

# Adaptation of Tendon Structure and Function in Tendinopathy With Exercise and Its Relationship to Clinical Outcome

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**Context:** Exercise is seen as the most evidence-based treatment for managing tendinopathy and although the type of exercise used to manage tendinopathy may induce adaptation in healthy tendons, it is not clear whether these adaptations occur in tendinopathy and if so whether they are associated with improved clinical outcomes. **Objective:** The aim of the study was to synthesize available evidence for adaptation of the Achilles tendon to eccentric exercise and the relationship between adaptation (change in tendon thickness) and clinical outcomes among people with Achilles tendinopathy. **Evidence Acquisition:** The search was performed in September 2018 in several databases. Studies investigating the response (clinical outcome and imaging on ultrasound/magnetic resonance imaging) of pathological tendons (tendinopathy, tendinosis, and partial rupture) to at least 12 weeks of eccentric exercise were included. Multiple studies that investigated the same interventions and outcome were pooled and presented in effect size estimates, mean difference, and 95% confidence intervals if measurement scales were the same, or standard mean difference and 95% confidence intervals if measurements scales were different. Where data could not be pooled the studies were qualitatively synthesized based on van Tulder et al. **Evidence Synthesis:** Eight studies met the inclusion and exclusion criteria and were included in the review. There was strong evidence that Achilles tendon thickness does not decrease in parallel with improved clinical outcomes. **Conclusions:** Whether a longer time to follow-up is more important than the intervention (ie, just the time per se) for a change in tendon thickness remains unknown. Future studies should investigate whether exercise (or other treatments) can be tailored to optimize tendon adaptation and function, and whether this relates to clinical outcomes.

**Keywords:** tendon adaptation, tendinitis, tendinosis, physical activity

Tendinopathy is a general term indicating any abnormal state of a tendon, including pain, dysfunction, and, but not necessarily, pathology.<sup>1,2</sup> Pathological tendons are defined as having abnormal changes on imaging (eg, increased signal intensity on magnetic resonance imaging [MRI] or hypoechoic regions in ultrasound) or on histological investigations.<sup>2</sup> Histological changes that can be seen in tendinopathy include increased water content, increased amounts of proteoglycans and glycosaminoglycans, fascicular disorganization, neurovascular ingrowth, and changes in cell phenotype.<sup>3,4</sup> Pathological tendons (ie, those with imaging or histological abnormalities) may not necessarily be painful. Pain-free tendons with pathology are common and measures of structural changes, at any given time, cannot be used to determine whether a tendon is perceived painful.<sup>5</sup>

Tendon, like muscle, is a plastic tissue that adapts to ensure it can “cope” with habitual loading. This plasticity may be via transduction mechanisms, that is, the fibroblasts linking to the extracellular matrix via integrins, which enable the cell to detect and adapt to the mechanical loading. Tendon material properties or tendon structure (eg, increased fibril size, additional enzymatically derived cross-links between fibrils) and tendon morphology or size (eg, increased cross-sectional area [CSA], thickness) may adapt to load.<sup>6</sup> Bohm et al<sup>7</sup> recently reviewed studies investigating adaptation of healthy human tendon to mechanical loading and found consistent evidence for increased stiffness following high load interventions

that bring about large tendon strains (>70% maximal voluntary contraction or >70% 1 repetition maximum).

The question that now arises is whether a change in tendon structure (ie, tendon size) occurs in tendinopathy following exercise interventions and whether these changes are associated with clinical symptoms. Exercise is seen as the most common evidence-based treatment for managing tendinopathy,<sup>8</sup> and although the type of exercise used to manage tendinopathy may induce adaptation in healthy tendons, it is not clear whether these adaptations occur in tendinopathy and if so whether they are associated with improved clinical outcomes. A prior systematic review<sup>9</sup> did not support a relationship between observable structural change (MRI and ultrasound) and improved clinical outcomes when treated by eccentric exercise, but this was based on imaging (structural changes, eg, echogenicity) outcomes with poor reliability,<sup>10</sup> bringing into question the validity of the conclusions. A further systematic review<sup>11</sup> concluded that there is moderate evidence for an association between clinical outcomes and tendon thickness and tendon neovascularization in tendinopathy, but included cointerventions with exercise that may influence tendon adaptation (eg, injection therapy). Given the uncertainty in the literature and methodological limitations, a review that focuses on reliable imaging outcomes and exercise interventions without confounding cointerventions is warranted. This will allow athletic trainers and other clinicians to make informed decisions about the potential mechanisms to target when delivering exercise interventions for people with Achilles tendinopathy.

## Objective

The aim of this review is to synthesize current evidence that reports a change in tendon structure (change in tendon thickness) in

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Achilles tendinopathy in response to exercise (>12 wk) and whether this relates to change in clinical outcomes (self-reported pain and function). The focus is on reliable outcomes of a change in tendon structure and studies measuring eccentric exercise from single-cohort studies as well as those studies comparing eccentric exercise with another intervention or wait and see. This review may inform clinical practice and future studies regarding optimal exercise interventions to achieve a change in tendon structure.

