# Platelet-rich plasma in the conservative treatment of painful tendinopathy: a systematic review and meta-analysis of controlled studies

I. Andia[†], P. M. Latorre[‡], M. C. Gomez[‡], N. Burgos-Alonso[‡],
M. Abate[§], and N. Maffulli[††,*]

[†]Regenerative Medicine Laboratory, BioCruces Health Research Institute, Cruces University Hospital, 48903 Barakaldo, Spain, [‡]Primary Care Research Unit of Bizkaia, BioCruces Health Research Institute, Bilbao, Spain, [§]Department of Medicine and Science of Aging, University G. d'Annunzio, Chieti-Pescara, Chieti Scalo, Italy, and [††]Center for Sports and Exercise Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, Mile End Hospital, 275 Bancroft Road, London E1 4DG, UK

*Correspondence address. Center for Sports and Exercise Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, Mile End Hospital, 275 Bancroft Road, London E1 4DG, UK. E-mail: n.maffulli@qmul.ac.uk

## Abstract

**Background:** Platelet-rich plasma (PRP) seeks to meet the multifaceted demand of degenerated tendons providing several molecules capable of boosting healing.

**Areas timely for developing research:** PRP is used for managing tendinopathy, but its efficacy is controversial.

**Sources of data:** Electronic databases were searched for clinical studies assessing PRP efficacy. Methodological quality was evaluated using the methods described in the Cochrane Handbook for systematic reviews.

**Areas of agreement:** Thirteen prospective controlled studies, comprising 886 patients and diverse tendons were included; 53.8% of studies used identical PRP protocol.

**Areas of controversy:** Sources of heterogeneity included different comparators, outcome scores, follow-up periods and diverse injection protocols, but not PRP formulation *per se*.

**Growing points:** Pooling pain outcomes over time and across different tendons showed that L-PRP injections ameliorated pain in the intermediate-long term compared with control interventions, weighted mean difference (95% CI): 3 months, −0.61 (−0.97, −0.25); 1 year, −1.56 (−2.27, −0.83).

However, these findings cannot be applied to the management of individual patients given low power and precision.

**Research:** Further studies circumventing heterogeneity are needed to reach firm conclusions. Available evidence can help to overcome hurdles to future clinical research and bring forward PRP therapies.

## Introduction

Painful tendon conditions are frequent in orthopedics and sports medicine, and challenging to treat. The term tendinopathy describes a common painful condition with reduced functional capacity of the tendon associated with the histopathological findings of intra-tendinous failed healing response.[1] Tendon degeneration may occur when tissue breakdown exceeds the rate of tissue healing due to extrinsic factors such as tendon overload, excessive mechanical stimulation, training errors, fatigue, environmental conditions and/or chemical stresses (fluroquinolone antibiotics, corticosteroids).[2] Alternatively, the capacity for tissue repair can be reduced or impaired because of intrinsic factors such as advanced age, or genetic predisposition. Also, the capability for tissue repair may be weakened and tendon turnover disrupted due to pathological biochemical changes associated with metabolic diseases such as diabetes mellitus, hypercholesterolemia or gouty arthritis among others.[3,4] These observations also suggest that factors affecting microcirculation may play an important role in the development of tendinopathies.

Current treatments to manage tendinopathy include activity modifications, palliative medications and physiotherapy often complemented with extracorporeal shock wave therapy. Patients may benefit from conservative treatments in the form of eccentric training or heavy slow resistance training.[5] When conservative care fails, a wide range of injection therapies including prolotherapy, sclerosing agents, anesthetics, corticosteroids, botox or autologous blood are among the treatment options, which have evolved with current physiopathological knowledge.

Relatively, new biological therapies developed in the field of regenerative medicine, such as platelet-rich plasma (PRP), seek to meet the multifaceted demand of the tendinopathic tendon by providing several molecules capable of boosting healing mechanisms and counteracting degenerative processes. Upon degranulation, platelets secrete diverse signaling proteins that may modify the pathological status of the tendon by modulating angiogenesis, inflammation or cell activation.[6–10]

Research findings on the use of PRP injections in tendinopathy show that they can increase cell number,[6] stimulate precursor cell differentiation[11,12] and collagen fiber density,[13] and restore tissue architecture.[14] Moreover, it appears that molecules released from PRP may modify the way local cells and peripheral nerves react to the molecular changes that occur in tendinopathy, providing a biological basis for PRP effects in pain modulation. There is evidence of an inflammatory molecular microenvironment with the presence of PGE2 and COX2.[15] Signaling molecules present in PRP, mainly hepatocyte growth factor, reduce the production of pain associated molecules such as PGE2, COX-1 and COX-2 by tendon cells.[16] Up-to-date preclinical research on PRP has not evidenced any difference in its mechanism of action in different tendons.[6–13]

Currently, the clinical use of PRP in painful tendons is widespread, but its efficacy remains controversial. A recent retrospective cross-sectional survey,[17] representative of clinical practice in sports medicine settings, has shown moderate pain improvement (>50%) in most recalcitrant tendinopathies treated with PRP injections. However, the use of accurate reliable data to support the wide adoption of PRP therapies is essential if the growing demand for musculoskeletal lesions in large medical markets such as those for treating sports-associated pathologies is to be met from limited resources.

Despite efforts to distinguish among PRP products,[18] the different blood-derived products are most often gathered under the same category, including pure-PRP, leukocyte and PRP and autologous blood. However, treatments with autologous blood differ from PRPs, as the former is mainly composed of red blood cells (95%) in contrast to PRPs, which generally do not contain erythrocytes but merely platelets (pure-PRP) and, optionally leukocytes (leukocyte rich, PRP, L-PRP). Common thinking is that PRPs are not uniform and cannot be fairly assessed against each other.

The utility of autologous blood-derived products has been examined in three recent meta-analyses.[19–21] Taking a broad view across all musculoskeletal tissues (hard and soft) and various conditions, Sheth *et al.*[19] have addressed the efficacy of autologous blood and PRPs by pooling pain data, as assessed by VAS, across different conditions, ranging from ACL surgery to tendinopathy. This study confirmed 'uncertainty about the evidence to support the use of PRP'. Pooling data from all musculoskeletal conditions obviate the marked diversity among tissues, and also the heterogeneity of blood-derived products. In addition, two other meta-analyses have focused on PR-fibrin augmented arthroscopic surgery of the rotator cuff, and have reported no benefits[14] or limited benefits in the rate of re-tears in patients with small- or medium-sized tears, but not in massive tears.[21] A more recent qualitative review in lateral chronic elbow tendinopathy suggested that PRP may be of benefit over standard treatment as a second-line intervention.[22]

PRP is a controversial area in orthopedics and sports medicine. Methodological limitations of current PRP research in tendinopathy hamper conclusions and progress. The present study had three objectives: to investigate the effects of PRP in pain by using all controlled studies of PRP in tendinopathy; to examine the clinical efficacy in patient self-reported specific scales for pain and symptom severity stratifying studies using the same condition, PRP product and protocol and to identify the potential sources of heterogeneity among current studies to anticipate shortcomings in future studies.

## Materials and methods

### Search strategy

A comprehensive systematic literature search was performed until week 3 March 2014. The databases searched were MEDLINE, EMBASE, OrthoEvidence and The Cochrane Library Clinical Trials Database. The search included human clinical studies, written in English, Italian, French or Spanish. The following search algorithm was used to search in MEDLINE via Pubmed: (tendinopathy/OR tendinitis/OR tendinosis/ OR tendonosis/OR tendon injuries/OR shoulder/OR rotator cuff/OR supraspinatus/OR elbow/OR epicondylitis/OR patellar tendon/OR Achilles tendon) AND (PRP/OR platelet-rich fibrin/OR platelet concentrate) AND (cohort-study OR case control OR clinical trial).

