Extracorporeal shockwave therapy in the treatment of patellar tendinopathy

A randomized, double-blind, placebo-controlled trial

Persson Krogh, Thøger; Kaae Astrup, Jacob; Kyed, Charlotte; Fredberg, Ulrich

Published in:
Translational Sports Medicine

DOI (link to publication from Publisher):
10.1002/tsm2.246

Publication date:
2021

Document Version
Accepted author manuscript, peer reviewed version

DR. THØGER PERSSON KROGH (Orcid ID : 0000-0002-3382-8088)

Article type : Original Article

Extracorporeal shockwave therapy in the treatment of patellar tendinopathy: A randomized, double-blind, placebo-controlled trial

Thøger Persson Krogh[1,2], Jacob Kaae Astrup[1], Charlotte Kyed[1], Ulrich Fredberg[1,3,4]

1. Diagnostic Centre, University Research Clinic for Innovative Patient Pathways, Silkeborg Regional Hospital, Denmark.

2. Center for Sports Medicine, Regional Hospital of Northern Denmark, Hjørring, Denmark.

3. Research Unit of Rheumatology, Department of Clinical Research, University of Southern Denmark, Odense University Hospital, Denmark.

4. Institute of Sports Medicine Copenhagen, Bispebjerg Hospital, Copenhagen, Denmark.

The study was conducted at: Diagnostic Centre, University Research Clinic for Innovative Patient Pathways, Silkeborg Regional Hospital, Denmark.

Address correspondence to Thøger Persson Krogh, MD, PhD, Center for Sports Medicine, Regional Hospital of Northern Denmark, Hjørring, Denmark. (email: thogerkrogh@hotmail.com).

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

ABSTRACT

Background: Patellar tendinopathy is a common injury in athletes.

Hypothesis/Purpose: To examine whether extracorporeal shockwave therapy (ESWT) was more effective than placebo in the treatment patellar tendinopathy.

Methods: Thirty-six athletes were randomly assigned to receive either three ESWT treatments or three placebo treatments. The primary endpoints were changes in pain while walking, at rest, and when the tendon was squeezed on a 0–10 numeric rating scale. Secondary outcomes included treatment satisfaction and ultrasonographic outcomes.

Results: After 12 weeks, ESWT was more effective than placebo regarding pain while walking, mean difference [MD] 1.4, $P = 0.011$). There was no difference in pain at rest, MD 0.4, $P = 0.404$) or pain when the tendon was squeezed, MD 0.3, $P = 0.221$). Regarding the secondary outcomes, ESWT was more effective than placebo with regard to patient-rated treatment effect, but no improvements were observed in the ultrasonographic outcomes.

Conclusion: Improvement was observed after 12 weeks in the ESWT group regarding pain while walking but not regarding pain at rest, when the tendon was squeezed, and on ultrasonography. These findings provide limited support for the use of ESWT, but the clinical relevance is still unclear.

Key Words: Patellar tendinopathy, jumper's knee, tendinosis, ultrasonography, shockwave, ESWT, randomized placebo-controlled trial.

INTRODUCTION

Patellar tendinopathy (PT) also known as jumper's knee, is a common tendinous disorder in both competitive and recreational athletes.[1,2] PT is the preferred term for persistent patellar tendon pain and loss of function related to mechanical loading.[3] Participation in sports that involve jumping, running, or cutting maneuvers like volleyball, basketball, handball, and football carries a high risk of PT.[1,4,5] Overuse of the patellar tendon from continuous and repetitive stress is the most widely

accepted theory explaining this injury that leads to pain, reduced function, and time away from sports.[2,6]

Exercise may be the best treatment for PT. Eccentric, concentric (heavy slow resistance training), and isometric training protocols have demonstrated positive results.[7,8] However, PT, like most other tendinopathies, can be resistant to treatment. This has led to the development of a wide range of therapies with the aim of achieving better or faster recovery.[9-13] Around 1980 extracorporeal shockwave therapy (ESWT) was introduced as a treatment for renal stones by means of stone disintegrating (lithotripsy).[14] Since the 1990s ESWT has been assessed for treatment of elbow tendinitis, calcific deposits in the rotator cuff, and plantar fascitis.[15-17] From the start of the millennium, trials investigating the efficacy of ESWT in PT began to appear.[18,19] In recent years systematic reviews have concluded that there is evidence, however limited, supporting the use of ESWT in PT.[19,20]

Our main objective was to determine whether three ESWT treatments were more effective than placebo in the treatment of athletes with PT evaluated by ultrasonographic changes and changes in pain while walking, at rest, and, when the tendon was squeezed 12 weeks after treatment. ESWT is a treatment where mechanical force is applied to the tendinopathic tissue through pressure waves (kinetic energy of acoustic shockwaves). The mechanism behind ESWT in tendinopathy is thought to be through cascades of inflammatory and catabolic processes, following the mechanical stimulus of ESWT and leading to tendon remodeling, regeneration, and removal of damaged matrix constituents.[21-23] Another possible mechanism is through the induction of transient nerve degeneration of the free nerve fiber endings, sensory nerve fibers and neuromuscular junction.[24-26] Finally, in tendons with calcific deposition studies have demonstrated the ability of ESWT to disintegrate the deposit leading to resorption.[27-31]

METHODS

Study design and participants

Between September 2005 and May 2007, 63 patients with PT were assessed for eligibility, and 36 were included in this double-blind RCT. The patients had been referred to the Rheumatology Unit at Silkeborg Regional Hospital by general practitioners or by other rheumatology/orthopedic departments. The treatments were either three sessions of ESWT or placebo, and 18 patients were randomly allocated to each group. The a priori hypothesis (null hypothesis) was that there was no

additional effect from adding ESWT to the rehabilitation other than the effect of the rehabilitation on itself.

