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Ultrasound-Guided Injection Therapy with Platelet-Rich Plasma in Recreational Athletes with Patellar Tendinopathy: A Randomized, Single Blinded, Placebo-Controlled Trial with 3 months follow-up.

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ABSTRACT

Background: Patellar tendinopathy is a common injury in athletes.

Hypothesis/Purpose: To examine whether 1 injection of platelet-rich plasma (PRP) was more effective than placebo (saline) in the treatment of athletes with patellar tendinopathy.

Methods: Twenty-four athletes with patellar tendinopathy of at least 6 months' duration were randomly assigned to receive either a blinded injection of PRP (n = 12) or saline (n = 12). The primary endpoint was improvement in Victorian Institute of Sports Assessment-Patella (VISA-P) score at 3 months. Secondary outcomes included changes in pain at rest, while walking, and when the tendon was squeezed. Ultrasonographic outcomes were changes in tendon thickness, the presence and size of a central hypoechoic area, and color Doppler activity.

Results: No difference between the PRP group and the saline group could be observed with regard to the primary outcome, VISA-P score mean difference 5.4 (95% confidence interval –5.5 to 16.4, P = 0.316). There were no statistically significant differences observed in any of the secondary outcomes.

Conclusion: In this blinded, randomized, controlled trial, there was no improvement in VISA-P score, ultrasonography, or any other outcome measures 3 months after an injection of PRP compared to a saline injection.

Key Words: Patellar tendinopathy, jumper's knee, tendinosis, growth factors, platelet-rich plasma, ultrasonography, injection therapy, VISA-P, 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, 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 injection therapies with the aim of achieving better or faster recovery.[9,10] Only a few of these therapies have been assessed in randomized controlled trials.[11] In sports medicine platelet-rich plasma (PRP) has been an area of interest during the last 10–15 years. In the treatment of injuries to ligaments, muscles and tendons, PRP is increasingly being used despite the limited scientific data supporting its effectiveness.[12] Theoretically, injecting PRP into a tendinopathic tendon could stimulate repair mechanisms and promote tendon healing through release of platelet growth factors (GF) like platelet-derived epidermal GF, platelet-derived GF, transforming GF, insulin-like GF, vascular endothelial GF, endothelial cell GF, and basic fibroblast GF.[13-15]

Our main objective was to determine whether 1 injection of PRP was more effective than 1 saline injection in the treatment of athletes with PT evaluated by changes in VISA-P score (Victorian Institute of Sport Assessment Questionnaire – Patellar Tendon) as primary outcome and secondarily ultrasonography.

METHODS

Study design and participants

Between August 2009 and August 2014, 37 patients with PT were assessed for eligibility, and 24 were included in this single-blind RCT. The patients had been referred to the Rheumatology Unit at Silkeborg Hospital by general practitioners or by other rheumatology/orthopedic departments. The local injection treatments were PRP or isotonic saline and 12 patients were randomly allocated to each group.

Inclusion criteria were symptoms located in the proximal part of the patellar tendon with more than 6 months duration, related to exercise, and with no effect of a standard rehabilitation program. The

clinical diagnosis was tenderness to palpation at the inferior pole of the patella with the knee fully extended.[16] 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.[17]

Exclusion criteria were age younger than 18 years, PT treatment with glucocorticoid injection or any other injection within the last 6 months, previous PT surgery, and known inflammatory diseases (e.g. rheumatoid arthritis, psoriasis arthritis, or inflammatory bowel disease).

The diagnosis was verified in all patients by the physician who also performed the inclusion, randomization, and treatment procedures. Outcome was assessed 3, 6, and 12 months after injection. Three physicians were assigned to the study as treating physicians and outcome assessors. Patients who did not achieve a satisfying treatment response (assessment and decision made by the patient) at 3 or 6 months had the option to discontinue the study and receive the standard treatment available at the department. There was no further trial follow-up in patients who opted out.

The study was approved by the institutional review board. The study protocol was registered and approved by the scientific ethics committee at Central Jutland Region Denmark (No. 20080067). The protocol can be accessed at www.hospitalsenhedmidt.dk/siteassets/fil-link/protocol.pdf. All participants gave written informed consent. The study was carried out in accordance with the Danish law and the Declaration of Helsinki.

Randomization and group allocation

Sequence generation: Eligible participants were randomly assigned in permuted blocks of 6, using a simple “shuffling envelopes” procedure, to PRP or saline injection.

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

Masking

As part of the blinding technique, a 54-mL venous blood sample was obtained from all the patients. The time from blood sampling to intervention was approximately 20 minutes, injectants were prepared out of sight of the patients, and all patients were blindfolded while receiving the intervention. Prior to the intervention, all patients received ultrasound (US)-guided injection of 10–

15 mL lidocaine (10 mg/mL) in the peritendon of the patellar tendon. The patient was blinded to the treatment, but the treating physician was not. In most cases the outcome assessor at 3-, 6-, and 12-month follow-up was the same as the treating physician, but the previous results were not available until after the completion of the study.

