45 The Role of Orthobiologics in the Management of Tendon and Fascia Injuries in Sports

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45.1 Introduction

Orthobiologics have emerged as a promising treatment modality, seeking to enhance musculoskeletal regeneration and repair. This overarching term comprises many developing treatments, including isolated growth factors, platelet-rich plasma (PRP), cell-based therapies, and scaffolds. Preclinical studies and initial enthusiasm have resulted in substantial research efforts. Preliminary results of these efforts suggest improved function, decreased pain, and early return to play in several different soft tissue injuries; however, true reproducible soft tissue regeneration has not been demonstrated [1, 2].

As in all athletes, tendon and fascia injuries are very prevalent in basketball players. Common tendon and fascia injuries in athletes will be addressed in this chapter including patellar tendinopathy, Achilles tendinopathy, Achilles tendon rupture, plantar fasciitis, and rotator cuff pathology. The optimal treatment for soft tissue injuries is under debate, but most can be managed with conservative measures, including rest, icing, physical therapy, and analgesics for symptomatic relief. While these treatments are often effective, there is increasing interest in the role of orthobiologics in promoting healing, reducing pain, and enabling early return to play [3]. This chapter will relay the most current evidence regarding the efficacy of different orthobiologics for the treatment of tendon injuries in athletes [1].

45.2 Orthobiologics

45.2.1 Corticosteroids

Corticosteroids have long been used as anti-inflammatory agents in the treatment of soft tissue injuries in athletes. Corticosteroids can be given intravenously or orally for a systemic effect or injected (intra-muscular, intra-articular, intra-bursal, intra-tendinous, or peritendinous) for a more local effect. Either way, corticosteroids are well known for their ability to induce symptomatic relief.

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Corticosteroids decrease leukotrienes, prostaglandins, thromboxane A2, and prostacyclin, as well as by stabilize lysosomal membranes of inflammatory cells, decreasing vascular permeability, altering neutrophil chemotaxis and function. They also possess the ability to cross cell membranes and influence RNA transcription and subsequent protein production [4, 5].

Several clinical studies have reported improved outcomes with corticosteroids injections for soft tissue injuries in athletes. Levine et al. have reported improved return to play following corticosteroids and anesthetic injection for severe hamstring injuries in 58 National Football League (NFL) players. They have also reported no complications related to the injection [6]. Stahl et al. performed a prospective, randomized, double-blinded study to assess the effect of methylprednisolone on medial epicondylitis. They have reported short-term improvement in symptoms at 6 weeks follow-up in the experimental group; however, later follow-ups did not differ with regard to pain [7]. For the treatment of Achilles tendinopathy, corticosteroids have shown no benefit when compared to nonsteroidal anti-inflammatory drugs (NSAIDs) [8].

The use of corticosteroids should be carefully considered due to its significant side effects. There are several potential reported systemic side effects of corticosteroids including, but not limited to, diabetes, weight gain, hypertension, and psychosis when used systemically. Local injections in high concentrations may also confer systemic side effects, as well as local side effects [5]. Nichols performed a meta-analysis reporting on the complications associated with the use of corticosteroids in the treatment of athletic injuries. He reported local side effects including tendon weakening and rupture, postinjection pain flares, subcutaneous fat atrophy, and skin hypopigmentation. As for specific rates for tendon ruptures, he reported plantar fascia rupture to be the most common (53.7%), quadriceps/patellar tendon rupture rates were 9.5%, Achilles tendon rupture rates were 8.4%, and biceps tendon rupture rates were as high as 8.4% as well [9].

Fact Box

The use of corticosteroids should be carefully considered, mainly due to its significant side effects, which includes significant rates of tendon rupture, muscle weakness, and atrophy. However, in select cases their use is applicable and has shown favorable results.

45.2.2 Platelet-Rich Plasma (PRP)

The use of PRP for the management of soft tissue injuries has become increasingly common over the last decade [10, 11]. This is probably due to its potential benefits including its safety, efficient delivery of growth factors, and proteins that might modify acute and chronic pathology, and the potential for expedited recovery from soft tissue injuries used in isolation or as adjunctive treatment [11].

PRP is created by the process of centrifugation of a patient's own blood to produce small-volume plasma with high platelet concentration. Platelets contain an abundance of growth factors (transforming growth factor [TGF]-b1, platelet-derived growth factor, basic fibroblast growth factor, vascular endothelial growth factor, epidermal growth factor, insulin-like growth factor [IGF]-1), which may modify the inflammatory response and impact cell differentiation and proliferation [12–14]. Previous literature has defined PRP as any plasma volume with a platelet concentration above baseline [15]. However, recent literature supports defining PRP as a volume of plasma that has a platelet count of over one million platelets per milliliter (mL) [16, 17]. PRP with a platelet concentration above this proposed cutoff is thought to have a clinically significant impact on tissue healing [17, 18]. However, other authors reported that increased platelet concentration beyond the physiologic level did not improve functional graft healing in an anterior cruciate ligament (ACL) [19] and medial collateral ligament (MCL) animal models [20]. More recent studies are aiming to define optimal concentrations to

be used to induce healing according to the specific injured tissue [21–23].

Preparation protocols vary between the many available commercial PRP systems. Generally, blood is drawn from the patient and is mixed with an anticoagulant. Subsequently, a 1- or 2-step centrifugation separates the red blood cells, platelet-poor plasma, and the "buffy-coat". The buffy-coat which contains the highly concentrated platelets and leukocytes and the plasma is then isolated for a second centrifugation (when a manual system is utilized). Prior to the injection, some commercial systems recommend "activation" of the platelets using thrombin or calcium chloride, in order to induce platelet degranulation and release of growth and differentiation factors [24]. A recent analysis of the reporting of PRP processing for musculoskeletal conditions (105 studies) showed that only 11.5% of studies reported on all necessary variables of PRP processing required to repeat the protocol [25]. Moreover, there was no consensus in the machines to be used to prepare the PRP (manual or automatic), number of spins, speed, and time of centrifugation. Automated commercial systems and manual processing methods are used to minimally manipulate desired blood fractions to concentrate LR-PRP and LP-PRP but have been found to produce product variations in blood cell and growth factor concentrations [26–30]. In this regard, both systems can produce similar results when performed correctly [31].

