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Platelet-rich plasma in tendon-related disorders: results and indications

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Abstract
Purpose Platelet-rich plasma (PRP) is currently the most exploited strategy in the clinical practice to provide a regenerative stimulus for tendon healing. The aim of the present study was to systematically review the available evidence on the treatment of the main tendon disorders where PRP is currently applied.
Methods A systematic review of the literature was performed on the use of PRP as a treatment for tendinopathies focusing on the following sites: Achilles tendon, patellar tendon, rotator cuff tendons, and lateral elbow tendons. The following inclusion criteria for relevant articles were used: clinical trials written in English language up to 21 June 2016 on the use of PRP in the conservative or surgical treatment of the aforementioned tendinopathies.
Results The research identified the following clinical trials dealing with the application of PRP in the selected tendons: 19 papers on patellar tendon (6 being RCTs: 4 dealing with PRP conservative application and 2 surgical), 24 papers on Achilles tendon (4 RCTs: 3 conservative and 1 surgical), 29 on lateral elbow tendons (17 RCTs, all conservative), and 32 on rotator cuff (22 RCTs: 18 surgical and 3 conservative).
Conclusion Patellar tendons seem to benefit from PRP injections, whereas in the Achilles tendon, PRP application is not indicated neither as a conservative approach nor as a surgical augmentation. Lateral elbow tendinopathy showed an improvement in most of the high-level studies, but the lack of proven superiority with respect to the more simple whole-blood injections still questions its use in the clinical practice. With regard to rotator cuff pathology, the vast majority of surgical RCTs documented a lack of beneficial effects, whereas there is still inconclusive evidence concerning its conservative application in rotator cuff disorders.
Level of evidence Systematic review of level I–IV trials, Level IV.

Keywords PRP · Achilles tendon · Patellar tendon · Rotator cuff · Lateral elbow · Tendinopathy · Growth factors · Review

Introduction

Tendon-related disorders are rather common in sports medicine and orthopaedic practice, representing a major cause of functional impairment, and their high prevalence is responsible for a marked reduction in sport practice and working ability as well [63, 65]. Despite being an "old problem", the knowledge about tendon physiopathology has been long biased by the "inflammation" paradigm: it was just in the last decades that new theories have been prevailed, suggesting that inflammation is not the main aetiologic pathway, but just a side-finding in a more complex scenery [22, 88]. "Tendinopathy" is the term currently used in the clinical practice to define a wide spectrum of clinical conditions which affect

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several locations, with patellar and Achilles tendons, rotator cuff and extensor mechanism at the lateral elbow epicondyle being the most commonly affected anatomical sites. The intrinsic low healing potential of tendon tissue and the "degenerative" nature of the tendinopathic process stimulated basic researchers and clinicians to test new solutions aimed at increasing the tissue regeneration potential [82]. Among the emerging options to provide a regenerative stimulus in a tissue characterized by a poor healing capacity such as tendon, platelet-rich plasma (PRP) is currently the most exploited strategy in the clinical practice [25].

The particular nature of PRP makes this product applicable both as a conservative treatment, by a simple injective approach, and as an augmentation during surgical procedures [103]. It can be delivered directly into the lesion site and, once activated, the platelet concentrate becomes a gel allowing the secretion of the bioactive molecules in situ [7]. Its autologous nature makes it patient- and physician-friendly, and the lack of some side effects linked to more traditional medications is another point of strength of this particular approach, thus explaining the raising success it has encountered in recent times. A flourishing literature has been released on this particular topic; however, no conclusive findings have emerged, also due to the large inter-product variability and the heterogeneous therapeutic protocols used for the different applications in the clinical practice [102]. Moreover, since tendons with different biomechanical and anatomical features are treated by this approach, PRP might determine a different outcome depending on the specific condition considered, and the understanding of the currently available evidence for the different tendinopathy conditions may be of clinical relevance to provide indications for PRP use in the clinical practice.

Thus, the aim of the present study is to systematically review the available evidence on the treatment of the main tendon disorders where PRP is currently applied in the clinical practice: patellar tendinopathy, Achilles tendinopathy, rotator cuff tendinopathy, and lateral elbow tendinopathy.

Materials and methods

A systematic review of the literature was performed on the use of PRP as a treatment for tendinopathies focusing on the following sites: patellar tendon, Achilles tendon, rotator cuff tendons, and lateral elbow tendons. The search was conducted on the PubMed database on 21st June 2016 using the following formulas:

1. for the patellar tendon: (patellar tendon OR patellar tendinopathy OR jumper's knee OR jumper) AND (PRP OR platelet rich plasma OR platelet gel OR platelet derived growth factors OR platelet concentrate OR PRGF OR ACP OR autologous conditioned plasma OR platelet lysate OR platelet rich fibrin OR platelet rich membrane);
2. for the Achilles tendon: (Achilles tendon OR Achilles tendinopathy) AND (PRP OR platelet rich plasma OR platelet gel OR platelet derived growth factors OR platelet concentrate OR PRGF OR ACP OR autologous conditioned plasma OR platelet lysate OR platelet rich fibrin OR platelet rich membrane);
3. for the lateral elbow tendinopathy: (lateral elbow OR tennis elbow OR elbow tendinopathy OR elbow extensor tendons OR lateral epicondylitis) AND (PRP OR platelet rich plasma OR platelet gel OR platelet derived growth factors OR platelet concentrate OR PRGF OR ACP OR autologous conditioned plasma OR platelet lysate OR platelet rich fibrin OR platelet rich membrane).
4. for the rotator cuff tendons: (rotator cuff OR rotator cuff tendinopathy OR shoulder tendon) AND (PRP OR platelet rich plasma OR platelet gel OR platelet derived growth factors OR platelet concentrate OR PRGF OR ACP OR autologous conditioned plasma OR platelet lysate OR platelet rich fibrin OR platelet rich membrane).

Screening process and analysis were conducted separately by two independent observers. First, the articles were screened by title and abstract. The following inclusion criteria for relevant articles were used during the initial screening of titles and abstracts: clinical trials, written in English language, with no time limitation on the use of PRP in the treatment of the aforementioned tendinopathies. Exclusion criteria were articles written in other languages, case reports, reviews, or studies analysing other applications of PRP. In the second step, the full texts of the selected articles were screened, with further exclusions according to the previously described criteria. Reference lists from the selected papers were also screened. Relevant data were then extracted and collected in a unique database with the consensus of the two observers to be analysed for the purposes of the present manuscript.

Results

The research in the PubMed database identified the following clinical trials dealing with the application of PRP for the treatment of tendon-related disorders in the 4 selected anatomical sites: 19 studies on patellar, 24 on Achilles, 29 on lateral elbow, and 32 on rotator cuff tendons (Fig. 1). Results will be reported separately for each one of these anatomical districts; while the high-level trials will be discussed in the following paragraphs, more details of the

