soldiers treated for mid-portion Achilles tendinopathy (mid-AT), are currently lacking.
- In a non-military population, the MIC for VISA-A was found to be 14 points after 12 weeks and 7 points after 24 weeks.

What this study adds

- In soldiers, thresholds for MIC VISA-A were 6.97 points (95% CI: 4.18 to 9.76) after 26 weeks (post-treatment) and 7.37 points (95% CI: 4.58 to 10.2) after 1 year of follow-up.

- In soldiers, the post-treatment threshold for PASS-RTA was 95.5 points (95% CI: 92.2 to 97.8) after 26 weeks.

How this study might affect military practice or policy

- Values for MIC VISA-A can be used to determine the number of responders in clinical trials, or to a certain treatment in clinical practice, and also by clinicians to interpret changes scores in light of the probability that an individual soldier with mid-AT experiences a meaningful change.
- The PASS-RTA VISA-A may guide clinicians in rehabilitating soldiers treated for mid-AT.

Introduction

Mid-portion Achilles tendinopathy (mid-AT) is defined as persistent Achilles tendon pain 2 to 7 cm proximal to the calcaneus, and with loss of function related to mechanical loading.[1, 2] Mid-AT is most common between the ages of 30 and 50 years.[3] Symptoms can be long lasting despite state-of-the-art treatment.[4, 5] In the general population, up to 60% reports pain after 5 years of follow-up,[6] and 37% still experiences some level of pain and reduced function after 10 years of follow-up.[4] Mid-AT is also very common among soldiers, and can have a profound impact on physical activity levels and military operational readiness.[7, 8] A previous diagnosis of tendinopathy is considered the strongest risk factor for mid-AT.[2, 7]

The Victorian Institute of Sport Assessment – Achilles (VISA-A) is recommended as a patient-reported outcome measure (PROM) to evaluate the clinical course of mid-AT.[2, 3] VISA-A is a validated, disease-specific questionnaire that assesses pain, function in daily living, and sporting activity.[9] Despite thorough validation, the responsiveness of VISA-A, that is, the ability to detect true changes in health status, may depend on several factors including population characteristics, interventions, and period of follow-up.[10, 11]

The minimal important change (MIC) is defined as a threshold for a minimal within-person change over time, above which patients perceive themselves importantly changed.[11] The MIC has limited generalisability across patient groups.[10] No studies so far have estimated the MIC for VISA-A in soldiers with mid-AT. Moreover, no MIC for mid-AT has been reported beyond a 24-week follow-up period,[5, 12, 13] hampering the current interpretation of long-term follow-up VISA-A change scores.

The patient-acceptable symptom state (PASS) is defined as the threshold beyond which patients consider themselves to be well.[14] MIC and PASS are complementary as they reflect the patients' perspectives of 'feeling better' (MIC) and 'feeling good' (PASS).[14] A PASS indicating return to presymptom activity level (PASS-RTA) for soldiers treated for mid-AT is currently lacking. Such a threshold may aid in preventing a recurrence of mid-AT.

Therefore, our objective was to determine post-treatment both the MIC VISA-A and PASS-RTA VISA-A in soldiers treated with a conservative programme for mid-AT. Additionally, we aimed to determine MIC VISA-A at 1 year of follow-up.

Methods

Study design and setting

The data were collected as part of a large prospective cohort study (https://www.toetsingonline.nl/to/ccmo_search.nsf/Searchform?OpenForm, file number ToetsingOnline NL69527.028.19), aimed to evaluate a conservative treatment programme for soldiers suffering from mid-AT. The study was conducted at the Sports Medicine Centre of the Department of Training Medicine and Training Physiology of the Royal Netherlands Army, Utrecht, the Netherlands.

Eligibility criteria

Consecutive patients, consulting the Sports Medicine Centre for mid-AT between July 2019 and January 2021, were eligible for inclusion based on the following criteria: (1) military personnel (18-60 years) in active duty; (2) a clinical diagnosis of mid-AT;[2] and (3) symptoms for 2 months or more. In case of bilateral symptoms, only the side with the lowest score on the VISA-A questionnaire was included into the analysis.

Participants were excluded on the basis of: (1) concomitant insertional Achilles tendinopathy (ins-AT); (2) signs of a complete Achilles tendon rupture; (3) prior Achilles tendon surgery; (4) use of statins, fluoroquinolones, or corticosteroids[15] and (5) a previous diagnosis of rheumatoid arthritis, diabetes mellitus or psoriasis.[15] All participants were recruited by the main researcher (MP, physical therapist).

Patient and baseline characteristics

The following patient characteristics were retrieved at baseline: age (years), height (cm), weight (kg), body mass index (%), gender (male/female), symptom duration (months) and baseline VISA-A score.[9]

Conservative treatment programme

The 26-week conservative treatment programme used in this study has been published in detail.[16] In short, this programme consisted of: patient education;[2] focused extracorporeal shockwave therapy (four weekly sessions during the first 4 weeks); an individualised exercise programme on a stair climber or cross-trainer (at least two weekly sessions during the first 8 weeks); followed by a return to running programme (up to three weekly sessions from week 8 to 26).[16]

Study procedures

The follow-up measurements for this study consisted of a self-administered, written VISA-A questionnaire,[9] a 7-point Global Perceived Effect (GPE) scale,[11] and a so-called anchor question (yes/no): 'Have your mid-AT symptoms recovered to such an extent that you were able to return to your presymptom activity level?'[14]

VISA-A scores can range from 0 to 100, where 100 equals a perfect asymptomatic score. The GPE expresses self-perceived recovery as 1: very much improved; 2: much improved; 3: little improved; 4: no change; 5: a little deterioration; 6: much deterioration and 7: very much deterioration.

VISA-A was taken at baseline, at the end of the conservative treatment programme (after 26 weeks), and at 1-year post-treatment (after 78 weeks). The GPE was taken after 26 weeks and at 1 year of follow-up (after 78 weeks). The anchor question was evaluated post-treatment.

Statistics

Analyses were performed using SPSS (IBM SPSS Statistics for Windows, V.25.0, IBM, Armonk, New York, USA) and according to the recommendations of Terwee et al.[11] Baseline characteristics of our study population were presented with appropriate measures of central tendency and dispersion. The MIC was estimated using the predictive modeling method (MIC-predict), which is an anchor-based method relating VISA-A change scores to the GPE.[11, 17] First, the correlations between the numeric VISA-A change scores (after 26 weeks and at 1 year of follow-up), and corresponding categorical GPE's were calculated using Spearman's rank correlation coefficients.[18] Validity was assumed at a correlation of at least 0.30.[11] When data were deemed valid for estimation of the MIC the 7-point GPE was dichotomised to 'not improved' (scores 4-7) and 'improved' (scores 1-3).[11, 17] In case the percentage of improved patients was not approximately 50%, the adjusted MIC-predict was used.[11]

The PASS-RTA was estimated using receiver operating characteristic (ROC)-analysis in SPSS, by plotting the VISA-A post-treatment scores after 26 weeks to the return to presymptom activity level outcomes. The area under the curve (AUC) was interpreted as 'failed': 0.5-0.6; 'poor': 0.6-0.7; 'fair': 0.7-0.8; 'good': 0.8-0.9; and 'excellent': 0.9-1.0.[19] Youden's index was calculated to maximise sensitivity and specificity, using the formula: (sensitivity + specificity)-1. The PASS-RTA was determined with the Youden's index value closest to 1. Finally, the 95% CIs around MICs and PASS-RTA were calculated.[20]

Ethical considerations

The study was conducted according to the principles of Good Clinical Practice, and was approved by the ethics committee METC Brabant, Tilburg, the Netherlands (number of approval 1921). Participants gave informed consent to participate in the study before taking part.

Results

A total of 40 soldiers were included in this study. None were lost to follow-up. Patient characteristics are presented in Table 1.

Table 1. Patient characteristics of active soldiers with mid-AT .

Characteristics	Total group (n=40) Mean ± SD
Age (years)	40.1 ± 9.4
Height (cm)	185.1 ± 5.9
Weight (kilograms)	93.8 ± 13.2
Body Mass Index (%)	27.4 ± 3.3
Gender (male/female)	38/2
Duration of symptoms (months)	13.0 ± 16.5
Baseline VISA-A score	59.4 ± 17.3

Mid-AT, mid-portion Achilles tendinopathy; SD, standard deviation; cm, centimeter; VISA-A, Victorian Institute of Sport Assessment – Achilles tendon.

Spearman's rank correlation coefficients between VISA-A change scores and the GPE at 26 weeks and between VISA-A change scores and the GPE at 1 year of follow-up, were 0.46 (*p* 0.003) and 0.53 (*p* 0.000), respectively. Both values met the minimum threshold of 0.30 for assuming validity of the anchor.[11] Dichotomisation of the GPE indicated improvement in 95% (38/40) of all patients after 26 weeks and in 93% of all patients (37/40) at 1 year of follow-up. As the percentage of patients reporting improvement largely exceeded 50%, the adjusted MIC-predict was used to correct for bias (i.e., overestimation of the MIC).[17] The adjusted MIC-predict was 6.97 points (95% CI: 4.18 to 9.76) after 26 weeks and 7.37 points (95% CI: 4.58 to 10.2) after 1 year of follow-up post-treatment.

The post-treatment PASS-RTA was 95.5 points (95% CI: 92.2 to 97.8) (Figure 1). The corresponding AUC was 0.896 (95% CI: 0.728 to 1.000).

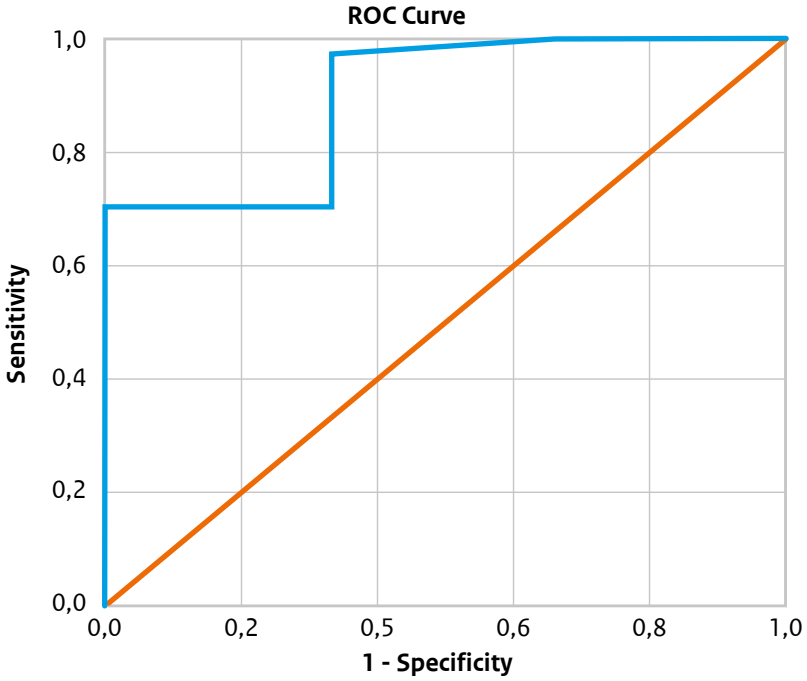

Figure 1. *The ROC curve.*
The ROC curve expresses the ability of VISA-A to distinguish patients that were able to return to their presymptom activity level from patients who were unable to return to their presymptom activity level. Diagonal segments are produced by ties.
PASS-RTA, patient acceptable symptom state for return to pre-symptom activity level; ROC curve, receiver operating characteristic curve; VISA-A, Victorian Institute of Sport Assessment – Achilles tendon.