Inclusion criteria were symptoms in the proximal part of the patellar tendon of more than 6 months duration that were related to exercise. The clinical diagnosis was tenderness to palpation at the inferior pole of the patella with the knee fully extended.[32] The ultrasonographic criteria were funnel-shaped swelling in the proximal part of the tendon of more than 1 mm compared to the distal part of the tendon and a central hypoechoic area in the proximal part of the tendon > 2 mm in diameter with increased color Doppler activity indicating hyperaemia.[33]

Exclusion criteria were age younger than 18 years and older than 60 years, glucocorticoid injection or any other type of injection therapy within the last 6 months, previous PT surgery, clinical or ultrasonographic suspicion of partial or total rupture of the tendon.

The diagnosis was verified in all patients by the physician who also performed the inclusion and outcome assessments at 2, 4, and 12 weeks. A study nurse performed the randomization and ESWT treatment procedures (at baseline, 2, and 4 weeks). Two physicians were assigned to the study as inclusion and outcome assessors. The study was approved by the institutional review board. The study protocol was registered and approved by the scientific ethics committee at Central Region Denmark (No. M-Åa-20040156). All participants gave written informed consent. The study was carried out in accordance with Danish law and the Declaration of Helsinki.

Randomization and group allocation

Sequence generation: Eligible participants were block randomized in permuted blocks of 6, using a simple “shuffling envelopes” procedure, to undergo ESWT or placebo treatment.

Allocation concealment and implementation: To ensure concealment of the assigned intervention, the study nurse obtained the shuffled, opaque, sealed envelope containing the participant’s assigned intervention.

Masking

To ensure concealment of the assigned intervention, the study nurse attached either an active or a placebo membrane (that blocks all pressure waves) to the ESWT equipment and carried out the treatment in a separate room after the examination by the physician was finished. Neither the

patients nor the physician knew the assigned treatment. The study nurse did not participate in other parts of the study than the randomization and treatments at baseline, 2, and 4 weeks.

Sonographic evaluation

Patients were examined in a supine position. The knees were flexed 90 degrees to avoid waving of the tendons in the gray-scale images and thickness measurements, Figure 2A.[33] Figure 2C shows a healthy patellar tendon with key anatomical landmarks. Figure 2D-E shows longitudinal and transverse images of patellar tendinopathy. We used a high quality ultrasound scanner (EUB 9000, Hitachi Medical) with a 14 MHz linear transducer. The patellar tendon was scanned longitudinally and transversally. By switching between longitudinal and transversal scanning, a 3-dimensional impression of the structure was obtained. When the thickest point of the tendon was found, a longitudinal scan was performed in which the thickness of the tendon was measured perpendicular to the greatest width of the tendon (the "true" tendon thickness).[33] A maximum discrepancy of 0.3 mm between the longitudinal and transverse measurements was accepted. If the difference between the two measurements was 0.3 mm or less, the longitudinal measurement was used. If the difference was more than 0.3 mm, both measurements were repeated until the difference was 0.3 mm or less.[34] The anterior-posterior thicknesses of both the whole tendon and the central hypoechoic area were measured, Figure 2D.

Color Doppler ultrasonography was performed in the longitudinal plane by moving the transducer from side to side, locating the part with the most Doppler activity. Knees were fully extended to avoid compression of the blood vessels in the patellar tendon, Figure 2B.[33] The region of interest (ROI) in a longitudinal scan was a 0.5-cm area limited by the superficial and the profound borders of the patellar tendon at the place with the most Doppler activity. Doppler settings were the same for all patients, with a gain setting just below the noise level and the V-Scale set to 350. We ranked the color Doppler activity from grade 0–4, Figure 3A–E. Grade 0: no activity, grade 1: 1–2 single vessels, grade 2: Doppler activity in less than 25% of the ROI, grade 3: Doppler activity in 25–50% of the ROI, and grade 4: Doppler activity in more than 50% of the ROI.[35,36] This technique is similar to the modified Öhberg score in which the number of vessels is counted on a 0–4 scale.[35,37] This way of quantifying color Doppler activity has previously been assessed in lateral epicondylitis in the common extensor tendon of the elbow regarding reliability and agreement.[38] Figure 3F shows the presence of color Doppler activity in the central hypoechoic area in a transverse scan.

Interventions

Three ESWT treatments were given at intervals of 14 days (baseline, 2, and 4 weeks). The first treatment comprised 1500 pulses, the following two 3000 pulses, all given at maximal tolerable energy flux density, depending on patient's pain tolerance. The maximal energy flux density was 0.29 mJ/mm^2. Equipment: The shockwave machine (Orthospec, Medispec, Ltd; Germantown, MD, USA) is an FDA-approved electrohydraulic system. It contains a saline water-filled chamber, in which there is an electrode that ignites a spark (electrical charge) that evaporates water and creates an acoustic shockwave. This shockwave is reflected off the walls of the ellipsoidal reflector and is focused, forming a "therapy zone" of 46 x 134 mm with increasing energy density. Because of the size of the therapy zone, imaging was not needed to pinpoint the tendinopathic area. The shockwave probe was aligned along the point of maximal pain on palpation in the proximal part of the patellar tendon. Before every treatment, a new electrode was applied. Transmission gel was applied between the membrane and the knee to optimize shockwave transmission. No local anesthetics were used. The treatment was performed with the patient seated in an upright position with the knee flexed to 90 degrees. A specialized energy absorbing membrane was used for placebo treatment. The placebo membrane contains a gel-like energy absorbing material. The patient was informed that the treatment could be painful but that there was an inter-individual variability in pain perception. The post-treatment protocol was the same in all participants. Patients were recommended to minimize the strain on the patellar tendon for 4 days, and thereafter gradually increase rehabilitation below the pain limit in accordance with the provided home therapy rehabilitation program, www.sportnetdoc.com (jumper's knee).[39] The rehabilitation protocol was based on strengthening (including eccentric training), stretching, and coordination.[40]

Outcomes

At all visits, baseline, 2, 4, and 12 weeks a clinical and an ultrasonographic examination was performed by a physician, and the symptom severity, was assessed by questionnaires.

Baseline characteristics, patellar tendinopathy medical history, patient-rated outcome questionnaires, exercise/sporting history, clinical and US assessments are listed in Table 1.

