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Platelet-rich plasma: evidence for the treatment of patellar and Achilles tendinopathy—a systematic review

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Abstract Platelet-rich plasma (PRP) has been introduced in the clinical practice to treat a growing number of different musculoskeletal pathologies. It is currently applied in the treatment of Achilles and patellar tendinopathies, which are common sport-related injuries very challenging to manage. Aim of the present paper was to review systematically the available clinical evidence concerning the application of PRP in the treatment of patellar and Achilles tendinopathy. A systematic review of the literature was performed according to the following inclusion criteria for relevant articles: (1) clinical reports of any level of evidence, (2) written in the English language, (3) with no time limitation and (4) on the use of PRP to treat conservatively Achilles and patellar tendinopathy. Twenty-two studies were included and analyzed. Two studies on patellar tendinopathy were randomized controlled trials (RCTs), whereas just one RCT was published on Achilles tendon. All the papers concerning patellar tendon reported positive outcome for PRP, which proved to be superior to other traditional approaches such as shock-wave therapy and dry needling. In the case of Achilles tendon, despite the encouraging findings reported by case series, the only RCT available showed no significant clinical difference between PRP and saline solution. The main finding of this study was the paucity of high-level literature regarding the application of PRP in the management of patellar and Achilles

tendinopathy. However, the clinical data currently available, although not univocal, suggest considering PRP as a therapeutic option for recalcitrant patellar and Achilles tendinopathies.

Keywords PRP · Tendinopathy · Achilles · Patellar · Systematic review

Introduction

Platelet-rich Plasma (PRP) has been introduced in the clinical practice to treat a growing number of different musculoskeletal pathologies, and, currently, it is the most exploited biological strategy to modulate tissue response to damage with the aim of stimulating regeneration in tissues characterized by a low intrinsic healing potential [1, 2].

Although a clear and univocal definition of PRP is still lacking and there are several different formulations currently available on the market, differing in terms of cell content, platelet concentration rate, activation methods and many other features [3], the biological pinnacle of this treatment option is well recognized: it is related to the peculiar action exerted by different growth factors (GFs) and other molecules contained in PRP and playing a crucial role in tissue homeostasis and regeneration. Several *in vitro* and animal studies [4–7] have investigated specific GFs, such as b-FGF, PDGF, TGF-beta, IGF and VEGF, which are involved in tissue regeneration with different roles, from the stimulation of fibroblast chemotaxis to extracellular matrix synthesis, cell migration and proliferation. The possibility of having several of these autologous GFs contained in physiological proportions, the ease of production and the possibility of minimally invasive administration are the most attractive features of PRP, which

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easily explain why its application has become so common in the fields of orthopaedics and sport medicine. Furthermore, recently the use of PRP for the treatment of musculoskeletal injuries has been derestricted, and even professional athletes can be treated by this approach without any fear of breaking doping regulations [8]. The most common application of PRP in orthopaedics is for the treatment of degenerative pathologies, such as chondropathy and tendinopathy [9–11]. However, despite its extensive use, there is actually a lack of robust scientific evidence to support its application to treat these pathologies, and it is still not clear whether PRP provides a superior clinical outcome with respect to more traditional approaches. Recently there have been some level I trials addressing the issue of PRP for the management of knee chondropathy [12–14], whereas there are still many unsolved questions concerning tendinopathies, especially concerning patellar and Achilles pathologies: these are common and very invalidating conditions affecting a considerable amount of the sport-active population [15–18]. The evidence gleaned from in vitro studies suggests that tendon problems are related to a chronic degenerative mechanism that leads to a gradual “disarrangement” in tendon ultrastructure, responsible for a functional impairment often associated with worsening symptoms over time [19, 20]. Since the overall tissue quality is affected, the management of tendinopathies is very challenging and often just temporary symptomatic relief can be obtained, without achieving a complete healing due to the impossibility of having a *restitutio ad integrum* in the damaged tissue. Treatment strategies range from physical to instrumental therapy and also include injective treatment with traditional products (corticosteroids and sclerosing agents), but surgical approaches can also be proposed [21, 22]: none of them has proven to be fully effective, and sometimes the treatment might even be detrimental in the long term, such as in the case of corticosteroid injections performed to relieve symptoms in athletes engaged in a strict agonistic schedule.

In this scenario, the introduction of a biological strategy such as PRP seems to provide a new and encouraging treatment option that is meant to address not just the symptoms but mainly the underlying problem of tendon tissue degeneration. However, the commercial success of PRP to treat tendinopathies has not been backed up by solid scientific evidence, and the miracle aura surrounding this approach should be reconsidered in light of scientific evidence.

The aim of the present paper is to review systematically the available clinical evidence concerning PRP application for the treatment of Achilles and patellar tendinopathies, to understand the real potential and the limits of this biological strategy for this specific therapeutic indication.