### Selection of studies

Two review authors independently assessed each title and abstract of all the articles identified by the above methods. All clinical trials, comparative cohorts that provided scientific evidence on efficacy of PRP injection versus other therapies were eligible for inclusion. The experimental treatment had to be any PRP, including autologous blood only as comparator of PRP. The outcome had to be reported in terms of pain and/or function. Publications only assessing sonographic structure and neovascularization in the same cohorts were excluded. The studies had to provide enough data to compare the mean score in each comparative group to enable calculation of weighted mean differences (WMDs), and/or standardized mean difference (SMD). Where data were insufficient, the corresponding author of the article was contacted twice 4 weeks apart. If the corresponding author did not provide outcome data, the article was excluded from the meta-analysis. Other illustrative data described below were extracted, and the study was merely assessed for quality. Full texts were obtained for all studies matching the inclusion criteria. The final list of eligible studies was separately reviewed by two authors and confirmed by a third investigator.

## Data extraction and management

Extraction of the data was independently performed by at least two reviewers in each case, and the authors of several trials were contacted for additional information. The following data were extracted: design, setting, country, patient population and number of patients in each group, anatomical location of the tendinopathy, experimental intervention including data pertinent to PRP products, i.e. platelet and leukocyte content (when not specifically described by the authors, we have used pre-defined values from the manufacturer), system of activation and injected volume, control intervention and the treatment procedures described as blind or US-guided injection, single or multiple injections, needling/fenestrations, associated anesthetics and outcome instruments, mean, standard deviation (SD) and/or standard error (SE).

Data related to methodological quality were also extracted and examined as described below.

## Assessment of methodological quality in included studies

We used the Cochrane Handbook for Systematic Reviews of Interventions[23] as a guidance to assess 'risk of bias'. Two reviewers independently assessed the risk of bias, by means of a pre-defined domain-based evaluation sheet, which included support for evaluation on the following domains: adequacy of the method used to generate the allocation sequence and concealment, the level of blinding (clinician, patient or outcome assessor), attrition and reporting bias (see Table 1). Then, the criteria are scored as 'YES' (+) (low risk of bias), NO (−) (high risk of bias) or UNCLEAR (?).[17] A trial was considered to be at low risk of bias when it concealed allocation and blinded participants and outcome assessors, if it reported complete outcome data and there was no selective reporting.[23] If one or more of these key domains were not met, the trial was considered at high risk of bias and, if these issues were not properly clarified, it was considered as unclear with respect to risk of bias.[23] Percentage of agreement between reviewers was 90%. The main topic of discordance was for allocation concealment, when the adjective 'opaque' was overlooked in the description of envelopes.

## Measures of treatment effects

Prior to reviewing the data, we specified that only outcomes that were common to two or more studies would be pooled. We grouped studies according to follow-up time as 1 month, 2 months, 3 months, 6 months, 1 year and 2 years.

We summarized pain outcomes by pooling the visual analogue scores (VAS), and calculation of WMD. In addition, the SMD was used to allow the comparison between composite scales at the different periods of follow-up.

In the case of pain as measured by VAS, we calculated the WMD as the difference between two means and 95% confidence interval (CI).

The SMD expresses the size of the intervention effect in each study relative to the variability observed in that study. We calculated SMD, as the difference in the mean outcome between groups (intervention and control), divided by an estimate of the within-group SD. Corresponding 95% CIs were calculated for all point estimates.

In both instances, outcome measures were weighted by study size and the inverse of the variance, and pooled using the random-effects model of DerSimonian and Laird.[24]

## Evaluation of heterogeneity

Heterogeneity between studies was quantified using the $I^2$ statistic. We chose an $I^2$ value of <25% to represent low heterogeneity, and an $I^2$ value of >75% to indicate high heterogeneity.[25,26] Sensibility assays were performed when studies showed high heterogeneity. Tests for significance were two tailed, and $P < 0.05$ was considered to be significant.

## Results

### General characteristics of the included studies

The results of the search are reported in Figure 1. There were 13 eligible studies (Table 2) and 15 articles,[27–41] as two studies[29,37] were long-term follow-ups from the studies by de Vos *et al.*[29] and by Peerbooms

**Table 1** Guidelines for assessing the risk of bias

| Type of bias | Description | Relevant domains in the collaboration's 'risk of bias' tool |
| --- | --- | --- |
| Selection bias | Systematic differences between baseline characteristics of the groups that are compared | • *Sequence generation*. Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups<br>• *Allocation concealment*. Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrollment |
| Performance bias | Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest | • *Blinding of participants and personnel*. Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective<br>• Other potential threats to validity |
| Detection bias | Systematic differences between groups in how outcomes are determined | • *Blinding of outcome assessment*. Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective<br>• Other potential threats to validity |
| Attrition bias | Systematic differences between groups in withdrawals from a study | • *Incomplete outcome data*. Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions were reported, and any re-inclusions in analyses performed by the review authors |
| Reporting bias | Systematic differences between reported and unreported findings | • *Selective outcome reporting*. State how the possibility of selective outcome reporting was examined by the review authors, and what was found |

Adapted from Higgins JPT, Altman DG, Sterne, JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (eds). *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org.

*et al.*[37] The included studies were published between 2010 and 2014; all were parallel-group studies except one three-arm investigation.[31] There were 12 RCT and 1 non-randomized controlled study. The majority of these studies were conducted in Europe (*n* = 7), the remaining six were carried out in the USA,[30,34] Turkey,[32] Egypt,[35] South Korea[39] and India.[38] Patients were treated in hospitals, and outpatient orthopedics and sports medicine clinics settings.

The characteristics of the studies/subjects and designs are presented in Table 2. One author[34] did not provide VAS mean values for the groups at baseline and during follow-up and so this study was not included in the quantitative analysis. Overall, data on 636 patients were included in the meta-analysis. Three hundred and thirty-five patients had PRP injections and 331 patients a control treatment. The number of treated patients ranged from 230 in the Mishra *et al.*[34] to 23 in the Dragoo *et al.* study.[30] The follow-up periods varied from 1 month to 2 years. PRP was injected in different tendons. Upper limb tendinopathy was in the subject of nine studies: seven on chronic elbow tendinopathy[27,33–36,38,40] and two studies on supraspinatus tendinopathy.[32,39] Lower
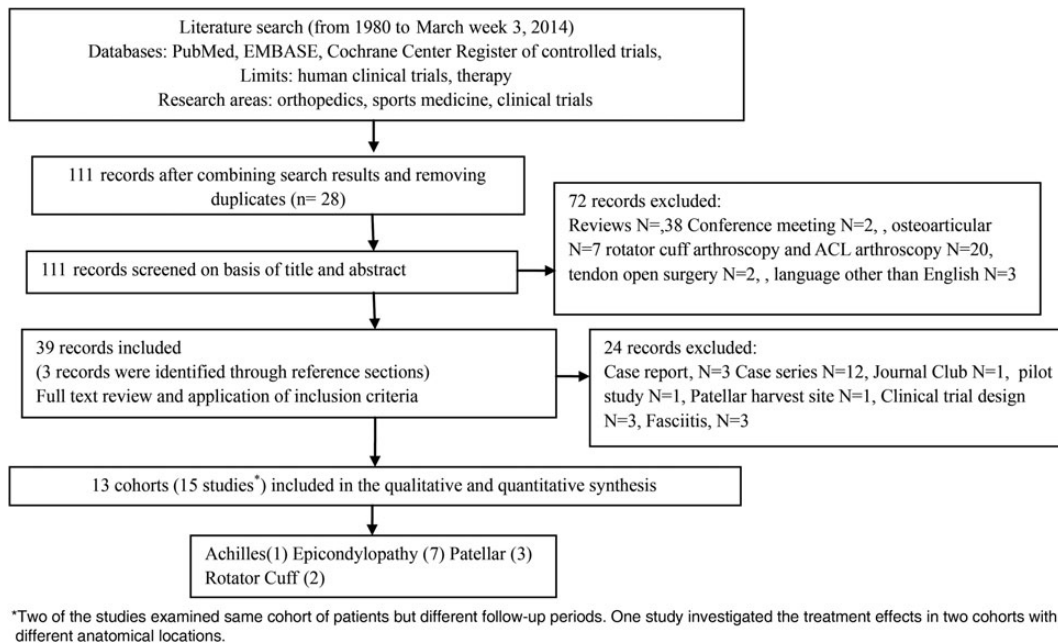
**Fig. 1** Flow diagram of study selection.