The primary efficacy outcomes were changes in pain while walking, at rest, and when the patellar tendon was squeezed. Pain while walking and at rest were assessed on a 0–10 numeric rating scale: 0 = no pain, 10 = worst pain imaginable.[41] Pain experienced when the tendon was gently squeezed

by the outcome assessor using the thumb and index finger was assessed on a 0–3 numeric rating scale. The patient was asked to state whether palpation tenderness was present or absent. The examiner graduated the pain reaction as 0 = none, 1 = light, 2 = modest, or 3 = severe, in relation to spontaneous pain response and ward movement.[42] Patient-rated treatment effect was rated on a 6-point Likert scale: 1 = worse, 2 = no improvement, 3 = improved a little, 4 = moderate improvement, 5 = improved a lot, and 6 = cured.[43] US outcomes included changes in tendon thickness (mm), thickness of the central hypoechoic area (mm), and color Doppler activity (0–4). The sports-specific baseline characteristics included 1) the amount of time spent on sports (hours per week); despite PT are you active in sports (1 = no, 2 = a little, 3 = very, and 4 = with no limitations), despite PT are you participating in competitive sporting events like match or competition: (yes/no); the effect of injury on sport performance: to what extent has the PT compromised your level of performance (1 = not at all, 2 = a little, 3 = moderate, 4 = a lot, 5 = ceased). Safety and adverse events: all patients were evaluated for safety, including all reported adverse events.

Statistical analysis

For a 2-sample pooled *t* test of a normal mean difference with a 2-sided significance level of 0.05, assuming a common standard deviation of 2.0 points on a 0–10 numeric rating scale, a sample size of 16 patients per group is required to obtain a power of at least 80% to detect a mean difference of 2.0 points. Thus, enrolling 18 patients in each group as the intention-to-treat population would correspond to a statistical power of 85% to detect a mean difference of 2.0 points after 12 weeks.
The intention-to-treat (ITT) population, which consisted of participants randomized to either shockwave or placebo after signing an informed consent statement, was assessed for efficacy and safety at 2, 4, and 12 weeks. The primary analyses were based on the ITT population. In case of missing data or drop-outs, last observation carried forward data were used. Levene's test was used as test for homogeneity of variance. The between-group difference in treatment effect for all outcomes was based on a 2-sample *t* test. Mean delta-values were changes from baseline to all follow-up time points. The analyses were performed by using SPSS version 17.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

The two groups were similar at baseline with *P*'s ≥ *0.39* except for the following baseline characteristics where the *P* values were closer to statistical significance: color Doppler activity *P* = 0.15, right knee affected *P* = 0.087, and analgesics use *P* = 0.1.

All study participants were actively engaged in sports. Average time spent on sports per week was 7.7 hours. Seventy-five percent of the participants took part in one sporting event and 25% in two sporting events. The sports included were handball 33%, running 31%, soccer 19%, badminton and tennis 11%, volleyball 6%, fitness, gymnastics, skiing, and triathlon 3%. As shown in Table 1, PT had a negative impact on sports performance and the ability to remain active in sports.

Missing Data

Of the 36 included participant, 15 participants in the shockwave group completed the 12 weeks follow-up and 17 participants in the placebo group. Two participants, one from each group, never showed up for the second treatment at 2 weeks. At 4 weeks, two participants from the shockwave group never showed up, Figure 1. In addition, for the US outcomes, there were three cases of missing data for the measurement of thickness of the central hypoechoic area and one case of missing data for measurement of tendon thickness. In the case of both drop-outs and missing data, the last observation carried forward approach was applied.

Clinical outcomes

Table 2 shows the mean scores at baseline and the delta-values at 2, 4, and 12 weeks for pain while walking, pain at rest, pain when the patellar tendon was squeezed, and the US outcomes.

Primary endpoints: At 12 weeks, there was a statistically significant difference between the shockwave group and the placebo group regarding pain while walking: mean difference, 1.4 (95% confidence interval CI, 0.4 to 2.5, *P* = 0.011). There was no statistically significant difference between the shockwave group and the placebo group regarding pain at rest: mean difference, 0.4 (95% CI, –0.6 to 1.5, *P* = 0.404) and pain when the tendon was squeezed: mean difference, 0.3 (95% CI –0.2 to 0.9, *P* = 0.221).

Secondary outcomes: Patient-rated treatment effect demonstrated a statistically significant difference at 12 weeks in favor of shockwave treatment: mean difference, 1.0 (95% CI, 0.3 to 1.7, *P*

= 0.007). None of the sport specific outcomes or the US outcomes demonstrated any statistically significant difference between the shockwave group and the placebo group at 12 weeks, Table 2.

Safety: There were no reports of any adverse events in any of the groups.

DISCUSSION

PT is a common injury in athletes.[1,2] In this study all participants were active in sports and spent an average of 7.7 hours per week on sports activities. At baseline most of the participant's activity levels were reduced and performance levels substantially lowered. The disease duration was 27.0 months on average, 39% were previously treated with glucocorticoid injection, and 47% had been using analgesics. US showed definite signs of tendinopathy, with the presence of an increased tendon thickness, a central hypoechoic area in the patellar tendon and increased color Doppler activity.[44] This indicates that the study cohort was severely affected by the PT and thus a priori a hard-to-treat population.

In this study, three sessions of shockwave therapy administered at 2-week intervals resulted in a statistically significant improvement compared to placebo at 12 weeks (end of study) regarding pain while walking and patient-rated treatment effect, but no effect regarding pain at rest and when the tendon was squeezed. Nor could an effect be demonstrated regarding sport activity or the ability to participate in competitive sporting events. During the follow-up there were single time points where statistically significant differences could be demonstrated regarding pain at rest and when the tendon was squeezed. However, the clinical value of these incoherent findings is limited. Previous RCTs have shown very limited support for the use ESWT in the treatment of PT.[45] It is therefore interesting in our study to observe that pain while walking demonstrated an effect favoring ESWT with an improvement from baseline to 12 weeks of 1.5 points (36.6%) on a 0–10 numeric rating scale compared to only 0.03 points (0.9%) in the placebo group. This result was supported by the patient-rated treatment effect. However, it is important to remember that this was a short-term study of 12 weeks, and what is observed in studies with a longer follow-up period is that patients with tendinopathies tend on average to improve over time.[46-48] Furthermore, the baseline value (pain while walking) in the shockwave group was higher than in the control group, although the difference was not statistically significant. But due to regression toward the mean, the chance of observing an improvement was a priori greater in the ESWT group.

