Effect of High-Volume Injection, Platelet-Rich Plasma, and Sham Treatment in Chronic Midportion Achilles Tendinopathy

A Randomized Double-Blinded Prospective Study

Anders Ploug Boesen,*†‡ MD, PhD, Rudi Hansen,† PT, MSc, Morten Ilum Boesen,§ MD, PhD, Peter Malliaras,‖ BPhysio (Hons), PhD, and Henning Langberg,¶ DrMed, PhD, DMSc
Investigation performed at the Institute of Sports Medicine, Bispebjerg Hospital, Copenhagen, Denmark

Background: Injection therapies are often considered alongside exercise for chronic midportion Achilles tendinopathy (AT), although evidence of their efficacy is sparse.

Purpose: To determine whether eccentric training in combination with high-volume injection (HVI) or platelet-rich plasma (PRP) injections improves outcomes in AT.

Study Design: Randomized controlled trial; Level of evidence, 1.

Methods: A total of 60 men (age, 18-59 years) with chronic (>3 months) AT were included and followed for 6 months (n = 57). All participants performed eccentric training combined with either (1) one HVI (steroid, saline, and local anesthetic), (2) four PRP injections each 14 days apart, or (3) placebo (a few drops of saline under the skin). Randomization was stratified for age, function, and symptom severity (Victorian Institute of Sports Assessment–Achilles [VISA-A]). Outcomes included function and symptoms (VISA-A), self-reported tendon pain during activity (visual analog pain scale [VAS]), tendon thickness and intratendinous vascularity (ultrasonographic imaging and Doppler signal), and muscle function (heel-rise test). Outcomes were assessed at baseline and at 6, 12, and 24 weeks of follow-up.

Results: VISA-A scores improved in all groups at all time points ($P < .05$), with greater improvement in the HVI group (mean ± SEM, 6 weeks = 27 ± 3 points; 12 weeks = 29 ± 4 points) versus PRP (6 weeks = 14 ± 4; 12 weeks = 15 ± 3) and placebo (6 weeks = 10 ± 3; 12 weeks = 11 ± 3) at 6 and 12 weeks ($P < .01$) and in the HVI (22 ± 5) and PRP (20 ± 5) groups versus placebo (9 ± 3) at 24 weeks ($P < .01$). VAS scores improved in all groups at all time points ($P < .05$), with greater decrease in HVI (6 weeks = 49 ± 4 mm; 12 weeks = 45 ± 6 mm; 24 weeks = 34 ± 6 mm) and PRP (6 weeks = 37 ± 7 mm; 12 weeks = 41 ± 7 mm; 24 weeks = 37 ± 6 mm) versus placebo (6 weeks = 23 ± 6 mm; 12 weeks = 30 ± 5 mm; 24 weeks = 18 ± 6 mm) at all time points ($P < .05$) and in HVI versus PRP at 6 weeks ($P < .05$). Tendon thickness showed a significant decrease only in HVI and PRP groups during the intervention, and this was greater in the HVI versus PRP and placebo groups at 6 and 12 weeks ($P < .05$) and in the HVI and PRP groups versus the placebo group at 24 weeks ($P < .05$). Muscle function improved in the entire cohort with no difference between the groups.

Conclusion: Treatment with HVI or PRP in combination with eccentric training in chronic AT seems more effective in reducing pain, improving activity level, and reducing tendon thickness and intratendinous vascularity than eccentric training alone. HVI may be more effective in improving outcomes of chronic AT than PRP in the short term.

Registration: NCT02417987 (ClinicalTrials.gov identifier).

Keywords: eccentric training; high-volume injection; tendinopathy; platelet-rich plasma; ultrasonography; Achilles tendon

Chronic midportion Achilles tendinopathy (AT) is a common overuse injury that is often longstanding and difficult to manage. The lifetime prevalence of AT is reported to be 52% in former runners, and the annual incidence is 7% to 9% in current runners.[52] Several studies have reported that the incidence of AT in runners accounts for 6% to 18% of all injuries.[21,42,58] The condition affects both sexes but has a higher incidence in middle-aged men.[3,14] The clinical findings in tendon overuse injuries are a combination of pain, swelling, and inability to perform strenuous activity.[8,32] Overloading is thought to be essential in the development of the condition.[8] AT occurs most commonly in the midportion of the tendon, and the pain mechanism is not completely

The American Journal of Sports Medicine, Vol. 45, No. 9
DOI: 10.1177/0363546517702862

understood. Most of the histological findings in tendinopathy represent ingrowth of new vessels with associated nerve endings, chronic degeneration (rather than inflammation), and micro tears of the tendinous tissue.[28,35]

The ingrowth of new vessels and nerves (neurovascularization) from the ventral side of the tendon is thought to be the main pain generator in AT.[12,30] However, the role of neovascularization in the pathogenesis of overuse tendon disease is largely unknown.[12,30] Doppler ultrasonographic imaging has demonstrated intratendinous vascularity in Achilles tendons with tendinopathy.[49] Abnormal abundance of vessels was found in the ventral aspect of the tendon adjacent to Kager's triangle. These vessels were accompanied by ingrowth of proliferating group III and IV nerves that are hypothesized to be integral in pain transmission.[48] The association between pain and intratendinous vascularity is not absolute, as tendons with intratendinous vascularity may not be painful,[11,36] whereas tendons without intratendinous vascularity may be painful.[22] However, evidence indicates a higher degree of pain in pathologic tendons with intratendinous vascularity compared with pathologic tendons without intratendinous vascularity.[15]

No gold standard regimen exists for the treatment of AT, but it seems crucial to include progressive tendon loading as part of the treatment.[4,41] For more than a decade, eccentric training has been widely used in the treatment and prevention of chronic AT,[3,4] and more recently an active rehabilitation regimen using heavy, slow resistance training has shown good results in patellar tendinopathy[38] and AT,[7] although pain and functional outcomes did not differ significantly with the eccentric program in either study. Other treatment modalities include load modification, analgesic and nonsteroidal anti-inflammatory drugs, ice therapy, manual therapy, and correction of biomechanics and functional issues throughout the kinetic chain.[3,41,52] Shockwave, injection therapy, and surgery may be offered in recalcitrant cases.[40,41] For most treatments of AT, aside from exercise interventions, few randomized controlled trials (RCTs) have been published,[51] and best practice is probably largely influenced by individual presentation (eg, extent of pain or extent of muscle atrophy/weakness) as well as experience of the clinician.

High-volume injection (HVI) involves a large volume of saline, steroid, and local anesthetic injected into the interface between the midportion of the Achilles tendon and peritendinous tissue and Kager's fat pad.[12,30] The high volume is thought to have a mechanical effect on neurovascular ingrowth and adhesions between the tendon and peritendinous tissue but may also have effects on pain and local sensitization.[12,30] A case series study performed by Chan et al[12] found that HVI in patients with chronic AT significantly reduced pain and improved function both at short-term follow-up (2 weeks) and after an average of 30.3 weeks of follow-up. Further case series studies by the same group, investigating the effect of HVI in chronic tendinopathy, have shown the same promising results in terms of pain, symptoms, function, and reduced tendon thickness and intratendinous vascularity on ultrasonography imaging.[19,30,43,44,47] These findings should be interpreted with caution, given that these studies are case series with no control group.

