Impact, diagnostic imaging and prognosis of Achilles tendinopathy

Tjerk Sleeswijk Visser

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Colophon

ISBN:	978-94-6506-341-6
Cover design:	Ridderprint | www.ridderprint.nl
Layout and printing:	Ridderprint | www.ridderprint.nl

Financial support for this thesis was provided by:

Erasmus MC Foundation, Rotterdam

Erasmus Trustfonds, Rotterdam

Printing of this thesis was kindly supported by:

Department of Orthopedics & Sports Medicine Erasmus University Medical Center, Erasmus University Rotterdam Graduate School, Xcelsior, van Dinter Den Haag, De Gangmakerij, LINK, LEUK Orthopedie, Bauerfeind, Push, ChipSoft, ABN AMRO and Wetenschapsfonds HMC

Impact, Diagnostic Imaging and Prognosis of **Achilles Tendinopathy**

Impact, diagnostische beeldvorming en prognose van **achilles tendinopathie**

Proefschrift

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

Prof.dr. A.L. Bredenoord

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

dinsdag 15 oktober 2024 15:30 uur

door

Tjerk Sieuwert Otmar Sleeswijk Visser
geboren te Voorburg.

Erasmus University Rotterdam

PROMOTIECOMMISSIE

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Chapter 1

General Introduction

PREFACE

"War will be always, until mankind reaches a point where it becomes extinct or destroys itself." This powerful saying by Achilles, a legendary Greek warrior known for his strength, in Homer's poem "The Iliad" reflects the nature of human struggle. The name "Achilles tendon" originates from his story, where he was struck in the heel by an arrow during the Trojan War. The arrow pierced the tendon, which connects the calf muscles to the heel bone, and led to his downfall. Consequently the tendon was named after him due to the belief that it was his only weak spot. The Achilles tendon is the largest tendon in the human body and is responsible for transmitting forces from the calf muscles to the heel bone, allowing for forceful propulsion during activities such as running and jumping.[1]

Just as Achilles faced the challenges of war, many people nowadays have their own battle, although on a different battleground – their struggles to stay healthy and physically active. One such battle is fought against a condition known as Achilles tendinopathy. Achilles tendinopathy is a condition that involves localized pain, thickening of the tendon, and impaired load-bearing capacity.[2-4] While the cause of Achilles tendinopathy is not related to the mythological weakness of Achilles, the name serves as a reminder of the injury prone nature of the tendon. Clinicians and researchers are continuously trying to understand the exact causes and manage the effects of this often debilitating condition. This thesis explores the impact, diagnostic imaging modalities and prognosis of Achilles tendinopathy, aiming to contribute in the ongoing ´battle´ to alleviate its burden.

IMPACT

Achilles tendinopathy is commonly seen in physically active individuals in middle age, with an incidence rate of 2-3 cases per 1,000 Dutch general practice registered patients.[5-7] The incidence of Achilles tendinopathy has increased in the past decade, partly due to the growing number of people participating in physical activities.[5,6] However, not all patients with Achilles tendinopathy are physically active and the increased prevalence of potential intrinsic risk factors as body weight or insulin resistance may also play a role in the increased incidence.[5,6] Runners have a high risk of experiencing an Achilles tendon injury in their lifetime, with a cumulative incidence rate of 52%.[8] The impact of this condition on patients is often measured using various outcome measures.[9] These measures, such as pain intensity, functional limitations, and quality of life, provide valuable insights into the severity and progression of the condition. However, an important issue in research and in the field of Achilles tendinopathy specifically is the heterogeneity of the outcome measures used which limits comparability of study's findings.[9]

The treatment of Achilles tendinopathy is often variable in clinical practice and more uniformity is necessary.[6] Several treatment options for Achilles tendinopathy are available with conservative treatment being the primary approach.[6,10] Calf muscle strengthening exercises are an important part of the treatment of Achilles tendinopathy as patients with Achilles tendinopathy have large deficits in plantar flexor strength and endurance.[11,12] The single-leg heel rise endurance test (HRET) is a frequently used test to assess calf muscle strength endurance.[12,13] A problem in the assessment of calf muscle strength and endurance is that the non-symptomatic limb cannot generally be used as reference and normative values for the HRET are currently lacking.[11,14]

Achilles tendinopathy can cause severe pain and reduced load-bearing capacity, resulting in a decreased quality of life.[2,7,8] Qualitative research indicates that some patients with this condition experience a negative impact on their social activities, self-perceived fitness levels, and overall sense of identity.[15-17] One exploratory study showed that individuals with Achilles tendinopathy have lower quality of life scores compared to normative data.[16] Similarly, other musculoskeletal conditions can also impact quality of life, albeit to varying degrees.[18-21] Understanding how Achilles tendinopathy affects quality of life can guide scientific research and help develop targeted management plans that address specific domains.

There is currently limited knowledge regarding the impact of Achilles tendinopathy on work performance, healthcare utilization, and costs.

DIAGNOSTIC IMAGING

Achilles tendinopathy can affect both the insertional and midportion region of the tendon (Figure 1), which have different anatomical features and loading profiles.[22] Achilles tendinopathy is mainly a clinical diagnosis, with imaging being used to confirm the diagnosis.[2,10] The diagnostic criteria for Achilles tendinopathy (local pain, thickening and impaired load-bearing capacity) are considered to be reliable.[23] A key diagnostic criterion is the location of pain, as distinguishing between midportion and insertional Achilles tendinopathy affects initial treatment and prognosis.[23,24] As subjective self-reported pain is one of the clinical criteria for establishing the diagnosis, it is essential to know if patients with Achilles tendinopathy can accurately localize their pain, information which is currently unknown.

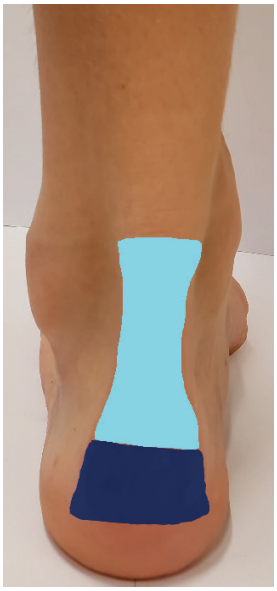

Figure 1. Visual presentation of the Achilles tendon with the light blue region representing the midportion part of the tendon and the dark blue region indicating the insertional part of the Achilles tendon.

Physical examination typically involves assessing the thickness of the tendon and determining if there is tenderness upon palpation.[3] The tendon is examined by applying gentle pressure between the index finger and thumb along the entire length of the tendon, from the musculotendinous junction to the calcaneal insertion.[3] Patients are then asked if they feel any pain during palpation.[3,23] Pain on palpation and self-reported (location of) pain are considered valid clinical tests.[23] As the presence of tendon thickening is not always necessary to diagnose Achilles tendinopathy, experts agree that the clinical diagnosis can be established when there is localized pain during tendon-loading activities and

recognizable tenderness upon Achilles tendon palpation. Despite the challenges inherent in diagnosing Achilles tendinopathy, experts concur that the above-mentioned criteria are reliable.[2,3]

The use of imaging to diagnose Achilles tendinopathy is a topic of debate.[2] In cases where not all clinical diagnostic criteria are present, imaging can play an important role to confirm the diagnosis.[2,25] When imaging is used, ultrasound is the preferred modality as it is a cheap and accessible method.[25] Conventional X-rays are typically only used to exclude bony abnormalities and MRI may be considered if ultrasound is unavailable, prior to potential surgery or when the findings on ultrasound are not consistent with the clinical picture.[25] The Ultrasound Tissue Characterization (UTC) procedure is a reliable technique that allows for accurate depiction of Achilles tendon geometry and structure.[26-29] The UTC is a customized tracking and ultrasonographic data-collection device that provides objective, standardized measurements, which in practice are often translated to conventional ultrasound.[26] The UTC procedure is carried out by positioning participants prone on an examination table with a maximal dorsiflexion angle of the ankle. A multi-frequency 5-16 MHz linear-array transducer is used, which is placed in a transverse position to the Achilles tendon (Figure 1). The transducer in the UTC tracking and data-collection device moves automatically from proximal to distal over a distance of 12 cm, collecting digital transverse images at regular intervals of 0.2 mm which result in a three-dimensional data block (Figure 2).

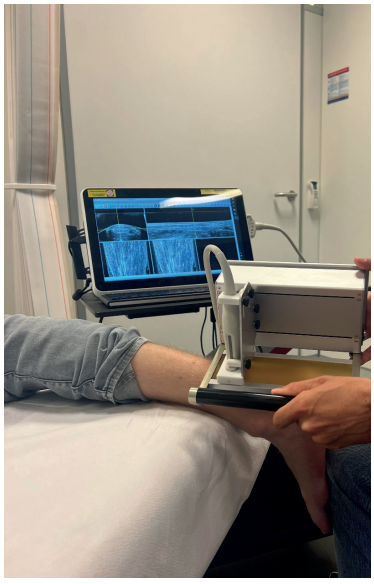

Figure 2. The Ultrasound Tissue Characterization procedure.

The typical appearance of the Achilles tendon on ultrasound is a pattern of parallel fibrillar lines in the longitudinal plane and a round-to-oval shape in the transverse plane.[25] The

Achilles tendon is typically viewed in two planes and the maximum anterior-posterior tendon thickness is commonly measured in the transversal plane (Figure 3).

Achilles tendinopathy is ultrasonographically characterized by increased tendon thickness (Figure 3), decreased tendon structure and neovascularization.[26,30,31] Doppler ultrasonography can detect the increased blood supply.[31,32] However, a significant drawback of imaging is that findings suggestive for tendinopathy are present in 25% of asymptomatic Achilles tendons, which can lead to overdiagnosis and overtreatment.[33] Another problem with imaging is that reference values for tendon geometry and structure are lacking for the general population.[33] The current cut-off value of 6 mm in maximum Achilles tendon thickness is accepted as a reference standard, but is based on small cross-sectional studies in specific populations, and it is likely that tendon geometry is influenced by personal characteristics.[25]

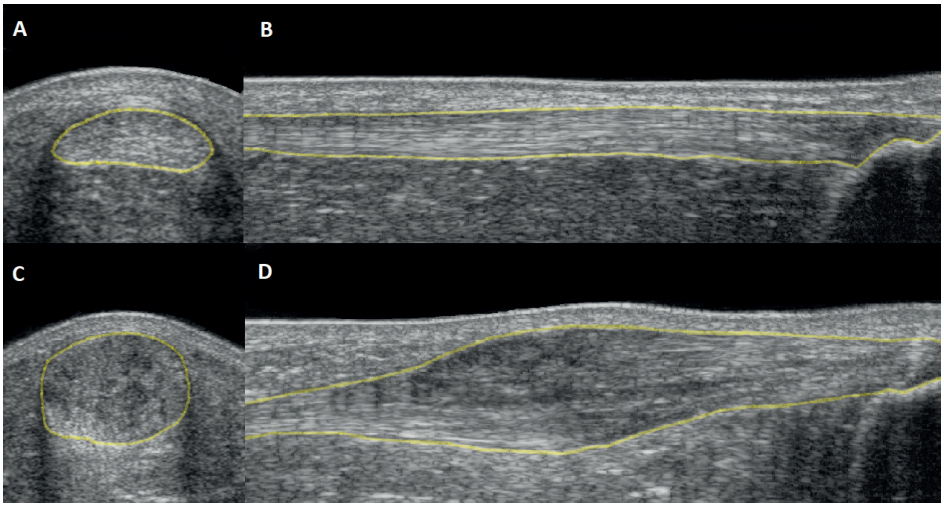

Figure 3. Visualisation of the Achilles tendon using Ultrasound Tissue Characterization in a healthy individual (A + B) and a patient with midportion Achilles tendinopathy (C + D), with increased tendon thickness. In image A + C the transversal view is shown and in image B + D the tendon is viewed in the longitudinal plane. The yellow line represents the border of the Achilles tendon.

PROGNOSTIC FACTORS

The conservative therapy for Achilles tendinopathy consists of load-management, education and exercise therapy. However, this treatment may not be very effective in first line care, as one-thirds of patients with new-onset Achilles tendinopathy continue to experience symptoms at one-year follow-up.[34] At ten years of follow-up, even up to a quarter of patients remain symptomatic.[35]

In clinical practice, it is essential to have the ability to anticipate the recovery of patients and identify those who will likely endure chronic symptoms. However, knowledge of prognostic factors for patients with Achilles tendinopathy is currently lacking, with imaging having no prognostic value, and only limited evidence for an association between having a metabolic disorder and developing persistent symptoms.[34,36]

The past years it has become increasingly clear that socio-economic status plays a role in prevalence of disease and treatment outcomes. Socio-economic factors such as income, age, level of education, ethnicity, and place of residence have been found to significantly affect the incidence and outcomes of various diseases.[37-39] Individuals with low socio-economic status are particularly vulnerable to chronic diseases and musculoskeletal conditions, resulting in worse outcomes.[37,40] The role of socio-economic status in the occurrence and treatment of Achilles tendinopathy is still unclear.

AIMS AND OUTLINE OF THIS THESIS

The aims of this thesis are to evaluate the impact of Achilles tendinopathy, to assess the role of ultrasonographic imaging and to assess socio-economic status as prognostic factor in Achilles tendinopathy patients.

Currently, there is considerable variation in the outcome measures used for Achilles tendinopathy, which can have implications for patient care, as healthcare professionals and researchers are unable to adequately interpret, compare, and synthesize study results for meta-analyses. In **Chapter 2** we performed an international Delphi survey and consensus meeting to agree to a set of core outcome measures for clinical trials on Achilles tendinopathy. This will advance the comparability between future studies in this field.

Calf muscle strengthening exercises are an important part of the treatment of Achilles tendinopathy. A frequently used test to assess calf muscle strength endurance is the single-leg heel rise endurance test (HRET). In **Chapter 3** we established normative values for the HRET in a large population of healthy individuals as these are currently lacking for the general population.

In **Chapter 4** we investigated the impact of Achilles tendinopathy on quality of life and compared this to other prevalent musculoskeletal conditions. We also studied the impact of Achilles tendinopathy on work performance and health care utilization as well as the associated costs of Achilles tendinopathy.

It is useful to know whether patients with Achilles tendinopathy can adequately localize their pain and distinguish between the insertional and midportion region as this effects prognosis and treatment. In **Chapter 5** we evaluated the level of agreement between patient-reported pain using a standardized pain map and the physician-determined clinical diagnosis of Achilles tendinopathy.

Ultrasound Tissue Characterization is a valid imaging method to evaluate tendon structure and is widely used in clinical research, but knowledge on the reliability of tendon thickness measurements is lacking. In **Chapter 6** we determined the intra-rater and inter-rater reliability for Achilles tendon thickness measurements using UTC and assessed if these measurements can be reliably translated to conventional ultrasound.

In **Chapter 7** we obtained reference values for Achilles tendon thickness on ultrasound in a large asymptomatic population and compared these to patients with Achilles tendinopathy. These values can help clinicians distinguish between normal morphological changes and abnormalities and enhance the diagnostic process.

Knowledge on health disparities between different populations can help clinicians to optimize treatment for the individual patient. In **Chapter 8** we evaluated if socio-economic status, measured by factors such as place of residence, age, gender, education level and

income, has effect on symptom severity and response to standardized treatment in patients with Achilles tendinopathy.

The clinical implications and relevance of the findings of this thesis are discussed in **Chapter 9** as well as perspectives for future research**.**

In **Chapter 10** a summary of the thesis in both English and Dutch language is presented.

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Chapter 2

ICON 2023—International Scientific Tendinopathy Symposium Consensus: the core outcome set for Achilles tendinopathy (COS-AT) using a systematic review and a Delphi study of healthcare professionals and patients

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[#]shared first authorship

Under review

ABSTRACT

Objectives: To develop a core outcome set for Achilles tendinopathy (COS-AT) for use in clinical trials.

Methods: We performed a five-step process including: (I) a systematic review on available outcome measurement instruments, (II) an online survey on truth and feasibility of the available measurement instruments, (III) an assessment of the methodological quality of the selected outcome measurement instruments, (IV) an online survey on the outcome measurement instruments as COS, and (V) a consensus in-person meeting. The OMERACT guidelines with 70% threshold for consensus were followed.

Results: We identified 233 different outcome measurement instruments from 307 included studies; 177 were mapped within the ICON core domains. 31 participants (12 patients) completed the 1st online survey. 22/177 (12%) outcome measurement instruments were deemed truthful and feasible and their clinimetric properties were evaluated. 29 participants (12 patients) completed the 2nd online survey and three outcome measurement instruments were endorsed: the Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire, the single-leg heel rise test, and evaluating pain after activity using a Visual Analogue Scale (VAS, 0-10). 12 participants (1 patient) attended the final consensus meeting, and 1 additional outcome measurement instrument was endorsed: evaluating pain on activity/loading using a VAS (0-10).

Conclusion: It is strongly recommended that the identified COS-AT will be used in future clinical trials evaluating effectiveness of an intervention. This will facilitate pooling of data and progression of knowledge about Achilles tendinopathy. As COS-AT is implemented further evidence on clinimetric properties of included measures should lead to its review and refinement.

INTRODUCTION

Achilles tendinopathy is the clinical diagnosis for load-related pain and disability localized to the Achilles tendon.[1] This condition frequently leads to chronic symptoms with poor quality of life and substantial healthcare consumption.[2,3] To effectively evaluate recovery of Achilles tendinopathy and treatment effectiveness, reliable and valid outcome measurement instruments are necessary.[4-6] Currently, there is considerable variation in the outcome measures used to assess interventions; this can have implications for patient care, as healthcare professionals and researchers are unable to adequately interpret, compare, and synthesize study results in meta-analyses.[5,7,8] The importance of developing a Core Outcome Set (COS) for clinical trials is emphasized by both the Outcome Measures in Rheumatology (OMERACT)[9] and the Core Outcome Measures in Effectiveness Trials (COMET)[10] initiative. These organizations also offer detailed guidelines for the development of a COS.[10,11] For inclusion in a COS, outcome measurement instruments must be both feasible (considering cost, patient burden, and availability in the clinical setting) and of sufficient quality (valid, responsive, reliable, and interpretable).[9,11]

In 2018, a Delphi study was conducted at the International Scientific Tendinopathy Symposium Consensus (ICON) to establish core domains for tendinopathy.[7] Expert clinicians and researchers in tendinopathy, as well as patients with tendinopathy at different anatomical sites, identified nine tendinopathy-specific core domains: patient overall rating, participation, pain on activity, disability, function, physical function capacity, quality of life, psychology, and pain over a specified time frame.[7] The next step is to use these core domains as a guide to develop core outcome sets for each of the common tendinopathies. A core outcome set for Achilles tendinopathy (COS-AT) is currently lacking.

The primary aim is to develop this COS-AT through a systematic search for outcome measurement instruments that map to core tendinopathy domains, methodological quality assessment and a 3-round Delphi including an in-person consensus meeting. After defining the COS-AT, it should be used in future clinical trials evaluating effectiveness of an intervention for Achilles tendinopathy.

METHODS

Study protocol

At the International Scientific Tendinopathy Symposium (ISTS) 2018 an Achilles tendinopathy consensus group was formed.[5] This group worked collaboratively on prospective registration of the study protocol on the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42020156763). The project was also registered in the COMET database (www.comet-initiative.org, reference number 1323).

The medical ethical committee of Erasmus MC University Medical Center confirmed that the Medical Research Involving Human Subjects Act (WMO) did not apply to our study (MEC-2021-0279).

To identify the core outcome set for Achilles tendinopathy, we predefined 5 steps based on recommended methodology[9,11]: 1) a systematic review on available outcome measurement instruments, 2) an online survey (1st round Delphi) on truth and feasibility, 3) assessing methodological quality of selected instruments, 4) an online survey (2nd round Delphi) on the core outcome set, and 5) an in-person consensus meeting (3rd round Delphi). The results of the first step have been published elsewhere.[5] The process of the complete study is described in detail below.

Panel selection

The steering committee (KS, PM and RJDV) was formed in collaboration with the initiator of the COS development in tendinopathies (BV). The steering committee performed the recruitment and selection of the broader COS-AT consensus group. There was a call for potentially eligible participants during the International Scientific Tendinopathy Symposium (ISTS) in September 2018 in Groningen, the Netherlands. Some participants were also recruited afterwards via snowball methods and contacts of the steering group. The COS-AT consensus group was important for the design process and inclusion of patients throughout the project. For the Delphi parts of the process, an expert panel was selected. In the process of panel selection, our objective was to ensure a comprehensive representation of both clinicians and researchers (professional participants) and people with lived experience of having Achilles tendinopathy (referred to as patients). To achieve this, we employed a two-pronged approach.

Firstly, to recruit patients, we enlisted the assistance of the COS-AT consensus group.[5] This group was tasked with identifying and engaging potential patients for participation. To promote diversity, we strived to constitute a patient panel that exhibited a representative distribution in terms of gender and country of residence. Anticipating a substantial time gap between the two rounds of the Delphi survey and as we required patients with Achilles tendinopathy to have current or recent (<3 months) symptoms of Achilles tendinopathy, the individuals recruited for round 1 differed from those in round 2. We anticipated a minimum number of ten patient participants for both surveys and one for the in-person consensus meeting. Upon expressing their interest to participate, patients were promptly provided with a detailed email outlining the entirety of the process, along with an explicit explanation of their specific role within the panel. During all rounds, patients had equal voting rights as professional participants.

Secondly, in the process of the selection of professional participants, we aimed to include representatives possessing varied backgrounds (both academic and clinical) and expertise,

striving to ensure an equitable and proportional distribution based on gender and country of residence. To identify suitable professional participants, we used www.expertscape.com, a website that ranks professionals from clinical and academic domains based on their publications within specific medical fields (search term 'Achilles tendon' with search date 1st June 2021). We contacted these selected professional participants via email, extending invitations to participate in the panel. Once professional participants expressed their interest to participate, they received an email with an explanation of the process and their exact role. Hereafter, informed consent from all participants (both patients and professional participants) was obtained.

Systematic review

Step 1 – A systematic review on all available outcome measurement instruments

We set up a search strategy to identify all available outcome measurement instruments used in prospective studies including patients with Achilles tendinopathy.[5] We mapped the outcome measurement instruments into predefined health-related core domains (data have been published elsewhere).[7]

Consensus process

Step 2 – Online survey to evaluate Truth and Feasibility of outcome measurement instruments (first round Delphi procedure)

All original outcome measurement instruments within the core domains for tendinopathy and identified by the systematic review[5] were evaluated during an international online survey using LimeSurvey (LimeSurvey GmbH, Germany), a software package designed for safe distribution of online surveys. The description of the outcome measurement instruments from the literature was used verbatim, so the experts (patients and professional participants) could rate exactly what had been used in the literature. Within the identified outcome measurement instruments, there were instances where multiple outcome measurement instruments described similar aspects but with slight variations. For example, pain on palpation was assessed using different formats such as a yes/no responses, a 0-10 Visual Analogue Scale (VAS), and a 5-point Likert scale. To ensure a comprehensive evaluation, we separately assessed these variations in measurement and presented them exactly as they were used in the literature. The international panel consisting of the selected professional participants and patients was invited to complete the survey. The selection process of the outcome measurement instruments in this second step was initiated according to the OMERACT filters, which uses Truth, Discrimination, and Feasibility as the core or the pillars for instrument selection.[9] In this step we focused on the pillars Truth (which core domain is covered and '*Is there a match with the target domain?*') and Feasibility ('*Is the outcome measurement instrument practical to use?*'). The specific outcome measurement instruments were displayed and these questions were

asked for every identified outcome measurement instrument. The respondents to the survey had four response options for the specific outcome measurement instrument to be: 1) NOT truthful and NOT feasible, 2) truthful but NOT feasible, 3) NOT truthful but feasible or 4) truthful AND feasible. An outcome measurement instrument was assessed in step 3 if it met the *a priori* decision criteria: ≥70% agree the outcome measurement instrument is both truthful and feasible. Conversely, outcome measurement instruments that received agreement from less than 70% of the respondents were not assessed in step 3.

Step 3 – Performing a quality assessment of the endorsed outcome measurement instruments

For this step, we only used outcome measurement instruments that were found to have content and concept match (were found to be truthful) and were feasible to use. This step consisted of a systematic review to assess the measurement properties of the selected outcome measurement instruments.

To ensure a standardized approach, we adhered to the OMERACT guideline for instrument selection in core outcome measurement sets.[9,11] This guideline uses the pillars Truth (do the numeric scores make sense?) and Discrimination (can it discriminate between groups of interest?). A search strategy (online Supplementary file 1) was performed by a medical librarian, using a focused search that was based on the 1) specific patient population of Achilles tendinopathy; 2) outcome measurement instrument names and 3) measurement properties (construct validity, test-retest reliability, responsiveness, sensitivity to change, minimum important difference and patient acceptable state). The following databases were searched for published and unpublished trials up to 17 March 2022: Embase, Medline ALL, Web of Science Core Collection, Cochrane Central Register of Controlled Trials, CINAHL and SPORTDiscus.

After duplicate removal, two researchers (RJDV, TSV) independently screened the studies based on title and abstract. Disagreements were resolved by consensus. Studies were deemed eligible if they investigated the measurement properties of the outcome measurement instruments in a population of patients with Achilles tendinopathy. The same two reviewers independently applied the eligibility criteria to the full texts, with any disagreements settled through consensus or, if necessary, with the involvement of a third reviewer (KGS). The selected studies were then grouped based on the outcome measurement instrument examined.

After this stage, the methods of the selected studies were critically appraised using the OMERACT and COSMIN (COnsensus-based Standards for the selection of health Measurement Instruments) guidelines.[12] Two researchers (IvdAS, SES) with methodological expertise from the collaborating group independently assessed the methodological quality of the selected studies. Selected studies were assessed on the performance of the outcome

measurement instrument (adequate/equivocal/poor) and the quality of the methods used in the particular study (good/moderate/poor). Disagreements were resolved by consensus. Studies with a high risk of bias according to this quality assessment were excluded from evidence synthesis. Subsequently, a Summary of Measurement Properties table was made per outcome measurement instrument, based on the OMERACT guidelines. This table covered extracted data of the 1) Truth (target domain); 2) Feasibility; 3) Truth (construct validity which included hypothesis testing [convergent validity] and testing of known group differences) and 4) Discrimination (test-retest reliability, responsiveness, clinical trial discrimination and thresholds of meaning) per included study. We performed a best evidence synthesis, which was based on the quality of the included studies, the number of good quality studies, the consistency across studies and the performance in each property. This resulted in a final synthesis rating that was categorized as 1) Go (green), 2) Cautious (amber), 3) Stop (red) or 4) No data. As we expected evidence for certain outcome measurement instruments to be absent or very limited in the specific population of Achilles tendinopathy patients, we decided not to reject outcome measurement instruments with no available data on clinimetric properties at this stage.

Step 4 – An online survey on outcome measurement instruments as COS-AT (second round Delphi procedure)

The outcome measurement instruments identified during the systematic review (step 1) that were found to be feasible and within the relevant core domain for tendinopathy (step 2) and assessed for their methodological quality (step 3) were rated during an international Delphi survey. The same international panel of professional participants was invited to participate as well as a new sample (≥10) of patients with Achilles tendinopathy. For each included outcome measurement instrument, we displayed the results of step 1 and 2 to the participants and asked whether this outcome measurement instrument should be part of the COS. The respondents to the survey had three response options: agree (yes), disagree (no), or unsure. An outcome measurement instrument was regarded as part of the COS if it met the *a priori* criterion decision: ≥70% agree. An outcome measurement instrument was not regarded as part of COS if ≥70% disagree. If 30-70% agree, the outcome measurement instrument was discussed during the in-person meeting (step 5).

Step 5 – Defining the COS-AT during a consensus meeting at ISTS 2023 (third round Delphi procedure)

The results from the first three steps were collated and circulated to all members of the panel prior to the consensus meeting, which was held at the ISTS 2023 in Valencia (Spain) on November 9th 2023. All professional participants were asked to attend the meeting as well as several patients. At this consensus meeting, any item not already included or excluded from the outcome set (agreement between 30% and 70%), was

discussed and voted upon. Voting at this meeting was anonymous and recorded using specific software (Mentimeter AB, Stockholm, Sweden). The choices at this meeting were only 'agree' or 'disagree' (with the outcome measurement instrument being part of the COS). An outcome measurement instrument was endorsed if ≥70% agreed. An outcome measurement instrument was provisionally endorsed if 30-70% agreed. An outcome measurement instrument was not endorsed if < 30% agreed.

Equity, Diversity, and Inclusion statement

The author group consist of a representative sample of men and women and both junior and experienced researchers from a variety of disciplines and from different countries. The panel consists of both patients and professional participants from different countries and with a representative distribution of gender and we strived for a diversity in country of residence.

RESULTS

We commenced this study in September 2018, with regular meetings by the steering committee to design the study, facilitate data collection and interpretation. The project was completed in November 2023.

We contacted 68 professional participants based on the Expertscape search. 35 did not want to participate of did not respond. 33 professional participants were selected to participate in the panel. The characteristics of the professional participants and patients who completed the Delphi surveys and attended the in-person consensus meeting are displayed in Table 1.

Table 1. Characteristics of the participants completing the first and second Delphi survey. Abbreviations; PPs: professional participants, NA: Not applicable

	Survey 1		Survey 2		In-person consensus meeting	
Characteristic	PPs	Patients	PPs	Patients	PPs	Patients
N	19	12	17	12	11	1
Gender: men (%)	10 (53)	8 (66)	12 (71)	6 (50)	8 (73)	1 (100)
Age: median (min-max) years	48 (29-68)	42 (28-56)	54 (30-69)	46 (29-68)	54 (32-68)	49
Role						
Clinician and researcher	13	-	14	-	10	-
Researcher/scientist only	6	-	3	-	1	-
Tendinopathy cases per month		NA		NA		
None	7		4		1	
At least 4	1		0		0	
Between 5 and 10	3		3		2	
Between 11 and 15	4		3		4	
More than 16	2		5		1	
Other[†]	2		2		3	
Years managing tendon problems		NA		NA		
None	1		1		0	
At least 4	2		0		0	
Between 5 and 10	2		2		0	
Between 11 and 15	1		1		3	
More than 16	12		12		8	
Other[†]	1		0		0	
Profession		NA		NA		
Physiotherapist	12		8		7	
Orthopaedic Surgeon	3		5		2	
Sports physician	1		2		1	
General Practitioner	1		1		0	
Other	1 (Biomedicine)		1 (retired orthopaedic surgeon)		1 (rheumatologist)	
Currently have a tendon problem	1	12	-	12	-	1
History of a tendon problem	9	5	-	8	-	1

	Survey 1		Survey 2		In-person consensus meeting	
Characteristic	PPs	Patients	PPs	Patients	PPs	Patients
Countries where work						
Australia	5	3	2	1	4	0
United Kingdom	3	5	2	3	2	0
United States of America	4	0	3	3	2	0
The Netherlands	2	0	4	2	1	0
Sweden	3	1	2	2	1	0
Italy	1	0	2	0	0	0
Canada	1	0	1	0	0	0
Belgium	0	1	0	1	0	0
Spain	0	1	0	0	0	1
Ireland	0	1	0	0	0	0
China	0	0	1	0	0	0
Denmark	0	0	0	0	1	0

† Not further specified.

Step 1 – A systematic review on all available outcome measurement instruments

In brief, there were 9,376 studies identified and 307 studies were finally included.[5] 233 different outcome measurement instruments across all domains were identified, and 177 outcome measurement instruments were selected within the predefined core domains – previously reported.[7] These outcome measurement instruments were used for the next step in the COS-AT process.

Step 2 – Online survey to evaluate Truth and Feasibility of outcome measurement instruments (first round Delphi procedure)

The first online survey was sent to the participants at 1st November 2021. 31 participants completed the survey. 12 (39%) participants were patients and 19 were professional participants. In total, 13 (42%) participants were women and 18 (58%) man. 177 different outcome measurement instruments across all core domains were assessed. More than 70% of the participants agreed that 22 (12%) outcome measurement instruments are both truthful and feasible (online supplementary file 2). The full results of the survey are presented in online supplementary file 3.

Step 3 – Performing a quality assessment of the endorsed outcome measurement instruments

We identified 4,878 potentially relevant publications for assessing the quality of the endorsed outcome measurement instruments in step 3. Figure 1 shows a flowchart of the article selection process. After duplicate removal, 2,119 publications were screened based on the title and abstract. Eight articles were relevant but were excluded because they were not original research articles (e.g. systematic review, scoping review). 42 articles were screened in the full text. 27 articles fulfilled the eligibility criteria and were critically appraised by the methodological experts using the COSMIN criteria.[12] A summary of the methodological measurement properties, as also presented to the participants in the 2nd round of the Delphi procedure, was made and is presented in supplementary File 4. There were no available data on the quality of 13/22 (59%) outcome measurement instruments. The remaining 9 outcome measurement instruments showed low quality evidence on their clinimetric properties, with very few studies examining responsiveness, clinical trial discrimination and thresholds of meaning. Moreover, structural validity (when assessed) was not or only partially according to COSMIN guidelines.