Despite a significant on average reduction in pain in the shockwave group, it is worth noting that, in addition to what is listed in Table 2, only one patient became pain free (compared to three in the control group) and that the sport-specific outcomes regarding sports activity and ability to participate in competitive events did not show any improvement. Taking all these aspects into account, the observed positive effect of shockwave therapy should be interpreted with caution, and the clinical relevance of this treatment should still be considered as questionable. Notwithstanding the limitations in the study, our present short-term RCT is the first placebo-controlled RCT on PT to demonstrate positive effects of ESWT. Larsson et al. concluded in a review in 2012 based on one RCT that there was limited evidence to support ESWT.[45] Mani-Babu et al. concluded in a review and meta-analysis from 2014 that the evidence was limited but studies indicated that ESWT could be a promising treatment option.[20] In a more recent review from 2018, Korakakis et al. found moderate-level evidence that ESWT had no short (3 months) or mid-term (5–6 months) effect on PT.[19] This conclusion was based on pooled data from five RCTs with an overall low risk of bias.[19] Two of the included RCTs had study designs similar to those in our study.[46,47] The demographic characteristics were similar, but the participants in our study had a longer disease duration and spent more hours on sports per week. Thijs et al. (2016) found no effect of adding three sessions of ESWT to an eccentric exercise program.[46] Nor did Zwerver et al. (2011) find an effect, when they compared three sessions of ESWT as solitary treatment to placebo in athletes during the competitive season.[47]

The optimal therapeutic ESWT dose regarding energy level, number of treatment sessions and number of impulses has not been well established. This task is complicated by a great diversity in the published ESWT protocols and the ongoing fundamental question concerning whether ESWT actually has a clinically important effect.[49] There are no strong evidence-based standardized guidelines for the number of sessions needed when using ESWT in tendinopathies. Several trials have reported using 3 sessions, but that number represents more tradition and personal experience from the clinicians than solid evidence.[50,51] The preliminary ESWT trials on plantar fascitis and lateral epicondylitis were conducted in 3 sessions and the succeeding studies often adopted this protocol, which was also the case for our current study.[15,17,52] In our study the ESWT protocol included 3 treatment sessions at 2-week intervals, with 1500–3000 impulses per session at the highest energy flux density that could be tolerated. But on PT there is no evidence to support this or any other ESWT protocol, according to the review by Schmitz et al.[53] In the review by Korakakis et al., no effective protocol for PT could be documented, but for Achilles tendinopathy they found

some evidence to suggest a protocol that included 3 treatment sessions.[19] A reason to recommend multiple ESWT sessions is supported by Takahashi et el. in their study on a cumulative effect of ESWT when looking at induction of nerve fiber degeneration as part of a pain relieving effect of ESWT.[26] In recent years attention has been called to the possibility that people may respond differently to ESWT. Waugh et al. have investigated the biological response from ESWT in tendinopathy through peritendinous microdialysis.[23] Following their results it is possible that only some of the treated patients respond biologically to the ESWT, suggesting that when using the present ESWT protocols some are responders and some are non-responders.[23] For the last decade a leading argument for ESWT has been its ability to treat musculoskeletal disorders with calcifications, especially in rotator cuff disease, which is one of the most intensively investigated area of ESWT.[49] However, Surace et al. (from 2020) concluded in a Cochrane meta-analysis on rotator cuff disease, including 32 trials and 2281 participants, that there were very few clinically important benefits from ESWT. In addition they found no between-group differences in pain and functional outcomes in participants who did or did not have calcific deposits in the rotator cuff.[49] This conclusion challenges some of the fundamentals of ESWT in its ability to treat conditions with calcific deposits.[31]

Imaging

At baseline and at 2, 4, and 12 weeks follow-up, the patellar tendon was assessed ultrasonographically regarding tendon thickness, thickness of the central hypoechoic area, and color Doppler activity. At none of the follow-up assessments were any changes observed regarding any of the three US parameters compared to the control group. The repair and regeneration of tendinous tissue is a time-demanding process. It is possible that the 12-week observation in our study was too short to demonstrate US changes. However, corticosteroid injection used in the treatment of PT has previously shown a significant reduction in tendon thickness after only 1 month and tendon thickness has been showed to decrease following rehabilitation after 3 months.[8,41] Limited evidence exists on US following ESWT in patients with PT, and to our knowledge, this is the first study to assess these US parameters. It is important to include imaging like US in clinical trials. US is widely used to support the initial clinical diagnosis.[37,54] The US image is also known to change over time without a strong relation to symptoms.[40,55,56] When US is included in clinical trials, we gain

knowledge on how the US image can change over time and its relation to symptoms, which can help to define what has clinical importance.

Side effects. There were no serious adverse events, no infections, and no dropouts due to adverse events. The number of participants in this study was relatively small and the average follow-up time short. This means that infrequent side effects or side effects developing over a longer time period were unlikely to be discovered in this trial. The overall safety of ESWT has been documented in a review by Schmitz et al. (2015) based on cumulative data from studies covering all orthopedic conditions where ESWT has been applied.[53]

Limitations

The study was designed as a double-blind study with blinding of both the patient and the outcome assessor. It is, however, likely that the patient-blinding was insufficient. The treatment itself induces pain, and we gave 1500 and 3000 impulses at the highest possible energy level in accordance with the pain limit. The placebo treatment did not involve any energy; hence it was painless. The patients, however, had little prior knowledge of shockwave therapy because we were among the first in the country to test it, but all participants were informed that the treatment could cause pain. The information about pain during treatment might therefore have provided an opportunity to distinguish placebo from active treatment. This risk of insufficient blinding could have led to increased satisfaction in the active group and the reverse in the placebo group. The blinding difficulties in ESWT studies have previously been addressed by Schmitz et al. in a ESWT study on plantar fasciitis questioning patient blinding and allocation concealment.[57]

