Ultrasound evaluation of Achilles enthesis in inflammatory and non-inflammatory processes: a systematic review and meta-analysis

N. Desai[1], J.F. Baker[1,2], J. Bucci[3], E.Y. Kissin[3]

[1]Department of Medicine, University of Pennsylvania, Philadelphia, PA;
[2]Corporal Michael J. Crescenz VA Medical Center, Philadelphia, PA;
[3]Department of Medicine, Boston University Medical Center, Boston MA, USA.

Abstract

Objective

Ultrasound evaluation of the Achilles tendon has been utilised to assess involvement at the entheses in the setting of various inflammatory, metabolic, and mechanical processes. The purpose of this systematic review was to evaluate the differences in ultrasound findings at the Achilles enthesis between inflammatory tendinopathy (IT) versus non-inflammatory tendinopathy (NIT).

Methods

A review of all studies involving ultrasound evaluation of IT or NIT (mechanical or metabolic) affecting the Achilles enthesis was performed by searching the Embase, PubMed and Medline databases from start until October 2020. We assessed study quality and extracted summary data from each individual study. We used random-effects meta-analysis to determine the average proportion of affected anatomic sites across all studies for each abnormality, weighting the analysis based on the size of each individual study.

Results

Achilles enthesis thickening was more frequent in the symptomatic IT (sIT) group (37.8%) compared to the unspecified IT (25%), NIT (11.2%) and healthy control (2.7%) groups. Increased vascularity at the enthesis was more common in the NIT (23.4%) group compared to the IT (9%), sIT (8.6%) and healthy control (0.1%) groups. Erosions were more common among the IT (17.3%) and sIT (14%) groups compared to the NIT (2.2%) and healthy controls (0.3%) groups.

Conclusion

While Achilles enthesis thickening, Doppler signal and calcaneal erosions discriminate IT from healthy subjects, erosions are more likely to distinguish IT from NIT than thickening or Doppler signal. Additional study is needed to quantify the diagnostic performance of ultrasound at this location given the frequency of abnormalities in NIT.

Key words

inflammation, meta-analysis, tendinopathy, ultrasonography, enthesitis, Achilles tendon

Nancy Desai, MD
Joshua F. Baker MD, MSCE
Justin Bucci, MD
Eugene Y. Kissin, MD

Please address correspondence to:
Eugene Y. Kissin,
Division of Rheumatology,
Department of Medicine,
Boston University School of Medicine,
72 East Concord Street, Evans 501,
Boston, MA 02118, USA.
E-mail: eukissen@bu.edu

Received on October 6, 2021; accepted in revised form on February 9, 2022.

Competing interests: none declared.

Introduction

Ultrasound (US) evaluation has become increasingly popular in the assessment of entheses in participants with suspected underlying inflammatory, metabolic, and mechanical processes (1, 2). The enthesis is the anatomical region where tendons, ligaments, or articular capsules integrate into bone. To improve consistency of scoring, the enthesis has been designated as within 2 mm of the bony cortex (3-6) although this does not correspond to any known anatomic or physiologic demarcation. Typically, an enthesis without underlying pathology in adults should be avascular and without erosions (7-9). Inflammation of this region, known as enthesitis, can be a clinical manifestation of underlying inflammatory disorders such as spondyloarthropathies (10). Traumatic, mechanical overuse and metabolic conditions can also cause pathologic changes at the enthesis (11, 12). Among all aetiologies of enthesitis, one of the most commonly involved sites is the Achilles tendon enthesis (13-15).

Traditionally, clinical evaluation has played a primary role in identifying enthesitis. However poor interobserver reliability and lack of accuracy in its diagnosis has necessitated the development of several scoring systems (16). Consequently, alternate imaging modalities such as magnetic resonance imaging (MRI) and US have also become more frequently utilised to help address these shortcomings. Compared to MRI, US has several practical advantages including relatively low cost, ease of access to multiple anatomical sites, as well as increased sensitivity and specificity for peripheral entheses lesions (17). In order to analyse lesions, a majority of studies in this review utilised the OMERACT (3, 6) or GUESS (18) criteria for US lesions to help identify active inflammatory and structural lesions of enthesitis in addition to changes secondary to prior inflammation (19).

The objective of this systematic review was to compare the rates of reported abnormalities in the Achilles enthesis in patients with established systemic inflammatory conditions, as compared to conditions not related to systemic autoimmune diseases, such as metabolic or mechanical abnormalities of an enthesis (20). Characterising the differences in US findings in inflammatory (IT), noninflammatory (NIT) and healthy controls can be helpful in strengthening the role of US as a diagnostic tool.

Materials and methods

This systematic review was reported in accordance with PRISMA guidelines (21).

Literature search

In collaboration with a medical librarian, a search strategy was developed. We systematically searched the Embase, PubMed, and Medline databases from start until October 2020 using mesh terms ((“Fascia” OR “Achilles Tendon” OR “Calcaneus”)) AND ultrasound AND (“Arthritis, Reactive” OR “Spondylarthritis” OR “Spondyloarthropathies” OR “Arthritis, Psoriatic” OR “Arthritis, Rheumatoid” OR “Spondylitis, Ankylosing” OR “Inflammatory Bowel Diseases” OR “Psoriasis” OR “Obesity” OR “Diabetes Mellitus” OR “Metabolic Diseases” OR “Tendinopathy” OR “Enthesopathy” OR “Stress, Mechanical”).

Selection of studies

Studies that were identified as potentially relevant were initially screened by title and abstract followed by a review of full text articles to assess for inclusion eligibility. Studies were limited to English language, human studies. One author [N.D.] applied additional predefined exclusion criteria, which included poster or conference abstracts, case reports, limited case series with less than 10 participants, lack of original data, studies not focused on Achilles tendon enthesis and studies in children. Studies that did not report tendon abnormalities by individual parameter (*i.e.* thickness, vascularity, erosions) or did not report abnormalities as a proportion of tendons or participants were also excluded. The identification process and reasons for exclusions are further detailed in Figure 2. An additional author [J.B.] performed blinded secondary review of the articles and any differences were then adjudicated by a third reviewing author [E.K.].