limb tendinopathies were in the subject of four studies: three on patellar tendinopathy[30,31,41] and one on Achilles tendinopathy.[28]

## Methodological features of the studies

The details of the 'risks of bias' of the included studies are shown in Table 3. Figure 2 displays a quantification synthesis of the risk of bias. De Jonge *et al.*[29] and Gosens *et al.*[37] studies were not appraised separately as they were the long-term follow-up to the de Vos *et al.*[28] and Peerbooms *et al.*'s[36] studies.

Overall, there are four studies with low risk of bias,[28,32,33,36] three studies with unclear risk of bias[31,35,41] and six studies with high risk of bias.[27,30,34,38–40] In general, most studies presented low risk of bias when allocating patients, blinding participants and undertaking outcome assessment, and reporting data attrition, but presented uncertainty for masking allocation (selection bias) and selective reporting. Additionally, blinding of personnel presented high risk of bias, but all studies were included even though they may have been considered at high risk of bias.

Of the 13 investigations included in the risk of bias evaluation, 10 adequately reported the randomization method.[27,28,30,32–34,36,38–40] Three other studies mentioned that the clinical trial was randomized but did not report further details.[31,35,41]

Five of the 10 studies adequately reported masking the allocation[28,30,32,33,36] but in other seven studies this was not specified.[27,31,34,35,38,39,41] One study did not use adequate allocation concealment.[40]

Eight studies blinded the participants.[27,28,30,32–34,36,39] Care providers were blinded in 4 studies[28,30,32,34] and outcome assessors in 10 studies.[27,28,32–34,36,38–41] Filardo *et al.*[31] and Omar *et al.*[35] did not mention whether the characteristics of the control group were comparable with those of the experimental group.

## Incomplete outcome data

All trials reported any participants lost to follow-up with the exception of Filardo *et al.*,[31] Omar *et al.*[35] and Rha *et al.*[39] The included trials had dropout percentages <30%, with the exception of Creaney *et al.*,[27] Mishra *et al.*[34] and Krogh *et al.*[33] with 31, 47 and

**Table 2** Conservative management of tendinopathy: characteristics of the studies included in the meta-analysis

| Study/clinicaltrial.gov identifier | Study design/follow-up | Condition | Patient population | PRP product (*n*) | Control product (*n*) | Injection procedure | Outcome instruments |
|---|---|---|---|---|---|---|---|
| Creaney et al.[27] | Randomized/6 months | Chronic elbow tendinopathy | Resistant to eccentric loading therapy | 1.5 ml L-PRP (plt: 2.8×) (*n* = 80) | Blood (*n* = 70) | Two monthly US-guided injections into clefts of hypoechoicity (no needling) | PRTEE |
| De Vos et al.[28] NCT00761423 De Jonge et al.[29] | Randomized/6, 12, 24 weeks (de Vos) 12 months (de Jonge) | Achilles midportion tendinopathy | Minimal duration of symptoms 2 months, excluded if previous full eccentric program or PRP | 4 ml L-PRP (plt: 4–8× WBC: 6×) buffered pH: 7.4, no activation and eccentric exercises (*n* = 27) | Saline and eccentric exercises (*n* = 27) | Single US-guided injection | VISA-A, patient satisfaction, return to sport |
| Dragoo et al.[30] NCT01406821 | Randomized/3, 6, 12 and >26 weeks | Patellar tendinopathy | Persistence of symptoms after 6 weeks (12 sessions) of physical therapy with eccentric exercises | 6 ml L-PRP (plt: 4–8× WBC: 6×) buffered, pH: 7.4, no activation (*n* = 9) | Dry needling, (*n* = 12) | Single US-guided injection, 10 penetrations into the injured area All patients received 3 ml bupivacaine with epinephrine (1:10$^5$) | VISA-P, Tegner, Lysholm, SF-12 |
| Filardo et al.[31] | Non-controlled, (matched for age, sex and sports level)/6 months | Patellar tendinopathy | Chronicity >3 m and recalcitrant to conservative and surgical treatment only in the PRP the group | 5 ml L-PRP (plt: 6×; WBC: NR) Ca$^{2+}$ activated + physical therapy (*n* = 15) | Physical therapy (*n* = 16) | Three blind injections/ biweekly US guided? | EQ-VAS, Tegner score |
| Kesikburun et al.[32] | Randomized/3, 6, 12 and 24 weeks and 1 year | Rotator cuff tendinopathy | Chronicity >3 months tendinosis or partial tear by MRI | 5 ml L-PRP (plt: 4–8× WBC: 6×) buffered pH:7.4, no activation (*n* = 20) | 5 ml saline (*n* = 20) | Single injection, injected into the center of the lesion and the edges of the tear at four sites. All patients received 1 ml 1% lidocaine | WORC, VAS, SPADI, Neer impingement sign (VAS) and passive range of motion (goniometry) |