US assessments that could have been relevant but not included in this study were the evaluation of tendon calcifications and patellar bone spur formation. Since disintegration of calcium deposition is a mechanism known to be induced by ESWT, a pre and post treatment US evaluation would have been of interest.[29-31]

This is an old study with the last patient included in 2007. This could lead to concerns regarding study quality since the focus on adequate reporting and limiting the risks of bias has increased substantially since then. Nevertheless, the study complied with the CONSORT recommendations and methodological rigor as expected in current RCTs.[58] However, there are issues that relate to the

time that the study was designed. The study protocol was approved by the local ethical committee, but the prespecified outcomes were not available in a public database like https://clinicaltrials.gov. The Victorian Institute of Sport Assessment (VISA) questionnaire has for the past decade been the most commonly used primary outcome assessment in trials on PT.[59] In a more recent study design, the VISA questionnaire would also have been included in this study. In this study, changes in pain were chosen as primary outcome based on pain while walking, at rest, and when the tendon was squeezed. However, the outcomes did not uniformly point in the same direction since only pain while walking demonstrated a statistically significant difference. From a patients'/athletes' point of view, this was probably the most important outcome since it relates to physical activity. But from a methodological point of view, with the primary outcomes predefined as equal, the result was that two out of three primary outcomes did not show any positive effect of ESWT.

The small sample size could make it difficult to demonstrate statistically significant differences that would be revealed in larger study population. However, when searching for a clinically relevant difference between an active treatment and a placebo control group, results from even small studies are of high importance.

In conclusion, in athletes with PT, three sessions of ESWT compared to placebo resulted in an improvement in pain while walking at 12-week follow-up compared to placebo but not regarding pain at rest and pain when the tendon was squeezed. ESWT does not ameliorate US changes in the tendon. The clinical relevance of these findings is uncertain, but they do provide support for future investigations of the role of ESWT.

Funding:

Medispec provided the shockwave machine during the study period. Santax Medico and Medispec gave an unrestricted grant of 10,000 Danish crowns each to the Silkeborg Regional Hospital for nursing and secretarial assistance.

Reference List

(1) Florit D, Pedret C, Casals M, Malliaras P, Sugimoto D, Rodas G. Incidence of Tendinopathy in Team Sports in a Multidisciplinary Sports Club Over 8 Seasons. *J Sports Sci Med* 2019;18:780-788.

(2) Khan KM, Maffulli N, Coleman BD, Cook JL, Taunton JE. Patellar tendinopathy: some aspects of basic science and clinical management. *Br J Sports Med* 1998;32:346-355.

(3) Scott A, Squier K, Alfredson H et al. ICON 2019: International Scientific Tendinopathy Symposium Consensus: Clinical Terminology. *Br J Sports Med* 2020;54:260-262.

(4) Janssen I, van der Worp H, Hensing S, Zwerver J. Investigating Achilles and patellar tendinopathy prevalence in elite athletics. *Res Sports Med* 2018;26:1-12.

(5) Lian OB, Engebretsen L, Bahr R. Prevalence of jumper's knee among elite athletes from different sports: a cross-sectional study. *Am J Sports Med* 2005;33:561-567.

(6) Tran PHT, Malmgaard-Clausen NM, Puggaard RS et al. Early development of tendinopathy in humans: Sequence of pathological changes in structure and tissue turnover signaling. *FASEB J* 2020;34:776-788.

(7) van Ark M, Cook JL, Docking SI et al. Do isometric and isotonic exercise programs reduce pain in athletes with patellar tendinopathy in-season? A randomised clinical trial. *J Sci Med Sport* 2016;19:702-706.

(8) 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;19:790-802.

(9) Nuhmani S. Injection therapies for patellar tendinopathy. *Phys Sportsmed* 2019;1-6.

(10) van Ark M, Zwerver J, van den Akker-Scheek I. Injection treatments for patellar tendinopathy. *Br J Sports Med* 2011;45:1068-1076.

(11) Malliaras P, Cook J, Purdam C, Rio E. Patellar Tendinopathy: Clinical Diagnosis, Load Management, and Advice for Challenging Case Presentations. *J Orthop Sports Phys Ther* 2015;45:887-898.

(12) Chen PC, Wu KT, Chou WY et al. Comparative Effectiveness of Different Nonsurgical Treatments for Patellar Tendinopathy: A Systematic Review and Network Meta-analysis. *Arthroscopy* 2019;35:3117-3131.

(13) Everhart JS, Cole D, Sojka JH et al. Treatment Options for Patellar Tendinopathy: A Systematic Review. *Arthroscopy* 2017;33:861-872.

(14) Chaussy C, Brendel W, Schmiedt E. Extracorporeally induced destruction of kidney stones by shock waves. *Lancet* 1980;2:1265-1268.

(15) Rompe JD, Hopf C, Küllmer K, Witzsch U, Nafe B. Extracorporeal shockwave therapy of radiohumeral epicondylopathy-- an alternative treatment concept. *Z Orthop Ihre Grenzgeb* 1996;134:63-66.

(16) Rompe JD, Rumler F, Hopf C, Nafe B, Heine J. Extracorporal shock wave therapy for calcifying tendinitis of the shoulder. *Clin Orthop Relat Res* 1995;196-201.

(17) Rompe JD, Hopf C, Nafe B, Burger R. Low-energy extracorporeal shock wave therapy for painful heel: a prospective controlled single-blind study. *Arch Orthop Trauma Surg* 1996;115:75-79.

(18) van Leeuwen MT, Zwerver J, van den Akker-Scheek I. Extracorporeal shockwave therapy for patellar tendinopathy: a review of the literature. *Br J Sports Med* 2009;43:163-168.

(19) Korakakis V, Whiteley R, Tzavara A, Malliaropoulos N. The effectiveness of extracorporeal shockwave therapy in common lower limb conditions: a systematic review including quantification of patient-rated pain reduction. *Br J Sports Med* 2018;52:387-407.