Sonographic evaluation

A high-end ultrasound scanner (HI VISION 900, Hitachi Medical) with a 14 MHz linear transducer was used. Patients were examined in a supine position. For the gray-scale images and thickness measurements the knees were flexed 90 degrees to avoid waving of the tendons, Figure 2A.[17] Figure 2B demonstrates the knees fully extended to avoid compression of the blood vessels in the patellar tendon necessary for color Doppler assessment.[17] Figure 2C shows a healthy patellar tendon with key anatomical landmarks. Figure 2D shows a longitudinal image of PT and demonstrates the anterior-posterior thicknesses measurement of both the whole tendon and the central hypoechoic area. Figure 2E shows a transverse image of PT. For the tendon thickness measurement, 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).[17] A maximum discrepancy of 0.3 mm between the longitudinal and transverse measurements was accepted. If the difference between the 2 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.[18]

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. 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.[19,20] This technique is

similar to the modified Öhberg score in which the number of vessels is counted on a 0–4 scale.[19,21] Figure 3F shows the presence of color Doppler activity in the central hypoechoic area in a transverse scan.

Interventions

US-guided injection technique was performed with the knee in a neutral position, probe positioned long axis to the patellar tendon, and the needle in a distal to proximal orientation, Figure 4. A 0.8x50-mm 21 gauge 2-inch needle was used to inject 6 ml of either PRP or saline (0.9%) using an antiseptic peppering technique by making 1 skin portal and about 5–7 tendon perforations evenly distributed in the hypoechoic area of the patellar tendon just distal to the apex patella. Three physicians (rheumatologists) were assigned to the study to perform the US guided injections. They had between 5 and 20 years of experience in performing US guided interventions. The PRP was prepared as follows: 54 mL of whole blood (autologous) was collected in a 60-mL syringe containing 6 ml sodium citrate (anticoagulant) and then placed in a disposable cylinder in a centrifuge for 15 min at a speed of 3,200 RPM. Platelets were collected using the Recover® GPS® II system (Biomet Biologics Inc., Warsaw, IN). The outcome of this process is approximately 6 mL of PRP with a platelet concentration increased on average by 8-fold compared to whole blood.[22] To achieve a physiologic pH, the PRP was buffered with 8.4% sodium bicarbonate. The PRP was injected immediately after preparation. The post-treatment protocol was the same for 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 web-based home therapy rehabilitation program from www.sportnetdoc.com.[23] This standard rehabilitation program was in accordance with the PT recommendations based on strengthening (including eccentric training), stretching, and coordination.[23]

Outcomes

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

The primary efficacy outcome was changes in VISA-P after 3 months.[24] Secondary outcomes were changes in pain at rest, when walking, and when the patellar tendon was squeezed. VISA-P is a

validated and commonly used patient-reported outcome measure, ranging from 0–100 points, with 100 indicating optimal function.[24] Previous studies have shown that healthy individuals have a mean score around 95 points and athletes with PT have a mean score ranging from 48–56.[24-26] In a study by Hernandez-Sanchez et al. the minimal detectable change in VISA-P was found to be 11.1.[27] We used an approved Danish version of the VISA-P. Pain at rest and pain while walking were assessed on a 0–10 numeric rating scale: 0 = no pain, 10 = worst pain imaginable.[28-31] Pain experienced when the tendon was gently squeezed by the outcome assessor using the thumb and index finger was assessed on a 1–4 numeric rating scale. The patient was asked to state whether palpation tenderness was present or absent. The examiner graduated the pain reaction as 1 = none, 2 = light, 3= modest or 4 = severe, with spontaneous pain response and ward movement.[32] 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.[33,34] US outcomes included changes in tendon thickness (mm), thickness of the central hypoechoic area (mm), presence of a central hypoechoic area (yes/no), and color Doppler activity (0–4). This way of quantifying color Doppler activity and measuring tendon thickness has previously been assessed regarding reliability and agreement in lateral epicondylitis in the common extensor tendon of the elbow.[35] The sports-specific baseline characteristics included the amount of time spent on sports (hours per week): despite PT are you still active in sports (1 = no, 2 = a little, 3 = very, and 4 = with no limitations), despite PT are you still participating in competitive sporting events like match or competition: (yes/no), Injury affects 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 and duration of any post-injectional pain.

Statistical analysis

The statistical power of this study was based on the need for a feasible sample size (less than 30 participants in total) enabling us to detect a treatment difference in the primary outcome of the patients' self-reported changes in VISA-P score for the PRP vs. saline groups. A priori calculations were initially made on a projected 12-month result. Because of a substantial dropout rate, with only a few patients left after 3 months, the 3-month data were chosen post hoc as the primary outcome (all participants still in the study). Secondary analyses at 6 and 12 months were based on both last

observation carried forward and per protocol. In this study, we set the minimum clinically important change in VISA-P score to 20 points.

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 15 VISA-P points, a sample size of 10 patients per group is required to obtain a power of at least 80% to detect a mean difference of 20 VISA-P points. Thus, enrolling 12 patients in each group as the intention-to-treat population would correspond to a statistical power of more than 85% (87.7%) to detect a mean difference of 20 in the VISA-P score after 3 months.

