

Nonoperative Treatment of Midportion Achilles Tendinopathy: A Systematic Review

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Objective: The aim of this systematic review is to provide an easily accessible, clear summary of the best available evidence for nonoperative treatment of midportion Achilles tendinopathy.

Data Sources: MEDLINE, CINAHL, and Embase through April 2007. Search terms: *achilles tendon* or *tendo achilles* or *triceps surae* or *tendoachilles* or *tendo-achilles* or *achilles* AND *tendinopathy* or *tendinosis* or *tendonitis* or *tenosynovitis*.

Study Selection: Of 707 abstracts reviewed, 16 randomized trials met our inclusion criteria.

Data Extraction: Data extracted from each paper included: patient demographics (age and sex), duration of symptoms, method of diagnosis, treatments, cohort size, length of follow-up, pain-related outcome data, and secondary outcome data.

Data Synthesis: The primary outcome measurement was change in numeric pain score. Focal tenderness, tendon thickness, and validated outcome scores were used secondarily. Eccentric exercises were noted to be equivalent to extracorporeal shockwave therapy (1 study) and superior to wait-and-see treatment (2 trials), traditional concentric exercise (2 of 3 trials), and night splints (1 study). Extracorporeal shockwave therapy was shown to be superior to a wait-and-see method in 1 study but not superior to placebo in another. Sclerosing injections were shown to be superior to placebo in 1 study, but local steroid treatment was beneficial in 2 of 3 studies. Injection of deproteinized hemodialysate and topical glyceryl nitrate application were beneficial in 1 trial each.

Conclusions: Eccentric exercises have the most evidence of effectiveness in treatment of midportion Achilles tendinopathy. More investigation is needed into the utility of extracorporeal shockwave therapy, local corticosteroid treatments, injections of sclerosing agents or deproteinized hemodialysate, and topical glyceryl nitrate application.

Key Words: Achilles, tendinopathy, midportion, nonoperative treatment

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INTRODUCTION

Overuse injuries occur frequently in athletes, with some authors estimating that they account for up to half of all athletic injuries.¹ The Achilles tendon is among the most prone to overuse injury, with tendon problems accounting for up to 18% of injuries in runners and 4% of patients presenting to sports medicine clinics.^{2–6} The literature is replete with multiple conservative treatment protocols and results for treating these conditions, but access to and use of the literature is complicated by inconsistent diagnoses and confusing terminology.

We will use terminology suggested by Maffulli et al, using the term *tendinopathy* when referring to a diagnosis based on “pain, swelling, and impaired performance” and reserving more specific terms, including *tendonitis* or *tendinosis* for cases when inflammation or degeneration has been confirmed.^{7,8} Achilles tendinopathy has been classified as insertional (within 2 cm of its insertion) and midsubstance (2 to 6 cm proximal to its insertion) and is felt by many to represent two distinct clinical entities.⁹ Additional discrimination should be made between acute Achilles tendon injuries and more chronic degenerative processes. Multiple risk factors and predispositions to the development of tendinopathy in both locations have been identified and discussed in recent reviews on this subject.^{8,10–12} The aim of this systematic review is to provide an easily accessible, clear summary of the best available evidence for nonoperative treatment of midportion Achilles tendinopathy. Our primary focus will be to evaluate data from randomized controlled trials relating to change in numeric pain score. Additionally, we provide a brief summary of other outcome data.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria

Papers included in this review are randomized controlled trials for treatment of Achilles tendinopathy. We included only papers that focused on midsubstance Achilles tendinopathy. Retrospective or nonrandomized papers, review papers without original data, and papers examining tendinopathy of multiple tendons without separate outcome data for Achilles tendinopathy were excluded. Papers that focused on insertional tendinopathy or failed to localize the tendinopathy in the tendon were also excluded (Table 1).

Literature Review

A MEDLINE search limited to human and English articles for *achilles tendon* or *tendo achilles* or *triceps surae* or

tendoachilles or *tendo-achilles* or *achilles* as well as *tendinopathy* or *tendinosis* or *tendonitis* or *tenosynovitis*, yielding 499 citations. The same search strategy was used to search Embase and the Cumulative Index to Nursing and Allied Health Literature (CINAHL), resulting in 657 and 114 citations, respectively. Finally, a search of the Cochrane Central Register of Controlled Trials was undertaken using the search term *Achilles* located 194 citations.

Combining these results and removing duplicate citations yielded a total of 707 papers. The title and abstracts of these studies were reviewed, and 596 were excluded. Reasons for exclusion included: review papers and others with no outcome data (339), papers unrelated to Achilles tendinopathy (135), case series (31), papers describing tendon rupture (42), papers focusing on specific medical conditions associated with Achilles tendinopathy (48), and inability to locate a copy in English (1).