Discussion

This is the first study to report VISA-A thresholds for both MIC and PASS-RTA, in soldiers treated with a standard care programme for mid-AT. Our values for MIC can be used to identify responders in clinical trials, or to a certain treatment in clinical practice, and also by clinicians to interpret VISA-A changes scores in light of the probability that an individual soldier experiences a meaningful change.[11] The PASS-RTA provides an estimate for soldiers to return to their presymptom activity level.

We have found an adjusted MIC-predict value of 6.97 points (95% CI: 4.18 to 9.76) after 26 weeks (post-treatment) and an adjusted MIC-predict value of 7.37 points (95% CI: 4.58 to 10.2) at 1 year of follow-up. The post-treatment PASS-RTA was 95.5 points (95% CI: 92.2 to 97.8) in our study. Two remarks need to be made to put our results for MIC and PASS-RTA into

perspective. First, when evaluating treatment progress in soldiers with mid-AT, it is important to acknowledge that in a general population VISA-A scores can be expected to improve 21 points, on average, following state-of-the-art treatment.[21]
Second, in a systematic review, Iversen et al.[22] reported that mid-AT patients rarely achieve VISA-A scores equal to those of uninjured healthy controls.[22] The authors concluded that a VISA-A score of 90 points can be considered full recovery from mid-AT.[22]

We can compare our MIC of 6.97 points post-treatment with a recent non-military study by Lagas et al. [5] in mid-AT patients that reported a comparable MIC value of 7 points (95% CI: -10 to 28) after 24 weeks of treatment. In the latter study, the MIC was found to be higher after 12 weeks of follow-up, as the authors reported a value of 14 points (95% CI: 3 to 19). We were unable to retrieve studies estimating MIC VISA-A beyond a 24-week follow-up period. Therefore, we cannot compare our MIC after 1 year of follow-up to the existing literature.

Concerning PASS, Lagas et al.[5] reported values of 50 points (95% CI: 47 to 70) after 12 weeks and of 60 points (95% CI: 38 to 80) after 24 weeks. Their PASS value at 24 weeks was considerably lower than our PASS-RTA of 95.5 points after 26 weeks. Our higher PASS-RTA may well be the result of generally high physical requirements for soldiers, with respect to work and sports. It should be acknowledged that different PASS definitions may make comparisons difficult: our PASS-RTA focused on the resumption of presymptom activity level, while Lagas et al.[5] estimated a PASS defined as a general acceptable symptom state.

Two more non-military studies have estimated the MIC VISA-A in mid-AT,[12, 13] using different statistical methods. De Vos et al.[12] suggested a MIC value between 10 to 15% of the VISA-A scale reporting a value of 12 points. Tumilty et al.[13] defined the MIC as the minimum score or higher achieved by 75% of the patients in their longitudinal study, reporting a value of 16 points after 12 weeks. The statistical methods used in these two studies do not meet the current definition of MIC,[11] since they do not estimate either a minimal within-person change over time or provide an actual threshold above which patients perceive themselves importantly changed.

Currently, there is discussion about the concept of MIC in the literature, questioning the validity of published values.[11] The discussion mostly relates to inconsistencies in clinical terminology used for MIC and to a variety of methods used to estimate MIC values, of which some are less methodologically sound.[11] Therefore, Terwee et al.[11] conducted a systematic review aiming to provide practical guidance for estimating methodological sound MIC values, discussing three anchor-based methods: the MIC-predict method, the MIC-roc method, and the Mean change method or MIC-mean method.[11] We have used the MIC-predict method, which uses logistic regression analysis to estimate the MIC, with the dichotomised GPE as our dependent variable and the VISA-A change score as the independent variable.[11, 17] The MIC-predict method is based on the predicted probability that, on the basis of the observed VISA-A change score, a patient belongs to the improved group on the GPE.[11, 17] The MIC-roc method

uses ROC statistics and is based on the ability of a measurement instrument to distinguish improved from not improved patients on an anchor.[11] The MIC-roc is defined as the value for which the sum of the proportions of misclassifications ([1-sensitivity] + [1-specificity]) is the smallest.[11] The MIC-predict method and MIC-roc method should be used over the MIC-mean method, as they provide an actual threshold between improved and not improved patients, while the MIC-mean does not reflect a threshold for minimal improvement, but rather a mean in a (usually small) subgroup of patients reporting 'little improvement'. The MIC-predict method is considered the most appropriate anchor-based method, as it is more precise than the MIC-roc and can be corrected for bias if the percentage of patients reporting improvement is not about 50%.[11]

Strengths and limitations

We have conducted our study according to recent recommendations for MIC studies.[11] We used the proposed definition of MIC to avoid inconsistency in terminology (e.g., minimal clinical important difference, minimal important difference, meaningful change threshold, minimal detectable change), as seemingly interchangeable terms sometimes refer to different concepts.[11]

A disadvantage of all anchor-based methods is the concern about reliability and validity of the anchor question, as recall bias may occur over time.[11] Therefore, in advance, we calculated the correlation between the VISA-A change scores and corresponding GPEs, which indicated that our data were suitable for estimating the MIC.[11]

For MIC studies, a minimum sample size of 100 patients has been recommended.[11] Although we have included 40 soldiers in our study, we cannot substantiate this being an actual limitation, as we have found significant results for MIC values and PASS-RTA. This may be the consequence of using the currently preferred MIC-predict method, that has shown to increase statistical power in MIC studies compared to the MIC-roc method.[17]

Although the soldiers included in this study were all recreational runners and mostly male (38/40), they held a variety of military job functions that reflect the variety in physical activity levels within the military.

Recommendations for future studies

We have estimated MICs for improvement. A MIC for improvement may not be the same as a MIC for deterioration.[11] Therefore caution is warranted when generalising our MICs to individuals reporting deterioration. Future studies may address if, and to what extent, MIC VISA-A values for improvement differ from values indicating deterioration.

Finally, we would like to emphasize that mid-AT and ins-AT are considered different clinical entities in the literature,[23] with different responses to treatment.[24, 25] Therefore we would like to recommend that future studies aiming to estimate the MIC in Achilles tendinopathy perform analyses for mid-AT and ins-AT separately.

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Chapter 7.

Prognostic value of ultrasound tissue characterisation for a recurrence of mid-portion Achilles tendinopathy in military service members: a prospective cohort study

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Abstract

Introduction
Tendon structure in mid-portion Achilles tendinopathy (mid-AT) appears poorly associated with symptoms. Yet, degenerative tendon changes on imaging have been associated with an increased risk for mid-AT. We aimed to investigate the prognostic value of ultrasound tissue characterisation (UTC) for a mid-AT recurrence in service members reporting to be recovered following standard care.

Methods
Mid-portion aligned fibrillar structure was quantified post-treatment in 37 participants. Recurrences were determined after 1 year of follow-up, based on self-perceived recurrence (yes/no) combined with a decrease in post-treatment Victorian Institute of Sports Assessment – Achilles score of at least the minimal important change of 7 points. Receiver operating characteristic curve analyses were used to determine a threshold for dichotomization of outcomes for aligned fibrillar structure (normal representation/under-representation). Using multivariable logistic regression, the association between a mid-AT recurrence (yes/no) and the dichotomised aligned fibrillar structure was determined.

Results
Eight participants (22%) experienced a recurrence. The threshold for aligned fibrillar structure was set at 73.2% (95% CI: 69.4 to 77.8) according to Youden's index. Values below this threshold were significantly associated with a mid-AT recurrence (odds ratio (OR) 9.7 (95% CI: 1.007 to 93.185). The OR for a mid-AT recurrence was 1.1 (95% CI: 1.002 to 1.150) for each additional month of symptom duration. The explained variance of our multivariable logistic regression model was 0.423; symptom duration appeared to be a better predictor than aligned fibrillar structure.

Conclusions
This study identified mid-portion aligned fibrillar structure and symptom duration as potential prognostic factors for a mid-AT recurrence in military service members. The threshold for aligned fibrillar structure of 73.2% can guide preventative interventions (e.g., training load adjustments or additional tendon loading programmes) aiming to improve tendon structure to minimise the future recurrence risk.
Trial registration number https://www.toetsingonline.nl/to/ccmo_search.nsf/Searchform?OpenForm, file number ToetsingOnline NL69527.028.19

What is already known on this topic
- Degenerative Achilles tendon changes on imaging have been associated with an increased risk for mid-portion Achilles tendinopathy (mid-AT).

What this study adds
- An under-representation of aligned fibrillar structure in the Achilles tendon mid-portion as quantified with ultrasound tissue characterisation, that is, below a threshold of 73.2%, significantly increases the risk of a mid-AT recurrence (odds ratio 9.7, 95% CI: 1.007 to 93.185) in military personnel.

- Every additional month of symptom duration increases the risk of a mid-AT recurrence (OR 1.1, 95% CI: 1.002 to 1.150) in military personnel.

How this study might affect military practice or policy

- Mid-portion aligned fibrillar structure and symptom duration can be used to identify individuals at risk for a mid-AT recurrence.
- The threshold for aligned fibrillar structure can guide preventative interventions (e.g., training load adjustments or additional tendon loading programmes) aiming to improve tendon structure to minimise the future recurrence risk.

Introduction

Mid-portion Achilles tendinopathy (mid-AT) is defined as persistent Achilles tendon (AT) pain, located 2 to 7 cm proximal to the calcaneus, and with loss of function related to mechanical loading [1, 2]. This disorder is most common between the ages of 40-59 years [3], typically affecting athletes [4] and service members [5, 6]. Mid-AT can be a career-ending injury for professional athletes [4], while in service members it may have a profound impact on activity levels and military operational readiness [5, 6]. In professional football, recurrence rates are as high as 27% [4]. A prior lower limb tendinopathy is considered to be the strongest risk factor for the development of mid-AT [2, 5, 7].

The treatment of mid-AT is initially conservative, with tendon loading programmes currently representing the best evidence based practice-treatment [2]. Not all patients seem to respond adequately to these programmes, since up to half of them reports seeking one or more alternative treatments after 5 years of follow-up [8]. Although most patients eventually recover [2], still 19% of them experiences symptoms after 10 years [9].

Histologically, mid-AT is characterized by degenerative changes that may progress as a result of tendon loading [3, 10], in rare occasions (4%) leading to a tendon rupture [3]. Degenerative tendon pathology can also exist in the absence of symptoms [11, 12]. The exact pathophysiology and source of nociception of mid-AT are currently unknown [2, 10, 12].

Ultrasound Tissue Characterisation (UTC) is an imaging modality that can quantify the AT structure into four echo types (I-IV), discriminating aligned fibrillar structure (echo types I + II) from disorganised tendon structure (echo types III + IV) [13]. Growing evidence indicates that AT structure is poorly associated with self-reported symptoms [14-16], as measured with the Victorian Institute of Sports Assessment – Achilles (VISA-A) questionnaire [17]. Yet, UTC has been found to be able to discriminate symptomatic from asymptomatic ATs, using a threshold for aligned fibrillar structure [13]. Taking into account that degenerative AT changes on imaging have been associated with an increased risk of developing mid-AT [18], we hypothesised that UTC may have prognostic value in predicting a mid-AT recurrence. Insight in variables predicting a recurrence may help to identify individuals at risk, and allow for targeted

preventive strategies [2, 6]. Our objective was to determine the validity of UTC as a predictive modality for a mid-AT recurrence, in service members treated successfully with a conservative programme for mid-AT.