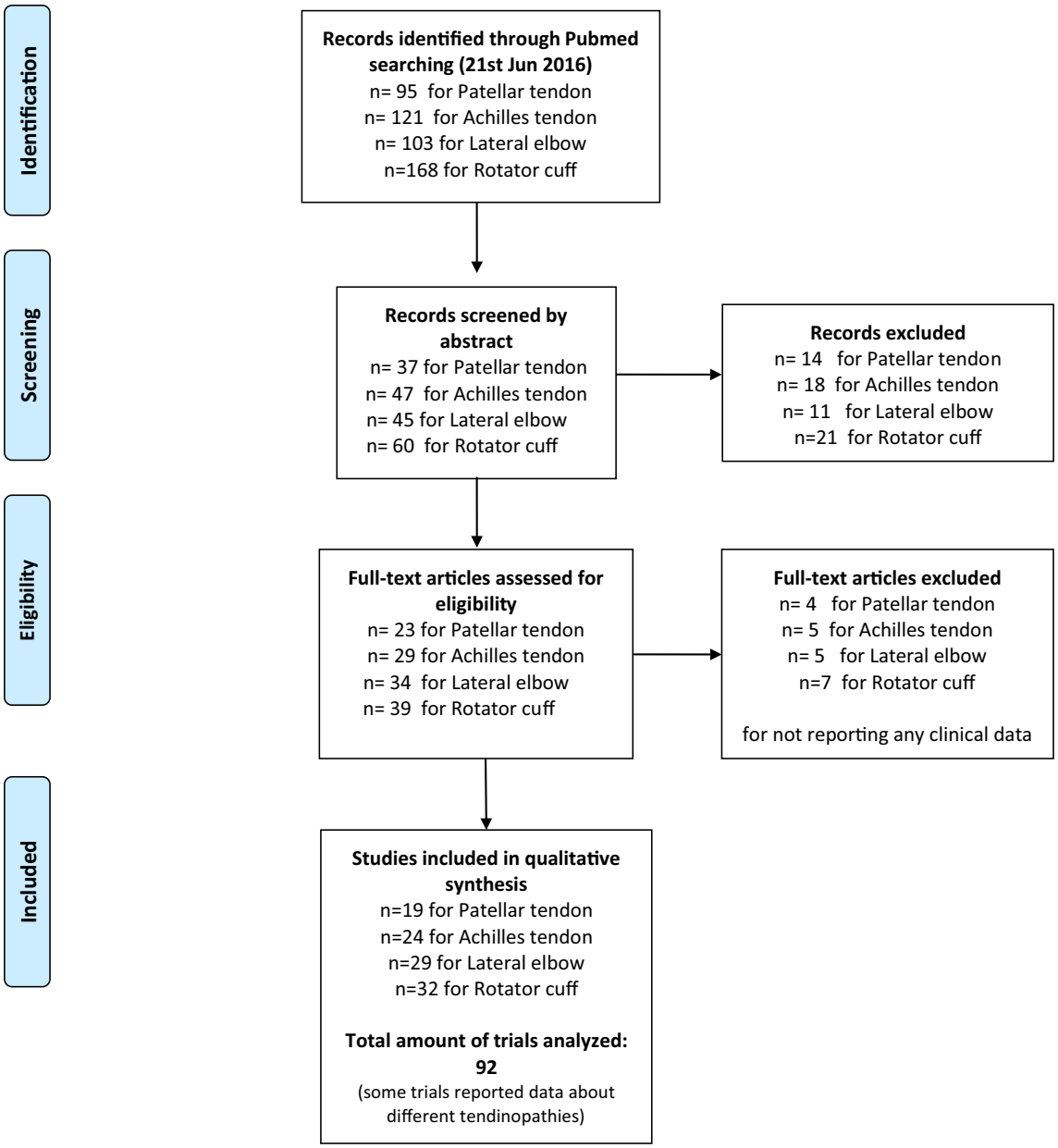

Fig. 1 PRISMA flow diagram summarizing the paper selection process

other published studies included in the analysis are reported in Tables 1, 2, 3, and 4. Furthermore, a critical appraisal of all the RCTs included in the review has been performed and reported separately as an additional file (see Additional file 1).

Patellar tendon

Nineteen papers [11, 15–17, 28–30, 32, 41, 52–54, 59, 67, 95, 105, 107, 113, 115] have been published on the treatment of patellar tendinopathy. All but two PRP were used as a conservative injective treatment for the management of tendinopathy not responsive to other previous therapeutic attempts. Looking at the level of evidence of the published trials, the surgical papers were randomized controlled trials (RCTs), whereas only 4 out of 17 papers dealing with conservative management were RCTs (Table 1).

The studies describing the intra-operative PRP application were authored by De Almeida et al. [17] and Seijas et al. [95], who injected PRP in the patellar tendon gap site after ACL reconstruction. In both trials, results were in favour of PRP group: a better pain control was documented in the initial post-op phases [17, 95] and, at 6-month

follow-up, MRI evaluation showed also a better tissue healing after PRP administration in the harvest site [17].

Looking at the conservative treatment, the literature showed overall good results, but heterogeneous therapeutic protocols, differing in terms of number of injections performed and time interval between administrations. Some authors performed a single injection, in some cases followed by a second one only when a poor clinical outcome was reported, whereas other authors opted for a multiple injection regimen (2 or even 3 injections) ab initio. In most of the published studies, the injective treatment was followed by a rehabilitation programme.

Table 1 Synopsis of the clinical trials dealing with PRP application in the patellar tendon

Publication	Level of evidence	N Patients	Pathology	Therapeutic Protocol	Platelet count and leukocytes	Activation	F-up	Main findings
Wesner et al. PLOS ONE 2016 [113]	Level IV Case series	21 patients	Patellar tendinopathy	1 injection of PRP	Platelets count: n.a. Leukocytes: n.a.	n.a.	3 months	PRP injection was effective in improving function and pain.
Seijas et al. ARCH ORTHOP TRAUMA SURG 2016 [95]	Level I Randomized controlled trial	44 patients: n= 23 PRGF n= 21 surgery alone	ACL injury	ACL reconstruction using patellar tendon graft, and application of PRGF at the donor site after graft harvesting Control group: ACL reconstruction alone	Platelets count: n.a. Leukocytes: n.a.	Ca-chloride	24 months	PRGF application provided faster improvement in pain but no long-term difference in clinical scores
Zayni et al. MUSCLES LIGAMENTS TENDONS J. 2015 [115]	Level II Randomized controlled trial	40 patients: n= 20 one injection n= 20 two injections	Patellar tendinopathy	1 vs 2 Injections of PRP (at two weeks interval)	Platelets count: 2x basal value Leukocytes: no	no	2-year (minimum)	Two injections of PRP provided better results when compared to a single injection.
Crescibene et al. J BLOOD TRANSFUS 2015 [15]	Level IV Case series	7 patients	Patellar tendinopathy	3 ultrasound-guided injections of PRP at one week interval	Platelets count: 2.2x basal value Leukocytes: n.a.	Ca-gluconate	24 months	PRP injection is a valid option for patients with patellar tendinopathy with significant pain reduction
Kaux et al. J SPORT MED PHYS FITNESS 2015 [53]	Level IV Case series	22 patients	Patellar tendinopathy	1 ultrasound-guided injection of PRP	Platelets count: 884.88 ± 70.82 x 10^3 per mm ^{3} Leukocytes: no	Ca-chloride	6 months	Single injection of PRP can improve symptoms of patellar tendinopathy unresponsive to other conservative therapies.
Kaux et al. ACTA ORTHOP BELG 2015 [52]	Level IV Case series	20 patients	Patellar tendinopathy	1 ultrasound-guided injection of PRP	Platelets count: 8-9 x 10^5 per mm^3 Leukocytes: no	Ca-chloride	12 months	Significant improvement in pain and function
Kaux et al. J SCI MED SPORT 2015 [54]	Level I Randomized controlled trial	20 patients: n= 10 one PRP injection n=10 two PRP injections	Patellar tendinopathy	1 vs 2 ultrasound-guided injections of PRP (at one week interval)	Platelets count: 8.5–9 x 10^5 per mm^3 Leukocytes: no	Ca-chloride	12 months	No statistical inter-group differences between one or two injections.
Dallaudière et al. J VASC INTERV RADIOL 2014 [16]	Level IV Case series	41 patients	Patellar tendinopathy	1 ultrasound-guided injection of PRP	Platelets count: 900,000 ± 25,000 per mm^3 Leukocytes: 200 ± 35 per mm^3	n.a.	mean 20.2 months	PRP injection allows rapid tendon healing and functional recovery
Dragoo et al. AM J SPORT MED 2014 [28]	Level I Randomized controlled trial	23 patients: n =13 ultrasound-guided dry needling n = 10 PRP injection	Patellar tendinopathy	1 ultrasound-guided dry needling 1 ultrasound-guided injection of PRP	Platelets count: n.a. Leukocytes: yes	n.a.	6 months	PRP administration provided faster recovery at 12 weeks evaluation, whereas no clinical difference was reported at the final 26 weeks follow-up. 3 patients in dry needling group failed and were treated by PRP injection.
Charousset et al. AM J SPORT MED 2014 [11]	Level IV Case series	28 patients: n =17 professional athletes n =11 semi-professional athletes	Patellar tendinopathy	3 ultrasound-guided injections of PRP	Platelets count: 2x basal value Leukocytes: no	no	2 years	Satisfactory results in athletes with chronic patellar tendinopathy and faster return to previous sport practice.
Vetrano et al. AM J SPORT MED 2013 [105]	Level I Randomized controlled trial	46 patients: n = 23 PRP n = 23 ESWT	Patellar tendinopathy	2 ultrasound-guided injections of PRP at one week interval 3 focused extracorporeal shock wave therapy	Platelets count: 0.89 - 1.1 x 10^6 per mm^3 Leukocytes: n.a.	no	12 months	PRP administration provided significantly better improvement than ESWT in VISA-P and VAS scores at 6- and 12-month follow-up.
Filardo et al. INT ORTHOP 2013 [32]	Level IV Case series	43 patients	Patellar tendinopathy	3 ultrasound-guided injections of PRP at two weeks interval	Platelets count: n.a. Leukocytes: n.a.	Ca-chloride	mean 48.6months	Multiple injections of PRP provided a good clinical outcome showing stable results up to medium-term follow-up. Patients affected by bilateral pathology and presenting a longer history of pain obtained significantly poorer results.
Mautner et al. PM&R 2013 [67]	Level IV Case series	27 patients	Patellar tendinopathy	ultrasound-guided injection of PRP (number of injections depending on global improvement)	Platelets count: n.a. Leukocytes: n.a.	no	15 months	Moderate improvement of symptoms and good satisfaction rate were found.
de Almeida et al. AM J SPORT MED 2012 [17]	Level I Randomized controlled trial	27 patients: n = 12 PRP n = 15 surgery alone	ACL injury	PRP added to the site of patellar tendon harvest after ACL reconstructive surgery Control group: ACL reconstruction alone	Platelets count: 1,185,166 ± 404,472 per mm^3 Leukocytes: 0.91 ± 0.81 x 10^3 per mm^3	Thrombin and Ca-chloride	6 months	PRP injection reduced pain in the immediate post-operative period. PRP did not improve patients' functional scores after ACL reconstruction with a patellar tendon graft.
Gosens et al. INT ORTHOP 2012 [41]	Level II Comparative study	36 patients: n= 14 with previous treatment before PRP injection n= 22 without previous treatment before PRP injection	Patellar tendinopathy	1 injection of PRP	Platelets count: n.a. Leukocytes: n.a.	no	mean 18.4 months	PRP injection provided statistically significant improvement. No significant difference was observed among patients who received or did not receive previous therapeutic approaches.