PRP can further be stratified to leukocyte (neutrophil)-rich PRP (LR-PRP) and leukocyte-poor PRP (LP-PRP) according to the white blood cell concentration. It has been suggested that LR-PRP can produce pro-inflammatory effects by induction of interleukin-1β (IL-1β), tumor necrosis factor (TNF)-α, and metalloproteinases, which may adversely affect tissue healing [32–35]. Recent two case series by Hanisch et al. have found no significant difference in effect between LR-PRP and LP-PRP for Achilles tendinopathy [36]. Many variables contribute to the preparation of what is broadly named PRP, thus the discovery of the optimal preparation method for each unique type of patient, tissue, and injury remains elusive.

Fact Box

The World Anti-Doping Agency (WADA) does not prohibit PRP use generally; however, use of independent growth factors (such as PDGF, VEGF, IGF-1, and FGF) is prohibited. Stem-cell-based therapies may or may not be prohibited, depending on how the cellular material is manipulated or modified for use [37].

45.2.3 Cell-Based Therapies

The rationale for use of mesenchymal stem cells (MSC) is the potential to improve symptoms and possibly augment healing of tissues that have relatively poor intrinsic healing ability such as cartilage, muscle, tendon, ligament, meniscus, and soft tissue to bone interfaces. Although preclinical studies suggest promising potential for MSC to enhance tissue healing, there is limited clinical data to support the use of MSC for the management of musculoskeletal pathologies. These mostly unsubstantiated therapies are being aggressively marketed directly to athletes, with unproven claims regarding their efficacy on outcomes and early return to play.

45.2.3.1 Bone Marrow Aspirate Concentrate (BMAC)

As one of the few techniques approved by the United States Food and Drug Administration (FDA) for the delivery of stem cells, bone marrow aspirate concentration (BMAC) has gained popularity in recent years [38]. Aside from progenitor cells, BMAC is reported to contain an abundance of growth factors and cytokines [33, 39, 40]. All together the contents of BMAC are thought to promote neogenesis, tissue regeneration, immunomodulatory, and anti-inflammatory effects [38, 41].

Bone marrow aspirate is usually performed by percutaneous aspiration of trabecular bone of the iliac crest due to the ease of procurement, relatively low donor site morbidity and a high concentration of progenitor cells [42] (Fig. 45.1). Using a small syringe and multiple aspirations at

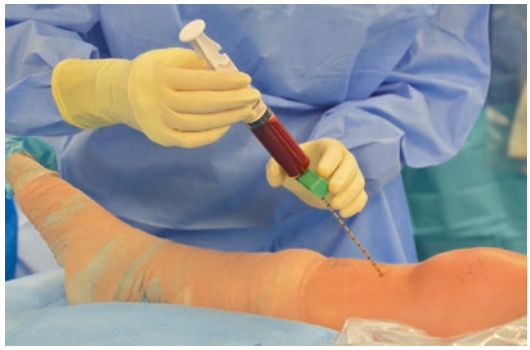

Fig. 45.1 Bone marrow aspiration from proximal tibia

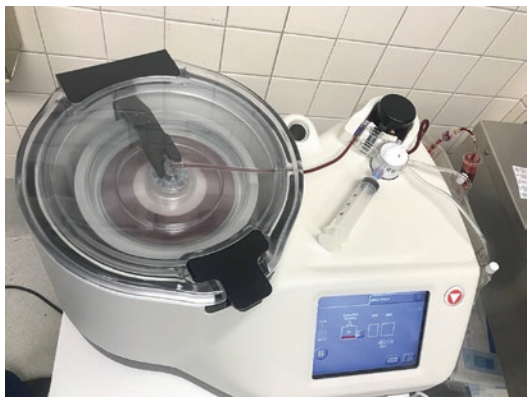

Fig. 45.2 Bone marrow aspiration centrifugation

different locations have been reported to increase progenitor cells concentration [43]. The bone marrow aspirate is then centrifuged in order to separate the mesenchymal stem cells (MSC) [44, 45] (Fig. 45.2). MSC concentration following centrifugation is still relatively low and is estimated to be around 0.001–0.01% [45]. Moreover, the true number of viable MSC that are actually delivered into the lesion is unknown, regardless of the tissue used to procure the cells. To increase the number of MSC, the cells are to be transferred to a lab and undergo cell isolation and culture expansion. However, such laboratory processing of cell preparations is prohibited in the United States, by the Food and Drug Administration (FDA).

Many preclinical and clinical studies have supported the use of BMAC, mainly for the treatment of cartilaginous and articular pathologies (e.g., meniscal injuries) [46–51]; however, there is a paucity of studies supporting the use of BMAC for the treatment of soft tissue injuries.

45.2.3.2 Other Cell-Based Therapies

MSC were first discovered in bone marrow; however, later studies revealed their presence in fetal tissue (umbilical cord and placenta), as well as in adult tissue (adipose tissue, periosteum, blood vessels, synovium, endometrium, dermis, and more) [52–54].

Commonly used MSC sources are autologous adipose tissue and allogenic amniotic tissue. Amniotic tissue contains higher concentrations of MSC when compared to the aforementioned BMAC, with concentrates of 0.9–1.5% [55]. Advantages for the use of amniotic stem cells are high plasticity and pluripotency of the cells, low immunogenicity, high capability to differentiate to major cell lineages, and the lack of donor site morbidity [55]. Adipose tissue is also a common source of MSC due to the abundance of MSC in adipose tissue and the relative ease of access and harvesting of adipose tissue. Adipose MSC are autologous and therefore also raise less ethical concerns [56].