The intention-to-treat (ITT) population, which consisted of participants randomized after signing an informed consent statement and subsequently opening an envelope informing them whether they had a dose of PRP or saline, were assessed for efficacy and safety 3 months after injection. The primary analyses were based on the ITT population. Secondary analysis at 6 and 12 months were based on both per protocol due to the huge attrition and the exploratory nature of these analyses and last observation carried forward. 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).

RESULTS

The two groups were demographically similar at baseline ($P > 0.05$) except that the PRP group had more participants with right-sided PT, $P = 0.042$ (Table 1). Clinically, the PT appeared to be more severe in the PRP group: VISA-P: $P = 0.048$ and pain while walking $P = 0.024$. Regarding previous treatments Table 1 lists analgesics use and glucocorticoid injections. In addition 3 participants in the PRP group had previously been treated with sclerosing injections (not within 6 months of study participations) and two of these participants had also been treated with shock wave therapy. One participant from each group had been treated with acupuncture. None of the participants had previously been treated with PRP or other blood-products. Nine participants, 5 from the PRP group

and 4 from the saline group had tried supervised rehabilitation from a physiotherapist. All study participants were actively engaged in sports. Each participant took part in between 1 to 3 different sports (1.8 in average): running, 58%; soccer, 42%; badminton, fitness, or biking, 13%; skiing, 8%; squash, karate, or handball, 4%. Average time spent on sports per week was 5.5 hours. 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 12 patients in each treatment arm, only 4 patients in the PRP group (33%) and 3 in the saline group (25%) completed the entire 12 months' trial period (Figure 1). The patients not completing the 12 months' follow-up left the study due to an unsatisfactory effect of the initial treatment. All patients were assessed with regard to the primary outcome at 3 months. Two participants, 1 in each group, did not complete the patient-rated outcome assessments including VISA-P after 3 months. Last observation carried forward was applied in the event of missing values. There were no missing US assessments at 3 months.

Clinical outcomes

Table 2 shows the mean scores at baseline and at 3 months for VISA-P, pain at rest, pain while walking, pain when the patellar tendon was squeezed, and the US outcomes.

VISA-P: At 3 months (primary endpoint), there was no statistically significant difference between the PRP and saline groups: mean difference, 5.4 (95% CI, –5.5 to 16.4, P = 0.316), Table 2. Our a priori sample size considerations did not take into account the huge dropout after 3 months. For this reason, data are presented as 3-month data (no attrition). The 6- and 12-month VISA-P scores are presented in Table 3. This table includes both per protocol and last observation carried forward (LOCF) statistics, but we emphasize that these data are not strong with regard to statistical power.

Secondary outcomes: None of the 3 secondary pain assessments (pain at rest, pain while walking, and pain when the patellar tendon was squeezed) demonstrated any statistically significant difference between the PRP and saline groups at 3 months, Table 2. Ultrasonographic evaluation: No statistically significant differences between the two groups were observed at 3 months

regarding: tendon thickness, thickness of central hypoechoic area, presence of a central hypoechoic area, and color Doppler activity, Table 2.

Safety: No events led to hospitalization in any of the groups, and there were no reports of infections following the injection therapies. The median duration of additional post-injectional discomfort in the patellar tendon area following the injection therapy was 7.5 minutes (range 0 to 10,080 min) in the saline group and 900 minutes (0 to 28,800 min) in the PRP group.

DISCUSSION

In this study, a single injection of PRP was not significantly superior to a saline injection with regard to showing an improvement in the primary outcome, VISA-P scores over a 3-month period in patients with PT. The same picture was observed regarding the secondary outcomes, with no between-group differences regarding pain at rest, pain while walking, and pain when the tendon was squeezed. The patient-rated effect of the treatment did not show any difference between the two groups.

On joining the study, most of the participant's activity levels were reduced and performance levels substantially lowered. The disease duration was 26.9 months on average, half of the participants had at some point been treated with glucocorticoid injection however not within 6 months of study enrollment, and US showed definite signs of tendinopathy. This indicates that the study cohort was severely affected by the PT and thus a priori a hard-to-treat population. This study was designed as a 12-month follow-up RCT. The pre-defined intention was to present the 12-month data as the primary outcome, but due to the very large drop-out following the unsatisfactory effect in both treatment arms, the 3-month data are presented as the primary outcome. The reason why many patients withdrew from the trial was that the injection therapies used did not provide the pain relief the participants had expected, an indication of the failure of the active treatment in our study during the first 3 months. On joining this study, the participants were told that at any time after 3 months they would have the option to leave the study and receive other treatments if the initial treatment had not had a satisfactory pain-reducing effect. The number of patients who chose to leave the study after 3 months (50%) is greater than that observed in 2 similar patient-blinded studies by Dragoo et al., with 6-month dropout rates of 26%, and by Scott et al., with 12-month dropout rates of 21%.[36,37] In two other RCTs with almost identical study protocols assessing the effect of PRP in patients with lateral epicondylitis and Achilles tendinopathy, similar huge dropout rates of 57% and 54% were

