47 The Role of Orthobiologics in the Management of Cartilage and Meniscal Injuries in Sports

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47.1 Cartilage Injuries

47.1.1 Introduction

Articular cartilage injuries in the athlete represent a significant source of pain and disability, resulting in time lost from play and predisposing athletes to early joint degeneration and shortened athletic careers [1, 2]. Athletes competing in sports requiring repetitive, high-impact loading such as basketball are particularly susceptible to chondral injuries secondary to acute traumatic episodes or repeated loading over time. A systematic review of 11 studies, comprising 931 American basketball, football, and endurance running athletes reported chondral defects to be present in up to 36% of knees [3]. Combined with the rising incidence of athletic participation at all levels of competition, a growing incidence of sports-related injuries to the articular cartilage has been reported [4–6], with a consequential increase in surgical procedures being performed annually for chondral injuries [7–10].

Particularly in basketball players, the integrity of articular cartilage is essential to optimize joint motion and minimize friction while providing support for the mechanical joint stresses placed across the knees during jumping, running, and cutting [11]. However, due to the poor inherent healing capacity of cartilage, secondary to the aneural, avascular nature of chondrocytes, the intrinsic potential for repair is minimal, with injured cartilage substituted by fibrocartilage [12–16]. Moreover, continued loading on injured cartilage has been shown to result in the accumulation of degradative enzymes and cytokines, leading to disruption of the collagen ultrastructure, resulting in further chondral damage [17–19]. As such, articular cartilage injuries represent a therapeutic challenge in the athlete due to the high functional demands placed on the articular surfaces and the athlete's desire to return to the same or higher levels of competition following injury [20].

The goal of returning athletes to pre-injury levels quickly following chondral injuries while minimizing the risk for development of long-term

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chondral degeneration has led to increased interest in the use of minimally invasive treatment options [21–24]. Specifically, increased attention has focused on the use of orthobiologics both as an isolated, nonoperative treatment modality and as an adjunct therapy during operative cartilage restoration procedures to promote cartilage healing and regeneration [6, 20, 22, 24]. Orthobiologics are defined as naturally occurring substances in the human body used to improve healing of injured cartilage, muscle, tendon, ligaments, and fractures [16]. Orthobiologics currently utilized for the treatment of sport-related chondral injuries include platelet-rich plasma (PRP), bone marrow aspirate concentrate (BMAC), and mesenchymal stem cells (MSC). The purpose of this chapter is to review the current literature on the use of orthobiologics in the treatment of articular cartilage injuries in the athlete.

47.2 Platelet-Rich Plasma

The use of PRP in isolation or as an adjunct to surgery for the treatment of sports-related chondral injuries in the athlete has gained significant interest in recent years [25–28]. PRP is defined as harvested autologous biological blood, concentrated via centrifuge to contain 1.5–2 to around a ninefold increase in platelet concentration compared with baseline endogenous serum levels [29, 30] or more than one million platelets per milliliter of serum although these values may not be agreeable by all, and reports of higher concentrations exist as well as commercially available products [31, 32] (Figs. 47.1 and 47.2). Injection of PRP leads to platelet activation, while also stimulating the release of various growth factors and cytokines [22, 30]. These biologic mediators include vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), insulin-like growth factor-1 (ILGF-1), interleukin-1β, interleukin-10, and tumor necrosis factor-β [33]. These growth factors and cytokines have been shown to activate biologic pathways, providing anti-inflammatory effects, while stimulating matrix synthesis, endothelial growth, angiogene-

Fig. 47.1 Platelet-rich plasma (PRP) before centrifugation

Fig. 47.2 Platelet-rich plasma (PRP) after centrifugation

sis, collagen synthesis, cell proliferation, and cell differentiation to initiate tissue healing [15, 16, 22, 34–37]. PRP preparations are traditionally divided based on leukocyte concentration, separated into leukocyte-rich PRP (LR-PRP) and leukocyte-poor PRP (LP-PRP) preparations [18, 38]. Prior studies have shown that LR-PRP creates a less ideal environment for chondral repair and detrimental to clinical outcomes through the expression of pro-inflammatory markers and catabolic cytokines [39, 40].

The widespread use of PRP, coupled with the relative ease and safety of obtaining autologous PRP with little risk to the patient, have made the use of PRP an attractive option for the management of cartilage injuries [33, 41]. However, there remains limited evidence on the efficacy of PRP for the treatment of cartilage injuries, particularly in the athlete. As such, while the majority of clinical investigations have examined outcomes associated with PRP use in non-athletes, multiple investigations have reported superior outcomes associated with the use of PRP treatment in younger patients with less severe degenerative chondral changes in the knee, comparable to the athletic population. Kon et al. compared 50 patients with symptomatic knee osteoarthritis (OA) undergoing three PRP injections to 100 patients treated with either high-molecular-weight hyaluronic acid (HA) or low-molecular-weight HA. The authors found that PRP provided improved outcomes and a longer duration of efficacy in reducing pain and symptoms based on visual analog scale (VAS) and International Knee Documentation Committee (IKDC) scores [42]. When analyzed based on patient age and degree of osteoarthritic changes, superior results were reported in younger and more active patients with lower degrees of cartilage degeneration. Cole et al. similarly reported in their double-blind, randomized controlled trial of patients with unilateral knee OA comparing LP-PRP to HA injections that patients with mild OA and lower body mass index experienced significantly better outcomes [43]. Meanwhile, the systematic review by Campbell et al. examining three meta-analyses comparing the use of PRP injection to the knee versus corticosteroids, HA, oral nonsteroidal anti-inflammatory drugs, or placebo found increased benefit for using PRP with reduced pain, improved range of motion, and quality of life in patients with focal chondral defects and early mild to moderate osteoarthritis [44]. Moreover, assessing athletes at the end of their career with chronic knee pain secondary to degenerative chondral lesions of the knee, Papalia et al. analyzed 48 professional soccer athletes randomized into two groups receiving either three injections of hybrid HA (HHA; $n = 24$ athletes) or three injections of PRP ($n = 23$ athletes) [45]. While athletes in the HHA group demonstrated significantly superior results when compared to the PRP group at 3 and 6 months follow-up, no significant differences in outcomes were reported by 12 months.