Materials and methods

A systematic review of the literature was performed on the use of PRP to treat patellar and Achilles tendinopathies. The search was made on the PubMed database on July 20, 2014, using the following criteria:

1. to identify clinical studies regarding patellar tendinopathy: (patellar OR patellar tendinopathy OR jumper’s knee) and (PRP OR platelet-rich plasma OR platelet gel OR platelet-derived OR platelet concentrate).
2. to identify clinical studies regarding Achilles tendinopathy: (Achilles OR Achilles tendinopathy) and (PRP OR platelet-rich plasma OR platelet gel OR platelet-derived OR platelet concentrate).

The guidelines for Preferred Reporting Items for Systematic Reviews and Meta-analysis were used [23]. The screening process and analysis were performed separately by 2 independent researchers.

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 reports of any level of evidence, written in the English language, with no time limitation, on the use of PRP to treat conservatively Achilles and patellar tendinopathy. Studies reporting the application of PRP as a biological augmentation during patellar and Achilles surgical repair were excluded from analysis. Other exclusion criteria were as follows: case reports, articles written in other languages and reviews. In the second step, the full texts of the selected articles were screened, with further exclusions according to the previously described criteria. Moreover, articles not reporting clinical results were excluded.

Reference lists from the selected papers were also screened. Relevant data were then extracted and collected in a single database with the consensus of the two observers to be analyzed for the purposes of the present manuscript.

Results

Twenty-two studies were included in the present analysis. Nine studies focused specifically on patellar tendinopathy, 9 on Achilles tendinopathy whereas 4 papers reported data on both the aforementioned tendon disorders.

Patellar tendinopathy

Thirteen papers in total met the inclusion criteria and were analyzed. Two of them are randomized controlled trials

Table 1 Clinical studies on patellar tendinopathy

Publication	Level of evidence	N patients	Therapeutic protocol	Platelet count and leukocytes	Follow-up	Overall results of PRP therapy
Filardo et al. Injury [27]	Level IV-case series	20 PRP	3 Injections of PRP 3 weeks apart	Platelet count: $6 \times$ basal value (mean 6,28 billions plts per injection)	6 months	+Clinical outcome
Filardo et al. Int Orthop. [11]	Level III-comparative study	31 in total (15 PRP + rehabilitation vs. 16 rehabilitation alone)	3 Injections of PRP 2 weeks apart	Leukocyte-rich PRP Platelet count: $6.1 \times$ basal value (mean: 6.5 billions plts per injection)	6 months	+Clinical outcome
Volpi et al. J Sports Med Phys Fitness [29]	Level IV-case series	9 Patellar tendons	1 US-guided PRP injection by peppering technique	Leukocyte-rich PRP Platelet count: $8 \times$ basal value	24 months	+Clinical outcome
Ferrero et al. J Ultrasound [30]	Level IV-case series	24 Patients (28 patellar tendons)	2 US-guided injections of PRP at a mean interval of 3 weeks	Leukocyte-rich PRP Not assessed (n.a.)	6 months	+Clinical outcome
Gosens et al. Int Orthop [32]	Level IV-case series	36	1 Injection of 3 ml PRP by peppering technique	N.a.	Mean 18 months	+Clinical outcome
Mautner et al. PM&R [33]	Level IV-retrospective study	27 Patients	1 PRP injection if 80 % global improvement; a second or even more injections performed in case of poorer results	N.a.	6 months	+Clinical outcome
Verrano et al. AJSM [24]	Level I single blind randomized trial	46 In total (23 PRP vs. 23 ESWT)	2 US-guided injections of PRP 2 weeks apart by peppering technique versus 3 session of ESWT at 48–72 h interval	Platelet count: $3\text{--}5 \times$ basal value (mean $0.89\text{--}1.1 \times 10^9/\text{ml}$) Leukocyte: n.a.	12 months	+Clinical outcome
Filardo et al. Int. Orthop. [10]	Level IV-case series	43 PRP (11 bilateral cases)	3 US-guided injections of PRP 2 weeks apart	Platelet count: $5.2 \times$ basal value Leukocyte-rich PRP	Mean 48 months	+Clinical outcome
Dragoo et al. AJSM [25]	Level I-double-blind randomized trial	23 (10 PRP vs. 13 dry needling)	1 Injection of PRP + US-guided needling VS US-guided dry needling alone	N.a.	6 months	+Clinical outcome
Dallandiere et al. J Vasc Interv Radiol [34]	Level IV-case series	15 Lower limb tendinosis (not specified how many Achilles and patellar tendons)	1 US-guided injection of 3 ml PRP	Platelet count: 9×10^5 plt/ mm^3 Leukocyte-poor PRP	Mean 20 months	+Clinical outcome
Kaux et al. J Sports Med Phys Fitness [35]	Level IV-case series	20	1 Injection of 6 ml of PRP	N.a.	3 months	+Clinical outcome
Charrouset et al. AJSM [36]	Level IV-case series	28 (professional or semi-pro athletes)	3 Weekly US-guided injections of 6 ml PRP	N.a.	2 years	+Clinical outcome

Overall results of PRP therapy are synthetically expressed by “+” in case of positive and by “–” in case of negative outcomes

(RCT), whereas the others are 10 case series and 1 comparative not randomized trial (Table 1).