**continued**

**Table 2** Continued

| Study/clinicaltrial.gov identifier | Study design/follow-up | Condition | Patient population | PRP product (*n*) | Control product (*n*) | Injection procedure | Outcome instruments |
|---|---|---|---|---|---|---|---|
| Krogh *et al.*[33] NCT01109446 | Randomized Three arms/3 months | Chronic elbow tendinopathy | Patients with symptoms for >3 months | 3–4 ml L-PRP (plt: 4–8× WBC: 6×) buffered pH: 7.4, no activation (*n* = 20) | Saline: 3 ml *n* = 20; Glucocorticoid; (1 ml triamcinolone + 2 ml lidocaine) (*n* = 20) | Single injection All patients received 10–15 ml lidocaine before intervention US guided | PRTEE (pain and function analysed separately), VAS (pain and pain duration caused by the treatment) US and color Doppler activity |
| Mishra *et al.*[34] NCT00587613[a] | Randomized multicenter /4, 8, 12, 24 weeks | Chronic elbow tendinopathy | Patients with symptoms for >3 months Failed conventional therapy | 3 ml L-PRP (plt: 4–8× WBC: 6×) buffered pH: 7.4, no activation, (0.5% bupivacaine and epinephrine to block injection site) (*n* = 116) | Bupivacaine: 2–3 ml (*n* = 114) | Single injection. Peppering technique in both groups (five penetrations of the tendon) | VAS, PRTEE |
| Omar *et al.*[35] | Randomized/6 weeks | Chronic elbow tendinopathy | Patients with pain and tenderness | L-PRP (plt > 2×) Vol: NR, activation: NR (*n* = 15) | Corticosteroid (*n* = 15) | Single blind injection | VAS, DASH, |
| Peerbooms *et al.*[36] NCT00757289 Gosens *et al.*[37] | Randomized /4, 8, 12 weeks and 6, 12 and 24 months | Chronic elbow tendinopathy | Chronic patients (medial region) | 3 ml L-PRP (plt: 4–8× WBC: 6×) buffered pH: 7.4, no activation (*n* = 51) | Corticosteroids triamcinolone + bupivacaine (*n* = 49) | Single blind injection, multiple small depots Bupivacaine before PRP | VAS, DASH |
| Raeissadat *et al.*[38] | Randomized /4, 8 weeks and 6 and 12 months | Chronic elbow tendinopathy | Chronic patients (>3 months) Pain >5/10 | 2 ml L-PRP (plt: 4.8× WBC: ~1×) (2 ml 1% lidocaine) (*n* = 30) | 2 ml autologous blood (2 ml 1% lidocaine) (*n* = 31) | Single blind injection Peppering technique | VAS, modified Mayo performance index, PTT |
| Rha *et al.*[39] | Randomized *n* = 39 25% drop out/6 weeks. 3 and 6 months | Supraspinatus tendinopathy | Pain >5/10 since >6 months, tendinosis or partial tear <1 cm (US), unresponsive to conservative treatments for at least 3 months | 3 ml L-PRP + dry needling (*n* = 16) | Dry needling (*n* = 14) | Two injections monthly US guided | VAS, SPADI, US |

| | | | | | | |
|---|---|---|---|---|---|---|
| Thanasas *et al.*[40] | Randomized /6 weeks, 3 and 6 months | Chronic elbow tendinopathy | No previous injections, symptoms since 3 months | 3 ml L-PRP (plt: 5.5× WBC: 6×) buffered pH: 7.4, no activation + physiotherapy (*n* = 14) | Autologous blood + physiotherapy (*n* = 14) | Single US-guided injection, peppering technique | VAS, Liverpool Elbow score/ |
| Vetrano *et al.*[41] | Randomized/2, 6 and 12 months | Patellar tendinopathy | Athletes | 3.5 ml PRP, platelet 3×–5×, CaCl$_2$ activation (*n* = 23) | ESWT (*n* = 23) | Two injections, biweekly, US guided | VAS, VISA-P, Blazina scale |

Anatomical location of the tendinopathy, participants, interventions (description of PRP products, controls and injection procedures) and type of outcome measures.
ABI, autologous blood injection; CTRL, control; DASH, Disabilities of the Arm, Shoulder and Hand; ESWT, Extracorporeal shock wave therapy; FHSQ, foot health status questionnaire; L-PRP, leukocyte-platelet rich plasma; NR, non-reported; plt, platelets; P-PRP, pure platelet-rich plasma; PRTEE, patient-related tennis elbow evaluation; PTT, pressure pain threshold; RCT, randomized controlled trial; SPADI, Shoulder Pain and Disability Index; US, ultrasound; VAS, visual analogue scale; VISA, Victorian Institute of Sports Assessment; VISA-P-Patella, VISA-A-Achilles; WBC, white blood cells; WORC, Western Ontario Rotator Cuff Index (WORC).
ᵃWithheld.

73%, respectively. Eight trials undertook intention-to-treat analyses.[27,28,32,33,36,38,39,41]

## Selective reporting

Seven studies presented low risk of bias of selective reporting.[32,33,35,36,38,39,41]

Five trial protocols of the 13 reported the registration number in Clinicaltrials.gov.[27,32–34,36] Outcomes of interest were pre-specified in the trial registration document in all studies, except for study NCT00587613 which was not included in the quantitative analysis.[34]

## Sources of clinical heterogeneity among studies

Although significant heterogeneity was noted in studies comparing PRP with other interventions, we have pooled pain outcome assessments pertaining to similar time points for follow-up, but trials critically differed in methodological and clinical aspects (comparators, injection protocols, outcome scores and total follow-up duration). High-quality studies in Achilles tendon,[28] and in chronic epicondylopathy[33] did not report VAS scores for pain, thus, although relevant, these studies could not be included.

## Control groups

Most studies were controlled with injectable interventions, but two studies were controlled with physical therapy,[31] or extracorporeal shock wave therapy.[41] The active comparators were corticoid in three studies;[33,35,36] autologous blood in three studies;[27,38,40] saline was used in three studies[28,32,33] and dry needling (sham control) in two studies.[30,39]

## PRP products

All studies used autologous PRP. Importantly, 92.3% of studies used L-PRP; 58% of these trials (seven studies) used the Biomet protocol. The methods for obtaining the L-PRP, single versus double spinning, varied among studies; 75% of L-PRP studies (nine studies) performed single spinning. Seven of the nine studies used the GPS III protocol consisting of single

**Table 3** Risk of bias assessment

| | Creaney 2011[27] | De Vos 2010[28] | Dragoo 2014[30] | Filardo 2012[31] | Kesikburun 2013[32] | Krogh 2013[33] | Mishra 2013[34] | Omar 2012[35] | Peerbooms 2010[36] | Raeissadat 2014[38] | Rha 2012[39] | Thanasas 2011[40] | Vetrano 2013[41] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Random sequence generation (selection bias) | + | + | + | ? | + | + | + | ? | + | + | + | + | ? |
| Allocation concealment (selection bias) | ? | + | + | ? | + | + | ? | ? | + | ? | ? | − | ? |
| Blinding of participants and personnel (performance bias): all outcomes (participants) | + | + | + | ? | + | + | + | ? | + | − | + | − | ? |
| Blinding of participants and personnel (performance bias): all outcomes (personnel) | − | + | + | ? | + | − | + | ? | ? | − | − | − | ? |
| Blinding of outcome assessment (detection bias) | + | + | ? | ? | + | + | + | ? | + | + | + | + | + |
| Incomplete outcome data (attrition bias) | − | + | − | ? | + | + | + | ? | + | + | − | + | + |
| Selective reporting (reporting bias) | ? | ? | − | ? | + | + | − | + | + | + | + | ? | + |
| Risk of bias | b | a | b | c | a | a | b | c | a | b | b | b | c |

Risk of bias assessment: low risk of bias: [a], six or more (+)/seven.

High risk of bias: [b], five or less (+)/seven.

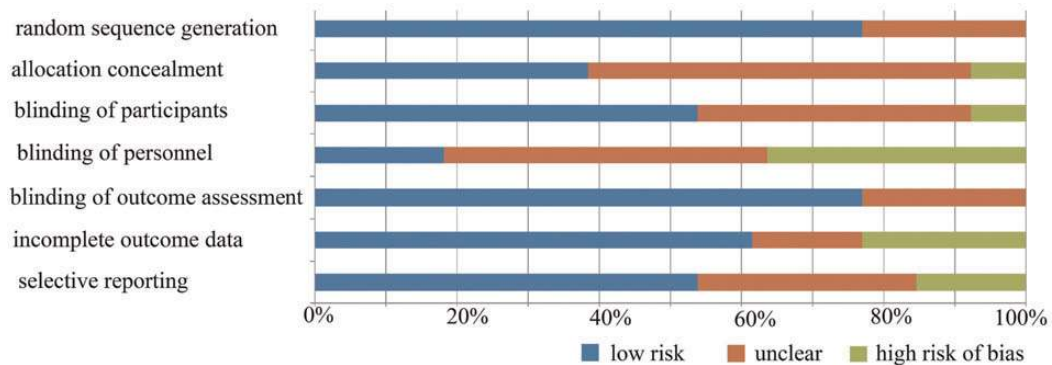Unclear risk of bias: [c], 3(?)/seven.

