

# Platelet-rich plasma (PRP) to treat sports injuries: evidence to support its use

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**Abstract** Tissue repair in musculoskeletal lesions is often a slow and sometimes incomplete process. In sports patients or professional athletes, the impact of musculoskeletal lesions on life and work is great, and the fast recovery of full efficiency and return to competition is of primary importance. The clinical improvement offered by available treatments is not always sufficient for highly demanding patients to return to their previous level of activity. The search for a minimally invasive solution to improve the status of the chondral surface of the injured joint is therefore highly desirable, especially in these patients. Platelet-rich plasma (PRP) is a procedure that allows to obtain a natural concentration of autologous growth factors. The attractive possibility to use the patients' own growth factors to enhance reparative process in tissues with low healing potential, the promising preliminary clinical findings and the safety of these methods, explain the wide application of this biological approach. The aim of this review is to analyse the existing published studies to look for scientific evidence in preclinical studies or in the results obtained through PRP application in humans that supports the efficacy of PRP and its use for the treatment of tendinous, ligamentous, cartilaginous and

muscular injuries. The analysis of the literature shows promising preclinical results but contradictory clinical findings for the treatment of sport injuries. High-quality studies are required to confirm these preliminary results and provide scientific evidence to support its use.

**Keywords** Platelet-rich plasma · Sport · Musculoskeletal · Injury

## Introduction

Tissue repair in musculoskeletal injuries is often a slow and sometimes incomplete process [15, 74, 76]. The real cost of these injuries to society includes not only money spent on healthcare but also the loss of work. In sports patients or professional athletes, the impact of musculoskeletal lesions on life and work is great, and the fast recovery of full efficiency and return to competition is of primary importance [82]. The optimal treatment for these injuries should therefore aim to restore patients to their pre-injury status in a safe, cost-effective way and as quickly as possible.

In recent years, several studies revealed a complex regulation of growth factors (GFs) for the normal tissue structure and the reaction to tissue damage and an important role and effectiveness of using growth factors for healing the damaged tissue [43, 66, 71, 78]. Therefore, the use of growth factors is thought to be useful in clinical practice, because it promotes rapid healing with a high-quality tissue and allows an early and safe return to unrestricted activity. Platelet-rich plasma (PRP) is a simple, low cost and minimally invasive way to obtain a natural concentration of autologous growth factors and is currently being widely experimented in different fields of medicine for its ability to aid the regeneration of tissue with a low

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healing potential. Fields of application are sports medicine, orthopaedics, dentistry, dermatology, ophthalmology, plastic and maxillofacial surgery, etc. [33, 86]. The rationale for using platelets in so many fields for the treatment of different tissues is because PLTs constitute a reservoir of critical GFs and cytokines, which may govern and regulate the tissue healing process that is quite similar in all kinds of tissues. In fact, the response to an injury is coordinated and regulated by mediators and cellular events, which are common to most tissues during the inflammatory, reparative and remodelling phases. PLTs participate predominantly in the early inflammation phases and degranulation produces a great number of GFs that initiate and maintain the healing process [53, 94]. In this view, the positive effects of platelet concentrate injections on tissue healing might be attributed to the higher content and secretion of GFs, which can be placed directly into the damaged tissue in physiological proportions [21]. In fact, with respect to the injection of purified individual growth factors or experimental associations of growth factors, PRP has the theoretical advantage of containing various growth factors and molecules with a natural balance of anabolic and catabolic functions, possibly optimizing the tissue environment and favouring the healing process [4]. Moreover, the risk of allergy or infection is negligible, due to the autologous nature of the platelet extract [86]. Finally, although growth factor secretion occurs mainly in the first hour, it has been seen that platelets remain viable for 7 days and continue to release growth factors, therefore suggesting that one single injection into the damaged tissue might be a sufficient treatment in most clinical applications [62].

Therefore, the reason for the recent worldwide clinical application of this appealing innovative approach would appear clear. Nevertheless, the existing data on PRP use in preclinical and clinical studies are controversial [26, 82].

Whereas the literature on the role of isolated growth factors in tissue regeneration is abundant, there is a lack of animal and clinical studies to demonstrate the real potential of PRP to promote musculoskeletal soft tissue repair.

The aim of this review is to analyse the existing published studies and look for scientific evidence in preclinical studies (Table 1) or in the results obtained through PRP application in humans (Table 2) that supports the efficacy of PRP and its use for the treatment of tendinous, ligamentous, cartilaginous and muscular injuries.