observed after 3 months.[20,38] Another explanation as to why it was hard to motivate participants to stay in the study after 3 months could be the lack of supervised rehabilitation/training. In 3 previous PRP RCTs, all participants were assigned to a therapist with supervised rehabilitation and follow-up sessions.[36,37,39] In our study, the participants did not receive supervised rehabilitation but were given an online rehab program to follow.[23] This program consisted of the same rehab recommendations described in the other studies.[8] When participants are instructed by therapist on an individual basis and guided to secure optimal rehab, they are probably more likely to remain in a study. Furthermore, the motivation to remain in a study is presumably greater when a therapist acknowledges the training effort and boosts the moral of the participants during the follow-up period. If we had assigned a therapist to each participant, we would probably have had more success in reducing drop-outs at 6 and 12 months as initially intended. It is, however, important to note that in this case it is the rehab and/or the nursing that keeps participants in the study and not necessarily the effect of the injection therapy.

Several trials, reviews, and meta-analysis have investigated PRP in the treatment of PT. [12,40-42] However, to date only 3 RCTs have assessed the efficacy of PRP in the treatment of PT.[36,37,39] In these 3 RCTs, 3 different PRP preparation kits were applied. There is an ongoing and unsettled debate regarding what should be the preferred PRP preparation method.[43,44]

Vetrano et al. (2013) compared 2 US-guided PRP injections over 2 weeks (n = 23) to 3 sessions of extracorporeal shock wave therapy (n = 23).[39] The PRP preparation system was MyCells Autologous Platelet Preparation System. Participants were not blinded to the treatment. The VISA-P PRP score was not significantly different compared to shock wave therapy at 2 months, but it was at 6 and 12 months. At 12 months, the VISA-P score in the PRP group improved by 36 points compared to 21.5 in the shock wave group. A comparison to our results is not straight forward because this study was not blinded, there are no directly comparable time points, and the PRP preparation kit was different.

Dragoo et al. (2014) compared 1 US-guided leukocyte-rich PRP injection (n = 10) to US-guided dry needling (n = 13).[37] Both the patient and the outcome assessor were blinded to the treatment. VISA-P score in the PRP group improved by 25.4 points compared to 4.6 in dry needling group. However, at 26 weeks there was no statistically significant difference between the groups. They concluded

that PRP accelerates the recovery of PT, but the effect dissipates over time. Regarding the platelet extraction count, Dragoo et al. used the Biomet GPS III PRP preparation system, which is very similar to the GPS II kit used in our study.[37,45] At 12-week follow-up, both studies demonstrated the same limited VISA-P changes in the control groups, whereas the PRP group improved significantly, but only in the Dragoo study and not in our study.[37] Patient characteristics appeared to be comparable. Our injections procedure involved 5–7 penetrations of the tendinopathic area compared to 10 penetrations in the Dragoo study. Another difference was that we injected saline in the control group in addition to making tendon penetrations, whereas Dragoo et al. performed dry needling.

In a multicenter study, Scott et al. (2019) compared US-guided injection of either leukocyte-rich PRP (n = 19) or leukocyte-poor PRP (n = 19) to a saline injection (n = 19).[36] The PRP preparation system was Arthrex ABS-10060. The baseline characteristics were almost identical to those in our study. Patients were blinded to the treatment. They concluded that at no time points (6, 12, 24, 52 weeks) was leukocyte-poor or leukocyte-rich PRP more effective than a saline injection assessed using VISA-P score. As in our study, Scott et al. were unable to show any significant differences in VISA-P changes between participants given PRP and those given a saline injection. Of interest is the fact that all groups improved compared to baseline, whereas in our study no significant improvement from baseline was observed (all P's > 0.15) One could speculate that this was due to the supervised gym-based rehabilitation program in the Scott study and no supervised training in our study.

In summary, including our study, 4 RCTs have investigated PRP in the treatment of PT. The study by Scott et al. and our study found no positive effect of PRP, whereas Dragoo et al. and Vetrano et al. could demonstrate some positive short-term results.[36,37,39] Even though the design of our study is similar to that of Dragoo et al., the conclusions are different because we found no effect of PRP.

Imaging

At baseline and at 3-month follow-up, the patellar tendon was assessed ultrasonographically regarding tendon thickness, thickness of the central hypoechoic area, presence of a central hypoechoic area, and color Doppler activity. After 3 months, PRP had no effect on these 4 US parameters compared to the control group. This study is the only RCT on PRP to include imaging (US) of the patellar tendon as an outcome measure. Ferrero et al. evaluated the PRP effect after 6 months in a PRP trial with no control group.[46] At 6 months, they observed a reduction in tendon

thickness, presence of central hypoechoic area, and power Doppler activity. But since there was no control group and no randomization, it is impossible to know whether the observed changes are the results of PRP, needling procedure, time, natural healing, or other explanations. The repair and regeneration of tendinous tissue is a time-demanding process. It is possible that the 3 months' observation in our study was too short to demonstrate US changes. However, corticosteroid injection has previously been shown to significantly reduce tendon thickness after only 1 month.[28] We believe that it is important to include imaging like US in clinical trials. US is widely used to support the initial clinical diagnosis.[21,47] The US image is also known to change over time without a strong relation to symptoms.[48-50] 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. Comparing the two treatment arms, there was a tendency toward post-injectional discomfort in the patellar tendon area lasting longer in the PRP group than in the saline group. This has also been documented in a previous trial on lateral epicondylitis in which the same PRP preparation system was used.[38] Since the patellar tendons in both groups were perforated as part of the injection procedure, this is not the reason for the observed difference in post injectional pain. We therefore conclude that it is the PRP that exerts a physiological effect in the tissue, causing the prolonged period of pain. 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.