The two RCT both documented positive results for PRP treatment. In particular, the first study, on 46 patients, was authored by Vetrano et al. [24], who compared 2 PRP injections versus 3 sessions of Shock Waves: at 6- and 12-month follow-up, PRP offered a superior clinical outcome according to VISA-P and VAS pain scores. Drago et al. [25] randomized 23 patients, affected by recalcitrant patellar tendinopathy, to receive a single session of ultrasound-guided dry needling combined or not with a leukocyte-rich PRP injection. PRP administration contributed to accelerating recovery time: at 3 months, the PRP group recorded a superior outcome in terms of VISA score with respect to the control group, even if at 6 months, results were comparable between groups, thus showing that PRP acted mainly by accelerating the early phases of tissue repair and remodeling. Furthermore, three patients treated by dry needling alone failed and required surgical intervention, whereas no failure was reported in the PRP group. Currently, this is the only double-blind RCT available for patellar tendon pathology.

Looking at case series, Filardo et al. [26] published the results obtained in a cohort of 20 male patients treated by three intra-tendinous injections: a significant functional increase and pain reduction were achieved, and 80 % of patients were able to go back to sport activity in a mean of 4 months after treatment. A later comparative study by the same group [27] showed that PRP therapy followed by an eccentric rehabilitation protocol in 15 patients affected by recalcitrant tendinopathy (i.e., non-responsive to previous treatments) could provide good clinical results, comparable to those achieved by a group of less complicated patients that were treated for the first time in their medical history by rehabilitation alone. The same authors subsequently documented [28] stable results with the same PRP formulation and therapeutic protocol (3 injections at 2 weeks interval) up to 4.5 years of follow-up, although inferior results were recorded in patients affected by bilateral lesions and longer symptom duration. Interestingly, ultrasound (US) evaluation showed a gradual reduction in neovascularization (evaluated by power Doppler) over time, even if no correlation was found between imaging and clinical outcome. Volpi et al. [29] treated 9 patients by a single PRP injection using the peppering technique. At 24 months, satisfactory results were reported and also MRI revealed an improved tendinous structure. Conversely, Ferrero et al. [30] applied a two-PRP-injections protocol in 28 patellar tendons and also in this case obtained a good outcome at 6-month evaluation. Furthermore, US evaluation revealed a reduction in the hypochoic areas in the majority of tendons, and also an improvement in fibrillar echotexture and reduced hypervascularity by power

Doppler. Another case series by Van Ark et al. [31] included 5 patients treated by a single injection of PRP followed by a rehab program and revealed a significant increase in VISA-P score up to 26 weeks. Gosens et al. [32] treated 36 patients with a single intra-tendinous injection of PRP and evaluated them by VISA-P score and VAS for pain up to a mean of 18-month follow-up. The results were statistically significant, and a good rate of return to pain-free sport activity was found. Moreover, the authors reported a lower clinical outcome in patients previously treated by corticosteroids or sclerosing injections or surgical management. Mautner et al. [33] evaluated 27 patients affected by patellar tendinopathy at mean of 15-month follow-up by considering the improvement of subjective symptoms on a Likert scale: 59 % of patients reported moderate-to-complete resolution of the symptoms (>50 % of improvement). Similar findings were reported in small cohorts of patients by Dallaudiere et al. [34] and Kaux et al. [35], who also suggested the benefit of PRP. Finally, Charrouset et al. [36] used PRP to treat 28 professional or semiprofessional athletes not responsive to other conservative treatments. At 2-year evaluation, a significant increase was reported in all clinical scores adopted and 75 % of patients were able to regain the same pre-injury sport activity level within 3 months.

Achilles tendinopathy

Twelve papers in total met the inclusion criteria and were analyzed. Only one trial was a double-blind RCT, whereas the others were all case series (Table 2).

The aforementioned double-blind RCT was published by de Vos et al. in 2010 and was followed by a second paper dealing with the same patients evaluated at longer follow-up (1 year). The authors compared PRP versus saline injections in patients affected by chronic mid-portion Achilles tendinopathy for more than 2 months [37]. Fifty-four patients, aged from 18 to 70 years, were included and treated by a single injection by needling technique of either 4 mL of non-activated PRP or 4 mL of saline solution. After the injection, patients were assigned to a standardized rehabilitation program based on eccentric exercises. Prospective evaluations were performed for up to 24 weeks using the VISA-A questionnaire, patient satisfaction and return to sport. The results showed improvements in both treatment groups without any significant inter-group difference in any parameter considered. In a later article [38], the authors reported the results at 1 year of follow-up where they confirmed no difference in clinical outcome or in time to return to sport. The ultrasonographic evaluation showed a reduction in neovascularization, reduction in antero-posterior thickness and improvement in overall tendon structure in both groups, even in this case without