Fact Box

Multiple investigations examining outcomes following the use of PRP for the treatment of articular cartilage injuries have reported improved outcomes in younger patients with lower degrees of cartilage degeneration [46–48].

Few studies have examined the impact of PRP for the treatment of chondral lesions about the hip, with limited data in athletic patients. Dallari et al. examined 111 patients aged 18–65 years old, randomized to three groups, receiving three weekly injections of either PRP, PRP + HA, or HA [49]. The authors reported that patients receiving PRP alone had lower VAS pain scores at 2, 6, and 12 months follow-up, along with significantly better Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores at 2 and 6 months. Meanwhile, Battaglia et al. performed a non-blinded, randomized trial comparing PRP versus HA in 100 consecutive patients with hip OA. Harris Hip Score (HHS) and VAS pain scores were found to be significantly improved between 1 month and 3 months follow-up in both groups. However, progressive worsening of symptoms was reported between 6 months

and 12 months follow-up despite scores remaining significantly improved when compared to preoperative values [50]. Moreover, no significant differences were found between the PRP or HA groups at any time point, while a significant association was appreciated between higher Kellgren-Lawrence (K-L) OA grade (Grade IV) and VAS score over the course of the investigation. As such, the use of PRP for chondral lesions affecting the hip of the athlete remains largely unknown and warrants further investigation.

In addition to the lack of high-quality studies examining the efficacy of PRP in athletes with chondral injuries, a major limitation to the use of PRP for the treatment of cartilage defects remains the lack of standardization and variability in PRP preparation techniques. The development of proper terminology to describe and classify the many different available PRP products and the variability in their characteristics is essential, especially when comparing results between various studies and analyzing the benefits of such treatments. The need for improved terminology, categorization, and classification has emerged in recent years with the growing number of reported studies using various PRP products and resulted in several classification systems. The first described and most comprehensive classification system is the Dohan Ehrenfest classification [32], which is based on cell content (mostly leukocytes) and fibrin architecture. Four main families were defined in this classification: Pure platelet-rich plasma (P-PRP)—or leukocyte-poor platelet-rich plasma (LP-PRP)—products are preparations without leukocytes and with a low-density fibrin network after activation; leukocyte- and platelet-rich plasma (L-PRP) products are preparations with leukocytes and with a low-density fibrin network after activation; pure platelet-rich fibrin (P-PRF)—or leukocyte-poor platelet-rich fibrin—are preparations without leukocytes and with a high-density fibrin network; and leukocyte- and platelet-rich fibrin (L-PRF) products are preparations with leukocytes and with a high-density fibrin network. Two other classification systems were proposed in recent years, which were more directed toward sports medicine applications. These are the Mishra classification and the PAW (platelet, activation, white cells) classification [34, 51]. Mishra et al. [51] proposed a classification that takes into consideration the presence of leukocytes, activation of platelets, and platelets concentration.

This classification established four types of PRP: an L-PRP solution (type 1 PRP), an L-PRP gel—with activation (type 2 PRP), a P-PRP solution (type 3 PRP), and a P-PRP gel—with activation (type 4 PRP). Each type can be described as an A or B subtype, with the A subtype standing for ≥X5, the blood concentration of platelets, and the B subtype standing for <X5, the blood concentration of platelets. The PAW classification [34] has similarities with the Mishra classification and is based on the absolute number of platelets, the manner in which platelet activation occurs, and the presence or absence of white cells. Different concentrations of platelets, leukocytes, and other growth factors in the final PRP preparation have been reported due to the availability of various commercial PRP preparation systems, resulting in wide variability in the contents of the final PRP product [25, 47, 52]. This inconsistency may account for the variable and oftentimes conflicting results among studies [25, 53, 54]. Moreover, lack of transparency and detail in reporting preparation techniques in many studies has made comparisons between studies difficult [55]. Further questions regarding the number of injections, timing of doses, use of LP-PRP versus LR-PRP, and the volume of injection require further studies to establish a gold standard protocol for the preparation and use of PRP in athletes [27, 33, 54].

Fact Box

There remains substantial discrepancy in PRP preparation techniques, injection contents, and delivery methods, warranting additional studies to better define the optimal treatment protocol for use in the athlete [16, 18, 30, 49, 50, 56].

Many more preparations are being investigated for their efficacy in cartilage injuries such as PRP-conjugate preparations and autologous conditioned serum (ACS). There is recent interest in creating PRP conjugates with other biologics (such as hyaluronic acid) to enhance healing through the properties of both materials [31, 57, 58]. However, there is no sufficient evidence to support its efficacy in athletes. ACS products such as Regenokine (marketed in the US) and Orthokine (marketed in Europe) have shown some success in the management of cartilage pathology. Although, most studies have reported efficacy in osteoarthritis [38, 59, 60], ACS is commonly used in athletes, particularly in Europe.