Full text of the remaining 111 articles was obtained. Eighty-one papers were then excluded because they were not randomized controlled trials. Two papers that included tendinopathy at multiple sites and failed to report separate outcomes for the Achilles tendons in the series were also excluded, leaving 28 papers.^{5,13-39}

The Cochrane Database of Systematic Reviews was consulted, and no additional papers were located. Finally, an exhaustive review was performed of the reference sections of each paper included in the study as well as all review articles on the subject published in the last 5 years in search of other articles meeting inclusion criteria. One additional paper was identified.⁴⁰ From all sources described above, a total of 29 studies were identified.

Upon detailed review of the inclusion criteria of the 29 studies, 10 did not specifically localize the tendinopathy to the midportion of the tendon,^{14,15,22,23,26,28,32-34,39} and 3 focused primarily on insertional tendinopathy.^{21,38,40} All 13 were excluded. The remaining 16 studies are the focus of this review. The search strategy is summarized in Figure 1.

Statistical Analyses

Statistical analyses from the included studies were used in determining statistical significance of the data, and *P* values

are reported as calculated by the authors of the original studies. When data were not statistically significant and no specific *P* values are reported, the data are reported as such.

RESULTS

Demographics

Demographic data from the 16 studies included in this review, including author, journal, publication year, patient age and sex, duration of symptoms, number of patients enrolled and percent follow-up, activity level, and the method of diagnosis of Achilles tendinopathy were recorded. The majority of studies include a predominance of men with a mean age between 30 and 50 years. Most are at least recreational athletes, and about half of the studies use ultrasound to confirm the diagnosis.

Outcomes

The studies included in this review used a wide range of outcome measures with little consistency between studies. Most of the studies attempted to quantify pain by using a variety of numeric pain scales. Other common outcomes measures included range of motion, return to activity, peak torque measurements, pain with a variety of provocative tests, and change in tendon diameter when measured with ultrasound. We chose to focus on change in numeric pain score as our primary outcome variable. Other data are summarized for reference.

Randomized Controlled Trials Comparing Eccentric Exercise With Controls

Five prospective randomized controlled trials were identified comparing eccentric exercises to controls for midportion Achilles tendinopathy (Table 2). Four trials showed statistically significant improvement in pain score with eccentric exercise compared with control,^{24,25,29,36} and one trial showed no significant difference.⁵

Randomized Controlled Trials Evaluating Variations of Eccentric Exercises, Splints, or Insoles

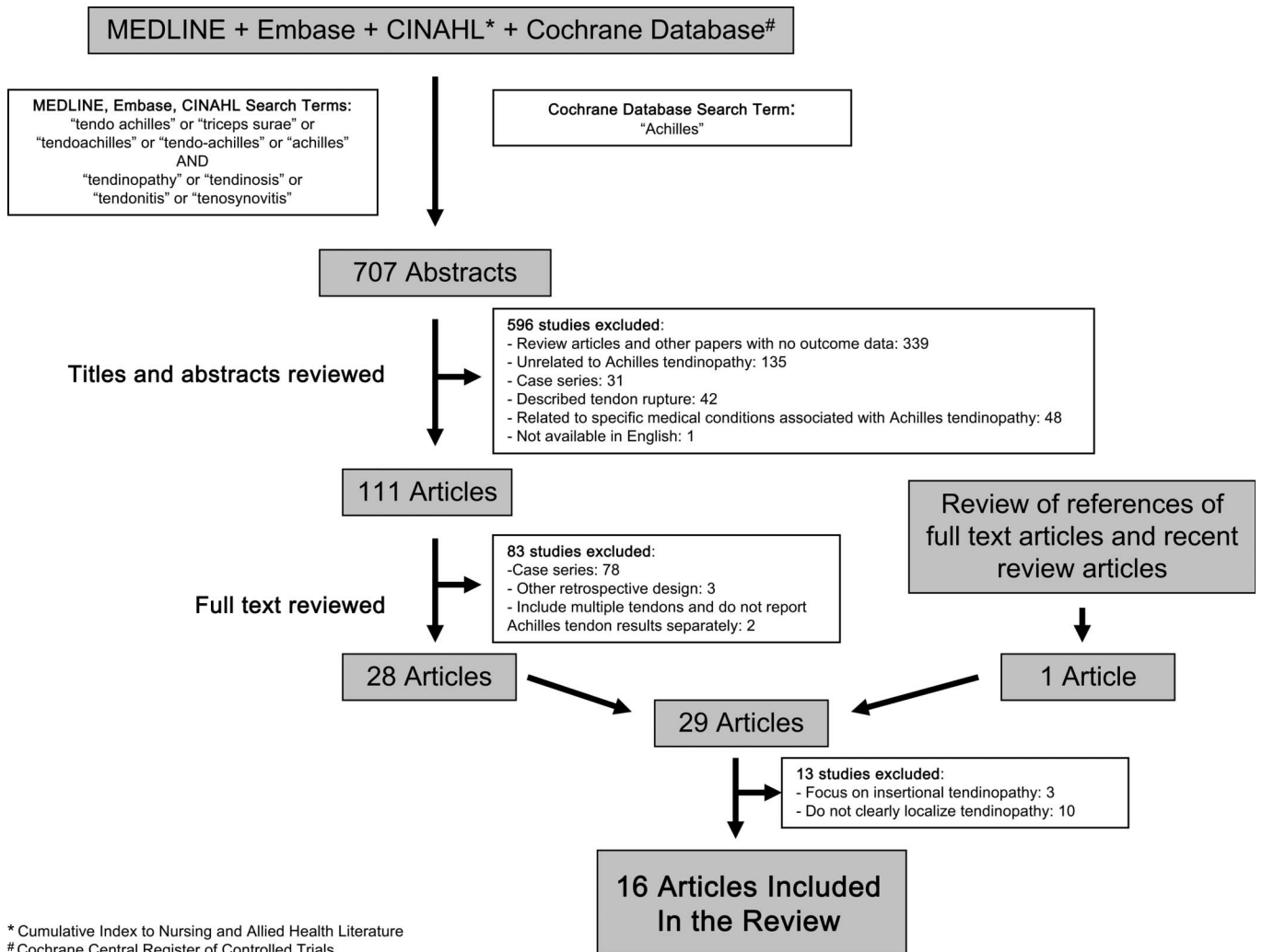
A recent randomized trial in Sweden demonstrated that restricting running and jumping for 6 weeks in patients undergoing eccentric training for Achilles tendinopathy had no impact on pain scores at 1 year after initiation of treatment.³¹ Roos et al found that eccentric exercises resulted in significantly lower pain scores after 12 weeks when compared with night splints alone.³⁰ In the same study, they were unable to demonstrate any difference in pain score when comparing those who performed eccentric exercises and wore night splints to patients who received either treatment alone. Similarly, Mayer et al demonstrated no difference in pain score when comparing eccentric exercises with custom fit insoles,²⁵ although the insole group was noted to have significantly better pain scores than controls (Table 3).