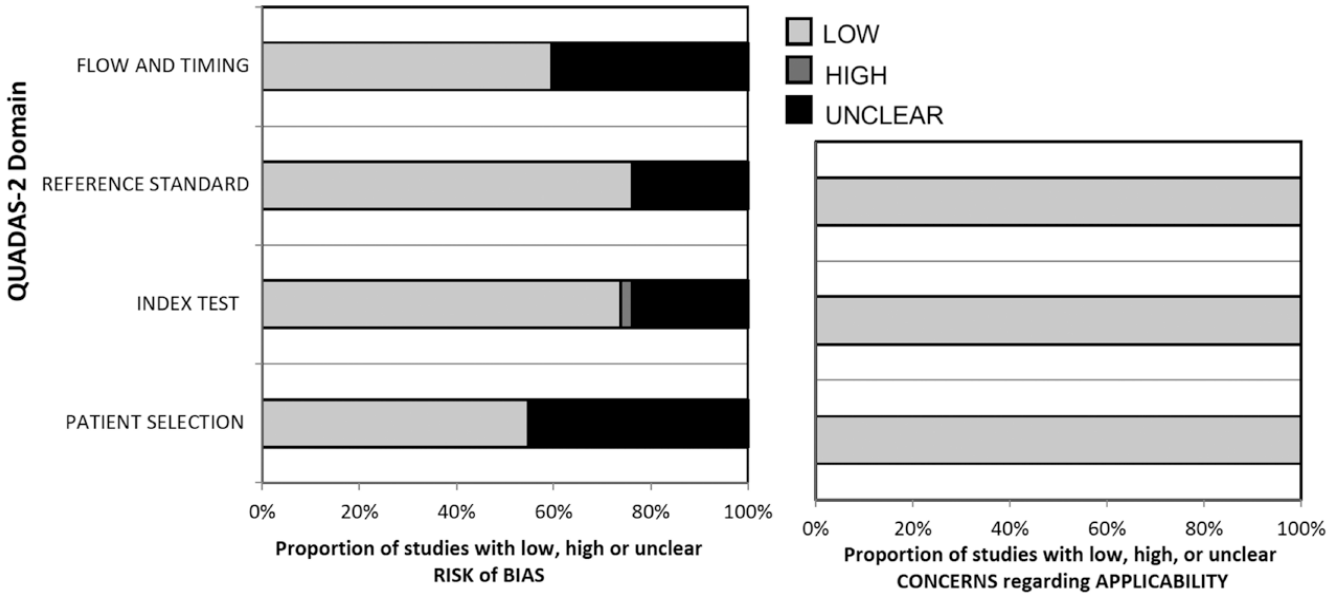

Fig. 1. Assessment of study using the QUADAS-2 tool (18, 19). QUADAS: Quality Assessment of Diagnostic Accuracy Studies.

Data extraction

A predefined data form was created to extract US findings from the included studies. Specifically, these findings were proportion of tendons assessed with abnormal tendon thickness, presence of Doppler signal, presence of erosions at the enthesis, and mean Achilles enthesis thickness. To help focus the scope of this review, additional US lesions of enthesitis such as hypoechogenecity, presence of enthesophytes or calcifications were not included as these lesions had not previously been thought to distinguish inflammatory from non-inflammatory disease. Hypoechoic lesions are well described due to mucoid degeneration and focal tears (22-24), enthesophytes are commonly found due to age, and in fact, enthesophytes at the Achilles enthesis were found to be the most common elementary lesion found in asymptomatic healthy adults (25-27). Indeed, for the Belgrade Ultrasound Enthesis Score, discrimination between spondylarthritis related enthesitis and mechanical enthesitis were best achieved by scoring Doppler or erosions as 4 points, while enthesophytes, calcifications or hypoechoic lesions only scored 1 point (28).

Assessment of study quality

All the included studies were critically assessed utilising the QUADAS-2 tool, which was developed to assess diagnostic accuracy studies (29, 30). The results from this assessment are included in the Supplementary file (Tables S7-S8). Figure 1 demonstrates the proportion of included studies with a low, high, or unclear risk of bias as well as the proportion of studies with low, high, or unclear concerns regarding applicability to this systematic review. There was one included study that had a high risk of bias and no studies with a high concern regarding applicability.

Statistical analysis

For our data analysis, we used random-effects meta-analysis to determine the average proportion of affected anatomic sites across all studies within each subgroup (separated by IT, NIT, healthy controls, spondyloarthropathy etc.) for each abnormality. We then weighted the analysis based on the size of each individual study (per location assessed). The effect of heterogeneity was quantified using forest plots and the I^2 statistic (31). We assumed that estimates could vary across studies related to real differences in study design as well as sampling error.

Results

Our initial database search resulted in 3034 publications. After screening for language, duplicates, and other exclusion criteria in the title and abstract, 185 potentially relevant articles remained for full-text review. Ultimately, 42 publications were included in the final review. A summary of the results comparing prevalence of abnormal thickness, vascularity and erosions can be seen in Figure 3. Further data on individual studies including heterogeneity measures are included in Supplementary Tables S1-S11.

Characteristics of the included studies

All 42 studies reported on the use of ultrasound to evaluate the Achilles enthesis in participants with underlying inflammatory, mechanical, or metabolic conditions as well as healthy control subjects. Several of the studies included more than one of these groups. A total of thirty-two studies included systematic inflammatory conditions, specifically 15 studies on psoriatic arthritis, 11 on undifferentiated spondyloarthropathy, 2 studies on reactive arthritis, 2 with IBD- associated arthritis, 4 on rheumatoid arthritis and 1 with systemic lupus erythematous. Fifteen of the studies included participants with underlying metabolic or mechanical disorders and 19 studies on healthy controls. The age of participants in the included studies ranged from 20 to 75 years. All the studies utilised ultrasound technology for evaluation at the Achilles enthesis. In terms of ultrasound findings evaluated