### Platelet growth factors and PRP

Platelets are commonly known for their role in haemostasis, but they also play a key role in mediating the healing of the damaged tissue, because of their capacity to release growth factors from their  $\alpha$ -granules [53, 94]. Platelets contain storage pools of growth factors including platelet-derived growth factor (PDGF), transforming growth factor (TGF- $\beta$ ), platelet-derived epidermal growth factor (PDEGF), vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF-1), fibroblastic growth factor (FGF) and epidermal growth factor (EGF) [32, 33, 35, 86]. Alpha granules are also a source of cytokines, chemokines and many other proteins [1] variously involved in stimulating chemotaxis, cell proliferation and maturation, modulating inflammatory molecules and attracting leucocytes. Moreover, platelets store antibacterial and fungicidal proteins to prevent infections, proteases such as metalloprotease-4 and coagulation factors [1]. Besides alpha granules, platelets also contain dense granules, which store and release, upon activation, ADP, ATP, calcium ions, histamine, serotonin and dopamine [65]. Finally, platelets contain lysosomal granules that can secrete acid

**Table 1** Preclinical studies: effects on musculoskeletal tissues documented for blood derivatives

Tissue	Effects
Tendon	Stimulation of gene expression of the matrix molecules, tendon cell proliferation, synthesis of angiogenic and other GFs Activation of circulation-derived cells Increase of neovascularization and metabolic activity Increase of maturation in tendon callus, stiffness, ultimate stress and force at failure
Ligament	Improvement in histological and biomechanical properties (used as collagen-PRP hydrogel)
Cartilage	Decrease of cartilage fibrillation and synovial membrane hyperplasia and hemorrhage (ACS) Acceleration of chondrocytes expansion Enhancement of MSC proliferation and chondrogenic differentiation
Muscle	Acceleration of satellite cell activation (ACS) Increase of diameter of regenerating fibres (ACS) Stimulation of myogenesis Increase of protein expression of myoD (38-kD) and myogenin Acceleration of recovery time after strain injury

**Table 2** PRP applications in humans: clinical evidence for the treatment of sports lesions

Pathology	Study	Level	Patients	F up	Results
Elbow tendinopathy	Mishra Pavelko (2006)	2	20	2 years	+ Enhanced healing and functional recovery vs. bupivacaine injections
	Peerbooms et al. (2010)	1	100	1 year	+ Reduced pain and increased function, exceeding the effect of corticosteroid injection (better initially, then declined)
Rotator cuff tear	Maniscalco et al. (2008)	4	1	6 months	+ Pain relief and ROM recover after surgical repair Complete integrity of the rotator cuff under the fibrin membrane by MRI
	Randelli et al. (2008)	4	14	2 years	+ No adverse events Good and stable clinical results after arthroscopic surgical repair
Achilles lesion/tendinopathy	Sanchez et al. (2007)	3	12	32–50 months	+ No wound complications in surgically repaired tendons Earlier recovery of ROM and a faster return to jogging and sport Lower cross-sectional area
	Filardo et al. (2010)	4	1	18 months	+ Fast tissue repair and return to competitive sports activity in partial tendon tear
	De Vos et al. (2010)	1	54	24 weeks	– Same results in pain and activity improvement compared with a saline injection
Patellar tendinopathy	Kon et al. (2009)	4	20	6 months	+ Marked improvement in knee function and quality of life PRP has to be associated with physiotherapy
	Filardo et al. (2010)	3	31	6 months	+ Marked clinical improvement in chronic refractory patellar tendinopathy, comparable with less severe cases Greater improvement in the level of sports activity in PRP group
ACL tear	Orrego et al. (2008)	2	108	6 months	+ Enhancing maturation (MRI) – No effect on tunnel widening
	Silva et al. (2009)	3	40	3 months	– No MRI difference compared to controls
	Radice et al. (2010)	3	50	3–12 months	+ 48% reduction in the time required to achieve a complete homogeneous graft signal when PRP was used for surgical ACL augmentation
Cartilage lesion/degeneration	Sanchez et al. (2003)	4	1		+ Rapid resumption of symptom-free athletic activity after surgical treatment for knee cartilage avulsion
	Sanchez et al. (2008)	3	60	5 weeks	+ Better pain control and physical function improvement vs hyaluronan injections
	Kon et al. (2010)	4	91	1 year	+ Clinical improvement Better results in early degeneration and younger patients Worsening from 6 to 12 months

hydrolases, cathepsin D and E, elastases and lisozima [2, 89], and most likely other not yet well-characterized molecules, whose role in the tissue healing process should not be underestimated. The fact that platelets secrete growth factors and active metabolites means that their applied use can have a positive influence in clinical situations requiring rapid healing and tissue regeneration. PRP is a minimally invasive method to obtain a concentrate of platelets and therefore autologous growth factors and many other bioactive molecules, and their administration in the form of

platelet gel might be a further advantage by providing an adhesive support that can confine their secretion to the chosen site [2].