Table 2 Clinical studies on Achilles tendinopathies

Publication	Level of evidence	N patients	Protocol	Platelet count and leukocytes	Follow-up (months)	Overall results of PRP therapy
Gaweda et al. Int J Sports Med [39]	Level IV-case series	14	1 Injection of 3 ml PRP	Not assessed (n.a.)	18	+Clinical outcome
Volpi et al. J Sports Med Phys Fitness [29]	Level IV-case series	3	1 US-guided PRP injection by peppering technique	Platelet count: $8 \times$ basal value Leukocyte-rich PRP	24	+Clinical outcome
deVos et al. JAMA [37]	Level I-double-blind randomized trial	27 PRP versus 27 saline solution	1 US-guided injection of 4 ml PRP by peppering technique versus 1 injection of 4 ml saline	N.a.	12	–(No inter-ground difference at any follow-up evaluation both in clinical outcome and in US evaluation)
deJonge et al. Am J Sports Med [38]	Level IV-case series	14	1 Injection of 2.5–3–5 ml PRP	Platelet count: $4.2 \times$ basal value (mean 1048×10^9 plts/L per injection) Leukocyte-rich PRP	14	+Clinical outcome
Finoff et al. PM&R [40]	Level IV-case series	14	1 Injection of 2.5–3–5 ml PRP	Platelet count: $4.2 \times$ basal value (mean 1048×10^9 plts/L per injection) Leukocyte-rich PRP	14	+Clinical outcome
Owens et al. Foot and Ankle Int [41]	Level IV-case series	10	1 Injection of 6 ml PRP	N.a.	24	+Clinical outcome
Monto et al. Foot and Ankle Int [42]	Level IV-case series	30	1 Injection of 4 ml PRP	N.a.	24	+Clinical outcome
Ferrero et al. J Ultrasound [30]	Level IV-case series	24 (30 Achilles tendons)	2 US-guided injections of 6 ml of PRP + percutaneous tenotomy at a mean interval of 3 weeks	N.a.	6	+Clinical outcome
Deans et al. J Foot and Ankle Surgery [43]	Level IV-case series	26 (2 bilateral cases)	1 Injection of PRP; 2 patients received a second injection after 6 weeks	N.a.		+Clinical outcome
Mautner et al. PM&R [33]	Level IV-retrospective study	27	1 PRP injection if 80 % global improvement; a second or even more injections performed in case of poorer results	N.a.	6	+Clinical outcome
Murawski et al. Foot Ankle Spec [45]	Level IV-retrospective study	32	1 Injection of 3 ml PRP by peppering technique	N.a.	6	+Clinical outcome

Overall results of PRP therapy are synthetically expressed by “+” in case of positive and by “–” in case of negative outcomes

any significant inter-group difference. Based on the results of this trial, the authors showed no evidence to support the use of PRP as an injective treatment for Achilles tendinopathy.

Looking at other available studies, Volpi et al. [29] injected a single dose of PRP in 3 patients and achieved a good clinical outcome at the first 3-month evaluation,

which was later confirmed at 2 years. Gaweda et al. [39] injected PRP in 14 patients (15 tendons in total) with non-insertional Achilles tendinopathy. A significant increase was recorded in clinical scores at the final evaluation at a mean of 18 months, and ultrasonography revealed normalization of peritendineum, reduction in tendon thickening and reduction in hypoechoic lesions. Furthermore, after

an initial increase for up to 3-month follow-up, power Doppler showed a reduction in tendon vascularity. The clinical efficacy of PRP has also been suggested by Finoff, Owens and Dallaudiere [34, 40, 41]. Finoff et al. [40] treated chronic tendinopathy with US-guided needle tenotomy and PRP injections. The study focused on differently located tendinopathies, among which 14 Achilles tendons were treated. Mean follow-up evaluation was carried out at 14 months (range 3.5–25 months), and the investigators found a significant decrease in pain and concomitant functional recovery. No correlation was found between clinical outcome and parameters such as age, BMI, smoking status, tendinopathy location, symptom duration or PRP platelet concentration. Owens et al. [41] retrospectively reviewed a small cohort of 10 patients all treated by intra-tendinous PRP injections. Evaluation items included Foot and Ankle Ability Measure, Foot and Ankle Ability Measure Sport and Short Form Health Survey (SF-8). An improvement was found in each of these clinical scores, but MRI evaluation did not reveal a better radiographic appearance in the majority of tendons treated.

