The Role of Orthobiologics for the Management of Ligament and Muscle Injuries in Sports

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46.1 Introduction

The use of orthobiologics has become increasingly common in the field of sports medicine to enhance healing of soft tissue injuries. Despite some promising outcomes reported and the surge in orthobiologic use in sports medicine, clarity is lacking with regard to the proper indications, optimal orthobiologic product for each indication, preparation method and dosage, as well as application method and protocol [1–3]. These variabilities have led to inconsistencies in both preclinical and clinical reported results. Therefore, establishing an optimal treatment protocol for the various soft tissue sports injuries still presents a challenge due to the number of independent variables and absence of high-quality evidence [4]. When attempting to optimize orthobiologic treatment for a specific musculoskeletal injury, one has to consider additional important factors which can affect treatment outcomes, such as the local environment as well as tissue biomechanics and load vectors, which may influence optimal adherence, stability, and potency of the orthobiologic agent in the injured tissue [5].

The purpose of this chapter is to review the best current evidence and recommendations on several orthobiologic treatment approaches in the management of common ligament and muscle injuries in basketball. In addition, regulatory aspects will dictate potential utilization based upon geographic considerations (i.e., in and outside the United States).

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46.2 Ligament Injuries

Ligament injuries in basketball represent some of the most severe injuries in terms of time loss from play and are responsible for a substantial burden of injury. Some of these injuries (knee cruciate ligament injuries; ankle ligament injuries) may often require surgical management and could lead to a permanently reduced level of sports performance or even be career ending.

The clinical use of platelet-rich plasma (PRP) for soft tissue injuries is based on previous preclinical studies investigating its effect on tendons, muscles, and ligaments. Several basic science studies have supported the application of growth factors to increase collagen synthesis and for healing enhancement in ligament tissue [6, 7]. Early studies of PRP use for ligament tissue in animal models have shown promising healing potential for both medial collateral ligament (MCL) and anterior cruciate ligament (ACL) injuries [8–10]. These basic science studies have assisted in supporting and developing the concepts of PRP use for ligament healing in the clinical setting, as well as provide promising future directions.

46.2.1 Anterior Cruciate Ligament

Anterior cruciate ligament (ACL) tears are among the most common severe sports-related injuries and therefore ACL reconstruction surgery is one of the most frequently performed procedures in the field of sports medicine [11]. ACL surgery relies upon both technical and biologic factors to assure the highest likelihood of success. Various strategies have been attempted over the years to improve ACL reconstruction (ACLR) outcomes such as targeting the biologic healing process to improve the graft's healing capacity and incorporation hoping to shorten return to sports duration and reduce failure rates. For this purpose, bio-regenerative/orthobiologic treatment options have shown potential to improve graft incorporation and strength from gene activation level through microenvironment optimization in order to possibly delay or prevent early progression to osteoarthritis [12].

46.2.1.1 Basic Science and Preclinical Evidence

Important preclinical work in the last two decades has provided the basis to improve bio-regenerative approaches to enhance ACL graft healing. Many of the previous investigated regenerative agents contain various growth factors (GFs) which have demonstrated positive effects on various biological processes necessary for ACL healing such as cell proliferation, cell migration, angiogenesis, and extracellular matrix (ECM) production in both in vivo and in vitro studies [13]. The fibroblast, the primary cell in the ACL, has receptors for many of these GFs, such as transforming GF b-1 (TGF-b1), fibroblast GF-2 (FGF-2), platelet-derived GF (PDGF), insulin-like GF, epidermal GF, and vascular endothelial GF (VEGF). Therefore, these GFs have been the focus of many preclinical studies. For example, TGF-b1, FGF-2, and basic-FGF have been shown to have a role in the repair process of a torn ligament by regulating and improving cellular proliferation and ECM production, as well as affect mesenchymal stem cells (MSCs) differentiation into fibroblasts [6, 14, 15]. PDGF has been shown to stimulate fibroblast growth, cell migration, and a biologic cascade reducing the postoperative release of proinflammatory factors [16], therefore potentially improving graft ligamentization and incorporation potentially reducing graft failure risk [17]. TGF-b1 was reported to potentially stimulate initial and overall healing in both histologically and biomechanically tested partial ACL tears in animal models [18, 19]. Kondo et al. reported significantly improved biomechanical and histologic healing properties of injured ACLs treated with TGF-b1 in a rabbit ACL injury model when compared with controls [18]. Marui et al. reported that TGF-b1 application resulted in up to ×1.5 increase in collagen synthesis compared with controls in both ACL and MCL fibroblasts [7]. VEGF-augmented grafts demonstrated improved vascularization and fibroblast infiltration compared to controls following ACL reconstruction in a sheep model although increased graft laxity was evident at 12 weeks [20]. More recently, blocking VEGF has been reported to reduce angiogenesis, graft maturation, and bio-

mechanical strength following an ACL reconstruction model in rats [21].

Murray et al. investigated the application of clotted PRP in the gap of a transected ACL in a porcine ACL repair model, reporting no beneficial effect for PRP use compared with controls. They concluded that the fibrin clot used was not sufficiently biologically stable and may have prematurely dissolved in the intra-articular environment and synovial fluid containing plasmin [22]. These observations led to the development of scaffolds to hold the PRP at the ACL injury site and protect it from the intra-articular environment and from early degradation. In a later study, the same group added PRP to a collagen hydrogel showing significantly increased cellular metabolic activity, a reduced apoptotic rate, and collagen production stimulation in cells from immature and adolescent animals although less effect was achieved in adult animal cells [23]. In a later study from the same group, Vavken et al. combined a collagen scaffold with autologous platelets, demonstrating significantly improved ACL repair outcomes in a porcine model. They reported primary repair augmented with a collagen-PRP hydrogel resulted in superior tissue mechanical properties compared with suture repair alone [24].