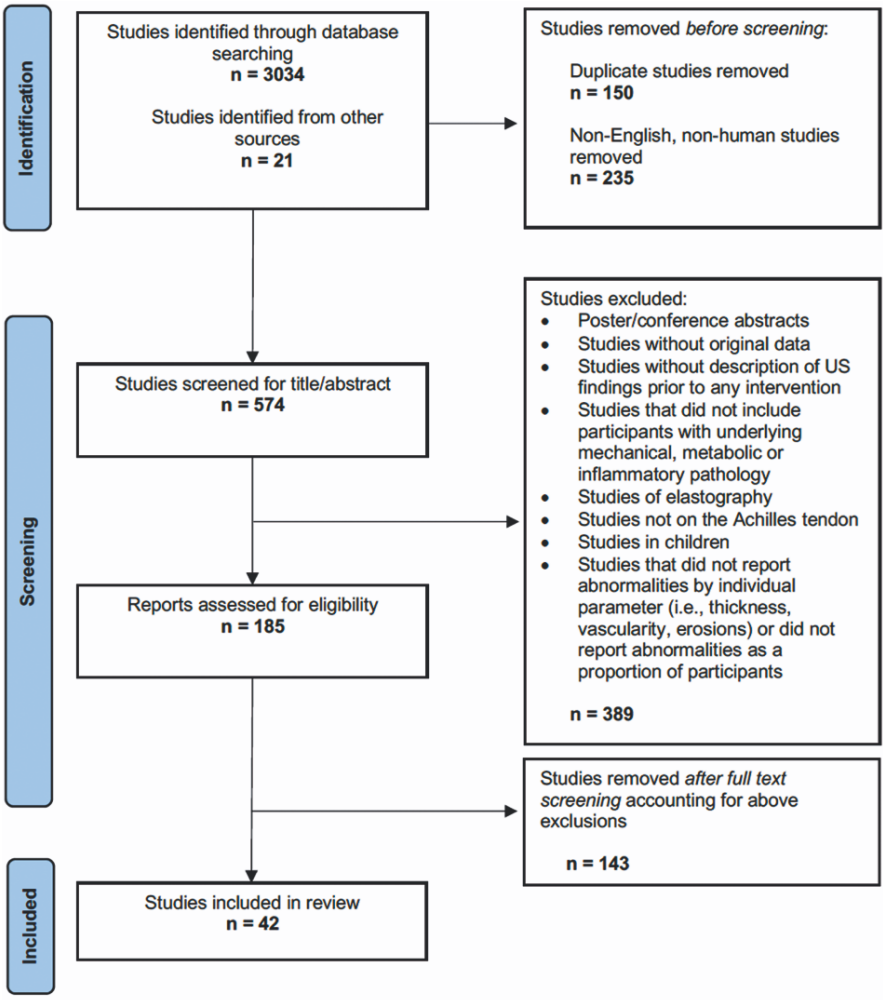

Fig. 2. PRISMA flow diagram for research strategy and study selection and inclusion (17). PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses.

by the studies, 31 investigated tendon thickness, 30 investigated vascularity, and 33 studies investigated erosions. While there was some variation in the definition of increased thickness, most studies defined increased thickness at the Achilles enthesis as >5.29 mm per OMERACT criteria and measured thickness at the anterior-posterior diameter (3). Studies also varied in their assessment of vascularity and subjective reporting of pain and clinical tenderness to palpation.

Increased thickness at the Achilles enthesis

Supplementary Table S4 provides a detailed description of included studies that evaluated differences in enthesis thickness. Among all participants with IT, 25.0% (95% confidence interval 20.3–29.6%) were found to have abnormal thickening at the Achilles enthesis in comparison to 11.2% (95% CI 4.6–17.9%) of participants with NIT and 2.7% (95% CI 1.3–4.1%) of healthy controls. (Number of subjects in IT=1,669, NIT=211, healthy controls=434, number of studies in IT=22, NIT = 6, healthy controls=12).

When identifying studies that reported results based on number of tendons, thickening of the Achilles tendon was found in 23.1% (95% CI 18.5–27.6%) of participants with IT in comparison to 24.6% (95% CI 8.8–40.4%) of participants with NIT and 0.1% (95% CI -0.1–0.4%) of healthy controls. In the subgroup of IT participants specified as having symptomatic Achilles tendinopathy (sIT), thickening of the enthesis was found in 37.8% (95% CI 13.7–61.9%). (Number of subjects in IT=1624, sIT=137, NIT=211, healthy controls=290, number of studies in IT=21, sIT=4, NIT=6, healthy controls=9). Studies that published specific measurements of Achilles enthesis thickness reported an average thickness of 5.23 mm in underlying IT groups (n=147, studies=4), 5.94 mm in symptomatic IT groups (n=31, studies=2), 5.26 mm in NIT groups (n=249, studies=6) and 4.23 mm in healthy participants (n=210, studies=5). (Fig. 3 and 4).

Increased vascularity at the Achilles enthesis

Supplementary Table S5 lists studies that examined vascularity at the Achilles enthesis. Among all participants with IT, 9.0% (95% CI 6.8–11.1%) were found to have increased vascularity at the Achilles enthesis in comparison to 23.4% in NIT (95% CI 10.0–36.9%) and 0.1% in healthy control groups (95% CI 0–0.3%). In the subgroup of IT participants specified as having abnormal vascularity per updated OMERACT criteria (6), 7.2% (95% CI 1.8–16.0%) were found to have abnormal findings. There was not specifically defined data regarding Doppler signal within 2 mm of enthesis attachment in the NIT group. In the subgroup of IT participants specified as having sIT, increased vascularity of the enthesis was found in 8.6% (95% CI 0-17.6%). (Number of subjects in IT=1731, sIT=129, NIT=320, healthy controls=499, number of studies in IT=22, sIT=4, NIT=10, healthy controls=14) (Fig. 3).

Increased prevalence of erosions at the Achilles enthesis

Supplementary Table S6 lists studies that examined erosions at the Achilles enthesis. When comparing the incidence of erosions, the rate in IT was 17.3%, (95% CI 12.0–22.6%). In contrast, erosions were noted only in 2.2% of NIT participants (95% CI 0.1–4.3%) and 0.3% (95% CI 0-0.7%) of healthy controls. In the subgroup of IT participants specified as having sIT, erosions at the enthesis were found in 14.0% of the participants (95% CI 6.7–21.3%). (Number of subjects in IT=2071, sIT=256, NIT=221, healthy controls=564, number of studies in IT=30, sIT=8, NIT=7, healthy controls=17) (Fig. 3).