Methods

Study design and setting

This study was conducted at the Sports Medicine Centre of the Department of Training Medicine and Training Physiology of the Royal Netherlands Army, Utrecht, the Netherlands. Data were collected from January 2020 to July 2022 as part of a larger prospective cohort study (https://www.toetsingonline.nl/to/ccmo_search.nsf/Searchform?OpenForm, file number ToetsingOnline NL69527.028.19).

Study population

Consecutive patients referred to the Sports Medicine Centre for AT were eligible for inclusion according to the following criteria: (1) military personnel in active duty (18-60 years), (2) a clinical diagnosis of mid-AT [2], and (3) symptoms for at least 2 months. Participants were excluded on the basis of concomitant insertional Achilles tendinopathy, or on the presence of factors that may have adversely affected the mid-portion AT structure: (1) signs of a complete AT rupture, (2) prior surgery to the AT, (3) use of statins, fluoroquinolones or corticosteroids [19], and (4) a previous diagnosis of rheumatoid arthritis, diabetes mellitus or psoriasis [19]. In case of bilateral symptoms, only the side with the lowest score on the VISA-A questionnaire was included in the study.

Ultrasound Tissue Characterisation

We used UTC for the assessment of mid-portion AT structure [13]. UTC is an imaging modality that can quantify tendon structure into four echo types: intact and aligned tendon bundles (echo type I); less integer and waving tendon bundles (echo type II); mainly fibrillar matrix (echo type III); and mainly amorphous matrix with loose fibrils, cells, or fluid (echo type IV) [13]. Combined, echo types I + II represent aligned fibrillar structure, whereas echo types III + IV can be seen as disorganised tendon structure (Figure 1 and 2). The UTC scans were collected and processed according to a standardised protocol, that showed excellent intra-rater and inter-rater reliability in the same patient group used for this study [20]. Post-treatment UTC scans from our previous study [14] were used as baseline measurements for the current study. A single examiner in UTC (MAP) collected these scans. An independent researcher (MTAWM), blinded to the VISA-A scoring, processed all UTC scans to quantify mid-portion tendon structure. The percentage of aligned fibrillar structure in the tendon mid-portion was used as outcome for this study.

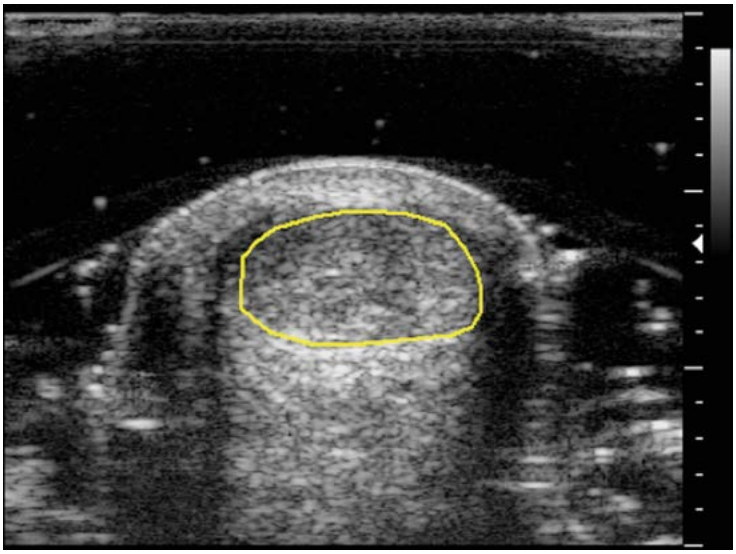

Figure 1. *Short-axis greyscale image in the Achilles tendon mid-portion. The yellow circle marks the anatomical borders of the Achilles tendon.*

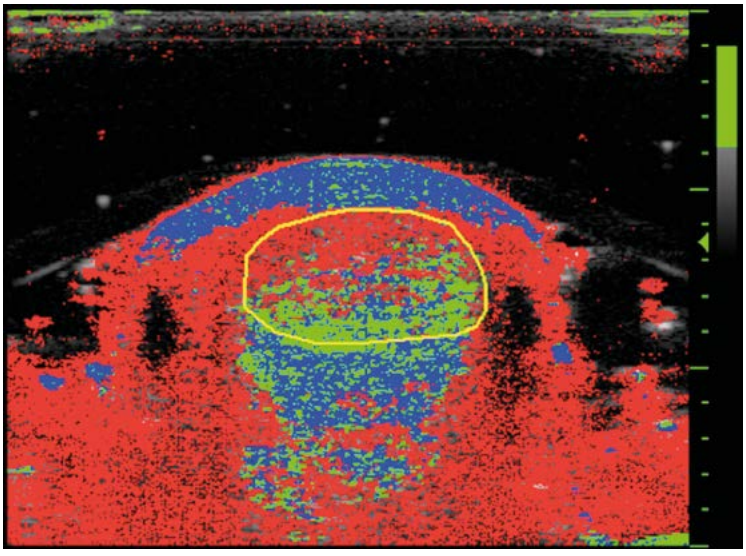

Figure 2. *Short-axis UTC-image in the Achilles tendon mid-portion. The yellow circle marks the anatomical borders of the Achilles tendon. Echo type I = colored green, echo type II = colored blue, echo type III = colored red, and echo type IV = colored black. Echo types I + II represent aligned fibrillar structure, whereas echo types III + IV can be seen as disorganised Achilles tendon structure.*

Baseline characteristics

At baseline, the following patient characteristics were retrieved: age (years), Body Mass Index (BMI, %), sex (male/female), symptom duration (months), mid-portion echo types I + II (%), and VISA-A.

VISA-A is a validated, disease-specific questionnaire to assess pain, function in daily living and sporting activity [17]. Scores range from 0 to 100, where 100 equals a perfect asymptomatic score.

Study measurements

All patients underwent a conservative treatment programme [14] and were evaluated directly post-treatment and after 1 year of follow-up. The post-treatment measurements for this study consisted of a written VISA-A questionnaire followed by a UTC examination [14, 20].

VISA-A was taken again after 1 year of follow-up, extended with the following additional items: (1) 'Since the UTC-scan was taken, have you experienced AT pain and reduced function (yes/no)?'; (2) 'Upon yes, for how long were these symptoms present?'; (3) 'What was the maximum score for pain (NRSmax) (0: no pain, 10: worst conceivable pain)?'; (4) 'Have you received any additional treatments for your AT?'; (5) 'Upon yes, which treatments (e.g., exercises, medication, surgery)?'.

Recurrence of mid-portion Achilles tendinopathy

Post-treatment, all patients were asked if they perceived themselves as recovered and functioning at their pre-symptom activity level (yes/no). Participants answering 'yes' were classified as recovered and were included in the current study. Individuals answering 'no' were excluded from this study.

A recurrence was determined after 1 year of follow-up post-treatment. We defined a recurrence either as: (1) the presence of AT pain and reduced function due to mid-AT symptoms (yes/no), combined with a decrease in post-treatment VISA-A score of at least the minimal important change (MIC) of 7 points, as assessed for this particular cohort [21], or (2) a self-reported recurrent episode in the past year, from which the participant was recovered at follow-up.

Statistics

The characteristics of our study population were presented in 2 groups (mid-AT recurrence yes/no) with appropriate measures of central tendency and dispersion.

We used univariate logistic regression to test if covariates, that is, age, BMI, sex, symptom duration, and baseline VISA-A scores, differed between groups.

Subsequently, a receiver operating characteristics (ROC) curve was created for aligned fibrillar structure to distinguish a mid-AT recurrence from a non-recurrence. For this, the post-treatment percentages of aligned fibrillar structure were plotted against mid-AT non-recurrences (coded: 0), and mid-AT recurrences (coded: 1). The area under the curve (AUC) was interpreted as follows: failed, 0.5-0.6; poor, 0.6-0.7; fair, 0.7-0.8; good, 0.8-0.9; and excellent, 0.9-1.0 [22]. Youden's index was calculated to maximise sensitivity and specificity, using the formula: (sensitivity + specificity) -1. The optimal cutoff point for aligned fibrillar structure to distinguish a recurrence from a non-recurrence was determined with the Youden's index value closest to 1. The 95% CI around this cutoff point was calculated [23].

Next, outcomes for aligned fibrillar structure were dichotomised using this cutoff point as a threshold. All scores equal to or higher than this threshold were coded '0', indicating a normal representation of aligned fibrillar structure within the AT mid-portion. Scores below this threshold were coded '1', indicating an under-representation of aligned fibrillar structure within the tendon mid-portion.

Logistic regression was used to determine the strength of the potential association with 95% CI between a recurrent episode (0, no; 1, yes) as dependent variable, and the dichotomised aligned fibrillar structure. We considered a multivariable logistic regression model to adjust this association for covariates that statistically differed between groups ($p<0.05$) at baseline. The Nagelkerke R^2 was used to express the proportion of variance of the dependent variable explained by the multivariable model (Nagelkerke, 1991).

Analyses were performed using SPSS (IBM SPSS Statistics for Windows, V.25.0, IBM, Armonk, New York, USA).

Ethical considerations

Approval for the study was granted by the Ethics Committee METC Brabant, Tilburg, the Netherlands (number of approval 1921). All participants provided written informed consent for anonymous use of their data.

Results

A total of 40 participants were treated with the conservative treatment programme, without loss to follow-up. Post-treatment, 37 participants reported recovery and were included in this study (Figure 3). Three participants had not yet returned to their pre-symptom activity level and were therefore excluded (Figure 3). Baseline characteristics of the participants are reported in Table 1.

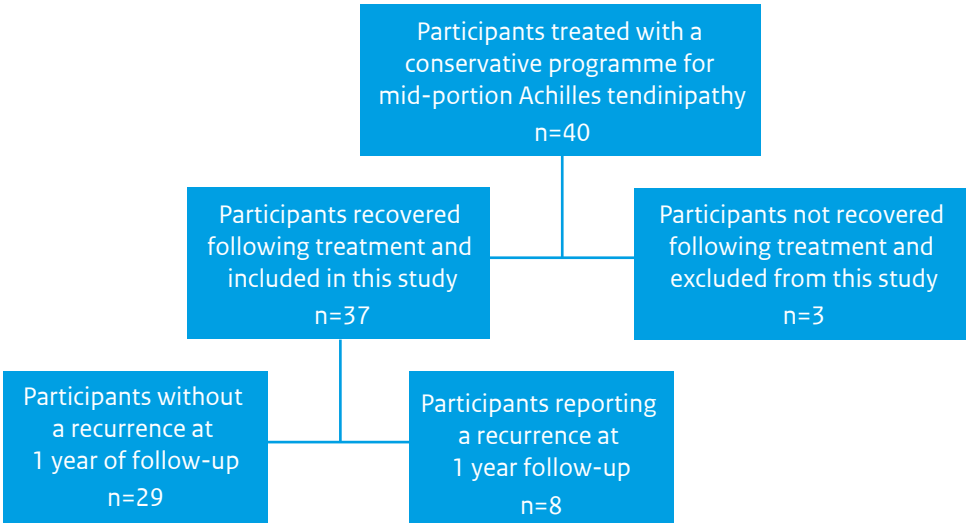

***Figure 3**. Flow diagram of the participants in the study.*

Table 1. Baseline characteristics of the participants.

Measure	Mid-AT non-recurrences (*n* = 29)	Mid-AT recurrences (*n* = 8)	*P value*	Total group (*n* = 37)
Age (years; mean ± SD)	40.4 ± 9.4	37.0 ± 8.2	0.354	39.7 ± 9.1
Body Mass Index (%; mean ± SD)	27.4 ± 2.6	27.1 ± 4.9	0.816	27.4 ± 3.2
Sex (% male)	28 (96.6%)	7 (87.5%)	0.348	35
Symptom duration (months; median ± IQR)	8.0 ± 10.0	12.0 ± 53.0	0.041	8.0 ± 12.0
VISA-A score (mean ± SD)	59.9 ± 16.9	56.8 ± 22.1	0.651	59.2 ± 17.8

Mid-AT, mid-portion Achilles tendinopathy; VISA-A, Victorian Institute of Sport Assessment – Achilles; SD, standard deviation; IQR, interquartile range.