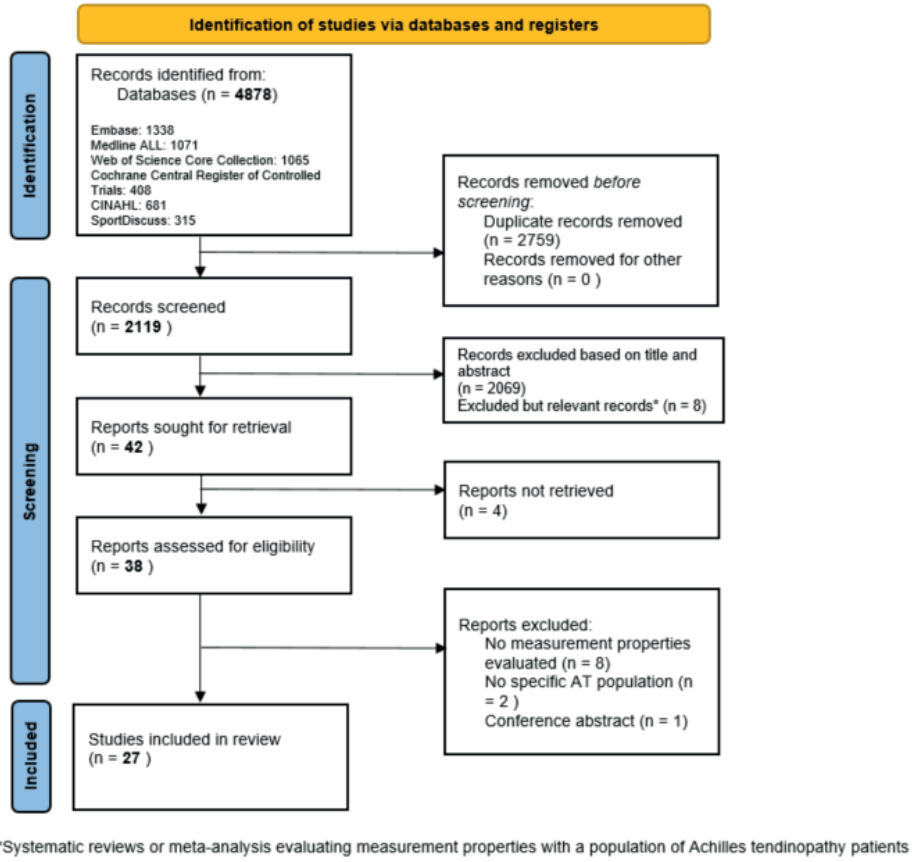

Figure 1. Flowchart of the article selection process for the research question related to the quality of the outcome measurement instruments. Abbreviations; AT: Achilles Tendinopathy.

Step 4 - An online-survey on outcome measurement instruments as COS-AT (second round Delphi procedure)

The second online survey was sent to the participants at 25th July 2023. For each included outcome measurement instrument, we displayed the results of step 2 and 3 to the participants and asked whether this outcome measurement instrument should be part of the COS-AT. 29 participants (12 patients (41%); 11 (38%) women and 18 (62%) men) completed the online survey of whom 11 (38%) were women and 18 (62%) were men. The results of this survey are displayed in online Supplementary File 5 (Table 1). More than 70% of the participants agreed that 3 of the 22 outcome measurement instruments should be included in the COS-AT. These outcome measurement instruments were 1) the (Victorian Institute of Sports Assessment-Achilles) VISA-A questionnaire[13], 2) the single-leg heel rise

test[14-16] and 3) evaluating pain after activity using a Visual Analogue Scale (VAS, from 0-10, with 0 indicating no pain). There were no measurements that were excluded at this stage (i.e., ≥70% disagreement). On 19 (86%) of the outcome measurement instruments, the *a-priori* decision criteria (either ≥70% agree or disagree) were not reached. These 19 outcome measurement instruments were evaluated in Step 5.

Step 5 - Defining the COS-AT during a consensus meeting at ISTS 2023 (third and final round Delphi procedure)

During the ISTS 2023 in Valencia (Spain) 11 professional participants (33% of the total clinician/researcher panel) and 1 patient (man) were present. All participants received an email with detailed information about the results of step 3 and 4. An introduction to the session was performed by the steering committee, and the 19 outcome measurement instruments not already included or excluded from the COS, were discussed and voted upon. 1 item was endorsed, 10 provisionally endorsed and 8 were not endorsed (online supplementary file 6, Table 1). In combination with the results of Step 4 a COS could be defined, comprising 4 outcome measurement instruments, which are displayed in Table 2.

Table 2. Endorsed outcome measurement instruments for the Core Outcome Set for Achilles tendinopathy (COS-AT).

Outcome measurement instrument	Domain	Endorsement (rate of agreement)
VISA-A questionnaire.	Disability	Endorsed in 2nd Delphi round (86%)
Single-leg heel rise test.*	Physical function capacity	Endorsed in 2nd Delphi round (76%)
Evaluating pain after activity using a VAS (0 -10)	Pain on activity/loading	Endorsed in 2nd Delphi round (72%)
Evaluating pain on activity/ loading using a VAS (0-10)	Pain on activity/loading	Endorsed after in-person consensus meeting (75%%)

Abbreviations; VISA-A: Victorian Institute of Sports Assessment-Achilles, VAS: Visual Analog Scale,
* Testing Calf muscle strength by asking the patient to perform a maximum number of single leg heel raises. [Unable/ Able, number of heel raises, Work (Joule), cm above the ground (measured from the heel)]

Notes during the in-person consensus meeting

During the final in-person consensus meeting, several key topics emerged, underlining the perspectives of the professional participants and the patient. All participants agreed that outcome measurement instruments should be as straightforward as possible; simpler measures are deemed more reliable, while those that are more extensive are often seen as having less construct validity. For example, a 0-10 Visual Analogue Scale (VAS), should be preferred over a 0-100 VAS. Additionally, there was a call for greater specificity in certain outcome measurement instruments, such as evaluating pain after activity.

A notable area of discussion revolved around the classification of certain outcome measurement instruments. For example, the use of co-interventions as outcome measurement instrument was viewed by some as essential to proper methodology, and thus not essential to a specific COS, whereas others believed it should be included in the COS-AT. Similarly, the relevance of pain location was debated. While some considered its assessment crucial in clinical diagnosis and argued it should be a part of diagnostic criteria rather than the COS-AT, others disagreed and voted for this outcome measurement instrument as part of the COS-AT.

DISCUSSION

This is the first core outcome set for Achilles tendinopathy (COS-AT). Experts (patients, clinicians and researchers) agreed on 4 outcome measurement instruments to be part of the COS-AT and 6 outcome measurement instruments were provisionally endorsed. The 4 endorsed outcome measurement instruments are 1) the VISA-A questionnaire, 2) the single-leg heel rise test, 3) evaluating pain after activity using a VAS (0 -10) and 4) evaluating pain on activity/loading using a VAS (0-10). These outcome measurement instruments cover the domains pain on activity/loading, physical function capacity and disability, which means that the other identified core domains[7] (patient overall rating, participation, function, quality of life, psychology, and pain over a specified time frame) are not covered by outcome measurement instruments of the COS-AT.

The in-person consensus meeting highlighted the need for more detailed specification of the evaluation of pain after activity, where clarity is lacking on the exact timing of measurement. When this outcome measurement instrument is used in clinical trials, it should be explicitly stated when it is measured (e.g. an hour after activity or a day after activity) and what 'activity' exactly entails (e.g. walking or running). While current pain assessments in the COS-AT utilize the VAS, we suggest the Numerical Rating Scale (NRS) can also be used as a potentially more practical alternative, as the panel considered both measures largely interchangeable when used consistently on a 0-10 scale. It is possible to use a 0-100 scale if this is deemed more appropriate in certain contexts. In that case, the scores could be converted for meta-analysis.

During the meeting, there was also considerable debate as to whether the use of co-interventions and the location of pain should be part of the COS-AT. Voting results showed 64% being opposed to their inclusion. Upon reviewing these results, we believe it's crucial to emphasize that both measures are significant for sound methodology and diagnostic assessment respectively. However, their suitability as part of the COS-AT warrants further consideration and a considerable degree of reservation.

It also became clear that high quality studies into all different clinimetric properties of the outcome measures are lacking. Only moderate evidence was available for some outcome measurement instruments. Especially on construct validity – with inclusion of structural validity and cross-cultural adaptation, which are not assessed in the current study following OMERACT guidelines – and responsiveness, clinical trial discrimination and thresholds of meaning more research is needed.

Clinical and research implications

The development of the COS-AT carries significant clinical and research implications. The introduction of standardized outcome measurement instruments, as derived in this study, offers several potential benefits. The COS-AT will enhance the ability to conduct meaningful meta-analyses in the future, providing a more robust foundation for advancing our understanding of interventions for Achilles tendinopathy. The adequate evaluation and comparison of interventions will facilitate evidence-based decision making for professional participants in the future. This could lead to more effective and personalized treatment strategies, ultimately improving patient care and outcomes. It is strongly recommended that the selected COS-AT will be used in future research, although this does not preclude the use of other outcome measurement instruments. For example, if an intervention is aimed to improve or evaluate psychosocial factors in Achilles tendinopathy patients it is still appropriate to include an outcome measurement instrument that covers this specific domain (along with the COS-AT).

It is crucial to recognize that the implementation of the COS-AT may face certain barriers. Researchers and clinicians accustomed to using a variety of outcome measurement instruments may require time to adapt to this standardized approach.[17,18] Lack of awareness and familiarity of the recommended COS-AT could also potentially form a barrier to effective implementation.[19] Another barrier might be that other more general health-related outcome measurement instruments are considered important in specific clinical settings. Adding disease-specific outcome measurement instruments to this set might not be feasible. To facilitate effective implementation of the COS-AT, researchers and clinicians need to be informed about the benefits of the COS-AT and why they are relevant to patients.[18] Another facilitator of implementation of the COS-AT is the use of an international panel with both professional participants and patients in the consensus process.[17,18] It should be noted that the exclusion of some outcome measurement instruments from the COS-AT, such as pain on tendon palpation or assessment of psychosocial factors, does not diminish their relevance. These measures are still regarded to be important in the evaluation and management of Achilles tendinopathy.

Feature box
The ICON group Achilles recommends that:
Clinical trials should include the agreed core outcome set for Achilles tendinopathy (COS-AT) as a minimum, so that future meta-analyses will be able to better estimate treatment effects.
This COS-AT should be used alongside clinical trial reporting guidelines (e.g. CONSORT and ICON PART-T) in reporting clinical trials.
Further evaluation of the COS-AT measurement instrument clinimetric properties is warranted – e.g. for validity, reliability, responsiveness and feasibility – as recommended in the OMERACT and COSMIN guidelines.
New outcome measurement instruments should be further developed covering the core domains of patient overall rating, participation, function, quality of life, psychology, and pain over a specified time frame.
The COS-AT represents the minimal reporting requirement, but should not prevent the use of other outcome measurement instruments in trials or clinical practice.

Strengths and Limitations

A strength of the consensus process for selecting the COS-AT is that we engaged a diverse group of participants, with various professions and nationalities, each possessing expertise in providing healthcare or performing research within the field of tendinopathy. It's important to acknowledge that there was limited diversity of professional participants and patients from regions other than the UK, US, Australia, and Europe and only 1 patient and 11 professional participants were present at the final consensus meeting. However, our participant pool for both surveys comprised a representative sample, with more than 10 patients having Achilles tendinopathy. While there are no specific OMERACT criteria for the attendance rate of an in-person meeting, we feel this as a limitation of this process, due to the international nature of the design and the planned meeting during a specific conference. However, the majority of the endorsed COS-AT was already established in Step 4 of the process by 29 experts (12 patients). One additional outcome measurement instrument was added after discussion during the in-person meeting. This collective effort ensures that the resulting COS-AT contains outcome measurement instruments holding genuine significance for patients with Achilles tendinopathy. Additionally, the consensus process was carried out without external funding influence. This independence strengthens the integrity of our COS-AT development. The prospective registration of the protocol is also a strength of this consensus process.

There were several limitations in the development of the COS-AT. One notable challenge was the limited or low-quality evidence for many of the identified outcome measurement instruments. This may introduce uncertainty into the reliability and validity of the selected COS components. For example, the VISA-A has been criticised in terms of its psychometric properties.[20,21] This might not be clearly noticeable in the quality assessment table (online supplementary File 4) we used in the process. This table was based on OMERACT guidelines, and as a result, structural validity and cross-cultural adaptation were not assessed, while COSMIN guidelines include these as part of construct validity. Especially regarding

structural validity, most studies did not determine this aspect of validity and when it was reported, it was not done using a unidimensional structure. The ongoing inclusion of the VISA-A in the COS-AT (as for any other outcome measure) should be considered against those reviews, and in light of further evaluation of its psychometric properties. However, a notable strength of the VISA-A is that is has been cross-culturally adapted and validated in a broad spectrum of languages.[22-28] Another reason why it is currently useful to include the VISA-A questionnaire (as well as VAS related to loading) in the COS-AT is the fact that most previous clinical studies used these outcome measurement instruments.[5,7,8] With the aim of improving the ability to synthesize data for meta-analyses in the future, it is likely of benefit that future clinical trials can also be statistically compared against previous ones.

Another possible limitation is that we have not included recently developed outcome measurement instruments – as our evidence search census date was March 2021. For example, the TENDINopathy Severity Assessment – Achilles (TENDINS-A) has been recently developed from interviews with patients and clinicians having adequate content validity,[29] as well as excellent reliability and structural validity.[30] The VISA-A has also been recently developed for sedentary individuals and might be included in the future.[31] Our scan of the literature since the census date has not identified any other outcome measurement instruments that would have likely changed the outcome of our COS-AT. When new measurement instruments become available the COS-AT will need to be reviewed and if deemed appropriate it would need a revision with the current COS-AT as foundation.

What comes next?

Future research should focus on evaluating the clinimetric properties of specific outcome measurement instruments, which have limited evidence but were included in the COS-AT. Furthermore, the COS-AT currently does not cover several core domains in tendinopathy, including patient overall rating, participation, function, psychological factors, quality of life, and pain over a specific time frame.[7] Future research should focus on assessing the reliability and validity of outcome measurement instruments within these core domains or to develop new instruments to determine their potential inclusion in the COS-AT. Valid imaging outcomes could be developed for use alongside the COS-AT, but were not included in this process as imaging was not included as core domain.

Knowledge dissemination plays a crucial role in ensuring the widespread adoption of the COS-AT within research and clinical practice.[32] Efforts should be directed towards effectively communicating the importance of this COS-AT, hereby enhancing its integration into clinical practice guidelines, and facilitating its use in future clinical trials. Continuous engagement with relevant stakeholders, such as professional participants and patients, is important to ensure that the COS-AT will be used widely, ultimately advancing the standardization and quality of care for individuals with Achilles tendinopathy.

CONCLUSION

This is the first extensive 5-step process to develop a core outcome set for Achilles tendinopathy (COS-AT). The core outcome set for clinical trials of Achilles tendinopathy consists of 4 outcome measurement instruments that are: 1) the VISA-A questionnaire, 2) the single-leg heel rise test, 3) evaluating pain after activity using a VAS (0 -10) and 4) evaluating pain on activity/loading using a VAS (0-10). Patients and professional participants agreed on these 4 outcome measurement instruments to be part of the COS-AT. It is strongly recommended that the selected COS-AT will be used in future clinical trials evaluating effectiveness of an intervention for Achilles tendinopathy, although this does not prevent the use of other outcome measurement instruments.

FOOTNOTES

Funding

The authors from the steering group (RJDV, KS, PM, BV) have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors. Within this 5-year project, multiple authors have been supported by specific research fellowships and/or grants that were not directly related to the COS-AT development. One author (DM) mentioned indirect support by the National Institute for Health Research Barts Biomedical Research Centre (NIHR203330).

Competing interests

None declared.

Patient consent for publication

Requested and obtained.

Ethics approval

The medical ethical committee of Erasmus MC University Medical Center confirmed that the Medical Research Involving Human Subjects Act (WMO) did not apply to our study (MEC-2021-0279).

Acknowledgements

The steering committee would like to acknowledge the contributions to this project of the Achilles tendinopathy Working group, the professional participants and the patients, who donated their time voluntarily. This project would not have been feasible without their help. We would like to acknowledge Peter Stig Magnusson and Jarrod Antflick, who contributed actively during specific phases of this project, but decided to retract their role as co-author.

SUPPLEMENTARY MATERIAL

All supplementary material can be found online.

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Chapter 3

Normative values for calf muscle strength-endurance in the general population assessed with the Calf Raise Application: A large international cross-sectional study

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Submitted

ABSTRACT

Objectives: To establish normative values for calf muscle strength-endurance, adjusted for personal characteristics

Methods: 500 individuals without current or previous symptoms of Achilles tendinopathy or recent lower limb immobilization were included. The primary outcome measures were the number of repetitions, total work (J), total vertical displacement (cm) and peak height (cm) upon the single-leg Heel Rise Endurance Test (HRET), assessed using the validated Calf Raise Application. A multiple quantile regression model was developed, incorporating covariates (personal characteristics) previously identified to significantly impact HRET metrics. Median (50.0th percentile) and 95% reference intervals (2.5th-97.5th percentiles) were derived.

Results: Of the 500 participants included, 55% were female and the majority (88%) participated in sports and physical activities. Median (dominant/non-dominant leg) number of repetitions was 25/24, total work was 1374/1325 J, vertical displacement was 192/186 cm and peak height was 9.3/9.6cm. There was no significant difference between the dominant and non-dominant leg for any of the HRET metrics. Lower physical activity levels, female gender, and higher body mass index (BMI) were associated with lower HRET metrics.

Conclusions: Outcomes of the HRET are influenced by personal characteristics, with female gender, higher BMI, and lower physical activity levels being associated with lower HRET metrics. We have developed an openly accessible calculator for estimating normative HRET metrics (www.achillestendontool.com/HRET). This can be a valuable tool for healthcare providers to monitor personalized trajectories of recovery and provide well-informed rehabilitation guidance. Documenting more than the number of repetitions is important when assessing calf muscle function using the HRET.

INTRODUCTION

The strength-endurance of the plantar flexors is frequently assessed in clinical practice and research using the single-leg heel rise endurance test (HRET).[1,2] The results obtained from this test are valuable for evaluating impairment severity, tracking recovery of Achilles tendon injuries, assessing exercise program effects on functional abilities and guiding return-to-sport recommendations.[2-4]

Normative values of tests are often used as a reference for evidence-based clinical practice.[5] The contralateral limb cannot always be used as a reference for comparison as it does not always reflect optimal function.[6,7] Consequently, it is important to have HRET normative values for both limbs. The existing literature suggests that a "normal" HRET performance comprises approximately 25 heel raises, with age, sex, body mass index (BMI), and activity level influencing the results in Swedish individuals.[6,8] Although the HRET has good test-retest reliability, a limitation of the test is that it relies on the total number of repetitions performed, without taking into account the quality of movement.[6,9] For example, individuals can complete numerous repetitions, but not raise the heel very high. More objective metrics, such as total work or peak height, are considered scientifically more robust than the number of repetitions and are deemed important measures of calf muscle tendon unit function.[10-13] The recently developed Calf Raise Application can reliably assess these metrics.[14] However, normative values for these HRET metrics in the general population are lacking.[2,12]

The primary objective of this study was to establish normative HRET values in a large population of healthy individuals, using objective metrics such as number of repetitions, total work (J), total displacement (cm) and peak height (cm). The secondary aim was to assess how HRET metrics are influenced by personal characteristics, including age, gender, BMI and activity level.

METHODS

Study design

The study was designed at the Erasmus MC University Medical Centre (NL) in collaboration with the University of Leicester (UK) and the University of Waikato (NZ). The local Medical Ethics Committee (Southwest-Holland, the Netherlands) approved the study protocol (MEC-2020-0585). The trial was prospectively registered (Netherlands Trial Register, NL9010) and we adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[15]

Protocol deviations

In the initial study registration, 'total work' and 'total vertical displacement' were listed as secondary outcomes, but were reclassified as primary outcomes. Similarly, 'repetitions' and 'peak height,' were not initially registered, but were included as primary outcome measures. These decisions were based upon further clinical assessment and post-registration discussions within our research team. The correlation between structure and calf muscle strength-endurance was prospectively registered but can't be reported at this stage as it requires specific software, which, as of now, has not been developed and validated by the manufacturer.

Participants

The study was conducted at the outpatient departments of two large universities (Erasmus MC University Medical Centre and University of Leicester) from October 2020 to June 2023. The study was paused from November 2020 to May 2022 due to Covid-19 restrictions. These restrictions also compelled us to limit sample size to 500, which is a reduction of 100 participants compared to the pre-defined protocol.

We aimed to include a sample of participants that accurately reflects the general population, with an even distribution of both gender and across decades of life. To recruit participants, a comprehensive announcement was disseminated through internal websites and various social media platforms, including Twitter (now X), Facebook, and LinkedIn. Interested individuals were screened remotely. Those meeting eligibility during remote screening were scheduled for an appointment with a researcher, during which further screening assessments were conducted.

Inclusion criteria were: (1) at least 18 years of age, (2) no current or prior history of Achilles tendon pain or stiffness, (3) no localized fusiform thickening of the Achilles tendon on palpation, and (4) a full score on the adapted (questions 1 to 5) Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire. [16,17] Exclusion criteria were: (1) a history of Achilles tendon or ankle surgery, (2) any lower-limb injury requiring immobilization within

the past 12 months, and (3) known systemic inflammatory disorders/internal diseases that may cause Achilles tendon abnormalities.

Eligible participants were asked to sign an informed consent form before data collection. Subsequently, participants were asked to fill out a more comprehensive survey to collect demographic data (age, sex, height, mass, and BMI), health status details (presence of comorbidities, smoking, medication use) and sports activities information. Physical Activity Level (PAL) was assessed using a 6-point Likert scale.[6]

Procedures

After completing the survey, participants performed the HRET. During this test, participants were instructed to assume a single-leg stance on a 10° incline board barefoot with the knee in full extension and the trunk erect. Video recordings of each HRET were obtained using the specialized Calf Raise Application.[14,18] A device (IPad or IPhone, Apple Inc., Cupertino, United States) was used to record the test (see Figure 1). The device was placed upright in a fixed position (in a stand on a flat base) to the side of participants.

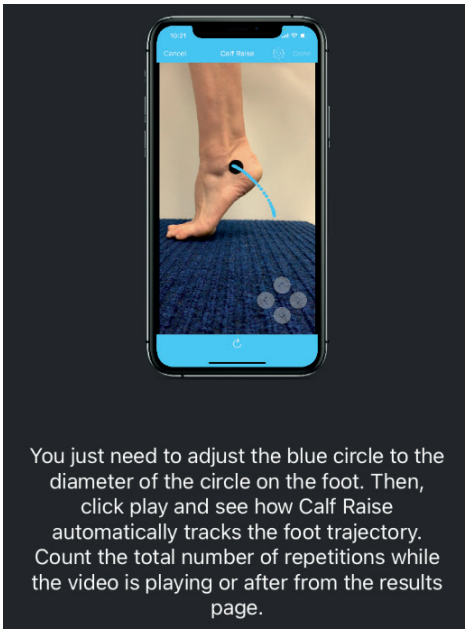


Figure 1. Example of the Calf Raise Application. A round sticker with a diameter of 2.5 cm is placed just below the distal tip of the lateral malleolus. The Calf Raise Application tracks this sticker using computer vision algorithms. As the participant goes up, the heel with the adjusted sticker moves upwards and forwards in the screen.

Participants were allowed fingertip support at shoulder height on the wall in front of them. The objective of the test was to raise the heel as high as possible on each repetition, returning it to the incline board, and performing as many repetitions as possible while minimizing anterior movement. A digital metronome set at 60 beats per minute guided the test, with participants ascending on one beat and descending on the next (i.e., 30 repetitions per minute). To acclimate to the metronome pace, each participant performed 10 bilateral standing heel rises as a warm-up prior to testing.

Participants were informed of the test termination criteria: 1) the heel can no longer be lifted from the incline board, 2) the pace of the digital metronome can no longer be followed, 3) the knee angle or trunk position can no longer be maintained, or 4) more than fingertip support on the wall is needed for balance. If a termination criterion was observed, a verbal prompt was given. Testing was terminated when there was no response to two consecutive prompts. Throughout the testing procedure, participants received verbal instructions to maintain the specific parameters, including heel excursion, cadence, balance support, and knee angle. The HRET was conducted once on each leg, and the order of testing was quasi-randomized, based on the moment of inclusion. A 2-minute rest period was provided to participants following the completion of the first single-leg HRET, after which the test was repeated using the opposite limb.

Outcome measures

By tracking the vertical displacement of the round sticker on the foot of participants and based on the mass (kg) of individuals, the Calf Raise Application calculates various metrics. The primary outcome measures in this study were the number of repetitions, total positive work (J), total vertical displacement (cm) and peak height (cm). These Calf Raise Application metrics are validated and show excellent reliability.[14,19] Secondary outcome measures, as reported in the application, were vertical height loss (%) and peak power (W). The exact working mechanism and validation of the Calf Raise Application have been described in detail elsewhere.[14,19]

Statistical analysis

Given the objective of establishing normative values and the skewed distribution of the data, we used quantile regression for the analysis as it estimates medians without imposing distributional assumptions. Potential differences in HRET metrics between the dominant and non-dominant leg were analysed using a Mann-Whitney U-test. When no statistically significant differences were observed, mean HRET metrics were used to develop the quantile regression model. Initially, bivariate models were constructed to examine the relationship between each covariate (age, gender, height, mass, BMI, leg dominance, and PAL) and the HRET metrics. Subsequently, a multiple quantile regression model was developed, incorporating the covariates that demonstrated a significant influence on HRET

metrics. The median (50.0th percentile), lower (2.5th), and upper (97.5th) percentile values of the regression models were extracted to present HRET metrics as median with a 95% (2.5th to 97.5th percentiles) reference interval (RI). A covariate was excluded from the multiple regression model if the following two criteria were met: 1) it exhibited a weak/negligible ($r<0.3$)[20] correlation coefficient and 2) the removal of the covariate did not impact the model's 'accuracy,' as indicated by the stability of the R^2 value. To evaluate the influence of each covariate on HRET metrics, the 95% confidence intervals (CI) were extracted to allow estimation of the impact of each covariate. We adhered to the CHecklist for statistical Assessment of Medical Papers (CHAMP) statement for the statistical analysis and presentation of results.[21] IBM SPSS Statistics (version 28.0.1.0) were used for all analyses, and significance was set at $p < 0.05$.

RESULTS

Flow of participants through the study

A total of 547 asymptomatic persons were screened for eligibility and 500 of these participants were included (n=300 at Erasmus MC and n=200 at University of Leicester). A flowchart of the study is presented in online supplementary file 1 (supplementary figure 1). In five participants, the HRET metrics could not be extracted due to recording/technical errors; there was a complete dataset of 495 participants.

The participant characteristics are displayed in Table 1. More than half of the participants were female (55%) and the majority (88%) participated in sports activities. Eight participants did not want to disclose their gender. The age of the participants ranged between 18 and 81 years.

Table 1. Participant characteristics. Values are means with standard deviation (SD) unless otherwise described.

Participant characteristics (n=500)	Mean (SD) / Median [IQR]		
	Overall	**Female**	**Male**
Population demographics			
Age (years)	30 [22-50]	34 [23-52]	28 [21-45]
Gender (Male/Female/Other; n)	218/274/8	274	218
Height (cm)	174 [168-180]	169 [164-173]	181 [176-186]
Mass (kg)	71 [64-80]	66 [60-73]	78 [72-87]
BMI (kg/m^2)	23.3 [21.7-25.6]	23.1 [21.3-25.4]	23.6 [22.2-26.0]
Leg dominance (Right/Left/Both/unknown)	442/46/10/2	234/30/8/2	198/18/2/0
General health and comorbidities			
Sports participation (yes/no)	439/61	234/40	197/21
Physical Activity Level (PAL; 1-6)	5 [4-6]	5 [4-5]	5 [4-6]
Medication use (yes/no; n)	128/372	86/188	41/177
Smoking (never/current/stopped)	439/28/33	245/13/16	187/15/16
Alcohol consumption (units/week)	4 [1-8]	3 [1-6]	5 [2-10]
Comorbidities* (yes/no; n)	52/448	37/237	15/203

Abbreviations; **BMI**: Body Mass Index (kg/m2), **PAL**: Physical Activity Likert Scale; 1-6, 1 = Hardly any physical activity, 2 = Mostly sitting, sometimes walk, easy tasks/play, 3 = Light physical activity for about 2-4 times a week (e.g., fishing, talking, dancing), 4 = Moderate exercise 1-2 hours a week (jogging, swimming, gymnastics), 5 = Moderate exercise at least 3 hours a week (jogging, swimming, gymnastics), 6 = Hard or very hard exercise regularly and several times a week during which the physical exercise is great (jogging, rugby, football).
*Comorbidities included: diabetes, hypercholesterolemia, hypertension, heart/vessel diseases and thyroid disease.

Normative values for HRET metrics

The median (95% RI) number of repetitions completed was 25 (13-50) for the dominant leg and 24 (12-51) for the non-dominant leg. The normative values (median, 95% RI) for the number of repetitions, total work, total displacement, and peak height are presented in Table 2. The normative values for the secondary outcome measures are presented in online supplementary file 1 (supplementary Table 1) as well as the normative data for the right and the left leg (Supplementary Table 2).

Table 2. Normative data for the HRET metrics of the primary outcome measures.

Normative values HRET metrics (n=483)	Median (95%RI)*		
	Overall	**Female**	**Male**
Dominant leg			
Repetitions (n)	25 (13 – 50)	24 (13 – 43)	26 (14 – 53)
Total work (Joule)	1374 (609 – 2676)	1204 (608 – 2151)	1676 (623 – 2935)
Total displacement (cm)	192 (86 – 376)	182 (84 – 343)	210 (91 – 405)
Peak height (cm)	9.3 (5.2 – 13.0)	9.2 (5.5 – 12.5)	9.4 (4.9 – 13.9)
Non-dominant leg			
Repetitions (n)	24 (12 – 51)	23 (11 – 48)	26 (13-62)
Total work (J)	1325 (539 – 2786)	1130 (488 – 2098)	1623 (662 – 3168)
Total displacement (cm)	186 (84 – 380)	174 (75 – 361)	204 (100 – 448)
Peak height (cm)	9.6 (5.6 – 13.8)	9.4 (5.4 – 12.7)	10.1 (5.7 – 14.1)

Abbreviations: HRET; Heel Rise Endurance Test, RI; Reference Interval. * Values are median with 95% reference interval (2.5^{th} and 97.5^{th} percentile)

There was no statistically significant difference between the dominant and the non-dominant side for any of the HRET metrics nor a correlation between leg dominance and HRET metrics (supplementary file 1, supplementary Table 3 and supplementary Table 4). Bivariate analyses revealed that there was a significant correlation between gender (r=0.20,p<0.001), height (r=0.17,p<0.001), BMI (r=-0.28, p<0.001) and PAL (r=0.23, p<0.001) with the number of repetitions. Total work significantly correlated with gender (r=0.45, p<0.001), height (r=0.52, p<0.001), mass (r=0.33, p<0.001) and PAL (r=0.19, p<0.001). Gender (r=0.23, p<0.001), height (r=0.26, p<0.001), BMI (r=-0.32, p<0.001) and PAL (r=0.21, p<0.001) significantly correlated with total displacement. There was a significant correlation between gender (r=0.12, p=0.009), height (r=0.20, p<0.001), and BMI (r=-0.15, p<0.001) with peak height. Results of the bivariate analyses for the secondary outcome measures are presented in supplementary file 1. The results of the multiple quantile regression model with estimates of the relevant parameters on the different HRET metrics are displayed in Table 3 (and supplementary file 1, supplementary Table 5 for the secondary outcome measures).

Table 3. Estimates (95%CI, p-value) of the effect of the parameters on the different HRET metrics derived from the multiple quantile regression analysis adjusted for age, height (cm), mass, BMI, sex and physical activity level (PAL). Examples on how to employ the normative equations based on two fictional patients are provided in the lower part of the table.

Parameter	Repetitions	Total work	Vertical displacement	Peak height
Intercept	41.2 (35.4, 47.0)	-2084 (-3329, -839)	156.7 (-25.7, 339.2)	3.3 (-2.4, 9.0)
Age	XX	XX	XX	XX
Height	††	19.5 (12.1, 27.0)	1.0 (0.8, 2.0)	0.044 (0.015, 0.074)
BMI	-0.61 (-0.84, -0.38)	XX	-5.5 (-7.4, -3.5)	-0.069 (-0.13, -0.10)
Mass	XX	2.6 (-2.0, 7.3)	XX	XX
Gender	-2.7 (-4.4, -1.1)	-164.3 (-296.8, -31.8)	-12.8 (-31.2, 5.7)	††
PAL 2	3.6 (-3.8, 10.9)	-211.4 (-649.9, 227.1)	-18.7 (-79.8, 42.4)	XX
PAL 3	-2.6 (-5.4, 0.27)	-185.3 (-354.1, -16.6)	-29.4 (-52.9, -5.9)	XX
PAL 4	-0.93 (-3.3, 1.4)	-135.6 (-275.8, 4.6)	-22.4 (-41.9, -2.8)	XX
PAL 5	0.43 (-1.6, 2.5)	33.9 (-86.2, 154.1)	5.9 (-10.9, 22.6)	XX

Normative equation*	Intercept + age + height + BMI + gender + PAL
Example A	Female, 53 years, 29 kg/m^2, 165 cm, 79 kg, PAL 3
Example B	Male, 25 years, 21 kg/m^2, 184 cm, 71 kg, PAL 5
Repetitions**	41.2 – 0.61 x (BMI) – 2.7 x (gender) + PAL
A: 18 (12 – 33)	41.2 – 0.61 x (29) -2.7 x (1) – 2.6
B: 29 (16 – 55)	41.2 – 0.61 x (21) -2.7 x (0) + 0.43
Total work**	-2084 + 19.5 x (height) + 2.6 x (mass) – 164.3 x (gender) + PAL
A: 989.3 (531.7-1651.0) J	-2084 + 19.5 x (165) + 2.6 x (79) – 164.3 x (1) – 185.3
B: 1722.5 (824.6-3108.2) J	-2084 + 19.5 x (184) + 2.6 x (71) – 164.3 x (0) + 33.9
Vertical displacement**	156.7 + 1.0 x (height) – 5.5 x (BMI) -12.8 x (gender) + PAL
A: 126 (69-246) cm	156.7 + 1.0 x (165) – 5.5 x (29) – 6.5 x (1) – 29.4
B: 231 (117-430) cm	156.7 + 1.0 x (184) – 5.5 x (21) – 6.5 x (0) + 5.9
Peak height**	3.3 + 0.044 x (height) – 0.069 x (BMI)
A: 8.6 (5.0-11.7) cm	3.3 + 0.044 x (165) – 0.069 x (29)
B: 9.9 (5.8-13.6) cm	3.3 + 0.044 x (184) – 0.069 x (21)

* Gender: male = 0, female = 1, PAL 6= 0

** Values are median (mm) with 95% RI (2.5th percentile, 97.5th percentile)

†† Covariate removed from the multiple quantile regression model as it exhibited a weak/negligible (r<0.3)[20] correlation coefficient and the removal of the covariate did not impact the model's 'accuracy,' as indicated by the stability of the R^2 value.