**Fig. 2** Quantification synthesis of risk of bias.

spin procedure, and collection of 3–6 ml of the buffy coat, which contains high concentrations of platelet (×4–8) and leukocytes (>5×) along with an undetermined number of erythrocytes; L-PRP was buffered with $NaHCO_3$ prior to injection of 3–6 ml of the product (GPS III system, Biomet Biologics LLC, Warsaw, IN, USA). Four of the seven studies performed with this protocol were sponsored by Biomet Biologics LLC, Warsaw, IN.

$CaCl_2$-PRP activation prior to injection was reported in two studies.[37,38]

### Injection procedures

Six studies reported the use of local anesthetics associated with PRP intervention.[28,30,32–34,38] Needling was reported in six studies.[30,32–34,38–40] Six studies performed blind injections.[28,30,32,34,36,38] Regarding the number and interval between injections, nine studies[28,30,32–36,38,40] performed a single injection, three studies performed two injections either monthly[27,39] or biweekly[41] and one study performed one injection each alternate week for a total of three injections.[31]

## Therapeutic effects of PRP injections

Pain ratings on a visual analogue scale (VAS) were used in 10 of the 13 studies (11 articles).[30–32,34–41] From these, one author did not provide his data.[34] Another study used VAS to monitor pain caused by intervention and how long it lasted.[33] Finally, we pooled VAS data from nine studies.[30–32,35,36,38–41]

Results at baseline and different follow-up periods are reported in Figure 3. Overall, PRP was not better than control interventions at 1, or 2-month follow-up. A small significant effect in pain reduction was found at 3 months, WMD (95% CI), −0.61 (−0.97, −0.25).

Regarding the pooled data at 6 months, heterogeneity was high ($I^2$ = 88.2%). We performed a sensibility assay, deleting the studies one by one and analyzing the repercussion of this action in the analysis. Deleting the studies by Filardo et al.[31] and Dragoo et al.,[32] heterogeneity was reduced ($I^2$ = 54.8%), WMD −1.04 (−1.64, −0.44). A large effect of PRP was reported in two trials with 100 and 31 participants compared with corticosteroids[29] and physical therapy,[31] whereas investigators from two trials of 30 and 46 participants reported a small effect of PRP;[39,41] no effect of PRP compared with autologous blood was reported in one trial with 28 patients.[35] Dragoo et al.[30] performed an approach 'by protocol' at 6 months with merely eight participants in the PRP group and nine participants in the control group; three patients from the control group received PRP treatment after control treatment failure at 12 weeks.

A significant effect in pain reduction was found at 1 year,[32,38,39,41] WMD (95% CI), −1.56 (−2.29, −0.83). Large effects in favor of PRP were reported in two trials with 100 and 46 patients 1 year after the intervention.[38,40]
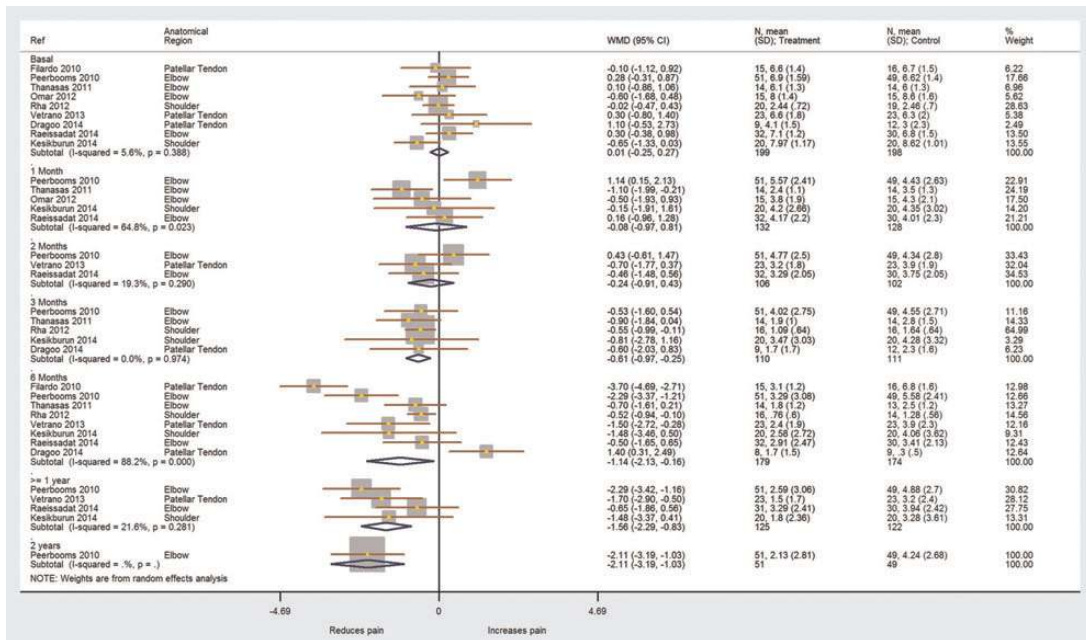
**Fig. 3** Forest plot of WMD showing temporal effect on pain scores of PRP compared with treatment for control patients. Results are expressed as stratified by follow-up time points. Diamonds indicate the pooled relative risk estimates. Squares represent point estimates around which 95% CI. *N*, number of patients; SD, standard deviation.

## Composite outcome measurements (pain and function)

For the lower limb, the composite outcome measurements used were VISA-A,[28] VISA-P,[30,41] Tegner,[30,31] Mayo Clinic performance index[38] and Blazina scale.[32,40] For the upper limb, the DASH,[35,36] PRTEE,[27,33,34] SPADI[39] and Liverpool elbow score[40] were used. These scores, addressing more than one aspect of the patient's health status, mostly pain and function, were rated using self-reported questionnaires, and found to be reliable and valid to measure the severity of tendinopathy. However, we did not pool the standardized mean differences because of the functional diversity of these conditions.

## Subgroup analysis: chronic elbow tendinopathy treated with one injection of L-PRP

Pooled VAS and outcome data from four studies[33,36,38,40] showed a small effect in overall improvement (composite scores) at 3 months in

pain, SMD −0.74 (95% CI, −1.45 to −0.03) and at 6 months, SMD −1.16 (95% CI, −2.23 to −0.08) but with significant heterogeneity ($I^2 = 69\%$) (Fig. 4A). Pooled functional outcome data[27,33,36,39] showed a small significant effect at 3 months, SMD, −0.298 (95% CI, −0.545 to −0.051) (Fig. 4B).

## Adverse effects

No complications or adverse events were reported in relation to PRP injections apart from injection-related pain (local pain and discomfort after PRP injection).