After 1 year of follow-up, 8 out of 37 participants reported a mid-AT recurrence, with a median symptom duration of 15.0 weeks (IQR 43.0 weeks). Mean VISA-A of this group was 94.4 (SD 5.3) post-treatment, and 78.6 (SD 12.3) after 1 year of follow-up. Mean aligned fibrillar structure was 71.2% (SD 13.0). No patients reported additional treatment. In the non-recurrence group, VISA-A was 95.3 (SD 6.4) post-treatment and 98.5 (SD 3.2) after 1 year of follow-up; mean aligned fibrillar structure was 74.2% (SD 13.0).

Seven of these 8 individuals reported a recurrent episode combined with a decrease in VISA-A score exceeding the MIC. One subject reported a recurrent episode (NRSmax 8 combined with impaired function for at least 2 weeks) in the past year from which he was fully recovered.

The ROC curve is presented in Figure 4. The AUC was interpreted as fair (0.616; 95% CI: 0.393 to 0.840). Youden's index indicated an optimal cutoff point for aligned fibrillar structure at 73.2% (95% CI: 69.4 to 77.8), with a sensitivity of 66% and specificity of 75%. Dichotomisation of outcomes for aligned fibrillar structure resulted in 21 participants considered to have a normal representation of aligned fibrillar structure, and 16 participants with an under-representation of aligned fibrillar structure.

Univariate logistic regression indicated that symptom duration was the only variable that significantly differed between groups (p=0.041). Symptom duration was therefore included in our multivariable model. The odds ratio (OR) of the association between mid-AT recurrence and aligned fibrillar structure was 5.7 (95% CI: 0.967 to 33.600), with a Nagelkerke R^2 of 0.168. For symptom duration, an OR of 1.1 (95% CI: 1.003 to 1.133) and Nagelkerke R^2 of 0.258 were found.

Multivariate logistic regression indicated that the odds for a mid-AT recurrence in a subject with an amount of aligned fibrillar structure below the threshold of 73.2%, compared to a subject with an amount of aligned fibrillar structure of 73.2% and higher, was 9.7 (p=0.049) (OR 9.7, 95% CI: 1.007 to 93.185). The odds for a mid-AT recurrence within the first year was 1.1 (p=0.044) (OR 1.1, 95% CI: 1.002 to 1.150) for each additional month of symptom duration.

The explained variance of the model was 0.423 (Nagelkerke R^2), representing the amount of variation of the recurrent episodes that could be explained by the included variables.

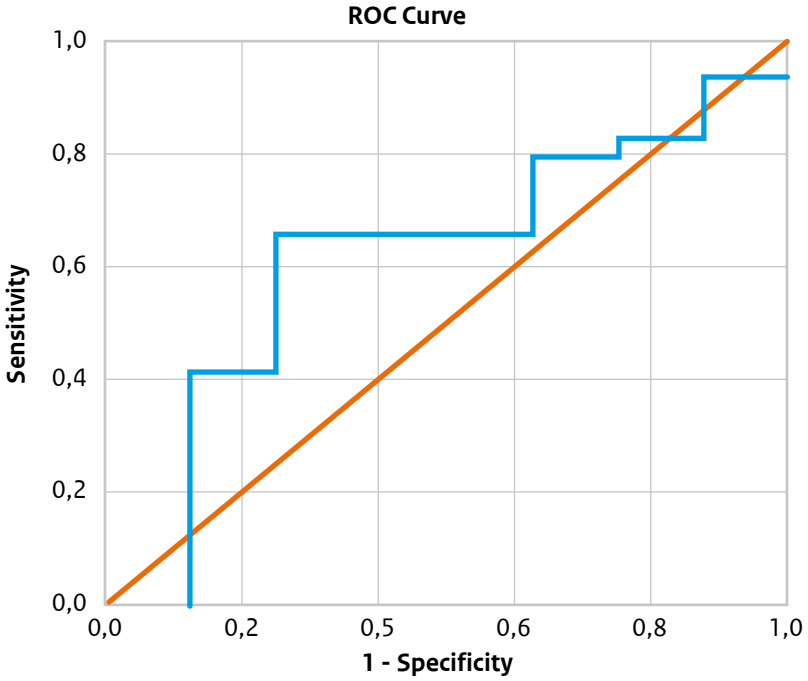

Figure 4. *Receiver operating characteristic (ROC) curve.*
The ROC curve (in blue) expresses the ability of mid-portion aligned fibrillar structure to distinguish participants with a mid-portion Achilles tendinopathy recurrence from those without a recurrence. Diagonal segments are produced by ties.

Discussion

The objective of this study was to determine the prognostic value of UTC for a mid-AT recurrence in military service members reporting to be recovered following conservative care. Our results indicate that an under-representation of mid-portion aligned fibrillar structure post-treatment, that is, below a threshold of 73.2%, was significantly associated with a recurrence (OR 9.7, 95% CI: 1.007 to 93.185). Moreover, every additional month of symptoms slightly increased the risk of a mid-AT recurrence within the first year (OR 1.1, 95% CI: 1.002 to 1.150). The explained variance of our multivariable logistic regression model was considerable (Nagelkerke R^2 0.423). It should be noted that the explained variance from the univariate logistic regression analysis indicates that symptom duration appeared to be a better predictor than aligned fibrillar structure, with variances of 0.258 and 0.168, respectively.

Clinicians can use the threshold for aligned fibrillar structure to identify individuals at risk after successful conservative treatment, allowing for preventative interventions to improve tendon structure (e.g., training load adjustments or complementary tendon loading programmes) to

minimise future risk for a recurrence [2, 6]. To our current knowledge, no study so far has investigated the potential of UTC to predict a mid-AT recurrence.

Various prognostic UTC characteristics of the AT structure have been reported in asymptomatic and symptomatic individuals [6, 7, 15, 16, 24]. Steinberg et al. [6] aimed to determine whether baseline mid-portion tendon structure was a risk factor for a wide range of musculoskeletal injuries during an infantry commander's course. Subjects with echo type III > 8.5% (OR 1.69, 95% CI: 1.35 to 2.12) were found to be at highest risk for injury [6]. In football players, Docking et al. [7] investigated whether pre-season AT structure was related to the development of AT symptoms during the season, and to symptom severity. Neither tendon AP diameter nor the extent of disorganised tendon structure were found to be predictive for symptom development or symptom severity. In a large cohort of first-year students without a previous history of AT, Wezenbeek et al. [24] could not identify echo type II as a risk factor for mid-AT. Due to a marginal representation of disorganised tendon structure in their study, this outcome did not allow for any conclusions concerning increased risk of mid-AT [24]. In patients with mid-AT, two studies reported pre-treatment aligned fibrillar structure not to be predictive for clinical outcome, as measured with VISA-A [15, 16].

Although the collection of UTC scans is highly standardised, the processing of these scans to quantify tendon structure allows variation, as UTC operators have the ability to select an anatomical region of interest (ROI) for quantification of tendon structure [13, 20]. A large variety in selecting ROI's is seen across studies [7, 13-15]. As UTC echo patterns vary along the anatomical course of the AT [13, 20], selecting different ROI's are most likely a source of quantitative variation in UTC echo typing, possibly contributing to different study outcomes when evaluating (prognostic) characteristics of UTC. According to current consensus, mid-AT is defined on the basis of symptom location, that is, symptoms located > 2 cm above the superior calcaneal insertion of the AT [2]. For reasons of standardisation and uniformity in clinical terminology [25], we adhered to this definition when quantifying mid-portion tendon structure in our study, by selecting a ROI starting 2 cm proximal to the calcaneus, and continuing up to the myotendinous junction or to a length of 7 cm. The first 2 cm of the AT proximal to the calcaneal insertion were not included into our analysis, since this part of the tendon is defined as the AT insertion [2]. Although our method for quantifying the AT mid-portion is not applicable to individuals with a free AT ≤ 2 cm, no such patients were included in our study. Since significantly shorter free ATs have been repeatedly observed in asymptomatic cohorts compared to symptomatic cohorts [26, 27], our method may well be limited to tendinopathy populations.

We set the threshold for aligned fibrillar structure at 73.2% (95% CI: 69.4 to 77.8) according to the Youden's index value closest to 1, as this value is most accurate in distinguishing individuals with a mid-AT recurrence from those without a recurrence. Van Schie et al. [13] reported a similar threshold for aligned fibrillar structure (75%) to be most accurate in discriminating symptomatic from asymptomatic ATs. Both our threshold and that of van Schie et al. [13] are not indicative of normative values of mid-portion aligned fibrillar structure,

as studies have reported much higher percentages in asymptomatic populations: 92.5% in military personnel [6], 96.3% in freshman students [24] and 99.2% in football players [28]. In a large cohort study (n=508) investigating normative values for UTC of asymptomatic AT structure, an overall sample percentage for aligned fibrillar structure of 97.3% was reported [29].

Strengths and limitations

The present study has several strengths. We used UTC to assess mid-portion AT structure, as conventional grey scale sonography is limited in quantifying intra-tendinous structure, relies largely on the subjective interpretation of ultrasound images, and has greater operator dependency, in contrast to UTC [7]. Moreover, we quantified mid-portion tendon structure analogous to the generally accepted definition of mid-AT based on symptom location [2], as uniformity in clinical terminology facilitates the communication between clinicians and researchers [25]. Finally, in defining a mid-AT recurrence, we used a population specific VISA-A MIC of 7 points, as recently assessed for this particular cohort [21].

With regard to the definition of a mid-AT recurrence, several methodological choices made in the present study have to be taken into account. First, we cannot rule out that individuals defined as recovered in our study experienced a mid-AT recurrence beyond the 1-year follow-up period. Second, one included participant reported a mid-AT recurrence in the past year, from which he was fully recovered at follow-up; we do not know the potential influence of recall bias in this particular case. Third, we considered the combination of both patient perspective (re-occurrence of mid-AT symptoms yes/no) and clinically important decrease in post-treatment VISA-A to establish a mid-AT recurrence, to be a valid reflection of a mid-AT recurrence. If we had chosen to use merely VISA-A, some patients might not have considered a decrease of the MIC to reflect a true recurrence.

Conclusions

This study identified mid-portion aligned fibrillar structure and symptom duration as potential prognostic factors for a mid-AT recurrence in military service members. A threshold for aligned fibrillar structure of 73.2%, as quantified with UTC, can guide preventative interventions aiming to improve tendon structure to minimise the risk of a mid-AT recurrence. Future studies are needed to verify our findings.

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Chapter 8.

General discussion

1. Aims of this thesis

This thesis aimed to improve the clinical evaluation and decision-making process in military healthcare aimed at service members with Achilles tendinopathy (AT), with a primary focus on mid-portion Achilles tendinopathy (mid-AT). A total of six studies were undertaken, with three core themes being the subject of research:

I. ultrasonographical assessment and clinical role of mid-portion Achilles tendon structure
II. clinical effectiveness of extra corporeal shockwave therapy (ESWT) on the Achilles tendon
III. population-specific thresholds for the Victorian Institute of Sport Assessment – Achilles (VISA-A) questionnaire, related to mid-AT

The primary objective of our work was to evaluate ultrasound tissue characterization (UTC) of the mid-portion Achilles tendon structure as an outcome measure for mid-AT. More specific, we assessed the intra-rater and inter-rater reliability of processing UTC scans, the validity of UTC for self-reported symptoms, and the prognostic value of UTC for a recurrence of mid-AT.