Table 1 continued

Publication	Level of evidence	N Patients	Pathology	Therapeutic Protocol	Platelet count and leukocytes	Activation	F-up	Main findings
Ferrero et al. J ULTRASOUND 2012 [29]	Level IV Case series	28 patients	Patellar tendinopathy	2 ultrasound-guided injections of PRP at mean 3 weeks interval	Platelets count: n.a. Leukocytes: n.a.	n.a.	6 months	PRP injection resulted in a significant and lasting improvement of clinical symptoms and led to a better tendon structure
Volpi et al. J SPORT MED PHYS FIT 2010 [107]	Level IV Case series	9 patients	Patellar tendinopathy	1 ultrasound-guided injection of PRP	Platelets count: 8x basal value Leukocytes: yes	no	24 months	Significant clinical improvement after 3 months, with stable results up to 2 years. MRI improvement in patellar tendon structure.
Filardo et al. INT ORTHOP 2010 [30]	Level II Comparative study	31 patients: n= 15 PRP n= 16 control	Patellar tendinopathy	3 ultrasound guided injections of PRP at two weeks interval Physiotherapy	Platelets count: 6.5 ± 1.5 x 10^5 per mm^3 Leukocytes: n.a.	Ca-chloride	6 months	PRP treatment showed statistically significant improvement in knee function and quality of life.
Kon et al. Injury 2009 [59]	Level IV Case series	20 patients	Patellar tendinopathy	3 injections of PRP at three weeks interval	Platelets count: 6,28 billion per injection Leukocytes: yes	Ca-chloride	6 months	PRP injection was a safe procedure, and provided a significant improvement over time, allowing the majority of patients to go back to sport activity.

Two RCTs [54, 115] investigated the correlation between clinical results and number of PRP administrations, with controversial results. In both studies, 40 patients were included and randomized to receive one or two PRP injection at two-week intervals. Kaux et al. [54] failed to show any significant beneficial effect related to the 2-injection protocol, whereas Zayni et al. [115] documented superior clinical outcome in patients treated by multiple PRP injections. Up to now, the low number of patients evaluated in these trials does not allow to draw any reliable conclusion on the usefulness of multiple vs single-injection protocols. The other published RCTs compared PRP injections versus external shock wave therapy (ESWT) [105] and dry needling [28]. In the study authored by Vetrano et al. [105], 46 patients were randomized to receive either 2 PRP injections (at 2-week interval) or 3 weekly sessions of ESWT. Results were overall positive, but the best outcome was obtained in the PRP group, where patients experienced a more significant pain reduction and a higher functional recovery at 6 and 12 months after treatment. In the trial by Dragoo et al. [28], 23 patients were included and randomized to receive a single PRP injection or dry needling alone: the authors documented that, at 12 weeks of follow-up, only the PRP group presented a statistically significant improvement in pain and functional scores. These differences were not maintained at the final 26-week evaluation when the clinical outcomes were comparable between groups and, in both cases significantly better than basal evaluation.

The positive results described in the aforementioned RCTs were confirmed by lower-quality studies which reported, in all cases, encouraging results for PRP therapy [11, 29, 30, 32, 41, 59, 67, 107].

Achilles tendon

Twenty-four papers [15, 16, 18–21, 29, 31, 35, 39, 43, 50, 56, 61, 67, 73–76, 91, 92, 94, 107, 113] have been published on the treatment of Achilles tendon diseases. Twenty papers describe PRP application as a conservative management for chronic Achilles tendinopathy, whereas in 4 trials PRP was used as adjuvant in the treatment of acute tendon rupture either as intra-operative enhancer or as an injective approach in the first weeks after surgical repair. Looking at the level of evidence of the published trials, only 4 papers were RCTs: 3 of them dealt with chronic Achilles tendinopathy and 1 with acute tendon rupture (Table 2). As described for the patellar tendon, the analysis of the available literature reveals a large variability among therapeutic protocols, with authors preferring a single PRP injection and others adopting instead multiple administrations at various intervals.

Looking at PRP application to manage chronic Achilles pathology, a significant discrepancy emerged between the results described by RCTs and case series. In fact, all the non-controlled studies [15, 16, 21, 29, 31, 35, 39, 43, 67, 73–76, 91, 107, 113] reported an encouraging clinical outcome, independently from the particular therapeutic protocol adopted, with good return to sport participation and beneficial effects lasting up to mid-term evaluation [31]. Conversely, the RCTs documented opposite results: the first double-blind RCT was authored by the group of de Vos et al. [19, 20], who compared a single non-activated intratendinous injection of PRP against a single injection of saline. Even though an overall improvement was described in both groups, the authors failed to show any significant inter-group differences and even US evaluation also revealed a comparable tendon structure at 12-month evaluation. Despite the robust study design, some aspects deserve to be reported since they could influence the strength of the study conclusions, such as the rather high mean age of the patients treated with minimal involvement in sport practice and sometimes only a short symptoms duration, and the control group which was not a real placebo administration since dry needling together with eccentric exercises could have a therapeutic potential, sufficient for these low demanding patients.

Similar results were reported also by Krogh et al. [61] who found no difference between PRP and saline solution 3 months after the injective treatment. Kearney et al. [56] published a RCT comparing PRP with a traditional rehabilitation programme and reporting very good results with PRP injections, quite superior to the ones documented for physiotherapy alone. However, no statistical significance could be reached, likely due to the low number of patients included (10 per group).

For what regards PRP application for acute Achilles tendon rupture, 3 out 4 papers documented no beneficial effect of PRP administration during and/or immediately after tendon suturing [18, 50, 94]. In particular, the RCT authored by Schepull et al. [94] revealed that PRP addition could be even detrimental in tissue healing since no biomechanical advantages and lower performance were reported in PRP patients with respect to the "suture-alone" group.

Table 2 Synopsis of the clinical trials dealing with PRP application in the Achilles tendon