(20) Mani-Babu S, Morrissey D, Waugh C, Screen H, Barton C. The effectiveness of extracorporeal shock wave therapy in lower limb tendinopathy: a systematic review. *Am J Sports Med* 2015;43:752-761.

(21) van der Worp H, van den Akker-Scheek I, van Schie H, Zwerver J. ESWT for tendinopathy: technology and clinical implications. *Knee Surg Sports Traumatol Arthrosc* 2013;21:1451-1458.

(22) Notarnicola A, Moretti B. The biological effects of extracorporeal shock wave therapy (eswt) on tendon tissue. *Muscles Ligaments Tendons J* 2012;2:33-37.

(23) Waugh CM, Morrissey D, Jones E, Riley GP, Langberg H, Screen HR. In vivo biological response to extracorporeal shockwave therapy in human tendinopathy. *Eur Cell Mater* 2015;29:268-280.

(24) Kenmoku T, Ochiai N, Ohtori S et al. Degeneration and recovery of the neuromuscular junction after application of extracorporeal shock wave therapy. *J Orthop Res* 2012;30:1660-1665.

(25) Ohtori S, Inoue G, Mannoji C et al. Shock wave application to rat skin induces degeneration and reinnervation of sensory nerve fibres. *Neurosci Lett* 2001;315:57-60.

(26) Takahashi N, Ohtori S, Saisu T, Moriya H, Wada Y. Second application of low-energy shock waves has a cumulative effect on free nerve endings. *Clin Orthop Relat Res* 2006;443:315-319.

(27) Kvalvaag E, Brox JI, Engebretsen KB et al. Effectiveness of Radial Extracorporeal Shock Wave Therapy (rESWT) When Combined With Supervised Exercises in Patients With Subacromial Shoulder Pain: A Double-Masked, Randomized, Sham-Controlled Trial. *Am J Sports Med* 2017;45:2547-2554.

(28) Kim YS, Lee HJ, Kim YV, Kong CG. Which method is more effective in treatment of calcific tendinitis in the shoulder? Prospective randomized comparison between ultrasound-guided needling and extracorporeal shock wave therapy. *J Shoulder Elbow Surg* 2014;23:1640-1646.

(29) Gerdesmeyer L, Wagenpfeil S, Haake M et al. Extracorporeal shock wave therapy for the treatment of chronic calcifying tendonitis of the rotator cuff: a randomized controlled trial. *JAMA* 2003;290:2573-2580.

(30) Bannuru RR, Flavin NE, Vaysbrot E, Harvey W, McAlindon T. High-energy extracorporeal shock-wave therapy for treating chronic calcific tendinitis of the shoulder: a systematic review. *Ann Intern Med* 2014;160:542-549.

(31) Huisstede BM, Gebremariam L, van der Sande R, Hay EM, Koes BW. Evidence for effectiveness of Extracorporal Shock-Wave Therapy (ESWT) to treat calcific and non-calcific rotator cuff tendinosis--a systematic review. *Man Ther* 2011;16:419-433.

(32) Cook JL, Khan KM, Kiss ZS, Purdam CR, Griffiths L. Reproducibility and clinical utility of tendon palpation to detect patellar tendinopathy in young basketball players. Victorian Institute of Sport tendon study group. *Br J Sports Med* 2001;35:65-69.

(33) Fredberg U, Bolvig L, Andersen NT, Stengaard-Pedersen K. Ultrasonography in evaluation of Achilles and patella tendon thickness. *Ultraschall Med* 2008;29:60-65.

(34) Bolvig L, Fredberg U, Rasmussen OS. *Textbook on musculoskeletal ultrasound - for beginners and trained*. 1. ed. Munksgaard Danmark, 2011.

(35) Sunding K, Fahlstrom M, Werner S, Forssblad M, Willberg L. Evaluation of Achilles and patellar tendinopathy with greyscale ultrasound and colour Doppler: using a four-grade scale. *Knee Surg Sports Traumatol Arthrosc* 2014.

(36) Krogh TP, Ellingsen T, Christensen R, Jensen P, Fredberg U. Ultrasound-Guided Injection Therapy of Achilles Tendinopathy With Platelet-Rich Plasma or Saline: A Randomized, Blinded, Placebo-Controlled Trial. *Am J Sports Med* 2016;44:1990-1997.

(37) Hoksrud A, Ohberg L, Alfredson H, Bahr R. Color Doppler ultrasound findings in patellar tendinopathy (jumper's knee). *Am J Sports Med* 2008;36:1813-1820.

(38) Krogh TP, Fredberg U, Christensen R, Stengaard-Pedersen K, Ellingsen T. Ultrasonographic Assessment of Tendon Thickness, Doppler Activity and Bony Spurs of the Elbow in Patients with Lateral Epicondylitis and Healthy Subjects: A Reliability and Agreement Study. *Ultraschall Med* 2013;34:468-474.

(39) Fredberg U. Patellar tendon rehabilitation program http://www.sportnetdoc.com/.

(40) Fredberg U, Bolvig L, Andersen NT. Prophylactic training in asymptomatic soccer players with ultrasonographic abnormalities in Achilles and patellar tendons: the Danish Super League Study. *Am J Sports Med* 2008;36:451-460.

(41) Fredberg U, Bolvig L, Pfeiffer-Jensen M, Clemmensen D, Jakobsen BW, Stengaard-Pedersen K. Ultrasonography as a tool for diagnosis, guidance of local steroid injection and, together with pressure algometry, monitoring of the treatment of athletes with chronic jumper's knee and Achilles tendinitis: a randomized, double-blind, placebo-controlled study. *Scand J Rheumatol* 2004;33:94-101.

(42) Fredberg U. Ultrasonography and pressure algometry in chronic Achilles and patellar tendinopathy: Ph.D. thesis. Faculty of Health Sciences, University of Aarhus; 2008.

(43) Fischer D, Stewart AL, Bloch DA, Lorig K, Laurent D, Holman H. Capturing the patient's view of change as a clinical outcome measure. *JAMA* 1999;282:1157-1162.