Comparable clinical results were also reported by Dallaudiere et al. [34]. A study by Monto et al. [42] confirmed the positive clinical outcome of the aforementioned papers. Thirty patients received a single US-guided injection of autologous PRP. Clinical evaluation was carried out using the American Orthopaedic foot and ankle score at 0, 1, 2, 3, 6, 12 and 24-month follow-up, and MRI/US evaluation was performed 6 months after treatment. Clinical results were positive, with a significant improvement with respect to the first evaluation; this improvement was confirmed up to the final follow-up at 24 months. MRI/US control scans revealed signs of tendon healing in 27 out of 29 patients. Two failures were recorded, and, interestingly, both cases were related to calcaneal pathology (insertional calcaneal tendinopathy and severe Haglund deformity). Similar findings were reported by Deans et al. [43] who treated 26 patients by a single PRP injection followed by a standardized rehabilitation protocol: significant improvement was documented at 6-week evaluation, with more than 80 % of patients reporting benefit in terms of pain and function recovery. Mautner et al. [33] published a retrospective, multi-centric, cross-sectional study analyzing clinical outcomes of 180 patients treated for different tendinopathies. The Achilles tendon was the third most common site treated (27 tendons), and the results were impressive, since 100 % of the patients reported a “moderate improvement to complete resolution” on a Likert scale: the Achilles group was the best to respond after PRP treatment. Interestingly, this trial included patients treated in 4 different medical centers, each employing its particular PRP formulation and therapeutic protocol. Another trial by Ferrero et al. [30] found good results at 6-month evaluation

in 24 patients treated by a single injection of PRP. Besides the good clinical outcome, follow-up US scans were also performed and revealed a widespread improvement in the fibrillar echo texture of the tendon and reduced hypervascularity as shown by power Doppler. More recently, Filardo et al. [44] showed that PRP could produce stable clinical benefit up to 4.5 years after the treatment. The authors found that, in 27 patients treated by 3 intra-tendinous injections, the clinical outcome was positive and sport participation was still possible at a stable level for up to the mean 54-month follow-up. Interestingly, the longest symptom duration correlated with a lower success rate of this biological approach.

The most recent published study was authored by Murawski et al. [45] who retrospectively assessed a cohort of 32 patients treated by a single PRP injection in the mid-substance of the Achilles tendon. Twenty-five patients were asymptomatic after 6 months, whereas the remaining 7 required surgical intervention; thus, the overall success rate for the therapy was estimated in about 80 % of cases.

Discussion

The main finding of the present study was the paucity of high-level literature regarding the application of PRP in the management of tendinopathy involving both patellar and Achilles tendons, thus making it very hard for clinicians and researchers to understand clearly the role of this biological approach in these common sport-related injuries. Up to the present, 22 studies have been published in total about these specific pathologies but just 2 of them (one for patellar and one for Achilles tendon) are double-blind RCTs, which is the best study design to provide robust and sound data to support (or deny) the efficacy of this treatment.

Considering patellar tendinopathy, all the reports suggest a favorable role of PRP in stimulating tendon healing and symptomatic relief. Two comparative trials have been performed, both randomized, the first one evaluating PRP against external shock waves [24] and the second one, a double-blind study, evaluating dry needling and PRP versus dry needling alone [25]. Both these trials documented superior results for PRP, that was at least capable of accelerating healing times as shown by Dragoo et al. [25]. PRP seems therefore to be a useful treatment option for recalcitrant patellar tendinopathy, which can be employed even in professional athletes and offers a good chance of beneficial effects as shown by Charrouset et al. [36]. Overall, the rate to return to sport activity was good in all the available trials, and even results at mid-/long-term evaluation were shown to be stable [28] without a significant rate of relapse. It also emerged that bilateral

involvement and long-lasting symptom duration could negatively affect the clinical outcome, and also previous injective or surgical treatments were linked to lower functional results.

The most controversial debate concerns Achilles tendinopathy, since the only double-blind RCT showed negative results for PRP, whereas the remaining trials (all case series) reported overall positive outcomes even at mid-/long-term evaluation. The authors of the aforementioned double-blind RCT revealed an improvement in both treatment groups (PRP and saline solution), without statistical difference in terms of clinical results between both at 6- and 12-month follow-ups. The same trend was observed after the ultrasonographic evaluation of the tendon structure over time. Despite these relevant findings, some limitations of the study should be taken into account before making a final pronouncement on the “inefficacy” of PRP: first of all, in the case of saline injections, needling itself might be a treatment which involves mechanical stimulation and bleeding of the degenerated tendon tissue, and therefore, the good results reported after saline injections cannot be ascribed only to a placebo effect. Furthermore, the mean age of patients was notably higher than the common sport-active population, and older age might impair patients’ responsiveness to the biological effect of PRP. Moreover, another fundamental aspect might be that PRP was not activated, based on the fact that its activation might be provided by contact with *in situ* autologous collagen: this way, however, platelet gel formation might be delayed and tendon contraction might squeeze the liquid PRP away from the injection site, thus reducing its potential beneficial effects. Based on these remarks, this study, despite its high methodological quality and the important contribution to the literature in this field, cannot be considered conclusive when assessing PRP inefficacy for this kind of pathology.