47.3 Bone Marrow Aspirate Concentrate

The popularity of BMAC has recently increased due to BMAC being one of the few procedures approved by the Federal and Drug Administration (FDA) for intra-articular, single-step delivery of MSCs [48]. In addition to MSCs, BMAC possesses hematopoietic stem cells, endothelial progenitor stem cells, and PDGFs that have been shown to improve tissue healing [61]. Despite only accounting for 0.001–0.01% of nucleated cells in standard BMAC injections [62], MSCs possess strong inherent regenerative properties. BMAC can presumably assist in the treatment of articular cartilage injuries, due to its regenerative potential, and ability to modulate the immune system via enhanced secretion of growth factors and cytokines [63–65]. The contents of BMAC have been shown to signal surrounding tissues to secrete growth factors and cytokines, including VEGF, PDGF, transforming growth factor-beta (TGF-β), bone morphogenetic protein (BMP)-2 and BMP-7, which are present in higher quantities when compared to PRP [22, 66]. These biologic modulators have been linked to chondrocyte proliferation, MSC differentiation, wound healing, as well as the suppression of potentially detrimental pro-inflammatory cytokines [67].

Clinically, BMAC augmentation has been shown to play a role in regenerating more hyaline-like repair tissue, improving patient-reported outcomes, and improving radiographic evidence of healing [68]. However, no current investigation has focused on the use of BMAC specifically in athletes. Chahla et al. reported in their systematic review that despite the lack of high-quality studies examining the use of BMAC for the treatment of early-onset OA, BMAC injection was a safe procedure with few reported adverse effects [66]. However, varying degrees of beneficial results with respect to the effect of BMAC for the treatment of chondral defects and early OA were reported, due to the high number of patients treated with and without an additional procedure. Meanwhile, Kim et al. reported outcomes of BMAC injection with adipose tissue in a case series of 75 knees ($n = 41$ patients) with knee OA (K-L grades I–IV) [69]. While statistical significance was not reported, VAS pain score, IKDC, short-form (SF)-36, Knee Injury and Osteoarthritis Outcome Score (KOOS), and Lysholm scores were found to be increased when compared to preoperative values by 12 months. Moreover, the authors noted a significant association between higher K-L grade and inferior clinical outcomes at final follow-up ($p = 0.02$).

Fact Box
Results following BMAC treatment for articular cartilage injuries have demonstrated improved outcomes in patients with lower grades of knee degeneration [60].

When utilized as a surgical adjunct, Gobbi et al. examined 15 patients with International Cartilage Repair Society (ICRS) grade IV knee chondral lesions (average size, 9.2 cm [4]) undergoing operative transplantation with BMAC covered with a collagen I/III matrix [70]. At 24 months, significant improvements in VAS pain score, IKDC, KOOS, Lysholm, Marx, SF-36, and Tegner scores were reported when compared to preoperative values. The presence of

hyaline-like tissue over the lesions was also reported based on magnetic resonance imaging (MRI) and histologic evaluation. Overall, superior outcomes were reported in patients with solitary cartilage defects and in patients with small lesions. Gobbi et al. further reported in their prospective cohort study of patients with ICRS grade 4 chondral lesions of the knee treated with HA-based scaffolds soaked in BMAC that clinical outcomes were correlated with the size of the chondral lesion treated [13]. Specifically, significantly better subjective IKDC scores and a trend toward a significantly better KOOS pain scores were found in patients with lesions smaller than 8 cm [4] compared to those with lesions larger than 8 cm [4] at final follow-up. For chondral defects of the talus, Giannini et al. compared the use of a single injection of BMAC ($n = 25$ cases) versus open autologous chondrocyte implantation (ACI) ($n = 10$ cases) versus arthroscopic ACI ($n = 46$ cases) in 81 patients with a mean age of 30 ± 8 years [71]. At second look arthroscopy with biopsy at 12 months, no significant difference in change in American Orthopaedic Foot and Ankle Society (AOFAS) score was appreciated between the three groups. However, BMAC was noted to permit a marked reduction in procedure morbidity and costs as a "one-step" procedure.

A recent systematic review by Migliorini et al. reported improved outcomes in patients receiving MSCs injections for knee osteoarthritis with 12 months follow-up. They included 18 studies and 1069 treated knees. Average age of patients was 57 years old. They reported improvement in patient-reported outcomes and a 12.7% local complications rate [15].

Hede et al. evaluated the clinical outcomes of ten patients treated with a one-step procedure using autologous BMAC and PRP on a collagen scaffold for large full-thickness cartilage lesions of the knee. They reported an increase in clinical outcome scores and pain scores at 1 and 2 years postoperatively. However, they also found that MRI and histology (from second-look arthroscopy that was performed in seven patients) have demonstrated repair tissue inferior to native hyaline cartilage [21].

Fact Box

When used as an adjunct during operative management, improved outcomes have been reported in patients with isolated chondral lesions or lesions measuring less than $8cm^2$ [2, 32].

Similar to PRP, the current literature examining the utilization of BMAC for athletic injuries remains lacking in high-quality studies focusing on athletes, as there remains limited evidence supporting the efficacy of the BMAC product, while standardized guidelines for preparation remain limited [16]. In addition, the ideal harvest site and technique, carrier for BMAC, number of BMAC treatments, injection timing, and volume remain poorly characterized [35].

47.4 Mesenchymal Stem Cells

MSCs have been shown to possess high plasticity while being immune-suppressive, anti-inflammatory, and capable of self-renewal. MSCs are known to produce proteins conducive to cartilage regeneration, making them perhaps the most promising stem cell option for articular cartilage repair [12, 35]. MSCs are present and can be harvested from various adult tissues, including bone marrow, peripheral blood, adipose tissue, and synovium. Recently, adipose-derived stem cells (ASCs) have gained increased popularity due to the ease of accessibility and harvest from liposuction aspirate or from the infrapatellar fat pad, resulting in minimal morbidity [37, 72]. Moreover, ASCs have been shown to possess up to 300-fold more stem cells per volume when compared to BMAC [9, 73] while maintaining their phenotype better over culture passages when compared with bone-marrow-derived MSCs [63, 72, 74].