Platelet-rich plasma (PRP) injection is commonly used in clinical practice to treat chronic tendinopathy.[23] The mechanism is believed to be a variety of growth factors, including platelet-derived growth factor, transforming growth factor β, and insulin-like growth factor, that promote a healing response.[29,37,50] One of the main advantages is that PRP is autologous and is prepared at the time of treatment (point of care); therefore, it has an excellent safety profile with almost no side effects.[23] The few level 1, randomized controlled clinical trials that have been published have not found clear evidence for improved clinical outcomes of PRP compared with placebo control.[20,23] Other studies have reported more promising results when examining the effect of PRP on other chronic tendinopathies.[18,24-26] Questions remain regarding the optimal composition of the PRP bolus[23,27] and number of injections. Prior RCTs in AT have administered only 1 injection,[20,23] whereas other studies have shown more positive outcomes with multiple injections.[13,24,59]

The aim of this study was to compare the effect of HVI, multiple PRP injections, and placebo injection, in combination with eccentric training, on pain and functional outcome in patients with chronic midportion AT. It was hypothesized that HVI or multiple PRP injections together with eccentric training would decrease AT pain and improve function outcome more than eccentric training alone (the placebo treatment consisted of sham injection and eccentric exercises).

METHODS

Study Design

The double-blinded, randomized prospective trial was performed at a large district hospital at the Institute of Sports

*Address correspondence to Anders Ploug Boesen, MD, PhD, Institute of Sports Medicine, Department of Orthopaedic Surgery M, Bispebjerg Hospital, Bispebjerg Bakke 23, DK-2400 Copenhagen, Denmark, and Department of Orthopaedic Surgery, Hvidovre Hospital, DK-2650 Hvidovre, Denmark (email: boesenanders@hotmail.com).

†Institute of Sports Medicine Copenhagen, Department of Orthopaedic Surgery M, Bispebjerg Hospital, and Center for Healthy Aging, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.

‡Department of Orthopaedic Surgery, Hvidovre Hospital, Hvidovre, Denmark.

§Department of Orthopaedics, Køge Sygehus, Køge, Denmark.

||Department of Physiotherapy, School of Primary Health Care Faculty of Medicine, Nursing and Health Science, Monash University, Frankston, Victoria, Australia.

¶CopenRehab, Institute of Social Medicine, Department of Public Health, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.

One or more of the authors has declared the following potential conflict of interest or source of funding: This work was supported by Arthrex Danmark A/S, Copenhagen, Denmark, with the Arthrex Double Syringe System. Arthrex Danmark A/S had no role in the design and conduct of the study; in the collection, management, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Medicine, Copenhagen, Denmark. The single-center study was advertised to sports medicine physicians, orthopaedic surgeons, physical therapists, and the general public. The primary analysis was performed after 24 weeks of follow-up, and blinding was disclosed for the primary researcher and subjects after the 24-week intervention. The study protocol (H-1-2010-052a) was approved by the local Ethics Committee of Region Copenhagen in accordance with the Helsinki declaration, and the study protocol was registered at ClinicalTrials.gov (Identifier: NCT02417987). All patients were informed of the risks associated with the study and gave written informed consent.

Patients

Patients with suspected AT contacted the main researcher by telephone or email, and detailed information about the study was given by telephone and by email. If patients were interested and suitable for inclusion, an appointment was made at the sports medicine institute. An experienced sports medicine physician (A.P.B.) evaluated the patients with a questionnaire, clinical examination, and ultrasonography for inclusion. Inclusion criteria were healthy males with clinical (thickness and pain) and ultrasonographic (tendon thickness and intratendinous vascularity) features of chronic midportion AT (approximately 2-7 cm proximal to the insertion on the calcaneus). The age inclusion criterion was 18 to 59 years, and symptoms should have been present for at least 3 months. Exclusion criteria were (1) clinical suspicion and ultrasonographic indication of other musculoskeletal injuries (eg, insertional disorders and tendon rupture), (2) the presence of diabetes or cardiovascular disease, or (3) previous injection with steroids or any kind of blood products (eg, PRP) or treatment with fluoroquinolones (which are known to cause tendinopathy[39]) during the last 6 months. More detailed information regarding the inclusion and exclusion criteria is provided at Clinical Trials.gov and in Appendix Table A1 (available online).

Procedures

A sports medicine physician (A.P.B.) prepared an HVI, a PRP injection, and a saline injection for every patient. The HVI consisted of five 10-mL syringes (total volume of 50 mL) containing a mixture of 10 mL 0.5% bupivacaine hydrochloride and 20 mg of Depo-Medrol (40 mg/mL methylprednisolone acetate) (Pfizer, New York, New York), followed by four 10-mL syringes containing injectable normal saline.[12]

The PRP injection was prepared by use of the Arthrex Double Syringe System in accordance with formal instructions.[1] The physician drew 10 mL of venous blood from the cubital vein in a closed double syringe system. The blood was then spun 1 time in a centrifuge (1500 rpm) for 5 minutes, and approximately 4 mL of the plasma (PRP) was obtained in the smaller inner syringes for infiltration.[1] No activator (eg, $CaCl_2$) was added before injection. A small amount (few drops) of the PRP was collected and frozen for later evaluation of platelet and growth factor concentration. Finally, 4 mL of isotonic saline was prepared in an identical syringe.

Randomization

Age and symptom severity were used to stratify patients into the 3 groups (HVI, PRP, and placebo) to ensure similarity between groups. Before randomization, patients were divided into age groups (<40 years and >40 years), and the 2 age groups were then stratified based on the Victorian Institute of Sports Assessment–Achilles (VISA-A) score (<50 and ≥50 points, of a possible 0-100 points). Randomization was then performed by use of sealed opaque envelopes. The patients were randomized into 1 of 3 groups (HVI, PRP, or placebo). The balance between the numbers in the groups was ensured by performing a block randomization (block size of 10).

After the randomization, an unblinded sports medicine physician (A.P.B) took a blood sample from the cubital vein of all patients (HVI, PRP, and placebo group) to prepare a PRP syringe. In all patients, both an HVI syringe and a placebo syringe were also prepared by the sports medicine physician (A.P.B) to ensure that each patient was blinded to this treatment. The same setup and procedures were performed 4 times with the first injection (HVI, PRP, or placebo) at baseline and 2-week intervals between each injection. The HVI injection was conducted only at baseline, whereas the following 3 treatments in the HVI group were placebo treatments to blind the patients (Appendix Table A2, available online). A covering sheath was placed around the syringe and hub of the needle so that the content of the injection was unknown to both the patients and the sports physical therapist (R.H.) who performed the training program and collected the VISA-A and visual analog pain scale (VAS) scores. Researchers involved in analyzing the ultrasonographic measurements and performing statistical analysis were blinded to group allocation. The only procedure that was not double blinded (only single blinded) was the ultrasonographic imaging (tendon thickness and intratendinous vascularity) performed by the same physician (A.P.B) performing the injections.