## Evidence Acquisition

**Inclusion Criteria.** Randomized controlled trials (RCTs), controlled trials, cohort studies, and case series were included. Studies investigating reliable measures of a change in tendon structure (outcome) following at least 12 weeks of exercise (interventions) among participants with Achilles tendinopathy were included. An additional outcome measure criterion was that studies needed to include at least 1 validated outcome measure for self-reported pain and/or function (eg, Victorian Institute of Sport Assessment-Achilles Questionnaire, Numeric Rating Scale).

**Study Type.** Randomized controlled trial design (eg, parallel group, factorial, cross-over), pseudo-randomized trials, and single-cohort studies were included. There were no restrictions based on date of publication.

**Population.** We included studies investigating participants with Achilles tendinopathy of any age, and duration of symptoms of at least 3 months. Only studies that clearly defined clinical diagnostic criteria for tendon-related pain (localized [insertion or midportion], Achilles tendon pain for >3 months, corresponding tenderness on palpation, thickening of the Achilles tendon 2 to 6 cm above the tendon insertion [for midportion only]), and demonstrated tendon pathology on ultrasound (tendon thickening, hypoechoic regions, and/or Doppler signal), MRI (tendon thickening and increased signal), or ultrasound tissue characterization (increase in abnormal echo types) were included. Studies also needed to exclude other potential causes of pain and interventions that could moderate tendon structure change following exercise such as systemic disease (eg, rheumatoid arthritis, psoriatic arthritis, or inflammatory bowel disease), positive neurological tests, reproduction of pain from movement of proximal joints (eg, back movement reproducing leg or foot pain), steroid injection in the last 3 months, and previous surgery to the affected tendon or joint.

**Tendon Structure Outcomes.** Includes tendon thickness or CSA measured with ultrasound or MRI. Measures of tendon thickness and CSA have demonstrated acceptable reliability.<sup>12-14</sup>

**Interventions.** Studies including exercise as a treatment or rehabilitation for Achilles tendinopathy were included. The only additional parameter was that exercise needed to be applied for 12 weeks or longer as a shorter intervention does not seem to bring about structural changes in the (healthy) tendon.<sup>7</sup> Any exercise frequency, load intensity, time under tension, and rest times were included with the exception of contraction type where only studies investigating eccentric exercise were included. Studies investigating other types of exercise (eg, heavy slow resistance [HSR]) were excluded because of the low number of studies and thus the ability to systematically review the literature.

**Exclusion Criteria.** Reviews, case studies, and opinion articles were excluded, as were animal and non-English language studies. Studies investigating tendon rupture/full thickness tears (eg, postsurgical intervention exercise) as well as those investigating other tendons that were not the Achilles tendon were excluded because their number was too low. Studies investigating nonexercise interventions alone (eg, manual therapy, taping, shockwave) were also excluded. Studies investigating shockwave or injections were excluded because they may influence a change in tendon structure.<sup>15-17</sup> Stretching was not considered an exercise intervention that is able to lead to a change in chronic tendon structure<sup>7</sup> and studies that investigated only stretching were thus excluded. Studies with cointerventions were excluded, as although they were unlikely to influence a change in tendon structure (eg, manual therapy or tape), they could influence the experience of pain. We also excluded studies investigating biomarkers because although exercise increases tendon collagen synthesis,<sup>18</sup> this biochemical response may not necessarily translate to tendon material or structural properties.<sup>19</sup> Studies investigating other types of tendon adaptation (eg, tendon mechanical properties, echo types investigated with ultrasound tissue characterization) were excluded too because of the low number of studies and thus the ability to systematically review the literature.

**Search Strategy.** The preferred reporting items for systematic reviews and meta-analyses statement protocol guidelines were followed in this systematic review.<sup>20</sup> The search was performed in November 2018 in the following databases: MEDLINE, CINAHL, EBSCO, and Google Scholar. Only terms relating to the intervention and population were searched. Adding the outcome resulted in a very low yield because most studies did not mention a change in tendon structure in the title, abstract, or keywords. No limits were applied (see Table 1 for MEDLINE example and subject headings for CINAHL and EBSCO). Several studies in the field of tendinopathy and the reference lists of final yield were screened to identify other eligible studies.