To facilitate uniform clinical terminology,[1] we quantified mid-portion tendon structure according to the generally accepted clinical definition of mid-AT based on symptom location,[2] i.e., 2 to 7 cm proximal to the calcaneal insertion. Additionally, we have quantified the area of maximum degeneration within the tendon mid-portion, to see if this might be better associated with symptoms.

Concerning the external validity of our work, it should be acknowledged that the military is a unique population that, despite an increasing number of female military service members in the last decades, still is a male dominant (88%) organization.[3] A culture of toughness, strict fitness requirements, and high physical demands for the job are elements that have been reported to distinguish cohorts of military service members from civilians cohorts.[4]

The participants included in our cohort studies (Chapters 3, 5, 6 and 7) were military service members, predominantly male, and all active in recreational running. They held a variety of military job functions that reflect the variety in physical activity levels in the military. The findings presented in this thesis may not be fully generalizable to non-military populations (i.e., general population or athletic population), or to specific military cohorts (e.g., special forces, logistic operators).

2. Main findings

Core theme I. Ultrasonographical assessment and clinical role of mid-portion Achilles tendon structure

Subtheme: Inter-rater reliability of conventional ultrasonography for Achilles tendon structure in asymptomatic military service members (Chapter 2)

In asymptomatic military service members, conventional ultrasonography showed:

1. almost perfect agreement in grading the mid-portion Achilles tendon structure using the modified four-graded Öhberg score (kw 0.87, 95% CI: 0.79, 0.95);
2. a very high interobserver correlation in measuring the mid-portion Achilles tendon anteroposterior diameter in short-axis plane (ρ 0.91, 95% CI: 0.87, 0.93) and long-axis plane (ρ 0.87, 95% CI: 0.83, 0.91), with no significant differences between the observers (Wilcoxon signed-rank test, $p > 0.05$);
3. absence of neovascularization in all subjects. Therefore, this phenomenon may be (predominantly) limited to pathological Achilles tendons;
4. that signs of mid-portion Achilles tendon degeneration are common (18.9 to 33.3%) in asymptomatic tendons.

Subtheme: Intra-rater and inter-rater reliability of UTC (Chapter 3)

Processing UTC scans in military service members with mid-AT is highly reliable in quantifying:

1. mid-portion Achilles tendon structure, that is, 2 to 7 cm proximal to the calcaneal insertion (intra-rater reliability, ICC 0.97 to 0.99; inter-rater reliability, ICC 0.98 to 0.99);
2. the area of maximum degeneration within the tendon mid-portion (intra-rater reliability, ICC 0.85 to 0.98; inter-rater reliability, ICC 0.92 to 0.98).

Subtheme: Association between Achilles tendon structure and self-reported symptoms (Chapter 5)

Pain and function (VISA-A) are negligibly associated with tendon structure (UTC) in military service members with mid-AT. Using various UTC-outcomes to quantify tendon structure, i.e., either aligned fibrillar structure (echo-type I + II) or disorganized tendon structure (echo-type III + IV), both analyzed within the tendon mid-portion and in the area of maximum degeneration within the tendon mid-portion, does not change the strength of the correlation with VISA-A (range: ρ -0.173 to 0.166).

Subtheme: Prognostic value of UTC for a recurrence of mid-AT (Chapter 7)

UTC appears to have prognostic value for a recurrence of mid-AT in military service members. Participants with an under-representation of mid-portion aligned fibrillar structure (post-treatment), i.e., below a threshold of 73.2% (95% CI: 69.4, 77.8), have shown to be at higher risk for a recurrence (odds ratio 9.7, 95% CI: 1007, 93185). Symptom duration can also be considered a prognostic factor, with every additional month of symptoms slightly increasing the risk of a recurrence within the first year (odds ratio 1.1, 95% CI: 1002, 1150).

Core theme II. Clinical effectiveness of ESWT on the Achilles tendon

A systematic review and meta-analysis of randomized controlled trials showed (Chapter 4):
1. moderate quality of evidence indicating that adding ESWT to a tendon loading program in mid-AT results in a clinical important improvement on VISA-A (MD 10.28, 95% CI: 7.43, 13.12);
2. very low quality of evidence indicating that ESWT is likely ineffective for insertional Achilles tendinopathy (ins-AT) (SMD -0.02, 95% CI: -0.27, 0.23).

Core theme III. Population-specific thresholds for the VISA-A questionnaire, related to mid-AT

We have estimated VISA-A thresholds for minimal important change and return to pre-symptom activity level (Chapter 6):
1. A VISA-A change score of 7 points, post-treatment (6.97, 95% CI: 4.18, 9.76) as well as after 1-year of follow-up (7.37, 95% CI: 4.58, 10.2), can be considered the minimal important change in military personnel with mid-AT;
2. In military personnel, a post-treatment VISA-A sum score of 96 points (95.5, 95% CI: 92.2, 97.8) or higher reflects the patient-acceptable symptom state for return to the pre-symptom activity level.

3. Lessons learned: incorporating the findings of this thesis in patient management

Core theme I. Ultrasonographical assessment and clinical role of mid-portion Achilles tendon structure

Subtheme: Conventional ultrasonography in asymptomatic Achilles tendons (chapter 2)

This study showed high inter-rater reliability of conventional ultrasonography for the assessment of Achilles tendon structure. Interestingly, it also provides an overview of asymptomatic mid-portion Achilles tendon structure in the military. While most tendons evaluated in this study were graded with normal structure, 18.9% showed signs of tendon degeneration. The prevalence of tendon degeneration increased with age, with a prevalence of 11% in subjects under 35 years to 33% in those of 35 years and older. It should be acknowledged that the majority of degenerated tendons displayed 'light' structural changes (82.1%); 'moderate' and 'severe' structural changes were found less frequently (17.9%) in asymptomatic Achilles tendons.

The results of this study indicate that ultrasonographic signs of mid-portion tendon degeneration are common in asymptomatic military personnel, putting in the ultrasonographic evaluation of military patients with mid-AT into perspective.

Subtheme: UTC as an outcome measure in mid-AT (Chapters 3, 5, and 7)

First, it should be emphasized that our UTC studies were conducted in a cohort of military service members treated with a conservative program for mid-AT. The applicability of UTC in asymptomatic cohorts (to monitor tendon adaptations to training loads, risk factors, etc.) or in surgical cohorts (to evaluate surgical techniques) are beyond the scope of this thesis.

Mid-AT is associated with degenerative tendon changes that may progress as a result of tendon loading,[1, 5, 6] predisposing patients to a partial or complete Achilles tendon rupture.[5, 7-10] Despite the fact that both rupture types are relatively rare within the spectrum of painful Achilles tendons,[5, 7] they can produce permanent functional impairment as a result of tendon elongation.[11, 12] Therefore, monitoring an Achilles tendons response to load or treatment may be warranted, to prevent progression of degeneration or even tendon rupture. This may be of particular importance in physically highly active individuals, like soldiers or athletes, for whom a rupture[5, 7] or permanent loss of function[11, 12] can have serious consequences. In Chapter 3, UTC was found to be a highly reliable imaging tool for quantifying the mid-portion Achilles tendon structure, as well as for quantifying the area of maximum degeneration within the tendon mid-portion.

Chapter 5 showed that mid-portion Achilles tendon structure and the area of maximum degeneration within the tendon mid-portion were negligibly associated with VISA-A scoring along the course of a conservative treatment program. These findings are in line with previous non-military studies.[13, 14] From this it can be concluded that, within the scope of mid-AT, tendon structure cannot be used as a biomarker for self-reported symptoms in military personnel. Hence, military clinicians are advised to use caution in assuming (causal) relationships between symptoms and tendon structure in patient management (e.g., loading advice, patient evaluation, treatment evaluation, requests for imaging). Moreover, patients should be informed that (changes in) symptoms are negligibly associated with mid-portion tendon structure.

Attention should be paid in case of suspected tendon rupturing. In general, complete Achilles tendon ruptures can be rather easily distinguished from mid-AT,[7] and are often diagnosed early after injury because of significant limitations in function, in contrast to partial Achilles tendon ruptures.[11] Partial tendon ruptures are clinically characterized by a sudden or sharp pain onset of pain, combined with an inability to fully load the Achilles tendon.[7, 11] As these symptoms overlap with those of tendinopathy, partial ruptures are often misinterpreted as aggravated AT.[7, 11] Yet, both injuries seem to require a different treatment approach. In case of a partial rupture, continued eccentric loading exercises aimed to reduce presumed tendinopathy symptoms may cause an Achilles tendon to lengthen, increasing the risk of functional impairments.[7, 11] In the treatment of partial ruptures, eccentric exercises, and tendon stretching in general, are not recommended in the first 12 weeks of conservative care,[7] as opposed to the state-of-the-art treatment of mid-AT.[15] Therefore, a correct diagnosis appears to be a precondition for providing appropriate care in patients suffering from painful mid-portion Achilles tendons.[7, 11] Ultrasonography may be warranted if there's uncertainty about the diagnosis, or in case of an unexpected course or change of symptoms.[2, 16]

In Chapter 7 we concluded that, despite negligible associations between pain/function and tendon structure (Chapter 5), a threshold for mid-portion aligned fibrillar structure of 73.2% appears to have prognostic value for a mid-AT recurrence. To our current knowledge, no previous studies have investigated the prognostic value of UTC for a mid-AT recurrence in military service members. In our study, participants with an under-representation of aligned fibrillar structure were almost 10 times more likely to experience a recurrent episode. Clinicians may use this threshold to identify military service members at risk for a recurrence, allowing for preventative interventions to improve tendon structure (e.g., training load adjustments or complementary tendon loading programs) to minimize the future recurrence risk.

II. Clinical effectiveness of ESWT on the Achilles tendon

Systematic reviews of randomized controlled trials are considered to represent the highest level of evidence in the hierarchy of research designs evaluating the effectiveness of interventions.[17] The results of our systematic review (Chapter 4) showed that in mid-AT, combining ESWT and exercise (i.e., tendon loading programs) has superior effectiveness over exercise alone, with a pooled VISA-A mean difference of 10.28 points. More recent studies have consistently reported that a VISA-A change score of 7 points represents the minimal important change in active individuals with mid-AT.[18, 19] Despite the fact that ESWT seems to result in a clinical important change in VISA-A scoring in mid-AT, no additional benefit of ESWT for ins-AT was found in our review.

According to clinical guidelines,[2, 16] first-line treatment for both mid-AT and ins-AT should consist of patient education, loading advice, and structural exercise therapy for a period of 12 weeks. In case of insufficient effectiveness, ESWT is recommended as secondary treatment for both tendinopathies, additional to continued exercise therapy. Based on the results of our review, in which several recent randomized controlled studies were included, we support combining ESWT and tendon loading exercises as treatment for mid-AT. Contrastingly, we cannot recommend using ESWT for ins-AT.

III. Population-specific thresholds for the VISA-A questionnaire, related to mid-AT

The ability of VISA-A to detect true changes in health status is both population-specific and context-specific.[20, 21] To our current knowledge, no studies so far have investigated such values for military service members. A VISA-A change score of 7 points was found to reflect the minimal important change, defined as a minimal within-person change over time above which military personnel with mid-AT perceive themselves importantly changed (Chapter 6).[20] This threshold can be used to interpret VISA-A change scores in military patients, or to determine the number of responders in clinical studies.