Intervention

Ultrasonography. Ultrasonography was performed with a Hitachi Hi Vision 900 (Hitachi Medical Corporation; 14-5 MHz linear array transducer). The color Doppler (CD) gain was set just below the level that produced random noise in the image. The Doppler settings were the same for all examinations. We chose CD and not power Doppler (PD) because the equipment in this study has higher sensitivity in the CD mode compared with the PD mode.

The Achilles tendons were scanned by the same experienced physician (A.P.B.) and were injected with the patients placed prone with a pillow under the distal tibia. The patients' feet were hanging freely in a relaxed, slightly plantarflexed position. So that patients did not see the injection procedure, they were instructed to not turn their head during the injection. All Achilles tendons were scanned in both longitudinal and transverse planes.[8-10] The tendons and peritendinous tissues were evaluated with CD, and the presence of maximum intratendinous vascularity in the longitudinal plane was recorded.[9] Intratendinous vascularity

was measured via a semiquantitative grading system with CD grades 0 through 5, where grade 0 indicated no CD; grade 1, 1 or 2 tiny foci; grade 2, less than 5% CD inside the region of interest (ROI); grade 3, 5% to 24% CD inside ROI; grade 4, 25% to 49% CD inside ROI; and grade 5, ≥50% CD inside ROI.[8,10] The Achilles tendons were examined for gray-tone changes, such as thickening (measured in the transverse plane), degeneration, hypo-echogenic areas, and the presence of any other surrounding soft tissue abnormality. CD was used to ascertain the presence of intratendinous CD. All data were stored as a DICOM file for postprocessing analysis.

The most symptomatic area (based on patient feedback upon palpation and ultrasonographic findings) was used as a marker for the injection between the anterior part of the tendon and the peritendinous tissue.

MuscleLab (Heel-Rise Test). The muscle functional evaluation conducted with MuscleLab (Ergotest Technology) consists of a standing 1-leg heel-rise test as described by Silbernagel et al.[54,56] Because the exercise treatment mainly consists of heel-rise exercises, the recovery of heel-rise performance has been suggested to be a measure of not only the effect of treatment but also the compliance with training.[53] The test has been shown to have good reliability in healthy subjects and good validity for subjects with chronic AT to measure the effect of treatment over time and the effect of the training compliance.[53] Briefly, the test was performed unilaterally with the subject standing on a small bench. The patient was instructed to reach as high as possible on each heel-rise with a frequency of 30 heel-rises per minute and to perform as many heel-rises as possible. The total amount of work performed (the total load used in the exercise [body weight] × total distance × gravity) in joules was used for data analyses.[53]

High-Volume Injection (HVI). The technique was identical to that suggested by Chan et al[12] and Humphrey et al.[30] Using an aseptic technique and helped by an assistant, the physician inserted a 21-gauge needle between the anterior aspect of the Achilles tendon and Kager's fat pad; the needle was attached to a connecting tube and was inserted under real-time ultrasonographic guidance. A mixture of 10 mL 0.5% bupivacaine hydrochloride and approximately 20 mg of Depo-Medrol was injected, immediately followed by 10 mL of injectable normal saline 4 times (total volume of 50 mL). The position of the needle was monitored continuously by ultrasonography during this phase, and the needle was moved gently across the anterior aspect of the tendon to ensure uniform effect over the symptomatic area. The saline was injected in bursts to maximize potential mechanical effect.[12] As mentioned, the HVI injection was conducted only at baseline, whereas the 3 treatments that followed during the trial were placebo treatments (described below).

Platelet-Rich Plasma (PRP). The PRP injection was prepared by use of the Arthrex Double Syringe System, as previously mentioned.[1] Using an aseptic technique and under real-time ultrasonographic guidance, the physician inserted a 21-gauge needle and injected the PRP between the tendon and peritendinous tissue just around the most affected area of the tendon. No local anesthetic was used for the injection procedure. Immediately after the injection, the patients remained prone for 10 minutes (the same in all groups). The PRP was prepared each time and the procedure was performed 4 times, with the first injection at baseline and with 2-week intervals between each injection.

Placebo. To maintain blinding conditions for all patients (HVI, PRP, and placebo group), as previously mentioned, a blood sample was taken with the same Arthrex system used for the PRP preparation. The patients in the placebo group were also positioned prone resembling the HVI and PRP procedures. The physician gave the impression of preparing an active treatment; that is, he left the examining room for several minutes. Using an aseptic technique, the physician inserted a 21-gauge needle under real-time ultrasonographic guidance. The needle was inserted in a more anterior direction, away from the tendon just under the skin, so as to not affect any tendinopathic or neovascular tissue. A few drops of isotonic injectable saline were injected. The needle was kept inserted for some time to resemble an active treatment protocol and thereby maintain blinding conditions. The placebo procedure was performed 4 times, as in the PRP group, with a 2-week interval during the trial.

Rehabilitation and Exercise Intervention. All patients received detailed instructions on the standardized rehabilitation and eccentric program recommended by Chan et al[12] and de Vos et al.[23] Exercise was prescribed by a blinded physical therapist (R.H.). Patients were allowed to walk on the injected leg immediately but were advised to refrain from sports activity, strenuous walks, running, or hard physical work during the first 72 hours. Thereafter, the 12-week daily eccentric exercise program was commenced twice a day (180 repetitions per day) as recommended by Alfredson et al.[4] Two days of rest from the eccentric exercise program and other activity that would stress the Achilles tendon was recommended just after the follow-up injections. All activity during the first 10 days had to be of low or moderate intensity with nonimpact fitness work (eg, cycling, swimming, and rowing). Activities were furthermore restricted to 3 or 4 times weekly at a maximum of 40 minutes. On day 10, the patients were allowed to resume running activities. Patients were told that initial running activities should be restricted to a maximum of 5 minutes 2 times per week, with low intensity the first week, and should be progressed only by 2 to 3 minutes per workout per week. Patients could increase the intensity of sports activities when they had only mild pain, defined as "load tolerance" (maximum score of 3 on a scale of 0-10, with 0 representing no pain and 10 representing maximum pain) and no increase in morning stiffness the following day.[23,53] The patients were advised to run only on flat surfaces and to avoid fast running, jumping, fast cutting movements, and activities that place high impact on the injured leg until running could be performed continuously for 30 minutes and with no discomfort. All patients consulted the physical therapist (R.H.) on days 14, 28, and 42 to adjust activity level, modify the eccentric program if needed (eg, increase load or adjust technique), or discuss any questions or problems concerning rehabilitation. If pain or discomfort occurred, the patients were instructed to decrease activity intensity and/or quantity. Patients were also instructed to avoid using other kinds of treatments or interventions during the follow-up period. After the 12-week program

consisting of eccentric training twice a day (180 repetitions per day), patients were encouraged to continue eccentric training 3 times a week (180 repetitions per day) from weeks 12 to 24.