## Discussion

Our systematic review examining the effectiveness of PRP injections for the conservative management of tendinopathy included 12 randomized controlled trials and 1 non-randomized controlled study, which individually were mostly of moderate quality according to the Cochrane criteria.[23] Pooled VAS data from nine
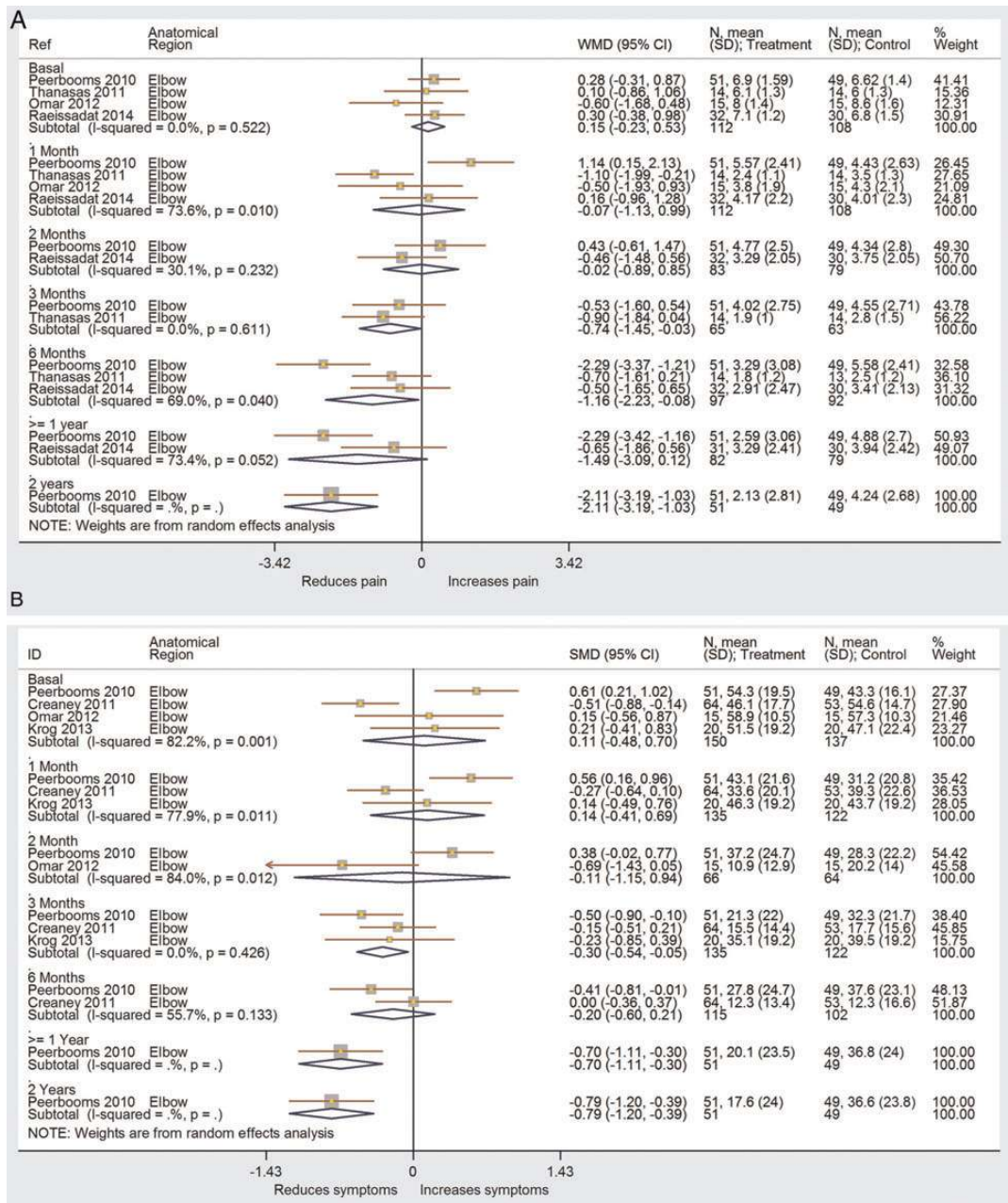
**Fig. 4** Pooled data of controlled studies examining PRP efficacy in epicondylitis. (**A**) Forest plot of WMD showing the temporal effect on pain scores of PRP compared with treatment for control patients. *N*, number of patients; SD, standard deviation. (**B**) Forest plot of standard mean difference (SMD) showing the temporal effect on composite scores (pain and function) of PRP compared with treatment for control patients. *N*, number of patients; SD, standard deviation.

studies showed that PRP has some beneficial effects in pain remission in the mid-term (36 months) compared with other existing interventions such as physical therapy,[31] anesthetics,[34] dry needling,[30,39] corticosteroids,[36] extracorporeal shock wave therapy[41] or autologous blood.[38,40] However, these results can be biased, as we excluded relevant studies that do not use VAS as outcome measurement.[27,28,33]

It would be interesting to know whether intermediate-long-term efficacy in favor of PRP could be related to improved tendon morphology, and whether changes in vascularity are related to the mechanism of action of PRPs.[9,42] For the time being, controlled human studies have not evidenced any changes in vascularity or echogeneicity attributable to PRP.[43–44] However, the relevance and validation of Doppler color and thickness assessments as outcome parameters for tendinopathy have not been established.

Not all PRP formulations are equally effective.[45,46] Strength of the current research is the fact that the composition of PRP products was very similar (L-PRP) in all trials. Indeed, most patients (97%) were treated with L-PRP containing high concentration of platelets and leukocytes.

Currently, the use of PRP in chronic elbow tendinopathy is widely investigated. Seven controlled studies using similar L-PRP product and protocols have examined the efficacy of PRP. This subgroup showed significant differences at 3 months. However, the analysis was hindered by different follow-up periods. Moreover, the severity of symptoms was assessed with four different scores, i.e. Liverpool elbow (1),[39] DASH (2),[35,36] PRTEE.[27,33,34] and Mayo score.[38] Additionally, these studies have used four different comparators, including corticosteroids,[33,36] saline,[33] anesthetics[34] and autologous blood.[27,38,39]

We point out that the PRP product *per se* does not vary, but the intervention procedure is different in the different studies. Whether PRP is applied with ultrasound guidance and delivered in a single depot into clefts of hypoechoicity, or delivered in multiple depots associated with needling/fenestration of tendinopathic tissue, which has a positive effect itself on tendon healing adds further variability.

In contrast to anesthetics and corticosteroids, which are injected peritendinously, PRP is most often injected intratendinously. However, ultrasonography shows that PRP spreads over the entire tendon.[47] Thus, when associating local anesthesia with PRP interventions,[30,32,34,36,38] care should be taken to avoid interferences with some of the biological actions of the PRP.[48]

Indeed, the association of PRP with anesthetics or corticosteroids can be potentially detrimental for peritendon cell proliferation and viability, as found in a highly controlled *in vitro* environment.[49] Also, corticosteroids deplete the tendon niche by inducing differentiation of tendon precursor cells into fatty and cartilage-like tissues.[49] For example, a high-quality study in chronic epicondylopathy[36] used intratendinous corticosteroid injections as comparator, which gives further advantage to PRP, because the former can induce tenocyte death or senescence.

Moreover, pooled intermediate effects, found on pain scores, was mainly based on the study of Peerbooms *et al.*[36] using corticosteroids as comparator.