Several preclinical studies have investigated the use of stem cells for the management of ACL tears. A recent systematic review of the available preclinical evidence of adult stem cells as a biological augmentation in the treatment of animal anterior cruciate ligament (ACL) injury was performed by Guo et al. [25]. Thirteen animal studies were included. Six of seven studies using bone marrow-derived mesenchymal stem (stromal) cells (BMSCs) reported a positive enhancement in histology, biomechanics, and biochemistry within 12 weeks postoperatively. Four studies using ACL-derived vascular stem cells showed a promoting effect in histology, biomechanics, and imaging within 8 weeks postoperatively. Two studies focusing on animal tendon-derived stem cells (TDSCs) and human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs) reported promotable effects for the early healing in a small animal ACL model. Authors concluded that BMSCs, ACL-derived vascular stem cells, TDSCs, and hUCB-MSCs were shown to enhance ACL healing during the early phase in small animal models. Oe et al. compared ACL regeneration between groups subjected to intra-articular injection of either fresh whole bone marrow cells (BMCs), cultured MSCs, or saline in partial ACL tears in a rat model [26]. They concluded that administration of fresh whole BMCs is an effective treatment for partial ACL rupture and reported nearly normal ligament healing and strength compared with controls. Similar findings were reported by Kanaya et al. following intra-articular injection of MSCs showing improved ligament healing with superior histologic features and a greater load-to-failure compared with nontreated controls in a rat model [27]. More recently, in another rat model, Lui et al. added tendon-derived stem cell sheets to ACL reconstructions. The treated knees exhibited higher intra-articular graft integrity with lower cellularity, improved cell organization and vascularity, as well as better tunnel-bone mineral density, bone volume, and better graft osteointegration compared to the control group [28]. A recent study by Hur et al. reported that the use of MSCs with ACL reconstruction decreased tunnel widening in rabbit model [29]. Sun et al. investigated the effect of human bone marrow stem cells (hBMSC)-CM on ACLR in a rat model and reported that hBMSC-CM accelerated graft-bone incorporation, midsubstance ligamentization and enhanced fibroblast proliferation, differentiation, and collagen synthesis [30].

46.2.1.2 Clinical Evidence

Clinical studies on the use of orthobiologics in ACL surgery have focused on the following applications: (1) Healing enhancement in partial tears with or without repair; (2) healing enhancement in ACLR graft, focusing on osteoligamentous integration into the tibial and femoral tunnels and maturation of the articular portion of the graft, and (3) graft harvest site healing.

Partial ACL Tears

Management of partial ACL tears presents a significant challenge to clinicians as the natural history of these lesions is poorly understood and due to the limited evidence regarding treatment

options. Although it is generally accepted that spontaneous healing capacity of the ACL following an injury is limited [31, 32], there are reports on spontaneous healing of partial ACL tears [33, 34]. More recently, Nguyen et al. reported an intrinsic healing response in the proximal third of human ACLs with typical spontaneous healing characteristics similar to the MCL, in a histological study investigating spontaneously reattached tibial ACL remnants [35]. This evidence prompted attempts to enhance the ACL's healing potential with or without repair.

ACL Healing Enhancement Without Repair

Seijas et al. reported a high return to sports rate in 19 professional soccer players with a partial ACL tear treated with intra-ligamentous application of platelet-rich growth factors (PRGF-Endoret) into the intact bundle (Fig. 46.3) [36]. Administration of 4 mL of this product, described by Anitua [37], was performed during arthroscopy using a spinal needle in both the proximal origin and the middle portion of the intact bundle (Fig. 46.1). An additional injection of PRGF (6 mL) was administered in the articular space at the end of the surgery,