Outcome Measures

The primary outcome measure in this study was the Danish version of the VISA-A questionnaire,[31] a valid and reliable self-administered tool used to assess pain and function among AT patients and to evaluate clinically relevant changes over time (effect of HVI, PRP, and eccentric training).[31,55] A VISA-A score of 100 points represents no pain and full function, and scores become progressively lower with worsening tendinopathy symptoms.[31]

The secondary outcome measures were pain during activity measured with a VAS (where 0 equals no pain and 100 is the worst pain imaginable; 0-100 mm), tendon thickness measured via ultrasonography (anterior-posterior diameter in transverse plane), intratendinous vascularity assessed by CD activity, and muscle function measured with the 1-leg heel-rise test.[53] A patient satisfaction questionnaire was administered after 12 weeks and 24 weeks of follow-up. The patients were asked to tick 1 of 2 boxes to indicate whether they were "satisfied" or "not satisfied" with the clinical outcome.[38] Furthermore, the patients were asked whether they had returned to running and the time frame of their return. The patients kept daily compliance diaries for the eccentric exercises.[23] At follow-up, the subjective adherence of the patients was determined by asking which percentage of the prescribed repetitions the patients had accomplished,[23] and an average of 75% or above the recommended repetitions (180 per day) was accepted as good compliance. All outcome measures were completed and performed at baseline (before first injections) and again at 6, 12, and 24 weeks.

Statistical Analysis

All data were analyzed in SigmaPlot (v11) by use of 2-way repeated-measures analysis of variance (ANOVA) with Student-Newman-Keuls post hoc test. A 1-way ANOVA was used to compare baseline demographics between treatment groups. Categorical data (satisfaction) were analyzed using a global 3×2 chi-square analysis. Setting the power to 0.80 (2-sided testing), with a hypothesis that groups should differ by at least 10 points on the VISA-A score, indicated that 16 patients in each group would be required. A total of 20 patients in each group were included to account for possible dropouts during the trial. Data are presented as the mean ± SEM unless otherwise stated. $P < .05$ was considered significant.

RESULTS

Patients

From January to August 2012, 96 male subjects (age 18-59 years) with diagnosed chronic AT were assessed for eligibility, and 60 male subjects were included. The flow of men with AT through the trial is shown in Figure 1. During the study, 1 patient in each group was lost to follow-up but the remaining 57 patients completed the trial with no missing data, and these 57 patients were included in the primary analysis. The 1 dropout in the HVI group did not show up for the 6-week follow-up and we were not able to contact him by phone or email. The 2 other dropouts (1 each in the PRP and placebo groups) left the trial after 6 weeks due to lack of compliance with the eccentric training regimen. The follow-up period ended May 2013.

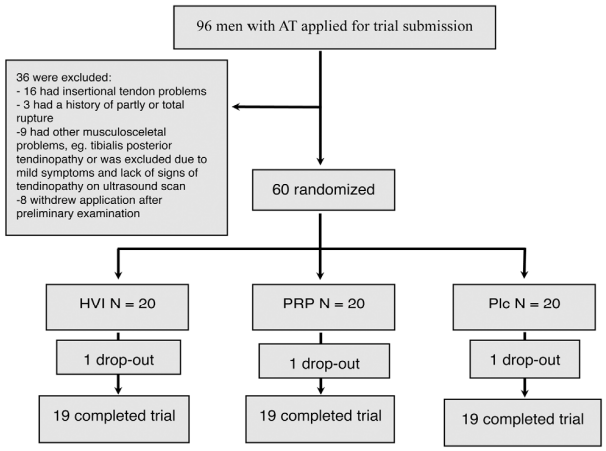

Figure 1. Flowchart of men with midportion Achilles tendinopathy (AT) through the trial. HVI, high-volume injection; PRP, platelet-rich plasma; Plc, placebo.

No significant differences were found at baseline between the groups regarding age, height, weight, VISA-A score, VAS score, and ultrasonographic findings (baseline characteristics, Table 1). No patients experienced any side effects of the injections during the study.

VISA-A Score

VISA-A scores improved in all groups at each follow-up ($P < .05$). Improvement in VISA-A was significantly greater ($P < .01$) in the HVI group (6 weeks = 27.1 ± 3.1 points; 12 weeks = 28.8 ± 4.1) versus PRP (6 weeks = 13.8 ± 4.1; 12 weeks = 14.8 ± 3.1) and placebo (6 weeks = 9.9 ± 3.3; 12 weeks = 10.6 ± 3.0) groups at 6-week and 12-week follow-up. At 24 weeks, VISA-A improvement was significantly greater ($P < .01$) in both the HVI (22.2 ± 4.6) and PRP (19.6 ± 4.5) groups compared with the placebo group (8.8 ± 3.3) (Figure 2).

VAS Score

VAS scores improved in all groups at each follow-up ($P < .05$). Decrease in VAS was significantly greater ($P < .05$) in the HVI group (48.5 ± 4.0 mm) vs PRP (37.3 ± 6.7 mm) and placebo (22.5 ± 4.9 mm) at 6-week follow-up and in the HVI (12 weeks = 44.9 ± 5.5 mm; 24 weeks =

TABLE 1
Characteristics of the HVI, PRP, and Placebo Groups[a]

	HVI (n = 19)	PRP (n = 19)	Placebo (n = 19)	Significance
Age, y	41.9 ± 12.2	43.1 ± 8.1	40.9 ± 6.6	.78
Weight, kg	83.6 ± 19.6	86.5 ± 20.6	89.7 ± 22.1	.16
Height, cm	182.6 ± 7.1	183.1 ± 19.4	183.5 ± 20.4	.76
Duration of symptoms, wk	24.7 ± 17.1	27.0 ± 34.0	30.8 ± 37.4	.71
Activity level				
Active in sports, n (%)	18 (95)	17 (89)	16 (84)	
Sedentary, n (%)	1 (5)	2 (11)	3 (16)	
Level of sports				
Competitive, n (%)	10 (56)	7 (41)	7 (44)	
Recreational, n (%)	8 (44)	10 (59)	9 (56)	
VISA-A score	52.5 ± 12.8	58.1 ± 12.4	59.2 ± 10.1	.57
VAS score, mm	55 ± 16	53 ± 21	45 ± 23	.94
Tendon thickness (US), mm	8.9 ± 1.9	8.3 ± 1.4	8.0 ± 1.7	.96
Intratendinous vascularity (CD), grade 0-5	3.2 ± 0.8	3.2 ± 0.8	2.9 ± 0.8	.98

[a]Data are presented as mean ± SD unless otherwise specified. CD, color Doppler; HVI, high-volume injection; PRP, platelet-rich plasma; US, ultrasonography; VISA-A, Victorian Institute of Sports Assessment–Achilles; VAS, visual analog scale for pain.

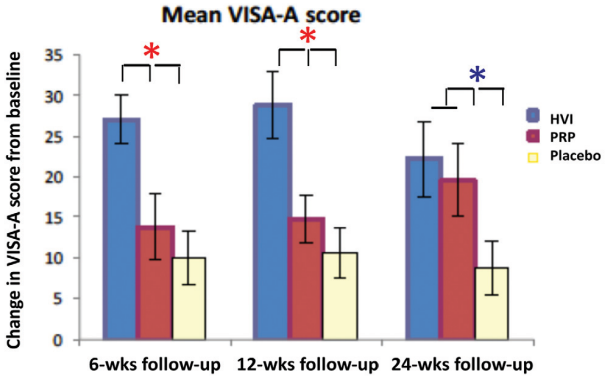

Figure 2. Mean changes in VISA-A score from baseline values at 6 weeks, 12 weeks, and 24 weeks of follow-up in patients with Achilles tendinopathy treated with either HVI (n = 19), PRP (n = 19), or placebo (n = 19). Time effect ($P < .05$) and group interaction ($P < .05$) were seen in all groups during follow-ups. Data are mean ± SEM. Red asterisk, $P < .01$, HVI vs PRP and placebo at 6-week and 12-week follow-up. Blue asterisk, $P < .01$, HVI and PRP vs placebo at 24-week follow-up. VISA-A, Victorian Institute of Sports Assessment–Achilles; HVI, high-volume injection; PRP, platelet-rich plasma; Plc, placebo.