Limitations

At baseline, we observed a difference in the two groups, indicating that the participants in the PRP group had signs of more severe PT than the participants in the saline group. A statistically significant difference was observed at baseline regarding VISA-P score and pain while walking. The same tendency was also observed in the PRP group regarding disease duration, tendon thickness, and color Doppler activity, but there was no statistically significant difference. We have no suspicion that the athletes with more severe PT were assigned to the PRP group due to any other

reason than random selection. The allocation concealment and implementation procedure described in Methods was followed and should not lead to any risk of bias. In a study with a small sample size (n = 24), a between-group baseline difference can occur. Since we compared differences from baseline (delta-values), any baseline differences between the two groups would not affect the results. One could speculate that in athletes with a less advanced PT the PRP effect could be more favorably. On the other hand, a more severe VISA-P score would leave more room for improvement, which would favor the active treatment if it was effective.

The small sample size in this study makes it underpowered to demonstrate smaller differences in outcomes between groups. However, when looking for clinically relevant differences between an active treatment and a placebo control group, the potential of an active treatment should be discovered even in smaller studies.

In this study only the patient was blinded, and in order to reduce risk of bias, blinding of the treating physician would have been desirable. The patient blinding was thoroughly planned and conducted but to what degree this blinding was successful was not evaluated in a post-treatment questionnaire.

At the end of the trial period, we did not ask participants specifically if they had pursued other ways of treatment while in the study. Nevertheless, any major change in treatment strategy from the participant would likely have been discovered from the clinical evaluation and discussion regarding if the treatment response had been satisfying.

Many questions remain unanswered with regard to PRP therapy. Issues such as PRP preparation technique, dose-response of PRP, number of injections, and anticoagulation technique could be important. Regarding the actual PRP platelet content, we did not test it ourselves but relied on the manufacturer's description. However, it would have been of interest to verify the content of each PRP solution due to the potential great variation in concentrations. The potential negative effects of local anesthetics on in-vitro tenocyte proliferation and viability in the presence of PRP have been discussed.[51,52] In our study, we did not mix lidocaine with either PRP or saline. All injections were guided by ultrasonography. Lidocaine was injected outside the tendon, around the peritendon, whereas the saline and PRP were injected intratendinously. Another potential issue is the use of sodium citrate as an anticoagulant because it could render the PRP less active.[52,53]

In conclusion, in athletes with PT, 1 injection of PRP compared to a saline injection did not result in improvement in VISA-P score or any other outcome after 3 months. Despite more than 10 years of use, there is insufficient scientific evidence to recommend PRP as part of the treatment of PT.

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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) Vander DT, Jelley W. Non-surgical treatment of patellar tendinopathy: A systematic review of randomized controlled trials. *J Sci Med Sport* 2020;23:118-124.

(12) Moraes VY, Lenza M, Tamaoki MJ, Faloppa F, Belloti JC. Platelet-rich therapies for musculoskeletal soft tissue injuries. *Cochrane Database Syst Rev* 2014;CD010071.

(13) de Mos M, van der Windt AE, Jahr H et al. Can platelet-rich plasma enhance tendon repair? A cell culture study. *Am J Sports Med* 2008;36:1171-1178.

(14) Borzini P, Mazzucco L. Tissue regeneration and in loco administration of platelet derivatives: clinical outcome, heterogeneous products, and heterogeneity of the effector mechanisms. *Transfusion* 2005;45:1759-1767.

(15) Foster TE, Puskas BL, Mandelbaum BR, Gerhardt MB, Rodeo SA. Platelet-rich plasma: from basic science to clinical applications. *Am J Sports Med* 2009;37:2259-2272.

(16) 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.

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

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

(19) 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.

(20) 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.

(21) 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.

(22) Eppley BL, Woodell JE, Higgins J. Platelet quantification and growth factor analysis from platelet-rich plasma: implications for wound healing. *Plast Reconstr Surg* 2004;114:1502-1508.

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

(24) 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.

(25) Frohm A, Saartok T, Edman G, Renstrom P. Psychometric properties of a Swedish translation of the VISA-P outcome score for patellar tendinopathy. *BMC Musculoskelet Disord* 2004;5:49.

(26) Zwerver J, Kramer T, van den Akker-Scheek I. Validity and reliability of the Dutch translation of the VISA-P questionnaire for patellar tendinopathy. *BMC Musculoskelet Disord* 2009;10:102.