Preclinical studies have supported the use of MSC for various applications. Most preclinical studies have concentrated on the effect of MSC in the treatment of articular cartilage pathology and bone healing [57–63]. Although the use of MSC for the treatment of soft tissue pathology has not been studied extensively, several preclinical studies have assessed the efficacy of MSC in rotator cuff pathology, with conflicting results. Gullota et al. and Yokoya et al. have reported that MSC promote healing of the rotator cuff in rat and rabbit models, respectively [64, 65]. Other studies by Gullota et al. and Chen et al. have raised doubts regarding the ability of MSC to improve rotator cuff healing when used in isolation [66–68]. A recent study by Ma et al. has shown potential benefit of human placenta-derived cells in patellar tendon injury in rats [69]. Many more clinical studies are in progress however to date, there is no high-quality evidence to support the use of MSC in the treatment of soft tissue injuries [70, 71].

Due to the exponential growth in cell-based treatments worldwide without standardization

and transparency, an international expert consensus proposed the DOSES tool for describing cell therapies, which was aimed to allow for better assessment and comparison of different treatments and techniques in the future [70]. This is of critical importance as lack of standardization and rigorous protocols may expose the athlete to serious adverse side effects and complications, including severe infections.

Cell-based therapies have an immense potential to improve management of soft tissue injuries in the athlete. However, more research is required to optimize the treatment protocol for each type of injury in regard to preparation techniques, dosing, delivery, and rehabilitation. Future research efforts should define the best indications and applications for biologic therapies in a way that maximizes both the benefit and the safety of the athlete.

45.3 Soft Tissue Injuries: Tendons and Fascia

The use of orthobiologics for tendon and fascia pathologies is less frequently studied compared to bone and cartilage pathologies [72]. Determining the optimal protocol for the treatment of tendon pathology should begin with differentiating acute tears from chronic degenerative and overuse tendinopathy or tendinosis. While in acute tears the goal may be to increase cellular proliferation and promote/enhance healing, in chronic tendinopathy the goal may more likely be to target the inhibition of matrix-degrading proteases and inflammatory mediators and possibly "jump-start" a healing response. Other considerations include the specific tendon involved, the location within the tendon (myotendinous junction, intra-tendon, or avulsion injuries), timing, and dosing [73].

45.3.1 Patellar and Quadriceps Tendinopathy

Tendinopathies of the extensor mechanism of the knee are common in both professional and amateur basketball players due to the repetitive jumping and loading subjected to the patellar and quadriceps tendons. The most common tendinopathy location of the extensor mechanism is the patellar tendon origin/proximal insertion (65–70% of the cases), followed by the quadriceps tendon insertion at the superior pole of the patella (20–25%), and the patellar tendon insertion on the tibial tuberosity (5–10%) [74]. Both patellar and quadriceps tendinopathies have been historically called "Jumper's knee" due to the high prevalence seen in athletes involved in jumping sports. Several classifications exist with regard to the severity of "jumper's knee" and are based on pain and sports performance [75, 76] and pain intensity [77] (Table 45.1). It has been reported that this injury is prevalent in up to 30% of basketball players. Lian et al. described an overall prevalence of "jumper's knee" of 14.2% in athletes in their report of 613 athletes with the highest prevalence reported in sports associated with high-impact ballistic/explosive loading of the knee extensor mechanism such as volleyball (44.6%) and basketball (31.9%) [78]. Zwerver et al. described a "jumper's knee" prevalence of 11.8% in non-elite basketball players in their report of 891 athletes [79].

Several clinical studies have supported the use of PRP injections for the management of patellar tendinopathy (Fig. 45.3). Dragoo et al. performed a randomized controlled trial comparing LR-PRP to dry needling for the management of patellar tendinopathy in 23 patients. At 12 weeks follow-up, the LR-PRP group improved significantly more than the dry needling group in regard to the Victorian Institute of Sports Assessment (VISA) score for patellar tendon (25.4 vs. 5.2 points, respectively, $p = 0.02$). At 26 weeks follow-up, both groups demonstrated a significant improvement, but there was no significant difference between the cohorts ($p = 0.66$). Of note, three patients crossed over from the dry needling group to the LR-PRP group and were excluded from the final >26 weeks analysis. Additionally, there was a between-group statistically significant age difference ($p = 0.04$); while patients in the dry needling group had a mean age of 40, patients in the LR-PRP had a mean age of 28 [80]. Vetrano et al.

Table 45.1 The different existing classifications for "Jumper's knee"

Stage/ grade	Blazina classification [75]	Ferretti classification [77]	Roels classification [76]
0		No pain	
I	Pain only following activity without functional impairment	Pain only following intense sports activity with no functional impairment	Pain at the infrapatellar or suprapatellar region following training or event
II	Pain during and following activity with satisfactory performance levels	Moderate pain during sports activity with no sports performance restriction	Pain at the beginning of activity, disappearing after warm-up and reappearing after activity completion
III	More prolonged pain during and following activity with progressively increasing difficulty in performing at a satisfactory level	Pain with slight sports performance restriction	Pain during and after activity. The patient is unable to participate in sports
IV		Pain with severe sports performance restriction	Complete rupture of the tendon
V		Pain during daily activity and inability to participate in sport at any level	

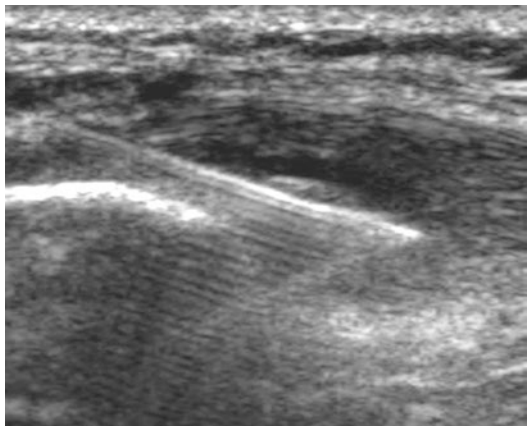

Fig. 45.3 Ultrasound-guided PRP injection for the management of patellar tendinopathy

performed a randomized controlled trial, enrolling 46 consecutive athletes with jumper's knee, and comparing between two ultrasound-guided injections of PRP (performed within 2 weeks) and three sessions of extracorporeal shock wave therapy (ESWT). Both groups significantly improved in symptoms at all follow-up assessments. At 2-months there were no significant differences between the groups in the VISA-patella, VAS, or Blazina scale scores, but, in 6- and 12-month follow-up, the PRP group showed a significantly greater improvement in all scores ($P < 0.05$ for all) [81]. Along with these randomized controlled studies, several other studies with a lower evidence level have also supported the use of PRP for the treatment of patellar tendinopathy [82–89].