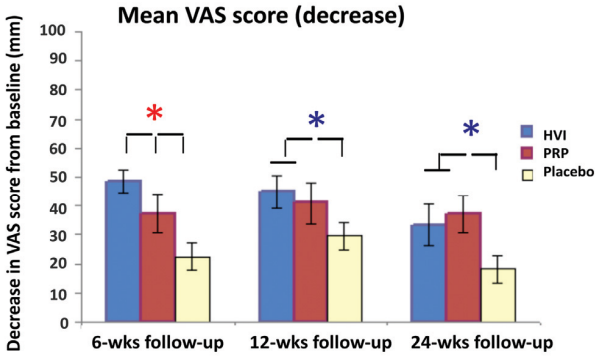

Figure 3. Mean changes in VAS score from baseline values at 6 weeks, 12 weeks, and 24 weeks of follow-up in patients with Achilles tendinopathy treated with either HVI (n = 19), PRP (n = 19), or placebo (n = 19). Time effect ($P < .05$) and group interaction ($P < .05$) were seen in all groups during follow-ups. Data are mean ± SEM. Red asterisk, $P < .05$, HVI vs PRP and placebo at 6-week and 12-week follow-up. Blue asterisk, $P < .05$, HVI and PRP vs placebo at 24-week follow-up. VAS, visual analog scale for pain; HVI, high-volume injection; PRP, platelet-rich plasma; Plc, placebo.

34.1 ± 6.5 mm) and PRP (12 weeks = 40.9 ± 7.0 mm; 24 weeks = 37.1 ± 6.2 mm) groups versus placebo (12 weeks = 29.5 ± 6.1 mm; 24 weeks = 18.1 ± 6.0 mm) at 12-week and 24-week follow-up ($P < .05$) (Figure 3).

Ultrasonography (Tendon Thickness and Intratendinous Vascularity)

Tendon thickness (maximum anterior-posterior diameter) showed a significant decrease ($P < .05$) in only the HVI and PRP groups. At 6 weeks and 12 weeks, the decrease in tendon thickness was larger ($P < .01$) in the HVI group (6 weeks = 1.9 ± 0.2 mm; 12 weeks = 2.0 ± 0.3 mm) versus PRP (6 weeks = 0.5 ± 0.2 mm; 12 weeks = 0.8 ± 0.2 mm) and placebo (6 weeks = 0.3 ± 0.1 mm; 12 weeks = 0.4 ± 0.2 mm). Furthermore, at 12 weeks a significant decrease ($P < .05$) was seen in the PRP group compared with placebo. At 24 weeks, a larger decrease was found ($P < .05$) in HVI (1.1 ± 0.3 mm) and PRP (1.0 ± 0.1 mm) groups versus placebo (0.4 ± 0.2 mm) (Figure 4).

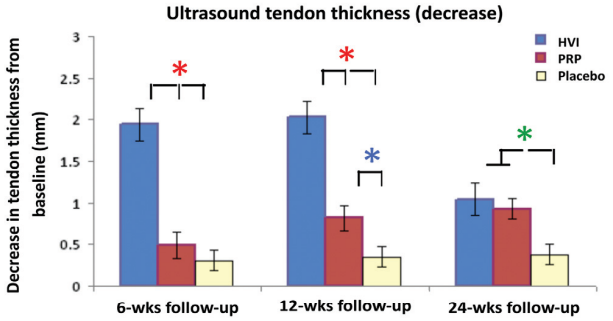

Figure 4. Mean changes in tendon thickness (ultrasonographic gray-tone) from baseline values at 6 weeks, 12 weeks, and 24 weeks of follow-up in patients with Achilles tendinopathy treated with either HVI (n = 19), PRP (n = 19), or placebo (n = 19). Time effects ($P < .05$) were seen in HVI and PRP groups during follow-up. Data are mean ± SEM. Red asterisk, $P < .01$, HVI vs PRP and placebo at 6-week and 12-week follow-up. Blue asterisk, $P < .05$, PRP vs placebo at 12-week follow-up. Green asterisk, $P < .05$, HVI and PRP vs placebo at 24-week follow-up. HVI, high-volume injection; PRP, platelet-rich plasma; Plc, placebo.

Regarding the intratendinous vascularity (Doppler activity) during intervention, a larger decrease was seen in the first 6 weeks in the HVI group (from 3.2 ± 0.2 at baseline to 0.8 ± 0.2) compared with both PRP (from 3.2 ± 0.2 at baseline to 2.8 ± 0.2) and placebo (from 2.9 ± 0.2 at baseline to 2.5 ± 0.3), respectively. After 12 weeks and 24 weeks, a decrease remained compared with baseline values in the HVI (12 weeks = 1.2 ± 0.2; 24 weeks = 1.7 ± 0.3), PRP (12 weeks = 2.2 ± 0.2; 24 weeks = 1.8 ± 0.3), and placebo (12 weeks = 2.2 ± 0.3; 24 weeks = 2.3 ± 0.4) groups (Appendix Figure A1, available online). No statistical measurement was performed, due to the fact that we used a semiquantitative grading system (grade 0-5; Appendix Figure A1, available online).

Muscle Function (Heel-Rise Test)

Muscle function improved in the entire cohort ($P < .001$) with no group interaction observed (Appendix Figure A2, available online).

Treatment Satisfaction

At 12 weeks, 16 patients in the HVI group (84%), 12 patients in the PRP group (63%), and 7 patients in the placebo group (35%) were satisfied with the treatment. After 24 weeks, 12 patients in HVI (63%), 11 patients in PRP (58%), and 8 patients in placebo (42%) groups were satisfied with the treatment. Treatment satisfaction differed between groups ($P < .05$), with HVI being the most satisfied overall during the intervention compared with placebo at both 12 weeks and 24 weeks ($P < .05$). At 24 weeks, no difference was seen between HVI (63%) and PRP groups (58%).

Thirteen patients (68%) in the HVI group, 10 patients (53%) in the PRP group, and 8 patients (42%) in the placebo group had returned to running during the trial period. The other patients in the study were able to perform other sports (eg, cycling, swimming, and rowing) that are considered less demanding for the Achilles tendon. The overall data concerning the patients returning to running showed that the HVI group returned a little bit earlier (from 10 days to 6 weeks from baseline) compared with both the PRP (from 3 to 8 weeks from baseline) and placebo (from 4 to 10 weeks from baseline) groups. No statistical measurement was performed on these data.

Concerning compliance with the eccentric training program, 70% of the patients performed more than 75% of the recommended repetitions during the 24-week trial, and the remaining 30% of patients performed between 50% and 75% of the recommended repetitions; no differences in compliance were found between groups. No complications (infections, hematomas, or ruptures) were reported after the injection treatments.