(27) Hernandez-Sanchez S, Hidalgo MD, Gomez A. Responsiveness of the VISA-P scale for patellar tendinopathy in athletes. *Br J Sports Med* 2014;48:453-457.

(28) 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.

(29) Alghadir AH, Anwer S, Iqbal A, Iqbal ZA. Test-retest reliability, validity, and minimum detectable change of visual analog, numerical rating, and verbal rating scales for measurement of osteoarthritic knee pain. *J Pain Res* 2018;11:851-856.

(30) Hjermstad MJ, Fayers PM, Haugen DF et al. Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. *J Pain Symptom Manage* 2011;41:1073-1093.

(31) Thong ISK, Jensen MP, Miro J, Tan G. The validity of pain intensity measures: what do the NRS, VAS, VRS, and FPS-R measure? *Scand J Pain* 2018;18:99-107.

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

(33) 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.

(34) O'Neill TA. An Overview of Interrater Agreement on Likert Scales for Researchers and Practitioners. *Front Psychol* 2017;8:777.

(35) 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.

(36) Scott A, LaPrade RF, Harmon KG et al. Platelet-Rich Plasma for Patellar Tendinopathy: A Randomized Controlled Trial of Leukocyte-Rich PRP or Leukocyte-Poor PRP Versus Saline. *Am J Sports Med* 2019;47:1654-1661.

(37) 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;42:610-618.

(38) Krogh TP, Fredberg U, Stengaard-Pedersen K, Christensen R, Jensen P, Ellingsen T. Treatment of lateral epicondylitis with platelet-rich plasma, glucocorticoid, or saline: a randomized, double-blind, placebo-controlled trial. *Am J Sports Med* 2013;41:625-635.

(39) Vetrano M, Castorina A, Vulpiani MC, Baldini R, Pavan A, Ferretti A. Platelet-rich plasma versus focused shock waves in the treatment of jumper's knee in athletes. *Am J Sports Med* 2013;41:795-803.

(40) Chen X, Jones IA, Park C, Vangsness CT, Jr. The Efficacy of Platelet-Rich Plasma on Tendon and Ligament Healing: A Systematic Review and Meta-analysis With Bias Assessment. *Am J Sports Med* 2018;46:2020-2032.

(41) Dupley L, Charalambous CP. Platelet-Rich Plasma Injections as a Treatment for Refractory Patellar Tendinosis: A Meta-Analysis of Randomised Trials. *Knee Surg Relat Res* 2017;29:165-171.

(42) Di Matteo B, Filardo G, Kon E, Marcacci M. Platelet-rich plasma: evidence for the treatment of patellar and Achilles tendinopathy-a systematic review. *Musculoskelet Surg* 2015;99:1-9.

(43) Oh JH, Kim W, Park KU, Roh YH. Comparison of the Cellular Composition and Cytokine-Release Kinetics of Various Platelet-Rich Plasma Preparations. *Am J Sports Med* 2015;43:3062-3070.

(44) Fitzpatrick J, Bulsara MK, McCrory PR, Richardson MD, Zheng MH. Analysis of Platelet-Rich Plasma Extraction: Variations in Platelet and Blood Components Between 4 Common Commercial Kits. *Orthop J Sports Med* 2017;5:2325967116675272.

(45) Kaux JF, Le Goff C, Renouf J et al. Comparison of the platelet concentrations obtained in platelet-rich plasma (PRP) between the GPS II and GPS III systems. *Pathol Biol (Paris)* 2011;59:275-277.

(46) Ferrero G, Fabbro E, Orlandi D et al. Ultrasound-guided injection of platelet-rich plasma in chronic Achilles and patellar tendinopathy. *J Ultrasound* 2012;15:260-266.

(47) 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.

(48) 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.

(49) 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.

(50) 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.

(51) Carofino B, Chowaniec DM, McCarthy MB et al. Corticosteroids and local anesthetics decrease positive effects of platelet-rich plasma: an in vitro study on human tendon cells. *Arthroscopy* 2012;28:711-719.

(52) Krogh TP, Fredberg U, Stengaard-Pedersen K, Christensen R, Jensen P, Ellingsen T. Authors' response. *Am J Sports Med* 2013;41:NP34-NP35.

(53) Callan MB, Shofer FS, Catalfamo JL. Effects of anticoagulant on pH, ionized calcium concentration, and agonist-induced platelet aggregation in canine platelet-rich plasma. *Am J Vet Res* 2009;70:472-477.