**Review Process.** Two reviewers (KF and PM) screened all titles and after excluding studies both abstracts and titles were screened and further studies were excluded. The full text of the remaining

**Table 1 Search Terms in Database**

Search term	Synonyms
Exercise (intervention)	Concentric, eccentric, isometric, heavy slow, load, physiotherapy, physical therapy, and strength training (title and abstract); exercise, exercise therapy, rehabilitation, resistance training (MeSH), concentric contraction, eccentric contraction, isometric contraction, exercise, physical therapy, resistance training, and rehabilitation (subject heading CINAHL); and exercise, exercise therapy, rehabilitation, and resistance training (subject heading EBSCO)
AND tendinopathy site (population)	Achilles, tendo-Achilles, tricep-surae, triceps, and triceps tendon (title and abstract); Achilles tendon (MeSH) (subject heading CINAHL); and Achilles tendon (subject heading EBSCO)
AND pathology (population)	Paratendinitis, pathological, and partial rupture (title and abstract); pathology, tendinopathy (MeSH) pathology, tendinopathy, and Achilles tendinopathy (subject heading CINAHL); and tendinopathy (subject heading EBSCO)

studies was screened. A third reviewer (SP) was also available to discuss eligibility of studies when this was not clear.

**Risk of Bias Assessment.** The risk of bias was evaluated by 2 independent assessors (KF and PM) and disagreements were resolved via consensus and adjudicated by a third author (SP) where necessary. Given that an RCT is the most appropriate design to answer our question, study quality was assessed using the Physiotherapy Evidence Database (PEDro) scale,<sup>21</sup> which has established reliability and validity.<sup>21,22</sup> The advantage of using the PEDro scale is that it penalizes cohort design studies where confounders such as regression to mean and natural recovery may influence outcomes.<sup>21</sup> The scale has 11 criteria (1 point per criterion) with a maximum score of 10 because the first question is not marked. A study with a low risk of bias was defined as having  $\geq 6/10$  score.<sup>21</sup>

**Data Extraction.** Data were extracted independently by 2 reviewers (KF and PM), using a recommended form.<sup>20</sup> A third reviewer (SP) was available to adjudicate when there was lack of consensus. Data extracted included study design, participant characteristics (including midportion or insertional tendinopathy), pathological tendon decrease, intervention, tendon structure outcome, and clinical outcome (eg, Victorian Institute of Sport Assessment-Achilles Questionnaire, Numeric Rating Scale). If there was more than 1 measurement scale used for the same construct, we included scales that were similar across most studies; otherwise we prioritized validated and disease-specific questionnaires. Outcome data were extracted for dichotomous (proportions and sample size) and continuous data (follow-up or change scores, SD, and sample size) to enable calculation of effect sizes (see "Data Synthesis and Analysis" section below). We extracted data at the follow-up times where tendon structure and clinical outcomes were both reported.

**Data Synthesis and Analysis.** We planned to perform meta-analyses among trials with similar characteristics (exercise interventions and comparator, outcome measures, and populations).<sup>23</sup> We planned to use random effects models, as clinical and methodological heterogeneity is likely to exist and may impact model findings. Where data could not be pooled, we qualitatively synthesized findings based on van Tulder et al<sup>24</sup> levels of evidence (Table 2). Although the synthesis according to van Tulder et al<sup>24</sup> should be based on RCTs and clinical controlled trials, it has often been used for other study designs.<sup>9,25,26</sup> Positive change in tendon thickness was defined as change toward the comparator group. Pathological Achilles tendons are reported to be thicker,<sup>27</sup> so a positive change is expected to be reduced thickness.

Where there were multiple studies (trials and single-cohort studies) that investigated the same interventions and outcome we calculated effect size estimates. Dichotomous outcomes were expressed as relative risk and 95% confidence intervals. Continuous

outcomes were expressed as mean difference (MD) and 95% confidence intervals if measurement scales were the same, or as standard mean difference and 95% confidence intervals if measurement scales were different. Standard mean difference effect sizes were interpreted as small (0.2), medium (0.5), and large (0.8).<sup>28</sup> The standard mean difference was adjusted (Hedges' adjusted  $g$ ) for small sample bias.<sup>23</sup>

## Evidence Synthesis

**Search Yield.** The search results are shown in Figure 1. Eight studies met the inclusion and exclusion criteria and were included in the review. Two studies<sup>29,30</sup> used the same cohort and investigated different follow-up times. Data from these studies were combined, so overall 8 studies and 7 unique cohorts were included.

**Risk of Bias.** Four studies had low risk of bias<sup>31-34</sup> and 4 had high risk of bias<sup>29,30,35,36</sup> (see Table 3). The mean risk of bias score was just over 5 out of 10 (5.3) and scores ranged between 2 and 8. The most common quality criteria not satisfied was blinding of subjects and therapists.