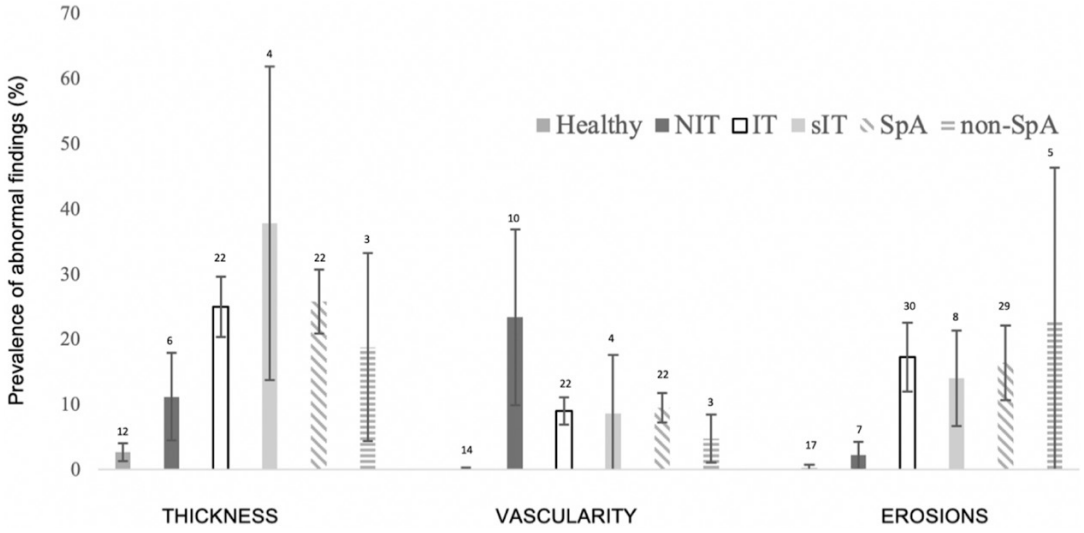

Fig. 3. Incidence (%) of abnormal thickness, vascularity, and erosions at the Achilles enthesis across the study design.
NIT: non-inflammatory tendinopathy; IT: inflammatory tendinopathy; sIT: symptomatic inflammatory tendinopathy; SpA: spondyloarthropathy; non-SpA: non-spondyloarthropathy.
*Error bars represent 95% confidence intervals, number of studies represented above each column.

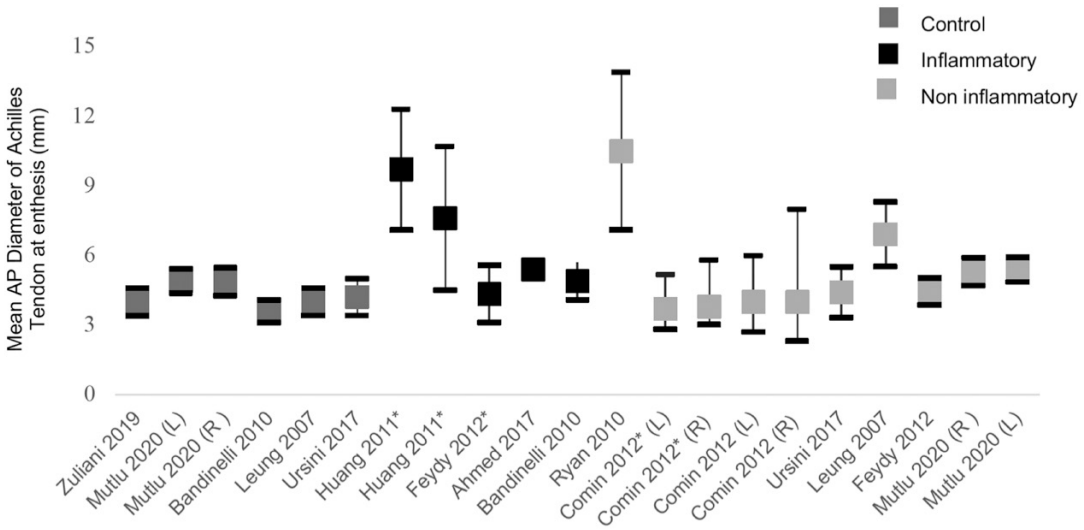

Fig. 4. Mean anterior-posterior diameter of the Achilles tendon reported at the enthesis across the study design in healthy controls, inflammatory and non-inflammatory groups.
L: left Achilles tendon data;
R: right Achilles tendon data.
*Indicates a study focusing only on symptomatic tendons in inflammatory disease.

Prevalence of Achilles enthesis thickness, vascularity, and erosions in spondyloarthropathy vs. other inflammatory conditions (i.e. RA, SLE)

In those with spondyloarthropathy (SpA), a subgroup of IT, Achilles enthesis thickening was noted in 25.8% (95% CI 20.8–30.7%) compared to 18.8% in the non-SpA group (95% CI 4.3–33.2). (Number of subjects in SpA=1550, non-SpA=119, number of studies in SpA=22, non-SpA=3). In the IT and SpA subgroup, increased vascularity was noted in 9.5% (95% CI 7.2-11.8%) compared to 4.8% (95% CI 1.1–8.5%) in the non-SpA group. (Number of subjects in SpA=1,609, non-SpA=122, number of studies in SpA=22, number of studies in non-SpA=3). Incidence of erosions was 16.4% (95% CI 10.7–22.1%) in the subgroup of SpA compared to 22.9% (95% CI 0–46.4%) in the non-SpA group. (Number of subjects in SpA=1,890, non-SpA=181, number of studies in SpA=29, non-SpA=5) (Fig. 3).