Abbreviations; **BMI:** Body Mass Index, **PAL:** Physical Activity Level.

DISCUSSION

In this large international cross-sectional study, we presented normative values for HRET metrics, adjusted for personal characteristics. We found that the median number of repetitions and peak height was 25 and 9.3 cm for the dominant leg and 24 and 9.6 cm for the non-dominant leg. There was no significant difference between the dominant and the non-dominant leg for any of the HRET metrics. Lower physical activity levels, female gender, lower body height, and higher BMI were associated with lower HRET metrics. For the primary outcome measures, we found no correlation between age and HRET metrics.

This study presents novel reference values for HRET metrics. The median number of repetitions achieved in the present investigation corresponds with previous findings.[6,19,22] Various studies have reported mean values for total work (ranging from 1800 to 3000 J) or peak height (ranging from 9 to 14.1 cm) in the uninjured legs of patients recovering from Achilles tendon rupture[11,22,23] or a small (38 participants) sample of healthy individuals.[10] Our median values for work (1380 J) and peak height (9.7 cm) are at the lower end of this spectrum. This discrepancy can potentially be attributed to the relatively small (38 – 96 participants) or selected (very active) study populations that are younger in age in previously published studies. The primary factor contributing to the observed variance in results is likely the methodology employed in the current study for collecting calf raise data, specifically the use of a marker placed below the lateral malleolus[14] rather than on the heel, as done in the aforementioned studies to attach a linear encoder[10,11,22]. This below malleolus placement is found to be more valid when using the Calf Raise Application,[14] but results in relatively lower values compared to using a marker positioned on the heel.[14]

Our results show that HRET metrics are influenced by personal characteristics. The findings that lower physical activity, higher BMI, lower body height and female gender are associated with lower HRET outcomes are consistent with previous findings.[6] We did not observe a correlation between age and the number of repetitions, which contrasts to earlier work showing a significant decline in number of repetitions for each passing decade of life.[6] A possible explanation for this may be that, despite the efforts to include a balanced population with regards to age and gender, the study population was relatively young with a mean (min-max) age of 36 (18-81) years as well as relatively active (supplementary file 1, supplementary Figure 2 and supplementary Figure 3). It is likely that other personal factors influence the results, like motivation[24] and self-confidence. We did encourage participants to perform maximally, but we are aware that psychological factors – which we did not consider – may affect outcome.

Clinical implications

Literature shows inconsistent findings with regards to the influence of leg dominance on the number of repetitions. While several studies reported no between-leg differences,[6,25] others reported the non-dominant side to exhibit greater strength[26] or a higher number of repetitions than the dominant side.[6,27] The current study did not find any difference between leg dominance and HRET performance. The inconsistent evidence makes it difficult to support or refute the use of the uninvolved side as a reference for comparison when evaluating HRET performance in clinical practice. This issue becomes particularly apparent in injured individuals where is it known that HRET performance is negatively impacted in both limbs.[6] To address this issue, clinicians may benefit from knowledge of reference values, adjusted for personal characteristics. We have developed an openly accessible web-based calculator for estimating normative HRET metrics (www.achillestendontool.com/HRET). This tool may be valuable for clinicians to monitor personalized trajectories of recovery and to provide well-informed rehabilitation guidance.

Strengths and limitations

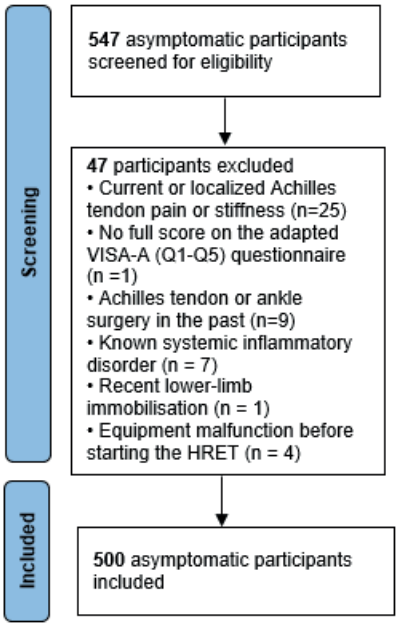
The strengths of this study lay in the design, with the inclusion of a large and international study population, a pre-defined protocol, the use of a validated openly accessible application to obtain outcome measures and the development of the open access tool for calculating normative HRET values, adjusted for personal characteristics to facilitate implementation in clinical practice. There are several limitations to this study. First, while the age range of the included participants was broad, the mean age of the study population was relatively young. This age may have led to the underestimation or absence of a correlation between age and HRET performance. Second, the normative values were derived exclusively from the Calf Raise Application. This application has demonstrated excellent validity and reliability, but our findings may not translate directly to normative values for other methods of assessing the HRET (such as the use of a linear encoder placed on the heel) or testing in different positions (e.g., no 10° incline or with shoes on) or with different cadence. However, this application is free for use and easily accessible for clinical and research use. Thirdly, during the design phase of the study we decided to collect the peak power and vertical height loss as outcome measures. Peak power is less relevant, because we used a metronome, resulting in more constant peak power values. Vertical height loss is known to be the least reliable and valid outcome measure.[14] We therefore present these metrics as secondary outcome measures.

CONCLUSION

Outcomes of the single-leg HRET are influenced by personal characteristics, with female gender, higher BMI, lower body height and lower physical activity levels being associated

with lower HRET metrics. The normative values for the HRET presented in this study (www.achillestendontool.com/HRET) may help clinicians in the in determining the severity of impairment or to evaluate treatment outcomes. We recommend metrics other than heel raise repetitions are used in research and practice as these are more scientifically robust and important measures of calf muscle tendon unit function.

SUPPLEMENTARY FILE 1.



Supplementary Figure 1. Flowchart of the study.

Supplementary Table 1. Normative values (median, 95% reference interval) of the secondary outcome measures (vertical height loss (%) and peak power (Watt)).

Normative values HRET metrics (n=483)	Median (95%RI)*		
	Overall	**Female**	**Male**
Dominant			
Peak power (Watt)	242 (132 – 463)	217 (120 – 377)	286 (152 – 521)
Vertical height loss (%)	22.1 (0.7 – 73.2)	20.2 (0.5 – 64.3)	24.0 (1.0 – 77.4)
Non-dominant			
Peak power (Watt)	249 (124 – 476)	220 (118 – 445)	284 (169 – 522)
Vertical height loss (%)	20.5 (0.9 – 71.6)	19.2 (0.8 – 74.9)	20.9 (1.3 – 70.3)

Abbreviations: HRET; Heel Rise Endurance Test, RI; Reference Interval
* Values are median with 95% reference interval (2.5^{th} and 97.5^{th} percentile)

Supplementary Table 2. Normative data for the HRET metrics for the left leg and right leg.

Normative values HRET metrics (n=495)	Median (95%RI)*		
	Overall	**Female**	**Male**
Left			
Repetitions (n)	24 (11 – 51)	23 (11 – 46)	26 (13-59)
Total work (J)	1304 (537 – 2743)	1125 (467 – 2097)	1622 (663 – 3024)
Total displacement (cm)	185 (80 – 379)	172 (74 – 353)	206 (97 – 418)
Peak height (cm)	9.7 (5.5 – 13.8)	9.4 (5.4 – 12.8)	10.1 (5.5 – 14.0)
Peak power (Watt)	249 (124 – 508)	213 (118 – 436)	281 (169 – 541)
Vertical height loss (%)	20.7 (1.0 – 71.5)	19.4 (0.9 – 73.1)	20.9 (1.3 – 70.3)
Right			
Repetitions (n)	25 (13 – 52)	24 (13 – 46)	27 (14 – 55)
Total work (Joule)	1379 (599 – 2755)	1203 (544 – 2147)	1676 (623 – 3094)
Total displacement (cm)	191 (86 – 377)	178 (83 – 347)	209 (91 – 431)
Peak height (cm)	9.3 (5.2 – 13.0)	9.2 (5.5 – 12.5)	9.4 (4.9 – 14.0)
Peak power (Watt)	242 (136 – 447)	218 (131 – 387)	290 (152 – 502)
Vertical height loss (%)	21.4 (0.7 – 72.4)	19 (0.5 – 65.9)	23.9 (1.0 – 77.4)

Abbreviations: HRET; Heel Rise Endurance Test, RI; Reference Interval. * Values are median with 95% reference interval (2.5th and 97.5th percentile)

Supplementary Table 3. Difference in HRET metrics between the dominant and the non-dominant leg for both sides.

	Mean difference	**P-value**
Left		
Repetitions (n)	-1.5	0.517
Total work (Joule)	-93.2	0.211
Total displacement (cm)	-17.9	0.164
Peak height (cm)	-0.05	0.886
Peak power (Watt)	-0.4	0.905
Vertical height loss (%)	-0.16	0.398
Right		
Repetitions (n)	-0.3	0.641
Total work (Joule)	-8.5	0.608
Total displacement (cm)	-6.1	0.311
Peak height (cm)	0.02	0.944
Peak power (Watt)	14.6	0.205
Vertical height loss (%)	-1.6	0.567

Abbreviations: HRET; Heel Rise Endurance Test

Supplementary Table 4. Correlation between leg dominance and the HRET metrics for the right and left leg separately.

	Correlation coefficient	p-value
Left		
Number of repetitions	-0.010	0.820
Peak height	0.003	0.941
Total displacement	0.020	0.655
Total work	0.013	0.776
Peak power	-0.033	0.472
Vertical height loss	-0.074	0.104
Right		
Number of repetitions	-0.008	0.863
Peak height	-0.024	0.592
Total displacement	0.005	0.917
Total work	-0.017	0.715
Peak power	-0.102	0.025
Vertical height loss	-0.012	0.792

Bivariate analyses for the secondary outcome measures

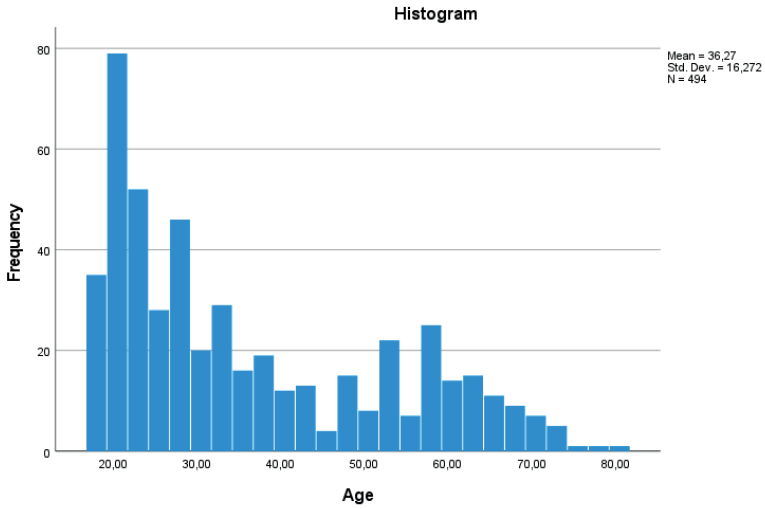
There was no significant correlation between any of the HRET metrics and vertical height loss. Age (r=-0.12, p=0.010) sex (r=0.49, p<0.001), height (r=0.52, p<0.001), weight (r=0.55, p<0.001) and PAL (r=0.12, p=0.009) significantly correlated with peak power.

Supplementary Table 5. Estimates (95%CI, p-value) of the effect of the parameters on the different HRET metrics for the secondary outcome measures, derived from the multiple quantile regression analysis adjusted for age, height (cm), mass, BMI, sex and physical activity level (PAL). An example on how to employ the normative equations based on two fictional patients is provided in the lower part of the table.

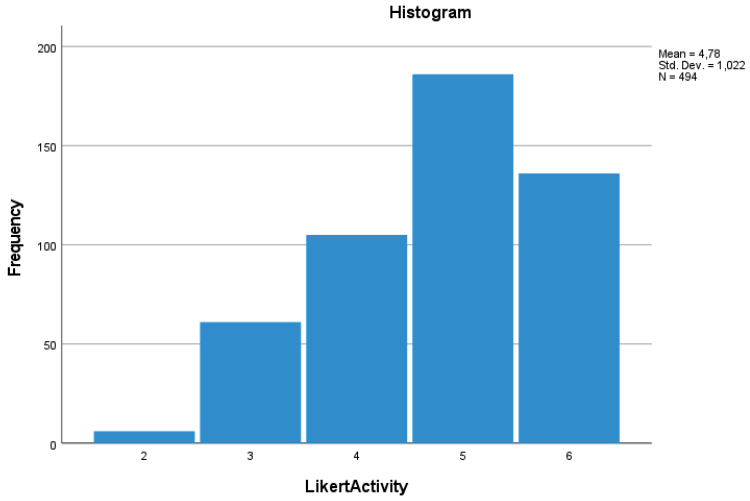
Parameter	Peak power
Intercept	-175.5 (-337.9, -13.1)
Age	-0.69 (-1.1, -0.28)
Height	1.7 (0.69, 2.6)
BMI	XX
Mass	2.4 (1.8, 2.9)
Sex	-17.8 (-35.0, -0.5)
PAL 2	-64.6 (-121.7, -7.6)
PAL 3	-2.5 (-25.1, 20.1)
PAL 4	-2.5 (-21.2, 16.2)
PAL 5	-4.8 (-20.8, 11.2)

Normative equation*	Intercept + age + height + BMI + sex + PAL
Example A	Female, 53 years, 29 kg/m^2, 165 cm, 79 kg, PAL 3
Example B	Male, 25 years, 21 kg/m^2, 184 cm, 71 kg, PAL 5
Peak Power**	-175.5 – 0.69 x (age) + 1.7 x (height) + 2.4 x (weight) – 17.8 x (sex) + PAL
A: 232.1 (146.1-302.9) W	-175.5 – 0.69 x (53) + 1.7 x (165) + 2.4 x (79) – 23.4 x (1) – 2.5
B: 285.7 (175.0-485.3) W	-175.5 – 0.69 x (25) + 1.7 x (184) + 2.4 x (71) – 23.4 x (0) – 4.8

* Sex: male = 0, female = 1, PAL 6= 0
** Values are median (mm) with 95% RI (2.5th percentile, 97.5th percentile)
Abbreviations; **BMI:** Body Mass Index



Supplementary Figure 2. Histogram of the distribution of age in the study population.



Supplementary Figure 3. Histogram showing the distribution of physical activity level (PAL) in the study population. Likert Scale; 1-6*, 1 = Hardly any physical activity, 2 = Mostly sitting, sometimes walk, easy tasks/play, 3 = Light physical activity for about 2-4 times a week (e.g., fishing, talking, dancing), 4 = Moderate exercise 1-2 hours a week (jogging, swimming, gymnastics), 5 = Moderate exercise at least 3 hours a week (jogging, swimming, gymnastics), 6 = Hard or very hard exercise regularly and several times a week during which the physical exercise is great (jogging, rugby, football).

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Chapter 4

Impact of chronic Achilles tendinopathy on health-related quality of life, work performance, healthcare utilisation and costs

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BMJ Open Sport & Exercise Medicine 2021;7:e001023

ABSTRACT

Objectives: To evaluate the impact of Achilles tendinopathy (AT) on quality of life (QoL), work performance, healthcare utilization and costs in adults with conservatively-treated chronic midportion AT

Methods: This cross-sectional survey-based study included 80 patients and took place in a sports medicine department of a large regional hospital in the Netherlands. Data were collected before any intervention was given. Primary outcome was the EuroQol questionnaire (EQ-5D). The EQ-5D expresses the percentage of moderate/major problems on the domains self-care, anxiety/depression, mobility, usual activities and pain/discomfort. Secondary outcomes were the number of previous healthcare visits, work performance during the period of symptoms and estimated annual direct medical and indirect costs per patient as result of AT.

Results: All 80 patients completed the questionnaires. The EQ-5D scores were low for the domains self-care (1%) and anxiety/depression (20%), and high for the domains mobility (66%), usual activities (50%), and pain/discomfort (89%). Patients with AT mainly reported an impact on work productivity (38%). Work absenteeism due to AT was present in 9%. The total median (IQR) number of annual healthcare visits was 9 (3-11). The total mean (SD) estimated annual costs were €840 (1420) per AT patient (mean and SD US $991 (1675)).

Conclusions: This study shows the large impact of Achilles tendinopathy on QoL and work productivity. This study also provides new information about the socio-economic impact of AT, which emphasizes that this common and longstanding disease causes substantial costs. These findings stress the need for optimized treatment and improved preventive interventions for AT.

INTRODUCTION

The term Achilles Tendinopathy (AT) entails the clinical triad of localized Achilles tendon pain, tendon thickening and impaired load-bearing capacity.[1-4] AT is frequently observed in middle-aged, physically active people.[1] The incidence rate of AT is 2-3 per 1,000 Dutch general practice registered patients and has risen in the past decade, probably as a result of an increasing amount of people performing sports activities.[2,5] Various treatment options are available and conservative treatment is the primary treatment of choice, but is not very effective.[6] Despite treatment two-thirds of the patients with new-onset AT remain symptomatic at one year follow up.[7] At 10-years follow up, still a quarter of the patients remain symptomatic.[7,8]

The restricting pain and impaired load-bearing capacity associated with AT is assumed to decrease quality of life (QoL).[1,4,9] Indeed, recent qualitative studies showed that some patients with AT describe profound impact on their life (e.g. their identity, social activities, and perceived levels of fitness). [10-12] One of these exploratory studies showed that AT is associated with a lower QoL score compared to normative data.[11] In this study – however – patients were included online without verifying the diagnosis of AT and the QoL scores were not compared to other musculoskeletal diseases. Additionally, a significant number of patients did not have AT at the time of inclusion, but experienced symptoms suggestive for AT in the past. This could have resulted in recall bias. Other musculoskeletal conditions also affect quality of life[13-16], with the magnitude of this impact varying among the conditions.[13-18] It is important to be informed about the magnitude of the impact on quality of life of specific diseases to be aware of the urgency on scientific agendas and it also aids in designing management plans when there is knowledge of the specific domains affected. This information is unknown in AT. Knowledge of the impact of AT on work performance, health care utilization and costs is currently also lacking.

The primary aim of this study is to evaluate the impact on QoL in conservatively treated patients with chronic midportion AT. The secondary aims are to assess the effect of AT on 1) work performance, 2) health care utilization and 3) estimated direct and indirect costs. We hypothesized the impact and socio-economic consequences of AT on QoL to be similar to other musculoskeletal conditions (such as lateral epicondylar tendinopathy, knee osteoarthritis, rheumatoid arthritis and chronic back pain).

METHODS

Study design

The study was designed at the Erasmus MC University Medical Centre (Rotterdam, the Netherlands) in collaboration with Haaglanden Medical Centre (Leidschendam, The

Netherlands). This cross-sectional study was part of a clinical trial, in which this part was completed before any intervention was given. The local Medical Ethics Committee (Southwest-Holland, the Netherlands) approved the study protocol (MEC 14-100). The trial was registered before commencement (ClinicalTrials.gov; NCT02996409).

Patient and Public involvement

Patients or public were not involved in the design and conduct of the study, the choice of outcome measures or the development of the research questions.

Patients

The study was conducted at the sports medicine department of a large regional hospital (Haaglanden Medical Centre), from December 2016 to January 2019. A study announcement was made through informing healthcare professionals (both medical and paramedical) and patients via letters, conferences and social media platforms. If patients passed a telephone and online screening, an appointment with the sports medicine physician was planned to assess eligibility. The main inclusion criteria were: (1) age 18-70 years, (2) painful swelling of the midportion of the Achilles tendon (2-7 cm proximal of the calcaneal insertion) (3) symptom duration of more than two months and (4) no response to at least six weeks of exercise therapy. The main exclusion criteria were: an Achilles tendon rupture, clinical suspicion of other tendinopathies (including insertional AT), inability to perform exercise therapy and previous surgical intervention for this condition. The full list of inclusion and exclusion criteria is displayed on ClinicalTrials.gov. Written informed consent was obtained from all subjects before inclusion.

Procedures

We obtained the outcome measures of this cross-sectional study before any intervention was given. Patients filled in several questionnaires directly following the inclusion appointment with the sports medicine physician. For the clinical trial, patients received either a peritendinous high-volume injection or a placebo injection. The results of this clinical trial have been published elsewhere.[19]

Outcome measures

Primary outcome measure

Quality of life was measured using the validated Dutch version of the EuroQol questionnaire (EQ-5D-3L). [20] The EQ-5D-3L consists of five questions involving the following dimensions: mobility, self-care, daily activities, pain, and anxiety/mood. Each domain consists of three response options: no problems, moderate problems and major problems. The results of the EQ-5D are dichotomized and expressed as the percentage of subjects with moderate or major problems (any problem) [21]. The EuroQol Visual Analogue Scale (EQ-VAS) was used

to evaluate self-rated current overall health status. The EQ-VAS consists of a tape ruler from 0 -100 (with 0 points being the worst imaginable health status).

Secondary outcome measures

We assessed work performance with a questionnaire by asking the number of lost days of work and a decrease in work productivity (yes/no) since the onset of symptoms. We corrected this secondary outcome measure for symptom duration, thereby displaying work performance outcome measures on an annual basis.

Healthcare utilization was expressed in the total annual number of healthcare visits, the type of healthcare provider, and type of treatment. Participants who reported visiting a healthcare provider, but could not specify the number of visits or treatments were recorded as missing data. Participants who reported visiting a sports medicine physician or orthopedic surgeon were assumed to have at least one consultation with a general practitioner (GP), as a referral from a GP to a medical specialist (e.g. sports physician or orthopedic surgeon) is required in the Netherlands. Participants who reported treatment with a certain number of injections, but did not specify the number of visits to a medical specialist were assumed to have an equal number of visits to a medical specialist as the number of injections.

We divided costs into two categories: direct costs as a result of medical consumption and indirect costs as a result of lost working days or decreased work productivity. The direct medical costs were calculated with the following formula: total number of visits/treatments multiplied with estimated medical costs for those visits/treatments. In 2016 the Dutch Healthcare Authority published a guideline for economic evaluations in healthcare.[22] Using this guideline we established medical costs per visit/treatment and estimated productivity costs per hour at €34.75 (US $38.57) per person.[22,23] Costs used for the economic evaluation are specified in supplementary file 1. Costs in dollars were calculated using the average exchange rate of the respective study period. We did not register the profession of the patients and therefore did not adjust the costs for type of profession. Indirect costs were calculated by lost working days/work productivity multiplied by the costs per working day. Costs per working day were calculated using the productivity costs per hour. To calculate indirect costs due to a decrease in work productivity we estimated reduced productivity without sickness absence at 1.0 hour per month. This is based on previous research on self-reported productivity loss in patients with musculoskeletal disorders.[24] The annual direct and indirect costs were adjusted for symptom duration, because we asked patients about these costs during their symptomatic period.

Statistical analysis

We assessed data for having a normal distribution using the Shapiro Wilk test. Normally distributed data are presented as mean with standard deviation (SD) and non-normally

distributed data as median with interquartile range (IQR). We chose to present costs (both in € and US $) as mean with standard deviation (SD), as we wanted to include the weight of outliers on both sides. A median value is also presented to provide a better interpretation of these data and improve the comparability to other studies. Completeness of data is specified in supplementary file 2. We used SPSS software (V.24.0.0.1; SPSS, USA) for statistical analysis. For the randomized controlled trial, of which this study was part, we performed a sample size calculation based on the primary outcome of the study. We estimated that 80 patients were needed to detect a clinically relevant between-group difference in the primary outcome.[19] As post-hoc power analyses are discouraged and this is a descriptive study, we refrained from performing an additional power calculation.

RESULTS

Patient population

All 80 patients that were included in the clinical trial completed the questionnaires for this cross-sectional study (missing data 0%). The median (IQR) age in our study population was 50 (44-54) years with 39 participants being male (49%). The median (IQR) Body Mass Index (BMI) was 25.7 kg/m^2 (23.9-30.0) and median (IQR) symptom duration was 63 weeks (40-127). All registered patient characteristics are shown in Table 1.

Table 1. Descriptive statistics of participants.

Characteristics (n=80)	Mean (SD) / Median [IQR]
Personal characteristics	
Age (years	50 [44-54]
Sex (Male/Female)	39/41
BMI (kg/m^2)	25.7 [23.9-30.0]
Injury-related factors	
AT (unilateral/bilateral; n)	52/28
Symptom duration (weeks)	63 [40-127]
VISA-A score (0-100)	42.8 (15.8)
Sports related factors	
Sports duration (hours/week)	4 [2.5-6.0]
AAS score (0-10)	5 [5.0-6.0]
Sport adaptation (none/reduced/stopped; n)	2/22/56
Work-related factors	
Sedentary work per working day (%)	68 [36-80]

Abbreviations: AT: Achilles tendinopathy, BMI: Body Mass Index, VISA-A: Victorian Institute of Sport Assessment Achilles, AAS: Ankle Activity Score
Values are displayed in frequencies and medians [interquartile range] / means (standard deviation).
Sports adaptation: patients who reported no change in sports activities, a reduce of sports activities or stopped performing sports activities.
VISA-A: A score range from 0 to 100 points (with asymptomatic persons expected to score 100 points) used for assessment of physical disability due to AT.25
AAS: A score range from 0 to 10 points (with 0 being unable to walk and 10 being physically active performing high intensity sports on a top level) which includes different sports, working activities and general activities used to assess the level of activity in persons.[26]

Primary outcome - Quality of Life

The majority of AT patients reported moderate or major problems (any problem) on the domains mobility (66%), usual activities (50%) and pain/discomfort (89%). Low frequencies were reported for the domains self-care (1%) and depression/anxiety (20%). Table 2 shows the distribution of EQ-5D scores in AT patients. Median (IQR) self-rated current overall health-status using the EQ-VAS score was 70 points (59-80).

Table 2. EQ-5D scores in patients with Achilles tendinopathy. Displayed values are the number of patients (%).

N = 80	No problems	Moderate problems	Severe problems
Mobility	27 (34%)	52 (65%)	1 (1%)
Self-Care	79 (99%)	1 (1%)	0 (0%)
Usual activities	40 (50%)	39 (49%)	1 (1%)
Pain/discomfort	9 (11%)	63 (79%)	8 (10%)
Anxiety/depression	64 (80%)	14 (18%)	2 (2%)

Secondary Outcomes

Work performance

Work absenteeism due to AT was reported in 9% of the patients. Within this 9%, the mean (SD) annual number of days that patients were unable to work due to AT was 7.8 (5.7). The median (IQR) annual number of days that the whole study population of patients was unable to work due to AT was 0 (0-0). 38% of the patients reported a decrease in work productivity.

Healthcare utilization

The median (IQR) total number of healthcare visits was 9 (3-11) per patient per year. The majority (84%) reported having visited a physiotherapist and 23% reported the use of foot orthoses prescribed by a podiatrist. 39% visited a GP, whereas 28% of the participants visited a sports medicine physician or orthopedic surgeon. 33% of all annual healthcare visits consisted of 'regular physiotherapy treatment' (e.g. exercise therapy, massage therapy and taping) performed by a physiotherapist. Table 3 demonstrates the frequencies of annual healthcare visits per type of healthcare provider. Table 4 shows the annual health care utilization per type of treatment.

Table 3. Annual health care utilization and medical costs per patient, per type of healthcare provider (n=80)

Health care provider	Patients using resource, no. (%)	Mean resource consumption (% of all healthcare visits)	Mean (SD) medical costs	Median (IQR) medical costs
Primary care (visits)				
General Practitioner	31 (39)	0.50 (4.6)	€17 (47)	€0 (0-17)
Physical therapist	67 (84)	9.7 (88.2)	€320 (598)	€176 (33-355)
Podiatrist	18 (23)	0.15 (1.4)	€23 (51)	€0 (0-0)
Other†	6 (8)	0.27 (2.4)	€20 (94)	€0 (0-0)
Secondary Care (visits)				
Sports medicine physician/ orthopedic surgeon	22 (28)	0.37 (3.4)	€36 (71)	€0 (0-42)
Total		10.8 (100)*	€415 (631)	€258 (131-480)

Abbreviations: IQR: interquartile range, SD: standard deviation

* Total median (IQR) annual healthcare visits was 9 (3-11).

† Another healthcare provider (e.g. osteopath, chiropractor or alternative medicine).

Differences between healthcare visits/costs and total visits/costs are due to rounding off

Table 4. Annual health care utilization and medical costs per patient, per type of treatment (n=80)

Health care resource	Patients using resource, no. (%)	Mean resource consumption (% of all healthcare visits)	Mean (SD) medical costs	Median (IQR) medical costs
Treatments (units)				
Physiotherapy*	67 (84)	3.6 (33)	€120 (363)	€0 (0-156)
Shockwave	35 (44)	2.6 (24)	€86 (222)	€0 (0-99)
Acupuncture/dry needling	16 (20)	1.7 (16)	€55 (267)	€0 (0-0)
Laser therapy/EPTE	7 (9)	0.33 (3)	€11 (47)	€0 (0-0)
Injection therapy†	8 (10)	0.06 (0.6)	€2 (9)	€0 (0-0)

Abbreviations: IQR: interquartile range, SD: standard deviation. EPTE: therapeutic percutaneous electrolysis
* 'Regular physiotherapy treatment' (e.g. exercise therapy, massage therapy and taping) performed by a physiotherapist.
† Prolotherapy, platelet-rich plasma or corticosteroids

Estimated direct and indirect costs

The mean (SD) total healthcare costs were €415 (631) (US $490) per patient per year (median and IQR €258 (131-480)). Physiotherapy treatments accounted for 77% of the total healthcare costs. Annual costs for healthcare use per type of healthcare provider are presented in Table 3. The annual costs per type of treatment are demonstrated in Table 4. Costs in US dollars ($) are specified in supplementary tables 3 and 4.

In patients who reported a decrease in work productivity, annual costs due to reduced work productivity were €417 (US $463) per employee. Total mean (SD) costs due to absenteeism and productivity loss are €425 (1319) (US $501) per AT patient per year. Total mean (SD) estimated annual direct and indirect costs are €840 (1420) (US $991) per AT patient. Costs from loss of work productivity and absenteeism accounted for 51% of the total costs.

DISCUSSION

We demonstrated in this cross-sectional study that Achilles tendinopathy (AT) is associated with a low QoL score, specifically on the domains mobility, usual activities, and pain/discomfort. Work absenteeism due to AT was low (reported in 9% of the patients), whereas more than one-third of the patients (38%) reported a reduction in work productivity due to AT. The total median annual number of healthcare visits was 9 and the total mean estimated annual direct and indirect costs are €840 (US $991) per AT patient.

Quality of life

The finding of a low QoL score in AT patients is in line with a recent exploratory study.[11] The median EQ-VAS score in the current study was comparable to patients with chronic patellar tendinopathy (70 vs. 68 points).[27] We also compared the score from the health-related QoL measure (EQ-5D) for AT to a large sample (n=3664) of the general Dutch population and different musculoskeletal diseases.[16] Having Achilles tendinopathy was associated with a worse mean QoL score, compared to those without a musculoskeletal disease, on all EQ-5D dimensions, except for self-care. Patients with AT reported a similar, if not worse, QoL score on the domains mobility, usual activities and pain/discomfort, compared to those with other musculoskeletal diseases, such as rheumatoid arthritis, osteoarthritis, lateral epicondylar tendinopathy (tennis elbow) and fibromyalgia. Figure 1 depicts the differences in QoL domain scores between these diseases.[16]

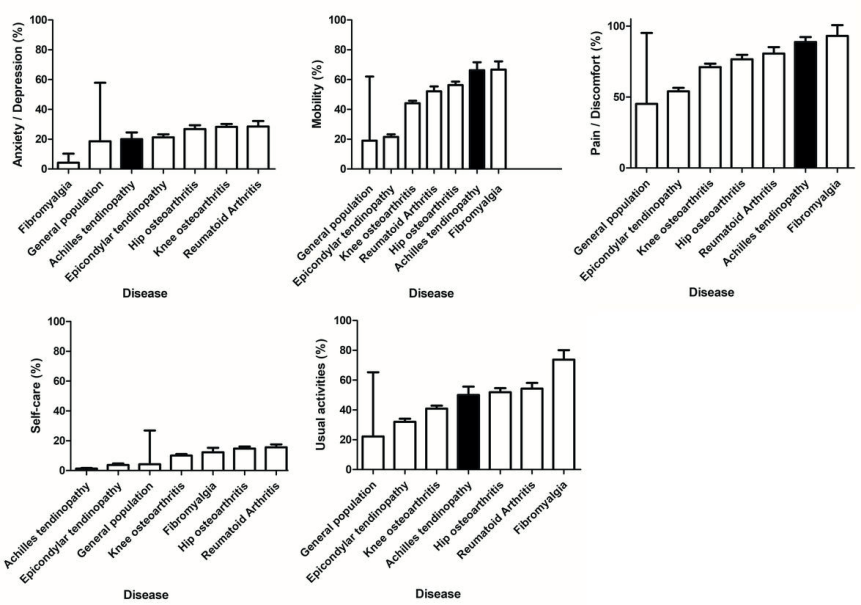

Figure 1. The EQ-5D scores for persons with musculoskeletal diseases per domain. DMC_3 study [16] Displayed values are percent with any (moderate and severe) problems (SE). EQ-5D: Euroqol five-item questionnaire for measuring health-related quality of life. General population: EQ-5D score in a large sample of the general population (no target on specific diseases) aged ≥ 25 years (n = 3664), weighted for age and sex in the Dutch population of 1998. DMC_3 study: Dutch population-based musculoskeletal complaints and consequenses cohort study.