PRP is defined as a blood derivate, generated by differential centrifugation of autologous whole blood, with a higher concentration of platelets compared with baseline blood. More specific elements of PRP have not been uniformly defined in the literature. In fact, a commonly accepted PRP concentration should be approximately 400% of the peripheral blood PLT count, and a clinically

valuable PRP typically should contain 1 million platelets or more per microlitre [61, 62]. However, in the literature, PRP concentrations have been reported to range widely [21], and the clinical efficacy of PRP has been demonstrated [21, 84] even with a less concentrated preparation.

The various preparation methods and the different platelet concentrations obtained, as well as other variables, such as activation modalities and presence of white blood cells within the platelet concentrate and many other aspects, are confounding factors when comparing the results obtained in different studies and complicate the research in this field, both in preclinical studies and in the evaluation of the effectiveness of this approach in humans for the treatment of musculoskeletal injuries.

### PRP for the treatment of tendon lesions

Tendon pathologies are a troublesome condition that affects a high number of athletes in every kind of sport. Pain and limited function often become a chronic problem, which can hinder performance and even contribute to athletes deciding to quit their career [76]. Currently, the treatments available offer mostly a partial recovery with unpredictable results, and both athletes and physicians have high expectations from this innovative biological approach. In fact, growth factors derived from platelets are already applied for the treatment of this tissue to improve and accelerate healing and recovery, and the majority of studies in this field involve preclinical and clinical applications on tendons.

Basic science studies have shown that healing tendon is responsive to the local application of growth factors and describe the role of many of the growth factors contained in the platelet alpha granules in tendon regeneration [18, 46]. TGF- $\beta$  increases the expression of procollagen types I and III and mechanical properties. PDGF-BB, IGF-1, VEGF and B-FGF promote tendon cell proliferation and tendon healing [7, 44, 66]. Releasate from PRP has been seen to stimulate the gene expression of the matrix molecules and tendon cell proliferation and promote the synthesis of angiogenic and other growth factors [3, 5, 25, 86, 88], and also activate circulation-derived cells, that also play an important role in the tissue healing process [42].

Animal studies have shown the usefulness of platelet concentrate for the treatment of tendon lesions. Aspenberg and Virchenko reported greater maturation in tendon callus and an increased force to failure and ultimate stress [8, 95], underlining an interplay between early regeneration and mechanical stimulation. In recent studies, Lyras et al. described the PRP-induced over-expression of IGF-1 and confirmed the improvement in mechanical properties in rabbit patellar tendon after resecting its central portion

[55, 56]. Histological examination showed a superior healing process, and the study of angiogenesis showed an increased neovascularization during the first phase, thus suggesting the enhanced and accelerated tendon healing process [57, 58]. The good results obtained in the first healing phase were confirmed in a bigger animal model at a longer follow-up. Bosch et al. reported the effect of a single intratendinous PRP treatment on surgically produced lesions in horses: after 24 weeks increased mechanical properties, better histological organization and an increased metabolic activity were found [13].

The first reports in humans are controversial. Some studies focused on the role of PRP application in surgery. Sanchez et al. [84] found a more rapid recovery in athletes undergoing PRP-enhanced Achilles tendon repair. The PRP-treatment group presented an earlier recovery of ROM and a faster return to jogging and sport, besides no wound complications and a lower Achilles cross-sectional area. Other authors suggest a possible role of PRP in improving results in patients undergoing arthroscopic rotator cuff repair. Maniscalco et al. reported a case of rotator cuff lesion where a membrane of autologous suturable fibrine with a high platelet concentration was used to close a 10-mm tear. Clinical examination after 6 months showed pain relief and ROM improvement, and the MRI evaluation showed the complete integrity of the cuff [59]. Randelli et al. evaluated the safety and results of PRP-augmented rotator cuff repair in a pilot study on 14 patients, with promising stable results at 24-month follow-up [80].