There are currently few studies examining the use of MSCs for the treatment of chondral injuries in athletes. However, MSCs have been shown to possess chondro-inductive properties in vitro, capable of inducing chondrocyte

proliferation and extracellular matrix production [75], resulting in encouraging clinical results and pain reduction without significant complications. A systematic review by Chahla et al. identified six studies examining intra-articular injections of stem cells within the knee for the treatment of cartilage injuries [75]. While no studies commented on the use of MSCs for athletes, all studies were noted to report improvement for patients with OA and focal chondral defects without significant adverse events. However, the authors noted that reported improvements were modest and that the presence of a placebo effect could not be ruled out. The retrospective cohort study by Kim et al. examined 20 patients with knee OA treated with MSC injection combined with PRP versus a pair-matched cohort of patients undergoing MSC implantation using a fibrin glue scaffold [23]. At a mean follow-up of 28.6 months, the authors reported significant improvement in IKDC and Tegner activity score in both groups compared to preoperative values, with significantly higher IKDC scores in the implantation group. Moreover, Nejadnik et al. compared outcomes between patients with chondral defects undergoing repair using ACI ($n = 36$) or bone-marrow-derived MSCs ($n = 36$), with outcomes measured at 3, 6, 9, 12, 18, and 24 months following treatment [76]. No significant differences between groups were reported based on Lysholm, IKDC, or Tegner activity scores, highlighting the effectiveness of bone-marrow-derived MSCs for focal cartilage lesions. Meanwhile, arthroscopic implantation of synovial MSCs in 10 patients with single chondral lesions of the femoral condyles was found to improve MRI features score, qualitative histology, and Lysholm score, but no improvement in Tegner activity level was reported [77]. Kyriakidis et al. have recently published a study on 25 patients undergoing treatment with ASCs implantation for focal cartilage defects of the knee with a 3-year follow-up [78]. Patient-reported outcomes significantly improved ($p < 0.05$), including IKDC, KOOS, Tegner, and VAS. Interestingly, histological analysis from two patients who underwent postoperative biopsies demonstrated the presence of hyaline-like tissue. Bastos et al. performed a randomized, controlled, and double-blinded study assessing the efficacy of culture-expanded MSCs injection with or without PRP in patients with knee osteoarthritis. They enrolled 47 patients in three groups, MSCs ($N = 16$), MSCs + PRP ($N = 14$), and corticosteroids ($N = 17$). They reported an improvement in most KOOS domains and global scores for the three groups in 1 and 12 months ($p < 0.05$). At 12-month follow-up, the corticosteroids group only showed significant improvement in the pain and function sub-scores, while the MSCs and the MSCs+PRP groups showed improvement in all KOOS domains and global scores (except quality of life for the MSCs+PRP group) [46].

Further research on the indication, safety, and efficacy of MSCs, particularly ASCs, for the treatment of athletic chondral-related injuries are warranted. Most current studies lack a control group, while in many other studies, additional therapeutic interventions and orthobiologics have been simultaneously added, preventing an accurate understanding of the contribution of MSCs to chondral healing. Similar to other orthobiologics, additional studies are necessary to better understand optimal harvest location, culture methods, cell concentration, and transplantation method for the treatment of cartilage injuries in athletes [77].

47.5 Meniscal Injuries

There are several inherent factors that create an unfavorable environment for healing of a meniscus tear. These include the avascular nature of the meniscus, the presence of synovial fluid and proinflammatory cytokines, and the repetitive load on the meniscus, which is virtually unavoidable. The avascular nature of the meniscus poses a significant challenge for meniscus tear healing. As demonstrated by Arnoczky and Warren, only the peripheral 10–30% of the meniscus is vascularized [79]. Furthermore, the presence of synovial fluid and proinflammatory cytokines has been shown to have a catabolic effect on meniscal healing [80].

In recent years, there has been growing interest in the role of orthobiologics in the treatment of meniscal pathology. There are several modalities for biologic augmentation of meniscal repair, including use of a fibrin clot, cytokines and growth factors, PRP, and cell-based therapies. Although most studies were focused on augmentation of meniscal repair, several studies have also assessed the efficacy of orthobiologics injections as a sole treatment for meniscal tears. Wei et al. hypothesized that PRP can enhance the healing of white on white meniscal tears [81]. Shin et al. have studied the effect of LR-PRP on healing of a horizontal medial meniscus tear in a rabbit model and found no significant differences in meniscal healing between the LR-PRP group and controls [82]. Ishida et al. reported an in-vitro and an in-vivo study in a rabbit model demonstrating increased healing with filling of the meniscal defect with a gelatin hydrogel delivery system for PRP [83]. Betancourt and Murrell presented a case of a 29-year-old woman improving after treatment with LP-PRP injections for a meniscal tear [84]. Blanke et al. reported on the use of percutaneous PRP injections of intrasubstance meniscal tears (grade 2) in ten recreational athletes. The injections were aimed at the affected site with the use of fluoroscopy guidance. Each patient received three sequential injections in a 7-day interval. Six patients (60%) showed improvement in outcomes and increased sports activity [85]. Literature on the effect of other injectables is limited. However, of note, Pak et al. have presented a case of a patient treated successfully with an ASC percutaneous injection [10].