(44) Cook JL, Khan KM, Harcourt PR, Grant M, Young DA, Bonar SF. A cross sectional study of 100 athletes with jumper's knee managed conservatively and surgically. The Victorian Institute of Sport Tendon Study Group. *Br J Sports Med* 1997;31:332-336.

(45) Larsson ME, Käll I, Nilsson-Helander K. Treatment of patellar tendinopathy--a systematic review of randomized controlled trials. *Knee Surg Sports Traumatol Arthrosc* 2012;20:1632-1646.

(46) Thijs KM, Zwerver J, Backx FJ et al. Effectiveness of Shockwave Treatment Combined With Eccentric Training for Patellar Tendinopathy: A Double-Blinded Randomized Study. *Clin J Sport Med* 2017;27:89-96.

(47) Zwerver J, Hartgens F, Verhagen E, van der Worp H, van dA-S, I, Diercks RL. No effect of extracorporeal shockwave therapy on patellar tendinopathy in jumping athletes during the competitive season: a randomized clinical trial. *Am J Sports Med* 2011;39:1191-1199.

(48) Smidt N, Van der Windt DA, Assendelft WJ, Deville WL, Korthals-de Bos IB, Bouter LM. Corticosteroid injections, physiotherapy, or a wait-and-see policy for lateral epicondylitis: a randomised controlled trial. *The Lancet* 2002;359:657-662.

(49) Surace SJ, Deitch J, Johnston RV, Buchbinder R. Shock wave therapy for rotator cuff disease with or without calcification. *Cochrane Database Syst Rev* 2020;3:CD008962.

(50) Thiel M. Application of shock waves in medicine. *Clin Orthop Relat Res* 2001;18-21.

(51) Speed CA. Extracorporeal shock-wave therapy in the management of chronic soft-tissue conditions. *J Bone Joint Surg Br* 2004;86:165-171.

(52) Buchbinder R, Ptasznik R, Gordon J, Buchanan J, Prabaharan V, Forbes A. Ultrasound-guided extracorporeal shock wave therapy for plantar fasciitis: a randomized controlled trial. *JAMA* 2002;288:1364-1372.

(53) Schmitz C, Csaszar NB, Milz S et al. Efficacy and safety of extracorporeal shock wave therapy for orthopedic conditions: a systematic review on studies listed in the PEDro database. *Br Med Bull* 2015;116:115-138.

(54) Warden SJ, Kiss ZS, Malara FA, Ooi AB, Cook JL, Crossley KM. Comparative accuracy of magnetic resonance imaging and ultrasonography in confirming clinically diagnosed patellar tendinopathy. *Am J Sports Med* 2007;35:427-436.

(55) Couppe C, Kongsgaard M, Aagaard P et al. Differences in tendon properties in elite badminton players with or without patellar tendinopathy. *Scand J Med Sci Sports* 2013;23:e89-e95.

(56) Fredberg U, Bolvig L. Significance of ultrasonographically detected asymptomatic tendinosis in the patellar and achilles tendons of elite soccer players: a longitudinal study. *Am J Sports Med* 2002;30:488-491.

(57) Schmitz C, Csaszar NB, Rompe JD, Chaves H, Furia JP. Treatment of chronic plantar fasciopathy with extracorporeal shock waves (review). *J Orthop Surg Res* 2013;8:31.

(58) Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.

(59) Visentini PJ, Khan KM, Cook JL, Kiss ZS, Harcourt PR, Wark JD. The VISA score: an index of severity of symptoms in patients with jumper's knee (patellar tendinosis). Victorian Institute of Sport Tendon Study Group. *J Sci Med Sport* 1998;1:22-28.

TABLE 1

Baseline Characteristics[a]

Characteristic	Shockwave (n = 18)	Placebo (n = 18)	Total (N = 36)
Age, y	32.3 ± 11.0	30.9 ± 10.0	31.6 ± 10.4
Female sex, n (%)	9 (50%)	7 (39%)	16 (44%)
Body mass index, kg/m^2	25.2 ± 3.6	25.3 ± 2.8	25.2 ± 3.2
Height, m	1.83 ± 0.07	1.85 ± 0.08	1.84 ± 0.07
Weight, kg	84.2 ± 12.5	87.4 ± 13.2	85.8 ± 12.8
Right knee affected, n (%)	9 (50%)	4 (22%)	13 (36%)
Previous patellar tendinopathy, n (%)	5 (28%)	3 (17%)	8 (22%)
Duration of symptoms, mo	26.9 ± 42.2	27.1 ± 16.1	27.0 ± 31.4
Median (range)	21.0 (6.0–192.0)	24.0 (7.0–60.0)	24.0 (6.0–192.0)
Previous glucocorticoid injection, n (%)	5 (28%)	9 (50%)	14 (39%)
Analgesics use, n (%)[b]	6 (33%)	11 (61%)	17 (47%)
Sport			
Amount of time spent on sports, hours/week	8.1 ± 5.1	7.3 ± 6.0	7.7 ± 5.5
Still active in sport (1–4)	2.3 ± 1.0	2.1 ± 1.1	2.2 ± 1.0
Participating in competitive sporting events, n (%)	8 (44%)	6 (33%)	14 (39%)

Injury affects sport performance (1–5)	4.2 ± 0.9	4.2 ± 0.7	4.2 ± 0.8
Pain scores			
While walking (0–10)	4.1 ± 2.4	3.4 ± 3.0	3.8 ± 2.7
At rest (0–10)	3.0 ± 2.3	3.1 ± 2.5	3.1 ± 2.4
Tendon squeezed (0–3)	1.8 ± 0.9	1.6 ± 0.9	1.7 ± 0.9
Ultrasound			
Tendon thickness, mm	8.8 ± 2.0	9.3 ± 1.4	9.0 ± 1.7
Thickness of central hypoechoic area, mm	6.9 ± 1.6	6.7 ± 0.7	6.8 ± 1.2
Color Doppler activity (grades 0–4)	2.5 ± 0.7	2.9 ± 1.0	2.7 ± 0.9

[a]Data are reported as mean ± SD unless otherwise indicated. SD, standard deviation; [b]Use of paracetamol and/or nonsteroidal anti-inflammatory drugs.