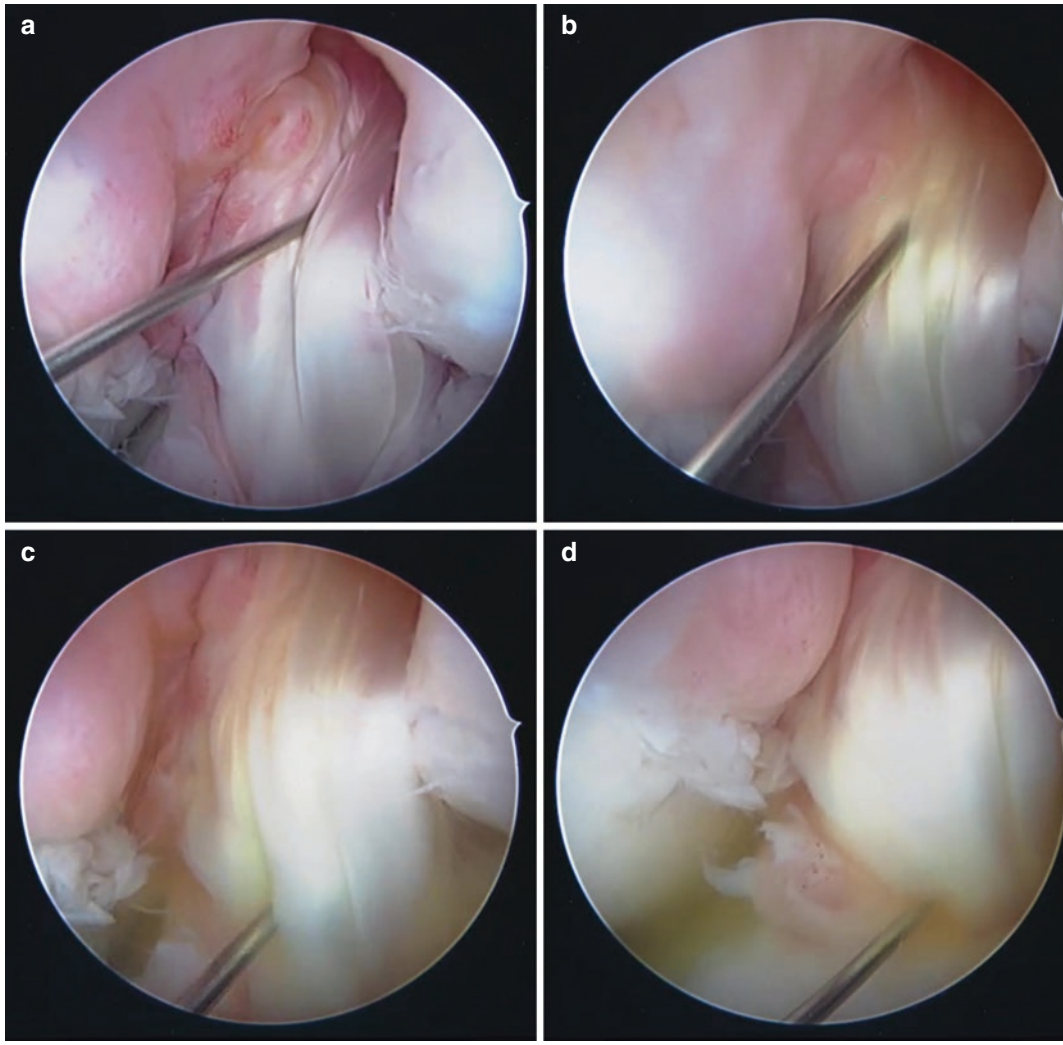

Fig. 46.1 Intraoperative PRP infiltration of a partial ACL tear with a mostly intact sheath into the proximal aspect of the tear (**a**). The ligament has an "inflated" appearance following the initial infiltration (**b**). Mid-substance ACL infiltration (**c**). Distal ACL aspect infiltration (**d**)

when the joint had been dried. Average time between injury to surgery in this study was 5.8 weeks. Eighteen of 19 players were able to return to their previous level of play, with 15 players (Tegner level 9) returning to play at an average of 16.20 weeks (1 re-rupture at 7 months), while the 3 patients playing at a higher level (Tegner level 10) returned at an average of 12.33 weeks. One patient was not able to return to sport due to significant cartilage lesions. No notable complications were reported in any of the patients in the study. A postoperative magnetic resonance imaging (MRI) at 1 year from surgery showed complete ligamentization and good anatomic organization of the remnant in all patients. In a recent study, Koch et al. evaluated 42 patients following an intra-ligamentous autologous conditioned plasma (ACP™, Arthrex, Florida, USA) by clinical scoring and functional performance assessment at a mean 33 months follow-up [38]. Failure was recorded in 4 patients (9.5%). Good to excellent results were reported on all outcome scores. Clinical examination showed marked improvements from the preoperative status in terms of the Lachman test, pivot shift phenomenon, and a significant reduction in AP laxity (rolimeter preoperative: 1.9 (SD 1.4); postoperative 0.6 (SD 1.8), $p = 0.001$) in all patients. Functional performance testing showed no significant differences between the injured and healthy side. Return to sport was achieved at a mean of 5.8 months (SD 3.6) in 71.1% of patients with a subjective return to pre-injury sports activity in 85.8% (SD 19%). Notably, the absence of a control group with equivalent pathology, it makes it difficult to conclude that the addition of PRP in either of these studies was responsible for the functional outcome.

Only one study reported the use of bone marrow aspirate concentrate (BMAC) for ACL tears. Centeno et al. published a small case series of 10 patients with ACL tears treated with a fluoroscopically guided intra-ligamentous injection of autologous bone marrow concentrate and PRP [39]. Assessments involved ACL laxity and tear grade on MRI and patients with partial and complete ACL tears with less than 1-cm retraction were included. Pre- and post-injection MRIs were obtained and objectively assessed through five different types of measurements of ACL pixel intensity for ligament integrity. Seven of ten patients showed improvement in at least four of five of these objective MRI measures. Improvements in mean visual analog scale (VAS) and mean Lower Extremity Functional Scale were documented, as well as mean reported improvement of 86.7%.

ACL Healing Enhancement With Partial Tear Repair

Gobbi et al. assessed the clinical outcomes of adding a PRP injection to ACL suture repair in addition to microfracture of the intercondylar notch in 58 athletes with partial ACL tears, with a 5-year follow-up [40]. They reported that 78% of the patients returned to their sports activities. They also reported a statistically significant decrease in side-to-side difference in anterior translation, from 4.1 mm (SD ¼ 1.6) preoperatively to 1.4 mm (SD ¼ 0.8) postoperatively at 5 years ($P < 0.05$). Four patients had a re-tear during sporting activity and underwent ACLR within 2 years from the primary repair surgery. The authors concluded that ACL repair + intercondylar notch microfracture + PRP was an effective technique to restore knee stability and function for acute partial ACL tears in young individuals.