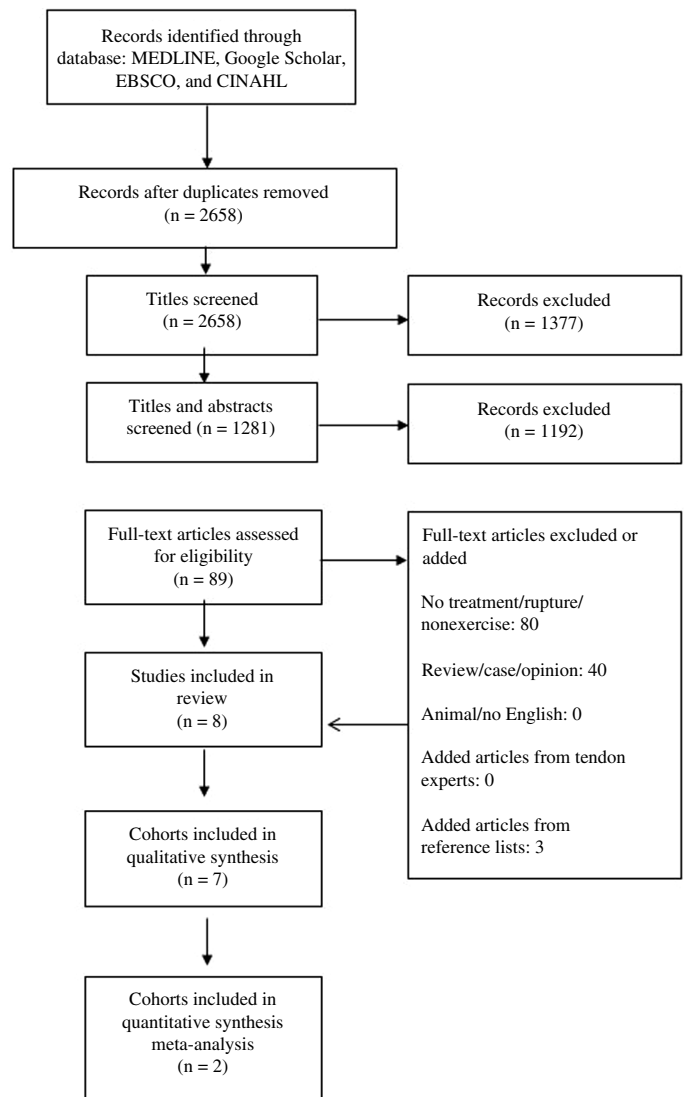
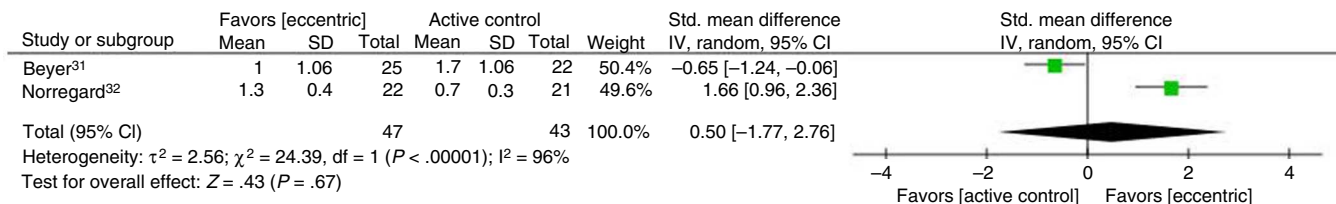


Figure 1 — Study selection flow chart.

Table 2 Level of Evidence<sup>24</sup>

Level of evidence	Measures
Strong	Consistent findings in multiple high-quality studies (n > 2)
Moderate	Consistent findings among multiple low-quality studies or 1 high-quality study
Limited	Findings from 1 low-quality study.
Conflicting	Inconsistent findings among multiple studies
No evidence	No studies found



**Figure 2** — Comparison of thickness outcomes measured by ultrasound between eccentric exercise (Alfredson protocol) and a heavy slow exercise protocol or stretching. CI, confidence interval; Std., standard.

**Table 3 PEDro Scale—Risk of Bias Assessment of Included Studies**

Study	EC	RTG	AC	SB	BS	BT	BA	KO	ITT	BG	MV	TS
Beyer <sup>31</sup>	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	7
Gärdin <sup>29</sup>	Yes	No	No	No	No	No	Yes	Yes	Yes	No	Yes	4
Norregard <sup>32</sup>	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	Yes	6
Petersen <sup>33</sup>	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	7
Richards <sup>35</sup>	Yes	N/A	N/A	N/A	N/A	No	Yes	No	Yes	No	No	2
Rompe <sup>34</sup>	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8
Shalabi <sup>30</sup>	Yes	No	No	No	No	No	Yes	No	Yes	No	Yes	3
Tsahie <sup>36</sup>	Yes	No	No	Yes	No	No	No	Yes	Yes	Yes	Yes	5

Abbreviations: AC, allocation was concealed; BA, blinding of all assessors; BG, between-group statistical; BS, blinding of all subjects; BT, blinding of all therapists; EC, eligibility criteria; ITT, intention to treat; KO, key outcome was obtained; MV, measures of variability; RTG, randomly allocated to groups; SB, similar at baseline; TS, Total score.

**Study Characteristics.** Characteristics of included studies are shown in Table 4. Most studies were RCTs<sup>31–34</sup> or prospective cohort studies.<sup>29,30,36</sup> There was 1 controlled clinical trial.<sup>35</sup> There were a total of 321 participants (173 men and 148 women) with mean age of 48 years (ranging from 42<sup>32</sup> to 51),<sup>30</sup> and mean duration of symptoms of 14 months.