Another less invasive application of PRP is under investigation, which evaluates its role in promoting the healing process in chronic tendinopathies through intratendinous injections. Mishra et al. [64] reported good results for the treatment of chronic severe elbow tendinosis. These promising results were confirmed by a recent double-blind, randomized controlled trial (RCT). Peerbooms et al. found that one PRP injection exceeds the effect of corticosteroid injections at 1-year follow-up [75]. In another recently published study, Kon et al. [48] described preliminary results with multiple PRP injections for the treatment of patellar tendinopathy and reported the safety and promising results underlying the need for concomitant rehabilitative treatment to apply a synergic biological and mechanical stimulation [95]. A further analysis confirmed the contribution of PRP to the healing process. Filardo et al. treated 15 patients affected by chronic jumper's knee, who had failed previous non-surgical or surgical treatments, with multiple PRP injections, and most of the patients improved markedly and returned to previous activities [30].

Multiple PRP injections have also been used for the treatment of acute partial rupture of the Achilles tendon in an athlete: the fast tissue repair, documented by magnetic

resonance and ultrasound imaging, allowed a swift return to full functionality and competitive sports activity [31]. Contrasting findings have been shown in case of chronic Achilles tendinopathy. De Vos et al. [26] performed a randomized trial comparing 27 patients treated with one PRP injection with patients treated with saline injections and found no difference in pain and activity improvement at 6-month follow-up. However, these results do not clearly demonstrate the uselessness of this PRP application: the average age of the patients was high, and older patients may respond less to platelet GF stimulus; the tendinopathies treated were mostly moderate, whereas severe recalcitrant tendinopathies were not evaluated; saline injections can affect the tissue by needle stimulation, and together with eccentric exercise contribute to confusing the results in the small group of patients evaluated; the follow-up was limited to 6 months, and only one injection was performed, whereas other studies obtained positive results with multiple applications. In fact, whereas good results have been obtained treating elbow tendinosis with one injection [26], in case of other locations a higher number could be needed, as previously reported for patellar tendinopathy [30, 48]. However, at the time being, there is a lack of scientific background to determine the proper number of injections required, and the clinical application protocol is based on the authors' personal experience, rather than evidence based.

Many aspects still need to be studied to define the optimal formulation, the proper dosage and timing of application, and to determine which patients, type of tendinopathy and phase of pathology may be better responder. Despite all of the factors to be clarified and the lack of scientific commonly accepted proof of its clinical efficacy, PRP is currently widely used for the treatment of tendinopathy. Several clinical and surgical trials are ongoing worldwide to support the preliminary data [65].

### **PRP for the treatment of ligament lesions**

The knee undergoes great forces during physical activity, due to its anatomical location; thus, it is not surprising that this joint is the most common site for a sport-related lesion, accounting for 15–30% of these injuries, many of them severe with ligament ruptures. Anterior cruciate ligament (ACL) lesions usually require surgical treatment and long-term rehabilitation and may result in functional impairment and permanent disability, as well as osteoarthritis in later life [74].

The material properties of a tendon autograft deteriorate during the remodelling phase after ACL reconstruction and are not completely restored even 12 months after surgery [16, 20]. Therefore, preventing graft deterioration after

ligament reconstruction or accelerating the restoration of the deteriorated graft is one of the goals of the new biological therapy approach. A series of studies on in situ frozen–thawed ligament in rabbits and ACL reconstruction with the autogenous bone–patellar tendon–bone graft in dogs have recently shown that a combined administration of TGF- $\beta$ 1 and EGF inhibits the deterioration of the grafts mechanical properties [9, 81, 100], whereas Nagumo et al. confirmed the TGF- $\beta$ 1 effect, but found that an application of EGF or PDGF-BB alone did not significantly affect the deterioration process [71].

Other studies focused on PRP supplementation. Murray et al. failed to show an improvement in the maximum tensile load or linear stiffness of the ACL repairs using PRP alone in a pig model, but he showed an improvement in the histological and biomechanical properties of the ACL when a scaffold of collagen-PRP hydrogel was used in both porcine and canine models [67–70]. Some preliminary findings suggest a potential effect of PRP on intraligamentous regeneration in humans. In an MRI study, Radice et al. recently demonstrated a 48% reduction in the time required to achieve a complete homogeneous graft signal when PRP was used for surgical ACL augmentation [79].