Publication	Level of evidence	N Patients	Pathology	Therapeutic Protocol	Platelet count and leukocytes	Activation	F-up	Main findings
Wesner et al. PLOS ONE 2016 [113]	Level IV Case series	28 patients	Achilles tendinopathy	1 injection of PRP	Platelets count: n.a. Leukocytes: n.a.	n.a.	3 months	PRP injection was effective in improving function and pain.
Krogh et al. AM J SPORTS MED 2016 [61]	Level I Randomized controlled trial	24 patients: n= 12 PRP n= 12 saline	Achilles tendinopathy	1 ultrasound-guided injection of PRP	Platelets count: 8x basal value Leukocytes: n.a.	n.a.	12 months	PRP injection did not provide better outcome with respect to placebo after 3 months
De Carli et al. KNEE SURG SPORTS TRAUMATOL ARTHROSC 2015 [18]	Level IV Case series	30 patients: n=15 surgery n=15 PRP	Achilles tendon rupture	Local injection of liquid PRP+ PRP membrane sutured to the peritenonium	Platelets count: n.a. Leukocytes: n.a	Thrombin Ca-gluconate	24 months	Addition of PRP to the surgical treatment did not offer superior clinical and functional results.
Salini et al. FRONT AGING NEUROSCI 2015 [91]	Level IV Case series	44 patients: 29 young (39.5±6.9 yy) n= 15 elderly (61.5±5.3 yy)	Achilles tendinopathy	3 ultrasound-guided injections of PRP at one week interval	Platelets count: 1.6x basal value Leukocytes: no	n.a.	12 months	PRP injections provided very satisfactory results in young subjects but also in aged people.
Oloff et al. FOOT ANKLE SPEC 2015 [75]	Level IV Case series	26 patients: n=13 surgery and PRP n= 13 PRP alone	Achilles tendinopathy	1 injection of PRP	Platelets count: 2x basal value Leukocytes: n.a	n.a.	10 months	PRP alone or PRP combined with surgery can produced similar improvement in both clinical outcomes and MRI imaging
Guelfi et al. FOOT ANKLE SURG 2015 [43]	Level IV Case series	73 patients	Achilles tendinopathy	1 ultrasound-guided injection of PRP (second injection for patients with minimal or no improvement)	Platelets count: n.a. Leukocytes: n.a	n.a.	mean 50.1 months	PRP treatment provided good clinical outcome in a large cohort of patients with mid–long-term follow-up.
Crescibene et al. J BLOOD TRANSFUS 2015 [15]	Level IV Case series	14 patients	Achilles tendinopathy	3 ultrasound-guided injections of PRP at one week interval	Platelets count: 2.2x basal value Leukocytes: n.a.	Ca-gluconate	24 months	PRP injection provided significant pain reduction
Filardo et al. BLOOD TRANSFUS 2014 [31]	Level IV Case series	27 patients	Achilles tendinopathy	3 ultrasound-guided injections of PRP at two weeks interval	Platelets count: 5x basal value Leucocytes: 1.2x basal value	Ca-chloride	mean 54.1 months	Significant improvement of VISA-A, EQ-VAS, Blanzina grade and Tegner Score, confirmed up to middle term evaluation.
Dallaudière et al. J VASC INTERV RADIOL 2014 [16]	Level IV Case series	54 patients	Achilles tendinopathy	1 ultrasound-guided injection of PRP	Platelets count: 900,000 ± 25,000 per mm^3 Leukocytes: 200 ± 35 per mm^3	n.a.	mean 20.2 months	PRP injection allowed rapid healing of tendinopathy with good tolerance
Kaniki et al ARTHROSCOPY 2014 [50]	Level III Retrospective comparative trial	145 patients: n= 73 PRP n=72 historical control	Achilles tendon rupture	2 injections of PRP during the first 2 weeks after the injury	Platelets count: n.a. Leukocytes: n.a	n.a.	2 years	No clinical benefit with PRP injection during tendon repair procedure.
Murawski et al. FOOT ANKLE SPEC 2014 [74]	Level IV Case series	32 patients	Achilles tendinopathy	1 injection of PRP	Platelets count: n.a. Leukocytes: n.a	n.a.	6 months	After PRP injection 78% patients had clinical improvement and avoided surgical intervention.
Kearney et al. BONE JOINT RES 2013 [56]	Level I Randomized controlled trial	20 patients n=10 PRP n=10 eccentric exercise	Achilles tendinopathy	1 injection of PRP	Platelets count: n.a. Leukocytes: n.a	n.a.	6 months	No inter-group statistically significant difference.
Monto et al. FOOT ANKLE INT 2014 [73]	Level IV Case series	30 patients	Achilles tendinopathy	1 ultrasound-guided injection of PRP	Platelets count: n.a. Leukocytes: n.a	no	24 months	Significant clinical improvement in 28 out of 30 patients.
Mautner et al. PM&R 2013 [67]	Level IV Case series	27 patients	Achilles tendinopathy	ultrasound-guided injection of PRP (number of injections depending on global improvement)	Platelets count: n.a. Leukocytes: n.a	n.a.	6 months	After PRP treatment, Achilles tendon patients showed complete resolution of symptoms.
Ferrero et al. J ULTRASOUND 2012 [29]	Level IV Case series	30 patients	Achilles tendinopathy	1 ultrasound-guided injection of PRP	Platelets count: n.a. Leukocytes: n.a.	n.a.	6 months	After PRP injection significant improvement at the 6-month evaluation was found in VISA-A score and tendon thickness.
Finoff et al. PM&R 2011 [35]	Level IV Case series	14 patients	Achilles tendinopathy	1 ultrasound-guided injection of PRP	Platelets count: 4.2x basal value Leukocytes: yes	no	14 months	PRP injection provided positive clinical results but not conclusive sonographic findings.
Deans et al. J FOOT ANKLE SURG 2012 [21]	Level IV Case series	26 patients	Achilles tendinopathy	1 injection of PRP	Platelets count: n.a. Leukocytes: n.a.	n.a.	6 weeks	Significant improvement in symptoms, activities of daily living, sport/recreation, QOL, and pain.

Table 2 continued

Publication	Level of evidence	N Patients	Pathology	Therapeutic Protocol	Platelet count and leukocytes	Activation	F-up	Main findings
Schepull et al. AM J SPORT MED 2011 [94]	Level II Randomized controlled trial	30 patients: n= 16 surgery + PRP n= 14 surgery alone	Achilles tendon rupture	1 injection of PRP	Platelets count: 3.673 ± 1.051 x 10^6 per mm^3 Leukocytes: n.a.	Ca-chloride	12 months	No significant inter-group differences regarding healing of Achilles tendon. Lower biomechanical performance in PRP-augmented group.
Owens et al. FOOT ANKLE INT 2011 [76]	Level IV Case series	10 patients	Achilles tendinopathy	1 injection of PRP	Platelets count: n.a. Leukocytes: n.a.	n.a.	24 months	Clinical but not MRI improvement up to 24 months
De Vos et al. JAMA 2010 [20] + De Jonge et al. AJSM 2011 [19]	Level I Randomized controlled trial	54 patients: n= 27 PRP n= 27 saline	Achilles tendinopathy	1 ultrasound-guided injection of PRP 1 ultrasound-guided injection of saline	Platelets count: n.a. Leukocytes: n.a.	no	52 weeks	No significant inter-group difference regarding pain and activity at final follow-up. No US differences in tendon structure between groups.
Gaweda et al. INT J SPORTS MED 2010 [39]	Level IV Case series	14 patients	Achilles tendinopathy	1 injection of PRP	Platelets count: n.a. Leukocytes: n.a.	n.a	18 months	Significant improvement was observed in the clinical and imaging results.
Volpi et al J SPORTS MED PHYS FITNESS 2010 [107]	Level IV Case series	3 patients	Achilles tendinopathy	1 ultrasound-guided injection of PRP	Platelets count: 8x basal value Leukocytes: yes	no	24 months	Significant clinical improvement after 3 months, with stable results up to 2 years.
Sanchez et al. AM J SPORT MED 2007 [92]	Level IV Case series	6 patients	Achilles tendon rupture	Intra-op. injection of un-clotted PRGF within the fascicles	Platelets count: 3.1x basal value Leukocytes: yes	Ca-chloride	6 months	Better outcome, less thickness in the treated tendons and faster sport return for PRP group.

Lateral Elbow Tendons

Twenty-nine papers [5, 8, 13, 14, 16, 35, 37, 38, 40, 42, 46, 51, 58, 62, 64, 67, 70–72, 77, 79, 83, 84, 96–98, 100, 113, 114] have been published on the treatment of lateral elbow tendinopathy, all of them focusing on PRP as conservative injective treatment. Looking at the level of evidence of the published trials, 17 papers were RCTs (Table 3). In the case of lateral elbow tendinopathy, a single PRP injection is by far the most preferred protocol (26 studies), with some authors performing a second or more injections due to the specific study protocol or in case of poor clinical response. The majority of the trials were controlled, and PRP was compared with different therapeutic approaches: autologous whole blood, corticosteroids, local anaesthetic, saline injections, or laser therapy.

The comparison between PRP and corticosteroids revealed overall superior results for the biological approach: Perbooms et al. [79] were the first ones to document better clinical outcome for PRP treatment at 1-year follow-up, and their results were confirmed by Gosens et al. [42] who evaluated the same cohort of patients at 2 years, pointing out that corticosteroid therapy is less durable and requires re-intervention much more frequently than PRP. The study by Gautam et al. [38] on a smaller group of patients confirmed the limited benefit of corticosteroid effects over time, both clinically and as observed at US evaluation. Also the RCTs authored by Yadav et al. [114], Lebiedzinski et al. [64], and Khaliq et al. [58] confirmed superior results for a single injection of PRP compared to corticosteroids. On the other hand, there are also 3 trials which did not reveal beneficial PRP effects [62, 72, 77]: despite these results, the low number of patients included is a major bias limiting the relevance of these trials.

Three trials compared PRP with local anaesthetic injections. The first one was published by Mishra et al. [70] and suggested, in a very small group of patients, a potentially superior performance of PRP. The same author, a few years later, published the results of a larger multicentre RCT [71] including 230 patients, where he could confirm the better clinical outcome of PRP both at 12 and 24 weeks compared to bupivacaine. Similar outcomes have been recently reported also by Behera et al. [5] in a RCT on a smaller group of patients.

The comparison between PRP and low-level laser therapy has been investigated in 2 contrasting trials [97, 100], showing in 1 case [97] comparable beneficial effects between the two treatments, and in the other case [100] a clear superiority of the biological treatment.

Controversial results have been found also in the 4 papers [14, 83, 84, 98] focused on the comparison with autologous whole-blood injections. In fact, the overall response after intra-tendinous injection of whole blood was quite satisfactory in all the published studies, without a clear advantage for PRP, in terms of pain relief and functional recovery, in particular at the mid-term evaluation. These findings foster further considerations on the importance of optimizing PRP formulation, since it seems clear that the healing potential of blood-derived products is deeply influenced by their cellular composition and by many other aspects that have still to be clarified. However, based on the available evidence, autologous whole blood seems to provide comparable clinical benefit in the treatment of lateral elbow tendinopathy with respect to the studied platelet concentrates.