Extracorporeal Shockwave Therapy

Two randomized controlled trials have evaluated extracorporeal shockwave therapy (ESWT) for midportion

TABLE 1. Inclusion and Exclusion Criteria

Inclusion Criteria
Randomized controlled trials of treatment of midsubstance Achilles tendinopathy
Randomized controlled trials of treatment of tendinopathy in multiple locations with separate outcome reporting for patient with midsubstance Achilles tendinopathy
Exclusion Criteria
No outcome data reported
Review papers without original data
Nonrandomized studies and study designs without a comparison group
No localization of tendinopathy within the Achilles tendon
Papers investigating insertional tendinopathy
Papers describing treatment of tendon rupture
Focus on patients with another medical condition with Achilles pathology – seronegative arthropathies, familial hypercholesterolemia, etc.



* Cumulative Index to Nursing and Allied Health Literature
Cochrane Central Register of Controlled Trials

FIGURE 1. Search strategy.

Achilles tendinopathy. With placebo ESWT as a control group, Costa et al were unable to demonstrate a statistically significant effect after 3 months of treatment.¹⁷ Rompe et al did demonstrate statistically significant improvements in pain at 16 weeks when compared with a wait-and-see group, but no benefit of ESWT over eccentric exercises was noted (Table 4).²⁹

Local Injections

Steroid Injections

Two randomized controlled trials used local steroid injections for midportion Achilles tendinopathy. Fredberg et al found decreased pain with ambulation 4 weeks after ultrasound-guided injection of triamcinalone around the Achilles tendon when compared with placebo.²⁰ However, DaCruz et al were unable to demonstrate any improvement in pain or more rapid return to function 12 weeks after methylprednisolone injection (Table 5).¹⁸ Fredberg et al noted 1 tendon rupture in their experimental group and none in the control, and DaCruz et al noted no ruptures in either the experimental or treatment groups.

Other Injections

One randomized controlled trial demonstrated significant improvements in visual analog pain score after injection with Polidocanol, a sclerosing agent, into areas of neovascularization when compared with injection of local anesthetic.¹³ Brown et al compared peritendinous injections of aprotinin with placebo injections and were unable to detect any significant differences in pain or return to sport in 1 year of follow-up.¹⁶ Pforringer et al demonstrated decreased tendon thickness and decreased pain overall under stress conditions and with palpation with local injection of deproteinized hemodialysate into patients with acute midportion Achilles tendinopathy (Table 5).³⁷

Other Conservative Treatments

Neeter et al noted decreases in pain with stairs and pain after activity 6 months after iontophoresis with dexamethasone compared with saline.³⁵ Paoloni et al investigated the use of topical glycerol nitrate and found significantly less pain with activity relative to control 24 weeks after treatment (Table 5).²⁷