Another challenge in ACL reconstruction is to achieve secure graft attachment to allow early range of motion and return to activity. One of the most commonly used grafts is the autologous bone–patellar tendon–bone graft, which offers the strongest healing potential because it relies mainly on bone-to-bone integration. In this context, the use of PRP to enhance the graft attachment is to be considered with caution, because of the not clear usefulness of PRP on bone graft integration. In fact, the effects of PRP on osteointegration are controversial, and some studies have even showed a negative effect on bone healing and regeneration [6, 96]. Due to donor-site morbidity problems related to this technique, some surgeons prefer alternative graft sources, and the use of hamstring tendons has been increasing. Although autologous hamstring grafts have less donor-site morbidity, they rely solely on tendon-to-bone healing. This process occurs slowly, thus leading to concerns about potential graft failure and joint instability. The use of GFs has been advocated to accelerate the integration process. Orrego et al. [73] showed an enhancing effect on the graft maturation process as evaluated by MRI signal intensity, but no significant effect of the platelet concentrate on the osteoligamentous interface or tunnel widening evolution was observed. Similarly, Silva et al. [91] used PRP after hamstring ACL reconstruction, but knee MRI performed after 3 months failed to show an acceleration of tendon-to-bone integration. However, some limitations, such as the low number of patients for each group and the possible insufficient sensitivity of MRI in detecting small

changes in the fibrous interzone, decrease the relevance of the results obtained in this study that have to be confirmed in wider studies.

Expression of growth factors, such as PDGF, TGF- $\beta$ 1 and B-FGF, has also been shown to be actively involved during the early stage of medial collateral ligament (MCL) healing, as well as in the ACL [49, 98]. MCL lesions are also a common knee ligament injury and have a high impact in the active population [52]. Despite the current treatments, radiographs have shown early signs of osteoarthritis in 13% of patients [54]. A method to accelerate and improve the healing of this ligament is therefore desirable to reduce recovery time, increase patient compliance with a shorter rehabilitation, increase the stability of the knee and reduce post-injury osteoarthritis. Unfortunately, clinical applications of the biological approach to favour MCL healing are not documented, and this treatment has not clearly proven to be effective even in animal models. Hildebrand et al. [40] reported improved ultimate load to failure, energy absorbed to failure and ultimate elongation values after using PDGF on ruptured rabbit MCL. In a further study, Letson et al. [51] showed a 73% improvement in ligament strength at only 12 days. Batten et al. [11] reported promising results of PDGF for healing ligaments if administered in appropriate doses soon after injury. Conversely, Spindler et al. [92, 93] showed that one-time dose administration of PDGF and TGF- $\beta$ 2 combination did not result in changes in any of the mechanical properties of the healed MCL in rabbit, whereas in another study he even demonstrated a decrease in the maximum load and energy absorbed to failure with chronic administration of TGF- $\beta$ . In general, experimental studies in animal models show a potential with the use of growth factors for ligament healing, but at the same time underline the profound implications on the results of the time, dose and method of growth factor administration.

The paucity of clinical evidence and the controversial animal studies suggest that the administration of growth factors carried in platelets should be performed with caution on humans and under strict observation in high-level trials to clarify the safety and efficacy of their application.

### PRP for the treatment of cartilage lesions

The incidence of articular cartilage pathology has grown due to the marked increase in sports participation and greater emphasis on physical activity in all age groups [22, 97]. The regeneration capacity of cartilage is limited [14, 15], and articular cartilage lesions represent a challenging problem for orthopaedic surgeons. In fact, most of the available treatments have controversial and unproven efficacy; often they may only offer temporary clinical relief

and functional improvement, and when they fail, the surgical approach is often unavoidable. Many surgical options have been proposed to treat chondral articular lesions: from the classic reparative techniques to the more recent and ambitious regenerative techniques. There is no agreement in the literature about the effective superiority of one technique over the others. However, most of these techniques have been proven to offer a satisfactory clinical outcome. Unfortunately, in case of athletes, other factors have to be taken into consideration. The marked clinical improvement is not always sufficient for highly demanding patients to return to their previous activity level, a decrease in results is often observed over time, and in every case, surgical cartilage treatments require a long postoperative phase, with a slow return to competition.

The search for a less invasive solution to improve the status of the chondral surface and allow a fast return to full activity is therefore highly desirable, especially for this kind of patient.