Rotator cuff

Thirty-two papers have been published on the treatment of rotator cuff disease [3, 4, 6, 9, 10, 12, 24, 36, 44, 45, 47–49, 57, 66, 67, 78, 85–87, 89, 90, 93, 104, 108–110, 112, 113, 116–118]. In 8 studies, PRP was used as conservative injective treatment for the management of chronic tendinopathy not responsive to previous therapeutic attempts, whereas in the remaining 24 papers, PRP has been used as augmentation during or immediately after arthroscopic cuff treatment. Looking at the level of evidence of the published trials, 3 out of 8 papers dealing with conservative management were RCTs, whereas 18 out of the 24 dealing with intra-operative or post-operative application were RCTs (Table 4).

In the case of PRP application as a conservative option for rotator cuff tendinopathy, while 5 case series [16, 67, 93, 108, 113] suggested a positive contribution of PRP to reducing pain and improving function at short-/mid-term follow-up, the 3 RCTs showed contrasting results. In particular, Kesikburun et al. [57] reported no differences in clinical scores and

Table 3 Synopsis of the clinical trials dealing with PRP application in the lateral elbow tendons

Publication	Level of evidence	N Patients	Pathology	Therapeutic Protocol	Platelet count and leukocytes	Activation	F-up	Main findings
Wesner et al. PLOS ONE 2016 [113]	Level IV Case series	23 patients	Lateral epicondylitis	1 injection of PRP	Platelets count: n.a. Leukocytes: n.a.	n.a.	3 months	PRP injection was effective in improving function and pain.
Tan et al. J ORTHOP SURG RES. 2016 [96]	Level IV Case series	56 patients	Lateral epicondylitis	3 injections of PRP at one week interval	Platelets count: 3x basal value	no	12 months	Three injections of PRP offered significant clinical improvement in the treatment of lateral epicondylitis
Palacio et al. REV BRAS ORTOP 2016 [77]	Level I Randomized controlled trial	60 patients : n= 20 neocaine n= 20 dexamethasone n= 20 PRP	Lateral epicondylitis	1 injection for each treatment group	Platelets count: n.a Leukocytes: n.a.	n.a.	6 months	PRP injection did not provide better results than corticosteroids or local anesthetic.
Tetschke et al. AM J PHYS MED REHABIL 2016 [97]	Level II Prospective comparative trial	52 patients: n= 26 PRP n= 26 low level laser therapy	Lateral epicondylitis	3 injections of ACP at one week interval 12 laser applications with two sessions per week	Platelets count: n.a Leukocytes: n.a.	n.a.	12 months	Both treatments provided a significant improvement of VAS and DASH scores. PRP injection showed a slight advantage compared to laser application.
Khaliq et al. J PAK MED ASSOC 2015 [58]	Level I Randomized controlled trial	102 patients: n= 51 corticosteroid n= 51 PRP	Lateral epicondylitis	1 injection of corticosteroid 1 injection of PRP	Platelets count: n.a Leukocytes: n.a.	n.a.	3 weeks	A single PRP injection demonstrated better improvement in term of pain control than corticosteroid injection.
Karaduman et al. J ORTHOP 2015 [51]	Level III Retrospective cohort study	90 patients : n= 36 PRP n= 44 surgery	Lateral epicondylitis	1 injection of PRP	Platelets count: 5x basal value	no	12 months	PRP injection demonstrated better results in term of pain relief and functional recovery in the short and midterm period.
Brkljac et al. J ORTHOP 2015 [8]	Level IV Case series	34 patients	Lateral epicondylitis	1 injection of PRP	Platelets count: n.a Leukocytes: n.a.	n.a.	6.5 months	PRP injection improved pain and function.
Yadav et al. J CLIN DIAGN RES 2015 [114]	Level I Randomized controlled trial	60 patients: n= 30 PRP n= 30 corticosteroid	Lateral epicondylitis	1 injection of PRP 1 injection of corticosteroid	Platelets count: 1 x 10^5 per mm^3 Leukocytes: n.a.	n.a.	3 months	PRP treatment demonstrated better results at long term evaluation with respect to corticosteroids.
Montalvan et al. RHEUMATOLOGY 2015 [72]	Level I Randomized controlled trial	50 patients: n= 25 PRP n= 25 saline	Lateral epicondylitis	2 ultrasound-guided injections of PRP at one month interval 2 ultrasound-guided injections of saline at one month interval	Platelets count: 1.6x basal value Leukocytes: no	n.a.	12 months	Two PRP injections did not show better results compared to saline injections.
Glanzmann et al. ARCH ORTHOP TRAUMA SURG 2015 [40]	Level II Prospective comparative trial	62 patients: n=35 one injection n= 26 two or three injections	Lateral epicondylitis	1 vs 2-3 injections of PRP (performed after 4 and 8 weeks)	Platelets count: 2.5x basal value Leukocytes: no	n.a.	6 months	At 6 months local pain reduction and improved function and quality of life. A second or third injection did not provide further beneficial effects.
Lebiedzinski et al. INT ORTHOP 2015 [64]	Level I Randomized controlled trial	120 patients: n=64 PRP n= 56 steroid + lidocaine	Lateral epicondylitis	1 injection of PRP 1 injection of corticosteroid	Platelets count: n.a. Leukocytes: n.a.	n.a.	12 months	ACP treatment provided long lasting beneficial effects with respect to corticosteroid injection.
Ford et al. HAND (NY) 2015 [37]	Level III Retrospective comparative trial	78 patients: n=28 PRP n=50 surgery	Lateral epicondylitis	1 injection of PRP	Platelets count: n.a. Leukocytes: n.a.	n.a.	mean 10.5 months for the PRP mean 11.7 months for the surgical group	PRP injection demonstrated similar outcomes in pain improvement and return to work when compared to surgery.
Gautam et al. J ORTHOP SURG (HONG KONG) 2015 [40]	Level I Randomized controlled trial	30 patients: n=15 PRP n=15 Corticosteroid	Lateral epicondylitis	1 injection of PRP 1 injection of corticosteroid	Platelets count: n.a. Leukocytes: n.a.	n.a.	6 months	PRP provided superior biological healing of the lesion and longer lasting beneficial effects.
Behera et al. J ORTHOP SURG 2015 [5]	Level I Randomized controlled trial	25 patients: n=15 PRP n=10 bupivacaine	Lateral epicondylitis	1 ultrasound guided injection of PRP 1 ultrasound guided injection of bupivacaine	Platelets count: 6-8 ×10^5 per mm^2 Leukocytes: no	Ca-chloride	12 months	PRP injection provided significantly superior improvement in pain and function.
Dallaudière et al. J VASC INTERV RADIOL 2014 [16]	Level IV Case series	220 patients	Lateral epicondylitis	1 ultrasound-guided injection of PRP	Platelets count : 900,000 ± 25,000 per mm^3 Leukocytes: 200 ± 35 per mm^3	n.a.	mean 20.2 months	The PRP treatment allows rapid healing of tendinopathy with good tolerance.
Tonk et al. Indian J ORTHOP 2014 [100]	Level II Prospective controlled trial	81 patients: n= 39 PRP n= 42 low level laser therapy	Lateral epicondylitis	1 injection of PRP 10 sessions of low level laser therapy	Platelets count: 509% basal value Leukocytes: n.a	no	12 months	PRP injection decreased pain up to 3 months. PRP was better than low laser therapy.