Eight studies (7 cohorts) investigated eccentric training.<sup>29–36</sup> Eccentric training involves 3 sets of 15 isolated eccentric exercises, both with straight and bent knee, performed twice daily.<sup>31</sup> Pain and discomfort are acceptable, and additional weight is added when the exercise becomes pain free. All studies executed the Alfredson protocol with exceptions from 2 studies.<sup>33,36</sup> In the study by Petersen et al,<sup>33</sup> the participants did the exercises 3 times per day and in the study by Tsehaie et al<sup>36</sup> the participants had a familiarization period for 4 weeks before the actual exercise period for 12 weeks started.

Only 2 studies<sup>31,32</sup> qualified for meta-analyses comparing eccentric exercise versus heavy slow exercise<sup>31</sup> or stretching<sup>32</sup> and the analyses showed an  $I^2$  of 96%, so we decided to present the individual results from each study (Table 5) as well as pooled data (Figure 2).

**Tendon Size Changes and Clinical Outcomes Findings with Eccentric Exercise in Achilles Tendinopathy.** Thickness, pain, and function outcomes: There is strong evidence to refute that Achilles tendon thickness decreases (normalization) in parallel with improvement in self-reported pain and function. Four cohorts with low risk of bias (all RCTs)<sup>31–34</sup> found either no change in parallel with improved self-reported clinical outcomes. There were heterogeneous between group differences with benefit of eccentric training compared to stretching (large effect) and inferior change in thickness of eccentric training compared to heavy slow resistance (moderate effect). Three cohorts with high risk of bias (all cohort studies) found either no change in tendon thickness<sup>29,30,36</sup> in parallel with improved self-reported clinical outcomes or that symptoms

improved before the Achilles size reduced.<sup>35</sup> Effect sizes were calculated and pooled where possible (see Table 5, Figure 2).

## Discussion

The aim of this review was to synthesize current evidence that reports a change in tendon structure (change in tendon thickness) in Achilles tendinopathy in response to exercise (>12 wk) and whether this relates to change in clinical outcomes (self-reported pain and function). We found that there was strong evidence that Achilles tendon thickness does not decrease in parallel with improved clinical outcomes. After 12 weeks of eccentric exercise only 2 studies<sup>31,32</sup> showed effect sizes not crossing zero regarding tendon thickness, but these showed heterogeneous differences between groups (compared with HSR<sup>31</sup> and stretching<sup>32</sup>). Further, the study by Norregard et al<sup>32</sup> was the only study that included participants with insertional tendinopathy, which could have affected the outcomes. The included cohort studies either reported no change in thickness at follow-up<sup>29,30,36</sup> or found that symptoms improved before the Achilles size reduced.<sup>35</sup>

Our findings suggest that the inconsistent changes seen in tendon thickness could be explained by time rather than eccentric exercise. However, in our effect size calculations we found that eccentric exercise was more effective [1.66 (0.96, 2.36)] than stretching in the study by Norregard,<sup>32</sup> but the study by Beyer et al<sup>31</sup> found no difference between both exercise groups (eccentric vs HSR) which suggests that loading maybe of importance. However, even in the original study by Norregard et al,<sup>32</sup> there was no significant difference between groups, but no exact  $P$  values or effect sizes were presented. The review by Rabello<sup>11</sup> concluded that there is moderate evidence for an association between clinical outcomes and tendon thickness and tendon neovascularization in