Current knowledge on the role of growth factors in determining the behaviour of chondrocytes is rapidly increasing, and many growth factors have been already identified to take part in the regulation of articular cartilage. TGF- $\beta$  increases chondrocyte phenotype expression, chondrogenic differentiation of MSCs, matrix deposition, decreases in the suppressive effects of inflammatory mediators IL 1 on proteoglycan synthesis in cartilage [34, 78], PDGF plays an important role in the maintenance of hyaline-like chondrogenic phenotype, increases chondrocyte proliferation and upregulates proteoglycan synthesis [87], IGF stimulates proteoglycan synthesis and slows their catabolism [60] and many other growth factors, such as FGF and HGF, are related to cartilage regeneration and metabolism with chondroinductive properties, independently or even more with additive effects and synergistic interaction [72].

All these factors are contained in platelet alpha granules, and the use of intra-articular injections of platelet concentrate might therefore represent a solution to promote cartilage healing. However, despite their wide clinical application and many trials ongoing worldwide, currently there is only scarce scientific evidence of the efficacy of PRP. Some studies on blood-derived growth factors have shown interesting preclinical results and a promising clinical outcome after the treatment of cartilage lesions in humans. Frisbie et al. [36] reported an improvement in lameness and a decrease in cartilage fibrillation and synovial membrane hyperplasia and haemorrhage after the administration of autologous conditioned serum (ACS) in horses with experimentally induced osteoarthritis. Gaissmaier et al. [37] investigated the effect of human platelet supernatant on chondrocytes in human articular biopsies and observed an acceleration of chondrocyte

expansion. Mishra described how PRP enhanced MSC proliferation and chondrogenic differentiation *in vitro* [65]. Baltzer et al. [10] recently showed the effectiveness of the treatment of cartilage degeneration through multiple injections of ACS in a randomized study in humans and an even higher effect in comparison with hyaluronan injections.

Regarding the use of PRP in humans, Sánchez et al. [85] published a case report where plasma rich in growth factors was used to treat an articular cartilage avulsion in a soccer player and achieved an accelerated and complete articular cartilage healing, with rapid resumption of symptom-free athletic activity. Subsequently, they applied platelet concentrate injections for knee osteoarthritis (OA) using hyaluronan injections as a control and showed better pain control and physical function improvement [83]. More recently, Kon et al. [47] published a pilot study of 100 patients treated with intra-articular PRP injections with evidence of safety, pain reduction and improved function. Only minor adverse events were detected such as a mild pain reaction and effusion after the injections, which persisted for not more than 2 days. In the 91 patients (115 knees), who completed the treatment and were available for the 2, 6 and 12-month follow-up, a statistically significant improvement was observed in all of the parameters evaluated. A tendency to worsen was observed at 1-year follow-up. The evaluation performed at 2-year follow-up confirmed the same trend with an overall worsening of the results obtained and showed a median duration of the beneficial effect of 9 months. However, a high range of effect persistency was observed. In fact, a greater and longer effect was found in young men, with a low BMI and a low degree of cartilage degeneration, whereas other patients presented less durable results [29].

However, despite this interesting finding, to our knowledge, no well-designed high-level studies have been reported in the literature to support the efficacy of intra-articular PRP injections, and the potential of this approach for the treatment of cartilage lesions still needs to be confirmed with large randomized trials.

### PRP for the treatment of muscle lesions

Muscular injuries, caused by contusion or strain, are common and disabling lesions, mainly occurring in competitive sports involving contact, sprinting, jumping and acceleration activities, and may account for the majority of missed days of practice in the elite athlete [33]. Despite the significance of this kind of lesion, the mainstay of treatment is mainly non-operative, thus allowing the body's native reparative function to heal: common recommendations are assistive modalities such as rest from activities, the application of ice, compressive dressing and elevation

of the injured limb [65]. PRP contains many of the bioactive proteins observed in the healing muscle tissue and has been therefore suggested as potential treatment to accelerate the healing process with an enhanced tissue quality.

Myogenesis is not restricted to prenatal development but also occurs in regenerating muscle after some injuries, and several growth factors have been suggested to be key regulators of muscle regeneration and myogenesis. B-FGF, IGF-1 and nerve growth factors have been identified as substances capable of enhancing muscle regeneration and improving muscle force in the strained injured muscle [43]. B-FGF and IGF-1 are potent stimulators of the proliferation and fusion of myoblasts, and *in vivo* mice treated muscles showed improved healing and significantly increased fast-twitch and tetanus strengths [63]. B-FGF, as well as VEGF and exercises, also increased local angiogenesis in healing rat gastrocnemius muscle [27, 28]. HGF is able to activate quiescent satellite cells, whereas TGF- $\beta$ 1 has a major influence on the reorganization of the extracellular matrix and supports other growth factors, specifically PDGF, stimulating satellite cell activation [39, 41]. The neutralization of B-FGF, IGF-1 and TGF- $\beta$ 1 in mouse muscle injury resulted in an attenuation of the healing response, thus showing the important role of these factors in promoting the healing process [50].