Table 3 continued

Publication	Level of evidence	N Patients	Pathology	Therapeutic Protocol	Platelet count and leukocytes	Activation	F-up	Main findings
Raeissadat et al. PAIN RES TREAT 2014 [84]	Level I Randomized controlled trial	40 patients: n= 20 PRP n= 20 autologous whole blood	Lateral epicondylitis	1 injection of PRP 1 injection of autologous whole blood	Platelets count in PRP : 220000 ± 23000 per mm^3 Leukocytes: yes	n.a.	8 weeks	PRP injection was more effective than autologous blood in pain control at 8 weeks evaluation.
Raeissadat et al. BMC SPORTS SCI MED REHABIL 2014 [83]	Level I Randomized controlled trial	64 patients: n= 33 PRP n= 31 autologous whole blood	Lateral epicondylitis	1 injection of PRP 1 injection of autologous whole blood	Platelets count: 4.8x basal value Leukocytes: 6740 ± 1396 per mm^3 in PRP group	no	12 months	PRP was not better than whole blood at long term follow-up in any parameter considered.
Krogh et al. AM J SPORTS MED 2013 [62]	Level I Randomized controlled trial	60 patients: n= 20 PRP n= 20 Glucocorticoid n= 20 Placebo saline solution	Lateral epicondylitis	1 ultrasound-guided injection of PRP 1 ultrasound-guided injection of corticosteroid 1 ultrasound-guided injection of saline solution	Platelets count : n.a. Leukocytes: n.a.	n.a.	3 months	No inter-group differences in pain reduction or disability at 3 months; PRP injection was more painful.
Mishra et al. AM J SPORT MED 2014 [71]	Level I Randomized controlled trial	225 patients: n= 112 PRP n= 113 bupivacaine	Lateral epicondylitis	1 injection of PRP 1 injection of bupivacaine	Platelets count : 5x basal value Leukocytes: yes	n.a.	6 months	Significantly better performance of PRP compared with control group (bupivacaine).
Chaudhury et al. SKELETAL RADIOL 2012 [13]	Level IV Case series	6 patients	Lateral epicondylitis	1 ultrasound-guided injection of PRP	Platelets count : n.a. Leukocytes: n.a	n.a.	6 months	After PRP, an increase in vascularization at ultrasound examination was deemed to promote better tendon healing.
Mautner et al. PM&R 2013 [67]	Level IV Case series	30 patients	Lateral epicondylitis	Ultrasound-guided injection of PRP (number of injections depending on global improvement)	Platelets count : n.a. Leukocytes: n.a	n.a.	15 months	93% success rate for PRP treatment (defined as moderate to complete resolution of symptoms).
Creaney et al. BR J SPORTS MED 2011 [14]	Level I Randomized controlled trial	150 patients: n=80 PRP n=70 autologous whole blood	Lateral epicondylitis	2 ultrasound-guided injections of PRP at one month interval 2 ultrasound-guided injections of autologous whole blood at one month interval	Platelets count in PRP: 652 ×10 ^{3} per mm^3 Leukocytes: n.a.	n.a.	6 months	Autologous whole blood and PRP can be used as effective second-line therapy. No inter-group difference reported.
Perbooms et al AM J SPORT MED 2010 [79] + Gosens et al. AM J SPORT MED 2011 [42]	Level I Randomized controlled trial	100 patients: n=51 PRP n=49 costicosteroid	Lateral epicondylitis	1 injection of PRP 1 injection of costicosteroid	Platelets count : n.a. Leukocytes: n.a.	no	2 year	Significantly better performance in PRP group in terms of pain relief and functional improvement.
Thanasas et al. AM J SPORT MED 2011 [98]	Level I Randomized controlled trial	28 patients: n= 14 autologous whole blood n= 14 PRP	Lateral epicondylitis	1 ultrasound-guided injection of autologous whole bood 1 ultrasound-guided injection of PRP	Platelets count: 235-1.292 x 10^3 per mm^3 Leukocytes: no	no	6 months	Statistically significant difference in pain control only at 6 weeks follow-up. No other inter-group difference.
Hechtman et al. ORTHOPEDICS 2011 [46]	Level IV Case series	30 patients	Lateral epicondylitis	1 injection of PRP	Platelets count : n.a. Leukocytes: n.a.	Ca-chloride	24 months	Encouraging results in term of pain reduction. High patient satisfaction rate (90%).
Finoff et al. PM&R 2011 [35]	Level IV Case series	6 patients	Lateral epicondylitis	1 ultrasound-guided injection of PRP	Platelets count: 4.2x basal value Leukocytes: yes	no	14 months	PRP injection demonstrated positive clinical results but not conclusive sonographic findings.
Mishra et al. AM J SPORT MED 2006 [70]	Level II Cohort study	20 patients: n= 15 PRP n= 5 control	Lateral epicondylitis	1 injection of PRP	Platelets count: 5.4x basal value Leukocytes: yes	no	mean 25.6 months	Best results in pain control and functional scores for PRP group at short term evaluation. Stable results up to middle term evaluation with 93% of patients satisfaction rate.

objective measurements between PRP and placebo groups in 40 patients evaluated up to 1 year of follow-up. Conversely, Rha et al. [87] found that 2 PRP injections (compared to dry needling alone) could contribute to improve symptoms and restore shoulder motility at 6 months in a study on 39 patients. The two RCTs differ in terms of applicative modalities: Kesikburun et al. used a single PRP injection in the subacromial space, whereas Rha et al. applied PRP by a peppering technique, that could have improved the effect of the biological agents. Finally, 1 RCT [47] investigated the effect of 3 weekly intra-articular PRP injections as a conservative management of chronic, partial supraspinatus tears in comparison with a standardized rehabilitation protocol. At the final 12-month evaluation, both treatment groups presented a significant clinical improvement, without any evident superiority of the biological treatment.

With respect to the surgical application, PRP has been widely used as a biological enhancer during or immediately after arthroscopic procedures. A fundamental aspect to consider is the wide variability among the techniques employed by different authors (more details are reported in Table 1), which makes study comparison difficult. Furthermore, various PRP products and application methods have been tested. Among the currently available RCTs, 10 studies [3, 9, 10, 36, 89, 90, 104, 109, 110, 118] failed to show any beneficial contribution of PRP augmentation compared to the surgical procedure alone. This means that no difference was observed in terms of clinical scores and/or re-tear rate at the MRI evaluation between the treatment groups. Three studies, despite confirming overall no inter-group difference in clinical scores and functional outcome at the final follow-up, suggested a potential, but still limited, contribution of PRP: in 1 case [45] it was observed that PRP injections after arthroscopic repair could determine a slightly lower VAS for pain score at 6 weeks, whereas in the second case [117], the authors observed a superior tendon vascularization only at the first 6-week Doppler

evaluation, thus leading to speculate that PRP might fasten the tendon healing process and, finally, Gumina et al. [44] revealed better appearance and tissue integrity at MRI evaluation. Oppositely, 5 RCTs clearly documented positive results after PRP administration. In particular, the research groups led by Jo [49], Malavolta [66] Zhang [116], and Pandey [78] documented lower re-tear rate when PRP was used as an augmentation, while Randelli et al. [85] and Pandey et al. [78]

Table 4 Synopsis of the clinical trials dealing with PRP application in the rotator cuff tendons