**Table 4 Summary of Main Study Characteristics**

Author, tendon	Study characteristics	Participant characteristics	Tendon outcome	Clinical outcome
Beyer <sup>31</sup> Midportion	RCT Eccentric exercise vs HSR exercise for 12 wk Outcomes at 12 and 52 wk Eccentrics: Alfredson protocol, 12 wk, 2×/d, 180 reps/d HSR 12 wk, 3×/wk, increased load over time as repetitions decreased over time.	Mean age = 48 y Mean duration = 18 mo 15 women and 32 men	Ultrasound ↓ tendon thickness ( $P < .001$ ) in eccentric (1 mm) and HSR group (1.7 mm). No between-group differences at 52 wk ( $P = .01$ ). Significant differences not reported for other outcomes.	Improved VISA-A at 0–52 wk ( $P < .001$ ). No difference between groups ( $P = .62$ ). Improvement in VAS while running at 0–52 wk ( $P < .001$ ) with no difference between groups ( $P = .71$ ).
Norregaard <sup>32</sup> Midportion and insertional 3–4 patients per group had insertional Achilles tendinopathy	RCT Eccentric training vs stretching exercises/gastrocnemius for 12 wk Outcomes after 12, 39, and 52 wk Eccentrics: Alfredson protocol, 12 w, 2×/d, 180 reps/d	Mean age = 42 y 22 women and 23 men Mean duration = 28 mo	Ultrasound ↓ tendon thickness (nonsignificant) in the stretch group (0.1 mm) and an increase in the eccentric group (0.6 mm) at 12 wk. ↓ tendon thickness ( $P = .001$ ) in the eccentric group (1.3 mm) and the stretch group (0.7 mm) at 52 wk, no between-group difference ( $P = .05$ ).	Improvements in symptoms ( $P = .05$ ) in the stretch group at 0–3 wk. Improvements in symptoms ( $P = .01$ ) and pain ( $P = .05$ ; KOOS) in the stretch group and in pain in the eccentric group ( $P = .05$ ) at 0–12 wk. No difference between groups. Improvements in symptoms ( $P = .01$ ) and pain ( $P = .05$ ; KOOS) in the eccentric group and in symptoms for the stretch group ( $P = .01$ ) at 0–52 wk. No difference between groups
Petersen <sup>33</sup> Midportion	RCT Eccentric exercise, eccentric training vs Airheel brace or a combination of eccentric training and Airheel brace for 12 wk Outcomes at 6, 12, and 54 wk Eccentrics: 12 wk, 3×/d, 270 reps/d	Mean age = 43 y Mean duration = 7 mo 40 women and 60 men	Ultrasound No change in the tendon diameter in any of the 3 treatment groups ( $P = .05$ ) at 12 wk. No thickness measures at 54 wk.	Improved AOFAS improved the eccentric group at 0–54 wk ( $P < .001$ ). No difference between groups. Significant differences not reported for other outcomes. Improvements in VAS in activities of daily living in the eccentric group at 0–54 wk ( $P < .001$ ). No difference between groups. Improvements in VAS in activities of daily living in the eccentric group from 0 to 6 wk ( $P = .001$ ). No further decrease in the Airheel-only group after 6 wk. Improvements in VAS in activities of daily living in the eccentric group from 0 to 12 wk ( $P = .001$ )
Richards <sup>35</sup> Midportion	CCT Eccentric training Outcomes at 2, 6, 12, and 52 wk. Eccentrics: Alfredson protocol, 12 wk, 2×/d, 180 reps/d	Mean age = 47 y Mean duration is not known 4 women and 5 men	Ultrasound and MRI ↓ tendon thickness ( $P = .09$ ) (4.4 mm) at 52 wk. Significant differences not reported for other outcomes.	Improved VISA-A at 0–52 wk. Significant differences not reported for other outcomes.
Rompe <sup>34</sup> Midportion	RCT Eccentric training vs shockwave therapy or wait and see for 12 wk Outcomes at 16 wk Eccentrics: Alfredson protocol, 12 w, 2×/d, 180 reps/d	Mean age = 49 y Mean duration = 11 mo 46 women and 29 men Midportion Achilles tendinopathy	Ultrasound No change in tendon thickness at 16 wk in none of the groups ( $P = .05$ ).	Improved VISA-A at 0–16 wk ( $P = .01$ ). No difference between treatment groups ( $P = .26$ ). Both intervention groups showed better results than the wait and see group only ( $P = .001$ ). Improvement in NRS score in load-induced pain at 0–16 wk ( $P = .01$ ). No difference between intervention groups ( $P = .49$ ). Both intervention groups showed better results than the wait and see group ( $P = .001$ ).

(continued)

Table 4 (continued)

Author, tendon	Study characteristics	Participant characteristics	Tendon outcome	Clinical outcome
Shalabi <sup>30</sup> Midportion (these studies used the same cohort, only follow-up that differ) Gårdin <sup>52</sup>	PC Eccentric training for 12 wk Outcomes at 12 wk and 4.2 y. Eccentrics: Alfredson protocol, 12 w, 2×/d, 180 reps/d	Mean age = 51 y Mean duration = 12 mo 9 women and 16 men	MRI ↓ tendon CSA ( $P = .05$ ) (0.8 mm) at 12 wk. No change in tendon thickness at 4.2 y ( $P = .18$ )	Improvements in Curwin scale at 0–12 wk ( $P = .01$ ) Improvements in Curwin scale ( $P < .001$ ) and function ( $P = .001$ ) at 4.2 y.
Tsehai <sup>36</sup> Midportion	PC Eccentric training for 16 wk Outcomes at 24 wk Eccentrics: Alfredson protocol, familiarization period for 4 wk before 12 wk, 2×/d, 180 reps/d	Mean age = 46 y Mean duration = 9 mo 12 women and 8 men	MRI No change in tendon thickness ( $P = .01$ ) ↓ tendon volume ( $P = .02$ ) (0.3 cm) at 24 wk. ↓ tendon CSA ( $P = .048$ ) (4.5 mm) at 24 wk.	Improved VISA-A score ( $P = .004$ ) at 24 wk

Abbreviations: AOFAS, American Orthopedic Foot and Ankle Society; CCT, controlled trial; CSA, cross-sectional area; HSR, heavy slow resistance; KOOS, knee injury and osteoarthritis outcome score; MRI, magnetic resonance imaging; PC, prospective cohort; RCT, randomized controlled trial; VAS, visual analogue score; VISA, Victorian Institute of Sport Assessment; VISA-A, VISA Achilles version; VISA-P, VISA patellar version.

tendinopathy, which is the opposite of what we conclude. The difference between this study and the 2 earlier reviews<sup>9,11</sup> is the methodology and we only investigated eccentric exercise (alone without any cointervention) by itself or compared with another intervention where it became clear that the number of studies, and therefore, the overall evidence, is scarce.