Impact on work

Rotator cuff tendinopathy, lateral epicondylar tendinopathy and patellar tendinopathy all negatively impact work productivity and result in increased rates of absence from work.[28-32] Work performance in AT patients was frequently decreased because of reduced work productivity. This is similar to research on upper extremity musculoskeletal disorders.[33] In patients with lateral epicondylar tendinopathy and rotator cuff tendinopathy, 56% had decreased work productivity while decrease in work productivity due to AT in our study was lower with 38%.[31,34] The impact of AT on work productivity is comparable to moderate knee osteoarthritis and patellar tendinopathy (40% and 36% decreased work productivity respectively).[31] The majority of the patient population in our study performed sedentary work (68%), which is conceivably less impacted by AT. The impact of AT may thus even be higher in populations with physical work.

Health care utilization and costs

Healthcare utilization is an important measure for public healthcare organizations. The burden is especially large in individuals with chronic pain conditions.[35] One previous study examined the health care utilization and costs for patients with lateral epicondylar tendinopathy.[36] Median number of annual physiotherapy visits was higher in AT patients compared to patients with lateral epicondylar tendinopathy (7 for AT versus 3 for lateral epicondylar tendinopathy), while the median number of medical specialist visits was comparable (1 for both disorders).[36]

Both indirect costs due to the inability to work and direct costs as a result of tendinopathy have not been extensively researched. In the United States direct semi-annual medical costs for conservatively treated patients with lateral epicondylar tendinopathy were US $168 (€151) per patient.[36] The total median annual medical costs per patient were slightly higher in conservatively treated patients with lateral epicondylar tendinopathy, knee osteoarthritis, and ankylosing spondylitis compared to conservatively treated AT patients (respectively €305, €660 and €451 versus €258).[36-38] Patients with fibromyalgia and chronic back pain reported slightly lower median annual medical costs for primary and secondary care compared to AT patients (respectively €190 and €131 versus €258).[38]

Socio-economic consequences of AT patients for the public are substantial, based on Dutch incidence rates of AT and the persisting nature of the condition.[7,8] The absolute socio-economic burden of Achilles tendinopathy in the Netherlands can be estimated at more than 21 million euros. Based on an incidence rate of 2.35 per 1,000 in general practice registered adult patients and a total of 5028 general practices (with an average of 2,095 patients per practice) in the Netherlands, the total number of annual new Dutch AT patients is estimated at 25,000.[5] The total socio-economic burden can therefore be estimated at 25.000 x €840 = €21.000.000 (US $24.780.000). This is likely to be an underrepresentation, as our study shows that only 39% of these patients visit a general practitioner and it is known that in an open population of runners sustaining AT, the majority is seeking other sources of primary healthcare than general practice (e.g. physiotherapy).[39]

Previous research indicated that surgery is performed in up to 24% of all AT patients in some countries.[40] Surgically treated AT patients were excluded in our study. Including these would lead to a significant increase in healthcare costs. Furthermore, we did not use costs of medication use and imaging in the comparison as we, contrary to the other studies, did not collect this information. An illustration of the possible impact if imaging costs were included in this study is provided in supplementary file 3. It is conceivable that work absence, healthcare utilization and healthcare costs would also be significantly higher if surgically-treated patients were included and medication use and imaging costs would have been included. Therefore, the actual impact of AT on work performance, health care utilization, and direct and indirect costs may be even larger than presented in this study.

Strengths and limitations

Our study is one of the first studies to evaluate the impact of AT on quality of life, work performance, health care utilization, and estimated direct and indirect costs. To assess the impact of AT on quality of life we used the reliable and validated EQ-5D questionnaire.[20] Data was complete for our primary outcome and was retrieved from a homogenous group of clinically-diagnosed AT patients. However, there are some limitations to this study. We asked patients about the duration of their symptoms and applied treatments retrospectively, which could have induced recall bias on these specific items. This may have inaccuracy in collection of these secondary outcome measures.

Secondly, loss in work productivity was measured using a binary response option ('yes' or 'no'), the amount of loss of work productivity was not specified. Thirdly, the study population may not be representative of all AT patients. Most patients included in this study had longstanding symptoms (median 63 weeks) and it is likely that patients with short living AT experience less impact on QoL, work performance, and visit less healthcare providers. Another limitation was that the direct costs were mainly based on assumptions of the national mean costs of treatments. The main reason for this is that we did not register accurate data of the profession of the patients. This might have provided a less accurate estimation of the direct costs.

Recommendations for future research

Our main recommendation for future research is to evaluate the effect of different treatments on quality of life scores in AT patients. This will gain more insight into the impact and effectiveness of different treatments. Secondly, it would be interesting to investigate the cost-effectiveness of different treatments. To better understand the economic impact of AT, future studies could research the specific underlying cause of the decreased work productivity.

CONCLUSION

We demonstrated the large impact of Achilles tendinopathy on quality of life, specifically on the domains mobility, pain/discomfort, and usual activities. The magnitude of this impact seems similar to other chronic musculoskeletal conditions, such as knee osteoarthritis and rheumatoid arthritis. AT impacts significantly on work, with more than one third of patients having decreased work productivity. Healthcare utilization, direct and indirect costs as a result of AT are substantial with a total mean estimated annual direct and indirect costs of €840 per AT patient. These costs seem similar to other chronic musculoskeletal conditions. The above mentioned socio-economic impact of AT stresses the need for optimized treatment and improved preventive measures.

SUPPLEMENTARY MATERIAL

All supplementary material is available online at: https://bmjopensem.bmj.com/content/7/1/e001023

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Chapter 5

Standardized pain mapping for diagnosing Achilles tendinopathy

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Journal of Science and Medicine in Sport. 2022 Mar;25(3):204-208.

ABSTRACT

Objective: To assess the level of agreement between patient-reported pain using a standardized pain map and the physician-determined clinical diagnosis of Achilles tendinopathy.

Design: Cross-sectional study.

Methods: Eligible patients were adults visiting a sports physician for symptoms in the Achilles tendon region. Patients completed a digital questionnaire and indicated one location on a pain map where they experienced their pain. The primary outcome measure was level of agreement (% and Kappa coefficient) between patient-reported pain on the pain map and the physician-determined clinical diagnosis (defined as localized pain associated with tendon-loading activities and pain on palpation with or without tendon thickening). The secondary outcome measure was the agreement between the location on the pain map (midportion/insertional region) with the clinical diagnosis of midportion/insertional Achilles tendinopathy.

Results: 110 patients (mean (SD) age 48 (13), 61% men) with pain in the Achilles region were included. In 102 (93%, Kappa = 0.86, CI 0.78-0.95) patients who indicated pain in the Achilles tendon region on the pain map, the clinical diagnosis of Achilles tendinopathy was made by the sports physician. 82% of the patients had the clinical diagnosis of tendinopathy in the specific region of the tendon they marked on the pain map (Kappa = 0.67, CI 0.54-0.79).

Conclusions: There is almost perfect agreement between patient-reported pain on a pain map and a physician-established clinical diagnosis of Achilles tendinopathy. There was substantial agreement between the localization of the pain that was selected by the patient and the diagnosis of insertional/midportion Achilles tendinopathy by the physician. This tool could potentially aid in adequate triage for specialized care and for researchers performing large epidemiological studies.

INTRODUCTION

Achilles tendinopathy is a tendon disorder with a substantial socio-economic impact and is characterized by persistent localized Achilles tendon pain related to mechanical loading.[1,2] It can affect both the insertional and midportion (2-7 cm proximal of the calcaneal insertion) region of the tendon.[3] Achilles tendinopathy is mainly a clinical diagnosis, with imaging being a supportive method. [4,5] The most frequently used diagnostic criteria of Achilles tendinopathy are localized Achilles tendon pain associated with tendon-loading activities, pain on Achilles tendon palpation and localized tendon thickening.[4] These three findings can be assessed reliably.[6] Experts agree that the clinical diagnosis can be established when there is localized pain associated with tendon-loading activities and pain on Achilles tendon palpation, as the presence of tendon thickening is not always necessary to make the clinical diagnosis.[4,5] While there remain challenges in the diagnosing of Achilles tendinopathy, there is agreement among experts about the above-mentioned criteria.[4,5,7]

The location of pain is a key diagnostic criterion and it is important to distinguish between the insertional and midportion region of the Achilles tendon. This location affects prognosis and initial treatment.[6,8] Because the clinical sign of subjective self-reported pain is one of the criteria for establishing the diagnosis it is important to know if patients with pain in the Achilles region can adequately localize their pain.[5]

Pain mapping is a tool for patients to indicate the location where they experience most of their pain and could assist in the diagnosis of musculoskeletal conditions.[9-12] Researchers previously suggested a self-administered pain map to be a useful and effective way to diagnose patients with patellar tendinopathy in a large group of subjects.[13] Knowing the reliability of using a self-administered standardized pain map for diagnosing Achilles tendinopathy could help clinicians with adequate triage. Additionally, in the near future it could be very helpful using digital support in first line care for the effective implementation of targeted treatment advices and in large epidemiological studies. The level of agreement between patient-reported pain using a pain map and the physician-determined clinical diagnosis of Achilles tendinopathy is currently unknown.

The primary objective of this study was to assess the level of agreement between patient-reported pain on a standardized pain map with the physician-determined clinical diagnosis of Achilles tendinopathy (defined as localized pain associated with tendon-loading activities and pain on palpation with or without tendon thickening). The secondary objective was to assess the level of agreement between the patient-reported location (midportion or insertional region) of the pain, marked on the standardized pain map with the physician-determined clinical diagnosis of midportion or insertional Achilles tendinopathy.

METHODS

Study design

This cross-sectional study was designed at the Department of Orthopaedic Surgery and Sports Medicine, Erasmus MC University Medical Center (Rotterdam, the Netherlands). The study received exemption for comprehensive application from the Medical Ethical Committee (MEC-2021-0033) of the Erasmus MC University Medical Center Rotterdam, the Netherlands. All patients provided digital informed consent for this study. We adhered to the STROBE guideline for reporting of cross-sectional studies and to the minimum reporting standards for tendinopathy studies according to the international consensus (ICON) statement.[14,15]

Patients

Adult patients were eligible when they were referred to the Orthopaedic Surgery and Sports medicine outpatient department of the Erasmus MC University Medical Center with symptoms in the region of the Achilles tendon. General practitioners or medical specialists referred these patients using a referral letter, where the region of the pain was stated. The inclusion period was between September 2018 and September 2020. Patients were included if they provided informed consent and if they completed the digital (baseline) questionnaire before their appointment. Patients were excluded if: (1) they did not record the location of their symptoms on the pain map, (2) the pain was not located in the Achilles tendon region or (3) the symptoms changed in the interval between completion of the digital questionnaire and the consultation with the sports physician.

Procedures

Patients were consecutively enrolled and asked to complete a digital questionnaire before their outpatient appointment. This questionnaire was send to patients using a software package (GEneric Medical Survey Tracker, GemsTracker) for secure distribution of questionnaires during clinical research. The baseline questionnaire consisted of questions on demographics, lifestyle, work, sports activity and injury characteristics. Based on this information, the Ankle Activity Score (0-10 points) was also established.[16] The baseline questionnaire also inquired the region where patients experienced most of their symptoms and patients were asked to indicate this on a standardized digital pain map. If patients had bilateral symptoms they were asked to mark the region of the tendon of the side where they experienced most pain. Figure 1 shows the pain map. Patients could choose one of three options (inferior side of the heel, posterior side of the heel in the insertional region of the Achilles tendon or the midportion region of the Achilles tendon). There was also one option stating ‘none of these regions’. Patients were also asked about the severity of pain during activities of daily living and sports activities (when applicable). Severity of pain was assessed using a Visual Analogue Scale (VAS, 0-10). The validated Victorian

Institute of Sports Assessment-Achilles (VISA-A) questionnaire was also completed. This questionnaire evaluates pain score and activity level and ranges from 0 to 100 (with lower scores corresponding with more pain and decreased activity).[17]

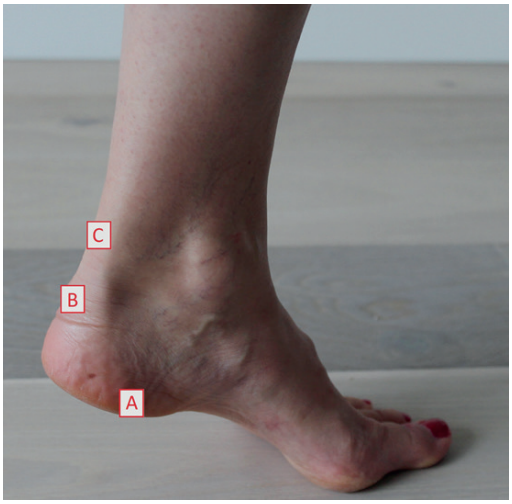

Figure 1. The standardized pain map included in the baseline questionnaire. The standardized pain map in the way it was provided to the patients. Descriptions in laymen terms in the way it was provided to the patients. A = bottom of the heel (attachment plantar tendon to the heel bone), B = back of the heel (attachment of the Achilles tendon to the heel bone), C = middle part of the Achilles tendon (2-7 cm above the attachment of the Achilles tendon to the heel bone). Patients indicating their symptoms to entail region A were excluded from the analysis as the pain was not located to the Achilles tendon region.

All patients then had a complete history-taking and clinical examination by a single senior sports medicine physician (Details omitted for review). The outpatient appointment was scheduled between one and maximal 7 days after the completion of the digital questionnaire. A study flow chart is presented in Figure 2. History-taking included whether patient's symptoms were associated with (sports) activities. Physical examination included assessing tendon thickening and pain on tendon palpation. Palpation of the tendon was performed by gently squeezing the Achilles tendon between the index finger and thumb, hereby palpating the entire length of the tendon from the musculotendinous junction to the distal calcaneal insertion. Patients were asked whether they experienced recognizable pain on palpation.[18] The location (midportion/insertion) of recognizable pain was recorded by the clinician. Presence of tendon thickening was assessed by the clinician on palpation.[6] Based on patient history and physical examination, a clinical diagnosis was made.

The clinical diagnosis of Achilles tendinopathy was established by the clinician if pain in association with Achilles tendon-loading activities and localized pain on Achilles tendon palpation were present. This could be with or without Achilles tendon thickening.

Data of history-taking and findings on physical examination, including the location of the diagnosis (insertional or midportion Achilles tendinopathy), were documented by the sports medicine physician using a standardized electronic format, to ensure consistency in data collection. All data were collected prospectively and analyzed after extraction from electronic medical records. From all patients the presence or absence of the diagnostic criteria were recorded.

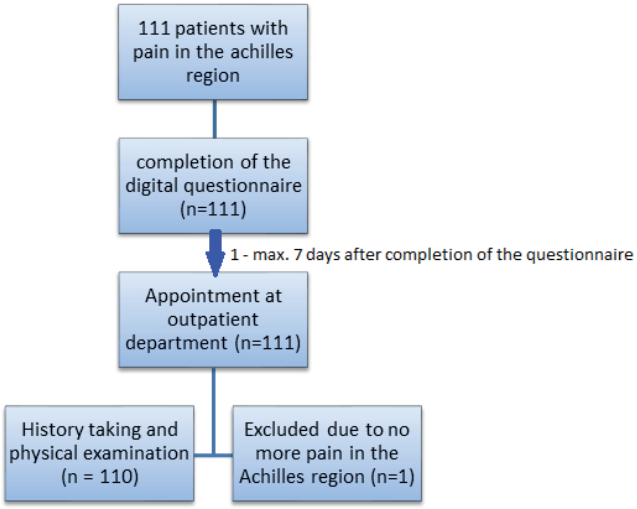

Figure 2. Study flow chart

Outcome measures

Primary outcome was the agreement between presence of patient-reported pain in the Achilles region on the standardized pain map and the physician-determined clinical diagnosis of Achilles tendinopathy.

The secondary outcome measure was the level of agreement between the marked patient-reported location of the pain (midportion region or insertional region of the Achilles tendon) on the standardized pain map with the physician-determined clinical diagnosis of midportion or insertional Achilles tendinopathy.

Statistical analysis

We assessed data for having a normal distribution using the Shapiro Wilk test. Normally distributed data are presented as mean with standard deviation (SD) and non-normally distributed data as median with interquartile range (IQR). We evaluated the utility of the pain map by determining the level (%) of agreement between the presence of patient-reported pain on the pain map and the physician-determined diagnosis. The level of agreement between the patient-reported pain map results and the physician-determined diagnosis was also calculated using the Cohen's Kappa coefficient and 95% confidence intervals (CI). We calculated both percent agreement and kappa based on recommendations in existing literature.[19] We interpreted a Kappa coefficient of 0–0.20 as slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61-0.80 as substantial and 0.81-1.0 as almost perfect agreement.[20] The same procedure was done for the location of the pain and the location of the diagnosis. We used SPSS software (V.24.0.0.1; SPSS, USA) for statistical analysis.

RESULTS

111 patients were referred to the outpatient department of the Erasmus MC because of symptoms in the region of the Achilles tendon. All referred patients received a digital questionnaire and completed the questionnaire before their appointment. One patient was excluded due to the fact that there was no pain in the Achilles tendon region anymore at the time of the appointment with the sports physician. The mean (SD) age in our study population was 48 (13) years with the majority (61%) being male. The mean (SD) Body Mass Index (BMI) was 26.2 kg/m^2 (4.5). The majority of the patients (76%) practiced one or more sports. Unilateral symptoms were reported in 65% of the patients. 38 of the 39 patients with bilateral symptoms had symptoms in the same region (midportion/insertional) of the tendon on both sides. Consequently, the same clinical diagnosis was made for both Achilles tendons in 38 of these 39 patients (97%). The patient characteristics are displayed in Table 1.

Table 1. Descriptive characteristics of the included patients. Abbreviations: SD: standard deviation, BMI: Body Mass Index, ADL: Activities of daily living, VISA-A: Victorian Institute of Sport Assessment Achilles.[17]

Characteristics (n=110)	Mean (SD), median[IQR]
Personal characteristics	
Age (years)	48.1 (13.3)
Sex (Male/Female; n)	67/43
BMI (kg/m^2)	26.2 (4.5)
Injury-related factors	
Symptom duration (weeks)	20 [8-52]
VISA-A score (0-100)	44.1 (19.4)
Pain location (unilateral/bilateral); n	71/39
Marked pain location on pain map (insertional/ midportion); n	52/58
Prior history of Achilles tendinopathy; yes (%)	8 (7.2%)
Prior history tendinopathy on other locations; yes (%)	50 (46%)
Pain during ADL (VAS 0-10)	4.8 (2.3)
Sports-related factors	
Participation in sports activities before injury; yes (%)	83 (76%)
Adaptation of sports activities due to the injury (none/reduced/stopped; n)	19/24/67
Pain during sports (VAS 0-10)	5.6 (3.0)
Ankle Activity Score; mean (SD)	5.1 (2.4)
Lifestyle-related factors	
Smoking (never/stopped/yes; n)	66/38/6
Alcohol use (units/week)	4.9 (4.3)
Current medication use; yes (%)	45 (41%)
Presence of comorbidities*; n(%)	46 (42%)
Work-related factors	
Type of work (active/sedentary/not applicable); n	42/60/8
Limitations in work; yes (%)	54 (49.1%)
Absenteeism from work; yes (%)	27 (24.5%)
Clinical findings	
Presence of tendon thickening; n (%)	77 (70%)
Presence of pain in association with Achilles tendon-loading activities; n (%)	110 (100%)
Presence of pain on tendon palpation; n (%)	104 (95%)

***** Specific registered comorbidities in the digital questionnaire were: Diabetes, Hypertension, Hypercholesterolemia, Cardiac and blood vessel disease, Ankylosing spondylitis, Psoriasis, Uveitis, Thyroid disease and Inflammatory bowel disease.

Primary outcome – Agreement of pain mapping with the clinical diagnosis of Achilles tendinopathy

The main clinical diagnostic criteria were present in the majority of the patients. The presence of pain associated with tendon-loading activities (100%) and recognizable pain on tendon palpation (95%) were very frequent, while the presence of localized tendon thickening had a lower frequency (70%).

In 102 (93%) of the patients who indicated pain in the Achilles tendon region on the standardized pain map, the clinical diagnosis of Achilles tendinopathy was made (Kappa = 0.86, 95% CI 0.78-0.95) .

In 6 (5%) patients another diagnosis was established, as there were none or 1 criteria present for the clinical diagnosis of Achilles tendinopathy (4 patients) or there were 2 criteria for Achilles tendinopathy but the clinical picture was more consistent with another diagnosis (2 patients). The list of these other diagnoses is provided in Table 2.

Two patients (2%) did not fulfil the predefined criteria for the clinical diagnosis of Achilles tendinopathy. One only had localized activity-related pain and the other one had localized activity-related pain and Achilles tendon thickening. These patients were not diagnosed with Achilles tendinopathy.

Table 2. List of other diagnoses

	Number of patients
None or only 1 criteria present for the clinical diagnosis of Achilles	
Soleus muscle strain	2
Posterior ankle impingement	1
2 criteria for Achilles tendinopathy but the clinical picture was more consistent with another diagnosis	
Retrocalcaneal bursitis without Achilles tendon pathology	1
Achilles midportion paratendinopathy	1
Neglected full-thickness Achilles tendon rupture	1

Secondary outcomes – Agreement of marked location (midportion/insertional) with the clinical diagnosis of Achilles tendinopathy

2 patients were clinically diagnosed with combined midportion and insertional Achilles tendinopathy and could therefore not be included in the analysis of the location specific (midportion/insertional) part. A total of 82% (89/108) of the patients had the clinical diagnosis of Achilles tendinopathy in the specific region of the tendon they marked on the pain map (Kappa = 0.67, CI 0.54-0.79).

In 36 of the 50 (72%) patients who indicated their symptoms in the insertional Achilles tendon region (marked this region on the pain map) the clinical diagnosis of insertional Achilles tendinopathy was made by the physician.

Out of the 58 patients who marked the midportion region on the pain map as the origin of their symptoms, 53 (92%) had the clinical diagnosis of midportion Achilles tendinopathy.

Patients who marked the bottom of the heel (location A on the pain map), were excluded from the analysis as they did not have symptoms located to the Achilles tendon region. Out of these 5 patients, 1 patient did have insertional Achilles tendinopathy. Six patients chose the option 'none of the displayed regions'. Two of these patients were diagnosed with insertional Achilles tendinopathy. One patient was diagnosed with posterior ankle impingement syndrome. The 3 remaining patients had a combination of diagnoses (insertional Achilles tendinopathy + retrocalcaneal bursitis and in two cases insertional Achilles tendinopathy + plantar fasciopathy).

DISCUSSION

This is the first study to explore the utility of a patient-administered standardized pain map for the diagnosis of Achilles tendinopathy. This study showed that in 9 out of 10 patients who reported pain in the Achilles tendon region on a pain map the clinical diagnosis of Achilles tendinopathy was made. The Kappa coefficient of 0.86 was considered to be almost perfect. There was also substantial agreement (82%, kappa = 0.67) between the location of most pain on the pain map and the location of symptoms that was established by the sports physician. This level of agreement was higher in patients who marked the midportion region compared to patients who marked the insertional region (92% vs. 72%). Overall, approximately 4 out of 5 patients selected the same region as the sports physician. These findings show that a patient-administered standardized pain map could aid clinicians and researchers in estimating the likelihood of the diagnosis Achilles tendinopathy. This is important information for the development of future self-management programs in first line healthcare and for accurate diagnosis in large epidemiological studies. The pain map could also be used as a screening tool for potentially eligible patients in clinical studies or for triage in clinical care.

Self-reported injury locations are frequently used as an outcome measure in epidemiological studies.[21-24] These locations are often interpreted as self-reported diagnoses, but for many injuries the agreement between pain location and a specific diagnosis is unknown. Several studies on Achilles tendinopathy did not use a pain map when assessing the location of the pain.[21,23,24] Other studies did use a pain map, but without knowledge of the agreement between this outcome measure and the diagnosis. It is therefore important that the level of agreement between self-reported outcome measures, such as a pain map, and specific diagnoses are known.

We compared the use of pain mapping in the current study with previous studies on this subject. A previous study used a self-administered pain map to classify participants with patellar tendinopathy.[13] 45 participants who were diagnosed with patellar tendinopathy with this method were asked to take part in a randomized control trial. In order to confirm eligibility to participate in this trial, participants were assessed by a senior sports medicine physician who confirmed the diagnosis of patellar tendinopathy in 44 of the 45 (97%) participants. This suggests the level of agreement between patient reported pain and the diagnosis of patellar tendinopathy to be similar compared to Achilles tendinopathy (97% vs 93%). In a recent randomized controlled trial, the same method was used for screening purposes.[25] While the pain map suggested the diagnosis of patellar tendinopathy in 101 subjects, this could only be confirmed in 76 subjects (75%) using clinical examination and ultrasound as confirmation.

Patients with knee osteoarthritis were able to adequately identify different pain locations on a pain map, with good test-retest reliability.[26] Trained researchers could reliably record

these locations, but the reported pain locations varied widely.[26] This heterogeneity of pain locations made it impossible to assess the level of agreement between pain map location and final diagnosis in patients with knee osteoarthritis.[26,27] Children aged 10 – 17 years with an orthopedic condition of the lower leg had a high level of agreement between the identified pain location on a pain map and the physician-determined location of the pain.[28] This level of agreement was similar compared to the current study (76% respectively vs. 82%). The diagnostic site was confirmed by an orthopedic surgeon, but because this study only focused on the pain location and diagnostic site and not on the exact diagnosis, a valid comparison between the two studies cannot be made.

The strengths of this study are the relatively large sample size and the inclusion of a homogenous group of patients with pain in the Achilles region. Data was collected prospectively and complete for our primary and secondary outcome measures and was obtained in a consistent way by a single sports medicine physician. There are some limitations to this study. These include the academic setting of the study, which may have led to the study population not being representative of the general population of patients with Achilles tendinopathy symptoms. Next to this, patients who do not localise pain to the Achilles region (e.g. to the bottom of the heel) may still have Achilles tendinopathy. In the current study, this was the case in 1 out of 5 patients who reported pain in the inferior heel region. There were also patients who chose the option 'none of the displayed regions' and were diagnosed with Achilles tendinopathy, either with or without the presence of another diagnosis (e.g. plantar fasciopathy). There may even be other regions that we did not evaluate, which could be representative for the diagnosis Achilles tendinopathy. Patients were referred by a medical doctor because of pain in the Achilles tendon region, which might have caused selection bias. An additional limitation is the amount of patients with bilateral symptoms, which could have led to inaccuracy in the results if symptoms entailed different regions (midportion/insertional) on both tendons or if a different diagnosis was made on both sides. In the current study this played a minor role as a large majority of these patients (97%) had symptoms in the same region and the same diagnosis was made on both sides. Another limitation is that this study was based on the clinical findings of a single sports physician and was not confirmed by a second examiner. However, several studies demonstrated that the clinical tests used in this study are reliable.[6]

Future research could focus on further developing the self-administered standardized pain map for patients with pain in the Achilles tendon region and the optimization of agreement between the pain map and physician-determined diagnosis. The figure used in this study could be improved by marking the specific regions on the Achilles tendon. Furthermore, patients could be asked about presence of tendon thickening. This could further improve the reported agreement. Hereafter, the self-administered pain map could be used in epidemiological studies on Achilles tendinopathy and as a screening tool for clinical studies. It could also be used in virtual consultation which may become necessary

in the current Covid-19 pandemic. Finally, the implementation of the pain map in primary care could be evaluated, where the pain map could be used for self-reported pain location and initial self-care.

CONCLUSION

This study demonstrates that a self-administered pain map could be useful for diagnosing Achilles tendinopathy. There was almost a perfect agreement between patient-reported pain on a standardized pain map and a physician-established clinical diagnosis of Achilles tendinopathy. There was also substantial agreement between the patient-selected location of the pain and the location-specific diagnosis (insertional or midportion Achilles tendinopathy) as determined by the physician. This self-reported outcome measure should be further developed, especially for the location-specific element of diagnosing Achilles tendinopathy (insertional versus midportion). This tool could aid healthcare providers and researchers for screening purposes and for performing large epidemiological studies.

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Chapter 6

Measuring ultrasonographic Achilles tendon thickness of the insertion is less reliable than the midportion

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Journal of Ultrasound in Medicine. 2024;43(4):713-722.

ABSTRACT

Introduction: Ultrasound is the preferred imaging method in the diagnostic process of Achilles tendinopathy (AT). Ultrasound Tissue Characterization (UTC) is a frequently used, standardized and valid method to assess tendon geometry in AT patients. It is unknown whether UTC is reliable for measuring Achilles tendon thickness.

The aim of the study was to assess intra- and inter-rater reliability of Achilles tendon thickness measurements using UTC in both asymptomatic individuals and patients with AT, and to evaluate if the reliability of thickness measurements differs between the midportion and insertional area.

Methods: 50 Patients with AT and 50 asymptomatic individuals were included. Using the conventional US and standardized UTC procedure maximum thickness was measured in the midportion and insertion region. To determine inter- and intra-rater reliabilities, the intraclass correlation coefficient (ICC) was used.

Results: The ICC values for inter- and intra-rater reliability were classified as 'excellent,' for the AT group (0.93 (95% CI: 0.88-0.96) and 0.95 (0.92-0.97)) and asymptomatic participants (0.91 (0.87-0.94) and 0.94 (0.92-0.96)). The reliability of measuring tendon thickness in the midportion region was 'excellent,' with both inter-rater (0.97 (0.95-0.98)) and intra-rater (0.98 (0.96-0.99)) ICC values indicating high levels of agreement. In the insertional region, ICC values for inter-rater (0.79 (0.69-0.87)) and intra-rater (0.89 (0.84-0.93)) reliability were 'moderate to good.'

Conclusion: We showed excellent reliability for measuring the US thickness of the midportion and good reliability of measuring the insertional region in patients with AT. Significantly lower ICCs were observed for the reliability of thickness measurements in the insertional region when compared to the midportion.

INTRODUCTION

Achilles tendon pain related to mechanical loading is commonly referred to as Achilles tendinopathy (AT).[1] Patients with AT are classified by location (midportion versus insertional AT) as this might affect the choice of treatment.[2,3] Individuals with AT experience a lower quality of life when compared to healthy people and AT has significant socio-economic consequences[4,5]. There is a need to optimize the diagnostic process for this patient group.[6] According to the current guidelines, ultrasound (US) is the preferred imaging method in the diagnostic process of AT.[2,7,8] One of the typical findings of AT on US examination is increased tendon thickening, with a cut-off value of approximately 7 mm being accepted as reference standard based on several small cross-sectional studies.[7,9-11]

Reliability of Achilles tendon thickness measurements using conventional US ranges from fair to excellent.[12-14] In the majority of the cases, only the reliability of measuring the Achilles tendon midportion area has been assessed.[14,15] No studies have evaluated the reliability of measuring the insertional area in AT patients.[14,15] Most of the reliability studies on ultrasonographic Achilles tendon geometry have a high risk of bias (e.g. a very specific selection of participants, inadequate blinding to prior findings/clinical information/reference standards/additional cues and no time interval between measurements), which limits drawing firm conclusions.[14,15] Implementing standardized US procedures is becoming more essential in clinical practice and is a suggested method to improve the reliability of tendon geometry measurements.[14,16,17] Ultrasound Tissue Characterization (UTC) is a customized tracking and ultrasonographic data-collection device that facilitates these standardized measurements (see supplementary file 1 for a detailed explanation of UTC).[9] To date, it is unknown whether a standardized US method is reliable for measuring Achilles tendon thickness and whether there is a difference in reliability when measuring the midportion versus the insertional area of the Achilles tendon. It is also unknown whether a standardized procedure improves this reliability when compared to conventional US measurements of geometry.

The primary aim of this study was to evaluate the intra- and inter-rater reliability of Achilles tendon thickness measurements using UTC in both asymptomatic individuals and patients with AT. The secondary aims were to evaluate if the reliability of thickness measurements differs between the midportion and insertional area and to determine whether tendon thickness measurements using UTC can be translated to conventional US.

MATERIALS & METHODS

Participants

We recruited a total of 100 participants, comprising 50 patients diagnosed with AT and 50 asymptomatic individuals. We included 25 patients with insertional AT and 25 patients with midportion AT. To be eligible for inclusion, AT patients had to meet the following criteria: 1) age ≥ 18 years, 2) the clinical diagnosis of AT established by the sports physician and 3) provide informed consent. The patients with AT were consecutively recruited between September 2020 and September 2022 from the outpatient department of Orthopaedic Surgery and Sports Medicine of Erasmus MC University Medical Centre, and the clinical diagnosis was established by a single sports medicine physician with nine years of clinical experience as a medical specialist (RJDV). The diagnosis was made based on the presence of gradual-onset pain in the Achilles tendon region during tendon-loading activities and recognizable and localized pain upon palpation of the Achilles tendon.[1,2,6,18] Insertional tendinopathy was diagnosed when the pain was located between the Achilles tendon insertion and the upper border of the calcaneus. Midportion tendinopathy was diagnosed when symptoms were located proximal to the upper border of the calcaneus (free tendon region).