However not all studies have found PRP to be beneficial in patellar tendinopathy; a recent level-I study by Scott et al. compared LR-PRP, LP-PRP, and normal saline injection in athletes with patellar tendinopathy for >6 months. They reported no significant differences in VISA-P, pain, or global rating of change among the three treatment groups at all time points [24]. Notably, this study did not indicate that PRP is ineffective, but rather it was no more effective than saline which in and of itself may have some therapeutic benefits.

Several preclinical and clinical studies involving the management of patellar tendinopathy using cell-based therapies. Ni et al. studied the use of tendon-derived stem cells (TDSC) in rat patellar tendon window defect model. They reported significantly higher ultimate stress and young's modulus of elasticity in the TDSC group and concluded that the use of TDSC had promoted earlier and better tendon repair in this rat model [90]. Pascual-Garrido et al. reported on eight patients with patellar tendinopathy where BMAC was used. A 5-year follow-up revealed significantly higher Tegner score, international

knee documentation committee (IKDC) score, and symptoms and sports subscales of the knee injury and osteoarthritis outcomes score (KOOS). They also reported that most patients said that they would have the procedure again if they had the same problem in the opposite knee [91]. Clarke et al. conducted a randomized controlled trial to compare skin-derived tenocyte-like collagen-producing cells to autologous plasma for refractory patellar tendinopathy. There was a significantly greater improvement of 8.1 points in the VISA score for patellar tendon in the cell group. Of note, one patient in the cell group had a late rupture and underwent surgery [92] (Table 45.2).

Fact Box

There is evidence to support the use of PRP injections in persistent patellar tendinopathy. Although, one recent level-I study has created doubt regarding this issue. More high-quality research will shed light on the precise indications, timing, dosing, and other relevant parameters in the athlete. Preliminary evidence suggests that cell-based therapies may play a role in the management of patellar tendinopathy.

45.3.2 Achilles Tendon Pathology

45.3.2.1 Achilles Tendinopathy

Achilles tendinopathy in the athlete can present in escalating severity, from a dull pain to a debilitating injury precluding play. Many conservative treatments have been introduced; however, management of Achilles tendinopathy remains a challenge in many athletes. A preclinical study by Solchaga et al. compared the effect of an intratendon delivery of recombinant human platelet-derived growth factor-BB (rhPDGF-BB), PRP, and corticosteroids in a rat Achilles tendinopathy model. Their results demonstrated increased stiffness and load-to-failure in the rhPDGF-BB when compared to the other groups [93].

Several prospective randomized controlled trials of LR-PRP injections for Achilles tendinopathies have failed to support its efficacy [94–96]. De Vos et al. randomized 54 patients, aged 18–70, with chronic Achilles tendinopathy to receive eccentric exercises with either an LR-PRP injection or a saline injection. They concluded that no greater improvement was observed in pain or activity level with the use of LR-PRP. DeJonge et al. performed a follow-up trial on the same patient population demonstrating similar results, including no difference in tendon appearance as viewed with ultrasonography at 1-year follow-up [97]. Similarly, a randomized controlled study performed by Krogh et al. found no improvement in Achilles VISA scores following a PRP injection when compared to a saline injection. They did, however, report a significant increase in tendon thickness in the PRP group [98].

Boesen et al. have also performed a randomized double-blinded prospective trial assessing the efficacy of PRP for the management of Achilles tendinopathy in 60 patients, aged 18–59. They compared the efficacy of eccentric exercises with either (1) a high-volume injection (HVI) of steroids, saline, and local anesthetics, (2) four PRP injections each 14 days apart, or (3) a placebo (a few drops of saline injected under the skin). Both the HVI and PRP group were found to be effective in reducing pain, improving activity level and reducing tendon thickness and vascularity [99]. Of note, these studies have not targeted the professional athlete population and perhaps may not be generalizable to this patient population. Also, for the elite athlete, reduced tendon thickness can potentially result in decreased strength and velocity, as well as harbor a risk for the dreadful Achilles tendon rupture.

There is limited evidence to support the use of cell-based therapy in Achilles tendinopathy. Usuelli et al. conducted a randomized controlled trial comparing PRP to adipose-derived stromal vascular fraction (SVF) for the management of Achilles tendinopathy. They reported significantly better functional and pain scores at 15 and 30 days in the SVF group ($P < 0.05$); however, no significant differences were measured between the groups in later follow-ups [100] (Table 45.3).

Table 45.2 Characteristics of level-I studies of orthobiologics in the management of patellar tendinopathy

Author	Year of publication	Athletes	Mean age	Type of intervention	Sample size		Intervention details		Number of injections	Follow-up (months)	Favorable result	Results
					Tested group	Control group	Tested group	Control group				
Vetrano et al.	2013	Yes	PRP-26.9, control-26.8	PRP	23	23	2 mL PRP	ESWT	2	12	Yes	Significantly better VISA-P, VAS, and modified Blazina scale in the PRP group
Dragoo et al.	2014	No	PRP-28, control-40[a]	LR-PRP	10	13	3 mL bupivacaine → 6 mL LR-PRP + dry needling	3 mL bupivacaine + dry needling	1	6	Yes	Significantly better VISA-P at for 12 weeks for the PRP group, no difference in 26 weeks. Significantly better Lysholm score for the control group at 26 weeks
Scott et al.	2015	Yes	LR-PRP-32, LP-PRP-33, NS-31	LR-PRPLP-PRP	1919	19	Two groups: 1. 2 mL Lidocaine → 3.5 mL LR-PRP + rehabilitation 2. 2 mL Lidocaine → 3.5 mL LP-PRP + rehabilitation	2 mL Lidocaine → 3.5 mL NS + rehabilitation	1	12	No	No significant change in VISA-P, pain scores or global rating of change among the 3 treatment groups at all time points
Clarke et al.	2011	No	36	Skin-derived tenocyte-like cells	33	27	Skin-derived tenocyte-like cells + autologous plasma	Autologous plasma	1	6	Yes	Significantly better VISA-P scores and faster improvement in the tested group. One patient in cell group had late patellar tendon rupture