Besides considerations regarding the level of evidence of the available studies, other controversial aspects should be considered. First of all, the marked inter-product variability and the different application strategies currently in clinical use have to be remembered. PRP is an off-the-shelf product whose characteristics can widely vary according to the different production techniques adopted. The different cell types and concentrations provided by different procedures and applied to the lesion site are a fundamental aspect since even small variations in GFs concentrations can produce different effects [3]. Timing and number of injections are also important and should be further investigated since they might influence clinical outcome. Another crucial aspect regards cellularity, since leukocytes, monocytes, macrophages and mast cells are contained in platelet concentrates and may play a role in the effects exerted on the tendon tissue. Furthermore, the storage

procedure, if used, is thought to have an impact on the amount and pattern of GFs released, and also the activation method may influence the results, due to the fact that activation may regulate the amount and speed of GFs release and also the molecules used may themselves exert their own effect on the physiology of tissue healing and remodeling, without forgetting that the timing of gel formation might also determine the amount of releasate actually being delivered into the treated area [3]. All these possible variables impede knowing the best formulations to adopt for the treatment of tendinopathies, and current clinical data do not allow any specific product feature to be linked to clinical outcome, either positively or negatively. In fact, good clinical outcomes were obtained with very different PRP formulations (e.g., with or without leukocytes) and injective protocols (e.g., one to three injections). In light of these findings, further high-quality studies are needed, with the aim of identifying the optimal PRP properties and applicative modalities to treat Achilles and patellar tendinopathy.

Another central aspect is the role of concurrent treatment: in fact, PRP is always associated with a rehabilitation protocol that itself plays a major role in the therapeutic process. It is impossible to assess the contribution of PRP administration to tendon healing alone, but some studies have suggested that biological stimulation can be enhanced by appropriate physical therapy (mainly based on eccentric exercises) to achieve a better clinical outcome [46]. Therefore, current indications suggest combining both approaches to treat this kind of patient with complex tendinopathies.

In conclusion, the clinical data available, although not univocal, suggest considering PRP as an option for the management of both patellar and Achilles tendinopathies. Clearly it must be remembered that there are marked anatomical and biomechanical differences between patellar and Achilles tendons, thus implying different etio-pathological pathways and probably inherent different responses to biological stimulation. However, based on the trials published, PRP seems useful for tendinopathies not responsive to other conservative treatments and, therefore, at the moment, it can be considered as a second-line approach for such conditions. Many questions are still open concerning basic biology of PRP and its most appropriate applicative modalities, as well as advantages and disadvantages with respect to other treatment approaches, and therefore, more high-level trials are needed to address these specific points and offer clear indications on the use of PRP for the treatment of patellar and Achilles tendinopathy.