Asymptomatic participants were consecutively recruited through informing potential participants via social media platforms (Twitter, Facebook, LinkedIn). To be eligible for inclusion, asymptomatic participants had to meet the following criteria: 1) age ≥ 18 years, 2) no current or past history of Achilles tendon pain or stiffness, 3) no localized tendon pain or nodular thickening upon palpation and 3) provide informed consent.

Procedures

The study was designed at the Erasmus MC University Medical Centre (Rotterdam, the Netherlands). The local Medical Ethics Committee (Southwest-Holland, the Netherlands) approved the study protocol (MEC-2020-0585, MEC-2021-0033). We adhered to the minimum reporting standards for reporting participant characteristics in tendinopathy research and to the guidelines for reporting reliability and agreement studies.[19,20] Supplementary File 2 shows a graphical description of the design of the study.

Patients with Achilles tendinopathy

Prior to their appointment at the outpatient department, patients completed a standardized digital questionnaire that encompassed demographic information, health status, and sports activities. Physical Activity Level (PAL) was assessed using a 6-point Likert scale.[21] Additionally, patients completed the Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire, ranging from 0-100.[22] A single senior sports physician (RJDV) conducted a comprehensive history taking and physical examination for each patient.

If the clinical diagnosis of AT was established, conventional US and Ultrasound Tissue Characterization were performed by the sports physician. Participants were positioned in a standardized manner, prone on an examination table with the ankle placed in maximum passive dorsiflexion and then supported by the examiner's knee (Supplementary File 1). A multi-frequency 5-16 MHz linear-array transducer (Terason, Burlington, United States) was used. The depth was set at 3.0 cm. The transducer was placed in a transverse position and perpendicular to the Achilles tendon.

The sports physician has 15 years of experience with US tendon imaging and UTC data collection and analysis. The procedures were conducted on the symptomatic side. Both sides were examined in cases of bilateral symptoms.

The same sports physician simultaneously conducted thickness measurements using conventional US as part of routine care. To minimize recall bias, the thickness measurements on the UTC scans were performed by the sports physician/researcher (RJDV) an average of 16 (standard deviation; SD:7) months after the UTC scan and the measurements on conventional US. The conventional US and UTC scan thickness measurements will be described more extensively below.

Asymptomatic population

If the inclusion criteria were met, participants were asked to complete a standardized questionnaire that included demographic information, health status, and details on their physical activity and participation in sports activities. Subsequently, a brief physical examination was conducted to evaluate the presence or absence of localized pain upon palpation of the Achilles tendon, as well as to assess localized thickening of the tendon using the Arc sign.[18] Finally, the UTC scan was carried out following a standardized protocol on both Achilles tendons by a single trained researcher (TSV). This researcher has three years of experience with US tendon imaging and UTC data collection and analysis. To mitigate the potential influence of anatomical variations, we included 25 left Achilles tendons and 25 right Achilles tendons in our study. The UTC thickness measurements on asymptomatic individuals were performed an average of 5 months (SD: 0.3) after the UTC scan.

Outcome measures

Conventional ultrasound

The largest anterior-to-posterior (AP) diameter of the Achilles tendon was estimated in the transversal view, in line with current clinical and research practice.[7,15] This section of maximum thickness was frozen and subsequently the thickness was directly measured in millimeter (mm), rounded to one decimal (Figure 1). This procedure was performed for the Achilles tendon midportion, insertional region, or both, based on the location of symptoms (data were only collected from the region(s) in which patients experienced symptoms).

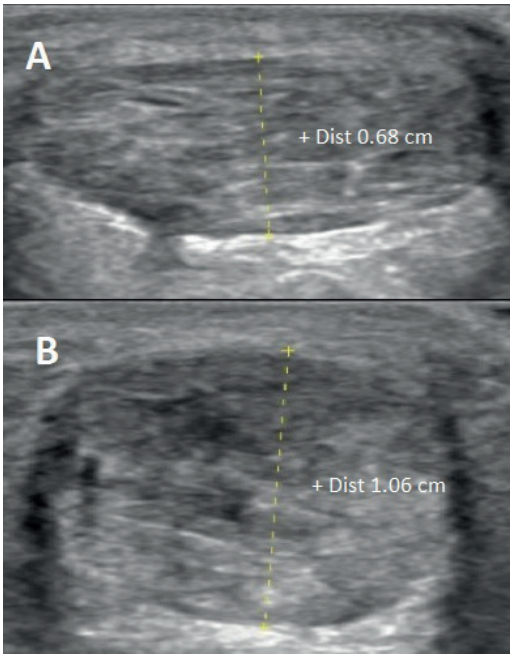

Figure 1. Achilles tendon thickness measurements with conventional ultrasound of the insertion (A) and midportion (B) of the tendon. The largest AP diameter of the Achilles tendon perpendicular to the latero-medial width was measured in the transversal view.[9] This section of maximum thickness was frozen and subsequently the thickness was measured directly (yellow dotted line).

Ultrasound Tissue Characterization

We utilized the UTC Imaging version 2020 (UTC Imaging, Stein, The Netherlands) for the standardized ultrasound assessment. This system involves a tracking device and conventional US equipment. The UTC scan was carried out following a standardized protocol. Participants were positioned in an identical manner to the conventional US procedure, prone on an examination table with a maximum passive dorsiflexion angle of the ankle obtained and then maintained by the researchers knee (Supplementary File 1). The same multi-frequency 5-16 MHz linear-array transducer (Terason, Burlington, United States) was used in a transverse and perpendicular position, moving automatically from proximal to distal over a distance of 12 cm to obtain a three-dimensional data block. The UTC tracking and data-collection device facilitated the collection of 'raw' digital transverse images at regular intervals of 0.2 mm. The exact working mechanisms of the UTC procedure have been described in detail in previous literature.[9,23,24] All scans were collected in a database and pseudonymized before initiating the measurements.

The maximum AP distance was measured manually by two independent researchers (RJDV and TSV) using a standardized procedure (Figure 2 and 3). First, the thickest part of both the midportion and insertion region of the tendon were estimated by the researchers in the longitudinal plane. Then, these regions of the tendon were assessed in the transversal plane and subsequently the maximum diameters of the tendon were measured. Measurements were performed using pixel size (rounded to one decimal), with 1 pixel corresponding to 0.062 millimeters (mm). Both raters were blinded to the conventional US measurements and each other's measurements. Both raters were aware of the disease condition (symptomatic vs. asymptomatic) but were blinded to clinical information such as localized tendon thickening and additional cues (e.g., age, height, symptom duration, gender, etc.). Measurements were performed in a consecutive order as varying the order of subjects was impractical.

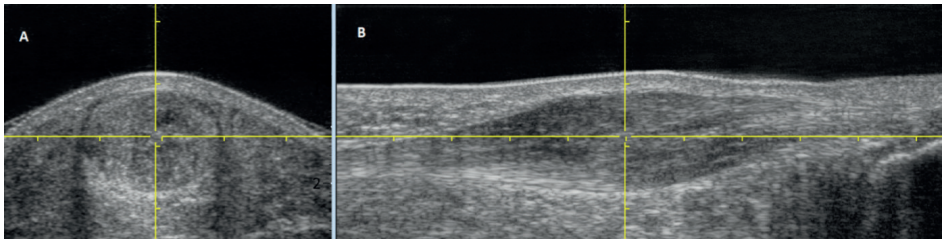

Figure 2. UTC image of the Achilles tendon. In the longitudinal plane (B), the thickest part of both the mid-portion and insertional region of the tendon were estimated. Subsequently, those regions were assessed in the transversal plane (A).

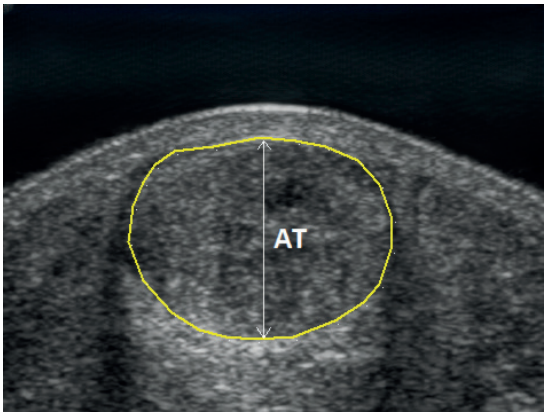

Figure 3. Achilles tendon thickness measurement with the UTC procedure of the midportion of the tendon. After identifying the thickest part of the tendon in the longitudinal plane the maximum AP diameter perpendicular to the latero-medial width (white solid line) was measured in the transversal plane. The yellow line identifies the periphery of the tendon.

For intra-rater reliability, a single researcher (TSV) performed thickness measurements in a consecutive order on all UTC scans a second time with an average time interval of 43 (SD; 1) days. This researcher was unaware of previous measurements (both his own and of the other rater).

Statistical analysis

A total of 100 participants were recruited. Descriptive statistics comprising mean and standard deviations were computed for the participants' characteristics and tendon thickness (maximum AP diameter in mm). During the measurement phase, both researchers also assessed whether data collection errors were present which refrained them from properly obtaining the outcome measurement. In case both researchers independently agreed that a UTC scan was not suitable to obtain the outcome measurement, we decided to exclude the scan in the analysis. If only one of both researchers assessed the scan as unsuitable for performing measurements, this was discussed between the two. In case there was no consensus, we decided to ask a third reviewer with experience in US data collection and analysis (SO) to assess the suitability of the UTC images. To determine inter- and intra-rater reliabilities, the intraclass correlation coefficient (ICC) was used. For both asymptomatic participants and those diagnosed with AT, the ICC ± 95% confidence interval (CI) was calculated for the maximum thickness in the midportion area and insertional area, using two-way random, single measurement on UTC scans. The reliability between conventional US and UTC measurements was also calculated for maximum thickness in the midportion and insertional region, using a two-way mixed, single measurement for

patients diagnosed with AT. An ICC value of less than 0.5, ranging from 0.5 to 0.75, ranging from 0.75 to 0.9 and above 0.9 were respectively classified as 'poor', 'moderate', 'good' and excellent.[25] We also calculated the standard error of measurement (SEM = √total mean square within people) and smallest real difference (SRD = 1.96 × SEM × √2).[26] Smallest real difference can also be referred to as minimal detectable change (MDC), which is calculated in the same manner. IBM SPSS Statistics (version 28.0.1.0) was used for statistical analyses.

RESULTS

One hundred UTC scans in the database were assessed by the two researchers. One UTC scan of a patient with insertional AT was excluded because of an artifact caused by a large air bubble within the scan gel (both researchers independently agreed on this). Consequently, 99 UTC scans were included in the analyses. The sports physician performed all thickness measurements of the conventional US in the remaining patients with AT (n=49).

The participants' characteristics are depicted in Table 1. Patients with AT had an average symptom duration of more than five years. Maximum tendon thickness using UTC is also displayed in Table 1. Mean ± SD tendon thickness in AT patients was 8.3 ± 2.2 mm (midportion) for patients with midportion AT and 5.4 ± 1.3 mm (insertion) for patients with insertional AT. There were significant differences in age and Body Mass Index (BMI) between the AT and asymptomatic group.

Table 1. Participant characteristics. Values are means with standard deviation (SD) unless otherwise described.

	Total Group (n=99)	Achilles tendinopathy patients (n=49)	Asymptomatic participants (n=50)	Mean difference (95%CI, p-value)
Age (years)	44.2 (14.5)	48.0 (13.5)	40.4 (14.5)	7.6 (2.0-13.2, p= 0.008)
Height (cm)	177.3 (8.6)	178.7 (7.8)	175.9 (9.2)	2.8 (-0.6-6.2, p= 0.105)
BMI (kg/m2)	25.3 (4.2)	26.6 (4.3)	23.9 (3.8)	2.7 (1.1-4.3, p= 0.001)
Gender (female/ male)	48/51	21/28	27/23	p= 0.267
Physical activity level (PAL; 1-6)†	4.6 (0.9)	4.5 (0.8)	4.8 (1.0)	-0.4 (-0.7-0.01, p= 0.058)
Symptom duration (weeks)	-	278 (375)	-	
VISA-A score	-	46.3 (18.0)	-	
Side (Left/Right/ Both)	39/41/19	14/16/19	25/25/0	-
Tendon thickness on UTC (mm; midportion)	-	8.3 (2.3)‡	5.5 (1.2)	2.8 (2.0 – 3.6, p < 0.001)
Tendon thickness on UTC (mm; insertion)	-	5.4 (1.4)‡	4.3 (0.69)	1.1 (0.59 – 1.6, p < 0.001)
Tendon thickness on US (mm; midportion)	-	8.2 (2.5)‡	-	-
Tendon thickness on US (mm; insertion)	-	5.8 (1.9)‡	-	-

‡Midportion thickness included 25 patients with midportion AT. Insertional thickness included 24 patients with insertional AT.

Abbreviations; **BMI**: Body Mass Index (kg/m2), **VISA-A**: Victorian Institute of Sports Assessment-Achilles, **AT**: Achilles tendinopathy, **PAL**: Physical Activity Likert Scale; 1-6†, 1 = Hardly any physical activity, 2 = Mostly sitting, sometimes walk, easy tasks/play, 3 = Light physical activity for about 2-4 times a week (e.g., fishing, talking, dancing), 4 = Moderate exercise 1-2 hours a week (jogging, swimming, gymnastics), 5 = Moderate exercise at least 3 hours a week (jogging, swimming, gymnastics), 6 = Hard or very hard exercise regularly and several times a week during which the physical exercise is great (jogging, rugby, football).

Overall, ICC values for inter-and intra-rater reliability using UTC were classified as 'excellent' for both AT patients and asymptomatic participants (Table 2). In symptomatic as well as asymptomatic individuals, reliability of measuring thickness in the midportion and insertional region were respectively classified as 'excellent' and 'moderate to good'. The 95% CIs of the ICC values did not overlap between the two regions, indicating a statistically significant difference in reliability of measuring Achilles tendon thickness

between the midportion and insertional region. The 95% CIs of the ICC values did overlap between the AT patient group and the asymptomatic group, indicating that disease status has no significant effect on reliability of measuring Achilles tendon thickness. The SRD for intra-rater reliability ranged between 1.22 mm (midportion) and 1.51 mm (insertion) for AT patients and between 0.78 (midportion) and 1.07 (insertion) for asymptomatic participants. For inter-rater reliability the SRD was 1.47 mm (midportion) and 2.46 mm (insertion) for AT patients and ranged between 0.84 mm (midportion) and 1.17 mm (insertion) for asymptomatic participants.

ICC values for the reliability between UTC and conventional US were classified as 'good' (0.81) for the insertional region and 'excellent' (0.96) for the midportion (Table 3). The SRDs between these two measurement techniques were 2.27 mm for the insertional area and 1.60 mm for the midportion area.

Table 2. ICC values for inter-and intra-rater reliability of tendon thickness measurements using UTC. Abbreviations; ICC: intraclass correlation coefficient, CI: Confidence interval, SEM: standard error of measurement, SRD: smallest real difference

	Inter-rater reliability			Intra-rater reliability		
	ICC (95% CI)	SEM (mm)	SRD (mm)	ICC (95% CI)	SEM (mm)	SRD (mm)
Overall (total, n=99)	**0.93** (0.91 – 0.95)	0.521	1.44	**0.96** (0.95 – 0.97)	0.399	1.11
Midportion (n=75)	**0.97** (0.95 – 0.98)	0.396	1.10	**0.98** (0.96 – 0.99)	0.345	0.96
Insertion (n=74)	**0.79** (0.69 – 0.87)	0.581	1.61	**0.89** (0.84 – 0.93)	0.408	1.33
Achilles tendinopathy patients (total, n=49)	**0.93** (0.88 – 0.96)	0.727	2.02	**0.95** (0.92 – 0.97)	0.492	1.36
Midportion (n=25)	**0.95** (0.90 – 0.98)	0.529	1.47	**0.96** (0.92 – 0.98)	0.439	1.22
Insertion (n=24)	**0.80** (0.61 – 0.91)	0.888	2.46	**0.87** (0.74 – 0.94)	0.543	1.51
Asymptomatic participants (total, n=50)	**0.91** (0.87 – 0.94)	0.366	1.01	**0.94** (0.92 – 0.96)	0.340	0.94
Midportion (n=50)	**0.94** (0.89 – 0.96)	0.301	0.84	**0.96** (0.93 – 0.98)	0.282	0.78
Insertion (n=50)	**0.71** (0.53 – 0.82)	0.421	1.17	**0.81** (0.69 – 0.89)	0.388	1.07

Table 3. ICC values for standardized and conventional US procedures. Abbreviations: UTC: Ultrasound Tissue Characterization, US: Ultrasound, ICC: intraclass correlation coefficient, CI: Confidence interval, SEM: standard error of measurement, SRD: smallest real difference

	Reliability between standardized UTC and conventional US procedures		
	ICC (95% CI)	SEM (mm)	SRD (mm)
Achilles tendinopathy patients (total, n=49)	**0.95** (0.91 – 0.98)	0.681	1.89
Midportion (n=25)	**0.96** (0.92 – 0.98)	0.577	1.60
Insertion (n=24)	**0.81** (0.62 – 0.91)	0.819	2.27

DISCUSSION

This is the first large-scale study to evaluate the reliability of Achilles tendon thickness measurements using a standardized US procedure for both the midportion and insertional region in AT patients as well as asymptomatic individuals. Overall, our findings indicate a high level of agreement between and within observers with respect to thickness measurements of the Achilles tendon. This observation holds true for both individuals who suffer from AT and those who are asymptomatic. Lower ICC and higher SRD values were observed for the thickness measurements in the insertional region when compared to the midportion. The reliability of thickness measurements between the standardized UTC procedure and conventional US was excellent for the midportion region and good for the insertional region.

Clinical relevance

These findings are relevant for the clinical setting, as current guidelines advise performing US as the first imaging modality of choice in the diagnostic process of patients with AT. For this reason, it is important to know the reliability of measuring Achilles tendon thickness in specific regions (the midportion and insertional region) where pathology is frequently observed. It is also relevant to have more knowledge of the reliability when using standardized US procedures, such as UTC, since these are gaining popularity in the clinical setting.[16,17] When US is used to monitor change in tendon diameter it is important to verify that changes exceed the SRD to be of relevance. This is illustrated when considering the range of SRD values observed in our study, which lie between 0.8 and 2.5 mm. This range must be interpreted in the context of the absolute mean values of Achilles tendon thickness, which we found to be between 4.3 and 8.3 mm. The SRD values represent a threshold for clinically meaningful changes in tendon thickness. When a change in tendon thickness less than the SRD is observed, it may be considered within the margin of measurement error.

Excellent reliability for measuring Achilles tendon thickness

Previous systematic reviews on the reliability of Achilles tendon thickness measurements using conventional US reported wide ranges for intra-rater (0.78-0.99 vs. 0.96 for the current study) and inter-rater (0.68-0.99 vs. 0.93 for the current study) ICC values.[14,15] These studies did not distinguish between the midportion and insertional region, did not use a standardized US procedure, such as the UTC, and did not include both AT patients and asymptomatic individuals, which may account for the discrepant findings. Notably, the SRD values observed in the current study were relatively higher (1.22-1.47 mm for midportion AT and 1.51-2.46 mm for insertional AT) than those reported in previous investigations (ranging between 0.007 and 0.84 mm).[14,15] This may be attributed to the heterogeneity of the study population evaluated as the previously mentioned studies only reported SRD values for the midportion region and the majority only included asymptomatic individuals. A study by Docking et al (2016) did use UTC and included both AT patients and asymptomatic individuals and reported a minimal detectable change (MDC) of 0.5 mm.[11] However, this was only based on intra-observer agreement after scanning eight Achilles tendons and without distinguishing between the midportion and insertional region.[11]

Lower reliability for measuring thickness of the insertional Achilles tendon region

We observed that the ICC values for Achilles tendon thickness measurements were lower for the insertional region compared to the midportion. To our knowledge, this is the first study to comprehensively evaluate thickness measurements in the insertional region, as previous investigations have focused solely on the midportion.[9,12,14,15,23,27] The diminished reliability of thickness measurements in the insertional region may be attributed to the unique anatomical properties of this region. Specifically, the insertional part of the tendon has a less straight course compared to the midportion. The appearance of tissue-structures on ultrasound are angle-dependent, a phenomenon referred to as anisotropy, where tissue structure might appear to be hypoechoic due to the positioning of the ultrasound probe.[7,28,29] The 'rotated' trajectory of the insertional region is more susceptible to anisotropy which may lead to angle-generated artifacts on ultrasonographic images, potentially resulting in reduced measurement reliability.[7,29] Our study is the first to show that it is likely that patients with midportion AT will be identified with increased thickness of the Achilles tendon midportion. However, the measurement error in the insertional area may be too large to detect a change in thickness between patients and asymptomatic individuals as the SRD values exceed the mean difference between insertional AT patients and asymptomatic individuals.

Conventional US procedure has similar reliability as standardized US procedure

Our study is the first in this field to compare a standardized US procedure (UTC) to the conventional US procedure. Only a limited number of studies have evaluated the application of UTC to the insertional region of the Achilles tendon[30,31], as the predominant body of literature primarily examines the use of UTC for identifying alterations in the tendon structure at the midportion.[9,27,32] In the current study, the reliability for thickness measurements between the two methods was excellent for the midportion region and good for the insertional region. This means that both procedures can be used in the clinical or research setting. It also emphasizes that our reliability results for the UTC-based approach can be extrapolated to the conventional US procedure. As conventional US is more readily available in most cases and is used in the clinical setting most often, it is useful to know that it is as reliable as the UTC procedure in assessing tendon thickness. Although for the insertional region, there might be a clinically relevant difference between both methods since the SRD was 2.27 mm (more than half of the mean maximum thickness in the patients with insertional AT).

Strengths and limitations

Our study has several strengths as we adhered to the relevant guidelines for conducting and reporting in reliability studies. The study was large enough to answer the specific research questions.[33] Participants and raters were representative and raters were blinded to each other's and previous measurements and to patient characteristics and additional cues.

Nonetheless, this study is subject to certain limitations that warrant consideration. First, thickness measurements of the Achilles tendon using conventional US were only conducted once and by a single physician as part of standardized routine care. Consequently, our capacity to assess intra- and inter-rater reliability for conventional US measurements was restricted, and we were only able to report on reliability between conventional US and UTC based on the measurements taken by that particular researcher. However, we were particularly interested in the translation of standardized (UTC) measurements to daily clinical practice, and we showed that there is an excellent to good reliability between both procedures.

Second, the experience in US between both raters ranged from three to 15 years. To reduce potential examiner influence, we used a standardized protocol for collecting and analyzing UTC data. Third, both raters were not blinded to disease status, and the order of examination was not varied, which could have induced information and recall bias respectively. For this reason, we decided to have at least eight months between the measurements of the conventional US and the UTC for one researcher (RJDV) and 16 weeks between the UTC scan and first UTC measurements (TSV). This makes recall bias less likely.

Next to this, the UTC data collection procedure in both groups was only performed by one rater. Consequently, we did not obtain data on the reliability of the UTC procedure itself. The finding of excellent to good reliability in translation from UTC measurements to conventional US makes it less likely that the UTC procedure itself has a large influence, which is confirmed by previous studies showing excellent reliability of the UTC scanning procedure.[27,34]

Future perspectives

Future research should focus on obtaining a large dataset of reference values for Achilles tendon thickness in asymptomatic individuals in order to adequately distinguish between changes characteristic of tendinopathy (increased tendon thickening) and 'normal' morphological appearance. The SRD values in both the midportion and insertional region identified in the current study will aid in interpreting these between-group differences. This will likely have a major impact on interpreting US assessment for patients with AT.

CONCLUSION

This study offers valuable insights into the reliability of US-based thickness measurements in patients with Achilles tendinopathy and individuals with asymptomatic Achilles tendons. We showed excellent reliability for accurately measuring the US thickness of the midportion and good reliability of measuring the insertional region in patients with Achilles tendinopathy. Significantly lower ICC and higher SRD values were observed for the reliability of thickness measurements in the insertional region when compared to the midportion. As the SRD values exceed the mean difference in tendon thickness between insertional AT patients and asymptomatic individuals, we recommend interpreting US thickness with caution in patients with insertional Achilles tendinopathy. Thickness measurements with the standardized US (UTC) procedure were similar to conventional US. In order to accurately discriminate between changes indicative of tendinopathy, such as increased tendon thickening, and morphological changes that fall within the range of normal variation, future research should prioritize the acquisition of ultrasonographic reference values for tendon thickness in symptomatic and asymptomatic individuals. This will likely impact on the role of US in assessing patients with AT.

SUPPLEMENTARY MATERIAL

All supplementary information is available online at: https://onlinelibrary.wiley.com/doi/full/10.1002/jum.16396

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Chapter 7

Normative ultrasound values for Achilles tendon thickness in the general population and Achilles tendinopathy patients: a large international cross-sectional study

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Scandinavian Journal of Science & Medicine in Sports. 2024; 34:e14665

ABSTRACT

Objectives: To obtain adjusted ultrasonographic reference values of the Achilles tendon thickness (maximum anterior-posterior distance) in adults without (previous) Achilles tendinopathy (AT) and to compare these reference values with AT patients.

Methods: 600 participants were consecutively included, comprising 500 asymptomatic individuals and 100 patients with clinically diagnosed chronic AT. The maximum tendon thickness was assessed using Ultrasound Tissue Characterization. A multiple quantile regression model was developed, incorporating covariates (personal characteristics) that were found to have a significant impact on the maximum anterior-posterior distance of the Achilles tendon. A 95% reference interval (RI) was derived (50th, 2.5th-97.5th percentile)

Results: In asymptomatic participants median (95%RI) tendon thickness was 4.9(3.8-6.9) mm for the midportion region and 3.7(2.8-4.8) mm for the insertional region. Age, height, Body Mass Index and sex had a significant correlation with maximum tendon thickness. Median tendon thickness for the midportion region was calculated with the normative equation -2.1+AGE*0.021+HEIGHT*0.032+ BMI*0.028+SEX*0.05. For the insertional region the normative equation was -0.34+AGE*0.010+ HEIGHT*0.018+BMI*0.022+SEX*-0.05. In the equations, SEX is defined as 0 for males and 1 for females. Mean (95%CI) difference in tendon thickness compared to AT patients was 2.7 mm (2.3-3.2, $p<0.001$) for the midportion and 1.4 mm (1.1-1.7, $p<0.001$) for the insertional region. Compared to the asymptomatic population 73/100 (73%) AT patients exhibited increased tendon thickening, with values exceeding the 95% RI.

Conclusions: This study presents novel reference values for the thickness of midportion and insertional region of the Achilles tendon, which were adjusted for personal characteristics. Our novel web-based openly accessible calculator for determining normative Achilles tendon thickness (www.achillestendontool.com) will be a useful resource in the diagnostic process.

INTRODUCTION

Achilles tendinopathy (AT) is the preferred term for local tendon pain related to mechanical loading.[1] It is frequently occurring (2-3/1,000 individuals)[2], longstanding (20-30% persisting symptoms at 10-year follow-up)[3,4], has a large impact on quality of life and is associated with substantial costs (840€/patient/year in a western European country).[5]

Ultrasound is the preferred method for imaging of the Achilles tendon according to the current guidelines.[6,7] In the longitudinal plane the Achilles tendon exhibits a pattern of parallel fibrillar lines, while in the transverse plane, it presents as a round-to-ovoid echogenic shape.[6] AT is ultrasonographically characterised by tendon thickening in the anterior-posterior direction and a decreased tendon structure.[8,9]

Imaging could aid in establishing the diagnosis of AT.[10] Currently, maximum Achilles tendon thickness is estimated at approximately 6 to 7 mm based on clinical experience and cross-sectional studies.[6,8,11-15] An important knowledge gap with imaging is that current normative values for Achilles tendon thickness may not be representative of the general population and no studies differentiated between the midportion and insertional region of the tendon.[16] Previous studies also showed a considerable deviation surrounding the normative values for Achilles tendon thickness.[14] It is likely that tendon thickness is influenced by personal characteristics. Obtaining reference values for Achilles tendon thickness and addressing important personal characteristics will aid clinicians in differentiating between AT and 'normal' morphological changes, which will facilitate personalized healthcare.

The primary aim of this study aim is to obtain ultrasonographic reference values of the Achilles tendon thickness (maximum anterior-posterior distance) in adults without (previous) Achilles tendinopathy. The secondary aim is to compare these reference values with tendon thickness in patients with clinically diagnosed AT.

METHODS

Study design

The study was designed at the Erasmus MC University Medical Centre (Rotterdam, the Netherlands) in collaboration with the University of Leicester (Leicester, United Kingdom) and conducted at the outpatient departments of these universities from October 2020 to July 2023. The study was temporarily halted between November 2020 and May 2022 because of Covid-19 related restrictions. These restrictions also forced us to adjust the number of participants to 500, which is a decrease by 100 participants compared to the pre-defined protocol. The local Medical Ethics Committee (Southwest-Holland, the Netherlands) approved the study protocol (MEC-2020-0585). The trial was registered before commencement (Netherlands Trial Register, NL9010). We adhered to the Strengthening the

Reporting of Observational Studies in Epidemiology (STROBE) guidelines for the reporting of observational studies.[17]

Participants and procedures

Asymptomatic population

A study announcement was made through informing potential participants via social media platforms (Twitter, Facebook, LinkedIn and internal websites). If participants expressed interest to participate and passed an online screening, an appointment with a researcher was planned to further assess eligibility and perform measurements in case of inclusion. The inclusion criteria were: (1) Age ≥18 years, (2) no current Achilles tendon pain or stiffness, (3) no localized fusiform thickening of the Achilles tendon on palpation, (4) no history of pain or stiffness in the Achilles tendon region and (5) full score on the adapted Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire (question 1 – question 5).[18,19] The exclusion criteria were: (1) Achilles tendon or ankle surgery in the past, (2) known systemic inflammatory disorders or internal diseases that can cause Achilles tendon abnormalities (e.g. Spondylarthropathy, Psoriatic Arthritis or Familial Hypercholesterolaemia) and (3) recent (past 12 months) lower-limb injury requiring immobilisation. Additionally, participants who experienced technical malfunctions with the UTC, such as an empty battery or software errors during scanning, were asked to schedule a new appointment. If rescheduling was not feasible for the participant, they were excluded to ensure the reliability of our data collection.

If the inclusion criteria were met, participants were asked to sign the written informed consent form. Subsequently, participants completed a more extensive questionnaire with collection of demographic data (age, sex, height, weight and Body Mass Index (BMI)), past medical history (presence of comorbidities), medication use (including past or current use of fluoroquinolones and statins), smoking and current and past physical activities. A 6-point Likert scale[20] and the Sports Activity Rating Scale[21] were used to rate physical activity. Thereafter a short physical examination was performed, assessing the amount of localised pain on Achilles tendon palpation (using a 0-10 Visual Analogue Scale; VAS) and localized fusiform tendon thickening using the Arc sign (positive when the area of swelling identified with palpation moves with ankle range of motion).[22] Subsequently, the UTC procedure was carried out on both Achilles tendons when the participant was eligible.

Achilles tendinopathy patients

All adult patients who visited the outpatient Department of Orthopedics and Sports Medicine of the Erasmus MC University Medical Centre with a clinical diagnosis of AT were eligible to participate. Patients were included if: 1) the clinical diagnosis of AT was established by the clinician, 2) informed consent was provided, 3) the baseline

questionnaire was completed and 4) the Ultrasound Tissue Characterisation (UTC) procedure was performed.

Patients completed a digital questionnaire prior to their appointment at the outpatient department. The questionnaire included information on demographics, lifestyle habits, comorbidities, work, injury characteristics, and physical activity level. The VISA-A questionnaire was also completed.[18] A single senior sports physician (RJDV) performed complete history taking and physical examination, which included assessing pain on tendon palpation and the presence/absence of tendon thickening. The clinical diagnosis was made based on history and physical examination. The clinician established the clinical diagnosis of AT if the pain was 1) located to the Achilles tendon region, 2) associated with Achilles tendon-loading activities AND 3) provoked on Achilles tendon palpation.[1,7,10,22] If the pain was localised at the level of the posterior calcaneus, insertional Achilles tendinopathy was diagnosed and if the pain was localized above the superior border of the posterior calcaneus, midportion Achilles tendinopathy was diagnosed. Hereafter, the UTC procedure was carried out on the symptomatic side. In case of bilateral symptoms, the side with the most severe complaints was scanned.

Outcome measures

Ultrasound Tissue Characterization (UTC)

Primary outcome measure was the maximum anterior-posterior (AP) distance of the Achilles tendon in transversal view (also referred to as thickness) using UTC. Achilles tendon thickness can be depicted with UTC.[8,11,23] The UTC is a customized tracking and ultrasonographic data-collection device that allows for objective, standardized measurements, which can be translated to conventional ultrasound.[8] The UTC Imaging version 2020 (UTC Imaging, Stein, The Netherlands), consisting of conventional ultrasound equipment (multi-frequency 5-16 MHz linear-array transducer) and a tracking device, was used. At each site, one single trained researcher (TSV and SO) performed all UTC scans. Participants were positioned prone on an examination table with a maximum tolerable dorsiflexion angle of the ankle.[8] The transducer was placed in a transverse position to the Achilles tendon and moved automatically from proximal to distal over a distance of 12 cm.[24] Images were stored using a specific code and analysis of the images was performed in a subsequent stage of the research project. Previous studies have described the UTC procedure in more detail.[8,11,12,23]

Image analysis of all UTC scans was performed by one trained researcher (TSV). This researcher was blinded to patient characteristics while performing the analyses. The maximum anterior-posterior distance was measured with the UTC software. In the longitudinal plane (sagittal view), we screened for the area of maximum thickness in the midportion and insertional region of the tendon (Figure 1). Hereafter this area was

evaluated in the transverse plane and in this view, we estimated the maximum thickness and measured it. The insertional region was defined as the area from the lowest Achilles tendon insertion on the calcaneus to the upper border of the posterior calcaneus. The midportion region was defined as the area proximal to the upper border of the posterior calcaneus.