Publication	Level of evidence	N Patients	Pathology	Therapeutic Protocol	Platelet count and leukocytes	Activation	F-up	Main findings
Wesner et al. PLOS ONE 2016 [113]	Level IV Case series	21 patients (+ 9 included in a RTC prematurely interrupted)	Rotator cuff tendinopathy	1 injection of PRP	Platelets count: n.a. Leukocytes: n.a.	n.a.	3 months	PRP injection was effective in improving function and pain.
Zhang et al. ACTA ORTHOP TRAUMATOL TURC. 2016 [116]	Level I Randomized controlled trial	62 patients: n=32 PRP n=30 control	Rotator cuff tear	Arthroscopic double-row repair + intra-op injection of PRP Arthroscopic double-row repair	Platelets count: n.a. Leukocytes: n.a.	Ca-chloride	12 months	PRP injection provided a significantly higher rate of tendon healing with respect to surgery alone.
Di Benedetto et al. ACTA BIOMED 2016 [24]	Level III Case-control study	32 patients: n=18 PRP n=18 control	Rotator cuff tear	Arthroscopic repair + intra-op. injection of PRP Arthroscopic repair	Platelets count: n.a. Leukocytes: n.a.	n.a.	12 month	PRP injection did not provide better tendon healing.
Flury et al. AM J SPORTS MED 2016 [36]	Level I Randomized controlled trial	120 patients: n=60 PRP n=60 control	Rotator cuff tear	Arthroscopic double-row repair + 1 injection of PRP Arthroscopic double-row repair	Platelets count: n.a. Leukocytes: n.a.	n.a.	24 months	The intraoperative injection of PRP showed no significant effect on the clinical and patient-reported outcomes up to 24 months.
Pandey et al. J SHOULDER ELBOW SURG 2016 [78]	Level I Randomized controlled trial	110 patients: n=56 PRP n=54 control	Rotator cuff tear	Arthroscopic single-row repair+ 1 injection of PRP Arthroscopic single-row repair	Platelets count: $4.74 \pm 0.3 \times 10^5$ per mm^3 Leukocytes: no	Ca-chloride	24 months	PRP injection demonstrated superior structural healing in a large rotator cuff tear, with higher vascularization of rotator cuff and surrounding tissues in the early phases.
Verhaegen et al. J SHOULDER ELBOW SURG 2016 [104]	Level I Randomized controlled trial	40 patients n=20 PRP n=20 control	Rotator cuff calcification	Arthroscopic debridement of the calcification + intra-op PRP injection Arthroscopic debridement of the calcification	Platelets count: n.a. Leukocytes: yes	n.a.	12 months	PRP injection did not demonstrate beneficial effect on rotator cuff healing.
Zumstein et al. J SHOULDER ELBOW SURG 2016 [118]	Level I Randomized controlled trial	35 patients: n=17 PRP n=18 control	Rotator cuff tear	Arthroscopic double-row repair with addition of PRP clots Arthroscopic double-row cuff repair	Platelets count: n.a. Leukocytes: yes	n.a.	12 months	PRP augmentation during double-row repair did not produce better clinical or structural outcomes.
Carr et al. AM J SPORTS MED 2015 [9]	Level I Randomized controlled trial	48 patients n=25 PRP n=23 control	Rotator cuff tendinopathy	Arthroscopic acromioplasty + 1 intra-op. sub-acromial PRP injection Arthroscopic acromioplasty	Platelets count: n.a. Leukocytes: yes	Autologous thrombin	24 months	PRP injection did not provide beneficial effect on clinical outcomes. Potentially detrimental effects of PRP to the long-term structural properties of the tendon
von Wehren et al. KNEE SURG SPORTS TRAUMATOL ARTHROSC 2015 [108]	Level III Comparative trial	50 patients n=25 ACP n=25 corticosteroids	Rotator cuff tear	1 sub-acromial ACP injection 1 sub-acromial steroid injection	Platelets count: n.a. Leukocytes: n.a.	n.a.	12 months	PRP application showed earlier benefit compared to corticosteroids, although no difference was reported at 6 and 12 months evaluation.
Ilhanli et al. IRAN RED CRESCENT MED J. 2015 [47]	Level I Randomized controlled trial	70 patients n=35 PRP n=35 physical therapy	Rotator cuff tear	3 intra-articular injections of PRP at one week interval; Standard physical therapy for 15 session	Platelets count: 2.1-2.5x basal value Leukocytes: 1.1-1.3x basal value	Ca-chloride	12 months	Comparable results between physical therapy and PRP
Wang et al. AM J SPORTS MED 2015 [109]	Level I Randomized controlled trial	60 patients: n=30 PRP n=30 control	Rotator cuff tear	Arthroscopic double-row cuff repair followed by 1 post-op PRP injection Arthroscopic double-row cuff repair	Platelets count: 470.000 per mm^3 Leukocytes: no	Ca-chloride	16 weeks	Sequential delivery of PRP in the post-op. did not improve early rotator cuff healing or functional recovery.
Hak et al. SPORTS HEALTH 2015 [45]	Level I Randomized controlled trial	25 patients: n=12 PRP n=13 saline	Rotator cuff tear	Arthroscopic single-row repair + PRP during surgery and after 4 weeks Arthroscopic single-row repair + saline during surgery and after 4 weeks	Platelets count: n.a. Leukocytes: n.a.	n.a.	6 weeks	PRP injections did not provide superior pain relief. No statistical inter-group differences in functional outcomes.
Werthel et al. INT J SHOULDER SURG 2014 [112]	Level I Randomized controlled trial	65 patients n 33 PRP n=32 control	Rotator cuff tear	Arthroscopic double-row suture bridge repair + intra-op. PRP injection Arthroscopic double-row suture bridge repair	Platelets count: n.a. Leukocytes: yes	n.a.	12 months	The injection of PRP did not demonstrate beneficial effects on tendon healing and functional outcome. Only a possible analgesic effect has been documented.
Malavolta et al. AM J SPORT MED 2014 [66]	Level I Randomized controlled trial	55 patients: n=28 PRP n=27 control	Rotator cuff tear	Single-row repair Single-row repair + intra-op. PRP injected at the tendon-bone interface	Platelets count: n.a. Leukocytes: n.a.	Autologous thrombin Ca- chloride	24 months	PRP treatment did not provide better functional results at 24-month follow-up for small- and medium-sized tears.
Zumstein et al. J SHOULDER ELB SURG 2014 [117]	Level I Randomized controlled trial	20 patients: n=10 PRP n=10 control	Rotator cuff tear	Arthroscopic double-row repair + PRP clots placed at the tendon-bone interface Arthroscopic double-row repair	Platelets count: n.a. Leukocyte: n.a.	n.a.	3 months	Application of PRP determined higher early vascularization that might potential predispose to an increased cellular response and healing potential.
Charousset et al. ARTHROSCOPY 2014 [12]	Level IV Case-control trial	70 patients: n=35 PRP n=35 control	Rotator cuff tear	Arthroscopic double-row repair + intra-op. PRP injection Arthroscopic double-row repair	Platelets count: n.a. Leukocytes: yes	Autologous Thrombin	24 months	The results did not show any inter-group difference in cuff healing. No statistically significant difference in re-tear rate.
Antuna et al. ACTA ORTHOP BELG 2013 [3]	Level I Randomized controlled trial	28 patients: n=14 PRP n=14 control	Rotator cuff tear	Arthroscopic repair + intra-op PRF injection Arthroscopic repair	Platelets count: n.a. Leukocyte: n.a.	n.a.	24 months	PRP application did not improve the clinical outcome and the healing rate compared with standard repair

Table 4 continued

Publication	Level of evidence	N Patients	Pathology	Therapeutic Protocol	Platelet count and leukocytes	Activation	F-up	Main findings
Jo et al. AM J SPORT MED 2013 [49]	Level I Randomized controlled trial	48 patients: n=24 PRP n=24 control	Rotator cuff tear	Arthroscopic double-row repair + PRP gel at the tendon-bone interface Arthroscopic single-row repair	Platelets count: 1000 x 10^3 per mm^3 Leukocyte: n.a.	Ca-gluconate	mean 15.9 months for PRP mean 17.3 months for control	The re-tear rate in the PRP group was significantly lower than control group. Clinical outcomes showed no statistical difference between groups.
Kesikburun et al. AM J SPORT MED 2013 [57]	Level I Randomized controlled trial	40 patients: n=20 PRP n=20 saline	Rotator cuff tendinopathy	1 ultrasound-guided injection of PRP into the sub-acromial space 1 ultrasound-guided injection of saline solution	Platelets count: n.a. Leukocyte: n.a.	no	1 year	No significant inter-group differences regarding quality of life, pain, disability, and shoulder range of motion at 1y follow-up.
Ruiz-Moneo et al. ARTHROSCOPY 2013 [90]	Level I Randomized controlled trial	63 patients: n=32 PRGF n=31 control	Rotator cuff tear	Arthroscopic double-row repair + intra-op PRP application Arthroscopic double-row repair	Platelets count: 600 x 10^3 per mm^3 Leukocytes: yes	Ca-chloride	1 year	No significant inter-group differences in cuff healing and in functional scores.
Weber et al. AM J SPORT MED 2013 [110]	Level I Randomized controlled trial	60 patients: n=30 PRP n=30 control	Partial rotator cuff tear	Arthroscopic single-row repair + PRP membrane clot placed onto the repair site Arthroscopic single-row repair	Platelets count: n.a. Leukocytes: n.a.	Ca-chloride	1 year	PRP treatment did not show significant improvement in perioperative morbidity, clinical outcomes, VAS and structural integrity. MRI showed comparable re-tear rate and tendon healing.
Scarpone et al. GLOB ADV HEALTH MED 2013 [93]	Level IV Case series	18 patients	Rotator cuff tendinopathy	1 injection of PRP	Platelets count: n.a. Leukocytes: n.a.	No	3 months	PRP injection provided a significant improvement in pain, function and MRI outcome.
Mautner et al. PM&R 2013 [67]	Level IV Case series	21 patients	Rotator cuff tendinopathy	Ultrasound-guided injection of PRP (number of injections depending on global improvement)	Platelets count: n.a. Leukocytes: n.a.	No	15 months	Overall good clinical results in term of pain control and functional recovery after PRP administration.
Rha et al. CLIN REHABIL 2013 [87]	Level I Randomized controlled trial	39 patients: n=20 PRP n=19 control	Tendinosis or partial tear of supraspinatus tendon	1 ultrasound-guided injection of PRP 1 ultrasound-guided dry needling procedure	Platelets count: n.a. Leukocytes: n.a.	n.a.	6 months	PRP administration determined significant reduction in pain and disability when compared to dry needling.
Gumina et al. J BONE JOINT SURG AM 2012 [44]	Level I Randomized controlled trial	80 patients: n=40 PRP n=40 control	Rotator cuff tear	Arthroscopic single-row repair + PRP membrane placed at the tendon-bone interface Arthroscopic single-row repair	Platelets count: >400 x 10^3 per mm^3 Leukocytes: 7 x 10^3 per mm^3	Ca-gluconate	mean 13 months	PRP group showed better tendon repair but not better functional outcome.
Rodeo et al. AM J SPORT MED 2012 [89]	Level I Randomized controlled trial	79 patients: n=40 PRFM n=39 control	Rotator cuff tear	Arthroscopic repair + intra-op. PRP membrane placed at the tendon-bone interface Arthroscopic repair	Platelets count: n.a. Leukocytes: n.a.	Ca-chloride	12 months	No differences in tendon-to-bone healing between the PRFM and control groups; no significant differences in healing by ultrasound at 6 and 12 weeks.
Bergeson et al. AM J SPORT MED 2012 [6]	Level III Cohort trial	37 patients: n=16 PRMF n=21 control	Rotator cuff tear	Arthroscopic single or double-row repair + intra-op. PRP membrane placed at the tendon bone interface Arthroscopic single or double-row repair	Platelets count: n.a. Leukocytes: n.a.	Ca-chloride	13 months	PRP treatment did not show difference in any clinical score. Re-tear rates were significantly higher in the PRP group.
Randelli et al. J SHOULDER ELB SURG 2011 [85]	Level I Randomized controlled trial	53 patients: n=26 PRP n=27 control	Rotator cuff tear	Arthroscopic single-row repair + intra-op. PRP injection Arthroscopic single-row repair	Platelets count: n.a. Leukocytes: n.a.	Autologous thrombin Ca-chloride	24 months	PRP treatment significantly reduced pain in the first post-op month and provided better clinical score than controls at 3 months. For grade I-II tears, PRP was able to provide better results even at 24 months.
Jo et al. AM J SPORT MED 2011 [48]	Level II Cohort trial	42 patients: n=19 PRP n=23 control	Rotator cuff tear	Arthroscopic double-row repair + PRP gel at the tendon-bone interface Arthroscopic double-row repair	Platelets count: 1400x10^3 per mm^3 Leukocytes: no	Ca-gluconate	16 months	PRP application did not provide better outcole compared to conventional repair at any time point.
Barber et al. ARTHROSCOPY 2011 [4]	Level III Case-control trial	40 patients: n=20 PRP n=20 control	Rotator cuff tear	Single or double-row repair + PRP membrane at the tendon-bone interface Single or double-row repair	Platelets count: n.a. Leukocytes: n.a.	n.a.	mean 28.3 months for PRP mean 33 months for control	PRP group presented lower re-tear rate with respect to controls.
Castricini et al. AM J SPORT MED 2011 [9]	Level I Randomized controlled trial	88 patients: n=43 PRFM n=45 control	Rotator cuff tear	Arthroscopic double-row repair + PRP membrane placed at the tendon-bone interface Arthroscopic double-row repair	Platelets count: n.a. Leukocytes: n.a.	Ca-chloride	mean 20.2 months	PRP did not improve the healing of the rotator cuff.
Randelli et al. DISABIL REHABIL 2008 [78]	Level IV Case series	14 patients	Rotator cuff tear	Arthroscopic repair + intra-op. PRP injection	Platelets count: n.a. Leukocytes: n.a.	Autologous thrombin Ca-chloride	24 months	The application of PRP was safe and effective and produced stable results over time.