TABLE 1

Baseline Characteristics[a]

Characteristic	PRP Group (n = 12)	Saline Group (n = 12)	Total (N = 24)
Age, y	34.5 ± 8.7	34.8 ± 7.8	34.7 ± 8.1
Female sex, n (%)	3 (25%)	2 (17%)	5 (21%)
Body mass index, kg/m^2	26.2 ± 3.9	24.5 ± 3.3	25.4 ± 3.6
Height, m	1.85 ± 0.1	1.83 ± 0.06	1.84 ± 0.09
Weight, kg	90.7 ± 19.6	82.3 ± 13.5	86.5 ± 17.0
Right knee affected, n (%)	9 (75%)	4 (33%)	13 (54%)
Previous jumpers knee, n (%)	2 (17%)	2 (17%)	4 (17%)
Duration of symptoms, mo	31.5 ± 31.3	22.8 ± 15.9	26.9 ± 24.3
Median (range)	24.0 (6.0–120.0)	18.0 (6.0–48.0)	24.0 (6.0–120.0)
Previous glucocorticoid injection, n (%)	8 (67%)	4 (33%)	12 (50%)
Analgesics use, n (%)[b]	7 (58%)	4 (33%)	11 (46%)
Sport			
Amount of time spent on sports, hours/week	6.8 ± 5.7	4.2 ± 3.7	5.5 ± 4.8
Still active in sport (1–4)	2.0 ± 0.6	1.9 ± 0.8	2.0 ± 0.7
Participating in competitive sporting events, n (%)	1 (8%)	2 (17%)	3 (13%)
Injury affects sport performance (1–5)	4.0 ± 1.0	3.8 ± 1.1	3.9 ± 1.0
VISA-P score (0–100)	44.3 ± 14.1	56.0 ± 13.1	50.2 ± 14.6
Median (range)	45.5 (23–64)	58.0 (31–76)	51.0 (23–76)
Pain scores			
At rest (0–10)	3.4 ± 2.5	2.8 ± 2.3	3.1 ± 2.3
While walking (0–10)	4.2 ± 2.5	2.3 ± 1.1	3.2 ± 2.1
Tendon squeezed (1–4)	3.0 ± 0.7	2.5 ± 0.8	2.8 ± 0.8
Ultrasound			
Tendon thickness, mm	7.9 ± 2.0	6.8 ± 2.0	7.3 ±2.0
Thickness of central hypoechoic area, mm	4.6 ± 3.1	4.7 ± 2.5	4.7 ± 2.7
Central hypoechoic area present, n (%)	10 (83%)	11 (92%)	21 (88%)
Color Doppler activity (grade 0–4)	2.8 ± 1.3	1.8 ± 1.6	2.3 ± 1.5

[a]Data are reported as mean ± SD unless otherwise indicated. PRP, platelet-rich plasma; SD, standard deviation; VISA-P, Victorian Institute of Sports Assessment-Patella. [b]Use of paracetamol and/or nonsteroidal anti-inflammatory drugs.

TABLE 2

Outcome Measurements and Group Differences[a]

	PRP group		Saline group		PRP vs Saline	
Outcome	Mean	SE	Mean	SE	Mean Difference (95% CI)	*P* Value
VISA-P (0–100)[b]						
At baseline	44.3	4.1	56.0	3.8		
Δ at 3 months	0.4	4.2	–5.0	3.2	5.4 (–5.5 to 16.4)	0.316
Patient-rated treatment effect at 3 months (1–6)	3.3	0.4	3.6	0.5	–0.3 (–1.6 to 1.0)	0.667
Pain at rest (0–10)						
At baseline	3.4	0.7	2.8	0.7		

Δ at 3 months	0.8	0.6	0.5	0.8	0.3 (–1.7 to 2.3)	0.735
Pain while walking (0–10)						
At baseline	4.2	0.7	2.3	0.3		
Δ at 3 months	0.9	0.7	0.1	0.5	0.8 (–0.9 to 2.5)	0.318
Pain tendon squeezed (1–4)						
At baseline	3.0	0.2	2.5	0.2		
Δ at 3 months	0.3	0.3	0.3	0.3	–0.1 (–0.8 to 0.7)	0.818
Tendon thickness, mm						
At baseline	7.9	0.6	6.8	0.6		
Δ at 3 months	0.1	0.3	0.6	0.3	–0.5 (–1.3 to 0.4)	0.263
Thickness of central hypoechoic area, mm						
At baseline	4.6	0.9	4.7	0.7		
Δ at 3 months	0.5	1.4	1.1	0.3	–0.6 (–3.5 to 2.3)	0.696
Central hypoechoic area present						
At baseline	0.8	0.1	0.9	0.1		
Δ at 3 months	0.1	0.2	0.2	0.1	–0.1 (–0.5 to 0.4)	0.713
Color Doppler activity (grade 0–4)						
At baseline	2.8	0.4	1.8	0.5		
Δ at 3 months	0.5	0.3	0.3	0.4	0.3 (–0.9 to 1.4)	0.643

[a]PRP, platelet-rich plasma; SE, standard error; CI, confidence interval; VISA-P, Victorian Institute of Sports Assessment-Patella; Δ, the difference from Baseline. [b]Primary outcome.