DISCUSSION

In this randomized, placebo-controlled clinical study of patients with chronic AT, treatment with HVI or PRP in combination with a 12-week eccentric training regimen was more effective in reducing pain symptoms, improving activity level and function, and reducing tendon thickness and intratendinous vascularity than eccentric training alone.

This study confirms the positive clinical effect of eccentric training but indicates that a combination treatment with HVI or multiple PRP injections is superior compared with eccentric training alone at the time points studied. Furthermore, HVI seems to be more effective at improving pain, function, and patient satisfaction than PRP in the short term (6 and 12 weeks) but not medium term (24 weeks).

The improvement in clinical functional scores (VISA-A), reduction of pain (VAS), and reductions in tendon thickness and intratendinous vascularity found on ultrasonography in the patient group receiving HVI are in line with the results of previous case series involving HVI in which subjects were assessed both retrospectively[12] and prospectively.[30,44] Some of these studies are comparable in regard to rehabilitation regimen and follow-up period, but none included a control group as in the current study. Based on the data in the current study, it is tempting to suggest that HVI is preferable to PRP in the management of chronic midportion AT. The HVI group in this study required only 1 injection, whereas the PRP group required 4 injections. The last 2 questions in the VISA-A rate ability to train, so it is conceivable that patients receiving HVI had a faster return to previous sporting activities (something that was not measured directly). A previous case series investigating HVI in midportion AT also reported a significant improvement in VISA-A scores at 1 month that was maintained at 3 months.[12]

Multiple potential concerns with HVI warrant discussion. The mechanisms of action are not clear, and although the effect may be partly mechanical, it is very likely that

the steroid has some effect on pain in the short term. It is well known that steroid injection is very effective at improving tendinopathy pain and function in the short term, but long-term outcomes of steroid injection are poorer compared with exercise.[17] Coombes et al[16] found that outcomes at 12 months in lateral elbow tendinopathy were worse among people who had steroid compared with placebo injection, regardless of whether rehabilitation exercises were prescribed to complement the injections. Our data show a small reduction in patient satisfaction in the HVI group at 24 weeks compared with 12 weeks, whereas satisfaction increased in the placebo group and remained about the same in the PRP group over this time frame. Long-term follow-up is required to determine whether benefits are eroded. Another interesting question is whether the steroid component is part of the positive effect of HVI or whether pain relief is provided mainly by the remaining components (local anesthetic and large volume of saline); a study is ongoing to compare HVIs with and without steroids.

A further potential concern of the HVI injection is that the dramatic short-term improvement in pain and function may lead to a faster than tolerated return to sporting activities. In some individuals, returning to sport after receiving steroid-containing injections without adequate rehabilitation of the muscle-tendon unit may increase the risk of further injury, such as a tendon rupture,[45] and the incidence of setbacks as seen in a few of the patients in the HVI group between 12- and 24-week follow-up. Anecdotal reports have linked steroid injection and tendon rupture,[57] but so far no rupture complications have been reported in the HVI literature. The more likely outcome of sudden return to sport may simply be symptom provocation once the steroid effect has subsided,[16] and this may partly explain late-term symptom recurrences observed after steroid injection.

To our knowledge, this is the first RCT to show a positive effect of PRP compared with placebo injection in AT. This is in contrast to previous studies that found no significant effect of PRP compared with placebo injection[20,23] as well as another study that compared autologous blood injection (ABI) (whole blood that has not been spun to concentrate the plasma) and placebo injection (dry needling).[6] One explanation for the different results could be that our study involved 4 injections at 2-week intervals, whereas previous studies used only 1 PRP injection[20,23] or 2 ABI injections.[6] A case study in chronic patellar tendinopathy using multiple PRP injections also showed positive clinical results in regard to function and pain.[13] The specific mechanisms behind the potential effect of PRP treatment in tendinopathy are not known, but the results give reason to believe that PRP has the potential to promote tendon healing. Given that histopathological changes in tendon tissue probably occur slowly,[2,3,37] that this might explain why gradual improvements in function (VISA-A) and pain (VAS) in the PRP group were seen in this study, whereas HVI had a more acute mechanical impact on the tendon tissue (breaking adhesions and potentially destroying neovessels and adjacent nerve-endings from the peritendinous tissue) just after the injection. PRP contains a large variety of growth factors (including tumor growth factor β, interleukin 1, interleukin 6, and insulin-like growth factor 1), all of which have shown the possibility to stimulate tendon tissue healing.[5,33,34,46] Repetition of injections may prolong the exposure of growth factors to the tendons and thereby influence the rehabilitation of the tendon tissue in a positive manner.

We were not able to accurately analyze the PRP in this study due to disturbances in the thawing process, but future studies need to determine whether the concentration of platelets and growth factors, the amount of bolus injected, and number of injections influence clinical outcome. A counter argument is that PRP influences pain mechanisms rather than leading to tendon healing and adaptation, and this is partly supported by the equivalent change in Achilles tendon thickness across the 3 groups in this study.

Another difference when comparing this study to the de Vos study[23] is the rehabilitation program. The eccentric training regimen was the same, but patients in the current study were allowed to begin gradual return to sports activities after 10 days based on a pain-monitoring model (pain should be minimal and an increase in pain after exercise should subside quickly). In the de Vos study, all patients were instructed to avoid weightbearing sporting activities for the first 4 weeks. Silbernagel et al[55] showed that allowing sport based on a pain monitoring system did not lead to an inferior outcome compared with stopping sport activity for 6 weeks during AT rehabilitation. To our knowledge, no evidence is available to suggest that total rest from weightbearing activities improves outcome.[55] It is important to note that participants in our study who received eccentric exercise only had a mean 9-point increase in VISA-A score after 24 weeks, whereas a similar group in the de Vos study had a more than 20-point increased on average. A possible explanation for the greater benefit from eccentric exercise in the de Vos study is slower return to sport. Exercise compliance was 70% in 75% of the cohort in the de Vos study, which is similar to our results, so this is unlikely to explain the discrepancy. The age of participants in the de Vos study was higher (PRP group, 49 years; placebo group, 50 years) than in our study (HVI, 42 years; PRP, 43 years; placebo, 41 years), which makes the poorer effect of eccentric exercises in our study difficult to explain. Whether a poorer performance and effect of the eccentric training alone contributed to benefit of the injection groups is not possible to conclude.

Limitations

We did not record the amount of weight (kilograms) that the groups used during exercise. We would expect that with earlier pain improvement in the HVI group, these patients were able to progress their load with rehabilitation sooner. Another limitation to the study is the relatively short-term (24-week) intervention period. Longer follow-up to determine who would ultimately succeed or fail would have been desirable. Nevertheless, this is the first RCT in chronic midportion AT to show positive results compared with placebo for PRP, and it is the first RCT to evaluate the effectiveness of HVI. The findings provide a sound foundation for future studies with longer follow-up.

As previously mentioned, we were not able to determine the exact concentration of platelets and growth factors in

the PRP, as planned. When we analyzed the samples, we found a large variation between them. We realized that the large variation was probably caused by platelets being broken down in the process of thawing the PRP samples. Thus, the analysis should have been conducted immediately on fresh samples just after centrifugation. Although we are not able to tell precisely the content of the PRP injected into each study subject, after the study we obtained one fresh sample and analyzed the PRP just after centrifugation. In this sample, the platelet concentration was approximately 2.5-fold higher compared with whole blood, as predicted by kit producers.