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References

- Cole BJ, Seroyer ST, Filardo G, Bajaj S, Fortier LA (2010) Platelet-rich plasma: where are we now and where are we going? *Sports Health* 2(3):203–210
- Kon E, Filardo G, Di Martino A, Marcacci M (2011) Platelet-rich plasma (PRP) to treat sports injuries: evidence to support its use. *Knee Surg Sports Traumatol Arthrosc* 19(4):516–527
- Tschon M, Fini M, Giardino R, Filardo G, Dallari D, Torricelli P, Martini L, Giavaresi G, Kon E, Maltarello MC, Nicolini A, Carpi A (2011) Lights and shadows concerning platelet products for musculoskeletal regeneration. *Front Biosci (Elite Ed)* 1(3):96–107
- Boswell SG, Cole BJ, Sundman EA, Karas V, Fortier LA (2012) Platelet-rich plasma: a milieu of bioactive factors. *Arthroscopy* 28(3):429–439
- Kajikawa Y, Morihara T, Sakamoto H et al (2008) Platelet-rich plasma enhances the initial mobilization of circulation-derived cells for tendon healing. *J Cell Physiol* 215(3):837–845
- De Mos M, Van der Windt AE, Jahr H et al (2008) Can platelet-rich plasma enhance tendon repair? A cell culture study. *Am J Sports Med* 36(6):1171–1178
- Torricelli P, Fini M, Filardo G, Tschon M, Pischedda M, Pacorini A, Kon E, Giardino R (2011) Regenerative medicine for the treatment of musculoskeletal overuse injuries in competition horses. *Int Orthop* 35(10):1569–1576. doi:10.1007/s00264-011-1237-3. Epub 2011 Mar 11
- Engebretsen L, Steffen K, Alsousou J, Anitua E, Bachl N, Devillee R, Everts P, Hamilton B, Huard J, Jenoure P, Kelberine F, Kon E, Maffulli N, Matheson G, Mei-Dan O, Menetrey J, Philippon M, Randelli P, Schamasch P, Schweltnus M, Verneq A, Verrall G (2010) IOC consensus paper on the use of platelet-rich plasma in sports medicine. *Br J Sports Med* 44(15):1072–1081. doi:10.1136/bjism.2010.079822
- Vannini F, Di Matteo B, Filardo G et al (2013) Platelet-rich plasma for foot and ankle pathologies: a systematic review. *Foot Ankle Surg*. doi:10.1016/j.fas.2013.08.00
- Filardo G, Kon E, Roffi A, Di Matteo B, Merli ML, Marcacci M (2013) Platelet-rich plasma: why intra-articular? A systematic review of preclinical studies and clinical evidence on PRP for joint degeneration. *Knee Surg Sports Traumatol Arthrosc*. doi:10.1007/s00167-013-2743-1
- Filardo G, Presti ML, Kon E, Marcacci M (2010) Nonoperative biological treatment approach for partial Achilles tendon lesion. *Orthopedics* 33(2):120–123. doi:10.3928/01477447-20100104-31
- Filardo G, Kon E, Di Martino A, Di Matteo B, Merli ML, Cenacchi A, Fornasari PM, Marcacci M (2012) Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: study design and preliminary results of a randomized controlled trial. *BMC Musculoskelet Disord* 23(13):229
- Cerza F, Carni S, Carcangiu A, Di Vavo I, Schiavilla V, Pecora A, De Biasi G, Ciuffreda M (2012) Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis. *Am J Sports Med* 40(12):2822–2827
- Sánchez M, Fiz N, Azofra J, Usabiaga J, Aduriz Recalde E, García Gutierrez A, Albillos J, Gárate R, Aguirre JJ, Padilla S, Orive G, Anitua E (2012) A randomized clinical trial evaluating plasma rich in growth factors (PRGF-Endoret) versus hyaluronic acid in the short-term treatment of symptomatic knee osteoarthritis. *Arthroscopy* 28(8):1070–1078
- Cook JL, Khan KM, Harcourt PR, Grant M, Young DA, Bonar SF (1997) A cross sectional study of 100 athletes with jumper's knee managed conservatively and surgically. The Victorian Institute of Sport Tendon Study Group. *Br J Sports Med* 31(4):332–336
- Lian OB, Engebretsen L, Bahr R (2005) Prevalence of jumper's knee among elite athletes from different sports: a cross-sectional study. *Am J Sport Med* 33:561–567
- Sobhani S, Dekker R, Postema K, Dijkstra PU (2013) Epidemiology of ankle and foot overuse injuries in sports: a systematic review. *Scand J Med Sci Sports* 23(6):669–686. doi:10.1111/j.1600-0838.2012.01509.x
- Kujala UM, Sarna S, Kaprio J (2005) Cumulative incidence of achilles tendon rupture and tendinopathy in male former elite athletes. *Clin J Sport Med* 15(3):133–135
- Riley G (2004) The pathogenesis of tendinopathy. A molecular perspective. *Rheumatology (Oxford)* 43(2):131–142
- Samiric T, Parkinson J, Ilic MZ, Cook J, Feller JA, Handley CJ (2009) Changes in the composition of the extracellular matrix in patellar tendinopathy. *Matrix Biol* 28(4):230–236
- Peers KH, Lysens RJ (2005) Patellar tendinopathy in athletes: current diagnostic and therapeutic recommendations. *Sports Med* 35:71–87
- Sussmilch-Leitch SP, Collins NJ, Bialocerowski AE, Warden SJ, Crossley KM (2012) Physical therapies for Achilles tendinopathy: systematic review and meta-analysis. *J Foot Ankle Res* 5(1):15
- Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 339:b2535
- Vetrano M, Castorina A, Vulpiani MC, Baldini R, Pavan A, Ferretti A (2013) Platelet-rich plasma versus focused shock waves in the treatment of jumper's knee in athletes. *Am J Sports Med*. doi:10.1177/0363546513475345
- Dragoo JL, Wasterlain AS, Braun HJ, Nead KT (2014) Platelet-rich plasma as a treatment for patellar tendinopathy: a double-blind, randomized controlled trial. *Am J Sports Med* 42(3):610–618
- Kon E, Filardo G, Delcogliano M, Presti ML, Russo A, Bondi A, Di Martino A, Cenacchi A, Fornasari PM, Marcacci M (2009) Platelet-rich plasma: new clinical application: a pilot study for treatment of jumper's knee. *Injury* 40(6):598–603
- Filardo G, Kon E, Della Villa S, Vincentelli F, Fornasari PM, Marcacci M (2009) Use of platelet-rich plasma for the treatment of refractory jumper's knee. *Int Orthop* 34(6):909–915
- Filardo G, Kon E, Di Matteo B et al (2013) Platelet-rich plasma for the treatment of patellar tendinopathy: clinical and imaging findings at medium-term follow-up. *Int Orthop* 37(8):1583–1589
- Volpi P, Quaglia A, Schoenhuber H, Melegati G, Corsi MM, Banfi G, de Girolamo L (2010) Growth factors in the management of sport-induced tendinopathies: results after 24 months from treatment. A pilot study. *J Sports Med Phys Fitness* 50(4):494–500
- Ferrero G, Fabbro E, Orlandi D, Martini C, Lacelli F, Serafini G, Silvestri E, Sconfienza LM (2012) Ultrasound-guided injection of platelet-rich plasma in chronic Achilles and patellar tendinopathy. *J Ultrasound* 15(4):260–266
- van Ark M, van den Akker-Scheek I, Meijer LT, Zwerver J (2013) An exercise-based physical therapy program for patients with patellar tendinopathy after platelet-rich plasma injection. *Phys Ther Sport* 14(2):124–130
- Gosens T, Den Ouden BL, Fievez E, van 't Spijker P, Fievez A (2012) 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* 36(9):1941–1946