ACL Reconstruction

Assessment of orthobiologics use in ACL reconstruction surgery has focused on three main parameters: (1) Maturation of the articular portion of the graft, (2) osteo-ligamentous integration of the graft into the tibial and femoral tunnels, and (3) clinical outcomes [41]. ACL graft maturation is most commonly assessed on MRI, with a low homogeneous intensity signal on T2-weighted and proton density-weighted MRI accepted as likely indicative of a maturing ACL graft. Several studies have shown improved graft maturation with PRP [42–45], while others reported no significant differences [46, 47]. A recent systematic review of 11 controlled trials concluded that PRP likely improves ACL graft maturation by up to 50% [17]. The authors suggested insufficient sample size as a potential explanation for lack of statistical significance

despite MRI improvement in measuring ACL graft maturation.

In the only study where histologic samples were obtained from PRP augmented ACL grafts, Sanchez et al. compared PRGF-assisted ACLRs (n = 22) to nonaugmented ACLRs (n = 15) in which a second-look arthroscopy was required (for either loose body or hardware removal, meniscal tears treatment, or cyclops lesions resection) at a minimum of 6 months [45]. Histologic analysis showed that newly formed connective tissue enveloping the graft was present in 77.3% of the PRP group compared to 40% in controls.

In a prospective randomized trial, Radice et al. compared 25 patients treated with ACLR in combination with PRP (GPS System, Biomet) to a control group of 25 patients who underwent surgery alone matched for age and gender [43]. They included 15 bone-patellar tendon-bone (BTB) autografts and 10 hamstrings autografts in each group. For the BTB autografts, 5 mL of activated PRP was added to an absorbable gelatin-compressed sponge (Gelfoam; Pfizer, Ixelles, Belgium) and sutured to the femoral plug and intra-articular parts of the graft, acting as a scaffold. For the hamstrings autografts, the same product was placed between the folded tendons and sutured in a similar manner. Monthly MRIs were performed from 3 to 9 months post-op to track the homogenization curve of the intra-articular portion of the graft, showing time to complete homogeneity in the PRP group was 177 days compared to 369 days in the control group. Moreover, in an analysis of the BTB autograft subgroup, the maturation time in the PRP group was 109 days versus 363 days in BTB controls. The authors concluded that PRP use in ACLR accelerates graft maturation by half of the expected time, with an additional reduction in maturation time from 12 months to 3.6 months when used in BTB autograft ACLR.

While several studies focused on the assessment of graft osteo-ligamentous integration (graft–bone tunnel incorporation) reported improved characteristics, there is a lack of sufficient evidence showing its correlation with clinical benefit of PRP use in ACLR [46, 48]. In a randomized, controlled, double-blind study, Vogrin et al. investigated the effects of PRP gel application in hamstring autograft ACL reconstruction in 50 patients (25 thrombin-activated PRP-soaked grafts and 25 controls) [47]. They reported MRI evidence of improved vascularization along the ACL graft–bone interface at 3 months in the PRP group, with improved anterior–posterior instrumented knee stability measurements using a KT-2000 (MEDMETRIC; San Diego, CA) arthrometer at 6 months. However, in another double-blind, randomized controlled trial (RCT) involving 100 patients undergoing ACLR with BTB allograft (50 treated with platelet-enriched gel and 50 controls), Nin et al. reported no difference in International Knee Documentation Committee (IKDC) scores and KT-1000 arthrometer measurements (MEDmetric, San Diego, CA). Ventura et al. reported no differences in knee injury and osteoarthritis outcome score (KOOS), Tegner scores, or anterior–posterior instrumented knee stability measurements using a KT-1000 (MEDMETRIC; San Diego, CA) measurements between the PRP-treated group and control subjects at six following ACLR, despite the evidence of significant difference in graft appearance [49]. Orrego et al. similarly found no significant benefit in both Lysholm and International Knee Documentation Committee (IKDC) scores at 6 months post-ACLR, despite a favorable effect of PRP on graft maturation. Other studies have similarly reported limited to no evidence to support the use of PRP to augment ACL graft–bone tunnel incorporation [50–53]. An interesting observation from the existing literature is that nearly all of the studies used (leukocyte-rich) LR-PRP formulations, which have been known to increase local tissue inflammation and thus may delay or alter healing [54].

In a recent retrospective cohort of 151 knees in 143 patients ≤21 years of age in which hamstrings autograft ACLRs were augmented with PRP and a porous collagen carrier, Berdis et al. reported a decreased rate of second ACL injury, as well as reduced rates of ACL revision surgery. The patients in this study also show higher return to preinjury level of competition, with 132 returning to competitive sports at a pre-injury level, out of which 39 basketball players, and at an average of 22 weeks postsurgery [55].

ACL Reconstruction + Stem Cells/Cell-Based Therapy

Recently, Alentorn-Geli et al. published clinical outcomes of 20 soccer players undergoing ACL reconstruction using BTB autograft infiltrated with adipose-derived regenerative stem cells (ADRC) at the end of the procedure, with a 12-month follow-up [56]. This cohort was compared to a historical, matched cohort of 19 soccer players undergoing the same procedure without ADRC. They reported no significant differences in outcomes improvement between groups across time ($p > 0.05$). All patients returned to sports after surgery, but 8 (40%) patients in the ADRC and 13 (68.4%) patients in the control group had lower Tegner activity score at 12 months postop.