Abbreviations: *ESWT* extracorporeal shock wave therapy, *NS* normal saline, *PRP* platelet-rich plasma, *LP-PRP* leukocyte-poor PRP, *LR-PRP* leukocyte-rich PRP, *VAS* visual analog scale, *VISA-P* Victorian Institute of Sport Assessment-Patella

[a]Significant difference in age between groups ($P = 0.04$)

Table 45.3 Characteristics of level-I studies of orthobiologics in the management of Achilles pathologies

Achilles tendinopathy	DeJonge et al.	2011	No	49.7	LR-PRP	27	27	4 mL LR-PRP	4 mL NS	1	12	No	No significant difference in VISA-A or sonographic parameters
Achilles tendinopathy	Kearney et al.	2013	No	PRP-47.8, control-49.9	PRP	10	10	3–5 mL PRP	Eccentric loading program	1	6	No	No significant difference in VISA-A
Achilles tendinopathy	Krogh et al.	2016	No	PRP-46.7, NS-51.8	LR-PRP	12	12	10–15 mL Lidocaine → 6 mL LR-PRP	10–15 mL Lidocaine → 6 mL NS	1	3	No	No significant difference in VISA-A. Significantly increased tendon thickness in PRP group
Achilles tendinopathy	Boensen et al.	2017	No	PRP-43.1, HVI-41.9, placebo-40.9	LP-PRP	20	(1) 20 (2) 20	4 mL LP-PRP + eccentric exercise	Two groups: 1. HVI—10 mL bupivacaine +20 mg methylprednisolone + ~40 mL NS + eccentric exercise 2. A few drops of NS under skin + eccentric exercise	4	6	Yes	HVI and PRP more effective in reducing pain (VAS), improving activity level (VISA-A), reducing tendon thickness and intra-tendinous vascularity. HVI may be better than PRP in the short term
Achilles tendinopathy	Usuelli et al.	2017	No	SVF-47.3, PRP-46.6	Adipose derived SVF vs. LR-PRP	21	23	4 mL SVF	4 mL LR-PRP	1	6	Yes	Better VAS, AOFAS Ankle-Hindfoot score and VISA-A in both groups. Significantly better early (15 and 30 days) improvement in the SVF group. No difference in later follow-up
Achilles tendon rupture	Zou et al.	2016	No	PRP-30.2, control-28.9	LR-PRP	16	20	3–4 mL LR-PRP + Achilles tendon repair	Achilles tendon repair	1	24	Yes	Significantly better SF-36, Leppilahti scores and ankle ROM for the LR-PRP group

Abbreviations: *AOFAS* American Orthopaedic Foot and Ankle Society, *HVI* high-volume injection, *NS* normal saline, *PRP* platelet-rich plasma, *LP-PRP* leukocyte-poor PRP, *LR-PRP* leukocyte-rich PRP, *SVF* stromal vascular fraction, *VAS* visual analog scale, *VISA-A* Victorian Institute of Sport Assessment-Achilles

45.3.2.2 Achilles Tendon Rupture

Complete rupture of the Achilles tendon is a devastating injury, with only 61.1–68% of professional National Basketball Association (NBA) players returning to play at a professional level [101, 102]. Most NBA players who do return to play suffer from a decline in performance, games, and minutes played when compared to pre-injured levels [101, 102].

Several preclinical studies have supported the potential benefit of platelets, PDGF, and tendon stem cells in promoting healing of injured Achilles tendon in rats and rabbits [103–111]. However, caution should be taken when trying to translate these results to humans, as differences between the species such as Achilles tendon size and loading can dramatically affect outcome [110, 112, 113]. Moreover, other studies have not shown positive effects in a long-term follow-up [114].

Several clinical studies assessed the efficacy of adding PRP to surgical Achilles tendon repair. Schepull et al. performed a randomized, single-blinded, controlled trial of 30 patients undergoing Achilles tendon repair. Sixteen patients were injected with 10 mL of PRP to the rupture site during primary repair and 14 were not. They found no significant differences in elasticity modulus or heel raise index. They did, however, report significant lower Achilles Tendon Total Rupture Score in the PRP group, suggesting a detrimental effect associated with the use of PRP (P = 0.014) [115]. De Carli et al. performed Achilles tendon repair using mini-open technique in 30 patients and tested the addition of two injections of PRP (one during surgery and another 14 days later). They reported no difference in structural and functional outcomes [116].

Sanchez et al. published a small case–control study of 12 athletes, in which 6 athletes were treated with preparation rich in growth factors (PRGF) during primary Achilles tendon repair. They reported earlier recovery of range of motion (ROM) and return to training activity [117]. Zou et al. performed a prospective study (n = 36) using LR-PRP as biologic augmentation to Achilles tendon repair with a 2-year follow-up. They reported improved functional outcomes (ankle ROM, Leppilahti score, and the SF-36 score) in the PRP group in both short- and mid-term follow-ups [118].

Literature reporting on biologic augmentation using cell-based therapy to Achilles tendon repair is scarce. Stein et al. reviewed retrospectively 27 patients (28 tendons) treated with open Achilles repair augmented with BMAC. Ten patients were injured while playing basketball. Mean follow-up was 29.7 months. Twenty-five (92%) patients returned to their sporting activity at an average of 5.9 months postoperatively. Mean Achilles Tendon Rupture Score was 91 [119].

Fact Box

Current best evidence does not support the use of PRP or cell-based therapies for the management of chronic Achilles tendinopathy and for augmentation during primary suture repair of Achilles tendon rupture.