Additionally, our work indicated that a post-treatment VISA-A sum score of 96 points or higher can be considered to represent the patient-acceptable symptom state for return to the pre-symptom activity level.[22] This threshold can guide the rehabilitation of military patients with mid-AT.

4. Emerging evidence and clinical observations in mid-AT

Despite the clinimetric focus of this thesis, it is important to discuss emerging evidence from other recent studies investigating AT, as well as relevant clinical observations from our own cohort studies related to patient management.

Currently, clinical guidelines recommend using VISA-A as a patient-reported outcome measure (PROM) for patients with mid-AT and ins-AT.[2, 16] Recently, a new PROM for the assessment of tendinopathy severity of the Achilles tendon (TENDINS-Achilles) was developed.[23] In contrast to the VISA-A questionnaire, the TENDINS-Achilles questionnaire better meets the current recommendations for the development of PROMS, reflecting the involvement of patients, in addition to researchers and clinicians, in the development process.

A recent study has shown that pain provocation tests have a clinically relevant prognostic value on patient-reported improvement,[24] as patients with less pain during pain provocation tests at baseline showed better improvements in pain, function, and activities after 24 weeks than patients with high baseline pain scores.

While eccentric loading programs have long been considered a superior exercise intervention, recent systematic reviews have indicated that various tendon loading programs seem equally effective, regardless of contraction type.[25-27] A wait-and-see policy is no longer recommended for chronic mid-AT, as all active treatments appear to perform superior.[26] Yet, a large number of patients do not respond adequately to tendon loading programs.[28]

In our cohort study (Chapter 5), the majority of included patients were referred by clinicians who specifically requested ESWT due to unsatisfactory results from a tendon loading program in primary care.[29] Additional to ESWT, our patients were subjected to an individualized exercise program on a stair master or cross-trainer, followed by a return-to-running program.[29] The mean VISA-A score improved from 59.4 points at baseline to 93.5 points post-treatment, indicating full recovery[30] from mid-AT. Contrastingly, no detectable improvement in aligned fibrillar structure was observed in the tendon mid-portion, nor in the area of maximum degeneration within the tendon mid-portion. These observations are in line with previous research indicating that recovery of symptoms precedes the (much slower) restoration of tendon structure.[31] This should be taken into account when managing mid-AT in military personnel. Whether Achilles tendon structure would have improved after 26 weeks if patients had performed traditional tendon loading exercises (e.g., isolated eccentric loading programs, concentric-eccentric programs) is questionable, since there is currently conflicting evidence on this topic.[13, 14]

A total of 22% of the participants who were fully recovered following conservative treatment in our study reported a recurrence at one year post-treatment (Chapter 7).[32] Symptoms in AT have been known to persist in the long term.[28, 33, 34] Our percentage of recurrences is similar to that of a recent study, concluding that one-fifth of patients with conservatively treated mid-AT have symptoms after 10 years, with most patients reporting fluctuating pain over time.[35]

Based on these findings, we recommend that military patients should be given realistic expectations about the possible long term prognosis of mid-AT, as well as the fluctuating course of symptoms over time.[35] This may help patients with persisting complaints to better understand their own symptoms.

Surgery may be warranted in patients with persistent symptoms despite treatment,[36-40] as growing evidence suggests a possible role for the plantaris tendon in mid-AT.[36-44] The plantaris tendon has shown similar tendinopathic changes as the Achilles tendon,[44] and is suggested to contribute to the development of mid-AT as a result of compressive forces and shearing forces with the medial side of the Achilles tendon.[36, 39, 40, 44] Patients with plantaris tendon involvement commonly report medial Achilles tendon pain and exhibit tendinopathic tissue changes in the medial region of the Achilles tendon.[36, 38, 40, 41, 44] Surgery consisting of plantaris tendon excision, and scraping of the ventromedial surface of the Achilles tendon aiming to release the richly vascularized fat tissue from the Achilles tendon, has been reported to improve both short term and long-term clinical outcomes (i.e., pain, function and tendon structure).[36-40]

Finally, emerging evidence indicates that psychosocial factors play an important role in patients with mid-AT, particularly in terms of daily life and valued activities.[45-47] These studies underline the need to recognize and adopt a more biopsychosocial approach in patient management. Recently, Slagers et al.[45] suggested that clinicians should pay particular attention to patients with lack of psychosocial readiness to return to sports, and also patients with kinesiophobia or catastrophizing thoughts when experiencing pain.[45] Addressing psychosocial factors and incorporating pain education in conservative treatment may enhance the compliance with exercise programs, which are currently the cornerstone of treatment aiming to improve pain and disability in mid-AT.[2, 47, 48]

5. Future research perspectives

- To further improve military health care in chronic AT, future studies may investigate the potential role of psychosocial factors in military service members;
- Future (military) studies may explore a possible association between using ultrasonography in mid-AT rehabilitation (i.e., a patient getting visual confirmation of their tendons structural status) and patient reported outcome measures (e.g., VISA-A, Tampa Scale for Kinesiophobia, Pain Catastrophizing Scale, and Injury Psychological Readiness to Return to Sport);
- With regard to VISA-A, we have estimated minimal important change values for improvement in military personnel. Change scores for improvement may not be the same as those indicating deterioration.[20] Therefore, future military studies may investigate if, and to what extent, change score values for improvement differ from values indicating deterioration;

- Our work indicated that an under-representation of mid-portion aligned fibrillar structure appears to be associated with an increased risk for a mid-AT recurrence. More studies are needed to verify our threshold for aligned fibrillar structure, as well as its potential as a modifiable risk factor in military service members;
- More high-quality randomized controlled trials are needed to verify our findings regarding the effectiveness of ESWT for mid-AT and ins-AT, as the number of studies included in our systematic review was limited, and the pooled sample of patients was relatively small;
- Finally, mid-AT and ins-AT are considered different clinical entities in the literature,[15] with different responses to treatment.[49, 50] Therefore, we recommend that future clinical studies perform analyses for both entities separately.

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Summary

Chapter 1. General introduction:
This thesis aimed to improve the clinical evaluation and decision-making process in military healthcare aimed at service members suffering from Achilles tendinopathy (AT), with a primary focus on mid-portion Achilles tendinopathy (mid-AT). A total of six studies were undertaken, with three core themes being the subject of research:

I. ultrasonographical assessment and clinical role of mid-portion Achilles tendon structure
II. clinical effectiveness of extracorporeal shockwave therapy (ESWT) for mid-AT and insertional Achilles tendinopathy (ins-AT)
III. population-specific thresholds for the Victorian Institute of Sport Assessment - Achilles (VISA-A) questionnaire, related to mid-AT

The primary objective of our work was to evaluate ultrasound tissue characterization (UTC) of the mid-portion Achilles tendon structure as an outcome measure for mid-AT. More specific, we assessed the intra-rater and inter-rater reliability of processing UTC scans, the validity of UTC for self-reported symptoms, and the prognostic value of UTC for a recurrence of mid-AT.

Chapter 2: In a cross-sectional study including 74 asymptomatic military service members (148 Achilles tendons), we investigated the inter-rater reliability of conventional ultrasonography for the assessment of mid-portion Achilles tendon: (1) structure; (2) anteroposterior diameter; and (3) neovascularization. Our findings showed:
1. almost perfect agreement (kw 0.87, 95% CI: 0.79, 0.95) in grading tendon structure;
2. a very high inter-observer correlation for the diameter measurement in short-axis plane (ρ 0.91, 95% CI: 0.87, 0.93) and long-axis plane (ρ 0.87, 95% CI: 0.83, 0.91), with no significant differences between the observers (Wilcoxon signed-rank test, $p > 0.05$);
3. absence of neovascularization in all participants, suggesting that this phenomenon may be (predominantly) limited to pathological tendons.

This study is of particular clinical interest as it provides an overview of asymptomatic tendon structure in the military. Ultrasonographic signs of mid-portion tendon degeneration were commonly encountered in asymptomatic Achilles tendons, with a prevalence that increased with age (< 35 years: 11%, > 35 years: 33%).

Chapter 3: In a prospective cohort study including military service members with mid-AT (n=50), we determined the intra-rater and inter-rater reliability of our protocol for processing UTC scans to quantify both the mid-portion Achilles tendon structure, and the area of maximum degeneration within the tendon mid-portion. The intraclass correlation coefficient (ICC) was calculated for echo-types I, II, III, IV, aligned fibrillar structure (echo-types I + II), and disorganized tendon structure (echo-types III + IV). For mid-portion tendon structure, all ICC values were excellent for intra-rater reliability (range: 0.97 to 0.99) and inter-rater reliability (range: 0.98 to 0.99). Regarding the area of maximum degeneration, intra-rater reliability showed excellent ICC values for all echo-types (range: 0.94 to 0.98), except for echo-type II (0.85). Inter-rater reliability showed excellent ICC values for all echo-types (range 0.92 to 0.98).

The processing UTC scans was found to be highly reliable for quantifying mid-portion Achilles tendon structure, as well as for the area of maximum degeneration within the tendon mid-portion.

Chapter 4: A systematic review and meta-analysis of randomized controlled trials was performed to assess the clinical effectiveness of ESWT for mid-AT and ins-AT separately. Moderate quality of evidence was found, indicating that adding ESWT to a tendon loading program in mid-AT results in a clinical important improvement on VISA-A (mean difference 10.28, 95% CI: 7.43, 13.12). Contrastingly, very low quality of evidence indicated that ESWT is likely ineffective for ins-AT (standardized mean difference -0.02, 95% CI: -0.27, 0.23).

Chapter 5: In non-military populations, growing evidence shows that self-reported symptoms in mid-AT are poorly associated with tendon structure. In a prospective cohort study including military service members with mid-AT (n=40), our objective was to assess the association between self-reported symptoms (VISA-A) and Achilles tendon structure (UTC) along the course of a conservative treatment program. Mid-portion tendon structure turned out to be negligibly associated with self-reported symptoms. Using various UTC-outcomes to quantify tendon structure, i.e., either aligned fibrillar structure (echo-type I + II) or disorganized tendon structure (echo-type III + IV), both analyzed within the tendon mid-portion and in the area of maximum degeneration within the tendon mid-portion, did not change the strength of the correlation with VISA-A (range: ρ -0.173 to 0.166). Therefore, tendon structure cannot be used as a biomarker for self-reported symptoms in military personnel with mid-AT.

Chapter 6: The ability of VISA-A to detect true changes in health status is both population-specific and context-specific. As such detecting values were lacking in military personnel with mid-AT, we estimated the minimal important change (MIC) and the patient-acceptable symptom state for return to the pre-symptom activity level (PASS-RTA) in a prospective cohort study (n=40). Our results indicated that a VISA-A change score of 7 points, both post-treatment (6.97, 95% CI: 4.18, 9.76) and after 1-year of follow-up (7.37, 95% CI: 4.58, 10.2), can be considered the MIC. A post-treatment VISA-A sum score of 96 points (95.5, 95% CI: 92.2, 97.8) or higher was found to reflect the PASS-RTA.

Chapter 7: Previous studies have shown that degenerative Achilles tendon changes on imaging are associated with an increased risk for mid-AT. In a prospective cohort study (n=37), we investigated the prognostic value of UTC for a mid-AT recurrence in military personnel reporting to be recovered following conservative care. Subjects with an under-representation of mid-portion aligned fibrillar structure (i.e., below a threshold of 73.2%, 95% CI: 69.4, 77.8) were almost 10 times more likely (odds ratio 9.7, 95% CI: 1007, 93185) to experience a recurrent episode.