47.6 Augmentation of Meniscal Repair

A recent randomized controlled trial investigated PRP augmentation of repaired vertical tears as compared to isolated suture repair. The results were favorable, with statistically significant functional outcome improvement, lower failure rates, and better healing on second look arthroscopy at 42 months after surgery in PRP-augmented repairs [14]. Another recent study by Everhart et al. found that PRP augmentation of isolated meniscus repairs resulted in significantly decreased failure rates at 3 years after surgery [86]. However, PRP augmentation of meniscus repairs with concomitant ACL reconstruction was found to have no difference in failure rates when compared to controls at the same time period. A number of smaller studies with lower levels of evidence have produced more mixed results, with some showing modest benefits in functional outcomes while others finding no benefits when compared to placebo [24, 56, 87, 88]. While promising, there remains significant heterogeneity in PRP preparation techniques as well as the type of tear being repaired, and future well-designed studies are needed to corroborate these early findings.

Fibrin clot augmentation has also proven to be an efficacious adjunct to meniscus repairs in several investigations. In an early investigation of five patients with complete radial tears of the posterolateral aspect of the lateral meniscus traditionally treated with meniscectomy, van Trommel et al. completed suture repairs enhanced with a fibrin clot [89]. On MRI assessment of three of the five patients at an average of 71 months after surgery, all menisci were completely healed with no evidence of degenerative change. Recently Ra et al. also utilized fibrin clot augmentation of complete radial tear repairs in 12 patients, which similarly results in excellent rates of healing and functional outcome improvement [90]. Fibrin clots have also been investigated in the repair of horizontal cleavage tears, with significant functional outcome improvement, but only a 70% healing rate on second look arthroscopy at 12 months after repair [36]. As with PRP augmentation, future large and well-designed studies are needed to confirm the preliminary benefits of fibrin clots in the healing of meniscus repairs.

Additionally, the use of BMAC in meniscus repair surgery has shown promise. In a basic science study using a rabbit model with avascular meniscal lesions, Koch et al. found that BMAC augmentation demonstrated macroscopic and histologic evidence of superior healing when

compared to PRP and no augmentation of suture repaired meniscus lesions at 6 and 12 weeks after surgery [91]. Another recent investigation by Piontek et al. utilized bone marrow aspirate injection and collagen wrapping of repaired meniscus lesions, finding favorable functional and radiographic outcome improvements at 2 years after surgery [92]. While preliminary, bone-marrow-derived augmentation techniques are being actively studied, with several ongoing clinical trials currently investigating BMAC and meniscus repair.

47.7 Conclusion

The popularity of orthobiologics for the use of cartilage and meniscal injuries in sports continues to increase. Current treatment guidelines for the use of orthobiologics for cartilage defects and meniscal tears based on type, size, location, and defect severity while accounting for patient's age, activity level, and desire to return to competition remain poorly characterized, requiring further research to define an optimal treatment algorithm. Such algorithm should also differentiate between the efficacy of orthobiologics for focal defects, osteochondritis dissecans (OCD), and osteoarthritis, as these pathologies may defer in many aspects. Despite most investigations reporting orthobiologics to be safe with few serious adverse effects, inconsistent and at times conflicting data has been reported. The discrepancy in outcomes requires standardization for orthobiologic processing while defining the optimal contents of orthobiologic preparations to allow for reliable comparison among studies. By defining a standard procedure, future basic science and clinical research utilizing well-designed randomized controlled trials are warranted to determine the long-term impact of chondral injuries in the knee of the athlete. Meanwhile, establishing short- and medium-term data for injuries within the hip and ankle is necessary to better understand the role of orthobiologics as a minimally invasive individual treatment or adjunct during operative intervention. Such limitations must be weighed against the popularity of orthobiologics in their use for the treatment of articular chondral and meniscal injuries in the athlete.

Take-Home Message

Despite the increased popularity of orthobiologics for the treatment of articular cartilage injuries, further investigations standardizing treatment preparation, contents, and protocols are necessary to better understand the efficacy and long-term effects of the use of orthobiologics in the athlete.

The role of orthobiologics in meniscal injuries is less understood, and current evidence does not allow making recommendations regarding the use of orthobiologics in meniscal injuries.

References

1. Drawer S, Fuller CW. Propensity for osteoarthritis and lower limb joint pain in retired professional soccer players. Br J Sports Med. 2001;35(6):402–8.
2. Engstrom B, Forssblad M, Johansson C, Tornkvist H. Does a major knee injury definitely sideline an elite soccer player? Am J Sports Med. 1990;18(1):101–5.
3. Flanigan DC, Harris JD, Trinh TQ, Siston RA, Brophy RH. Prevalence of chondral defects in athletes' knees: a systematic review. Med Sci Sports Exerc. 2010;42(10):1795–801.
4. Arendt E, Dick R. Knee injury patterns among men and women in collegiate basketball and soccer. NCAA data and review of literature. Am J Sports Med. 1995;23(6):694–701.
5. Jones SJ, Lyons RA, Sibert J, Evans R, Palmer SR. Changes in sports injuries to children between 1983 and 1998: comparison of case series. J Public Health Med. 2001;23(4):268–71.
6. Mithofer K, Peterson L, Mandelbaum BR, Minas T. Articular cartilage repair in soccer players with autologous chondrocyte transplantation: functional outcome and return to competition. Am J Sports Med. 2005;33(11):1639–46.
7. Ciccotti MC, Kraeutler MJ, Austin LS, et al. The prevalence of articular cartilage changes in the knee joint in patients undergoing arthroscopy for meniscal pathology. Arthroscopy. 2012;28(10):1437–44.
8. McCormick F, Harris JD, Abrams GD, et al. Trends in the surgical treatment of articular cartilage lesions in the United States: an analysis of a large private-payer database over a period of 8 years. Arthroscopy. 2014;30(2):222–6.