Discussion

In this systematic review and meta-analysis, we compared ultrasound findings at the Achilles enthesis among IT, NIT, and healthy control groups as well as the sIT and SpA subgroups. We found important differences between these groups when looking at these parameters. For example, abnormal Achilles enthesis thickness and the presence of erosions were more common in the sIT subgroup, compared to NIT and healthy groups. These lesions may be valuable in differentiating inflammatory conditions *versus* non-inflammatory conditions. However, vascularity was not a good discriminator of NIT and IT. Overall, these observations suggest that, while promising, the quantification of the value of ultrasound in distinguishing between IT and NIT requires further study. Studies directly comparing these two entities and aimed at quantifying the diagnostic test characteristics may provide further insight.

Given the low incidence of thickening in healthy controls, enthesis thickening is not generally thought to be a benign phenomenon (25, 27, 32-46) although this assertion has been called into question by several recent studies (9, 47, 48). In our review, we found a substantially increased prevalence of Achilles enthesis thickening in the IT participants compared to NIT participants and healthy controls in studies report-

ing abnormality as a proportion. When stratifying for patients with sIT, an even greater disparity was found between the IT and NIT groups. In the subgroup of studies that reported mean Achilles enthesis thickness in mm, thickness was also highest in the sIT group, though there were minimal differences between IT and NIT groups overall. Surprisingly, we noted similar rates of entheseal thickening between the SpA and non-SpA groups which was unexpected given the higher prevalence of entheseal involvement in patients with SpA. Achilles tendon thickening is a time-dependent process and consideration of disease duration and associated clinical features will improve the diagnostic value of this US lesion.

Overall, we noted that few published studies have directly examined the Achilles enthesis in mechanical and metabolic tendinopathies compared to inflammatory tendinopathy. A much more significant portion of studies evaluating mechanical tendinopathy have focused on Achilles tendon thickening at the midportion. This is most likely explained by the fact that the midportion of the Achilles is an especially vulnerable area to injury in the setting of poor vascular supply (49, 50). We did not include studies focused on the Achilles tendon midportion in this review to allow for greater discrimination in our results.

The presence of erosions in non-inflammatory conditions have been noted previously, although they have been observed in greater frequency in underlying inflammatory IT (51). Our findings corroborated this, as all the IT groups had a higher incidence of erosions in comparison to either NIT or healthy controls. We did find a relative lower incidence of erosions in the SpA subgroup in comparison to the non-SpA group. While there have been other studies that showed more erosive disease in RA in comparison with seronegative disease (52), we would not suggest drawing any conclusions based on the numerical difference between these groups as the confidence intervals for the data in each group overlapped. The incidence of erosions in healthy controls was nearly zero. Therefore, evaluation for more chronic changes such as presence of erosions is more likely to specify underlying inflammatory pathology compared to abnormal thickness or increased vascularity based on our results.

Surprisingly, increased Doppler signal was commonly reported in NIT and was similar in studies looking only at symptomatic tendons with underlying inflammatory conditions or spondyloarthropathy. Our finding differs from previous studies. For example, D'Agostino *et al*. noted that abnormal vascular flow detected by US within entheseal lesions was specific for SpA and was less prevalent in patients with mechanical low back pain and RA (54). Similar findings were reported by Baccouche *et al*. (55). Other studies have also described increased vascularity at other anatomical sites including the knee which can be used to distinguish inflammatory versus non-inflammatory conditions using colour Doppler ultrasound (56). Vascularity in NIT may be explained by abnormal tendon remodelling as part of the healing process or a response to mechanical stress stimuli (53). Vascularity in IT however, has been histologically linked to osteitis, increased osteoclast formation and therefore suggesting a possible link between vascularity and erosion formation (57). This potentially important detail would benefit from evaluation in future studies.

Additionally, we did not find meaningful differences in the incidence of abnormal Doppler signal between the non-SpA, SpA, IT, or symptomatic IT groups. There was also not a significant difference when looking only at studies utilising updated OMERACT criteria of Doppler signal within 2 mm of the bony cortex in IT. However, the studies evaluating non-inflammatory conditions did not specify whether the Doppler signal was necessarily within 2 mm of the cortical insertion. The presence of vascularity at the Achilles enthesis in healthy subjects was found to be rare, almost zero percent. This was an expected finding as the enthesis is an avascular structure in adults relying on blood supply from nearby periosteal arteries and bone marrow (15, 58).

Several systematic reviews have looked at the application of ultrasound at the Achilles enthesis in various underlying inflammatory conditions alone, with seronegative spondyloarthropathies being one of the most commonly studied (59). The utilisation of US to evaluate for disease activity has also been previously broached in several studies but results have been mixed regarding the association between abnormal thickening at the enthesis and disease activity (19, 60-62). To our knowledge, this is the first systematic review directly comparing the ultrasound findings at the Achilles enthesis between non-inflammatory and inflammatory groups. Given our results, the utilisation of ultrasound technology in the clinical setting may be more fruitful in differentiating underlying aetiology when directly comparing symptomatic patients rather than as a method to detect disease activity in asymptomatic inflammatory tendinopathies.

There were several limitations to this systematic review that may have affected the scope of our results. By including a myriad of underlying inflammatory conditions, a varied distribution of participant populations was grouped together. This may have contributed to increased heterogeneity of the results in the IT group. We addressed this by separating these groups in sub-group analyses. In addition, while many of the studies utilised the OMERACT or GUESS criteria to define characteristics at the enthesis, there was some variability in the definition of Achilles tendon thickness, vascularity, and erosions between several studies. This may also have contributed to heterogeneity between studies. By including both mechanical and metabolic conditions under the non-inflammatory category, underlying conditions thought to have some degree of low-grade underlying systematic inflammation such as chronic kidney disease and diabetes mellitus were included in this group (63-65). As detailed previously, other US lesions such as hypoechogenicity, enthesophytes and calcifications were excluded from this study which may also be regarded as a limitation of this study.

Conclusions

The presence of erosions or tendon thickening at the Achilles enthesis may

be helpful US abnormalities to help differentiate the underlying pathology in symptomatic patients. However, there remains a need for further studies aimed at directly comparing findings in inflammatory and non-inflammatory conditions. As might be expected, these utility of US abnormalities may not be as clinically useful for diagnosis of IT when looking at asymptomatic patients.