TABLE 2. Randomized Controlled Trials Comparing Eccentric Exercises With Controls

Author, Journal, and Year	Mean Patient Age (Range) and Sex	Duration of Symptoms	Method of Diagnosis	Intervention 1	Intervention 2	Cohort Size* and Length of Follow-up	Decrease in Pain Score	Other Outcome Data
Mayer† BJSM, 2007	38 (18 to 50); 100% male	Mean = 14 months	Painful nodule or pain over mid- portion of Achilles tendon	Physiotherapy: friction massage, ultrasound (1.5 W/cm ²)†, ice, and exercises (eccentric training, balance) × 10 sessions over 4 weeks	Control: normal activity	19/21 (90%); 4 weeks	Decrease in PES,‡ <i>P</i> < 0.05 Physiotherapy (eccentric exercises) = 55% Control = 10%	Increase in peak torque, NS§ Physiotherapy (eccentric exercises) = 15% Control = 5%
Rompe† AJSM, 2007	48; 39% male	All, >6 months	Pain 2 to 6 cm proximal to insertion with degenerative change noted on ultrasound	Eccentric exercises: 12 weeks	Control: wait-and-see	46/50 (92%); 16 weeks	Decrease in pain with loading,¶ <i>P</i> < 0.001 Eccentric exercises = 3.2 points Wait and see = 2.0 points	Subjective improvement, <i>P</i> = 0.001 Eccentric exercises = 60% Wait and see = 24% VISA-A** score, <i>P</i> = 0.001 Eccentric exercises = 75.6 Wait and see = 55.0
Silbernagel JMS, 2001	44 (19 to 77); 73% male	All, >4 months	Pain 2 to 6 cm proximal to insertion of tendon	Eccentric exercises: 12 weeks	Control: concentric exercises	37/49 (76%); 52 weeks	Decrease in median VAS†† pain score, NS Eccentric exercises = 28 points Concentric exercises = 18 points	Subjective full recovery, <i>P</i> < 0.05 Eccentric exercises = 60% Concentric exercises = 25% Patient satisfied with outcome, <i>P</i> < 0.05 Eccentric exercises = 70% Concentric exercises = 38% Have pain during activity, <i>P</i> < 0.05 Eccentric exercises = 26% Concentric exercises = 46% Return to initial activity level, NS Eccentric exercises = 55% Concentric exercises = 34%
Mafi KSSA, 2001	44; 55% male	All, >3 months	Pain 2 to 6 cm proximal to insertion with degenerative change noted on ultrasound	Eccentric exercises: 12 weeks	Control: concentric exercises	44/44 (100%); 12 weeks	Decrease in VAS pain score, <i>P</i> < 0.002 Eccentric exercises = 51 points Concentric exercises = 22 points	Resumed previous activity, <i>P</i> < 0.002 Eccentric exercises = 82% Concentric exercises = 36%
Niesen- Vertommen CJSM, 1992	35 (22 to 49); 59% male	Mean = 3.7 months	NR	Eccentric exercises: 12 weeks	Control: concentric exercises	17/17 (100%); 12 weeks	Decrease in pain score,¶ <i>P</i> < 0.01 Eccentric exercises = 4.7 points Concentric exercises = 3.0 points	

NR, not reported. *Number of tendons included (some patients had bilateral involvement). †Both Mayer et al and Rompe et al included a third group in their study (Table 3). ‡Pain Experience Scale: range, 0 to 100; higher score indicates greater pain. Decrease in pain score reported as a percentage only by the primary authors. §Not Significant: specific *P* value not reported in the original paper. ¶Numeric Pain Scale: range, 0 to 10; higher score indicates greater pain. **Victorian Institute of Sports Assessment, Achilles: range, 0 to 100; higher score indicates less severe symptoms. ††Visual Analogue Scale: range, 0 to 100; higher score indicates greater pain. ‡‡Not reported in the original paper.

TABLE 3. Randomized Controlled Trials Evaluating Variations of Eccentric Exercises, Splints, or Insoles