### Comparison With Earlier Evidence

In the Drew et al<sup>9</sup> systematic review, it was concluded that HSR exercise may be superior to other exercises in relation to tendon adaptation outcomes. This was based on a report of superior Doppler signal and tendon thickness outcomes with HSR compared with eccentric exercise in the Kongsgaard et al<sup>37</sup> patellar tendinopathy study. In Achilles tendinopathy, which was the focus of this review, a recent study compared HSR versus eccentric exercise and found no difference in tendon thickness change or improvements in clinical outcomes between the groups.<sup>31</sup> Based on these limited data, there is a lack of evidence (Achilles) that HSR is superior at adapting pathological tendon, but more evidence is needed before firm conclusions can be made. Theoretically, HSR may involve heavier load than the Alfredson eccentric program (up to 6 repetition maximum compared with up to 15 repetition maximum in eccentric exercise). However, there is no way of knowing whether this is the case because adherence and fidelity of either program are not reported, and the HSR program was performed double leg and the eccentric program single leg.

### Change in Tendon Structure With Exercise and Relationship to Clinical Outcome

There was within group clinical benefit in pain and function with exercise which was not paralleled with change in tendon thickness. Only one study found a between-group difference. Rompe et al<sup>34</sup> found that eccentric exercise or shockwave therapy improved Victorian Institute of Sport Assessment-Achilles version and NRS scores more than the wait and see group. However, no exercise regime seems to be superior regarding clinical outcomes in both Achilles and patellar tendinopathy patients.<sup>38</sup> To the authors' knowledge, there is only one study investigating fibril morphology and clinical outcomes. This study<sup>39</sup> found that fibril morphology became more normal (increase fibril density and decrease mean area) following HSR exercise in patellar tendinopathy. Although this suggests a relationship between microstructural tendon adaptation and clinical outcomes, caution is needed as the data are from only one study. Given that this is the only study to investigate tendon microstructure with biopsy, it raises the possibility that current imaging measures lack sufficient sensitivity to identify tendon adaptations that may be occurring in tendinopathy. In support of this, in the same study, the authors reported no change in tendon CSA, modulus, or stiffness.<sup>39</sup> A potential limitation of the biopsy procedure is that it could have contributed to changes in the tendon (eg, collagen type III and type I collagen expression).<sup>40</sup>

### Tendon Thickness

Unlike healthy tendon where change in thickness or CSA may indicate increased collagen content, change in pathological tendon thickness is more likely to indicate change in bound water and proteoglycan content.<sup>41</sup> Tendon thickening and increased proteoglycan content are an attempt to reduce permeability and fluid flow and load on tendon cells.<sup>42</sup> Preliminary evidence from the studies

**Table 5 Effect Size Pre–Post Eccentric Intervention on Tendon Thickness**

Study	PEDro score	Length of follow-up	Thickness in mm (SD) at baseline—follow-up	Thickness in mm (SD) at follow-up	Between-group difference (SMD)
Rompe <sup>34</sup>	8	16 wk	12.8 (4.1)	None	None
Tsahie <sup>36</sup>	5	24 wk	8.9–8.6	Not reported	No comparison group
Beyer <sup>31</sup>	7	52 wk	8.3 (1.06)	7.3 (1.06)	–0.65 (–1.24, –0.06)
Norregard <sup>32</sup>	6	52 wk	7.6 (not reported)	6.3 (0.4)	1.66 (0.96, 2.36)
Richards <sup>35</sup>	2	52 wk	15 (5.15)	10.6 (4.63)	No comparison group
Petersen <sup>33</sup>	7	54 wk	Not reported	None	None
Shalabi/Gärdin <sup>29,30</sup>	4	4.2 y	6.7 (2.0)	6.4 (2.0)	No comparison group

Abbreviation: SMD, standard mean difference.

included in this review suggests that the Achilles tendon does not change in thickness in parallel with improved clinical outcome in Achilles tendinopathy. Whether change in thickness is a mechanism for change in pain and the clinical relevance of a few millimeters' reduction in thickness are unknown. It is noteworthy that some tendons may increase collagen content and size, but reduce water content after an exercise intervention so overall their thickness does not change and in this case adaptation may only be detected by assessing mechanical properties. A recent study<sup>43</sup> investigating the long-term prognosis (5–15 y follow-up) in plantar fascia-related pain found a greater decrease than studies included in this review (in asymptomatic and symptomatic groups from 6.9 and 6.7 mm, respectively, to 4.3 mm in both groups). However, at follow-up, fascia thickness and echogenicity had normalized in only 24% of the patients in the asymptomatic group and fascia thickness decreased over time regardless of symptoms and had no impact on prognosis.