References

1. KLAUSER AS, TAGLIAFICO A, ALLEN GM *et al*.: Clinical indications for musculoskeletal ultrasound: a Delphi-based consensus paper of the European Society of Musculoskeletal Radiology. *Eur Radiol* 2012; 22(5): 1140-8. https://doi.org/10.1007/s00330-011-2356-3
2. MCALINDON T, KISSIN E, NAZARIAN L *et al*.: American College of Rheumatology report on reasonable use of musculoskeletal ultrasonography in rheumatology clinical practice. *Arthritis Care Res* (Hoboken) 2012; 64(11): 1625-40. https://doi.org/10.1002/acr.21836
3. WAKEFIELD RJ, BALINT PV, SZKUDLAREK M *et al*.: Musculoskeletal ultrasound including definitions for ultrasonographic pathology. *J Rheumatol* 2005; 32(12): 2485-7.
4. APOSTOLAKOS J, DURANT TJ, DWYER CR *et al*.: The enthesis: a review of the tendon-to-bone insertion. *Muscles Ligaments Tendons J* 2014; 4(3): 333-42.
5. SUDOŁ-SZOPIŃSKA I, KWIATKOWSKA B, PROCHOREC-SOBIESZEK M, MAŚLIŃSKI W: Enthesopathies and enthesitis. Part 1. Etiopathogenesis. *J Ultrason* 2015; 15(60): 72-84. https://doi.org/10.15557/jou.2015.0006
6. BALINT PV, TERSLEV L, AEGERTER P *et al*.: Reliability of a consensus-based ultrasound definition and scoring for enthesitis in spondyloarthritis and psoriatic arthritis: an OMERACT US initiative. *Ann Rheum Dis* 2018; 77(12): 1730-5. https://doi.org/10.1136/annrheumdis-2018-213609
7. BENJAMIN M, MCGONAGLE D: The enthesis organ concept and its relevance to the spondyloarthropathies. *Adv Exp Med Biol* 2009; 649: 57-70. https://doi.org/10.1007/978-1-4419-0298-6_4
8. CHANG EY, CHEN KC, HUANG BK, KAVANAUGH A: Adult inflammatory arthritides: what the radiologist should know. *Radiographics* 2016; 36(6): 1849-70. https://doi.org/10.1148/rg.2016160011
9. DI MATTEO A, FILIPPUCCI E, CIPOLLETTA E *et al*.: How normal is the enthesis by ultrasound in healthy subjects? *Clin Exp Rheumatol* 2020; 38(3): 472-8.
10. LI CA, KIM HO, LEE SY, LEE SI: Assessment of Achilles enthesitis in the spondyloarthropathies by colour Doppler energy ultrasound in the context of the 'enthesis organ'. *Scand J Rheumatol* 2010; 39(2): 141-7. https://doi.org/10.3109/03009740903273197
11. ABATE M, SCHIAVONE C, SALINI V, ANDIA I: Occurrence of tendon pathologies in metabolic disorders. *Rheumatology* (Oxford) 2013; 52(4): 599-608. https://doi.org/10.1093/rheumatology/kes395
12. FALSETTI P, CONTICINI E, BALDI C, BARDELLI M, CANTARINI L, FREDIANI B: Diffuse peripheral enthesitis in metabolic syndrome: a retrospective clinical and power Doppler ultrasound study. *Reumatol Clin* (Engl Ed). 2021 Feb 24 https://doi.org/10.1016/j.reuma.2020.12.005
13. KAELEY GS, EDER L, AYDIN SZ, GUTIERREZ M, BAKEWELL C: Enthesitis: A hallmark of psoriatic arthritis. *Semin Arthritis Rheum* 2018; 48(1): 35-43. https://doi.org/10.1016/j.semarthrit.2017.12.008
14. BENJAMIN M, TOUMI H, RALPHS J, BYDDER G, BEST T, MILZ S: Where tendons and ligaments meet bone: Attachment sites ('entheses') in relation to exercise and/or mechanical load. *J Anat* 2006; 208(4): 471-90. https://doi.org/10.1111/j.1469-7580.2006.00540.x
15. BRAUN J, KHAN MA, SIEPER J: Enthesitis and ankylosis in spondyloarthropathy: what is the target of the immune response? *Ann Rheum Dis* 2000; 59(12): 985-94. https://doi.org/10.1136/ard.59.12.985
16. KRISTENSEN S, CHRISTENSEN JH, SCHMIDT EB *et al*.: Assessment of enthesitis in patients with psoriatic arthritis using clinical examination and ultrasound. *Muscles Ligaments Tendons J* 2016; 6(2): 241-7. https://doi.org/10.11138/mltj/2016.6.2.241
17. MCGONAGLE D, MARZO-ORTEGA H, O'CONNOR P *et al*.: The role of biomechanical factors and HLA-B27 in magnetic resonance imaging-determined bone changes in plantar fascia enthesopathy. *Arthritis Rheum* 2002; 46(2): 489-93. https://doi.org/10.1002/art.10125
18. BALINT PV, KANE D, WILSON H, MCINNES IB, STURROCK RD: Ultrasonography of entheseal insertions in the lower limb in spondyloarthropathy. *Ann Rheum Dis* 2002; 61(10): 905-10. https://doi.org/10.1136/ard.61.10.905