Author, Journal, and Year	Mean Patient Age (Range) and Sex	Duration of Symptoms	Method of Diagnosis	Intervention 1	Intervention 2	Cohort Size* and Length of Follow-up	Decrease in Pain Score	Other Outcome Data
Silbernagel AJSM, 2007	46 (30 to 58); 53% male	All, >2 months	Painful nodule or pain over mid-portion of Achilles tendon	Eccentric exercise program including eccentric exercises × 12 weeks; no limits on physical activity	Eccentric exercise program including eccentric exercises × 12 weeks; no running or jumping allowed for the first 6 weeks	53/57 (93%); 52 weeks	Decrease in median VAS† pain score, NS Full activity = 3.5 points Limited activity = 4.0 points	VISA-A‡ score, NS Full activity = 85 Limited activity = 91 Toe raise (total work), NS Full activity = 2431 Joules Limited activity = 2058 Joules Range of motion, dorsiflexion, NS Full activity = 35 degrees Limited activity = 35 degrees
de Vos BJSM, 2006	45 (26 to 59); sex not reported	All, >2 months	Pain 2 to 7 cm proximal to insertion	Eccentric exercises × 12 weeks	Night splints × 12 weeks	63/70 (90%); 12 weeks§		Subjective patient satisfaction,¶ NS** Eccentric exercises, night splint = 48% Eccentric exercises = 63% VISA-A score, NS Eccentric exercises, night splint = 67.0 Eccentric exercises = 68.8
Roos SJMSS, 2004	46 (26 to 60); 48% male	86%, >3 months	Pain 2 to 6 cm proximal to insertion of tendon	Eccentric exercises × 12 weeks	Night splints × 12 weeks	23/29 (79%); 12 weeks§	Decrease in mean pain†† score, <i>P</i> = 0.04 Eccentric exercises = 22 points Night splints = 7 points	Difficulty with sports, NS Eccentric exercises = 27% Night splints = 50%
Roos SJMSS, 2004	46 (26 to 60); 48% male	86%, >3 months	Pain 2 to 6 cm proximal to insertion of tendon	Eccentric exercises × 12 weeks	Both eccentric exercises and night splints × 12 weeks	23/29 (79%); 12 weeks§	Decrease in mean pain†† score, NS Eccentric exercises = 22 points Both treatments = 14 points	Difficulty with sports, NS Eccentric exercises = 27% Both treatments = 58%
Roos SJMSS, 2004	46 (26 to 60); 48% male	86%, >3 months	Pain 2 to 6 cm proximal to insertion of tendon	Night splints × 12 weeks	Both eccentric exercises and night splints × 12 weeks	23/30 (77%); 12 weeks§	Decrease in mean pain†† score, NS Night splints = 7 points Both treatments = 14 points	Difficulty with sports, NS Night splints = 50% Both treatments = 58%
Mayer BJSM, 2007	38 (18 to 50); 100% male	Mean = 14 months	Painful nodule or pain over mid-portion of Achilles tendon	Individually fit semi-rigid insoles during all activities	Physiotherapy: friction massage, ultrasound (1.5W/cm ²), † ice, and exercises (eccentric training, balance) × 10 sessions over 4 weeks	19/21 (90%); 4 weeks	Decrease in PES,‡‡ NS Insoles = 65% Physiotherapy (eccentric exercises) = 55%	Increase in peak torque, NS Insoles = 20% Physiotherapy (eccentric exercises) = 15%
Mayer BJSM, 2007	38 (18 to 50); 100% male	Mean = 14 months	Painful nodule or pain over mid-portion of Achilles tendon	Individually fit semi-rigid insoles during all activities	Control: normal activity	18/20 (90%); 4 weeks	Decrease in PES,‡‡ <i>P</i> < 0.05 Insoles = 65% Control = 10%	Increase in peak torque, NS Insoles = 20% Control = 5%

*Number of tendons included (some patients had bilateral involvement). †Visual Analog Scale: range 0 to 10; higher score indicates greater pain. ‡Victorian Institute of Sports Assessment, Achilles: range 0 to 100, higher score indicates less severe symptoms. §Follow-up was carried longer (52 weeks), but crossover was allowed after the 12-week point. ¶Subjective patient satisfaction score: 100% indicates completely satisfied. **Not significant, *P* values not reported in the original paper. ††Numeric Pain Scale: range, 0 to 10; higher score indicates greater pain. ‡‡Pain Experience Scale: range, 0 to 100; higher score indicates greater pain. Decrease in pain score reported as a percentage only by the primary authors.

TABLE 4. Randomized Controlled Trials Evaluating ESWT

Author, Journal, and Year	Mean Patient Age and Sex	Duration of Symptoms	Method of Diagnosis	Intervention 1	Intervention 2	Cohort Size* and Length of Follow-up	Decrease in Pain Score	Other Outcome Data
Rompe† AJSM, 2007	48; 39% male	All, >6 months	Pain 2 to 6 cm proximal to insertion with degenerative change noted on ultrasound	ESWT: 2000 pulses of 0.1 mJ/mm ² ‡ at 8 pulses/s weekly × 3 treatments	Control: wait-and-see	46/50 (92%); 16 weeks	Decrease in pain§ with loading, <i>P</i> = 0.001 ESWT = 3.0 points Wait and see = 2.0 points	Subjective improvement, <i>P</i> = 0.001 ESWT = 53% Wait and see = 24% VISA-A score,¶ <i>P</i> = 0.001 ESWT = 70.4 Wait and see = 55.0
Rompe† AJSM, 2007	48; 39% male	All, >6 months	Pain 2 to 6 cm proximal to insertion with degenerative change noted on ultrasound	ESWT: 2000 pulses of 0.1 mJ/mm ² ‡ at 8 pulses/s weekly × 3 treatments	Eccentric exercises: 12 weeks	47/50 (94%); 16 weeks	Decrease in pain§ with loading, <i>P</i> = 0.001 ESWT = 3.0 points Eccentric exercises = 3.2	Subjective improvement, NS** ESWT = 53% Eccentric exercises = 60% VISA-A score, <i>P</i> = 0.26 ESWT = 70.4 Eccentric exercises = 75.6
Costa CORR, 2005	52; 43% male	All, >4 months	Pain with dorsiflexion and palpation of Achilles	ESWT: 1500 pulses of 0.2 mJ/mm ² monthly × 3 treatments	Placebo shockwave (air bubble interposition to dissipate shockwaves)	43/49 (88%); 13 weeks	Decrease in pain score,†† NS ESWT = 14 points Placebo = -5 points	Pain†† during walking, <i>P</i> = 0.12 ESWT = 21 points Placebo = 5 points Pain†† during sport, NS ESWT = 20 points Placebo = 4 points