CONCLUSION

Treatment with HVI or PRP in combination with a 12-week eccentric training regimen in chronic AT seems more effective in reducing pain, improving activity level, and reducing tendon thickness and intratendinous vascularity than eccentric training alone. HVI may be more effective in improving outcomes of chronic AT than PRP in the short term but not medium term.

ACKNOWLEDGMENT

The authors thank Dr Otto Chan (Independent Hospital, London, UK) and Dr Dylan Morrissey (Sports and Exercise Medicine, Queen Mary University of London, London, UK) for their guidance concerning the HVI treatment, technique, and procedure (to A.P.B., M.I.B., and H.L.); Peter Schjerling (Institute of Sports Medicine Copenhagen, Department of Orthopaedic Surgery M, Bispebjerg Hospital, and Center for Healthy Aging, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark) for his help with the statistical analysis; and all the colleagues at the Institute of Sports Medicine Copenhagen, Department of Orthopaedic Surgery M, Bispebjerg Hospital, and Center for Healthy Aging, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark, for their logistic help. All of these individuals were not compensated for their efforts and there is no conflict of interest.

REFERENCES

1. ACP™ Double Syringe System. Autologous conditioned plasma. Arthrex. http://www.brunmala.se/files/ACP_double_syringe_system.pdf Published 2009.
2. Alfredson H. Chronic midportion Achilles tendinopathy: an update on research and treatment. *Clin Sports Med*. 2003;22(4):727-741.
3. Alfredson H, Lorentzon R. Chronic Achilles tendinosis: recommendations for treatment and prevention. *Sports Med*. 2000;29(2):135-146.
4. Alfredson H, Pietilä T, Jonsson P, Lorentzon R. Heavy-load eccentric calf muscle training for the treatment of chronic Achilles tendinosis. *Am J Sports Med*. 1998;26(3):360-366.
5. Andia I, Sanchez M, Maffulli N. Tendon healing and platelet-rich plasma therapies. *Expert Opin Biol Ther*. 2010;10(10):1415-1426.
6. Bell KJ, Fulcher ML, Rowlands DS, Kerse N. Impact of autologous blood injections in treatment of mid-portion Achilles tendinopathy: double blind randomised controlled trial. *BMJ*. 2013;346:f2310.
7. Beyer R, Kongsgaard M, Hougs Kjaer B, Ohlenschlaeger T, Kjaer M, Magnusson SP. Heavy slow resistance versus eccentric training as treatment for Achilles tendinopathy: a randomized controlled trial. *Am J Sports Med*. 2015;43(7):1704-1711.
8. Boesen AP, Boesen MI, Koenig MJ, Bliddal H, Torp-Pedersen S, Langberg H. Evidence of accumulated stress in Achilles and anterior knee tendons in elite badminton players. *Knee Surg Sports Traumatol Arthrosc*. 2011;19(1):30-37.
9. Boesen AP, Boesen MI, Torp-Pedersen S, et al. Associations between abnormal ultrasound color Doppler measures and tendon pain symptoms in badminton players during a season: a prospective cohort study. *Am J Sports Med*. 2012;40(3):548-555.
10. Boesen MI, Boesen A, Koenig MJ, Bliddal H, Torp-Pedersen S. Ultrasonographic investigation of the Achilles tendon in elite badminton players using color Doppler. *Am J Sports Med*. 2006;34(12):2013-2021.
11. Boesen MI, Koenig MJ, Torp-Pedersen S, Bliddal H, Langberg H. Tendinopathy and Doppler activity: the vascular response of the Achilles tendon to exercise. *Scand J Med Sci Sport*. 2006;16(6):463-469.
12. Chan O, O'Dowd D, Padhiar N, et al. High volume image guided injections in chronic Achilles tendinopathy. *Disabil Rehabil*. 2008;30(20-22):1697-1708.
13. Charousset C, Zaoui A, Bellaiche L, Bouyer B. Are multiple platelet-rich plasma injections useful for treatment of chronic patellar tendinopathy in athletes? a prospective study. *Am J Sports Med*. 2014;42(4):906-911.
14. Cook JL, Khan KM, Purdam C. Achilles tendinopathy. *Man Ther*. 2002;7(3):121-130.
15. Cook JL, Malliaras P, De Luca J, Ptasznik R, Morris ME, Goldie P. Neovascularization and pain in abnormal patellar tendons of active jumping athletes. *Clin J Sport Med*. 2004;14(5):296-299.
16. Coombes BK, Bisset L, Brooks P, Khan A, Vicenzino B. Effect of corticosteroid injection, physiotherapy, or both on clinical outcomes in patients with unilateral lateral epicondylalgia: a randomized controlled trial. *JAMA*. 2013;309(5):461-469.
17. Coombes BK, Bisset L, Vicenzino B. Efficacy and safety of corticosteroid injections and other injections for management of tendinopathy: a systematic review of randomised controlled trials. *Lancet*. 2010;376(9754):1751-1767.
18. Creaney L. Platelet-rich plasma and the biological complexity of tissue regeneration. *Br J Sports Med*. 2011;45(8):611.
19. Crisp T, Khan F, Padhiar N, et al. High volume ultrasound guided injections at the interface between the patellar tendon and Hoffa's body are effective in chronic patellar tendinopathy: a pilot study. *Disabil Rehabil*. 2008;30(20-22):1625-1634.
20. de Jonge S, de Vos RJ, Weir A, et al. One-year follow-up of platelet-rich plasma treatment in chronic Achilles tendinopathy: a double-blind randomized placebo-controlled trial. *Am J Sports Med*. 2011;39(8):1623-1629.
21. de Jonge S, van den Berg C, de Vos RJ, et al. Incidence of midportion Achilles tendinopathy in the general population. *Br J Sports Med*. 2011;45(13):1026-1028.
22. De Jonge S, Warnaars JLF, De Vos RJ, et al. Relationship between neovascularization and clinical severity in Achilles tendinopathy in 556 paired measurements. *Scand J Med Sci Sports*. 2014;24(5):773-778.
23. de Vos RJ, Weir A, van Schie HTM, et al. Platelet-rich plasma injection for chronic Achilles tendinopathy: a randomized controlled trial. *JAMA*. 2010;303(2):144-149.
24. Dragoo JL, Wasterlain AS, Braun HJ, Nead KT. Platelet-rich plasma as a treatment for patellar tendinopathy: a double-blind, randomized controlled trial. *Am J Sports Med*. 2014;42(3):610-618.
25. Filardo G, Kon E, Di Matteo B, Pelotti P, Di Martino A, Marcacci M. Platelet-rich plasma for the treatment of patellar tendinopathy: clinical and imaging findings at medium-term follow-up. *Int Orthop*. 2013;37(8):1583-1589.
26. Filardo G, Kon E, Di Matteo B, et al. Platelet-rich plasma injections for the treatment of refractory Achilles tendinopathy: results at 4 years. *Blood Transfus*. 2014;12(4):533-540.
27. Foster TE, Puskas BL, Mandelbaum BR, Gerhardt MB, Rodeo SA. Platelet-rich plasma: from basic science to clinical applications. *Am J Sports Med*. 2009;37(11):2259-2272.