Wright-Carpenter et al. [99] used a gastrocnemius contusion model in mice to evaluate the role of the GFs released from ACS to support muscle healing: an accelerated satellite cell activation and an increased diameter of the regenerating fibres were found. Recently, Hammond et al. [39] applied PRP to a multiply loaded, eccentric muscle injury model in rats and obtained a significantly decreased full recovery time.

Despite these preclinical findings and preliminary promising results in humans [21, 33, 65], with an accelerated recovery in athletes and no excessive fibrosis, many aspects still need to be clarified, such as how, when and which dose. Intra-lesional injections appear to be the most reasonable approach, in order to directly stimulate the damaged site, but the proper timing of application is still unclear. The knowledge of the time-dependent processes occurring after muscle injury allows some speculations. Muscle injuries undergo a distinct set of overlapping healing phases [77]. Together with the trauma-induced myofibres degeneration, capillary rupture results in a hematoma that fills the gap with the elements responsible for the subsequent phases. Cytokines and GFs released start the inflammatory phase since the first day, and then the regenerative process during the first week post-injury. At the same time, the necrotic muscle gap begins to be replaced by a fibrotic tissue, which provides early support for myofibres, but as it becomes increasingly dense over

the course of 7–14 days, it restricts the myofibres regeneration [77]. Therefore, the platelet concentrate should be administered in this time frame in order to modulate the inflammation phase and support the regeneration processes before the development of the scar tissue. Regarding the PRP dose to be applied, it has to be underlined that there are some concerns about the application of the high concentration of GFs contained in PRP. In fact, fibrosis development has been suspected because of the involvement of high TGF- $\beta$ 1 level. TGF- $\beta$ 1 functions synergistically with PGE2 to balance the fibrosis level in the muscle healing process, [90] and the increase in TGF- $\beta$ 1 levels after PRP injection might be deleterious by inducing a fibrotic muscle healing [17].

Clinical use should therefore be performed with caution in robust scientifically controlled trials because, while preliminary findings are promising, there is a lack of literature supporting PRP safety and potential in modulating the healing of muscular injuries in human. The difficulties in this field are further increased by the introduction of this use of PRP to the WADA Prohibited List, prohibiting its use via intramuscular injection and restricting its applicability only for non-elite sports patients.

## Discussion

Since the introduction of platelet concentrates as topical adjuvant therapy to treat chronic leg ulcers in the late 1980 [45], the use of platelet products has been extended to many fields of medicine, with the aim of promoting the healing of various pathologies in numerous kinds of tissues. The attractive possibility of using patients' own growth factors to enhance reparative processes in tissues with low healing potential, the promising preliminary clinical findings and the safety of these methods, explain the wide use of this biological approach.

In fact, PRP and other blood derivatives, used alone or in combination with biomaterials, are under investigation in preclinical studies or even already used in clinical practice. Fields of application include dermatology, ophthalmology, dentistry, and cosmetic, plastic and maxillo-facial surgery [86]. In recent years, they have also been used to treat many pathologies in orthopaedics. PRP has been used to promote the healing of bone defects and non-unions, bone fractures, laminectomy, spinal fusion, joint arthroplasty and bone implant osteointegration [23, 30, 38, 86]. More recently, PRP injections have emerged as a fashionable non-invasive treatment also in sports medicine, where it is applied to treat acute or chronic tendinopathy, ligamentous or muscular injuries and cartilaginous disease.

Despite the wide use of these products, research into their clinical efficiency is still in its infancy, and only a

few, not well-designed, studies report some preliminary results. In particular, an analysis of the literature on the treatment of musculoskeletal injuries reveals a lack of evidence to support the use of PRP. Some interesting promising findings have been obtained, especially in pre-clinical studies, but in most cases results are still preliminary and controversial.

The complex regulation of growth factors in tissue balance and regeneration is still partial, and mechanisms of action of the growth factors administered with platelets are far from being fully understood. The difficulty in this field of research is further increased by the numerous products used, which makes it difficult to compare results obtained in different studies.