*Number of tendons included (some patients had bilateral involvement). †For results of eccentric exercise versus control, see Table 2. ‡Millijoules per square millimeter. §Numeric Pain Scale: range, 0 to 10; higher score indicates greater pain. ¶Victorian Institute of Sports Assessment, Achilles: range, 0 to 100; higher score indicates less severe symptoms. **Not Significant, specific *P* value not reported in the original paper. ††Pain Scale: range, 0 to 100; higher score indicates greater pain.

TABLE 5. Randomized Controlled Trials Evaluating Local Injection or Topical Application of Steroids, Sclerosing Agents, Aprotinin, or Deproteinized Hemodialysate, or Glyceryl Nitrate

Author, Journal, and Year	Mean Patient Age (Range) and Sex	Duration of Symptoms	Method of Diagnosis	Intervention 1	Intervention 2	Cohort Size* and Length of Follow-up	Decrease in Pain Score	Other Outcome Data
Fredberg SJR, 2004	35 (18 to 58); 62% male	50%, >2 months	Tenderness noted 2 to 4 cm proximal to insertion with mass noted on ultrasound	Injection of 20 mg triamcinolone in 4 mL × 1	Injection of 4 mL of placebo × 1	24/24 (100%); 4 weeks	Decrease in walking pain score, [†] $P < 0.02$ Triamcinolone = 2.9 points Placebo = 0.5 points	Tendon thickness, $P = \text{NR}$: Triamcinolone = 8.0 mm Placebo = 9.4 mm Local pain threshold, $P = \text{NR}$ Triamcinolone = 599 kPa Placebo = 460 kPa
DaCruz BJSM, 1988	28 (22 to 46); 64% male	NR	Pain in the midportion of the Achilles tendon	Injection of methylprednisolone (40 mg) × 1	Placebo injection × 1	34/42 (81%); 12 weeks	Decrease in pain score, [§] NS [¶] Methylprednisolone = 11 points Placebo = 11 points	Complete resolution of symptoms, NS Methylprednisolone = 32% Placebo = 33% Returned to at least 50% of normal activity, NS Methylprednisolone = 77% Placebo = 70%
Neeter SJMSS, 2003	38 (18 to 76); 60% male	All, >3 months	Pain 2 to 6 cm proximal to insertion of tendon	Dexamethasone iontophoresis: 20-min treatment every 3 to 4 days × 4 treatments	Saline iontophoresis: 20-min treatment every 3 to 4 days × 4 treatments	25/25 (100%); 26 weeks	Pain after activity,** $P < 0.05$ Dexamethasone = 17% Saline = 64% Pain with walking,** NS Dexamethasone = 14% Saline = 36% Pain with stairs,** $P < 0.05$ Dexamethasone = 0% Saline = 36%	Number of toe lifts performed, NS Dexamethasone = 14 Saline = 10
Alfredson KSSTA, 2005	50 (38 to 66); 45% male	All, >3 months	Tenderness noted 2 to 4 cm proximal to insertion with mass noted on ultrasound	Injection of sclerosing agent polidocanol (5 mg/mL) into neovascularized areas of tendon under ultrasound guidance × 2 injections	Injection of nonsclerosing lidocaine and epinephrine into neovascularized areas of tendon under ultrasound guidance × 2 injections	20/20 (100%); 12 weeks	Decrease in VAS pain score, ^{††} $P < 0.005$ Sclerosing injection = 48 points Placebo injection = 2 points	Percent of patients satisfied, $P = \text{NR}$ Sclerosing injection = 90% Placebo injection = 50%
Brown BJSM, 2006	46 (30 to 73); 64% male	All, >6 weeks	Pain on Achilles palpation and with activity, noninsertional	Injection of 30,000 IU ^{‡‡} aprotinin weekly × 3 treatments	Injection of placebo × 3 treatments	26/33 (79%); 52 weeks	Decrease in VAS pain score, ^{††} NS Aprotinin = 36.3 points Placebo = 32.3 points	Returned to sport, NS Aprotinin = 77% Placebo = 85% Number of hops before pain, NS Aprotinin = 7.4 Placebo = 5.5