19. FALCAO S, CASTILLO-GALLEGO C, PEITEADO D, BRANCO J, MARTIN MOLA E, DE MIGUEL E: Can we use enthesis ultrasound as an outcome measure of disease activity in spondyloarthritis? A study at the Achilles level. *Rheumatology* (Oxford) 2015; 54(9): 1557-62. https://doi.org/10.1093/rheumatology/keu399
20. MASCARENHAS S: A narrative review of the classification and use of diagnostic ultrasound for conditions of the Achilles tendon. *Diagnostics* (Basel) 2020; 10(11): 944. https://doi.org/10.3390/diagnostics10110944
21. MOHER D, SHAMSEER L, CLARKE M *et al*.: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015; 4(1): 1. https://doi.org/10.1186/2046-4053-4-1
22. MARTINOLI C, DERCHI LE, PASTORINO C, BERTOLOTTO M, SILVESTRI E: Analysis of echotexture of tendons with US. *Radiology* 1993; 186(3): 839-43. https://doi.org/10.1148/radiology.186.3.8430196
23. GIBBON WW, LONG G: Ultrasound of the plantar aponeurosis (fascia). *Skeletal Radiol* 1999; 28(1): 21-6. https://doi.org/10.1007/s002560050467
24. FALSETTI P, ACCIAI C, LENZI L, FREDIANI B: Ultrasound of enthesopathy in rheumatic diseases. *Mod Rheumatol* 2009; 19(2): 103-13. https://doi.org/10.1007/s10165-008-0129-x
25. GENC H, CAKIT BD, TUNCBILEK I, ERDEM HR: Ultrasonographic evaluation of tendons and enthesal sites in rheumatoid arthritis: comparison with ankylosing spondylitis and healthy subjects. *Clin Rheumatol* 2005; 24(3): 272-7. https://doi.org/10.1007/s10067-004-0997-1
26. SHAIBANI A, WORKMAN R, ROTHSCHILD BM: The significance of enthesopathy as a skeletal phenomenon. *Clin Exp Rheumatol* 1993; 11(4): 399-403.
27. GULDBERG-MØLLER J, TERSLEV L, NIELSEN SM *et al*.: Ultrasound pathology of the entheses in an age and gender stratified sample of healthy adult subjects: a prospective cross-sectional frequency study. *Clin Exp Rheumatol* 2019; 37(3): 408-13.
28. MILUTINOVIC S, RADUNOVIC G, VELJKOVIC K *et al*.: Development of ultrasound enthesitis score to identify patients with enthesitis having spondyloarthritis: prospective, double-blinded, controlled study. *Clin Exp Rheumatol* 2015; 33(6): 812-7.
29. WHITING P, RUTJES AW, REITSMA JB, BOSSUYT PM, KLEIJNEN J: The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol* 2003; 3: 25. https://doi.org/10.1186/1471-2288-3-25
30. BRISTOL UO: QUADAS-2 Assessments. https://www.bristol.ac.uk/population-health-sciences/projects/quadas/resources/: University of Bristol Medical School. p. resources to help with the application and presentation of QUADAS-2.
31. HIGGINS JP, THOMPSON SG: Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21(11): 1539-58. https://doi.org/10.1002/sim.1186
32. AYDIN SZ, FILIPPUCCI E, ATAGÜNDÜZ P, YAVUZ Ş, GRASSI W, DIRESKENELI H: Sonographic measurement of Achilles tendon thickness in seronegative spondyloarthropathies. *Eur J Rheumatol* 2014; 1(1): 7-10. https://doi.org/10.5152/eurjrheum.2014.002
33. WERVERS K, VIS M, RASAPPU N *et al*.: Modification of a sonographic enthesitis score to differentiate between psoriatic arthritis and young healthy volunteers. *Scand J Rheumatol* 2018; 47(4): 291-4. https://doi.org/10.1080/03009742.2017.1393695
34. ABATE M, DI CARLO L, SALINI V, SCHIAVONE C: Metabolic syndrome associated to non-inflammatory Achilles enthesopathy. *Clin Rheumatol* 2014; 33(10): 1517-22. https://doi.org/10.1007/s10067-014-2524-3
35. BANDINELLI F, MILLA M, GENISE S *et al*.: Ultrasound discloses entheseal involvement in inactive and low active inflammatory bowel disease without clinical signs and symptoms of spondyloarthropathy. *Rheumatology* (Oxford) 2011; 50(7): 1275-9. https://doi.org/10.1093/rheumatology/keq447
36. BANDINELLI F, PRIGNANO F, BONCIANI D *et al*.: Ultrasound detects occult entheseal involvement in early psoriatic arthritis independently of clinical features and psoriasis severity. *Clin Exp Rheumatol* 2013; 31(2): 219-24.