TABLE 2

Outcome Measurements and Group Differences

	Shockwave		Placebo		Shockwave vs Placebo	
Outcome	Mean	SE	Mean	SE	Mean Difference (95% CI)	*P* Value
Pain while walking (0–10)						
At baseline	4.1	0.6	3.4	0.7		
Δ at 2 weeks	0.9	0.4	–1.4	0.6	2.3 (0.8 to 3.8)	**0.004**
Δ at 4 weeks	0.9	0.4	–0.5	0.4	1.4 (0.2 to 2.6)	**0.028**
Δ at 12 weeks	1.5	0.4	0.03	0.3	1.4 (0.4 to 2.5)	**0.011**
Pain at rest (0–10)						
At baseline	3.0	0.6	3.1	0.6		
Δ at 2 weeks	0.9	0.3	–0.4	0.3	1.3 (0.4 to 2.2)	**0.008**
Δ at 4 weeks	0.6	0.5	–0.4	0.3	1.0 (–0.2 to 2.2)	0.104
Δ at 12 weeks	0.8	0.4	0.4	0.4	0.4 (–0.6 to 1.5)	0.404
Pain tendon squeezed (0–3)						
At baseline	1.8	0.2	1.6	0.2		
Δ at 2 weeks	0.2	0.2	–0.3	0.2	0.5 (–0.1 to 1.1)	0.100
Δ at 4 weeks	0.5	0.2	–0.1	0.1	0.6 (0.03 to 1.2)	**0.039**
Δ at 12 weeks	0.6	0.2	0.3	0.2	0.3 (–0.2 to 0.9)	0.221
Patient-rated treatment effect (1–6)						
at 2 weeks	2.8	0.2	2.0	0.2	0.8 (0.3 to 1.4)	**0.005**
at 4 weeks	3.0	0.3	2.5	0.2	0.5 (–0.2 to 1.2)	0.178
at 12 weeks	3.5	0.3	2.5	0.2	1.0 (0.3 to 1.7)	**0.007**
Tendon thickness, mm						
At baseline	8.8	0.5	9.3	0.3		
Δ at 2 weeks	0.1	0.2	0.4	0.1	–0.3 (–0.7 to 0.2)	0.195
Δ at 4 weeks	0.3	0.1	0.3	0.2	0.01 (–0.5 to 0.5)	0.982
Δ at 12 weeks	0.7	0.2	0.4	0.3	0.3 (–0.3 to 1.0)	0.280
Thickness of central hypoechoic area, mm						
At baseline	6.9	0.4	6.7	0.2		
Δ at 2 weeks	0.3	0.3	–0.02	0.2	0.4 (–0.4 to 1.1)	0.308
Δ at 4 weeks	0.5	0.3	0.1	0.2	0.4 (–0.4 to 1.1)	0.328
Δ at 12 weeks	1.2	0.4	0.5	0.5	0.7 (–0.7 to 2.0)	0.321
Color Doppler activity (grades 0–4)						

At baseline	2.5	0.2	2.9	0.2		
Δ at 2 weeks	0.0	0.2	0.1	0.2	–0.1 (–0.7 to 0.4)	0.671
Δ at 4 weeks	0.1	0.2	0.2	0.2	–0.1 (–0.6 to 0.4)	0.644
Δ at 12 weeks	0.7	0.3	0.4	0.2	0.3 (–0.4 to 1.1)	0.405
Still active in sport (1–4)						
At baseline	2.3	0.2	2.1	0.3		
Δ at 12 weeks	0.1	0.2	0.5	0.2	–0.4 (–0.9 to 0.2)	0.159
Participating in competitive sporting events, no/yes						
At baseline	0.4	0.1	0.3	0.1		
Δ at 12 weeks	0.1	0.1	0.2	0.1	–0.1 (–0.3 to 0.2)	0.641

SE, standard error; CI, confidence interval; Δ (delta-value), the difference from Baseline, calculated as the baseline value minus the follow-up value. A positive delta-value indicates an improvement from baseline and a negative delta-value indicates deterioration. Patient-rated treatment effect is not listed as a delta-value since there was no baseline value.

Figure legends:

Figure 1. Flow diagram of patients through the study.

Figure 2. (A) Photograph of knee flexed to 90 degrees and longitudinal probe position. (B) Photograph of knee in neutral position and longitudinal probe position. (C) Longitudinal ultrasonogram of a healthy patellar tendon. Probe position as demonstrated in Figure 2A. (D) Longitudinal ultrasonogram of patellar tendinopathy. Probe position as demonstrated in Figure 2A. Illustration of anterior-posterior thickness measurement of (1) patellar tendon (2) central hypoechoic area. (E) Transverse ultrasonogram of the patellar tendon just distal to the apex of the patella. Illustration of the central hypoechoic area. (a) Cortical surface of the apex of the patella. (b) Patellar tendon. (c) Cortical surface of tibia just proximal to the tuberosity of tibia. (d) Central hypoechoic area. Closed arrows mark the superficial border of the patellar tendon. Open arrows mark the deep border of the patellar tendon. Arrow heads mark the central hypoechoic area.

Figure 3. (A–E) Longitudinal ultrasonograms of the patellar tendon illustrating grading of color Doppler activity from grade 0 to 4. The grading is performed in the region of interest (ROI) defined as a 0.5 cm longitudinal part of the tendon with maximum color Doppler activity. A horizontal yellow line measuring 0.5 cm marks the superficial border of the ROI (the superficial border of the patellar tendon) and white dotted lines mark the proximal and distal borders. The deep border of the ROI is the profound border of the patellar tendon. Grade 0: no activity. Grade 1: 1–2 single vessels in the ROI. Grade 2: Doppler activity in less than 25% of the ROI. Grade 3: Doppler activity in 25–50% of the ROI. Grade 4: Doppler activity in more than 50% of the ROI. (F) Transverse ultrasonogram of the patellar tendon just distal to the apex of the patella illustrating presence color Doppler activity in the central hypoechoic area.

tsm2_246_f1.pptx