TABLE 5. (continued) Randomized Controlled Trials Evaluating Local Injection or Topical Application of Steroids, Sclerosing Agents, Aprotinin, or Deproteinized Hemodialysate, or Glyceryl Nitrate

Author, Journal, and Year	Mean Patient Age (Range) and Sex	Duration of Symptoms	Method of Diagnosis	Intervention 1	Intervention 2	Cohort Size* and Length of Follow-up	Decrease in Pain Score	Other Outcome Data
Pforringer CJSM, 1994	33 (18 to 55); sex not reported	All, <3 months	Thickened Achilles tendon by >2 mm compared to contralateral or mean on ultrasound	Injection of 5 mL mepivacaine and 5 mL of deproteinized hemodialysate × 3 at 0, 3, and 10 days	Injection of 5 mL mepivacaine and 5 mL of saline at 0, 3, and 10 days	60/60 (100%); 3 weeks	Decrease in pain score, §§ $P < 0.0002$ Deprotein hemodialysate = 4.8 points Placebo = 1.5 points	Decrease in tendon thickness, $P < 0.0001$ Deprotein hemodialysate = 27.2% Placebo = 14.2% Pain: stress conditions, $P < 0.02$ Deprotein hemodialysate = 0% Placebo = 25.0% Local tenderness, $P < 0.00001$ Deprotein hemodialysate = 16.7% Placebo = 70.0%
Paoloni JBJS Am, 2004	49 (24 to 77); 62% male	All, >4 months	Tender nodule 2 to 6 cm proximal to insertion with no tear by ultrasound	Transdermal glyceryl trinitrate 1.25 mg q24h for 24 weeks	Transdermal placebo patch q24h for 24 weeks	58/65 (89%); 24 weeks	Decrease in activity pain, ¶¶ $P = 0.03$ Glyceryl trinitrate = 1.9 points Placebo = 1.4 points Decrease in night pain, §§ NS Glyceryl trinitrate = 0.7 points Placebo = 0.5 points	Hop test pain, $P = 0.01$ Glyceryl trinitrate = 0.5 Placebo = 1.6 Decrease in local tenderness, §§ NS Glyceryl trinitrate = 1.5 points Placebo = 1.3 points

NR, not reported. *Number of tendons included (some patients had bilateral involvement). †Pain score: range, 0 to 10; higher score indicates increased pain. ‡Not reported by original author. §Pain Scale: range, 0 to 100; higher score indicates increased pain. ¶¶Not significant, specific P values not reported by original author. **Pain reported as either present or absent, no pain score utilized. ††Visual Analogue Scale: range, 0 to 100; higher score indicates increased pain. ‡‡International Units. §§Numeric Pain Scale: range, 0 to 10; higher score indicates increased pain. ¶¶Scale: 0 to 4; higher score indicates greater pain.

DISCUSSION

Eccentric Exercises

Eccentric muscle training for treatment of Achilles tendinopathy has been recommended since the mid-1980s.⁴¹ Theories on the mechanism of eccentric exercises in decreasing pain include more rapid strengthening of the calf muscle, stiffening and lengthening of the myotendinous unit, and decreased neovascularization in the region.^{24,30,42-44} Regardless of the mechanism, significant improvement in patient satisfaction and decreased pain were seen in 60% to 90% of patients, and it has been demonstrated to be superior to controls in 4 of the 5 randomized controlled trials outlined above. Performance of a meta-analysis on these data was prohibited by the heterogeneity of treatment groups, interventions, and outcome measures across the prospective trials evaluating eccentric exercises.

A recent randomized controlled trial attempting to reproduce the beneficial effects of eccentric exercise on Achilles tendinopathy showed mild improvement from baseline with eccentric exercises at 3 months and 1 year, but it was not able to demonstrate superiority of this technique to stretching.²⁶ This study included patients with midportion as well as insertional tendinopathy. Other work by the same authors has demonstrated insertional tendinopathy to be less responsive to eccentric exercises than midportion tendinopathy.^{45,46} Careful distinction between these conditions should be made in any future trials.