Although L-PRP is the preferred formulation by most clinical researchers, experimental research showed that L-PRP was more pro-inflammatory when injected in rabbits,[47] and increased the levels of MMPs when assayed in tenocyte cultures compared with pure PRP.[48] Assuming preliminary experimental results, pure PRP would be less inflammatory and could produce better outcomes. Hence, randomized trials designed to compare the effectiveness of L-PRP (leukocyte rich) versus pure PRP (leukocyte depleted) will help in defining the optimal PRP formulation to manage tendinopathy.[50] Currently, comparative effectiveness research in osteoarthritis is limited to one study that has shown similar clinical improvements, but L-PRP injections induced more swelling and pain than pure PRP.[51] Upcoming trials using pure PRP injections in different tendinopathy sites such as supraspinatus or elbow (registered with clinicaltrials.gov number NCT01614223, NCT01915979, NCT01945528) might be helpful to contrast different formulations.[52]

Regarding the protocols for PRP administration, critical issues such as optimal volume and number of injections are still unclear. The effect of PRP could essentially stem from the needle penetration in combination with injection of a relatively high volume. Thus, further studies using saline injections and needle scarifications are needed to clarify this issue. Ten of 13 studies, representing 73% of patients, performed a single application of the product, and whether two or more applications should be performed depending on the anatomical location or severity of the lesion is crucial, and merits further investigation. It seems logical that a single L-PRP

injection may not change the natural history of a long-standing chronic conditions.[28,53] Patients with a longer history of tendinopathy, and previous pharmacological (corticosteroid) or surgical treatments might be candidates for multiple PRP injections, as a single injection produced poorer results comparing with patients with no previous treatments.[54] In fact, a case series with a 3-year follow-up emphasizes the potential importance of a second injection in painful tendons unresponsive to a single injection.[54] Research addressing the number of injections and the interval between them may help to understand negative results.[55]

The present meta-analysis has important shortcomings. In addition to clinical heterogeneity from the inclusion of different tendons, the use of diverse comparators, and timing of outcome measures, the random error attributed to the low power and precision because of the small number of studies hinders reaching definitive conclusions.

The possibility of performing a tendon meta-analysis with relevant conclusions for health-care professionals and policy-makers is far from reality because upcoming studies, as registered in clinicaltrials.gov, also show important sources of heterogeneity, mainly different comparators not used up to now (i.e. prolotherapy) and diverse outcome scales and time points in addition to tendons in a variety of anatomical locations.

To build upon the current results, future studies should use identical time points and outcome tools as well as similar injectable comparators other than corticosteroids.

All the controlled studies included in this review had been published since 2010, reflecting the enormous interest on this topic caused by the growing use of PRP in tendinopathy. Currently, at least 12 controlled trials are being run, as registered in clinicaltrials.gov, aiming to examine the effectiveness of single or multiple injections of either L-PRP or pure PRP in different tendinopathy sites. However, effectiveness research comparing both L-PRP and pure PRP formulations is presently lacking.

Furthermore, whether PRP might be more effective when applied in certain temporal stages of tendon degeneration, or in selected patients should be investigated based on biomarker development for tendinopathies. Future studies that combine changes in tissue histopathology,[56] and match clinical symptoms with PRP response have the potential to help answering important questions regarding not only the mechanism of action of PRPs but identifying patients for whom this therapy is indicated.

## Conclusions

Currently, with the presently available studies, a meta-analysis evaluating the effects of PRP intervention in tendinopathy cannot inform clinical decision mainly because of clinical heterogeneity. In spite of the fact that pooling pain outcomes across different sites of tendinopathy showed that L-PRP injections ameliorated pain in the intermediate-long-term compared with control interventions, these findings cannot be applied to the management of individual patients. Although the PRP formulation was identical in most studies, the moderate quality of primary trials and the great procedural heterogeneity among studies hinder conclusive results. Essentially, main sources of heterogeneity included different comparators, varied outcome scales and follow-up periods, number of injections and the diverse injection protocols but not the PRP formulation *per se*. Chronic elbow tendinopathy, the most widely investigated tendinopathy, illustrates all these constraints. Overcoming these methodological limitations in future studies will help to advance PRP therapies. Moreover, exploring the potential and limitations of PRP therapies by identifying biomarkers that help defining the quality of PRP and/or the pathological features of the host tissue might be tackled in the next years if the full potential of PRP therapies is to be realized.

## References

1. Maffulli N, Kha KM, Puddu G. Overuse tendon conditions: time to change a confusing terminology. *Arthroscopy* 1998;14:840–3.
2. Abate M, Silbernagel KG, Siljeholm C, et al. Pathogenesis of tendinopathies: inflammation or degeneration? *Arthritis Res Ther* 2009;11:235.
3. Abate M, Schiavone C, Salini V, et al. Occurrence of tendon pathologies in metabolic disorders. *Rheumatology (Oxford)* 2013;52:599–608.

4. Abate M, Oliva F, Schiavone C, et al. Achilles tendinopathy in amateur runners: role of adiposity (Tendinopathies and obesity). *Muscles Ligaments Tendons J* 2012;2:44–8.

5. 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.

6. Anitua E, Andía I, Sanchez M, et al. Autologous preparations rich in growth factors promote proliferation and induce VEGF and HGF production by human tendon cells in culture. *J Orthop Res* 2005;23:281–6.

7. Anitua E, Sanchez M, Nurden AT, et al. Reciprocal actions of platelet-secreted TGF-beta1 on the production of VEGF and HGF by human tendon cells. *Plast Reconstr Surg* 2007;119:950–9.

8. Anitua E, Sanchez M, Nurden AT, et al. Autologous fibrin matrices: a potential source of biological mediators that modulate tendon cell activities. *J Biomed Mater Res A* 2006;77:285–93.

9. Andia I, Sánchez M, Maffulli N. Tendon healing and platelet rich plasma therapies. *Expert Opin Biol Ther* 2010;10:1415–26.

10. Andia I, Maffulli N. Platelet rich plasma for managing pain and inflammation in osteoarthritis. *Nat Rheum Rev* 2013. doi:10.1038/nrrheum.2013.141.

11. Chen L, Dong SW, Liu JP, et al. Synergy of tendon stem cells and platelet-rich plasma in tendon healing. *J Orthop Res* 2012;30:991–7.

12. Wang X, Qiu Y, Triffit J, et al. Proliferation and differentiation of human tenocytes in response to platelet rich plasma: an in vitro and in vivo study. *J Orthop Res* 2012;30:982–90.

13. Tohidnezhad M, Varoga D, Wruck CJ, et al. Platelet-released growth factors can accelerate tenocyte proliferation and activate the anti-oxidant response element. *Histochem Cell Biol* 2011;135:453–60.

14. Schnabel LV, Mohammed HO, Miller BJ, et al. Platelet rich plasma (PRP) enhances anabolic gene expression patterns in flexor digitorum superficialis tendons. *J Orthop Res* 2007;25:230–40.

15. Fredberg U, Stengaard-Pedersen K. Chronic tendinopathy tissue pathology, pain mechanisms, and etiology with a special focus on inflammation. *Scand J Med Sci Sports* 2008;18:3–15.

16. Zhang J, Middleton KK, Fu FH, et al. HGF mediates the anti-inflammatory effects of PRP on injured tendons. *PLoS One* 2013;8:e67303.

17. Mautner K, Colberg RE, Malanga G, et al. Outcomes after ultrasound-guided platelet-rich plasma injections for chronic tendinopathy: a multicenter, retrospective review. *PMR* 2013;5:169–75.

18. Dohan Ehrenfest DM, Rasmusson L, Albrektsson T. Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF). *Trends Biotechnol* 2009;27:158–67.

19. Sheth U, Simunovic N, Klein G, et al. Efficacy of autologous platelet-rich plasma use for orthopaedic indications: a meta-analysis. *J Bone Joint Surg Am* 2012;94:298–307.

20. Chahal J, Van Thiel GS, Mall N, et al. The role of platelet-rich plasma in arthroscopic rotator cuff repair: a systematic review with quantitative synthesis. *Arthroscopy* 2012;28:1718–27.

21. Zhang Q, Ge H, Zhou J, et al. Are platelet-rich products necessary during the arthroscopic repair of full-thickness rotator cuff tears: a meta-analysis. *PLoS One* 2013;8: e6973.