45.3.3 Plantar Fasciitis

The plantar fascia is prone to injury in basketball players due to the ballistic nature of motion required during the game, while jumping, running, cutting, and changing pace [120–123]. More specifically, Pau et al. demonstrated a significant increase in plantar peak pressure in women basketball players while attempting three-point shots and lay-ups [124]. Injuries can present either as a result of an acute injury or a more gradual presentation of chronic symptoms accompanied by acute exacerbations. The first line of treatment for plantar fasciitis in athletes is conservative management with rest, plantar fascia-specific stretching, NSAIDs, foot orthosis, and shock wave therapy [125]. When more conservative measures fail and when early return to play is sought, several local injections can be offered. Several injectables have been studied including Botulinum Toxin Type A (BTX-A) [126], corticosteroids [126], platelet-rich plasma (PRP) [127, 128], and amniotic-derived stem cells [129–132].

45.3.3.1 Corticosteroids

Corticosteroids are still commonly used for plantar fasciitis with 89% of the American Orthopaedic Foot and Ankle Society (AOFAS) surgeons performing an average of 13.9 injections per year [133]. Studies suggest short-term pain relief up to 3 months [134, 135], and better results with lower recurrence rates when ultrasound guidance is utilized [136]. However, high rates of plantar fascia rupture (53.7%) and fat pad atrophy have been reported following corticosteroids injections [9, 137–140]. In an effort to achieve better outcomes and mitigate the concerns regarding the adverse effects of corticosteroids, several injectables have been compared to corticosteroids.

45.3.3.2 Botulinum Toxin Type A (BTX-A)

Elizondo-Rodriguez et al. performed a randomized, double-blinded study, comparing BTX-A injection to the gastrocnemius muscle and a dexamethasone isonicotinate injection to the plantar fascia in 36 patients with plantar fasciitis. They found that the BTX-A group had a more rapid and sustained improvement in the functional scores measured [126].

45.3.3.3 PRP

Several level-I and level-II studies have compared the efficacy of PRP or corticosteroids injection for the treatment of plantar fasciitis [127, 141–153]. Most studies reported favorable outcomes of PRP over corticosteroids [127, 143, 145, 146, 149–153]. This statement was supported by two recent meta-analyses published by Singh et al. and Yang et al. [154, 155] Singh et al. performed a meta-analysis of 10 studies comparing PRP and corticosteroids for plantar fasciopathy. They concluded that PRP injections were associated with improved pain and functional scores at 3-months follow-up (p = 0.04 and p = 0.03, respectively), but there were no differences at 1-, 6-, and 12 months follow-ups [154]. Yang et al. included nine randomized controlled studies in their meta-analysis. They found greater long-term (24 weeks) pain relief with PRP injections when compared to corticosteroids (p = 0.03). However, there was no difference in pain relief in short (4 weeks) and intermediate (12 weeks) follow-up (p = 0.51 and p = 0.44, respectively), and also no difference in functional outcomes was observed ($p > 0.05$) [155]. The efficacy of a PRP injection for chronic plantar fasciitis was also compared to a platelet-poor plasma (PPP) injection in a study performed by Malahias et al. They reported significant improvement in pain relief and functional outcomes at 3- and 6-months follow-up in both groups. There was no significant difference between the two treatment modalities [156]. Due to the small sample sizes, relatively short follow-up periods, and the lack of data regarding adverse effects in most of these studies, large-scale high-quality studies are warranted.

45.3.3.4 Amniotic-Derived Products

A few studies investigated the role of amniotic-derived products for the treatment of plantar fasciitis. Cazzell et al. conducted a multicenter single-blinded, randomized, controlled trial to evaluate the safety and efficacy of micronized dehydrated human amniotic/chorionic membrane (mDHACM) for the treatment of plantar fasciitis. Fourteen sites enrolled 145 patients to receive one injection of either mDHACM or saline. At 3-months follow-up, there was a significantly greater decrease in VAS scores in the mDHACM group (76%) compared to the control group (45%) ($p < 0.0001$). Greater reduction in the Foot Function Index—Revised (FFI-R) scores was also observed in the mDHACM group (p = 0.0004). There were four serious adverse events that were determined as unrelated to the study procedures. Two patients in the treatment group complained of postinjection pain and one patient reported postinjection itching [132]. Zelen et al. published a randomized, controlled, single-blinded study reporting on 45 patients with chronic plantar fasciitis. Patients were randomized to receive 2 milliliters (mL) of 0.5% marcaine with either saline, 0.5 mL mDHACM, or 1.25 mL mDHACM. At 1-week follow-up, increase in AOFAS hindfoot scores was 2.2 for the control group and 38.7 and 33.7 for the 0.5 mL mDHACM and 1.25 mL mDHACM, respectively. At 8-weeks follow-up,

AOFAS scores were 12.9, 51.6, and 53.3, respectively. The mDHACM groups showed a significantly greater increase when compared to the control ($p < 0.001$ for all), but there was no dose-related difference between the two mDHACM groups [131]. Hanselman et al. performed a randomized, controlled, double-blinded trial comparing one or two injections of cryopreserved human micronized amniotic membrane (c-hAM) versus corticosteroids for patients with plantar fasciitis. Nine patients were randomized to receive c-hAM, and 14 patients were randomized to receive a corticosteroid injection. Patients were offered to undergo a second injection at 6-weeks follow-up and three patients from each group elected to do so. While the majority of outcome measures did not demonstrate a significant difference between the groups of patients who received one injection, patients receiving two injections of c-hAM had a greater improvement in Foot Health Status Questionnaire (FHSQ) pain score at 18 weeks ($p = 0.0113$) [129]. Werber performed a prospective, open-label case series using a cryopreserved micronized amniotic membrane and amniotic fluid product (PalinGen SportFLOW) in 44 patients with plantar fasciitis and/or Achilles tendinopathy. By the fourth-week postinjection, there was a significant decrease in the visual analog scale (VAS) ($p < 0.001$). Pain relief was sustained for the remainder of the study (up to 12 weeks). No adverse events were reported by any of the patients [130]. Early results of amniotic-derived injections for plantar fasciitis are encouraging. Further studies will hopefully allow determining the true role of these novel injectables (Table 45.4).