underlined better pain control after surgery in PRP group and also superior clinical scores at various follow-up evaluations.

Discussion

The main finding of the present manuscript is that PRP application may offer different outcomes according to the tendon disorders considered. Patellar tendons seem to benefit from PRP injections, whereas results in the Achilles tendon do not justify the application of the evaluated platelet concentrates, neither conservatively nor surgically. Less definitive appear the conclusions from the results on rotator cuff and elbow tendinopathies. The findings on the conservative treatment of rotator cuff are still too limited to provide viable indications; on the other hand, there is a more consistent literature with

an overall agreement on the lack of benefit of PRP surgical augmentation and only a few authors suggest its usefulness for some patient and lesion subcategories. Lateral elbow tendinopathy showed an improvement in most of the high-level studies, but the lack of proven superiority with respect to the more simple whole-blood injections still questions its use in the clinical practice.

The possibility to favour healing in tissues characterized by a low regenerative potential is highly attractive. In this light, PRP has gained increasing interest, being a fashionable treatment that allows to deliver a high concentration of autologous GFs and bioactive molecules in physiologic proportions, with low costs and in a minimally invasive way [102]. This explains the wide application of this blood derivative to several tissues and heterogeneous conditions in different fields of medicine, including tendinopathies [2, 33, 60, 80]. Even though several preclinical in vitro and in vivo studies support this rational and despite preliminary promising findings, the literature currently offers a more controversial scenery [25].

There is still a huge gap to be filled in order to understand how to translate the biological rational of PRP into a proven clinical benefit, to reach the goal of a new treatment to accelerate and improve healing in tissues with a low regenerative potential such as tendons. Some limits are due to the difficulties in producing high-level studies, but also to the application of concomitant treatments, the lack of standardization of PRP administration modality, and the combined physical therapy. This is an important aspect, since the synergic effect of biological and mechanical stimulation has been proven [106], and therefore rehabilitation should be shaped in terms of both timing and load applied to favourably interact with the application of PRP. Another key point, which is a major current limitation in the available studies, is the understanding of the right indications. Some findings already showed how some patient and lesion characteristics, such as bilateral lesions, long symptom duration, previous treatments, can influence the final outcome, but many other aspects are still unexplored [31, 32]. Older or sedentary patients may present a lower biological potential, in terms of both platelet concentrate and tissue response, but also the disease phase may play a key role. Even in the same tendon, traumatic or chronic lesions, degeneration or partial/complete rupture may present a different tissue homeostasis alteration and therefore a different response to the stimulation with platelet GFs and bioactive molecules [20, 34, 56, 94]. It is also important to remember the crucial role played by rehabilitation after PRP treatment: patients less compliant or unable to perform a proper rehabilitation protocol could respond less to the biological stimulation, thus obtaining lower clinical benefit.

The identification of lesion and patient that may benefit more from this treatment will allow from one side to plan studies without the blurring effect of the less responsive cases and, on the other side, to better select the treatment indication with benefit in terms of both clinical outcome for the patient and resource allocation for the healthcare system. The improvement in this direction will need a deeper understanding of both disease and healing mechanisms [99]. The path towards the optimization of PRP treatment also passes from other fundamental questions. Besides the identification of the best applicative modalities, which may heavily influence the effects on the treated tissue (conservative vs surgical application, single injection vs peppering technique, number and timing of injections, etc.), the nature of PRP itself will need a specific focus of the research efforts. In fact, under the acronym PRP there are countless procedures which lead to heterogeneous concentrates. Some authors tried to offer a classification framework to put some order into this multifaceted field [23, 27, 68], but the biological nature of this autologous one-step treatment approach does not favour sufficient standardization for a reliable and meaningful classification. Among the several aspects responsible for the high inter-product variability, one of the most debated is the different platelet concentrations provided by different procedures, since preclinical studies suggested how even small variations in platelet GFs concentrations may produce different effects [101, 111]. The release of bioactive molecules may be also affected by the activation method, which can determine both amount and release kinetic. Moreover, calcium chloride, thrombin, or in situ activation by contact with autologous collagen are also responsible for a different PRP gel formation. This may affect the molecules release from the fibrin net over time [26], as well as the persistency of the concentrate in the lesion site, since intra-tendinous injections present the challenge of a compact tissue where contraction may easily squeeze out a liquid PRP. Finally, a crucial aspect regards cellularity. In fact, leucocytes, monocytes, macrophages, and other cells are also present in variable proportions according to the procedure used to obtain PRP. In particular, lot of attention is currently placed on the possible negative effects of leucocytes, with in vitro studies showing deleterious effects in terms of inflammation, cell migration, and matrix molecules formation/degradation. These effects are not counteracted even by an increase in platelet concentration [69]. Nonetheless, in vitro studies may offer only a partial understanding on the role of these cells, which in vivo may have a threshold for their negative effects, while providing other effects, such as GFs release and chemotaxis, that could be useful and contribute to the tendon healing process [1, 81]. Thus, before a final verdict is given banning leucocytes, specifically designed preclinical studies should be performed in the animal model, also considering that most of the beneficial effects are reported by clinical studies where a leucocyte-rich PRP was used [1, 25].

The improvement in this field will pass through the understanding of the mechanism of interaction between PRP components and the aetiopathogenetic/regenerative tendon processes, as well as the identification of the best PRP features and application modality for each targeted condition together with the identification of the patient and lesion type that may benefit from this treatment. Finally, even though there is mainly an overall support on the safety of this biological approach, some isolated reports on adverse events [55] still suggest the need to document all PRP effects and clearly identify possible contraindications. Based on the data derived from the current literature, the use of PRP in tendon disorders should not be applied indiscriminately in the clinical practice, but rather as second-line treatment until further evidence will provide clear indications. Clinicians should be aware of the different potential of platelet concentrates according to the tendinopathy condition, as shown by the literature analysis, and offer correct expectations to patients undergoing PRP treatment.

Conclusion

The present systematic review on the most common tendinopathy conditions showed heterogeneous findings, as well as the difficulties in assessing indications, results, and limitations of PRP treatment. Based on the current evidence, patellar tendons seem to benefit from PRP injections, whereas results in the Achilles tendon do not justify the application of the evaluated platelet concentrates, neither conservatively nor surgically. The findings on the conservative treatment of rotator cuff are still too limited to provide viable indications; on the other hand, there is a more consistent literature with an overall agreement on the lack of substantial benefit of PRP surgical augmentation. Lateral elbow tendinopathy showed an improvement in most of the high-level studies, but the lack of proven superiority with respect to the more simple whole-blood injections still questions its use in the clinical practice.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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