22. Ahmad Z, Brooks R, Kang SN, et al. The effect of platelet-rich plasma on clinical outcomes in lateral epicondylitis. *Arthroscopy* 2013. doi:pii: S0749-8063(13) 00853-0. 10.1016/j.arthro.2013.07.272.

23. Higgins JPT, Green S (eds). Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0 [updated March 2011]. *The Cochrane Collaboration*, 2011. www.cochrane-handbook.org.

24. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.

25. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.

26. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.

27. Creaney L, Walla A, Curtis M, et al. Growth factor-based therapies provide additional benefit beyond physical therapy in resistant elbow tendinopathy: a prospective, double-blind, randomised trial of autologous blood injections versus platelet-rich plasma injections. *Br J Sports Med* 2011;45:966–71.

28. de Vos RJ, Weir A, van Schie HT, et al. Platelet-rich plasma injection for chronic Achilles tendinopathy: a randomized controlled trial. *JAMA* 2010;303:144–9.

29. de Jonge S, de Vos RJ, Weir A, et al. One-year follow-up of platelet-rich plasma treatment in chronic Achilles tendinopathy: a double-blind randomized placebo-controlled trial. *Am J Sports Med* 2011;39:1623–9.

30. Dragoo JL, Wasterlain AS, Braun HJ, et al. Platelet-rich plasma as a treatment for patellar tendinopathy: a double-blind, randomized controlled trial. *Am J Sports Med* 2014;42:610–8.

31. Filardo G, Kon E, Della Villa S, et al. Use of platelet-rich plasma for the treatment of refractory jumper's knee. *Int Orthop* 2010;34:909–15.

32. Kesikburun S, Tan AK, Yilmaz B, et al. Platelet-rich plasma injections in the treatment of chronic rotator cuff

tendinopathy: a randomized controlled trial with 1-year follow-up. *Am J Sports Med* 2013;41:2609–16.

33. Krogh TP, Fredberg U, Stengaard-Pedersen K, et al. Treatment of lateral epicondylitis with platelet-rich plasma, glucocorticoid, or saline: a randomized, double-blind, placebo-controlled trial. *Am J Sports Med* 2013;41:625–35.

34. Mishra AK, Skrepnik NV, Edwards SG, et al. Platelet-rich plasma significantly improves clinical outcomes in patients with chronic tennis elbow: a double-blind, prospective, multicenter, controlled trial of 230 patients. *Am J Sports Med* 2014;42:463–71.

35. Omar Aziza S, Maha EI, Amal SA, et al. Local injection of autologous platelet rich plasma and corticosteroid in treatment of lateral epicondylitis and plantar fasciitis: randomized clinical trial. *Egypt Rheumatol* 2012;34:43–9.

36. Peerbooms JC, Sluimer J, Bruijn DJ, et al. Positive effect of an autologous platelet concentrate in lateral epicondylitis in a double-blind randomized controlled trial: platelet-rich plasma versus corticosteroid injection with a 1-year follow-up. *Am J Sports Med* 2010;38:255–62.

37. Gosens T, Peerbooms JC, van Laar W, et al. Ongoing positive effect of platelet-rich plasma versus corticosteroid injection in lateral epicondylitis: a double-blind randomized controlled trial with 2-year follow-up. *Am J Sports Med* 2011;39:1200–8.

38. Raeissadat SA, Rayegani SM, Hassanabadi H, et al. Is platelet-rich plasma superior to whole blood in the management of chronic tennis elbow: one year randomized clinical trial. *BMC Sports Sci Med Rehabil* 2014;6:12.

39. Rha DW, Park GY, Kim YK, et al. Comparison of the therapeutic effects of ultrasound-guided platelet-rich plasma injection and dry needling in rotator cuff disease: a randomized controlled trial. *Clin Rehabil* 2013;27:113–22.

40. Thanasas C, Papadimitriou G, Charalambidis C, et al. Platelet-rich plasma versus autologous whole blood for the treatment of chronic lateral elbow epicondylitis: a randomized controlled clinical trial. *Am J Sports Med* 2011;39:2130–34.

41. Vetrano M, Castorina A, Vulpiani MC, et al. Platelet-rich plasma versus focused shock waves in the treatment of jumper's knee in athletes. *Am J Sports Med* 2013;41:795–803.

42. Finnoff JT, Fowler SP, Lai JK, et al. Treatment of chronic tendinopathy with ultrasound-guided needle tenotomy and platelet-rich plasma injection. *PMR* 2011;3:900–11.

43. Chaudhury S, de La Lama M, Adler RS, et al. Platelet-rich plasma for the treatment of lateral epicondylitis: sonographic assessment of tendon morphology and vascularity (pilot study). *Skeletal Radiol* 2013;42:91–7.

44. de Vos RJ, Weir A, Tol JL, et al. No effects of PRP on ultrasonographic tendon structure and neovascularisation in chronic midportion Achilles tendinopathy. *Br J Sports Med* 2011;45:387–92.

45. Dragoo JL, Braun HJ, Durham JL, et al. Comparison of the acute inflammatory response of two commercial platelet-rich plasma systems in healthy rabbit tendons. *Am J Sports Med* 2012;40:1274–81.

46. Sundman EA, Cole BJ, Fortier LA. Growth factor and catabolic cytokine concentrations are influenced by the cellular composition of platelet-rich plasma. *Am J Sports Med* 2011;39:2135–40.

47. Loftus ML, Endo Y, Adler RS. Retrospective analysis of postinjection ultrasound imaging after platelet-rich plasma or autologous blood: observational review of anatomic distribution of injected material. *AJR Am J Roentgenol* 2012;199:W501–5.

48. 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;28:711–9.

49. Zhang J, Keenan C, Wang JH. The effects of dexamethasone on human patellar tendon stem cells: implications for dexamethasone treatment of tendon injury. *J Orthop Res* 2013;31:105–10.

50. McCarrel TM, Minas T, Fortier LA. Optimization of leukocyte concentration in platelet-rich plasma for the treatment of tendinopathy. *J Bone Joint Surg Am* 2012;94:e1431–8.

51. Filardo G, Kon E, Pereira Ruiz MT, et al. Platelet-rich plasma intra-articular injections for cartilage degeneration and osteoarthritis: single- versus double-spinning approach. *Knee Surg Sports Traumatol Arthrosc* 2012;20:2082–91.

52. Parafioriti A, Armiraglio E, Del Bianco S, et al. Single injection of platelet-rich plasma in a rat Achilles tendon tear model. *Muscles Ligaments Tendons J* 2011;1:41–7.

53. Martin JI, Merino J, Atilano L, et al. Platelet-rich plasma (PRP) in chronic epicondylitis: study protocol for a randomized controlled trial. *Trials* 2013;14:410.

54. Gosens T, Den Oudsten BL, Fievez E, et al. Pain and activity levels before and after platelet-rich plasma injection treatment of patellar tendinopathy: a prospective cohort study and the influence of previous treatments. *Int Orthop* 2012;36:1941–6.

55. Dallaudière B, Meyer P, Hummel V, et al. Efficacy of second intra-tendinous platelet-rich-plasma injection in case of incomplete response of the first injection: three-year follow up experience. *Diagn Interv Imaging* 2013. doi:pii: S2211-5684(13)00199-X.

56. Maffulli N, Testa V, Capasso G, et al. Similar histopathological picture in males with Achilles and patellar tendinopathy. *Med Sci Sports Exerc* 2004;36:1470–5.