45.3.4 Rotator Cuff Pathology

Several level-I studies assessed the efficacy of PRP for the management of rotator cuff tendinopathy [157–160]. Rha et al. performed a double-blinded, randomized, controlled study comparing two injections of LR-PRP to two dry needling sessions for rotator cuff; they report better Shoulder and Disability Index (SPADI) Scores from 6 weeks to 6 months (17.7 vs. 29.5, $p < 0.05$) and reduced pain in the LR-PRP group [159]. Kesikburun et al. compared LR-PRP injection to a saline injection for rotator cuff tendinopathy with a 1-year follow-up. They have found no difference in Western Ontario Rotator Cuff Index [WORC], SPADI, or VAS of shoulder pain with the Neer test at 1-year follow-up ($p = 0.174$, $p = 0.314$ and $p = 0.904$, respectively) [157]. A recent systematic review of randomized controlled trials concluded that PRP may not be beneficial in the short term for rotator cuff disease. They did however state that this interpretation may be confounded by the lack of reporting of the cytology and characteristics of PRP [161] (Table 45.5).

Augmentation of rotator cuff repair with platelet-rich fibrin matrix (PRFM) has also been studied by several high-quality studies [162–182]. Saltzman et al. and Filardo et al. performed meta-analyses that demonstrated no improvement in clinical outcomes or retear rates with PRP augmentation [183, 184].

Hernigou et al. compared outcomes of rotator cuff repair with ($n = 45$) and without ($n = 45$) augmentation of BMAC derived from the iliac crest. At 6 months, 100% of the BMAC group demonstrated a healed rotator cuff on MRI, compared to 67% in the control group. Moreover, at 10-years follow-up, they found less additional ruptures in the BMAC group [71]. Kim et al. studied the effect of a single BMAC-PRP injection ($n = 12$) vs. rotator cuff exercise ($n = 12$) for rotator cuff tear. The BMAC-PRP group had lower VAS in 3 months ($p = 0.039$), but not in 3 weeks ($p = 0.147$). American Shoulder and Elbow Surgeons (ASES) scores increased significantly more in the BMAC-PRP group at 3 months ($p = 0.011$) [185] (Table 45.6).

Take-Home Messages

- There is sufficient evidence to recommend the use of PRP for patellar tendinopathy that is refractory to a first line of conservative treatment and that it is considered a safe treatment option. Although, recent level-I study has raised doubts regarding the benefits of PRP for patellar tendinopathy.

Table 45.4 Characteristics of level-I studies of orthobiologics in the management of plantar fasciitis

Author	Year of publication	Athletes	Mean age	Type of intervention	Sample size		Intervention details		Number of injections	Follow-up (months)	Favorable result	Results
					Tested group	Control group	Tested group	Control group				
Acosta-Olivo et al.	2016	No	44.8	PRP	14	14	Lidocaine +0.45 mL 10% Ca^{+2} Gluconate +3 mL PRP	2 mL Lidocaine +2 mL dexamethasone	1	4	No	No difference in VAS, AOFAS, and FADI scores.
Jain et al.	2015	No	55.6	LR-PRP	30	30	2.5 mL PRP	40 mg triamcinolone + Levobupivacaine hydrochloride	1	12	Yes	At 12-months the PRP group had better VAS, AOFAS, and roles-Maudsley scores. At 3- and 6-months follow-ups there was no significant differences between the groups
Mahindra et al.	2016	No	PRP-30.7, CS-34.9, NS-35.5	PRP	25	25	2.5-3 mL PRP	2 mL methyl-prednisolone or NS	1	3	Yes	At 3-months follow-up, the PRP group had significantly higher AOFAS scores. Other comparisons between PRP and CS were not statistically significant

(continued)

Table 45.4 (continued)

Author	Year of publication	Athletes	Mean age	Type of intervention	Sample size		Intervention details		Number of injections	Follow-up (months)	Favorable result	Results
					Tested group	Control group	Tested group	Control group				
Monto et al.	2014	No	PRP-51, CS-59	LR-PRP	20	20	6 mL bupivacaine → 3 mL PRP	6 mL bupivacaine → 1 mL methyl-prednisolone	1	24	Yes	Significantly greater post-treatment AOFAS scores. PRP was more effective and durable than CS injection
Sherpy et al.	2015	No	PRP-37.5, CS-38.5	LR-PRP	25	25	Mepivacaine → PRP	Mepivacaine → 1 mL triamcinolone	1	3	No	No significant difference in VAS and FHSQ at 3 months.
Tiwari et al.	2013	No	Not reported. Range 30–85	LR-PRP	30	30	5 mL PRP	1 mL Prilocaine +1 mL methyl-prednisolone	1	6	Yes	Significantly decreased VAS scores in the PRP group
Vahdatpour etal.	2016	No	PRP-45.4, CS-47.1	LR-PRP	16	16	3 mL PRP	1 mL Lidocaine +1 mL methyl-prednisolone	1	6	Yes/no	The PRP group had higher VAS scores at 1- and 3-months follow-ups, but lower scores at 6-months. Roles-Maudsley scores was lower in the PRP group at 1- and 3-months, but greater at 6 months.

Zelen et al.	2013	No	1. 51, 2. 56, NS-50	mDHACM	1. 15 2. 15	15	2 mL 0.5% Marcaine + 1. 1.25 mL mDHACM 2. 0.5 mL mDHACM	2 mL 0.5% Marcaine +1.25 mL NS	1	2	Yes	Greater decrease in VAS and FFI-R scores in the mDHACM groups. No difference between the mDHACM groups.
Hanselman et al.	2014	No	51	c-hAM	9	14	c-hAM ± repeat injection at 6 weeks	DepoMedrol ± repeat injection at 6 weeks	1/2	4.5	Yes	No difference in most outcomes for one injection. Greater FHSQ for patients receiving 2 c-hAM injections.
Cazzel et al.	2018	No	mDHA CM~49CS -53	mDHACM	73	72	1 mL mDHACM	1 mL NS	1	3	Yes	Greater decrease in VAS and FFI-R in the mDHACM group at 3 months.