The inter- and intra-rater reliability for AP-measurements have been shown to be excellent for AT patients (intra-class correlation coefficient (ICC) 0.93 and 0.95 respectively) as well as for asymptomatic participants (ICC 0.91 and 0.94).[25]

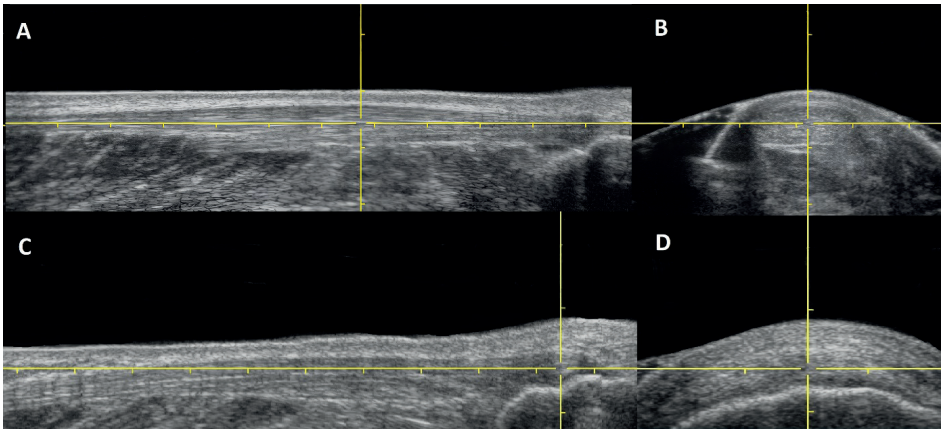

Figure 1. UTC image of the Achilles tendon. In the longitudinal plane (A and C), the thickest part of both the midportion and insertional region of the tendon were estimated. Subsequently, those regions were assessed in the transversal plane (B and D). A and B; midportion region of the Achilles tendon. C and D; insertional region of the Achilles tendon.

Statistical analysis

To establish normative equations for maximum AP distance of Achilles tendon thickness, the data from 500 subjects were inspected using scatter- and boxplots to identify outliers. Descriptive statistics were used for presentation of personal characteristics. Quantile regressions were used for analysis, given the expected skewed nature of the data and the aim to establish normative values. Quantile regression allows for estimations of medians and does not make distributional assumptions.[26] Potential differences in tendon thickness between the right and left leg were analysed using a Wilcoxon signed-rank test (in the case of non-normal distribution) for the midportion and insertion region. When no statistically significant differences were observed, data is presented as the mean tendon thickness for the midportion and insertional region. Bivariate models were constructed for each covariate (age, sex, height, weight, BMI, activity level, leg dominance, smoking, alcohol

consumption and presence of comorbidities) for the midportion and insertion region separately on both sides. Hereafter, a multiple quantile regression model was built using the covariates that significantly influenced the maximum anterior-posterior distance of the midportion and insertion region. Participants with missing data on any of the covariates that significantly influenced maximum AP-distance were omitted from the multiple regression analysis. The median (50.0th), lower (2.5th), and upper (97.5th) percentile values of the regression model's results were extracted to present tendon thickness as median with a 95% reference interval (RI) encompassing the 50th percentile within the range of the 2.5th to 97.5th percentiles. To effectively assess the influence of each covariate on tendon thickness, the 95% confidence intervals (CI) were also extracted. This allows the estimation of the impact of each covariate on tendon thickness for both the midportion and insertional region. For the secondary objective, we aimed to include 100 AT patients. We compared the tendon thickness between AT patients and asymptomatic individuals for the midportion and insertional region using a general linear model while adjusting for the variables that significantly differed between both groups. We adhered to the CHecklist for statistical Assessment of Medical Papers (CHAMP) statement for the statistical analysis and presentation of results.[27] IBM SPSS Statistics (version 28.0.1.0) were used.

RESULTS

A total of 684 persons were screened for eligibility and finally 500 asymptomatic participants and 100 AT patients, with complete data for the primary outcome measure of tendon thickness, were included. A flowchart and reasons for exclusions is presented in Figure 2. The main participants' characteristics are depicted in Table 1. Among the participants, 55% were female, while 8 participants did not want to disclose their sex. Patients with AT had a median [interquartile range (IQR)] symptom duration of 108 [50-260] weeks. Midportion AT was reported in 64 patients and 34 patients had insertional tendinopathy (2 patients had a combination of midportion and insertional AT). Bilateral symptoms were present in 36/100 (36%) of the AT patients.

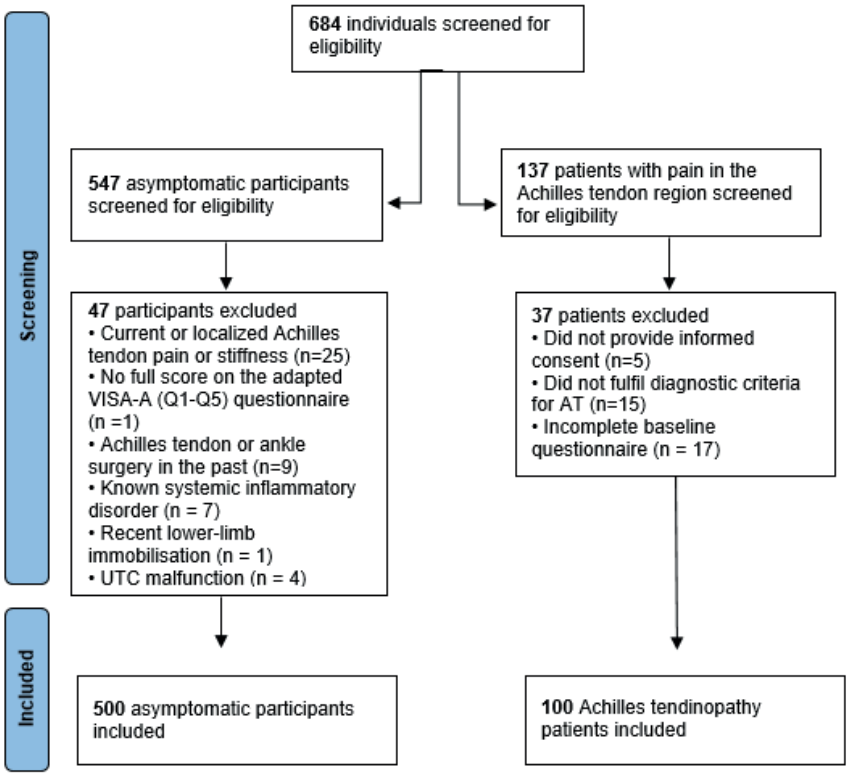

Figure 2. Flowchart of the study

Table 1. Participant characteristics. Values are means with standard deviation (SD) or medians with interquartile ranges [IQR] unless otherwise described. *Midportion thickness included 64 patients with midportion AT. Insertional thickness included 34 patients with insertional AT. 2 patients had a combination of midportion and insertional AT. ** = 95% reference interval. † = adjusted for age, height, sex, BMI and physical activity level. ‡ = comorbidities include diabetes mellitus, hypertension, hypercholesterolemia, heart-vessel disease and thyroid disease

	Total Group (n=600)	Achilles tendinopathy patients (n=100)	Asymptomatic participants (n=500)	Mean difference (95%CI, p-value)
Age (years)	34 [23-53]	48.0 (12.8)	30 [22-50]	11.8 (8.4-15.2, p < 0.001
Height (cm)	174.9 (9.5)	178.6 (8.8)	174.2 (9.5)	4.4 (2.4-6.4, p < 0.001)
BMI (kg/m2)	23.6 [21.8-26.2]	26.1 (4.5)	23.3 [21.7 – 25.6]	2.1 (1.3-2.9, p < 0,001)
Sex (female/male/ undisclosed, n)	317/275/8	43/57	274/218/8	p = 0.020
Physical activity level (PAL; 1-6)	5 [4 - 6]	3 [3 – 4]	5 [4 - 6]	p < 0.001
Symptom duration (weeks)	-	108 [50-260]	-	-
VISA-A score (0-100)	-	48.0 (17.5)	98.9 (3.3)	50.9 (49.3 – 52.6, p < 0,001)
Tendon thickness (mm; midportion)	-	9.2 (2.5)*	4.9 [3.8 – 6.9]**	2.7 (2.3-3.2, p < 0.001)†
Tendon thickness (mm; insertion)	-	5.7 (1.4)*	3.7 [2.8 – 4.8]**	1.4 (1.1-1.7, p < 0.001)†
Medication use (yes/no)	181/419	53/47	128/372	-
Smoking (current/past/never)	33/67/500	5/34/61	28/33/439	-
Presence of co-morbidities (yes/no)‡	71/529	19/81	52/448	-

Abbreviations; **BMI**: Body Mass Index (kg/m2), **VISA-A**: Victorian Institute of Sports Assessment-Achilles, **AT**: Achilles tendinopathy, **PAL**: Physical Activity Likert Scale; 1-6*, 1 = Hardly any physical activity, 2 = Mostly sitting, sometimes walk, easy tasks/play, 3 = Light physical activity for about 2-4 times a week (e.g., fishing, talking, dancing), 4 = Moderate exercise 1-2 hours a week (jogging, swimming, gymnastics), 5 = Moderate exercise at least 3 hours a week (jogging, swimming, gymnastics), 6 = Hard or very hard exercise regularly and several times a week during which the physical exercise is great (jogging, rugby, football).

Normative values for Achilles tendon thickness

There was no significant difference between the left and right leg for tendon thickness of the midportion region (5.06 vs 5.05 mm, p=0.728) and the insertional region (3.72 vs. 3.71 mm, p=0.967). Bivariate analyses revealed that age (r=0.46, p<0.001 and r=0.33, p<0.001), height (r=0.31, p<0.001 and r=0.34, p<0.001), BMI (r=0.17, p<0.001 and r=0.22, p<0.001) and sex (r=0.15, p<0.001 and r=0.25, p<0.001) had a correlation with maximum tendon thickness of the midportion and insertional region respectively. Leg dominance did not influence tendon thickness (r=0.032, p=0.48 for the midportion and r=0.007, p=0.87

for the insertion). The median (95% RI) AP thickness in asymptomatic individuals for the midportion region was 4.9 mm (3.8–6.9) and 3.7 mm (2.8–4.8) for the insertional region.

Age and height had the largest influence on tendon thickness, with older age and higher height being associated with increased values for tendon thickness (Table 2). In the bivariate analysis, male sex was found to be positively correlated with tendon thickness but this effect was not significant in the multiple quantile regression model (Table 2). The results of the multiple quantile regression model (n=492, R^2=0.22 for the midportion and R^2=0.16 for the insertion) with the relevant parameters is provided in Table 2. The data for the 8 participants who opted not to disclose their sex were excluded from the multiple quantile regression analysis.

Table 2. Estimates (95%CI, p-value) of the effect of the parameters on maximum Achilles tendon thickness derived from the multiple quantile regression analysis adjusted for age, height (cm), BMI and sex. Examples on how to employ the normative equations based on two fictional patients are provided in the lower part of the table. * Sex: male = 0, female = 1 ** Values are median (mm) with 95% RI (2.5th percentile, 97.5th percentile). Abbreviations; BMI: Body Mass Index

Variable	Parameter estimated in the Midportion region	Parameter estimated in the Insertional region
Intercept	-2.1 (-3.7, -0.35)	-0.34 (-1.6, 0.9)
Age	0.021 (0.017, 0.025, p=0.000)	0.010 (0.007, 0.012, p<0.001)
Height	0.032 (0.023, 0.041, p<0.001)	0.018 (0.012, 0.025, p<0.001)
BMI	0.028 (0.010, 0.045, p=0.003)	0.022 (0.009, 0.036, p=0.001)
Sex	0.054 (-0.11, 0.22, p=0.553)	-0.050 (-0.18, 0.78, p=0.446)

Normative equation*	Intercept + age + height + BMI + sex
Example A	Female, 23 years, 20 kg/m^2, 165 cm
Example B	Male, 58 years, 28 kg/m^2, 186 cm
Tendon thickness (midportion)**	-2.1 + 0.021 x (age) + 0.032 x (height) + 0.028 x (BMI) + 0.054 x (sex)
A: 4.3 (3.1-5.5) mm	-2.1 + 0.021 x (23) + 0.032 x (165) + 0.028 x (20) + 0.054 x (1)
B: 5.9 (4.6-7.9) mm	-2.1 + 0.021 x (58) + 0.032 x (186) + 0.028 x (28) + 0.054 x (0)
Tendon thickness (insertion)**	-0.34 + 0.010 x (age) + 0.018 x (height) + XX x (BMI) + XX x (sex)
A: 3.2 (2.7-4.1) mm	-0.34 + 0.010 x (23) + 0.018 x (165) + 0.022 x (20) – 0.050 x (1)
B: 4.2 (3.3-5.6) mm	-0.34 + 0.010 x (58) + 0.018 x (186) + 0.022 x (28) – 0.050 x (0)

Estimates of normative median (95% RI) values for tendon thickness of the midportion and insertional region are presented in Table 3.

Table 3. Estimates of the normative median (50th), lower (2.5th) and upper (97.5th) percentile values (upper, lower) of Achilles tendon thickness for the midportion and insertional part of the tendon, presented by sex for each decade of life. Estimates are for individuals with a body mass index of 24.0 kg/m^2 and a height of 183 cm (males) or 170 cm (females)

Age (years)	Male		Female	
	Midportion	Insertion	Midportion	Insertion
20	4.9 (4.1, 6.0)	3.7 (3.0, 4.8)	4.4 (3.1, 5.6)	3.3 (2.8, 4.2)
30	5.1 (4.2, 6.4)	3.8 (3.0, 4.9)	4.6 (3.2, 6.0)	3.4 (2.8, 4.4)
40	5.3 (4.4, 6.8)	3.9 (3.1, 5.1)	4.8 (3.3, 6.4)	3.5 (2.9, 4.5)
50	5.5 (4.5, 7.2)	4.0 (3.1, 5.2)	5.0 (3.5, 6.8)	3.6 (3.0, 4.7)
60	5.7 (4.6, 7.6)	4.1 (3.2, 5.4)	5.2 (3.6, 7.2)	3.7 (3.0, 4.8)
70	5.9 (4.7, 8.0)	4.2 (3.3, 5.6)	5.4 (3.7, 7.6)	3.8 (3.1, 5.0)
80	6.2 (4.8, 8.4)	4.3 (3.3, 5.7)	5.6 (3.8, 8.0)	3.9 (3.1, 5.2)

Difference between asymptomatic individuals and patients with Achilles tendinopathy

Patients with AT were on average older, taller, had a higher BMI and a lower physical activity level than the asymptomatic participants (Table 1). Maximum tendon thickness as measured with UTC is also displayed in Table 1. The mean difference (95%CI) in tendon thickness, adjusted for age, sex, height, BMI and physical activity level, between the asymptomatic population and AT patients was 2.7 mm (2.3-3.2, p<0.001) for the midportion and 1.4 mm (1.1-1.7, p<0.001) for the insertional region.

Using the normative equations for the median, lower (2.5th) and upper (97.5th) values of tendon thickness for each AT patient, we found that 73/100 patients (73%) had increased tendon thickening (a value larger than the 97.5th percentile).

DISCUSSION

In this large international cross-sectional study, we demonstrated that Achilles tendon thickness is influenced by personal characteristics. We found that age and height had the largest influence on maximum anterior-posterior distance. The mean difference in tendon thickness between asymptomatic persons and patients with Achilles tendinopathy was 2.7 mm for the midportion region and 1.4 mm for the insertional region. The majority of the AT patients (73%) had an increased tendon thickening outside the 95% reference interval.

This study presents novel reference values for the thickness of the midportion and insertional region of the Achilles tendon, which have been lacking in the literature. Currently, maximum Achilles tendon thickness is estimated at 6 to 7 mm based on clinical experience and cross-sectional studies.[13-15] These studies have reported a considerable deviation surrounding the normative values for Achilles tendon thickness in selected (e.g.

pre-dominantly military recruits or elite fencers)[13,14] or relatively small samples (ranging from 6 to a maximum of 100 individuals)[8,11,12]. These studies reported different mean values of tendon thickness ranging from 4.2 to 7.1 mm, without adjusting for personal characteristics.[8,11-15] The relatively small and/or selected study populations in these studies may account for the variation in findings and no studies differentiated between the midportion and insertional region of the tendon, while these are considered separate clinical entities based on the current guidelines.[7,28]

The influence of personal characteristics on Achilles tendon thickness has been evaluated once in the past. A larger study (n= 267) by Koivunen-Niëmela et al. in 1995 evaluated the influence of personal characteristics on Achilles tendon thickness in an asymptomatic population. A large proportion of the population were military recruits who were predominantly male between the ages of 18-29.[14] This study found that there was a significant correlation between tendon thickness and age, height, and weight, with tendon thickness increasing from 5.9 mm in those aged 10-17 years to 6.7 mm in those aged >30 years.[14] These findings are consistent with those of the current study that is performed on a larger scale and without a clear selection, which also found that tendon thickness is largely influenced by age and height.

Clinical implications

Imaging techniques have been found to aid in the diagnosis of Achilles tendinopathy, particularly in challenging cases where not all clinical diagnostic criteria are met.[7,10] It is, however, important to note that imaging may present a potential drawback, as findings suggestive for tendinopathy can be detected in 25% of asymptomatic Achilles tendons.[10,16] Additionally, our study shows that 27% of the patients with clinical diagnostic criteria for AT do not have increased Achilles tendon thickness outside the 95% reference interval. While abnormal imaging might increase the likelihood of AT, these findings challenge the use of imaging as gold standard for diagnosing AT.

Clinicians can benefit from having knowledge of reference values and parameters that impact on tendon thickness, which can help to distinguish between AT and normal morphological changes (www.achillestendontool.com).

Strengths and limitations

This study has several strengths. To our knowledge this is the largest cross-sectional study on this subject. We used strict methods, a pre-defined protocol and included an international cohort drawn from the general population which improves generalizability of the findings. Next to this, the outcomes of the quantile regression model are openly available, serving as a calculator for normative tendon thickness. The study also has limitations that must be acknowledged. First, only the maximum AP distance was used as an outcome measure in this study. While this is the most frequently used outcome

measure when assessing Achilles tendon geometry, it doesn't fully capture the geometry of the tendon. Future research could focus on obtaining normative values for different measures of tendon geometry (e.g. cross-sectional area and volume) as well as for tendon structure. Second, we predefined fusiform Achilles tendon thickening as an exclusion criterion for asymptomatic participants. This might jeopardize generalizability, as there might be persons without (previous) Achilles tendon pain but a local thickened tendon. This might have overestimated the difference in ultrasonographic tendon thickness between asymptomatic and symptomatic individuals. We acknowledge this, but we feel that this choice was justified as one of the diagnostic criteria for AT is localized tendon thickening. Third, we used the UTC procedure to obtain ultrasonographic values for Achilles tendon thickness. It is questionable whether the results of this sophisticated procedure can be extrapolated to the procedures using conventional ultrasound in daily clinical practice. Nevertheless, we have recently showed a clear agreement (ICC 0.95) in obtained Achilles tendon thickness between the UTC procedure and conventional ultrasound procedure in the clinical setting.[25]

PERSPECTIVE

Achilles tendon thickness is influenced by personal characteristics with older age and higher height being associated with increased values for Achilles tendon thickness. The normative ultrasonographic values for tendon thickness derived from this study can help clinicians to differentiate between physiological morphological changes and features consistent with Achilles tendinopathy. The openly accessible web-based calculator for normative values of Achilles tendon thickness adjusted by personal characteristics can be accessed at www.achillestendontool.com and may help clinicians to distinguish between ultrasonographic features of Achilles tendinopathy and normal morphological changes.

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Chapter 8

Low socioeconomic status is associated with worse treatment outcomes in patients with Achilles tendinopathy

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British Journal of Sports Medicine. 2024;2023-107633.

ABSTRACT

Objective: To assess whether there is a difference in symptom severity at baseline and 24-weeks follow-up between conservatively managed patients with Achilles tendinopathy (AT) with low socioeconomic status (SES) compared to those with high SES.

Methods: In this prospective cohort study, 200 patients with AT were included and treated according to current guidelines. We linked a neighborhood SES-indicator based on income, employment, and education level and divided the patient population into quintiles, with Q1 being the highest SES and Q5 the lowest. Symptom severity at baseline and follow-up was assessed using the Victorian Institute of Sports Assessment-Achilles (VISA-A) score. Treatment adherence was not measured. We used a general linear model and the mean VISA-A scores at baseline and at 6, 12- and 24-weeks follow-up were compared between Q1(n=45) and Q5(n=39), while adjusting for age, sex, body mass index (BMI), Ankle Activity Score, symptom duration and baseline VISA-A score.

Results: Patients had a median age of 51 years and median BMI of 25.4, 40% were female. 74%, 70% and 58% of the participants completed the VISA-A at 6, 12 and 24 weeks respectively. VISA-A scores at baseline were similar for Q1 and Q5 (43.9 and 41.8, p=0.591). At 24-weeks there was a mean (95% confidence interval) difference of 11.2 (1.0-21.3, p=0.032) points in favor of Q1 on the VISA-A score.

Conclusion: AT patients with low SES may have worse outcomes when treated using the current guidelines. The difference in VISA-A score at 24-weeks is larger than the Minimal Clinically Important Difference and might be clinically relevant, but comes with uncertainty due to large dispersion in the data. Clinicians need to consider the impact of social inequality when developing and implementing treatment plans.

INTRODUCTION

Achilles tendinopathy (AT) is characterized by localized pain in the Achilles tendon that results from mechanical loading.[1] AT is frequently occurring and often longstanding with substantial impact on quality of life.[2-5] The role of psychosocial factors In tendinopathy is scarcely studied, but believed to be important by experts.[6] Examples of socioeconomic factors include income, place of residence, age, sex, education, and ethnicity. Individuals with lower socioeconomic status (SES) may face barriers to accessing healthcare, leading to limited support during rehabilitation.[7,8] Limited health literacy is also associated with low SES and results to misunderstanding of medical information and reduced adherence to medical instructions.[9]

The outcome of various diseases is associated with socioeconomic factors.[10-12] Low SES leads to a higher incidence, more severe symptoms before treatment initiation and worse outcomes in several musculoskeletal conditions[10,13,14] Understanding the influence of SES on treatment outcomes in Achilles tendinopathy is crucial, as it could lead to more effective, tailored interventions (e.g. health literacy education and targeted support to improve access to healthcare). This could help bridge the health disparity gap in musculoskeletal care. It is unknown whether SES influences symptom severity and treatment effectiveness in patients with Achilles tendinopathy.

The primary objective of this study is to assess whether a disparity exists in the severity of symptoms at baseline between AT patients with low SES and those with high SES. The secondary aim is to investigate whether there is a difference in the effectiveness of standardized treatment after 24 weeks between AT patients with low and high SES.

METHODS

Study design

This prospective cohort study was conducted at the Department of Orthopedics and Sports Medicine, Erasmus MC University Medical Center (Rotterdam, the Netherlands). The local Medical Ethics Committee (Southwest-Holland, the Netherlands) approved the study protocol (MEC-2021-0033). All participants provided digital informed consent for this study. We adhered to the minimum reporting standards for tendinopathy studies as determined by the international consensus statement[15] and the CHecklist for statistical Assessment of Medical Papers (CHAMP) statement for the design, analysis and reporting of cohort studies.[16]

Patient and Public involvement

Prior to the start of the study, an electronic survey was performed, as part of the development of the Dutch multidisciplinary guideline on Achilles tendinopathy.[17] AT patients were asked about their treatment goals. Patients mainly described treatment goals to be: return to (pain free) participation in sports and (pain free) participation in activities of daily living (ADL).[18] Based on these treatment goals established by the patients we chose our outcome measures. As the Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire evaluates pain during daily living and sports activities, and return to participation in sports, we selected the VISA-A Score as primary outcome.[19] To complement this and address aspects not covered by VISA-A we included an assessment of patient satisfaction, reflecting individual treatment needs and experiences, as a secondary outcome.

Equity, diversion and inclusion statement

Our study, conducted in a single high income country, specifically investigated the effect of SES on the selected outcome measures. However, we acknowledge we did not evaluate the effects of race/ethnicity and marginalized groups as we did not obtain these data. The author team includes both junior and senior researchers and both men and women.

Patients

All adult patients who visited the outpatient department of Orthopaedics and Sports medicine of the Erasmus MC University Medical Center with symptoms in the Achilles tendon region were eligible to participate. These patients were referred by general practitioners or medical specialists. As per Dutch healthcare regulations the referral process is free for patients who have already met their deductible; otherwise, they are responsible for costs up to €385 (this amount is including costs for treatment and follow-up by the sports physician). The Erasmus MC, situated in an below average SES area, attracts

a broad spectrum of patients from across the country, encompassing both underserved and well-served populations. The inclusion period was between September 2018 and March 2023. Patients were included if: 1) the clinical diagnosis of Achilles tendinopathy was established by the physician, 2) informed consent was provided and 3) the baseline digital questionnaire was completed.

Procedures

Patients who were referred by a healthcare provider (general practitioner or medical specialist) because of pain in the Achilles tendon region were asked to complete a digital questionnaire before their appointment at the outpatient department. This questionnaire was sent within one week before the appointment to patients using GemsTracker (GEneric Medical Survey Tracker), a software package designed for clinical research assuring secure distribution of questionnaires. This baseline questionnaire consisted of questions on demographics (age, sex, postal code), lifestyle, comorbidities, work, injury characteristics and (sports) activity. Sports activity was rated using the Ankle Activity Score (range 0-10) (AAS).[20] The VISA-A questionnaire was also completed. A single senior sports physician (RJDV) performed complete history taking, physical examination and ultrasound examination on all patients. The scheduled duration of the consultation was one hour for all patients. Patients were specifically asked if their symptoms were associated with (sports) activities. Physical examination included the assessment of recognizable pain on palpation[21] and the presence/absence of localized tendon thickening. The clinical diagnosis was made based on physical examination and patient history. The physician established the clinical diagnosis of Achilles tendinopathy if 1) pain located in the Achilles tendon region in association with Achilles tendon-loading activities AND 2) localized pain upon Achilles tendon palpation that was consistent with their injury pain (e.g. experienced during loading activities) were present. This could be with or without Achilles tendon thickening. The imaging findings were discussed with the patients. All included patients received treatment advice based on the best available evidence and standard practices for Achilles tendinopathy at the time of inclusion. This approach was aligned with the prevailing recommendations in existing (inter)national guidelines, which included education, load management, and exercise therapy.[17,22,23] If patients already received (part of) this treatment advice, the sports physician aimed to optimize this cornerstone of treatment based on the context of the individual (e.g. changes in the exercise therapy program or education about the longstanding nature of tendinopathy and need for prolonged rehabilitation). All patients received a folder (see Supplementary Files 3 and 4 for the folders ‘insertional Achilles tendinopathy’ and ‘midportion Achilles tendinopathy’) which provided an overview of education, load management advice and progression of exercise therapy. The patient could voluntarily consult a physiotherapist for guidance if he or she desired. If so, the physician also instructed that the folder was a guide of the

treatment plan that could be used during the physiotherapy sessions. This is according to the Dutch multidisciplinary guideline.[17] Follow-up appointments were scheduled between 6 to 12 weeks as part of routine care and further follow-up appointments were made based on individual needs. The limited value of additional conservative treatments (e.g. ESWT or orthotic devices)[18] was discussed at the first appointment and considered during follow-up.

Socioeconomic status

We linked a neighborhood SES-indicator based on area information, which is in line with previous studies in this field.[24-26] The indicator was linked using patients' four-digit postal code. SES scores are calculated per postal code area by the Dutch Central Bureau for Statistics,[27] based on household income, educational level and employment status. The most recent socioeconomic data, published in 2019, were used.[27] We divided the SES scores into quintiles, based on the rank of the scores. Quintile 5 (Q5) was the quintile with the lowest SES (most deprived) and quintile 1 (Q1) was the quintile with the highest SES (least deprived, e.g. high income, high educational level and high employment rate). The Q1 and Q5 groups were used for the analyses, which has been shown to be a customary method for evaluating inequality.[28] This approach follows guidelines by the World Health Organization, highlighting the importance of focusing on the most extreme SES contrasts to effectively reveal significant effects on health outcomes and ensure findings are easily interpretable.[29]

Outcome measures

At 6-, 12- and 24-weeks patients were asked to complete a follow-up questionnaire including the VISA-A questionnaire and treatment satisfaction.

The primary outcome measure was the score on the VISA-A questionnaire at 24 weeks. This questionnaire evaluates pain scores and activity level and ranges from 0 to 100 (with lower scores corresponding with more pain and decreased activity).[19] The VISA-A is considered to be a reliable and responsive measure of symptom severity in people with AT.[30]

The secondary outcome measure of the study was the level of satisfaction with the treatment effect as reported by the patients. Treatment satisfaction was assessed using a four-point Likert scale, which consisted of the following categories: excellent, good, moderate, and poor.[31] In this study, we dichotomized the satisfaction score, as done previously.[31] Patients who rated their treatment satisfaction as excellent or good were considered to be satisfied, while those who rated it as moderate or poor were deemed unsatisfied.

The number of additional treatments (e.g. ESWT or orthotic devices) was also recorded. Treatment adherence to the exercise therapy and guidance of a physiotherapist were not registered in this study.

Statistical analysis

The dataset of included subjects was examined using scatterplots to identify any outliers or disparities. Missing data were recorded and the reasons behind missing data were carefully evaluated. For the primary outcome measure there was 26%, 30% and 42% of missing data at 6, 12 and 24 weeks respectively. As a substantial proportion (>10%)[32] of the primary outcome measure was missing (at 24 weeks follow-up), we performed the Little MCAR test.[33] The missingness of this data was found to be plausible for missing completely at random (MCAR), according to the non-significant (p=0.242) Little MCAR test. We performed a complete case analysis (CCA) utilizing pairwise deletion for both the primary and secondary outcome measures. We compared the VISA-A scores between Q1 and Q5 at baseline, 6, 12 and 24 weeks using a general linear model while adjusting for the following pre-defined set of variables that we also used in a similar prospective study: age, sex, BMI, AAS and duration of symptoms.[34] We did not detect any significant collinearity among the variables (supplementary file 5). Additionally, we adjusted for baseline VISA-A score as it significantly ($p < 0.001$ in univariate analysis) influenced the VISA-A scores at 6, 12 and 24 weeks follow-up. For the secondary outcome measure (patient satisfaction), we used a modified Poisson regression analysis adjusting for the same set of variables. These methods ensured unbiased analyses.[35-38]

When it is plausible that data is MCAR, conducting a complete case analysis does not introduce bias since the incomplete datasets can be considered representative of the entire dataset.[35,38,39] However, it is important to note that a CCA may lead to increased standard errors due to the reduced sample size resulting from missing data.[39] Additionally, as a substantial (>40%) amount of data is missing for the outcome measures, the results obtained from the analysis should be interpreted as hypothesis-generating rather than definitive.[39] To explore the robustness of our findings, a sensitivity analysis was performed using a (generalized) linear mixed-effects model for the primary and secondary outcome measures separately. IBM SPSS Statistics (version 28.0.1.0) were used for the CCA and the sensitivity analysis was conducted using R software, version 4.2.1. Used packages included 'nlme', 'GLMMadaptive', 'emmeans'. Residuals were checked for all models.

RESULTS

A total of 240 participants were potentially eligible for the study. We excluded 29 (12%) participants because they did not meet the criteria for the clinical diagnosis of AT and 11 (5%) participants were excluded as they did not provide informed consent. 200 participants fully completed the baseline questionnaire and were included in the study. For the primary outcome measure 148 (74%), 139 (70%) and 116 (58%) participants completed the questionnaire at 6, 12 and 24 weeks respectively. In Q1 and Q5 respectively 64% and 67% of the participants completed the questionnaire at 24-weeks.

The included participants had a median age of 51 years, were mainly male (60.5%), had a median symptom duration of 94 weeks and were active in sports before their injury in the majority of the cases (91%). The collected participants' characteristics are depicted in Table 1 for the overall population. Adjunct conservative therapies were performed during follow-up in 33 participants (17%), including Extracorporeal Shockwave Therapy (ESWT) (7%), orthotic devices (5%) and prolotherapy (2%). 10 patients with high SES (Q1) received adjunct therapies compared to 6 patients with low SES (Q5). This difference was not statistically significant (p=0.497).

Table 1. Descriptive statistics of participants.

	Participants' characteristics (n=200)
Population demographics	
Age, median [IQR], (years)	51 [40-57]
Sex (Male/Female)	121(61) / 79(39)
Height, mean (SD), (cm)	179.2 (9.3)
BMI, median [IQR], (kg/m^2)	25.4 [23.5-28.8]
Tendinopathy descriptors	
AT (unilateral/bilateral)	132(66) / 68(34)
Symptom duration, median [IQR], (weeks)	94 [39-213]
VISA-A score at baseline (0-100), mean (SD)	45.3 (18.7)
Pain location (midportion/insertion)	106(53) / 94(47)
General health and comorbidities	
Sports participation (yes/no)	183(92) / 17(8)
AAS score (0-10), median [IQR]	4 [4-7]
Sport adaptation (none/reduced/stopped)	32(16) / 42(21) / 126(63)
Prior history of tendinopathy (yes/no)	92(46) / 108(54)
Medication use (yes/no)	70(35) / 130(65)
Comorbidities* (yes/no)	54(27) / 146(73)

Abbreviations: SD: Standard Deviation, IQR: Interquartile Range, AT: Achilles tendinopathy, BMI: Body Mass Index, VISA-A: Victorian Institute of Sport Assessment Achilles, AAS: Ankle Activity Score
Data are presented as No. (%) unless otherwise specified. Sports adaptation: patients who reported no change in sports activities, a reduction in sports activities or stopped performing sports activities.
*Comorbidities included: diabetes, hypercholesterolemia, hypertension, heart/vessel diseases, uveitis, (inflammatory) bowel disease, rheumatism, thyroid disease and psoriasis

Symptom severity at baseline and SES

Data was complete for both VISA-A and baseline SES scores (Q1-Q5). Quintile 1 contained the largest proportion of AT patients (22.5%) and in all quintiles a larger proportion was male (Table 2). Table 2 shows the participant characteristics per quintile, which did not demonstrate statistically significant differences between the quintiles. VISA-A scores at baseline were similar for Q1 and Q5 (43.9 and 41.8, p=0.59. See Table 3).