Chapter 8. General discussion:

Lessons learned:

Core theme I. Ultrasonographical assessment and clinical role of mid-portion Achilles tendon structure:

Chapter 2: Conventional ultrasonography is highly reliable in the assessment of asymptomatic mid-portion tendon structure. Signs of tendon degeneration, especially 'light' structural changes, are common in asymptomatic military personnel. These findings put the evaluation of military patients with mid-AT into perspective.

Chapter 3: In military service members with mid-AT, UTC is highly reliable for quantifying Achilles tendon structure, and can therefore be used to evaluate treatment or monitor load, potentially contributing to preventing progression of Achilles tendon degeneration or rupture in patients with mid-AT.

Chapter 5: Achilles tendon structure (UTC) cannot be used as a biomarker for self-reported symptoms (VISA-A) in military personnel with mid-AT. Clinicians are advised to use caution in assuming (causal) relationships between self-reported symptoms and tendon structure in patient management (e.g., loading advice, patient evaluation, treatment evaluation, requests for imaging). Moreover, patients should be informed that (changes in) symptoms are negligibly associated with mid-portion tendon structure.

Chapter 7: An under-representation of mid-portion aligned fibrillar structure (UTC) appears to have prognostic value for a mid-AT recurrence in military service members. These findings may help to identify subjects at risk, allowing for preventative interventions to improve tendon structure (e.g., training load adjustments or complementary tendon loading programs) to minimize the future recurrence risk.

Core theme II. Clinical effectiveness of ESWT for mid-AT and ins-AT:

Chapter 4: Currently, in case of insufficient effectiveness from a tendon loading program, clinical guidelines recommend ESWT as secondary treatment for refractory mid-AT and ins-AT. While our findings support ESWT as additional treatment for mid-AT, we cannot recommend it for ins-AT.

Core theme III. Population-specific thresholds for the VISA-A questionnaire, related to mid-AT:

Chapter 6: The values for MIC can be used to interpret VISA-A change scores in military patients, or to determine the number of responders in clinical studies. Our threshold for the PASS-RTA can guide the rehabilitation of military personnel with mid-AT.

Future research perspectives:

- To further improve military health care in chronic AT, future studies may investigate the potential role of psychosocial factors in military service members.
- Future (military) studies may explore a possible association between using ultrasonography in mid-AT rehabilitation (i.e., a patient getting visual confirmation of their tendons structural status) and patient reported outcome measures (e.g., VISA-A, Tampa Scale for Kinesiophobia, Pain Catastrophizing Scale, and Injury Psychological Readiness to Return to Sport).
- With regard to VISA-A, we have estimated MIC values for improvement in military personnel. Change scores for improvement may not be the same as those indicating deterioration. Therefore, future military studies may investigate if, and to what extent, change score values for improvement differ from values indicating deterioration.
- Our work indicated that an under-representation of mid-portion aligned fibrillar structure appears to be associated with an increased risk for a mid-AT recurrence. More studies are needed to verify our threshold for aligned fibrillar structure, as well as its potential as a modifiable risk factor in military service members.
- More high-quality randomized controlled trials are needed to verify our findings regarding the effectiveness of ESWT for mid-AT and ins-AT, as the number of studies included in our systematic review was limited, and the pooled sample of patients was relatively small.
- Finally, mid-AT and ins-AT are considered different clinical entities in the literature, with different responses to treatment. Therefore, we recommend that future clinical studies perform analyses for both entities separately.

Nederlandse samenvatting

Hoofdstuk 1. Algemene inleiding:
Centraal in dit proefschrift staat het verbeteren van het klinische evaluatie- en besluitvormingsproces bij militairen met Achilles tendinopathie (AT), in het bijzonder mid-portion Achilles tendinopathie (mid-AT). Er zijn in totaal zes studies uitgevoerd, te clusteren naar de volgende kernthema's:

I. echografische beoordeling en klinische rol van mid-portion Achillespeesstructuur
II. klinische effectiviteit van extracorporale shockwavetherapie (ESWT) voor mid-AT en insertionele Achilles tendinopathie (ins-AT)
III. populatiespecifieke drempelwaarden op de Victorian Institute of Sport Assessment - Achilles (VISA-A) vragenlijst, betrekking hebbende op mid-AT

Het primaire doel van het onderzoek was het evalueren van ultrasound tissue characterization (UTC) van de mid-portion Achillespeesstructuur als uitkomstmaat voor mid-AT. Hiertoe hebben wij achtereenvolgens de intra- en inter-beoordelaarsbetrouwbaarheid van het kwantificeren van UTC-scans, de validiteit van UTC voor zelf-gerapporteerde symptomen, en de prognostische waarde van UTC voor een recidief mid-AT onderzocht.

Hoofdstuk 2: In een cross-sectionele studie is bij 74 asymptomatische militairen (148 Achillespezen) de inter-beoordelaarsbetrouwbaarheid van conventionele echografie onderzocht voor het beoordelen van drie aspecten van de mid-portion Achillespees: (1) structuur, (2) anteroposterieure diameter en (3) neovascularisatie. Onze bevindingen zijn:
1. een bijna perfecte overeenstemming (kw 0.87, 95% BI: 0.79, 0.95) in het graderen van peesstructuur;
2. een zeer hoge correlatie tussen de beoordelaars bij het meten van de diameter in het transversale vlak (ρ 0.91, 95% BI: 0.87, 0.93) en het longitudinale vlak (ρ 0.87, 95% BI: 0.83, 0.91), zonder significante verschillen tussen beide beoordelaars (Wilcoxon signed-rank test, $p > 0.05$);
3. een consistente afwezigheid van neovascularisatie bij alle deelnemers, wat er mogelijk op wijst dat dit fenomeen zich (voornamelijk) lijkt te beperken tot pathologische pezen.

Deze studie is van bijzondere klinische betekenis omdat het een overzicht geeft van de Achillespeesstructuur bij asymptomatische militairen. Echografische tekens van mid-portion degeneratie werden regelmatig aangetoond in asymptomatische pezen, met een prevalentie die toenam met de leeftijd (< 35 jaar: 11%, > 35 jaar: 33%).

Hoofdstuk 3: In een prospectieve cohortstudie bij militairen met mid-AT (n=50) hebben wij de intra- en inter-beoordelaarsbetrouwbaarheid van UTC onderzocht, zowel voor het kwantificeren van de mid-portion Achillespeesstructuur als voor de 'area of maximum degeneration' in de mid-portion van de Achillespees. De intra-class correlatiecoëfficiënt (ICC) is berekend voor echotypes I, II, III, IV, 'aligned fibrillar structure' (d.w.z. echotypes I + II samen) en 'disorganized tendon structure' (d.w.z. echotypes III + IV samen). Het kwantificeren van de mid-portion Achillespeesstructuur liet uitstekende ICC-waarden zien voor zowel de intra-

beoordelaarsbetrouwbaarheid (range: 0.97 tot 0.99) als voor de inter-beoordelaarsbetrouwbaarheid (range: 0.98 tot 0.99). De intra-beoordelaarsbetrouwbaarheid van het kwantificeren van de 'area of maximum degeneration' was uitstekend voor alle echotypes (range: 0.94 tot 0.98), behalve voor echotype II (0.85). De inter-beoordelaarsbetrouwbaarheid was uitstekend voor alle echotypes (range 0.92 tot 0.98). Het kwantificeren van zowel de mid-portion Achillespeesstructuur als de 'area of maximum degeneration' in de mid-portion van de Achillespees met UTC is zeer betrouwbaar gebleken.

Hoofdstuk 4: Een systematische review en meta-analyse van gerandomiseerde gecontroleerde klinische trials is uitgevoerd om de klinische effectiviteit van ESWT voor mid-AT en ins-AT afzonderlijk te bepalen. Een gemiddeld niveau van bewijskracht ('moderate quality of evidence') is gevonden voor de effectiviteit van het toevoegen van ESWT aan een kuitspierkrachtprogramma bij mid-AT: dit resulteert in een klinisch relevante verbetering op de VISA-A vragenlijst (mean difference 10.28, 95% BI: 7.43, 13.12). Daarentegen is ESWT niet effectief gebleken voor de behandeling van ins-AT (standardized mean difference -0.02, 95% BI: -0.27, 0.23), maar hiervoor is de bewijskracht zeer laag ('very low quality of evidence').

Hoofdstuk 5: Een toenemend aantal studies in niet-militaire populaties geeft aan dat zelf-gerapporteerde symptomen bij mid-AT een zwakke associatie vertonen met de structuur van Achillespezen. In een prospectieve cohortstudie hebben wij bij militairen met mid-AT (n=40) die deelnamen aan een conservatief behandelprogramma de associatie onderzocht tussen zelf-gerapporteerde symptomen (VISA-A) en Achillespeesstructuur (UTC). Mid-portion Achilles peesstructuur vertoonde geen noemenswaardige associaties met zelf-gerapporteerde symptomen. Diverse UTC-uitkomsten om Achillespeesstructuur te kwantificeren zijn gehanteerd, zowel 'aligned fibrillar structure' (echotype I + II) als 'disorganized tendon structure' (echotype III + IV), beiden geanalyseerd in de mid-portion van de Achillespees en in de 'area of maximum degeneration' in de mid-portion van de Achillespees. Geen van de uitkomsten resulteerde in een sterkere correlatie met de VISA-A (range: ρ -0.173 tot 0.166). Op basis van deze bevindingen is geconcludeerd dat de Achillespeesstructuur bij militairen met mid-AT niet kan worden gebruikt als biomarker voor zelfgerapporteerde symptomen.

Hoofdstuk 6: De mogelijkheid van VISA-A om veranderingen in gezondheidsstatus te kunnen detecteren is populatie-specifiek en context-specifiek. Omdat dergelijke detectiewaarden niet beschikbaar waren voor militairen met mid-AT, hebben wij in een prospectieve cohortstudie (n=40) waarden geschat voor 'minimal important change' (MIC) en 'patient-acceptable symptom state for return to the pre-symptom activity level' (PASS-RTA). Onze resultaten geven aan dat een veranderscore van 7 punten op de VISA-A vragenlijst, zowel tijdens afsluiting van de behandeling (6.97, 95% BI: 4.18, 9.76) als na 1 jaar follow-up (7.37, 95% BI: 4.58, 10.2), kan worden beschouwd als de MIC. De PASS-RTA werd na de behandeling geschat op een VISA-A-somscore van 96 punten of hoger (95.5, 95% BI: 92.2, 97.8).

Hoofdstuk 7: Voorgaande studies hebben aangetoond dat tekens van Achillespeesdegeneratie op beeldvorming zijn geassocieerd met een verhoogd risico op mid-AT. In een prospectieve cohortstudie (n=37) hebben wij, bij militairen die waren hersteld na een conservatief behandelprogramma, de prognostische waarde van UTC onderzocht voor een recidief mid-AT. Deelnemers met een ondervertegenwoordiging van 'aligned fibrillar structure' in de mid-portion van de Achillespees (d.w.z. onder een drempelwaarde van 73.2%, 95% BI: 69.4, 77.8) hadden bijna 10 keer meer kans (odds ratio 9.7, 95% BI: 1007, 93185) op een recidief.

Hoofdstuk 8. Algemene discussie:

Lessons learned:

Kernthema I. Echografische beoordeling en klinische rol van mid-portion Achillespeesstructuur:

Hoofdstuk 2: Conventionele echografie is zeer betrouwbaar gebleken voor het beoordelen van asymptomatische mid-portion Achillespeesstructuur. Tekens van peesdegeneratie, in het bijzonder 'lichte' structurele veranderingen, komen regelmatig voor bij asymptomatische militairen. Deze bevindingen plaatsen het echografisch onderzoek van militaire patiënten met mid-AT in perspectief.