Abbreviations: *AOFAS* American Orthopaedic Foot and Ankle Society, *c-hAM* cryopreserved human amniotic membrane, *CS* Corticosteroids, *ESWT* extracorporeal shock wave therapy, *FADI* Foot and Ankle Disability Index, *FFI-R* Foot Function Index—Revised, *FHSQ* Foot Health Status Questionnaire, *mDHACM* micronized dehydrated human amnion/chorion membrane, *NS* normal saline, *PRP* platelet-rich plasma, *LP-PRP* leukocyte-poor PRP, *LR-PRP* leukocyte-rich PRP, *VAS* visual analog scale

Table 45.5 Characteristics of level-I studies of orthobiologics in the management of rotator cuff tendinopathy

Author	Year of publication	Athletes	Mean age	Type of intervention	Sample size		Intervention details		Number of injections	Follow-up (months)	Favorable result	Results
					Tested group	Control group	Tested group	Control group				
Rha et al.	2013	No	PRP—52.2, control—53.9	LR-PRP	20	19	<1 mL Lidocaine → 3 mL LR-PRP	<1 mL lidocaine	2	6	Yes	Better Shoulder and Disability Index Scores and reduced pain in the PRP group
Kesikburun et al.	2013	No	PRP—45.5, NS—51.4	LR-PRP	20	20	1 mL lidocaine → 5 mL LR-PRP	1 mL Lidocaine → 5 mL NS	1	12	No	No difference in WORC, SPADI, or VAS of shoulder pain with the Neer test at 1-year follow-up
Ilhanli et al.	2015	No	PRP—59.2, control—59.7	LR-PRP	30	32	6 mL LR-PRP	Physical therapy	1	12	Y/N	PRP group had significantly better DASH scores; however, the physical therapy group had significantly better ROM and VAS
Nejati et al.	2017	No	PRP—52.5, control—53.9	LR-PRP	22	20	4 mL LR-PRP	Physical therapy	2	6	No	Physical therapy group had superior functionality, ROM, and decreased pain in the first and third months

Abbreviations: *DASH* Disabilities of Arm Shoulder and Hand questionnaire, *NS* normal saline, *PRP* platelet-rich plasma, *LP-PRP* leukocyte-poor PRP, *LR-PRP* leukocyte-rich PRP, *ROM* range of motion, *SPADI* Shoulder and Disability Index, *VAS* visual analog scale, *WORC* Western Ontario Rotator Cuff Index

Table 45.6 Characteristics of level-I studies of orthobiologics in the management of rotator cuff repair

Author	Year of publication	Athletes	Mean age	Type of intervention	Sample size		Intervention details		Number of injections	Follow-up (months)	Favorable result	Results
					Tested group	Control group	Tested group	Control group				
D'Ambrosi et al.	2016	No	PRP—57.9, control—62	PRP	20	20	16 mL PRP + repair	Repair alone	1	6	Yes	PRP leads to a reduction in pain during a short-term follow-up.
Ebert et al.	2017	No	PRP—59.7, control—59.5	LP-PRP	30	30	2–4 mL LP-PRP + repair	Repair alone	2	42	Y/N	Reduced pain and maximal abduction strength at midterm. No additional benefit to tendon integrity.
Holtby et al.	2016	No	PRP—59, control—59	LP-PRP	41	41	7 mL PRP + repair	Repair alone	1	6	No	PRP had short-term effect on pain; however, no significant impact on patient-related outcomes or structural integrity
Malavolta et al.	2014	No	PRP—55.3, control—54	LR-PRP	27	27	20 mL PRP + repair	Repair alone	1	24	No	No beneficial clinical results for PRP
Jo et al.	2015	No	PRP—60, control—60.9	LP-PRP	37	37	3 mL PRP gel + repair	Repair alone	3	12	Yes	PRP group had significantly decreased re-tear rate and increased cross-sectional area of the supraspinatus, but not the speed of healing
Randelli et al.	2011	No	PRP—61.6, control—59.5	LR-PRP	26	27	6 mL PRP + repair	Repair alone	1	24	Yes	Early reduced pain with PRP. Positive effect on healing of rotator cuff at long-term follow-up
Castricini et al.	2011	No	PRP—55.2, control—55.5	PRFM	43	45	PRFM + repair	Repair alone	1	16	No	PRFM did not improve rotator cuff healing

(continued)

Table 45.6 (continued)

Author	Year of publication	Athletes	Mean age	Type of intervention	Sample size		Intervention details		Number of injections	Follow-up (months)	Favorable result	Results
					Tested group	Control group	Tested group	Control group				
Gumina et al.	2012	No	PRP—60, control—63	LR-PRFM	39	37	PRFM + repair	Repair alone	1	12	No	PRFM group had improved integrity of the rotator cuff; however, no improvement in functional outcomes
Weber et al.	2013	No	PRP—59.7, control—64.5	LP-PRFM	30	30	PRFM clot + repair	Repair alone	1	12	No	No significant improvement in perioperative morbidity, clinical outcomes, or structural integrity
Zumstein et al.	2016	No	PRP— 65, control—66	LR-PRFM	17	18	PRFM + repair	Repair alone	1	12	No	No beneficial effect in clinical outcome, anatomic healing rate, mean postoperative defect size, and tendon quality

Abbreviations: *PRFM* platelet-rich fibrin matrix, *PRP* platelet-rich plasma, *LP-PRP* leukocyte-poor PRP, *LR-PRP* leukocyte-rich PRP, *PPP* platelet-poor plasma

- High-quality evidence supports the use of PRP injections for plantar fasciitis due to slightly greater efficacy compared to corticosteroids, accompanied by a presumed lower complications rate.
- Current literature is conflicting and heterogenous regarding the use of PRP for rotator cuff pathology, Achilles tendinopathy, and for biologic augmentation of Achilles tendon repair.
- Studies reporting outcomes of cell-based therapies for the management of soft tissue injuries are limited. Early studies on amniotic-derived injectables for plantar fasciitis are promising but are not sufficient to support formal clinical recommendations at this point in time.
- In general, orthobiologics have yet to be thoroughly studied in specific soft tissue injuries in athletes in general and basketball players in particular; however many studies are on their way, and they will shed light on the future of this sprouting field.

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