33. Mautner K, Colberg RE, Malanga G, Borg-Stein JP, Harmon KG, Dharamsi AS, Chu S, Homer P (2013) Outcomes after ultrasound-guided platelet-rich plasma injections for chronic tendinopathy: a multicenter, Retrospective Review. *PM R*. doi:[10.1016/j.pmrj.2012.12.010](https://doi.org/10.1016/j.pmrj.2012.12.010)
34. Dallaudière B, Pesquer L, Meyer P, Silvestre A, Perozziello A, Peuchant A, Durieux MH, Loriaut P, Hummel V, Boyer P, Schouman-Claeys E, Serfaty JM (2014) Intratendinous injection of platelet-rich plasma under US guidance to treat tendinopathy: a long-term pilot study. *J Vasc Interv Radiol* 25(5):717–723
35. Kaux JF, Croisier JL, Bruyere O, Rodriguez de la Cruz C, Forthomme B, Brabant G, Lapraille S, Lonneux V, Noel D, Le Goff C, Gothot A, Collette J, Crielaard JM (2014) One injection of platelet-rich plasma associated to a submaximal eccentric protocol to treat chronic jumper's knee. *J Sports Med Phys Fitness* [Epub ahead of print]
36. Charrouset C, Zaoui A, Bellaiche L, Bouyer B (2014) Are multiple platelet-rich plasma injections useful for treatment of chronic patellar tendinopathy in athletes? A prospective study. *Am J Sports Med* 42(4):906–911
37. De Vos RJ, Weir A, van Schie HT, Bierma-Zeinstra SM, Verhaar JA, Weinans H, Tol JL (2010) Platelet-rich plasma injection for chronic Achilles tendinopathy: a randomized controlled trial. *JAMA* 303(2):144–149
38. de Jonge S, de Vos RJ, Weir A et al (2011) One-year follow-up of platelet-rich plasma treatment in chronic Achilles tendinopathy: a double-blind randomized placebo-controlled trial. *Am J Sports Med* 39(8):1623–1629
39. Gaweda K, Tarczyska M, Krzyzanowski W (2010) Treatment of Achilles tendinopathy with platelet-rich plasma. *Int J Sports Med* 31(8):577–583
40. Finnoff JT, Fowler SP, Lai JK et al (2011) Treatment of chronic tendinopathy with ultrasound-guided needle tenotomy and platelet-rich plasma injection. *PM R* 3(10):900–911
41. Owens RF Jr, Ginnetti J, Conti SF, Latona C (2011) Clinical and magnetic resonance imaging outcomes following platelet rich plasma injection for chronic midsubstance Achilles tendinopathy. *Foot Ankle Int* 32(11):1032–1039
42. Monto RR (2012) Platelet rich plasma treatment for chronic Achilles tendinosis. *Foot Ankle Int* 33(5):379–385
43. Deans VM, Miller A, Ramos J (2012) A prospective series of patients with chronic Achilles tendinopathy treated with autologous-conditioned plasma injections combined with exercise and therapeutic ultrasonography. *J Foot Ankle Surg* 51(6):706–710
44. Filardo G, Kon E, Di Matteo B, Di Martino A, Tesei G, Pelotti P, Cenacchi A, Marcacci M (2014) Platelet-rich plasma injections for the treatment of refractory Achilles tendinopathy: results at 4 years. *Blood Transfus* 19:1–8. doi:[10.2450/2014.0289-13](https://doi.org/10.2450/2014.0289-13)
45. Murawski CD, Smyth NA, Newman H, Kennedy JG (2014) A single platelet-rich plasma injection for chronic midsubstance Achilles tendinopathy: a retrospective preliminary analysis. *Foot Ankle Spec* 7(5):372–376. doi:[10.1177/1938640014532129](https://doi.org/10.1177/1938640014532129)
46. Virchenko O, Aspenberg P (2006) How can one platelet injection after tendon injury lead to a stronger tendon after 4 weeks? Interplay between early regeneration and mechanical stimulation. *Acta Orthop* 77(5):806–812