PRP for ACL Harvest/Donor Site

Another utilization of PRP use in ACLR focused on its influence on donor site (graft harvest site) pain and healing, with several clinical studies presenting promising early results. De Almeida et al. reported that adding PRP to the patellar tendon harvest site resulted in better immediate postoperative pain scores, and less patellar tendon gapping on MRI at 6 months from surgery [57]. In a double-blind RCT, Seijas et al. reported decreased anterior knee pain following PRGF application to BTB harvest site in ACLR, compared to controls [58]. In another study, Cervellin et al. 128 did not find a significant difference in VAS pain scores, but the PRP group had a significantly higher VISA score [59]. A recent double-blinded RCT by Walters et al. in which PRP was applied to the harvest site in BTB ACLR showed less favorable results with similar levels of kneeling pain and patellar defect sizes in both the PRP and control groups [60].

Future Directions

New approaches are continuously being developed in an attempt to harness the advantageous regenerative properties in orthobiologics to enhance the existing healing potential of the ACL. One interesting direction was introduced by Murray et al. following many years of preclinical studies [61]. They introduced a technique using a collagen scaffold soaked with whole blood to deliver platelets in combination with a novel bio-enhanced primary repair technique using a suture stent, called: bridge-enhanced ACL repair (BEAR technique). Use of this technique in an animal model was reported to result in equivalent biomechanical properties between the repaired ACL equivalent and an ACLR at 3, 6, and 12 months postsurgery [24]. Furthermore, this novel technique of bio-enhanced repair prevented the development of cartilage lesions, which were seen 12 months after untreated ACL transection and ACLR in an animal model. In a recent first clinical trial with the using BEAR technique in humans, ten patients underwent treatment using the BEAR technique compared to ten hamstrings autograft ACLRs [62]. Authors reported that the BEAR group produced similar outcomes to ACLR with a hamstring autograft at 12 and 24 months postsurgery, measured by subjective and objective IKDC scores, stability measures by arthrometer, and in functional hop testing. The BEAR group presented with higher hamstring strength indices.

46.2.2 Medial Collateral Ligament (MCL)

Medial collateral ligament (MCL) injuries are the most common knee ligament injuries. Spontaneous healing and nonoperative management is the usual clinical scenario in the large majority of cases [63]. Thirty-five MCL injuries have been recorded in female collegiate and high-school basketball between 2009–2010 and 2013–2014 seasons, and 33 injuries in males [64]. While the MCL has shown to have good healing potential [31], it has been reported that these injuries can lead to chronic pain, laxity, joint instability, and possibly osteoarthritis [65]. These injuries often present a serious problem to athletes as they can result in significant time away from sports in the competitive context. Several attempts have been made to enhance the healing process of the MCL with orthobiologic therapies and restore the normal ligament functionality as much as possible.

Early preclinical evidence suggested promising properties of PRP use for MCL injury with enhanced healing potential in animal models [8–10]. However, later studies reported less favorable results. Yoshioka et al. observed significantly improved structural properties of rabbit MCLs treated with PRGF (LP-PRP) compared to controls [66]. Conversely, Amar et al. reported no histological or biomechanical differences between PRP-treated MCLs and controls in a rat model [67]. More recently, LaPrade et al. reported that either a single dose of platelet-poor plasma (PPP) or a 2-times dose of PRP at the time of injury did not accelerate ligament healing. Moreover, a 4-times dose of PRP resulted in a significant negative effect on collagen orientation and ligament strength (compared to a sham group) at 6 weeks post injury.

Reports on clinical use of PRP for the treatment of MCL injuries are limited with the majority being in the form of case reports [68–70]. Recently, Lundblad et al. reported the use of PRP injections for MCL injuries in 20 elite-level football players out of a prospective cohort of 130 players over three full seasons (2 players with MRI grade I; 17 players with MRI grade II; and 1 player with MRI grade III MCL injuries) [71]. There were no differences in lay-off times in players treated with PRP or not, in grade II MCL injury grading (n.s.). However, there is no information on which type of PRP was used, how many injections were administered, time from injury to injection, MCL area involved as well as post-injection protocol (variance in brace administration was reported in this study), all factors which substantially limit the quality of any conclusion drawn from this study with regard to the use of PRP for treatment of MCL injuries.

46.2.3 Ankle Sprains

Ankle sprains have been highlighted in most epidemiologic studies as the most common type of injury in basketball across age groups, genders, and all levels of play [72–76]. To date, there are very few high-level studies analyzing the use of PRP injections for ankle or high-ankle sprains, with two published RCTs (one for ankle sprains and one for high-ankle sprains). In a double-blinded placebo-controlled RCT, Rowden et al. compared ultrasound-guided LR-PRP injections with local anesthetic versus normal saline injection with local anesthetic for acute ankle sprains in 37 patients [77]. Primary outcome measures were VAS pain score and Lower Extremity Functional Sale (LEFS) on day 0 (baseline), day 3, and day 8. This study had various limitations, apart from the small sample size and short follow-up, with lack of documentation of ankle sprain grade. All patients were treated with a posterior splint with non–weight-bearing restrictions for 3 days. Pain medication was given at the physician's discretion with no documentation as well. The investigators found no statistical difference in VAS pain score or LEFS between the two groups. In a recent, small RCT in 21 patients with grade II lateral ankle sprain, 12 ankles were treated with a single PRP injection to the anterior talofibular ligament (ATFL) and rigid immobilization compared to a control group of 11 patients treated with rigid immobilization alone. The PRP group showed better pain reduction and better functional scores than the control group at 8 weeks, but clinical outcomes were similar in both groups at 24 weeks [78].