9. Oedayrajsingh-Varma MJ, van Ham SM, Knippenberg M, et al. Adipose tissue-derived mesenchymal stem cell yield and growth characteristics are affected by the tissue-harvesting procedure. Cytotherapy. 2006;8(2):166–77.
10. Pak J, Lee JH, Lee SH. Regenerative repair of damaged meniscus with autologous adipose tissue-derived stem cells. Bio Med Res Int 2014;2014.
11. Sakata R, Iwakura T, Reddi AH. Regeneration of articular cartilage surface: morphogens, cells, and extracellular matrix scaffolds. Tissue Eng Part B Rev. 2015;21(5):461–73.
12. Chang YH, Liu HW, Wu KC, Ding DC. Mesenchymal stem cells and their clinical applications in osteoarthritis. Cell Transplant. 2016;25(5):937–50.
13. Gobbi A, Scotti C, Karnatzikos G, Mudhigere A, Castro M, Peretti GM. One-step surgery with multipotent stem cells and Hyaluronan-based scaffold for the treatment of full-thickness chondral defects of the knee in patients older than 45 years. Knee Surg Sports Traumatol Arthrosc. 2017;25(8):2494–501.
14. Kaminski R, Kulinski K, Kozar-Kaminska K, et al. A prospective, randomized, double-blind, parallel-group, placebo-controlled study evaluating meniscal healing, clinical outcomes, and safety in patients undergoing meniscal repair of unstable, complete vertical meniscal tears (bucket handle) augmented with platelet-rich plasma. Biomed Res Int. 2018;2018:9315815.
15. Migliorini F, Rath B, Colarossi G, et al. Improved outcomes after mesenchymal stem cells injections for knee osteoarthritis: results at 12-months follow-up: a systematic review of the literature. Arch Orthop Trauma Surg. 2019:1–16.
16. Moatshe G, Morris ER, Cinque ME, et al. Biological treatment of the knee with platelet-rich plasma or bone marrow aspirate concentrates. Acta Orthop. 2017;88(6):670–4.
17. Ding C, Cicuttini F, Scott F, Cooley H, Boon C, Jones G. Natural history of knee cartilage defects and factors affecting change. Arch Intern Med. 2006;166(6):651–8.
18. Lohmander LS, Roos H, Dahlberg L, Hoerrner LA, Lark MW. Temporal patterns of stromelysin-1, tissue inhibitor, and proteoglycan fragments in human knee joint fluid after injury to the cruciate ligament or meniscus. J Orthop Res. 1994;12(1):21–8.
19. Mandelbaum B, Waddell D. Etiology and pathophysiology of osteoarthritis. Orthopedics. 2005;28(2 Suppl):s207–14.
20. Di Matteo B, El Araby MM, D'Angelo A, et al. Adipose-derived stem cell treatments and formulations. Clin Sports Med. 2019;38(1):61–78.
21. Hede K, Christensen BB, Jensen J, Foldager CB, Lind M. Combined bone marrow aspirate and platelet-rich plasma for cartilage repair: two-year clinical results. Cartilage. 2019:1947603519876329.
22. Holton J, Imam M, Ward J, Snow M. The basic science of bone marrow aspirate concentrate in chondral injuries. Orthop Rev. 2016;8(3):6659.
23. Kim YS, Kwon OR, Choi YJ, Suh DS, Heo DB, Koh YG. Comparative matched-pair analysis of the injection versus implantation of mesenchymal stem cells for knee osteoarthritis. Am J Sports Med. 2015;43(11):2738–46.
24. Pujol N, Salle De Chou E, Boisrenoult P, Beaufils P. Platelet-rich plasma for open meniscal repair in young patients: any benefit? Knee Surg Sports Traumatol Arthrosc. 2015;23(1):51–8.
25. Dohan Ehrenfest DM, Andia I, Zumstein MA, Zhang CQ, Pinto NR, Bielecki T. Classification of platelet concentrates (platelet-rich plasma-PRP, platelet-rich fibrin-PRF) for topical and infiltrative use in orthopedic and sports medicine: current consensus, clinical implications and perspectives. Muscles Ligaments Tendons J. 2014;4(1):3–9.
26. Redler LH, Thompson SA, Hsu SH, Ahmad CS, Levine WN. Platelet-rich plasma therapy: a systematic literature review and evidence for clinical use. Phys Sportsmed. 2011;39(1):42–51.
27. Sanchez M, Anitua E, Orive G, Mujika I, Andia I. Platelet-rich therapies in the treatment of orthopaedic sport injuries. Sports Med. 2009;39(5):345–54.
28. Xie X, Ulici V, Alexander PG, Jiang Y, Zhang C, Tuan RS. Platelet-rich plasma inhibits mechanically induced injury in chondrocytes. Arthroscopy. 2015;31(6):1142–50.
29. Deal JB, Smith E, Heard W, O'Brien MJ, Savoie FH 3rd. Platelet-rich plasma for primary treatment of partial ulnar collateral ligament tears: MRI correlation with results. Orthop J Sports Med. 2017;5(11):2325967117738238.
30. Nguyen RT, Borg-Stein J, McInnis K. Applications of platelet-rich plasma in musculoskeletal and sports medicine: an evidence-based approach. PM R. 2011;3(3):226–50.
31. Chen W-H, Lo W-C, Hsu W-C, et al. Synergistic anabolic actions of hyaluronic acid and platelet-rich plasma on cartilage regeneration in osteoarthritis therapy. Biomaterials. 2014;35(36):9599–607.
32. Ehrenfest DMD, Rasmusson L, Albrektsson T. Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte-and platelet-rich fibrin (L-PRF). Trends Biotechnol. 2009;27(3):158–67.
33. Fice MP, Miller JC, Christian R, et al. The role of platelet-rich plasma in cartilage pathology: an updated systematic review of the basic science evidence. Arthroscopy. 2019;35(3):961–76. e963
34. DeLong JM, Russell RP, Mazzocca AD. Platelet-rich plasma: the PAW classification system. Arthroscopy. 2012;28(7):998–1009.
35. Dimarino AM, Caplan AI, Bonfield TL. Mesenchymal stem cells in tissue repair. Front Immunol. 2013;4:201.
36. Kamimura T, Kimura M. Meniscal repair of degenerative horizontal cleavage tears using fibrin clots: clinical and arthroscopic outcomes in 10 cases. Orthop J Sports Med. 2014;2(11):2325967114555678.
37. LaPrade RF, Geeslin AG, Murray IR, et al. Biologic treatments for sports injuries II think tank-current con-