Hoofdstuk 3: Bij militairen met mid-AT is UTC zeer betrouwbaar gebleken om Achillesstructuur te kwantificeren. UTC kan daarom worden gebruikt voor het evalueren van een behandeling of voor het monitoren van belasting, en op deze wijze mogelijk bijdragen aan het voorkomen van progressie van degeneratie of een ruptuur bij patiënten met mid-AT.

Hoofdstuk 5: Achillespeesstructuur (UTC) kan niet worden gebruikt als biomarker voor zelf-gerapporteerde symptomen (VISA-A) bij militairen met mid-AT. Daarom wordt clinici geadviseerd voorzichtigheid te betrachten bij het veronderstellen van (causale) relaties tussen zelf-gerapporteerde symptomen en de structuur van pezen tijdens de behandeling van patiënten, bijvoorbeeld daar waar het gaat om belastingadvies, patiënt- en behandelingsevaluaties of aanvragen voor beeldvorming. Patiënten dienen adequaat te worden geïnformeerd over de verwaarloosbare associaties tussen (veranderingen in) symptomen en mid-portion Achillespeesstructuur.

Hoofdstuk 7: Een ondervertegenwoordiging van 'aligned fibrillar structure' (UTC) in de mid-portion van de Achilllespees lijkt prognostische waarde te hebben voor een recidief mid-AT bij militairen. De bevindingen van deze studie kunnen bijdragen aan het identificeren van individuen die een verhoogd risico lopen op een recidief. Preventieve interventies gericht op verbetering van de peesstructuur kunnen worden geadviseerd, zoals aanpassingen in trainingsbelasting of aanvullende kuitspierkrachtprogramma's, om zo de kans op een toekomstig recidief te beperken.

Kernthema II. Klinische effectiviteit van ESWT voor mid-AT en ins-AT:

Hoofdstuk 4: Indien een kuitspierkrachtprogramma onvoldoende effectief blijkt te zijn, adviseren klinische richtlijnen momenteel ESWT als secundaire behandeling voor persisterende mid-AT en ins-AT. Hoewel onze bevindingen het richtlijnadvies voor ESWT als additionele interventie kunnen ondersteunen voor mid-AT, geldt dat niet voor ins-AT.

Kernthema III. Populatiespecifieke drempelwaarden op de VISA-A vragenlijst, gericht op mid-AT:

Hoofdstuk 6: Onze waarden voor MIC kunnen worden gebruikt om VISA-A-veranderscores bij militaire patiënten in perpectief te plaatsen, of om het aantal responders in klinische studies te identificeren. Onze drempel voor de PASS-RTA kan richting geven aan de revalidatie van militairen met mid-AT.

Aanbevelingen voor toekomstig onderzoek:

- Om de militaire gezondheidszorg bij chronische AT verder te verbeteren, kunnen toekomstige studies een potentiële rol van psychosociale factoren bij militairen onderzoeken.
- Toekomstige (militaire) studies kunnen onderzoeken of er in de revalidatie van patienten met AT een mogelijk verband is tussen het gebruik van enerzijds echografie, waarmee een patiënt visuele bevestiging krijgt van de structurele status van zijn/haar Achillespees, en anderzijds patiënt-gerapporteerde uitkomstmaten zoals de VISA-A, Tampa Scale for Kinesiophobia, Pain Catastrophizing Scale of Injury Psychological Readiness to Return to Sport.
- Wij hebben op de VISA-A vragenlijst MIC-waarden voor verbetering geschat bij militairen. Veranderscores voor verbetering zijn mogelijk niet hetzelfde als waarden die verslechtering aangeven. Daarom kunnen toekomstige militaire studies onderzoeken of, en in welke mate, veranderscores voor verbetering verschillen van veranderscores die verslechtering aangeven.
- Onze werkzaamheden geven aan dat een ondervertegenwoordiging van ‘aligned fibrillar structure’ in de mid-portion van de Achillespees mogelijk is geassocieerd met een verhoogd risico op een recidief mid-AT. Er is meer onderzoek nodig om onze drempel voor ‘aligned fibrillar structure’ te verifiëren, evenals het potentieel hiervan als modificeerbare risicofactor bij militairen.
- Vanwege het beperkte aantal geïncludeerde studies en gepoolde patienten in onze systematische review zijn er meer gerandomiseerde gecontroleerde trials van hoge kwaliteit nodig om onze bevindingen ten aanzien van de effectiviteit van ESWT voor mid-AT en ins-AT te bevestigen.
- Tot slot worden mid-AT en ins-AT in de literatuur beschouwd als afzonderlijke klinische entiteiten, met verschillende reacties op de behandeling. Daarom adviseren wij toekomstige klinische studies de analyses voor beide entiteiten afzonderlijk uit te voeren.

Dankwoord

Tot slot wil ik graag een dankwoord richten aan eenieder die een bijdrage heeft geleverd aan de totstandkoming van dit proefschrift. Ik ben het Ministerie van Defensie dankbaar voor de mogelijkheid om deze studies uit te voeren. Daarnaast wil ik de militairen die hebben deelgenomen als proefpersoon aan de diverse studies danken voor hun vertrouwen en flexibiliteit. Een aantal mensen wil ik in het bijzonder bedanken.

Allereerst mijn promotor **prof. dr. Frank Backx**. Beste Frank, heel veel dank voor de kans om te promoveren. Hoewel dit PhD-traject geen onderdeel uitmaakte van een bestaande onderzoekslijn, geloofde jij in het verkennen van de toepassingsmogelijkheden van ultrasound tissue characterization (UTC) bij militairen. Dank voor het vertrouwen in dit project, voor de logistieke hulp, voor de inhoudelijke bijdragen, en voor de prettige wijze waarop dit traject is gesuperviseerd, met steun, heldere kaders, en ruimte voor professionele autonomie.

Mijn co-promotor **dr. Eric Bakker**. Beste Eric, ik heb heel veel respect voor de wijze waarop je mij gedurende dit traject hebt begeleid. In mijn optiek beschik jij over een unieke set onderzoeksvaardigheden die vormend zijn geweest voor de inhoud van dit proefschrift. Dank voor je laagdrempelige bereikbaarheid, voor je geduld, en voor je fenomenale reactietijd. Ik hoop dat we in de toekomst nog regelmatig samen kunnen werken.

Mijn co-promotor **dr. Pieter Helmhout**. Beste Pieter, fijne en integere collega, vanaf de start van dit traject ben jij betrokken geweest, en heb ik als beginnend PhD-onderzoeker telkens mogen terugvallen op jouw uitgebreide kennis en ervaring. Dank voor de immer heldere adviezen en suggesties, voor je oog voor detail, en natuurlijk voor het luisterende oor. Ik heb de lage drempel om bij je binnen te kunnen wandelen zeer gewaardeerd.

De commandanten van Trainingsgeneeskunde & Trainingsfysiologie (TGTF): **Lkol. b.d. Jos Pelzers, Lkol. Ronald Weemering, Kol. Leon Jans, Lkol. b.d. Rob Krekelberg, en Lkol. Hein van der Made**. Dank voor het stimmuleren en faciliteren van wetenschappelijk onderzoek bij TGTF, alsmede voor het creëren van de randvoorwaardelijke kaders voor dit PhD-traject.

De leden van de beoordelingscommissie: **Prof. dr. L.M.G. Hartgens, Prof. dr. J.M. van Laar, Prof. dr. C. Lucas, Prof. dr. C. Veenhof, en Prof. dr. W.O. Zimmermann**. Dank voor het lezen en beoordelen van dit proefschrift.

De co-auteurs: Dr. Amanda Isaac, Faridi van Etten-Jamaludin, en Marco Leeuw MSc. Jullie bijdragen zijn van groot belang geweest om de betreffende studies succesvol te kunnen afronden. Dear Amanda, many thanks for your valuable contribution to our study; Beste Faridi, hartelijk dank voor de hulp met het ontwikkelen van een goede zoekstrategie voor de systematische review; Beste Marco, dank voor jouw uitgebreide inspanningen, en natuurlijk voor de leuke samenwerking.

Paranimfen Chris Harts MSc en Caroline van de Graaf MSc. Beste Chris en Caroline, dank voor jullie betrokkenheid en hulp rondom de promotieplechtigheid.

De collega's van TGTF. Dank voor alle steun, en boven alles voor het creëren van een inspirerende, professionele, en gezellige werkomgeving.

De eerstelijns collega's van de Defensie Gezondheidszorg Organisatie. Dank voor jullie hulp bij het rekruteren van proefpersonen.

Prof. dr. Michel de Maeseneer. Beste Michel, dank voor de begeleiding en inhoudelijke bijdrage ten aanzien van hoofdstuk 2 van dit proefschrift, en tevens voor de interessante en leerzame stage op de afdeling radiologie van de Vrije Universiteit Brussel.

Meindert Martens MSc en Joeri van Dongen MSc. Beste Meindert en Joeri, dank voor het analyseren en kwantificeren van de UTC-scans. Ik heb de samenwerking als heel plezierig en constructief ervaren.

UTC-imaging, en in het bijzonder prof. dr. Hans van Schie.
Dank voor de adequate logistieke ondersteuning, voor de gedetailleerde instructie ten aanzien van het kwantificeren van UTC-scans, en tevens voor het sparren over wetenschappelijk onderzoek met UTC.

Thomas Winnink MSc. Beste Thomas, bedankt voor de leuke gesprekken en voor de reflecties op de diverse studies.

Lieve Marja en Cor. Dank dat jullie altijd voor ons klaar staan.

Lieve pap en mam en Inge. Pap, tijdens dit traject heb jij ons helaas moeten verlaten. Woorden schieten tekort om uit te drukken wat mam en jij door de jaren heen voor mij hebben betekend. Ik ben ontzettend trots op ons hechte gezin, en dankbaar voor alle steun, gezelligheid en warmte.

Lieve Saar en Max. Niets is mooier dan samen met jullie tijd te mogen doorbrengen, en jullie beiden te zien opgroeien.

Lieve Caroline. Lieve schat, dank voor jouw onvoorwaardelijke steun. Ik waardeer het zeer dat je mij de gelegenheid hebt geboden om met focus deze weg te bewandelen.
Samen met jou is alles veel leuker...

Biography

Marc A. Paantjens was born on August 16, 1976 in Sittard (the Netherlands). After completing secondary school (HAVO) at Scholengemeenschap St. Michiel in Geleen, he studied physiotherapy at THIM, International University of Applied Sciences in Utrecht, and obtained his bachelor's degree in 1998.

He has been in the service of the Royal Netherlands Army since 1999. Between 1999 and 2008 he worked as a military physical therapist in various health centers in primary care, and was deployed to Bosnia and Herzegovina (SFOR 9, November 2000 – May 2001). From 2009 to present he has been employed as a manual therapist and researcher for the department of military sports medicine of the Royal Netherlands Army in Utrecht.

He has always had a special interest in the musculoskeletal system. In 2008 he obtained his master's degree in Orthopaedic Manual Therapy (with honors) at the University of Applied Sciences Utrecht, where he worked part-time as a manual therapy teacher between 2009 and 2013. In 2018 he completed the master of science program in Musculoskeletal Ultrasonography for Physiotherapists, at SOMT University of Physiotherapy in Amersfoort.

During his education and work as a researcher, he became increasingly interested in scientific research, resulting in a PhD-program being initiated at the University of Utrecht in 2019.

He likes to spend his free time with his family, and enjoys running and fitness to stay fit.

Curriculum vitae

Curriculum vitae

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