Extracorporeal Shockwave Therapy

The two randomized controlled trials of ESWT included in this review suggest that it may be of utility in the treatment of chronic midportion Achilles tendinopathy. These trials employ low- to medium-energy ESWT (0.1-0.2 mJ/mm²) without the use of general anesthesia. Significantly greater effect was noted in the Rompe et al study, but its use of a wait-and-see group as a control raises concerns of a placebo effect with treatment.²⁹ In the Costa et al study, patients were blinded to the treatment they received, and the treatment effect was not significant.¹⁷

A recent randomized controlled trial investigating high-energy ESWT for insertional Achilles tendinopathy showed significant pain relief at 1 year.²¹ Investigation of the effect of ESWT therapy for tendinopathy in other anatomic locations has been extensive and contradictory, with numerous randomized trials showing success,⁴⁷⁻⁵⁵ as well as multiple randomized trials failing to show an effect.⁵⁶⁻⁶⁰ Interpretation of these data are complicated by inconsistent definition of low- and high-energy ESWT and the use of multiple techniques to generate the pulses. Clear definition of terms and consistent technique will be necessary in future randomized controlled trials in this area.

Local Steroid Therapy

The 3 randomized controlled trials described above present a mixed picture of the effect of local steroids on healing, with 2 studies indicating some benefit^{20,35} and the other detecting none.¹⁸ Accurate placement of the injection was confirmed by ultrasound by Fredberg et al, and the iontophoresis method used by Neeter et al does not require

accurate injection. DaCruz et al did not confirm the injection site with imaging, instead relying on the experience of the senior author for accurate placement. The difficulty of obtaining appropriate placement without imaging is noted by Fredberg et al and may contribute to the failure of DaCruz et al to show an effect of the steroid injection relative to placebo. The relatively short follow-up (4 weeks) obtained by Fredberg et al should also be considered when evaluating these data; short-term improvement may not correlate with long-term outcomes. A major concern for the use of corticosteroid injections in the treatment of tendonopathies is subsequent tendon rupture, as was observed in 1 study cited in this review.

The mechanism behind any positive effect of local steroids on chronic Achilles tendinopathy remains unclear. A recent paper questioning the prevailing opinion that inflammation is not present in chronic tendinopathy may point to an antiinflammatory mechanism.⁶¹ Several authors have hypothesized that any beneficial effects of corticosteroids in this condition are owed to other local steroid effects rather than suppression of inflammation, including lysis of tendon-peritenon adhesions or alteration of the function of pain-generating nociceptors in the region.⁶²⁻⁶⁴

At this time, there is not significant evidence from which to draw firm conclusions on the utility of local steroid treatments for midportion Achilles tendinopathy. Previous reviews on this subject have come to the same conclusion.^{63,64}

Sclerosing Injections

As alluded to above, the presence of neovascularization has been associated with painful midportion Achilles tendinopathy.⁴³ Sensory nerves traveling with these vessels have been implicated as possible pain generators, leading to the hypothesis that destruction of the vessels and nerves will lead to pain relief.⁶⁵⁻⁶⁷ If other authors can demonstrate success in using sclerotherapy similar to Alfredson et al, it may prove to be a useful alternative therapy.¹³ However, the demonstration that less invasive eccentric exercises are also capable of decreasing neovascularization relegate sclerosing injection therapy to those that fail or are not capable of performing eccentric exercises.⁴⁴

Other Conservative Treatments

Aprotinin injections have been used for treatment of tendinopathy throughout the body, with a placebo-controlled randomized controlled trial showing improved outcomes of patellar tendinopathy.⁶⁸ A drawback of aprotinin therapy is the formation of antibodies to the medication, possibly limiting its subsequent use.⁶⁹

Both deproteinized hemodialysate injections and topical glycerol nitrate application showed positive results in one study each. Both are believed to influence Achilles tendinopathy through their effects on fibroblasts' ability to synthesize collagen. Deproteinized hemodialysate is believed to make the environment of fibroblasts in the region more conducive to anabolic pathways.⁷⁰⁻⁷² Topical glycerol nitrate application increases local tissue nitric oxide concentrations, which are believed to improve fibroblast function and wound healing.^{27,73,74} The relatively short duration of symptoms and short follow-up in the Pforringer et al paper

limit conclusions that can be made regarding deproteinized hemodialysate treatment.

Mayer et al demonstrated decreased pain relative to controls at 4 weeks with custom insoles, but no improvement was noted relative to physical therapy, including eccentric exercises.²⁵ The use of heel pads in Achilles tendinopathy was evaluated in the mid-1980s by Lowdon et al and found to be ineffective.²³ This earlier study did not differentiate between insertional and midportion Achilles tendinopathy, and the heel pads used were not custom-fit, possibly influencing outcome. However, the relatively short follow-up in the Mayer study weakened their finding of a positive effect of custom insoles.

CONCLUSION

There is currently more evidence in support of eccentric exercises than the other interventions included in this review. This evidence, combined with their low cost and low risk, makes these exercises ideal first-line therapy. Alternative treatment should be considered in patients who are unable or unwilling to perform or have failed treatment with these exercises. ESWT, injections of sclerosing agents or deproteinized hemodialysate, and topical glyceryl nitrate application show promise in early studies without known complications to date, but significant additional study is needed. More investigation is needed into the utility of local steroid therapy.

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