As previously reported, there is no accepted definition of PRP. The concentrations provided by most of the procedures range widely, commonly from 4 to 8 times the concentration of platelets found in whole blood, and good results have been reported also with the use of lower concentrations. The number of platelets and their concentration applied to the lesion site are important factors. In fact, the dose of growth factors delivered is a delicate aspect to consider when analysing the results obtained. For example, Weibrich et al. [96] found an advantageous biological effect on bone regeneration in rabbits with a platelet concentration of approximately 1,000,000/ $\mu$ l, but no effect at lower concentrations, whereas the use of highly concentrated PLT preparations appeared to have paradoxically inhibitory effects, maybe ascribable to an inhibitory and cytotoxic effects of GFs at too high concentrations. Surely, GFs are potent molecules, and small variations in their concentrations can produce very different effects. Besides the appropriate dose, timing and length of intervention are areas requiring further investigation. The complex process of tissue healing, up to now only partially understood, should always be considered to coordinate the temporal presence of cells and signalling molecules appropriately [11].

Other factors are not of secondary importance when evaluating PRP properties and the results obtained with its application. Another debated aspect regards cellularity: in fact, not only platelets but also leucocytes, monocytes, macrophages and mast cells are contained in platelet concentrates. Some authors define PRP as only platelets and attribute better results to leucocyte depletion, because of the deleterious effects of proteases and reactive oxygen released from white cells; others consider them as a source of important cytokines and enzymes, which may be important also for the prevention of infections, and report that PRP significantly inhibits the growth of *Staphylococcus aureus* and *Escherichia coli* [35, 65].

The activation method of PRP is also controversial. Thrombin and calcium have historically been used to activate platelets, but other methods have been recently



chosen by other authors [4, 19], using different factors or calcium chloride alone as a clot activator, considering that calcium chloride has shown to be able to promote the formation of thrombin directly “in situ”, mimicking the physiological clotting process and enabling the release of growth factors. The activation method may influence the results. In fact, the amount and speed of GF release and activation may differ, and the molecules used may also influence the tissue with other mechanisms [12].

Finally, also factors specifically related to the tissue involved and the type and phase of the pathology may influence the results. There is increasing awareness that the microenvironment at the lesion site strongly influences the success of any biological therapeutic approach. In orthopaedics and sports medicine, another factor also plays an important role and has to be considered. The mechanical stimulus, due to normal tissue function or associated physiotherapies, may modify the microenvironment influencing cellular differentiation and tissue repair independently of the presence of stimulatory GFs [24] and may act synergically with the biological treatment in the healing process of musculoskeletal tissues [95].

In this landscape, the analysis of the mechanism of action and efficacy of PRP appears complicated by numerous factors, which play an important role and may bias the results obtained. Basic science studies have already shown the complex role of numerous growth factors in development, maintenance and repair of musculoskeletal tissues, and there is general agreement on the fact that GFs are a promising therapy for tissue regeneration if correctly administered. Although further preclinical studies may help in understanding the mechanism by which PRP affects tissue repair, they cannot obviate the practical difficulty of designing a multiple GF treatment in humans. In fact, animals are kept under carefully controlled conditions, and animal models provide important knowledge to develop more effective treatments, but intra-species and inter-species variability and several other conditions make still results difficult to interpret and compare.

Therefore, well-designed human studies are essential to demonstrate clearly the efficacy of PRP in humans. Unfortunately, the awareness of the potential of this biological approach, as well as its safety, reduced invasiveness and low costs, have led to a wide and indiscriminate use of blood-derived products in clinical practice, especially in sports medicine, where the speed of recovery and return to competition is even more important. Up to now, the literature contains only a limited number of studies on the effects of platelet-derived growth factors in humans. Some studies provide interesting results on the treatment of musculoskeletal injuries, especially for tendon lesions, but they are mainly case series or less robust trials, which need to be confirmed by further studies. PRP is an innovative

promising treatment approach, but wide randomized well-designed studies are still needed to improve preparation methods and treatment modalities and clarify its real potential. Waiting for more robust evidence to support its use for the treatment of musculoskeletal injuries, the clinical applications of platelet-derived growth factors should be limited to well-controlled trials.

## Conclusion

Current research aims to develop innovative approaches for the treatment of musculoskeletal tissues to accelerate healing with improved tissue quality and allow athletes to recover fully and return early to competition. PRP is a vehicle to provide numerous growth factors needed to promote the healing process and has been widely tested. The literature contains controversial preclinical studies and a few reports on applications for sports-related injuries in humans. Interesting findings underline a possible role of PRP in the treatment of musculoskeletal injuries, especially for tendon pathology, whereas for other tissues clinical evidence is still minimal. High-quality studies are required to confirm these preliminary results and provide scientific evidence to support its use.

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