Table 2. Participants' characteristics of the patients in each quintile. Data are presented as No. (%) unless otherwise specified. Abbreviations: BMI: Body Mass Index, AAS: Ankle Activity Score, SES: socioeconomic status

	Number of patients	Sex (M/F)	Age, median [IQR], (years)	AAS score, median [IQR]	BMI (kg/m^2), median [IQR]	Symptom duration , median [IQR] (weeks)
Quintile 1 *(highest SES score)*	45 (22.5)	28 (62) / 17 (38)	50.0 [43.5-56.5]	4.0 [4.0-5.5]	25.5 [24.0-27.7]	126 [60-356]
Quintile 2	37 (18.5)	20 (54) / 17 (46)	53.0 [49.0-59.5]	4.0 [4.0-5.0]	25.4 [23.0-28.9]	77 [43-206]
Quintile 3	38 (19.0)	26 (68) / 12 (32)	45.5 [35.8-53.3]	5.0 [4.0-8.0]	25.2 [23.6-29.3]	104 [33-299]
Quintile 4	41 (20.5)	24 (59) / 17 (41)	51.0 [34.5-56.0]	5.0 [4.0-8.0]	25.4 [22.8-28.1]	66 [37-154]
Quintile 5 *(lowest SES score)*	39 (19.5)	23 (59) / 16 (41)	52.0 [32.0-59.0]	5.0 [4.0-7.0]	26.0 [23.8-30.0]	68 [27-208]

Baseline SES and change in symptom severity during 24 weeks treatment

The effect of baseline SES scores on change in symptom severity (measured with VISA-A and patient satisfaction) is depicted in Table 3 and 4 (complete case analysis). At baseline, 6-weeks and 12-weeks there were no statistically significant differences in VISA-A score between Q1 and Q5. At 24-weeks, there was a mean (95% Confidence Interval; CI) difference of 11.2 (1.0-21.3, p = 0.03) points on the VISA-A score in favor of Q1 (Table 3 and Figure 1). Supplementary File 1 shows the dispersion of the VISA-A scores for the overall population and the individual and mean VISA-A scores over time for Q1 and Q5.

Table 3. Differences in VISA-A score between Q1 and Q5 at each time point (adjusted for sex, BMI, age, symptom duration and AAS). Values are displayed as mean (SD) P-values were Bonferroni corrected

	Group		Difference		95% CI for difference	
	Q1	Q5	Mean difference (± SE)	P value	Lower Bound	Upper Bound
Baseline (n = 45/39)	43.9 (20.9)	41.8 (17.9)	2.1 ± 3.9	0.59	-5.6	9.8
6 weeks* (n=35/29)	49.2 (18.8)	43.7 (18.7)	5.5 ± 4.6	0.24	-3.7	14.8
12 weeks* (n=32/28)	50.7 (19.5)	54.5 (20.1)	-3.8 ± 5.1	0.45	-14.0	6.3
24 weeks* (n=29/26)	66.4 (18.9)	55.2 (18.9)	11.2† ± 5.0	0.03	1.0	21.3

*= also adjusted for baseline VISA-A score. † This difference exceeds the Minimal Clinically Important Difference (MCID) of 7-points at 24-weeks.[40]
Abbreviations: BMI: Body Mass Index (kg/m^2), VISA-A: Victorian Institute of Sports Assessment-Achilles, AAS: Ankle Activity Score. CI: Confidence Interval

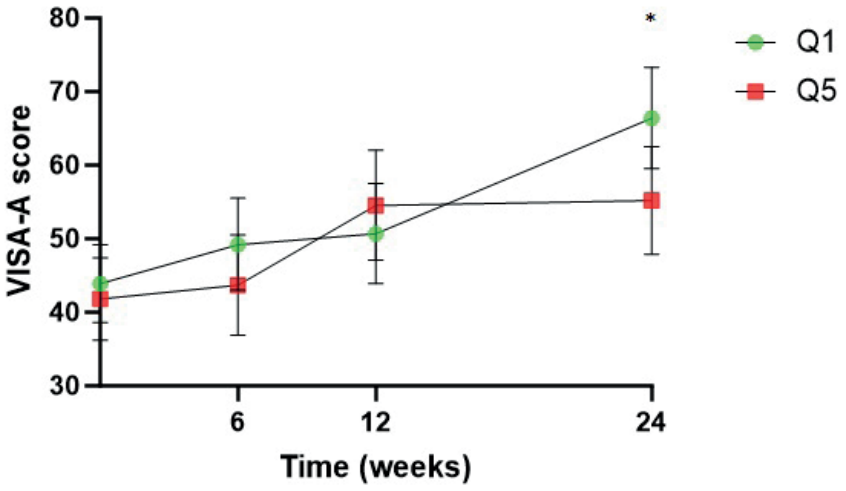

Figure 1. The difference in VISA-A between Q1 and Q5 at each time point (adjusted for sex, Body Mass Index, age, symptom duration, Ankle Activity Score and baseline VISA-A score). Values are displayed as mean ± 95% confidence interval. * Indicates statistically significant difference (p = 0.03) exceeding the Minimal Clinically Important Difference (MCID). We applied the Bonferroni adjustment to adjust for multiple comparisons.

There was no significant difference in treatment satisfaction between Q1 and Q5 at any of the follow-up time points (Table 4).

Table 4. Percentage satisfied with treatment results and the difference in treatment satisfaction between Q1 and Q5 at each time point.* The estimated difference is reported using risk ratio (RR). The RRs were derived using modified Poisson regression analysis.

	Group			
	Q1	**Q5**	**RR (95% CI)**	**P value**
6 weeks	58.3% (21/36)	63.3% (19/30)	0.94 (0.64 – 1.37)	0.75
12 weeks	56.3% (18/32)	53.6% (15/28)	1.07 (0.65 – 1.73)	0.80
24 weeks	77.4% (24/31)	69.2% (18/26)	1.10 (0.80 – 1.51)	0.56

*Adjusted for sex, BMI, age, symptom duration and AAS.
Abbreviations: BMI: Body Mass Index (kg/m^2), AAS: Ankle Activity Score. CI: confidence interval

The results of the sensitivity analyses for the comparison of VISA-A scores between Q1 and Q5 are displayed in Supplementary File 2. Mean (Standard Error; SE) VISA-A scores at baseline were similar for Q1 and Q5 (43.3 (2.6) and 43.6 (2.8)). At 24-weeks, there was a mean (SE) difference of 7.4 (5.3) points on the VISA-A in favor of Q1, but this difference was not statistically significant (p = 0.17) (Supplementary File 2, Table 1). The sensitivity analyses yielded similar results to the primary analysis for the comparison of treatment satisfaction (Supplementary File 2, Table 2).

DISCUSSION

To our knowledge, this is the first study to examine the effect of socioeconomic status in patients with tendinopathy. We found that AT patients with low SES have worse outcomes at 24-weeks follow-up when treated according to the current guidelines. Patients with low SES reported a mean VISA-A score that was 7 to 11 points lower at 24-weeks compared to patients with high SES. While this difference aligns with or exceeds the Minimal Clinically Important Difference (MCID) of 7 points [40,41], indicating potential clinical relevance, it is important to note that sensitivity analyses of the VISA-A scores only suggests a trend and did not demonstrate statistically significant differences between groups at all time periods, possibly due to the large dispersion of data. This highlights the need for cautious interpretation of these findings.

Comparison of current findings with the literature

The impact of SES on patients with Achilles tendinopathy has not been described before, but the relationship between SES and other musculoskeletal diseases has been studied

more extensively. Previous research shows a strong association between low SES and worse treatment outcomes in individuals with other musculoskeletal conditions such as rheumatoid arthritis and osteoarthritis.[42,43] These studies align with the outcomes of the present study, which revealed an association between low SES and increased pain and disability after 24 weeks of treatment in individuals with AT as measured with the VISA-A questionnaire.

Clinical implications

The present study has demonstrated that AT patients belonging to low socioeconomic status may experience inferior treatment outcomes compared to AT patients with higher SES when treated according to current guidelines. This observation has important clinical implications that require careful consideration by healthcare providers. Specifically, healthcare providers should be mindful of the SES of their patients while administering treatment.

A potential reason for the lower treatment effect in people with lower SES is a lack of understanding of their condition and suggested treatment and trust in their physician,[44] which may be addressed through improved patient education. Patient education has emerged as an important factor for improving treatment outcomes in general[45,46], and also plays a crucial role in improving treatment outcomes through knowledge gain in AT patients.[47] Patients belonging to lower SES groups may possess limited health literacy, which could impede their understanding of treatment recommendations and hinder their ability to adhere to the prescribed treatment plan.[9,48] Recognizing this, healthcare providers must take a proactive approach in providing comprehensive education and support to AT patients with lower SES. By ensuring that these patients possess a clear understanding of their treatment plan and the necessary steps required to achieve the best possible outcome, healthcare providers can empower them to actively participate in their own care.

In addition, it is crucial to recognize that individuals from lower SES groups often face multiple barriers in accessing healthcare services, such as access to physiotherapy or consultations with medical specialists.[8,49] Financial constraints and lack of insurance coverage can hinder their ability to seek and afford the recommended treatment.[7,8,49] Variations in physical activity engagement and adherence to exercise therapy could also affect AT recovery. Notably, in our study, the disparity between high and low SES groups primarily emerged between 12 and 24 weeks. This timing may reflect the challenges lower SES groups face in accessing continued physiotherapy support due to potential increased costs associated with prolonged rehabilitation. Consequently, healthcare providers may need to offer additional support to assist patients with lower SES in accessing affordable healthcare resources.

Strengths and limitations

This study has several strengths as we adhered to the CHAMP statement for analysis and reporting of the results and, to our knowledge, we performed the largest cohort study in AT patients. Nonetheless, this study has certain limitations that must be acknowledged. There was a substantial proportion of missing outcome data during the follow-up period. This issue arises due to the observational and longitudinal design of the study, in which the follow-up questionnaires were integrated into routine care. While we did not identify between-group differences in responders versus non-responders, the large proportion of missing outcome data warrants caution when interpreting the results. Additionally, the potential for unmeasured confounding must be considered as a limitation. While we adjusted for several known confounders, including age, sex, BMI, AAS, duration of symptoms, and baseline VISA-A score, there may be other unmeasured variables that could influence the outcomes. The nature of observational studies inherently limits our ability to control for all possible confounding factors. Thus, although the findings are statistically significant and clinically relevant, they should be interpreted as hypothesis-generating rather than definitive.[39] To provide a more comprehensive understanding of the results, we conducted a sensitivity analysis to explore the robustness of the findings. The sensitivity analysis revealed a clinically relevant difference, yet did not demonstrate statistical significance. One possible explanation for this discrepancy could be the substantial dispersion observed in the VISA-A scores (Supplementary File 1). The wide range of scores suggests considerable variability among the AT patients, which could impact the statistical significance of the findings. We did not observe any difference in treatment satisfaction between patients with low and high SES which may question the robustness of the findings of the VISA-A questionnaire. Recent studies have highlighted some shortcomings of the VISA-A, particularly concerning its content validity[50-52]. It is also unknown whether reduced health literacy influences the ability to complete the VISA-A, as shown in other PROMs used in musculoskeletal care.[53] This is especially relevant in our study design. However, the VISA-A continues to demonstrate sufficient reliability and responsiveness[30,51]. Next to this, the VISA-A has been cross culturally adapted in numerous languages (including the Dutch version of the current study).[54] We feel that the use of the VISA-A in our study is justified and that our study's findings and conclusions remain valid, but they should be considered along with the criticism on the psychometric properties of the VISA-A.

Another limitation is that we did not obtain data on treatment adherence and guidance of physiotherapists during treatment. This hinders a comprehensive understanding of the factors influencing the outcomes of patients with low SES and impedes a thorough analysis of the barriers they may face in receiving appropriate care.

Future research

The findings stress the need for future research to further examine the underlying mechanisms responsible for worse treatment outcomes among tendinopathy patients belonging to lower SES groups. Such qualitative investigations could identify barriers and facilitators, which in turn could inform specific interventions and strategies that can address these disparities and enhance treatment outcomes for all patients, irrespective of their SES status.

CONCLUSION

Low socioeconomic status may be associated with worse patient-reported outcomes in patients with Achilles tendinopathy who are treated according to the current guidelines. This highlights the need for clinicians to consider the impact of social inequality when developing and implementing treatment plans, and to explore tailored approaches that address the unique challenges faced by patients' subgroups. Future qualitative research should focus on this subgroup of patients with lower SES to better understand the reasons behind the lower treatment response, which can facilitate personalized treatment.

SUPPLEMENTARY MATERIAL

All supplementary material is available online at: https://bjsm.bmj.com/content/early/2024/04/03/bjsports-2023-107633

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Chapter 9

General discussion

DISCUSSION

Achilles tendinopathy is a frequently occurring and debilitating condition.[1,2] Knowledge in the field of Achilles tendinopathy is increasing rapidly, and recently resulted in the publication of clinical guidelines.[3,4] However, many questions remain unanswered. This thesis primarily aimed to evaluate the impact of Achilles tendinopathy, to examine the role of physical and ultrasonographical evaluation and to assess socio-economic status as prognostic factor in Achilles tendinopathy patients. By doing so we hope to contribute to an increased understanding of the condition and a more personalised approach for patients with Achilles tendinopathy.

IMPACT

To effectively evaluate the severity of Achilles tendinopathy and treatment effectiveness, reliable and valid outcome measures are necessary. Through a 5-step approach, including a systematic review, a 2-round Delphi survey, methodological quality assessment and an in person consensus meeting, we identified a core outcome set for clinical trials of Achilles tendinopathy (COS-AT). The following outcome measures were selected as part of the core outcome set: the Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire, the single-leg heel rise test, evaluating pain after activity using a Visual Analogue Scale (VAS, 0-10) and evaluating pain on activity/loading using a VAS (0-10). It is strongly recommended that future clinical trials should include the agreed core outcome set for Achilles tendinopathy (COS-AT) as a minimum. This will facilitate pooling of data and progression of knowledge about Achilles tendinopathy.

One important outcome measure selected by the patients and experts was the single-leg heel rise endurance test (HRET) which can be used to assess the strength-endurance of the plantar flexors. Muscle weakness of the plantar flexors is hypothesized to be an essential, modifiable risk factor for Achilles tendinopathy.[3,5,6] In contrast to individuals without symptoms, individuals suffering from Achilles tendinopathy exhibit significant reductions in both torque and strength-endurance of the plantar flexors.[7] Notably, these reductions are observed bilaterally, implying that it is unsuitable to consider the asymptomatic limb as a representative "healthy limb" or to use as a reference for comparisons with the symptomatic limb in research or clinical assessments.[7,8] In a large international cross-sectional study we presented normative values for App-based HRET metrics such as the number of repetitions, peak height, total displacement and total work. These normative values were adjusted for personal characteristics as we found that lower physical activity levels, female sex and higher BMI negatively influenced HRET performance. We found no significant difference between the dominant and non-dominant leg for any of the HRET metrics. This further stresses the clinical relevance of normative values for the

assessment of calf muscle strength and endurance. Clinicians can employ these normative values, openly available as calculator at www.achillestendontool.com/HRET, to assess whether a patient's strength-endurance falls within the established norms. This can aid in individualized patient evaluation and contribute to well-informed rehabilitation guidance. Furthermore, there is an opportunity for researchers to delve deeper into the prognostic significance and the utility of monitoring strength-endurance in relation to Patient-Reported Outcome Measures (PROMs).

The combination of the single-leg heel rise endurance test (HRET) and the associated normative values may also hold promising potential for screening individuals at risk of developing Achilles tendinopathy and identifying those with calf muscle strength deficits.[8,9] For example, individuals with a history of lower limb tendinopathy[5], professional athletes or individuals planning to increase their training load could be screened.[5] This early detection can enable healthcare providers to tailor preventive interventions (e.g. performing strengthening exercises of the plantar flexors) to address these deficits and potentially prevent the onset of Achilles tendinopathy. One of the significant benefits of using HRET in this context is its sensitivity to detect deficits in strength-endurance of the plantar flexors, which has been identified as a modifiable risk factor for Achilles tendinopathy.[6,7] However, there are some limitations to consider when using the HRET and normative values for preventive purposes. First, it's essential to acknowledge that while muscle weakness is a risk factor, Achilles tendinopathy is a multifactorial condition influenced by various factors such as biomechanical factors and non-modifiable patient characteristics.[5] Thus, HRET should be part of a broader assessment that takes these factors into account. Second, the effect of preventive calf muscle strengthening exercises has been scarcely studied, with only one study reporting no effect of this preventive intervention in a selected group (professional football players) and with only 2 sessions of exercises per week during the competitive season.[10] Third, it remains a question whether the HRET can be expected to serve as an effective screening tool or prognostic indicator for targeted training in the context of Achilles tendinopathy as the presence of pain in this population may influence the assessment. Patients with Achilles tendinopathy may be limited not only by muscle endurance but also by pain tolerance. This factor introduces a potential limitation, as the HRET assessment may not accurately reflect the true muscle endurance in this patient population. Current guidelines recommend calf muscle strengthening exercises as preventive strategy in a preseason period based on clinical expertise although it is acknowledged that literature on this is lacking.[3,11] Further research is needed to evaluate the potential use of preventive interventions for individuals with decreased calf muscle strength at risk of developing symptoms of Achilles tendinopathy.

Quality of life is an aspect which has been frequently overlooked when assessing tendinopathy-related outcomes. This recently led to an international group of experts (healthcare providers, researchers and patients) establishing quality of life as core domain

for tendinopathy.[12] We demonstrated that Achilles tendinopathy has a large impact on quality of life, with specifically the domains mobility, pain/discomfort and usual activities being affected. These findings are in line with a recent study, showing that patients with Achilles tendinopathy have a significantly reduced quality of life compared to the general population.[13]

We compared the score from the health-related quality measure (EuroQoL five-item questionnaire; EQ-5D) for Achilles tendinopathy to a large sample of the general Dutch population and different musculoskeletal conditions.[14] The results indicated that individuals with Achilles tendinopathy exhibited a notably lower mean quality of life score in comparison to those without any musculoskeletal conditions. This difference was observed across all EQ-5D dimensions, with the exception of self-care. It is worth highlighting that patients with Achilles tendinopathy reported similar, if not inferior, quality of life scores in key domains, including mobility, usual activities, and pain/discomfort, when compared to individuals with other musculoskeletal disorders such as rheumatoid arthritis, osteoarthritis, lateral epicondylar tendinopathy and fibromyalgia.[14]

The significant impact of Achilles tendinopathy on the domains mobility and pain/discomfort becomes even more apparent when we compare the quality of life scores of individuals with this condition to those of patients with cardiovascular diseases or cancer - conditions widely acknowledged for their debilitating nature. In comparison to individuals with cardiovascular disease, patients with Achilles tendinopathy report similar or lower quality of life scores in the domains of mobility and pain/discomfort (Figure 1).[15] Similar conclusions can be drawn when comparing the quality of life scores of patients coping with colorectal cancer[16] or those with prostate cancer[17] to Achilles tendinopathy patients (Figure 1).

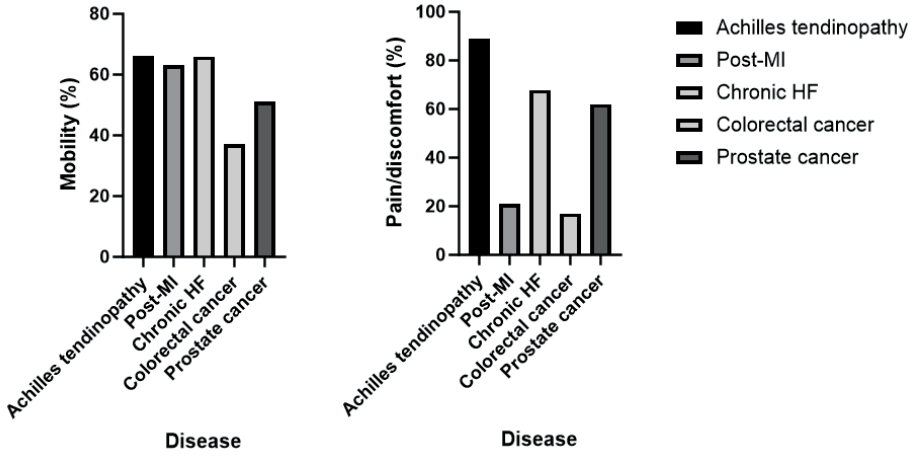

Figure 1. Comparison of the EQ-5D scores for Achilles tendinopathy patients with patients post myocardial infarction[18], patients with chronic heart failure[19], colorectal cancer[16] and prostate cancer[17]. Displayed values are percent with any (moderate and severe) problems. EQ-5D: EuroQoL five-item questionnaire for measuring health-related quality of life.

It is important to acknowledge that the conditions mentioned earlier typically have significantly more profound and far-reaching consequences than Achilles tendinopathy. Nevertheless, this comparison shows how individuals with Achilles tendinopathy experience a profound impact on their quality of life. If policymakers continue to focus on outcomes such as morbidity and mortality and less on quality of life, they will not adequately serve the population. These data should lead to a shift towards research on more effective treatments for musculoskeletal disorders and tendinopathies specifically. Two qualitative studies highlight the psychosocial impact of Achilles tendinopathy, with patients stating: ''*I no longer feel like I'm in control*'', ''*Wanting to run and I'm stuck here. Now I know there are worse things in life that can happen, but it's been horrible*'' and ''*I feel like there is nothing at the end of the tunnel*''.[20,21]

While our knowledge of Achilles tendinopathy is advancing, the existing body of research in the field is dominated by a focus on functional and disability-related outcome measures at the expense of psychosocial ones.[22] The predominant focus on these outcome measures does not support the concept of a more patient-centred approach in the management of Achilles tendinopathy. We recommend that clinicians and researchers integrate psychosocial factors into the evaluation and treatment of Achilles tendinopathy patients. This may not only improve the management of Achilles tendinopathy but may also promote greater adherence to evidence-based interventions such as exercise therapy.[23,24] It is

noteworthy that psychosocial outcome measures were not included in the core outcome set for clinical trials in Achilles tendinopathy. This omission may be attributed to the current absence of psychosocial outcome measures tailored specifically to the population of Achilles tendinopathy patients.

DIAGNOSTIC IMAGING

Clinical diagnosis

Achilles tendinopathy is a clinical diagnosis, with 3 key diagnostic criteria.[25] Patient history is crucial to diagnose Achilles tendinopathy as patients must have pain in the Achilles tendon region, which worsens on loading.[25] A second key diagnostic criterion is the presence of localized Achilles tendon pain, which can be assessed upon palpation of the Achilles tendon.[25,26] When evaluating the location of pain it is important to distinguish between the insertional and midportion region as it affects prognosis and treatment.[26,27] Our cross-sectional study demonstrated that Achilles tendinopathy patients could adequately localize their pain. This study showed that, with the use of a pain map, there was substantial agreement between the localization of the pain by the patient and the diagnosis of insertional/midportion Achilles tendinopathy by the physician. A third important diagnostic criterion is the presence of localized tendon thickening.[25] Experts agree that when all three clinical diagnostic elements are present, the clinical diagnosis is straightforward.[28] Previous research, using ultrasound as reference standard, indicated that these three findings show high diagnostic accuracy for diagnosing chronic midportion Achilles tendinopathy.[26] This leads us to the role of imaging in diagnosing Achilles tendinopathy. Is imaging useful in cases where not all three diagnostic criteria are present (e.g. localized tendon pain which is painful on palpation but without tendon thickening)? And is imaging indeed the reference or 'golden' standard?

Diagnostic imaging

Ultrasound serves as the preferred imaging modality for diagnosing Achilles tendinopathy.[3,4,29] Conventional X-rays are generally only used to assess for any potential bone-related abnormalities and in cases where ultrasound is not accessible, prior to potential surgical intervention, or when ultrasound results don't match with clinical findings, MRI may be considered.[3,29] A common finding of Achilles tendinopathy during ultrasound examination is an increase in tendon thickness in the anterior-posterior direction.[29] The reliability of measuring Achilles tendon thickness using conventional ultrasound techniques ranges from fair to excellent.[30-32] However, there has been a lack of research evaluating the reliability of measurements in the insertional area of Achilles tendinopathy patients. In addition to conventional ultrasound, the adoption of standardized ultrasound procedures is becoming

increasingly important in clinical practice to enhance the consistency of tendon geometry measurements.[32-34]

Ultrasound Tissue Characterization (UTC) is a customized tracking and ultrasonographic data-collection device designed to facilitate these standardized measurements.[31,35] In a comprehensive reliability study, we included 50 patients with Achilles tendinopathy and 50 asymptomatic individuals, demonstrating excellent reliability in measuring tendon thickness using UTC. Additionally, we showed that measurements of tendon thickness obtained through UTC can be reliably translated to conventional ultrasound. However, we observed significantly lower intra-class correlation coefficients when assessing the reliability of thickness measurements in the insertional region compared to the midportion. This study is the first to comprehensively evaluate thickness measurements in the insertional region, as previous research had primarily focused on the midportion.

Until recently, a value of 6 mm was being accepted as reference standard for maximum anterior posterior distance of the midportion region.[29,35,36] However, a significant gap in our understanding of imaging lay in the absence of reference values for Achilles tendon thickness within the general population. In a large international cross-sectional study we presented normative values for Achilles tendon thickness on ultrasound examination, adjusted with personal characteristics. Our findings reveal that age and height have the most substantial impact on the maximum anterior-posterior distance. The mean difference in tendon thickness between asymptomatic persons and patients with Achilles tendinopathy was 2.7 mm for the midportion region and 1.4 mm for the insertional region. Notably, this difference of 1.4 mm in thickness in the insertional region is smaller than the Smallest Real Difference (SRD) of 1.5 mm for intra-rater reliability we observed in insertional Achilles tendinopathy patients in our reliability study. This questions the use of ultrasound when evaluating tendon thickness in patients with insertional Achilles tendinopathy. Previous studies reported lower SRD values (ranging between 0.007 and 0.84 mm), but these studies solely evaluated the midportion region and the majority only included asymptomatic individuals.[32,37] Thus, this study raises the question whether characteristic changes indicative of tendinopathy can be observed in all Achilles tendinopathy patients, especially for patients with insertional Achilles tendinopathy. In patients with midportion Achilles tendinopathy, however, the SRD was smaller than the observed difference between patients and asymptomatic individuals.

Using the normative equations for the median, lower (2.5th) and upper (97.5th) values of tendon thickness for each Achilles tendinopathy patient in our large international study, we found that 27% of the patients that were clinically diagnosed as having Achilles tendinopathy did not have increased tendon thickening outside the 95% reference interval. In addition, ‘‘morphological changes’ (changes characteristic for tendinopathy) are present in up to 25% of asymptomatic Achilles tendons.[38] While imaging, such as ultrasound or UTC,

can provide valuable insights into the structural changes in the Achilles tendon, it is now evident that not all patients with clinical symptoms of Achilles tendinopathy exhibit the expected increase in tendon thickness. Conversely, a substantial proportion of individuals without symptoms display morphological changes indicative of tendinopathy on imaging. This disparity raises significant questions regarding the reliance on imaging for diagnosing and assessing Achilles tendinopathy. Experts already agree that imaging is not essential for diagnosing Achilles tendinopathy and current guidelines only recommend imaging in cases where the diagnosis is uncertain.[3,4,28] However, randomized control trials frequently (47%) use imaging in the diagnostic process.[3,28,39] In these RCTs local thickening of the tendon is often used but predominantly without specifying the criteria for when one speaks of increased tendon thickness.[3] Heterogeneous tendon structure with hypoechoic areas and presence of intratendinous/peritendinous Doppler flow are also regularly used for diagnosing Achilles tendinopathy on imaging[35,36,40,41], but also these criteria may be absent in patients with Achilles tendinopathy. For example, one study showed that areas of altered echogenicity were seen in 67% of patients and only 47% of the patients exhibited increased Doppler flow.[42] While it is hypothesized that radiological findings are similar for midportion and insertional Achilles tendinopathy[43] diagnostic criteria in RCTs on insertional Achilles tendinopathy are underreported compared to midportion Achilles tendinopathy.[3] We found only one RCT reporting radiologic criteria (solely the presence of calcifications was used) for diagnosing insertional Achilles tendinopathy.[44] The heterogeneity in radiologic criteria used for diagnosing Achilles tendinopathy on imaging and the lack of reporting radiologic criteria in these RCTs stress the need for clear diagnostic criteria. These diagnostic criteria (such as tendon geometry and structure, Doppler flow and intratendinous calcifications) should preferably be based on large international studies evaluating imaging findings of the Achilles tendon in both Achilles tendinopathy patients and asymptomatic individuals. Next to this, clinicians and researchers should form clear agreements how these diagnostic criteria are defined and how to reliably assess them, for example through a consensus process/study. Only after such studies we will be able to know if imaging truly has a place in the diagnostic process for Achilles tendinopathy.

If imaging does not have a place in the diagnostic process, does it have added value for evaluating response to treatment or as prognostic factor? There have been several studies which used imaging as secondary outcome measure when evaluating the effect of treatment.[45,46] It is hypothesized that mild degree of tendon thickening, neovascularization or hypo-echogenicity is indicative of a favourable response to treatment. However, numerous studies have showed that there is no clear relationship between radiographic findings and clinical severity in patients with AT and that imaging findings are not predictive/indicative for the response to treatment.[47-51]

If imaging is of limited value in the diagnostic process or as prognostic factor, the question arises if there are other potential benefits of using imaging in the management of Achilles

tendinopathy. Current guidelines advice to start treatment of Achilles tendinopathy with patient education as a cornerstone of the treatment together with load-management and progressive calf muscle strengthening exercises for at least 12 weeks.[3,4] This education should consist of 1) explanation about the condition, 2) explanation about the prognosis and 3) pain education and addressing psychological factors.[3] The significance of patient education has become increasingly evident in enhancing treatment results in general healthcare[52,53], and increasing patient's knowledge about their condition also plays an important role in improving treatment outcomes in Achilles tendinopathy.[54] Could patient education be improved with the use of imaging? Prior studies have demonstrated that collaborative image viewing with patients can enhance their comprehension of their condition, positively influence the nature of the interactions between the clinician and the patient, and can influence their health-related behavioural intentions.[55-57] Importantly, the use of ultrasound in patient education in patients with rheumatic and juvenile arthritis has led to improved treatment adherence.[58-60] Further research into the value of incorporating imaging into patient education for Achilles tendinopathy patients is necessary to determine if including imaging remains useful in the management of Achilles tendinopathy.

PROGNOSTIC FACTORS

Prognostic factors play an important role in modern medicine and can help healthcare providers estimate the course of a disease to tailor treatment strategies to individual patients. In the field of oncology for example, the identification of specific tumour characteristics, such as genetic mutations and biomarkers, has paved the way for more personalized and effective treatment options.[61] The current conservative treatment for Achilles tendinopathy may not be very effective as one-thirds of patients with new-onset Achilles tendinopathy remain symptomatic at one-year follow-up[62] and at ten years of follow-up, up to a quarter of patients continue to experience symptoms.[63] However, it is unclear which patients will have a (un)favourable response to treatment as knowledge of prognostic factors is currently limited.[3]

In a large prospective cohort study, we found that socio-economic status had effect on response to standardized treatment; at 24 weeks follow-up patients with high socioeconomic status reported significantly less symptoms compared to patients with low-socioeconomic status. The mean difference between both groups was 11 points on the Victorian Institute of Sports Assessment-Achilles (VISA-A) scale which is larger than the Minimal Clinically Important Difference (7 points) and therefore regarded as clinically relevant.[64,65] It was striking that the difference in VISA-A score mainly occurred between 12 and 24-weeks follow up, with a lack of improvement in patients with low socio-economic status. It could be that reduced access to healthcare and absence of guided rehabilitation for prolonged periods in patients with low socio-economic status

are a cause of this difference. Future research should focus on the underlying mechanisms for this difference in treatment response.

Several other studies have evaluated potential prognostic factors in patients with Achilles tendinopathy. Imaging and patient-specific factors as age, sex, BMI and duration of symptoms do not have any prognostic value for predicting long term outcome based on several studies with relatively small sample size.[3,66-68] More recently, one study examined the potential prognostic value of physical tests at baseline. It was found that patients with less pain during pain provocation tests at baseline (pain on palpation and pain with 10-hops) have a larger improvement in pain, function and activities after 24 weeks compared to patients with high baseline pain scores.[69] These identified and refuted prognostic factors are in contrast with findings in patients with patellar tendinopathy. In patients with patellar tendinopathy physical and pain-provoking test at baseline do not have any prognostic value[70] whereas higher age and longer symptom duration were found to negatively influence treatment outcome.[71] When evaluating prognostic factors in other tendinopathy locations some similarities, as well as numerous differences, can be found. A systematic review on prognostic factors in patients with rotator cuff tendinopathy showed evidence that high baseline pain, high baseline disability and a longer duration of symptoms were associated with an unfavourable outcome and sex and age were not associated with the outcome.[72] In patients with lateral elbow tendinopathy, greater baseline pain and disability were also associated with a poor long-term prognosis. Although it is debatable whether different tendinopathy locations can be directly compared, apart from patellar tendinopathy, a similarity in prognostic factors becomes apparent with greater baseline pain and disability negatively influencing treatment outcome in tendinopathy patients. Further research is needed to evaluate potential patient-specific prognostic factors such as activity/loading profiles and larger datasets are necessary to confirm or refute the prognostic role of age, sex, BMI and duration of symptoms in Achilles tendinopathy patients.