TABLE 3

Outcome Measurements and Group Differences at 6 and 12 months based on LOCF and Per Protocol[a]

	PRP group		Saline group		PRP vs Saline	
Outcome	Mean	SE	Mean	SE	Mean Difference (95% CI)	*P* Value
LOCF						
ΔVISA-P, 6 mo	–10.6	7.1	–7.5	4.1	–3.1 (–20.1 to 13.9)	0.711
ΔVISA-P, 12 mo	–13.6	8.0	–12.2	5.5	–1.4 (–21.5 to 18.7)	0.885
Per Protocol[b]						
ΔVISA-P, 6 mo	–29.8	6.9	–10.0	6.4	–19.8 (–40.8 to 1.2)	0.062
ΔVISA-P, 12 mo	–47.3	2.0	–34.0	5.5	–13.3 (–26.6 to 0.09)	0.051

[a]LOCF, last observation carried forward; PRP, platelet-rich plasma; SE, standard error; CI, confidence interval; VISA-P, Victorian Institute of Sports Assessment-Patella. ΔVISA-P, the difference from Baseline. [b]Per Protocol data are based on the actual number of patients still in study at 6 months (PRP: $n = 6$; saline: $n = 6$) and at 12 months (PRP: $n = 4$; saline: $n = 3$).

Figure Legends

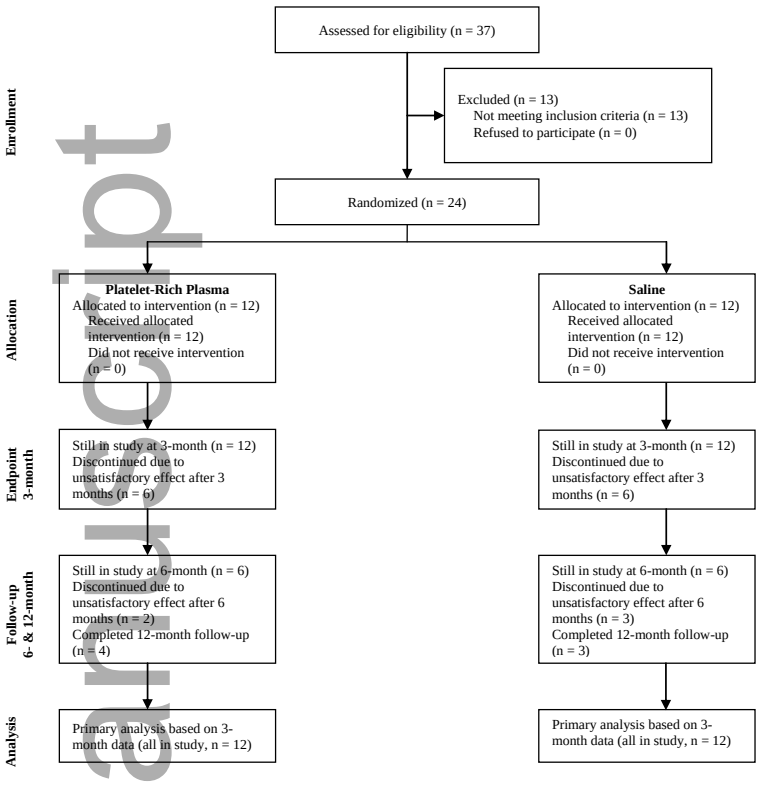
Figure 1. Flow diagram of patients through the study.

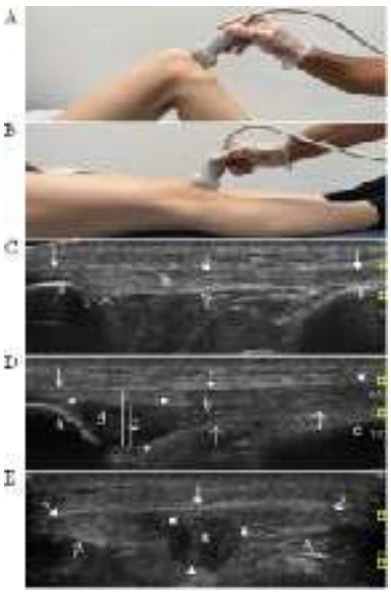
Figure 2. (A) Photograph of knee flexed to 90 degrees and longitudinal probe position. (B) Photograph of knee in a neutral position and longitudinal probe position. (C) Longitudinal ultrasonogram of a healthy patellar tendon. Probe position as demonstrated in Figure 2A. (D) Longitudinal ultrasonogram 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 illustrating 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.

Figure 4. Photograph of the platelet-rich plasma injection procedure.





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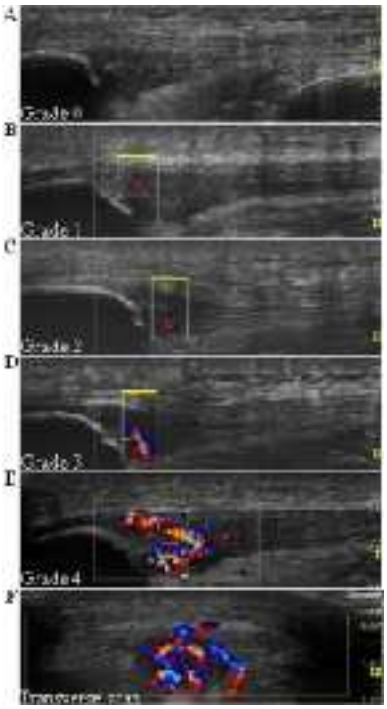

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