In another RCT, Laver et al. treated 16 elite athletes diagnosed with high ankle sprains, with either an ultrasound-guided LP-PRP injection to the antero-inferior tibiofibular ligament (AITFL) at initial presentation with a repeat injection 7 days later in conjunction with a rehabilitation program (eight athletes), versus a rehabilitation program alone (eight athletes) [79]. Primary outcomes were measured by return to play (RTP) and dynamic ultrasound studies. All patients followed the same rehabilitation protocol and RTP criteria. They reported the LP-PRP group returned to play in a shorter period of time (40.8 days) compared with the control group (59.6 days, $P < 0.006$). Only one patient had residual pain following RTP in the PRP group, whereas five patients had residual pain in the control group. No significant difference was seen on dynamic ultrasound examination in external rotation between the two groups 6 weeks

post injury. In another study, Samra et al. treated ten Rugby Union players with a single PRP injection into the AITFL within 14 days of an MRI confirmed ankle syndesmosis injury. A historical control group included 11 comparable Rugby Union players [80]. They reported a significantly shortened RTP time ($p = 0.048$). Additionally, athletes in the intervention group showed higher agility ($p = 0.002$) and vertical jump ($p = 0.001$), as well as a lower level of fear avoidance associated with rugby ($p = 0.014$). They concluded that a single PRP injection for high ankle sprains may accelerate a safe and successful return to Rugby Union, with improved functional capacity [80].

Fact Box

Current evidence has not shown PRP to be efficacious in acute ankle sprains; however, evidence suggests that LP-PRP injections may be beneficial in the management of high ankle sprains to reduce return-to-play time and decrease incidence of residual pain in elite athletes. Further high-quality evidence is needed to define the role of PRP and cell-based therapies in ankle and high-ankle sprains.

46.2.4 Ulnar Collateral Ligament of the Elbow Injuries

Ulnar collateral ligament (UCL) tears and subsequent medial elbow instability are highly prevalent and dreadful injuries in athletes participating in overhead throwing sports, particularly baseball pitchers. Additionally, javelin throwers, arm wrestlers, and collegiate wrestlers are also at risk for these types of injuries [81]. Since Jobe et al. performed the first medial ulnar collateral reconstruction in 1974, this once considered career-ending injury has become a surgically treatable pathology in most athletes with moderate to excellent rates (53–90%) of return to play at a professional level (depending on the author) [82, 83]. Although the Tommy John procedure has become the standard of care for UCL deficiency, orthobiologics may play a role in athletes during mid-season in order to postpone surgery, as an adjunct during surgery to promote healing or as a sole treatment in mild UCL injuries and patients who elect conservative treatment.

Literature supporting the use of orthobiologics in UCL injuries is limited. Dines et al. published a retrospective series of 44 baseball players with partial UCL tears treated with PRP injections and rehabilitation protocol [84]. They reported that 32 patients (73%) had a good to excellent outcome and that 67% of professional players returned to professional play. Podesta et al. treated 34 athletes who failed 2 months of conservative treatment for a partial UCL tear, with a PRP injection under ultrasound. They reported that 88% of patients returned to the same level of play without complaints and the average time to return to play was 12 weeks. Only one patient suffered persistent UCL instability and underwent surgery [85].

A recent study, McQueen et al. performed a comparative analysis of nonoperative treatment of UCL injuries in professional baseball players with or without PRP. The Health and Injury Tracking System (HITS) was reviewed, and the authors of the study found that players who received a PRP injection had longer time before returning to throwing (64 days vs. 51 days, $p < 0.001$); however, they concluded it might be due to a delay between the injury date and PRP injection (mean time from injury date to PRP injection was 14.5 days). There was no significant effect on the likelihood of surgical intervention [86].

More recently, Kato et al. published a series of 30 baseball players with partial or complete UCL injuries (9 grade 1 UCL injury; 13 grade 2; 8 grade 3) who failed 2 months of conservative treatment, and were treated with ultrasound guided trephination and an LP-PRP injection (ACP™, Arthrex, Florida, USA) [87]. They reported that 26 out of the 30 athletes were able to RTS at pre-injury level of play at an average of 12.4 weeks (range: 10–18), while four athletes required surgery (3 grade 2; 1 grade 3; 3 had distal tears; and 1 proximal). Improvements were recorded in visual analog scale (VAS) scores, Disabilities of the Arm,

Shoulder, and Hand (DASH) sports module scores, and sonographic ulno-humeral joint space opening with valgus stress.

To date, limited evidence exists on outcomes of management of UCL injuries using cell-based therapies.

46.2.5 Muscle Injuries

Muscle injuries are very common among athletes in general and basketball players in particular; In a recent prospective follow-up study of 59 male professional European basketball players, muscle injuries were found to have a higher incidence than ankle sprains, accounting for 21.2% of all injuries, with similar return to play (RTP) time of 7.6 ± 7.1 days for muscle injuries compared to 8.4 ± 9.5 days for ankle injuries [88]. This presents a significant problem for basketball team clinicians as management of muscle injuries can often be challenging no less than ankle injuries, as shown in this study [88]. Muscle injuries in the athlete can be classified into intrinsic and extrinsic injuries. Intrinsic muscle injuries occur most commonly at the myotendinous junction during eccentric contraction with tearing of the muscle fibers. Extrinsic muscle injuries in the athlete occur most commonly as a result of a contusion injury [89]. Conservative management has been the mainstay of treatment for most muscle injuries and usually consists of rest, ice, compression and elevation (RICE protocol), physiotherapy, NSAIDs, and time [90]. Aiming to promote early return to play, decrease recurrence rates and minimize fibrosis and subsequent muscle weakness, newer treatment modalities have been introduced into the field, including PRP and cell therapy [89, 91].