Tendon thickness has been shown to normalize after nonload interventions,<sup>44</sup> so clearly other mechanisms may explain change in this outcome. Maybe a longer time to follow-up is more important than the intervention (ie, just the time per se)? Another example, the stage of pathology, may also influence change in tendon thickness but is not considered by any study in this review.<sup>45</sup> For example, patellar tendons of volleyball players that were defined as “degenerative” based on the continuum model<sup>45</sup> on gray-scale ultrasound imaging (hypochoic regions and poor matrix alignment) were less likely to demonstrate change in tendon thickness over the course of a competitive season.<sup>46</sup>

### Incorporation of Evidence into Clinical Practice

This review found that the clinical outcomes improved with time, but there is still a great uncertainty whether tendon thickness changes in parallel with change in symptoms. Recent evidence suggests that different types of pathology may be less likely to resolve over time<sup>46</sup> and less responsive to exercise interventions,<sup>47</sup> suggesting that mechanisms for change in patient symptoms following exercise most likely extend beyond a change in tendon structure. However, there is a possibility that current imaging methods are not sensitive enough to identify a change in tendon structure. What the limited evidence base suggests is that a change in tendon thickness following exercise seems different in pathological versus healthy tendons.

### Recommendations for Future Research

Bohm et al<sup>7</sup> demonstrated in their systematic review that thickness of healthy tendon consistently increases following HSR and heavy

isometric interventions over a number of weeks, where the interventions with longer duration ( $\geq 12$  wk) seem to be more efficient to stimulate tendon change in several aspects. No study included in our review investigated eccentric exercise for more than 12 weeks and maybe this was the parameter missing for a change in tendon thickness. No studies utilizing elastography or more traditional measurement (ie, ultrasound) to investigate change in mechanical properties after exercise were identified. Given the lack of studies, no conclusions can be made about the relationship between change in mechanical properties with exercise and improvement in clinical outcomes in Achilles tendinopathy. Future studies should investigate whether pathological tendons respond to different exercise interventions (eg, applied for a longer period) or whether they have limited capacity for improvement in their mechanical properties. Finally, we acknowledge that stage of pathology as described in the continuum model<sup>45</sup> may influence tendon adaptation<sup>46</sup> and was not defined in studies in this review. However, it is important to note there is only prospective evidence for the continuum model utilizing imaging changes in patella tendons<sup>46</sup> alongside a RCT where participants with Achilles tendinopathy were divided by pathology (reactive vs. degenerative), to examine the effects of supplements and exercise on pathology and patient outcomes.<sup>47</sup> Whether change in tendon thickness is a mechanism explaining change in clinical outcome requires further investigation. Future studies should consider longer follow-up times and detailed reporting of exercise parameters (eg, load) to further elucidate the relationship between exercise adaptation (not only thickness) of pathological tendon mechanical properties in relation to clinical reporting outcomes. Considering other tendons (patellar, rotator cuff, and plantar fascia) and outcomes (tendon structure and mechanical properties), there is no clear evidence that a change in tendon structure improves in parallel with improved clinical outcomes due to lack of studies.

### Limitations

The key disadvantage of this review is there were limited studies utilizing eccentric training in Achilles tendinopathy. Thus, the only tendon and contraction type investigated in this review were the Achilles tendon and eccentric exercise. There was also limited description of load intensity and compliance, so it is not possible to draw firm conclusions regarding the relationship between load and tendon structure of pathological tendon. It is very possible that many exercise protocols did not achieve an adequate intensity for a change in tendon structure.<sup>7</sup> Further, the results from the single-arm studies should be interpreted with caution because the improvement cannot be differentiated from the confounders such as natural

history,<sup>48</sup> and this is reflected in our quality assessment. A further limitation is that the included studies report group averages, not individual data points. For example, individual data points are required to determine whether, in a given patient, tendon size and clinical outcome are trending in the same direction or not. Even if a study shows that, on group average, tendon thickness is decreasing and clinical outcomes are improving, the data do not demonstrate that these processes are occurring in the same individuals.

## Conclusions

For Achilles tendinopathy, 12 weeks of eccentric exercise appears to result in improved clinical outcomes (self-reported pain and function) over time, but this often happened in the absence of reduced tendon thickness. This review has progressed current knowledge by identifying this lack of relationship between a change in tendon structure in pathological tendon and clinical outcomes, which is observed in many other areas of the body. Overall, we conclude that we cannot say with any certainty that pathological Achilles tendon thickness do change with load.

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