28. Fredberg U, Stengaard-Pedersen K. Chronic tendinopathy tissue pathology, pain mechanisms, and etiology with a special focus on inflammation. *Scand J Med Sci Sports*. 2008;18(1):3-15.
29. Hansen M, Boesen A, Holm L, Flyvbjerg A, Langberg H, Kjaer M. Local administration of insulin-like growth factor-I (IGF-I) stimulates tendon collagen synthesis in humans. *Scand J Med Sci Sport*. 2013;23(5):614-619.
30. Humphrey J, Chan O, Crisp T, et al. The short-term effects of high volume image guided injections in resistant non-insertional Achilles tendinopathy. *J Sci Med Sport*. 2010;13(3):295-298.
31. Iversen JV, Bartels EM, Langberg H. The Victorian Institute of Sports Assessment–Achilles questionnaire (VISA-A)—a reliable tool for measuring achilles tendinopathy. *Int J Sports Phys Ther*. 2012;7(1):76-84.
32. Järvinen TA, Kannus P, Paavola M, Järvinen TL, Józsa L, Järvinen M. Achilles tendon injuries. *Curr Opin Rheumatol*. 2001;13(2):150-155.
33. Jeong DU, Lee C-R, Lee JH, et al. Clinical applications of platelet-rich plasma in patellar tendinopathy. *Biomed Res Int*. 2014;2014:249498.
34. Kampa RJ, Connell DA. Treatment of tendinopathy: is there a role for autologous whole blood and platelet rich plasma injection? *Int J Clin Pract*. 2010;64(13):1813-1823.
35. Kannus P, Paavola M, Paakkala T, Parkkari J, Järvinen T, Järvinen M. [Pathophysiology of overuse tendon injury]. *Radiologe*. 2002; 42(10):766-770.
36. Khan KM, Forster BB, Robinson J, et al. Are ultrasound and magnetic resonance imaging of value in assessment of Achilles tendon disorders? A two year prospective study. *Br J Sports Med*. 2003;37(2): 149-153.
37. Kjaer M, Langberg H, Heinemeier K, et al. From mechanical loading to collagen synthesis, structural changes and function in human tendon. *Scand J Med Sci Sports*. 2009;19(4):500-510.
38. Kongsgaard M, Kovanen V, Aagaard P, et al. Corticosteroid injections, eccentric decline squat training and heavy slow resistance training in patellar tendinopathy. *Scand J Med Sci Sports*. 2009; 19(6):790-802.
39. Lewis T, Cook J. Fluoroquinolones and tendinopathy: a guide for athletes and sports clinicians and a systematic review of the literature. *J Athl Train*. 49(3):422-427.
40. Lohrer H, David S, Nauck T. Surgical treatment for Achilles tendinopathy—a systematic review. *BMC Musculoskelet Disord*. 2016; 17(1):207.
41. Loppini M, Maffulli N. Conservative management of tendinopathy: an evidence-based approach. *Muscles Ligaments Tendons J*. 2011; 1(4):134-137.
42. Lysholm J, Wiklander J. Injuries in runners. *Am J Sports Med*. 15(2):168-171.
43. Maffulli N, Del Buono A, Oliva F, Testa V, Capasso G, Maffulli G. High-volume image-guided injection for recalcitrant patellar tendinopathy in athletes. *Clin J Sport Med*. 2016;26(1):12-16.
44. Maffulli N, Spiezia F, Longo UG, Denaro V, Maffulli GD. High volume image guided injections for the management of chronic tendinopathy of the main body of the Achilles tendon. *Phys Ther Sport*. 2013;14(3):163-167.
45. Metcalfe D, Achten J, Costa ML. Glucocorticoid injections in lesions of the Achilles tendon. *Foot Ankle Int*. 2009;30(7):661-665.
46. Mishra A, Woodall J, Vieira A. Treatment of tendon and muscle using platelet-rich plasma. *Clin Sports Med*. 2009;28(1):113-125.
47. Morton S, Chan O, King J, et al. High volume image-guided Injections for patellar tendinopathy: a combined retrospective and prospective case series. *Muscles Ligaments Tendons J*. 2014;4(2):214-219.
48. Ohberg L, Alfredson H. Ultrasound guided sclerosis of neovessels in painful chronic Achilles tendinosis: pilot study of a new treatment. *Br J Sports Med*. 2002;36(3):173-175; discussion 176-177.
49. Ohberg L, Lorentzon R, Alfredson H. Neovascularisation in Achilles tendons with painful tendinosis but not in normal tendons: an ultrasonographic investigation. *Knee Surg Sports Traumatol Arthrosc*. 2001;9(4):233-238.
50. Olesen JL, Heinemeier KM, Langberg H, Magnusson SP, Kjaer M, Flyvbjerg A. Expression, content, and localization of insulin-like growth factor I in human achilles tendon. *Connect Tissue Res*. 2006;47(4):200-206.
51. Rowe V, Hemmings S, Barton C, Malliaras P, Maffulli N, Morrissey D. Conservative management of midportion Achilles tendinopathy: a mixed methods study, integrating systematic review and clinical reasoning. *Sports Med*. 2012;42(11):941-967.
52. Scott A, Huisman E, Khan K. Conservative treatment of chronic Achilles tendinopathy. *CMAJ*. 2011;183(10):1159-1165.
53. Silbernagel KG, Gustavsson A, Thomeé R, Karlsson J. Evaluation of lower leg function in patients with Achilles tendinopathy. *Knee Surg Sports Traumatol Arthrosc*. 2006;14(11):1207-1217.
54. Silbernagel KG, Nilsson-Helander K, Thomeé R, Eriksson BI, Karlsson J. A new measurement of heel-rise endurance with the ability to detect functional deficits in patients with Achilles tendon rupture. *Knee Surg Sports Traumatol Arthrosc*. 2010;18(2):258-264.
55. Silbernagel KG, Thomeé R, Eriksson BI, Karlsson J. Full symptomatic recovery does not ensure full recovery of muscle-tendon function in patients with Achilles tendinopathy. *Br J Sports Med*. 2007;41(4):276-280; discussion 280.
56. Silbernagel KG, Thomeé R, Thomeé P, Karlsson J. Eccentric overload training for patients with chronic Achilles tendon pain—a randomised controlled study with reliability testing of the evaluation methods. *Scand J Med Sci Sports*. 2001;11(4):197-206.
57. Vallone G, Vittorio T. Complete Achilles tendon rupture after local infiltration of corticosteroids in the treatment of deep retrocalcaneal bursitis. *J Ultrasound*. 2014;17(2):165-167.
58. Van Middelkoop M, Kolkman J, Van Ochten J, Bierma-Zeinstra SMA, Koes B. Prevalence and incidence of lower extremity injuries in male marathon runners. *Scand J Med Sci Sports*. 2008;18(2):140-144.
59. Zayni R, Thaunat M, Fayard J-M, et al. Platelet-rich plasma as a treatment for chronic patellar tendinopathy: comparison of a single versus two consecutive injections. *Muscles Ligaments Tendons J*. 2015;5(2):92-98.