Muscle tissue regeneration is commonly limited by scar tissue formation, rather than by the rate of muscle regeneration [92, 93]. While the potential benefit of orthobiologics use for muscle injuries is not only early return to sports but also improved tissue healing with improved structural properties, potentially reducing the risk of recurrence, most clinical studies have only focused on return to sports rates and durations. With this in mind, Terada et al. performed a preclinical study assessing muscle healing of contusion-injured tibialis anterior muscle in mice with combined treatment of an oral antifibrotic agent (Losartan) and PRP [94]. The study showed increased muscle regeneration and function, along with decreased fibrosis in the experimental group. In vitro work has shown that PRP use can lead to myoblast proliferation, but not to myoblast differentiation, which is important in producing muscle tissue [95]. Furthermore, some growth factors contained in platelets, specifically myostatin and TGF-b1, have been proven detrimental to muscle regeneration [96, 97]. Several other preclinical studies involving the injection of PRP alone for gastrocnemius muscle injury in mice and rats have shown mixed results regarding the acceleration of tissue healing [98–103] performed controlled laboratory studies which suggested that platelet poor plasma (PPP) and PRP preparations subjected to a second spin to remove platelets led to the induction of myoblast cells into the muscle differentiation pathway [102, 103]. PRP that was not modified with a second spin led to induction into the muscle proliferation pathway. They concluded that these results suggests that PPP and LP-PRP subjected to a second spin to remove platelets could be used to stimulate muscle differentiation and subsequent muscle regeneration [102, 103].

Several studies have reported positive outcomes of autologous conditioned serum (ACS) and PRP injections for the treatment of muscle strains. Wright-Carpenter et al. have reported significantly shorter recovery time in a case–control study of professional sportsmen with various muscle strains who were treated with ACS [104]. Sanchez et al. have reported the use of PRP in muscle injuries of different severities in 21 professional soccer players. Their results suggested the PRP group required half the time to resume normal training activities when compared to matched historical controls [90]. Rossi et al. performed a randomized controlled trial comparing a rehabilitation program alone vs. a rehabilitation program plus a PRP injection for muscle injury (Hamstrings, quadriceps, and gastrocnemius) [105]. They presented significantly earlier full recovery (21 days vs. 2 days) and significantly lower pain scores in the PRP group.

We are unaware of clinical studies supporting the use of BMAC or other cell-based therapies in the management of muscle injuries.

46.2.6 Hamstring Muscle Injuries

Hamstrings injuries are one of the most common injuries in professional athletes and is also common in basketball [106], usually dictating a prolonged rest period and delayed return to play even in mild injuries. Hamid et al. published a randomized controlled trial of 28 patients comparing a rehabilitation program with and without a PRP injection for hamstrings injury [107]. They found shorter time to return to play in the PRP group (26.7 days) when compared to the rehabilitation alone group (42.5 days). Another recent prospective study by Bezuglov et al. reported similar results in 40 soccer players [108].

Other studies on outcomes of PRP injections in hamstrings injuries, however, do not support its use. Reurink et al. performed a double-blind, placebo-controlled, randomized study on 80 professional and recreational athletes with acute hamstrings injuries treated with two intramuscular injections of PRP or isotonic saline [109]. They found no benefit for intramuscular PRP injections for acute hamstrings tears. Several other studies reported the lack of benefit for intramuscular PRP injections for acute hamstrings tears [110–113].

Fact Box

Current literature does not provide sufficient evidence to support the use of PRP for muscle injury; however, many studies are relatively heterogenous regarding injury type and preparation method. Laboratory studies suggest PPP or LP-PRP with platelets removed may induce muscle regeneration. Further high-quality evidence is needed to define the role of PRP and cell-based therapies in muscle injuries.

Our personal approach to orthobiologics use for muscle injuries depends on the extent of muscle injury and would be considered in cases where true and significant muscle fibers disruption is confirmed on imaging studies. In cases where hematomas or seromas are present, they are evacuated under ultrasound guidance to decompress the area of injury; if and once the hematoma is evacuated, a platelet poor fraction (i.e., Fraction 1—F 1 in PRGF) is activated and injected into the injury site and adjacent peripheral healthy muscle (Fig. 46.2). We primarily prefer to use the platelet-poor fraction since it has a reduced concentration of the pro-fibrotic factor TGFβ-1, unlike the platelet-rich fraction, which is adjacent to the buffy coat layer or leukocytes sediment; Repeated ultrasound (US) or MRI imaging is used to follow healing progression and assess for excessive fibrosis which may predispose to reinjury. Repeated injections may be applied at a minimum of 1 week intervals and are based on US imaging (to assess muscle tissue damage) and symptoms.