37. EBSTEIN E, COUSTET B, MASSON-BEHAR V *et al*.: Enthesopathy in rheumatoid arthritis and spondyloarthritis: An ultrasound study. *Joint Bone Spine* 2018; 85(5): 577-81. https://doi.org/10.1016/j.jbspin.2017.11.014
38. HARMAN H, SÜLEYMAN E: Features of the Achilles tendon, paratenon, and enthesis in inflammatory rheumatic diseases: A clinical and ultrasonographic study. *Z Rheumatol* 2018; 77(6): 511-21. https://doi.org/10.1007/s00393-017-0314-4
39. ISHIDA SN, FURTADO RNV, ROSENFELD A, PROGLHOF JEP, ESTRELA GBQ, NATOUR J: Ultrasound of entheses in ankylosing spondylitis patients: The importance of the calcaneal and quadriceps entheses for differentiating patients from healthy individuals. *Clinics* (Sao Paulo) 2019; 74: e727. https://doi.org/10.6061/clinics/2019/e727
40. DI MATTEO A, FILIPPUCCI E, CIPOLLETTA E *et al*.: Entheseal involvement in patients with systemic lupus erythematosus: an ultrasound study. *Rheumatology* (Oxford) 2018; 57(10): 1822-9. https://doi.org/10.1093/rheumatology/key189
41. ŞERBAN O, PAPP I, BOCŞA CD *et al*.: Do ankle, hindfoot, and heel ultrasound findings predict the symptomatology and quality of life in rheumatoid arthritis patients? *J Ultrason* 2020; 20(81): e70-e82. https://doi.org/10.15557/jou.2020.0012
42. TOM S, ZHONG Y, COOK R, AYDIN SZ, KAELEY G, EDER L: Development of a preliminary ultrasonographic enthesitis score in psoriatic arthritis - GRAPPA Ultrasound Working Group. *J Rheumatol* 2019; 46(4): 384-90. https://doi.org/10.3899/jrheum.171465
43. WOODBURN J, HYSLOP E, BARN R, MCINNES IB, TURNER DE: Achilles tendon biomechanics in psoriatic arthritis patients with ultrasound proven enthesitis. *Scand J Rheumatol* 2013; 42(4): 299-302. https://doi.org/10.3109/03009742.2012.747626
44. ZULIANI F, ZABOTTI A, ERRICHETTI E *et al*.: Ultrasonographic detection of subclinical enthesitis and synovitis: a possible stratification of psoriatic patients without clinical musculoskeletal involvement. *Clin Exp Rheumatol* 2019; 37(4): 593-9.
45. MUTLU S, ERDEM TOSLAK I, INCI A, CEKIC B, YAVUZ A: Evaluation of the Achilles tendon using B-mode ultrasound and strain elastography in patients with chronic kidney disease. *J Ultrasound Med* 2021; 40(4): 771-8. https://doi.org/10.1002/jum.15453
46. URSINI F, ARTURI F, D'ANGELO S *et al*.: High prevalence of Achilles tendon enthesopathic changes in patients with type 2 diabetes without peripheral neuropathy. *J Am Podiatr Med Assoc* 2017; 107(2): 99-105. https://doi.org/10.7547/16-059
47. BAKIRCI S, SOLMAZ D, STEPHENSON W, EDER L, ROTH J, AYDIN SZ: Entheseal changes in response to age, body mass index, and physical activity: an ultrasound study in healthy people. J *Rheumatol* 2020; 47(7): 968-72. https://doi.org/10.3899/jrheum.190540
48. FILIPPUCCI E, SMERILLI G, DI MATTEO A, GRASSI W: Ultrasound definition of enthesitis in spondyloarthritis and psoriatic arthritis: arrival or starting point? *Ann Rheum Dis* 2021; 80(11): 1373-5. https://doi.org/10.1136/annrheumdis-2021-220478
49. GERVASIO A, BOLLANI P, BIASIO A: US in mid-portion Achilles tendon injury. *J Ultrasound* 2014; 17(2): 135-9. https://doi.org/10.1007/s40477-013-0023-z
50. MOLYNEUX P, CARROLL M, STEWART S, BRENTON-RULE A, ROME K: Ultrasound characteristics of the mid-portion of the Achilles tendon in runners: a systematic review protocol. *Syst Rev* 2017; 6(1): 108. https://doi.org/10.1186/s13643-017-0501-z
51. FALSETTI P, FREDIANI B, FIORAVANTI A *et al*.: Sonographic study of calcaneal entheses in erosive osteoarthritis, nodal osteoarthritis, rheumatoid arthritis and psoriatic arthritis. *Scand J Rheumatol* 2003; 32(4): 229-34. https://doi.org/10.1080/03009740310003721
52. ZAYAT AS, ELLEGAARD K, CONAGHAN PG *et al*.: The specificity of ultrasound-detected bone erosions for rheumatoid arthritis. *Ann Rheum Dis* 2015; 74(5): 897-903. https://doi.org/10.1136/annrheumdis-2013-204864
53. KAEDING C, BEST TM: Tendinosis: pathophysiology and nonoperative treatment. *Sports Health* 2009; 1(4): 284-92. https://doi.org/10.1177/1941738109337778
54. D'AGOSTINO MA, SAID-NAHAL R, HACQUARD-BOUDER C, BRASSEUR JL, DOUGADOS M, BREBAN M: Assessment of peripheral enthesitis in the spondylarthropathies by ultrasonography combined with power Doppler: a cross-sectional study. *Arthritis Rheum* 2003; 48(2): 523-33. https://doi.org/10.1002/art.10812
55. BACCOUCHE K, MANI L, ELAMRI N *et al*.: Musculoskeletal ultrasonography of the Achilles tendon and plantar fascia in spondyloarthritis patients. *Egypt Rheumatology* 2018; 40: 249-53.
56. BEITINGER N, EHRENSTEIN B, SCHREINER B *et al*.: The value of colour Doppler sonography of the knee joint: a useful tool to discriminate inflammatory from non-inflammatory disease? *Rheumatology* (Oxford) 2013; 52(8): 1425-8. https://doi.org/10.1093/rheumatology/ket136
57. MCQUEEN FM: Bone marrow edema and osteitis in rheumatoid arthritis: the imaging perspective. *Arthritis Res Ther* 2012; 14(5): 224. https://doi.org/10.1186/ar4035
58. TEMPFER H, TRAWEGER A: Tendon vasculature in health and disease. *Front Physiol* 2015; 6: 330. https://doi.org/10.3389/fphys.2015.00330
59. KAELEY GS, BAKEWELL C, DEODHAR A: The importance of ultrasound in identifying and differentiating patients with early inflammatory arthritis: a narrative review. *Arthritis Res Ther* 2020; 22(1): 1. https://doi.org/10.1186/s13075-019-2050-4
60. AYDIN SZ, KARADAG O, FILIPPUCCI E *et al*.: Monitoring Achilles enthesitis in ankylosing spondylitis during TNF-α antagonist therapy: An ultrasound study. *Rheumatology* 2009; 49(3): 578-82. https://doi.org/10.1093/rheumatology/kep410
61. RUTA S, ACOSTA FELQUER ML, ROSA J, NAVARTA DA, GARCÍA MONACO R, SORIANO ER: Responsiveness to therapy change of a global ultrasound assessment in spondyloarthritis patients. *Clin Rheumatol* 2015; 34(1): 125-32. https://doi.org/10.1007/s10067-014-2673-4
62. RUYSSEN-WITRAND A, JAMARD B, CANTAGREL A *et al*.: Relationships between ultrasound enthesitis, disease activity and axial radiographic structural changes in patients with early spondyloarthritis: data from DESIR cohort. *RMD Open* 2017; 3(2): e000482. https://doi.org/10.1136/rmdopen-2017-000482
63. DUNCAN BB, SCHMIDT MI, PANKOW JS *et al*.: Low-grade systemic inflammation and the development of type 2 diabetes: the atherosclerosis risk in communities study. *Diabetes* 2003; 52(7): 1799-805. https://doi.org/10.2337/diabetes.52.7.1799
64. COBO G, LINDHOLM B, STENVINKEL P: Chronic inflammation in end-stage renal disease and dialysis. *Nephrol Dial Transplant* 2018; 33: 35-40. https://doi.org/10.1093/ndt/gfy175
65. MIHAI S, CODRICI E, POPESCU ID *et al*.: Inflammation-related mechanisms in chronic kidney disease prediction, progression, and outcome. *J Immunol Res* 2018; 2018: 2180373. https://doi.org/10.1155/2018/2180373