FUTURE RESEARCH

This thesis has shed new light on the management of Achilles tendinopathy and has added to the accumulating knowledge regarding the impact, diagnostic imaging and prognosis of this condition. However, new questions have emerged ad several remain unanswered. We recommend future research to focus on answering the following questions:

1. What are the normative values of radiologic diagnostic criteria such as tendon structure, Doppler flow and intratendinous calcifications on imaging when evaluated in a large group of asymptomatic individuals and compared with Achilles tendinopathy patients?
2. Does the use of imaging in patient education improve treatment adherence or response to treatment?
3. What are the underlying mechanisms responsible for worse treatment outcomes among tendinopathy patients belonging to lower SES groups?

The approach to answer these research questions will depend on the type of the question. Some of these questions can only be answered when large amounts of participants will be included in new study projects. In numerous medical domains, 'Big Data' has emerged as a potential solution for addressing research questions. Examples are the Scandinavian Anterior Cruciate Ligament registry and the Dutch Arthroplasty Registry. In the field of tendinopathy this approach has not been used before. We propose the establishment of large (inter)national databases/registries for patients with Achilles tendinopathy. This initiative aims to advance our understanding of this debilitating condition and, ultimately, to prevent that future individuals being ´struck´ with Achilles tendinopathy will not experience a downfall as did the legendary warrior Achilles.

CLINICAL IMPLICATIONS OF THIS THESIS

Impact

- Future clinical trials should use the established core outcome set (COS-AT). This is a minimal reporting requirement and consists of the VISA-A questionnaire, the single-leg heel rise test, evaluation of pain after activity using a VAS (0-10) and evaluation of pain on activity/loading using a using a VAS (0-10).
- The single-leg heel rise is influenced by patient characteristics and health care providers may use the adjusted normative values to personalize and optimize rehabilitation programs.
- The impact of Achilles tendinopathy on quality of life is severe, especially in the domains mobility, pain/discomfort and usual activities. Estimated annual costs as a result of Achilles tendinopathy are €840 per AT patient. This socio-economic impact of AT stresses the need for optimized treatment and improved preventive measures.

Diagnostic imaging

- UTC can be reliably used to assess Achilles tendon thickness.
- Tendon thickness measurements of the Achilles tendon insertion are less reliable compared to the midportion.
- Achilles tendon thickness depends on personal characteristics with older age and higher height being associated with increased values for Achilles tendon thickness. The established normative ultrasonographic values for tendon thickness may help clinicians to differentiate between morphological changes and ultrasonographic features of Achilles tendinopathy.
- Not all patients with clinical symptoms of Achilles tendinopathy exhibit increased tendon thickening.

Prognostic factors

- Clinicians should consider the socioeconomic status of Achilles tendinopathy patients as this may play a role in the response to treatment.

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APPENDICES

Summary

Nederlandse samenvatting

PhD portfolio summary

List of publications

Dankwoord

Curriculum vitae

SUMMARY

The general aims of this thesis were to evaluate the impact of Achilles tendinopathy, to assess the role of ultrasonographic imaging and to assess socio-economic status as prognostic factor in Achilles tendinopathy patients. **Chapter 1** presents an overview of the available literature on Achilles tendinopathy with a focus on the impact, diagnostic imaging and prognostic factors.

IMPACT

There has been considerable variation in the outcome measures used for AT, which can have implications for patient care, as healthcare professionals and researchers are unable to adequately interpret, compare, and synthesize study results. In **Chapter 2** we performed an international Delphi survey and consensus meeting to agree to a set of core outcome measures for clinical trials on Achilles tendinopathy. The following outcome measures were selected as part of the core outcome set: 1) the Victorian Institute of Sports Assessment-Achilles (VISA-A) questionnaire, 2) the single-leg heel rise test, 3) evaluating pain after activity using a Visual Analogue Scale (VAS, 0-10) and 4) evaluating pain on activity/loading using a VAS (0-10). It is strongly recommended that future clinical trials should include the agreed core outcome set for Achilles tendinopathy (COS-AT) as a minimum.

Conservative treatment of Achilles tendinopathy partly consists of exercise therapy of the calf muscles, with the single leg heel-rise test (HRET) being frequently used to assess the strength endurance of the plantar flexors. A problem in the assessment of calf muscle strength and endurance is that the non-symptomatic limb cannot generally be used as reference and normative values for the HRET are currently lacking. In **Chapter 3** we performed a large international cross-sectional study and presented normative values for calf muscle strength, adjusted for personal characteristics. We found that the median number of repetitions were 24 for the left leg and 25 for the right leg and median peak height was 9.3-9.7cm. There was no significant correlation between leg dominance and any of the HRET metrics. Lower physical activity levels, female sex and higher BMI negatively influenced HRET performance. Except for peak power, we found no correlation between age and HRET performance. We have developed an openly accessible calculator for estimating normative HRET metrics (www.achillestendontool.com/HRET). This can be a valuable tool for healthcare providers to monitor personalized trajectories of recovery and provide well-informed rehabilitation guidance.

In **Chapter 4** we conducted a cross-sectional study, comprising 80 Achilles tendinopathy patients, to evaluate the impact of Achilles tendinopathy on quality of life, work performance, healthcare utilisation and costs in adults with conservatively treated

chronic midportion AT. The primary outcome was the EuroQol questionnaire (EQ-5D), which expresses the percentage of moderate/major problems on the domains self-care, anxiety/depression, mobility, usual activities and pain/discomfort. Secondary outcomes were the number of previous healthcare visits, work performance during the period of symptoms and estimated annual direct medical and indirect costs per patient as a result of AT. The EQ-5D scores were low for the domains self-care (1%) and anxiety/depression (20%), and high for the domains mobility (66%), usual activities (50%) and pain/discomfort (89%). Patients with AT mainly reported an impact on work productivity (38%). Work absenteeism due to AT was present in 9%. The total median (IQR) number of annual healthcare visits was 9 (3–11). The total mean (SD) estimated annual costs were €840 (1420) per patient with AT (mean (SD) US$991 (1675)).

We concluded that the impact of Achilles tendinopathy (AT) on quality of life is substantial, with especially the domains mobility, pain/discomfort and usual activities being affected. Next to this, we demonstrated that Achilles tendinopathy also leads to a significant decrease in work productivity and causes substantial costs.

Diagnostic imaging

As the clinical sign of subjective self-reported pain is a key criteria for establishing the diagnosis of Achilles tendinopathy we wanted to know if patients with pain in the Achilles region could adequately localize their pain. In **Chapter 5** we performed a cross-sectional study and evaluated the level of agreement between patient-reported pain using a standardized pain map and the physician-determined clinical diagnosis of Achilles tendinopathy. 110 patients with pain in the Achilles region were included and in 102 (93%, Kappa = 0.86, CI 0.78–0.95) patients who indicated pain in the Achilles tendon region on the pain map, the clinical diagnosis of Achilles tendinopathy was made by the sports physician. 82% of the patients had the clinical diagnosis of tendinopathy in the specific region (midportion/insertion) of the tendon they marked on the pain map (Kappa = 0.67, CI 0.54–0.79). This study demonstrated that there was substantial agreement between the localization of the pain selected by the patient and the diagnosis of insertional/midportion Achilles tendinopathy by the physician. The use of a pain map could be of value to researchers performing large epidemiological studies or aid in self-diagnosis and adequate triage for specialized care.

Ultrasound is the preferred imaging method in the diagnostic process of Achilles tendinopathy. Ultrasound Tissue Characterization is a frequently used, standardized method to assess tendon geometry in AT patients, but it has been unknown whether UTC is reliable for measuring Achilles tendon thickness. In **Chapter 6** we included 50 Achilles tendinopathy patients and 50 asymptomatic individuals and assessed the intra- and inter-rater reliability of Achilles tendon thickness measurements using UTC. Overall, we demonstrated excellent reliability for measuring tendon thickness using UTC. However,

significantly lower intra-class correlation coefficients were observed for the reliability of thickness measurements in the insertional region when compared to the midportion. Next to this, we showed that tendon thickness measurements using UTC can be reliably translated to conventional ultrasound.

In **Chapter 7** we obtained adjusted ultrasonographic reference values of the Achilles tendon thickness (maximum anterior-posterior distance) in adults without (previous) Achilles tendinopathy and compared these reference values with AT patients. In this large international cross-sectional study we demonstrated that Achilles tendon thickness is influenced by personal characteristics. We found that age and height had the largest influence on maximum anterior-posterior distance. The mean difference in tendon thickness between asymptomatic persons and patients with Achilles tendinopathy was 2.7 mm for the midportion region and 1.4 mm for the insertional region. The majority of the AT patients (73%) had an increased tendon thickening outside the 95% reference interval. Our novel web-based openly accessible calculator for determining normative Achilles tendon thickness (www.achillestendontool.com) will help clinicians distinguish between ultrasonographic features of Achilles tendinopathy and normal morphological changes.

Prognostic factors

As imaging does not have any prognostic value for Achilles tendinopathy patients, it is important to evaluate other potential patient specific prognostic factors. In **Chapter 8** we included 200 Achilles tendinopathy patients who were treated according to the current guidelines and evaluated if socio-economic status had effect on symptom severity and response to standardized treatment. We found that there was a mean difference of 11 points on the VISA-A questionnaire at 24-weeks follow-up in favour of patients with high socioeconomic status compared to patients with low SES. This difference in VISA-A score is larger than the Minimal Clinically Important Difference and thus clinically relevant. We advise healthcare providers to be mindful of the socioeconomic status of their patients while administering treatment. Future research should focus on this subgroup of tendinopathy patients with lower socioeconomic status to better understand the reasons behind the worse treatment response.

In **Chapter 9**, the key findings of this thesis are described in relation to both each other and the existing body of literature on Achilles tendinopathy. Several recommendations for future research are presented, aiming to enhance the knowledge on the impact, diagnostic imaging modalities and prognosis of Achilles tendinopathy.

NEDERLANDSE SAMENVATTING

De algemene doelstellingen van dit proefschrift waren het evalueren van de impact van achillespees klachten (achilles tendinopathie), het beoordelen van de rol van echografie en evalueren van socio-economische status als prognostische factor bij patiënten met achilles tendinopathie. In **Hoofdstuk 1** wordt een overzicht gegeven van de beschikbare literatuur over achilles tendinopathie met een focus op de impact, diagnostische beeldvorming en prognostische factoren.

Impact

Er is aanzienlijke variatie in de uitkomstmaten die worden gebruikt voor achilles tendinopathie, wat implicaties kan hebben voor de patiëntenzorg, aangezien zorgprofessionals en onderzoekers hierdoor niet goed in staat zijn om studieresultaten te interpreteren, te vergelijken en te analyseren in meta analyses. In **Hoofdstuk 2** hebben we een onder een groep van experts en patiënten een internationale Delphi-vragenlijst en consensus studie uitgevoerd om een set van uitkomstmaten voor klinisch onderzoek over achilles tendinopathie samen te stellen. De volgende uitkomstmaten werden geselecteerd: 1) de Victorian Institute of Sports Assessment-Achilles (VISA-A) vragenlijst, 2) de single-leg heel rise test, 3) het evalueren van pijn na activiteit met behulp van een Visuele Analoge Schaal (VAS, 0-10) en 4) het evalueren van pijn bij activiteit/belasting met een VAS (0-10). Het wordt aanbevolen om bij toekomstig klinisch onderzoek op het gebied van achilles tendinopathie minimaal deze uitkomstmaten te rapporteren.

De conservatieve behandeling van achilles tendinopathie bestaat gedeeltelijk uit oefentherapie van de kuitspieren, waarbij de single leg heel-rise test (HRET) vaak wordt gebruikt om de kracht en het uithoudingsvermogen van kuitspieren te beoordelen. Een probleem bij de beoordeling van de kracht en het uithoudingsvermogen van de kuitspieren is dat de niet-aangedane zijde niet standaard als referentie kan worden gebruikt en dat normaalwaarden voor de HRET momenteel ontbreken. In **Hoofdstuk 3** hebben we een grote internationale studie uitgevoerd en normaalwaarden voor kuitspierkracht gepresenteerd. Deze normwaarden zijn geadjusteerd voor persoonlijke kenmerken. We vonden dat het mediane aantal herhalingen 24 was voor het linkerbeen en 25 voor het rechterbeen en de mediane piekhoogte was 9.3-9.7cm. Er was geen significante correlatie tussen dominantie van het been en de HRET-parameters. Lagere niveaus van fysieke activiteit, vrouwelijk geslacht en een hogere BMI hadden een negatieve invloed op HRET-prestaties. Behalve voor piekvermogen vonden we geen correlatie tussen leeftijd en HRET-prestaties. We hebben een openbare calculator ontwikkeld voor het schatten van normaalwaarden van de HRET (www.achillestendontool.com/HRET). Dit kan een waardevol hulpmiddel zijn voor zorgverleners om hersteltrajecten te monitoren en patiënten te begeleiden bij hun revalidatie, rekening houdend met patiënt-specifieke kenmerken.

In **Hoofdstuk 4** hebben we een studie uitgevoerd om de impact van achilles tendinopathie op de kwaliteit van leven, werk en gezondheidsconsumptie te evalueren. We hebben daarvoor 80 patiënten geïncludeerd met achilles tendinopathie. De belangrijkste uitkomstmaat was hierbij de EuroQol-vragenlijst (EQ-5D), die het percentage van matige/grote problemen uitdrukt op de domeinen zelfzorg, angst/depressie, mobiliteit, gebruikelijke activiteiten en pijn/ongemak. Secundaire uitkomstmaten waren het aantal gezondheidszorg bezoeken, werkprestatie gedurende de periode van symptomen en de geschatte jaarlijkse directe medische en indirecte kosten per patiënt als gevolg van achilles tendinopathie. De EQ-5D-scores waren hoog voor de domeinen mobiliteit (66%), gebruikelijke activiteiten (50%) en pijn/ongemak (89%), wat betekent dat patiënten op deze gebieden veel problemen ervaarden. Patiënten met achilles tendinopathie rapporteerden voornamelijk een impact op werkproductiviteit (38%). Werkverzuim door achilles tendinopathie was aanwezig bij 9%. Het totale mediane (IQR) aantal jaarlijkse gezondheidszorgbezoeken was 9 (3–11). De totale gemiddelde (SD) geschatte jaarlijkse kosten waren €840 (1420) per patiënt met achilles tendinopathie.

We concludeerden dat de impact van achilles tendinopathie op de kwaliteit van leven aanzienlijk is, waarbij met name de domeinen mobiliteit, pijn/ongemak en gebruikelijke activiteiten worden beïnvloed. Daarnaast hebben we aangetoond dat achilles tendinopathie ook leidt tot een aanzienlijke afname in werkproductiviteit en aanzienlijke kosten met zich meebrengt.

Diagnostische beeldvorming

Achilles tendinopathie kan op basis van locatie worden geclassificeerd in tendinopathie van het middendeel en de insertie. Aangezien subjectieve zelf-gerapporteerde pijn een belangrijk criterium is voor het stellen van de diagnose achilles tendinopathie, wilden we weten of patiënten met pijn in de achillespeesregio hun pijn adequaat konden lokaliseren. In **Hoofdstuk 5** hebben we de mate van overeenkomst tussen door de patiënt gerapporteerde pijn, met behulp van een gestandaardiseerde pijnkaart, en de door de arts bepaalde klinische diagnose van achilles tendinopathie geëvalueerd. 110 patiënten met pijn in de achillespeesregio werden geïncludeerd en bij 102 (93%) patiënten die pijn in de achillespeesregio op de pijnkaart aangaven, werd de klinische diagnose van achilles tendinopathie gesteld door een sportarts. 82% van de patiënten had de klinische diagnose van tendinopathie in het specifieke gebied (middendeel/aanhechting) van de pees die ze op de pijnkaart markeerden (Kappa = 0.67, CI 0.54–0.79). Deze studie toonde aan dat er een aanzienlijke overeenstemming was tussen de door de patiënt geselecteerde lokalisatie van de pijn en de diagnose van insertie/middendeel achilles tendinopathie door de arts. Het gebruik van een pijnkaart kan van waarde zijn voor onderzoekers die grote epidemiologische studies uitvoeren of hulp bieden bij zelfdiagnose en adequate triage voor gespecialiseerde zorg.

Echografie is de beelvormingstechniek die de voorkeur geniet in het diagnostische proces van achilles tendinopathie. Ultrasound Tissue Characterization (UTC) is een veelgebruikte, gestandaardiseerde methode om de peesgeometrie bij achilles tendinopathie patiënten te beoordelen. Echter was het nog onbekend of UTC betrouwbaar is voor het meten van de dikte van de achillespees (een verdikte pees is een teken van achilles tendinopathie). In **Hoofdstuk 6** hebben we 50 patiënten met achilles tendinopathie en 50 asymptomatische personen geïncludeerd en de intra- en inter-beoordelaarsbetrouwbaarheid van metingen van de dikte van de achillespees met behulp van UTC beoordeeld. Over het algemeen vonden we uitstekende betrouwbaarheid voor het meten van de peesdikte met UTC. Echter observeerden we significant lagere correlatiecoëfficiënten voor de betrouwbaarheid van diktemetingen in de insertie regio (aanhechting gebied) van de pees. Daarnaast hebben we aangetoond dat diktemetingen van de pees met UTC betrouwbaar kunnen worden vertaald naar conventionele echografie.

In **Hoofdstuk 7** hebben we echografische referentiewaarden verkregen van de dikte van de achillespees (maximale anterieur-posterieure afstand) bij volwassenen zonder achilles tendinopathie en deze referentiewaarden vergeleken met achilles tendinopathie patiënten. In deze grote internationale studie hebben we aangetoond dat de dikte van de achillespees beïnvloed wordt door persoonlijke kenmerken. We vonden dat leeftijd en lengte de grootste invloed hadden op de maximale anterieur-posterieure afstand. Het gemiddelde verschil in peesdikte tussen asymptomatische personen en patiënten met achilles tendinopathie was 2.7 mm voor het middendeel en 1.4 mm voor het insertiegebied. De meerderheid van de achilles tendinopathie patiënten (73%) had een verdikte pees buiten het 95% referentie-interval. Onze nieuwe openbare calculator voor het bepalen van normaalwaarden van de dikte van de achillespees (www.achillestendontool.com) zal onderzoekers en zorgverleners helpen onderscheid te maken tussen echografische kenmerken van achilles tendinopathie en normale morfologische veranderingen.

Prognostische factoren

Aangezien beeldvorming een beperkte prognostische waarde heeft voor patiënten met achilles tendinopathie, is het belangrijk om andere potentiële en patiënt-specifieke prognostische factoren te evalueren. In **Hoofdstuk 8** hebben we 200 patiënten met achilles tendinopathie geïncludeerd die werden behandeld volgens de huidige richtlijnen en hebben we geëvalueerd of socio-economische status (SES) effect had op de ernst van symptomen en de respons op gestandaardiseerde behandeling. We vonden dat er een gemiddeld verschil van 11 punten op de VISA-A vragenlijst was bij een follow-up van 24 weken in het voordeel van patiënten met een hoge socio-economische status vergeleken met patiënten met een lage SES. Dit verschil in VISA-A score is bovendien klinisch relevant. We adviseren zorgverleners om rekening te houden met de socio-economische status van hun patiënten bij het behandelen van achilles tendinopathie. Toekomstig onderzoek

zou zich moeten richten op deze subgroep van tendinopathie patiënten met een lagere socio-economische status om de redenen achter de slechtere behandelingsrespons beter te begrijpen.

In **Hoofdstuk 9** worden de belangrijkste bevindingen van dit proefschrift beschreven in relatie tot elkaar en de bestaande literatuur over achilles tendinopathie. Er worden verschillende aanbevelingen voor toekomstig onderzoek gepresenteerd, met als doel de kennis over de impact, diagnostische beeldvorming en prognose van achilles tendinopathie te vergroten.

PHD PORTFOLIO SUMMARY

Courses	Organizer	ECTS
Erasmus MC - PhD Introduction session (2022)	Erasmus MC Graduate School	0.20
Erasmus MC - Scientific Integrity (2022)	Erasmus MC Graduate School	0.30
Erasmus MC - BROK® (Basic course Rules and Organisation for Clinical researchers) (2022)		1.50
Biomedical Writing for PhD candidates (LTC course) (2023)	Erasmus MC Graduate School, LTC course	1.50
Course - Presentation Skills (2023)		0.40
Introduction in MSK ultrasonography (2023)	NT-e (Dutch Trainingcentre for ultrasonography)	0.40
Erasmus MC - ESP03 Introduction to Data-analysis (2023)		1.00
Ultrasonography of the ankle/lower leg (2023)	NT-e (Dutch Trainingcentre for ultrasonography)	0.60
Course- Ethics, quality and safety in Healthcare (2024)		0.50
Basic Course on Cardiopulmonary Exercise Testing (CPET) (2024)		1.00
Course - Health & Innovation (2024)		1.00
Course - 'Change the system' (2024)		1.00
Course - Exercise Physiology (2024)		1.50
Course - Basics of Sports Medicine (2024)	Stichting Beroepsopleiding tot Sportarts	1.50
Advanced Basic (Paediatric) Life Support (2024)	Haaglanden Medisch Centrum	1.50
Teaching activities and student supervision		
Evaluation Minor Orthopedic Sporttraumatology (2022) *Weekly evaluation with all minor students*		0.80
Supervising SR bachelor students (2023) *Supervising and guiding three bachelor (year 2) students in their systematic review assignment*		0.50
Workgroup Research Students (2023) *Workgroup and education for master students doing their research internship - 'MOZ onderwijs*		0.40
Teaching/supervising minor students (2023) *Teaching/supervising minor students at the outpatient department (multiple students per week)*		3.00
Supervising Master student Stefano Brul (2024)		3.00

Extramural medical disciplines (2024) *Teaching master students about Sports Medicine as extramural specialty*	Leidsche Co-Raad	0.50
Conferences and (oral) presentations		
Oral presentation department meeting (2022) *Presentation on the socio-economic impact of running-related injuries/Achilles Tendinopathy, Impact of Achilles Tendinopathy and REVEAL Study Protocol*		0.10
Oral presentation – REVEAL study protocol – Radio Rijnmond (2022)	Radio Rijnmond	0.20
Oral presentation – REVEAL study protocol & imaging in Achilles tendinopathy – podcast with PhysioGlobal (2022)	PhysioGlobal	0.50
Oral presentation Department meeting (2022) *Presentation on the effect of SES and gender on AT – study protocol*		0.10
Oral Presentation Research visit Micheal Rathleff (2023) *Oral presentation during Research visit of Micheal Rathleff – Presenting PhD overview*		0.10
Oral presentation Soup & Science meeting (2023) *Oral presentation at the Soup & Science meeting (22-06) on the socio-economic impact of AT*		0.20
Oral presentation Department meeting (2023) *Oral presentation Department meeting 03/07 – Preliminary results of normative values on Achilles tendon geometry*		0.10
Oral presentation NT-e (Dutch Trainingcentre for ultrasonography) (2023) *Oral presentation at the NT-e (Dutch Trainingcentre for ultrasonography) on Normative ultrasound values of Achilles tendon geometry*		0.30
Oral presentation at ISTS 2023 (2023) *The impact of socioeconomic status and gender on symptom severity and response to treatment in patients with Achilles tendinopathy*	ISTS (International Scientific Tendinopathy Symposium)	1.00
Oral presentation at ISTS 2023 (2023) *Normative ultrasound values for Achilles tendon thickness in the general population and patients with Achilles tendinopathy: a large international cross-sectional study* Awarded best 2-minute oral poster pitch	ISTS (International Scientific Tendinopathy Symposium)	1.00

Poster presentation at ISTS 2023 (2023) *Measuring ultrasonographic thickness of the Achilles tendon insertion is less reliable than the midportion.*	ISTS (International Scientific Tendinopathy Symposium)	0.50
Oral presentation at Sport Medisch Wetenschappelijk Jaarcongres 2023 (2023) *The impact of socioeconomic status on symptom severity and response to treatment in patients with Achilles tendinopathy* Awarded 2nd price in 'Starpaper' session	VSG (Vereniging voor Sportgeneeskunde)	1.00
Oral presentation at Sport Medisch Wetenschappelijk Jaarcongres 2023 (2023) *Normative ultrasound values for Achilles tendon thickness in the general population and patients with Achilles tendinopathy: a large international cross-sectional study*	VSG (Vereniging voor Sportgeneeskunde)	1.00
Other scientific activities		
Reviewer for BMC Musculoskeletal disorders. (2022) Reviewer for Brazilian Journal of Physical Therapy (2024-now)		0.20
Soup & Science meetings (2023) *Biweekly presentations & discussion on research at the department of Orthopedics & Sports Medicine*		1.00
Evidence Based Espresso (2023) *Weekly Journal Club*		1.00
Regionaal Opleidingssymposium (OOR) (2024) *Conference attendance including multiple workshops*		0.50
Total Workload in ECTS		**30.9**

LIST OF PUBLICATIONS

This thesis

de Vos RJ, Silbernagel KG, Malliaras P, **Sleeswijk Visser TSO** et al.,

ICON 2023—International Scientific Tendinopathy Symposium Consensus: the core outcome set for Achilles tendinopathy (COS-AT) using a systematic review and a Delphi study of healthcare professionals and patients

Submitted for publication

Sleeswijk Visser TSO, O'Neill S, Hébert-Losier K, Eygendaal D, de Vos RJ

Normative values for calf muscle strength-endurance in the general population assessed with the Calf Raise Application: A large international cross-sectional study

Submitted for publication

Sleeswijk Visser TSO, van der Vlist AC, van Oosterom RF, et al.,

Impact of chronic Achilles tendinopathy on health-related quality of life, work performance, healthcare utilisation and costs.

BMJ Open Sport & Exercise Medicine 2021;7:e001023

Sleeswijk Visser TSO, van Es EM, Meuffels DE, Verhaar JAN and de Vos RJ

Standardized pain mapping for diagnosing Achilles tendinopathy.

Journal of Science and Medicine in Sport, Volume 25, Issue 3, 2022, Pages 204-208

Sleeswijk Visser TSO, Brul SL, O'Neill S, van Es EM, Eygendaal D and de Vos RJ

Measuring Ultrasonographic Thickness of the Achilles Tendon Insertion Is Less Reliable Than the Midportion in Healthy Tendons and Patients With Tendinopathy.

Journal of Ultrasound in Medicine, 2024, 43: 713-722

Sleeswijk Visser TSO, O'Neill S, Colaris J, Eygendaal D, de Vos RJ

Normative ultrasound values for Achilles tendon thickness in the general population and Achilles tendinopathy patients: a large international cross-sectional study

Scandinavian Journal of Science & Medicine in Sports. 2024; 34:e14665

Sleeswijk Visser TSO, Brul S, Deng J, Bonsel J, van Es E, Eygendaal D and de Vos RJ

Low socioeconomic status is associated with worse treatment outcomes in patients with Achilles tendinopathy.

British Journal of Sports Medicine 2024 Apr 3:bjsports-2023-107633. Epub ahead of print

Other publications

Sleeswijk Visser TSO, van Middelkoop M, Fokkema T, de Vos RJ

The socio-economic impact of running-related injuries: A large prospective cohort study. *Scandinavian Journal of Medicine and Science in Sports. 2021 Oct;31(10):2002-2009. Epub 2021 Jul 11.*

Le CY, **Sleeswijk Visser TSO**

The fear of developing knee OA after a traumatic knee injury - and how to prevent it?

British Journal of Sports Medicine 2023;57:1579-1580

Sleeswijk Visser TSO, de Vos RJ

Corticosteroïd injecties voor tendinopathie - back to the future?

Sport & Geneeskunde, december 2022

Sleeswijk Visser TSO, van Linschoten R, Vicenzino B, Weir A, de Vos RJ

Terminating corticosteroid injection in tendinopathy? Hasta la Vista Baby

Journal of Orthopaedic & Sports Physical Therapy. August 11, 2023 Volume 54 Issue 1 Pages 10-13

DANKWOORD

Graag wil ik via deze weg iedereen bedanken die mij op welke manier dan ook geholpen heeft om dit proefschrift te verwezenlijken. Allereerst veel dank aan alle **patiënten** die in grote getalen tijd hebben vrijgemaakt om deel te nemen aan de verschillende onderzoeken.

Robert-Jan, ontzettend bedankt voor de rol die jij als copromotor hebt gehad. Jouw enthousiasme voor onderzoek en de achillespees in het bijzonder werkten aanstekelijk. Je deur stond altijd open en soms hoefde ik maar met mijn ogen te knipperen of je had alweer naar een manuscript of revisie gekeken. Je hebt ervoor gezorgd dat ik enorm positief op de afgelopen periode terugkijk en hopelijk werken we in de toekomst nog eens samen.

Denise, erg veel dank dat jij mij de mogelijkheid hebt geboden om dit promotietraject te starten. Je hebt de functie van 'PhANIOS' in het leven geroepen ik waar ik nu de vruchten van mag plukken. Het is inspirerend geweest om te zien hoe jij als afdelingshoofd leiding geeft en betrokken bent bij iedereen op de afdeling.

Geachte Prof.dr. E.H.G. Oei, Prof.dr. J. Zwerver en Dr. M. van Middelkoop en de overige leden van de **promotiecommissie** bedankt voor jullie interesse, tijd en aandacht die jullie aan dit proefschrift hebben besteed. Ik hoop in de toekomst nog eens vaker van gedachten te wisselen over wetenschappelijk vraagstukken in de sportgeneeskunde.

Verder veel dank aan de **Erasmus MC Foundation** en het **Erasmus Trusfonds.** Jullie bijdrages zijn cruciaal geweest voor de totstandkoming van dit proefschrift. Ook de verschillende sponsoren wil ik graag bedanken voor het mede mogelijk maken van het drukken van dit proefschrift; de afdeling **Orthopedie & Sportgeneeskunde** van het **Erasmus MC,** de **Erasmus University Rotterdam Graduate School, Xcelsior, van Dinter Den Haag, De Gangmakerij, LINK, LEUK Orthopedie, Bauerfeind, Push, ChipSoft, ABN AMRO** en het **HMC Wetenschapsfonds.**

Robert en **Peter,** bedankt dat jullie mij als semi-arts de eerste stappen binnen de sportgeneeskunde hebben laten zetten, en ik kijk erg uit naar onze samenwerking de komende jaren.

Joep, Victor, Anne, Stef, Yoren en **Floris** bedankt voor jullie vriendschap, het is mooi om te zien hoe deze al vanaf de collegebanken in jaar 1 voortduurt. Ik hoop op nog veel borrels, etentjes, weekenden weg of poëtische avonden. Extra leuk dat jij, **Stef,** er vandaag als paranimf bij bent.

Ralph en **Boris,** als mede geneesco's waren jullie al vroeg met onderzoek bezig en dit werkte zeker stimulerend. Mooi dat jij, **Ralph,** mij vandaag als paranimf ondersteunt.

Annet en **Simone,** bedankt dat ik altijd bij jullie binnen kon lopen als ik iets niet wist en hoe jullie alle promovendi op de afdeling ondersteunen.

Max, Eline, Floris, Mark, Noor, Fleur, Myrthe, Joshua, Merel, Britt, Derek, Niels en iedereen van NC-424 bedankt voor alle koffies die ik uit prachtige mokken samen met jullie heb mogen nuttigen, alle dilemma's, gedeelde 'wetenschappelijke' broodjes kroket en uiteraard de potjes tafelvoetbal!

Karin, Peter en **Bill**, dank voor jullie enthousiasme en volharding in misschien wel het langstlopende project van dit proefschrift. Het was een hobbelige, lange en leerzame weg.

Papa, Mama, dank voor de onvoorwaardelijke steun en support en de liefde voor sport en bewegen die jullie mij hebben meegegeven. Samen met **Myrthe** en **Axel** hebben we de afgelopen jaren een aantal onvergetelijke reizen mogen meemaken, waarvan ik hoop dat er nog meer volgen. Het is ontzettend fijn om te weten dat ik altijd op jullie kan terugvallen.

Opi, Opa en Oma, erg bijzonder om dit proefschrift ook aan jullie te mogen overhandigen. Dank voor al jullie liefde en interesse.

Myrthe, wat ben ik elke dag nog steeds blij dat ik jou meer dan 8 jaar geleden tegen het lijf ben gelopen. Op de momenten dat ik zuchtend en steunend achter de laptop zat of SPSS vervloekte was jij er altijd om me op te vrolijken. Ik weet zeker dat we samen nog veel avonturen zullen meemaken.

CURRICULUM VITAE

Tjerk Sleeswijk Visser is geboren op 18-05-1995 in Voorburg. Na zijn middelbare schooltijd, starte hij met de studie Geneeskunde in Leiden. Zijn masterscriptie voerde hij uit onder begeleiding van dr. Robert-Jan de Vos aan het Erasmus MC. Na het succesvol afronden van de studie Geneeskunde deed hij klinische ervaring op als ANIOS cardiologie. In augustus 2022 startte hij zijn promotietraject op de afdeling Orthopedie en Sportgeneeskunde van het Erasmus MC, waar hij door Prof. dr. Denise Eygendaal en Dr. Robert-Jan de Vos werd begeleid. Dit combineerde hij met wekelijkse werkzaamheden als ANIOS orthopedie. Per 1 januari 2024 is hij in opleiding tot sportarts aan het Haaglanden Medisch Centrum. Hij woont samen met zijn vriendin Myrthe de Vos in Den Haag.