While the majority of muscle injuries are managed conservatively, another potential application of orthobiologics use for muscle injuries is in scenarios requiring surgical management. Such scenarios include: Complete or extensive musculo-tendinous junction (MTJ) avulsion in athletes, chronic symptomatic limiting injuries, and/or symptomatic nerve involvement. In such cases, for example in hamstrings and rectus femoris proximal injuries which are of severe definition in athletes, orthobiologics use could be considered during to surgery, with platelet-poor plasma fraction infiltration into and around the repair site (Fig. 46.3).

46.3 Summary

Orthobiologics have emerged in recent years as a safe and promising treatment option for musculoskeletal injuries and pathologies. However, evidence of its efficacy has been mixed and highly variable depending on the specific indication. Current evidence presents large heterogeneity in the various orthobiologic products, protocols, and characteristics making interpretation of existing literature a complicated task. Recent litera-

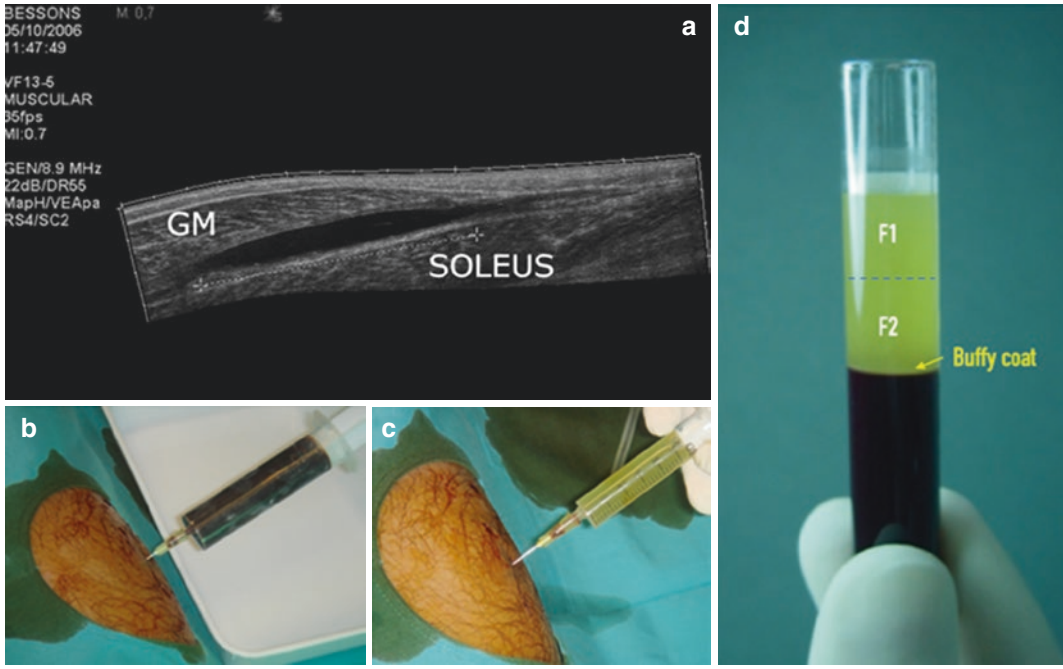

Fig. 46.2 (**a**) Ultrasound image of an extensive soleus muscle injury and the area of surrounding hematoma (Arrow; black area inside the muscle); (**b**) Hematoma evacuation using a 10 cc syringe; (**c**) Injection of platelet-poor plasma (PRGF F1 fraction, Endoret ® System) intramuscular injection using a 10 cc syringe; (**d**) PRGF fractions distribution following centrifugation

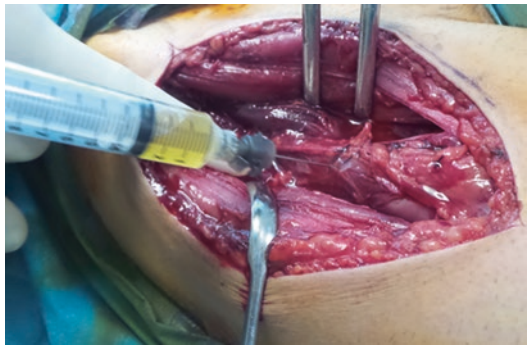

Fig. 46.3 Surgically repaired proximal rectus femoris MTJ injury. With platelet-poor plasma being injected into the repair site

ture has shown orthobiologics to have promising potential in improving tissue regeneration in laboratory and animal studies; however, results in the clinical setting have been mixed and variable in demonstrating consistent efficacy. Future high-quality large clinical trials are necessary to determine the true clinical value of these treatment options.

Take Home Messages

- The best available clinical evidence does not demonstrate efficacy of PRP injections for ACL reconstruction.
- There is currently insufficient high-quality evidence for the recommendation of PRP injections in high ankle sprains, but small clinical trials have shown promising efficacy for LP-PRP injections for high ankle sprains.
- There is sufficient evidence to consider the use of PRP for UCL injuries that are refractory to a first line of conservative treatment; however, there are conflicting results reported and athletes who have significant restrictions on time lines for return to sport must weigh that factor into the decision process.
- Current literature is conflicting and heterogenous regarding the use of PRP for muscle injuries, while preclinical stud-

ies suggest that PPP may hold promise for muscle injuries. Further high-quality clinical trials are necessary to validate this.

- There is lack of sufficient studies to support cell-based therapies for the management of soft tissue injuries and therefore concrete evidence-based clinical recommendations cannot be made.
- In summary, orthobiologics have yet to be thoroughly studied in specific soft tissue injuries in athletes in general and basketball players in particular. Future high-quality studies in these populations will unveil the true clinical value of this emerging field.

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