cepts, future research, and barriers to advancement, part 1: biologics overview, ligament injury, Tendinopathy. Am J Sports Med. 2016;44(12):3270–83.
38. Baltzer A, Moser C, Jansen S, Krauspe R. Autologous conditioned serum (Orthokine) is an effective treatment for knee osteoarthritis. Osteoarthr Cartil. 2009;17(2):152–60.
39. Braun HJ, Kim HJ, Chu CR, Dragoo JL. The effect of platelet-rich plasma formulations and blood products on human synoviocytes: implications for intra-articular injury and therapy. Am J Sports Med. 2014;42(5):1204–10.
40. Sundman EA, Cole BJ, Fortier LA. Growth factor and catabolic cytokine concentrations are influenced by the cellular composition of platelet-rich plasma. Am J Sports Med. 2011;39(10):2135–40.
41. Middleton KK, Barro V, Muller B, Terada S, Fu FH. Evaluation of the effects of platelet-rich plasma (PRP) therapy involved in the healing of sports-related soft tissue injuries. Iowa Orthop J. 2012;32:150–63.
42. Kon E, Mandelbaum B, Buda R, et al. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: from early degeneration to osteoarthritis. Arthroscopy. 2011;27(11):1490–501.
43. Cole BJ, Karas V, Hussey K, Pilz K, Fortier LA. Hyaluronic acid versus platelet-rich plasma: a prospective, double-blind randomized controlled trial comparing clinical outcomes and effects on intra-articular biology for the treatment of knee osteoarthritis. Am J Sports Med. 2017;45(2):339–46.
44. Campbell KA, Saltzman BM, Mascarenhas R, et al. Does intra-articular platelet-rich plasma injection provide clinically superior outcomes compared with other therapies in the treatment of knee osteoarthritis? A systematic review of overlapping meta-analyses. Arthroscopy. 2015;31(11):2213–21.
45. Papalia R, Zampogna B, Russo F, et al. Comparing hybrid hyaluronic acid with PRP in end career athletes with degenerative cartilage lesions of the knee. J Biol Regul Homeost Agents. 2016;30(4 Suppl 1):17–23.
46. Bastos R, Mathias M, Andrade R, et al. Intra-articular injection of culture-expanded mesenchymal stem cells with or without addition of platelet-rich plasma is effective in decreasing pain and symptoms in knee osteoarthritis: a controlled, double-blind clinical trial. Knee Surg Sports Traumatol Arthrosc. 2019:1–11.
47. Castillo TN, Pouliot MA, Kim HJ, Dragoo JL. Comparison of growth factor and platelet concentration from commercial platelet-rich plasma separation systems. Am J Sports Med. 2011;39(2):266–71.
48. Gobbi A, Chaurasia S, Karnatzikos G, Nakamura N. Matrix-induced autologous chondrocyte implantation versus multipotent stem cells for the treatment of large patellofemoral chondral lesions: a nonrandomized prospective trial. Cartilage. 2015;6(2):82–97.
49. Dallari D, Stagni C, Rani N, et al. Ultrasound-guided injection of platelet-rich plasma and hyaluronic acid, separately and in combination, for hip osteoarthritis: a randomized controlled study. Am J Sports Med. 2016;44(3):664–71.
50. Battaglia M, Guaraldi F, Vannini F, et al. Efficacy of ultrasound-guided intra-articular injections of platelet-rich plasma versus hyaluronic acid for hip osteoarthritis. Orthopedics. 2013;36(12):e1501–8.
51. Mishra A, Harmon K, Woodall J, Vieira A. Sports medicine applications of platelet rich plasma. Curr Pharm Biotechnol. 2012;13(7):1185–95.
52. Wasterlain AS, Braun HJ, Harris AH, Kim HJ, Dragoo JL. The systemic effects of platelet-rich plasma injection. Am J Sports Med. 2013;41(1):186–93.
53. Riboh JC, Saltzman BM, Yanke AB, Fortier L, Cole BJ. Effect of leukocyte concentration on the efficacy of platelet-rich plasma in the treatment of knee osteoarthritis. Am J Sports Med. 2016;44(3):792–800.
54. Southworth TM, Naveen NB, Tauro TM, Leong NL, Cole BJ. The use of platelet-rich plasma in symptomatic knee osteoarthritis. J Knee Surg. 2019;32(1):37–45.
55. Murray IR, Chahla J, Safran MR, et al. International expert consensus on a cell therapy communication tool: DOSES. JBJS. 2019;101(10):904–11.
56. Griffin JW, Hadeed MM, Werner BC, Diduch DR, Carson EW, Miller MD. Platelet-rich plasma in meniscal repair: does augmentation improve surgical outcomes? Clin Orthop Relat Res. 2015;473(5):1665–72.
57. Lee M-I, Kim J-H, Kwak H-H, et al. A placebo-controlled study comparing the efficacy of intra-articular injections of hyaluronic acid and a novel hyaluronic acid-platelet-rich plasma conjugate in a canine model of osteoarthritis. J Orthop Surg Res. 2019;14(1):314.
58. Russo F, D'Este M, Vadalà G, et al. Platelet rich plasma and hyaluronic acid blend for the treatment of osteoarthritis: rheological and biological evaluation. PLoS One. 2016;11(6):e0157048.
59. Arbel R. Orthokine. In: Bio-orthopaedics. Berlin: Springer; 2017. p. 561–9.
60. Fox BA, Stephens MM. Treatment of knee osteoarthritis with Orthokine®-derived autologous conditioned serum. Expert Rev Clin Immunol. 2010;6(3):335–45.
61. Yokoya S, Mochizuki Y, Natsu K, Omae H, Nagata Y, Ochi M. Rotator cuff regeneration using a bioabsorbable material with bone marrow-derived mesenchymal stem cells in a rabbit model. Am J Sports Med. 2012;40(6):1259–68.
62. Kasten P, Beyen I, Egermann M, et al. Instant stem cell therapy: characterization and concentration of human mesenchymal stem cells in vitro. Eur Cell Mater. 2008;16:47–55.
63. Chahla J, Mandelbaum BR. Biological treatment for osteoarthritis of the knee: moving from bench to bedside-current practical concepts. Arthroscopy. 2018;34(5):1719–29.
64. Dar A, Goichberg P, Shinder V, et al. Chemokine receptor CXCR4-dependent internalization and resecretion of functional chemokine SDF-1 by bone

marrow endothelial and stromal cells. Nat Immunol. 2005;6(10):1038–46.
65. Simmons PJ, Torok-Storb B. Identification of stromal cell precursors in human bone marrow by a novel monoclonal antibody, STRO-1. Blood. 1991;78(1):55–62.
66. Chahla J, Dean CS, Moatshe G, Pascual-Garrido C, Serra Cruz R, LaPrade RF. Concentrated bone marrow aspirate for the treatment of chondral injuries and osteoarthritis of the knee: a systematic review of outcomes. Orthop J Sports Med. 2016;4(1):2325967115625481.
67. Cotter EJ, Wang KC, Yanke AB, Chubinskaya S. Bone marrow aspirate concentrate for cartilage defects of the knee: from bench to bedside evidence. Cartilage. 2018;9(2):161–70.
68. Southworth TM, Naveen NB, Nwachukwu BU, Cole BJ, Frank RM. Orthobiologics for focal articular cartilage defects. Clin Sports Med. 2019;38(1):109–22.
69. Kim JD, Lee GW, Jung GH, et al. Clinical outcome of autologous bone marrow aspirates concentrate (BMAC) injection in degenerative arthritis of the knee. Eur J Orthop Surg Traumatol. 2014;24(8):1505–11.
70. Gobbi A, Karnatzikos G, Scotti C, Mahajan V, Mazzucco L, Grigolo B. One-step cartilage repair with bone marrow aspirate concentrated cells and collagen matrix in full-thickness knee cartilage lesions: results at 2-year follow-up. Cartilage. 2011;2(3):286–99.
71. Giannini S, Buda R, Cavallo M, et al. Cartilage repair evolution in post-traumatic osteochondral lesions of the talus: from open field autologous chondrocyte to bone-marrow-derived cells transplantation. Injury. 2010;41(11):1196–203.
72. Ruetze M, Richter W. Adipose-derived stromal cells for osteoarticular repair: trophic function versus stem cell activity. Expert Rev Mol Med. 2014;16:e9.
73. Aust L, Devlin B, Foster SJ, et al. Yield of human adipose-derived adult stem cells from liposuction aspirates. Cytotherapy. 2004;6(1):7–14.
74. Strioga M, Viswanathan S, Darinskas A, Slaby O, Michalek J. Same or not the same? Comparison of adipose tissue-derived versus bone marrow-derived mesenchymal stem and stromal cells. Stem Cells Dev. 2012;21(14):2724–52.
75. Bosetti M, Borrone A, Follenzi A, Messaggio F, Tremolada C, Cannas M. Human Lipoaspirate as autologous injectable active scaffold for one-step repair of cartilage defects. Cell Transplant. 2016;25(6):1043–56.
76. Nejadnik H, Hui JH, Feng Choong EP, Tai BC, Lee EH. Autologous bone marrow-derived mesenchymal stem cells versus autologous chondrocyte implantation: an observational cohort study. Am J Sports Med. 2010;38(6):1110–6.
77. Kraeutler MJ, Chahla J, LaPrade RF, Pascual-Garrido C. Biologic options for articular cartilage Wear (platelet-rich plasma, stem cells, bone marrow aspirate concentrate). Clin Sports Med. 2017;36(3):457–68.
78. Kyriakidis T, Iosifidis M, Michalopoulos E, Melas I, Stavropoulos-Giokas C, Verdonk R. Good mid-term outcomes after adipose-derived culture-expanded mesenchymal stem cells implantation in knee focal cartilage defects. Knee Surg Sports Traumatol Arthrosc. 2019:1–7.
79. Arnoczky SP, Warren RF. Microvasculature of the human meniscus. Am J Sports Med. 1982;10(2):90–5.
80. Taylor SA, Rodeo SA. Augmentation techniques for isolated meniscal tears. Curr Rev Musculoskelet Med. 2013;6(2):95–101.
81. Wei L-C, Gao S-G, Xu M, Jiang W, Tian J, Lei G-H. A novel hypothesis: the application of platelet-rich plasma can promote the clinical healing of white-white meniscal tears. Med Sci Monit. 2012;18(8):HY47.
82. Shin KH, Lee H, Kang S, et al. Effect of leukocyte-rich and platelet-rich plasma on healing of a horizontal medial meniscus tear in a rabbit model. Biomed Res Int 2015;2015.
83. Ishida K, Kuroda R, Miwa M, et al. The regenerative effects of platelet-rich plasma on meniscal cells in vitro and its in vivo application with biodegradable gelatin hydrogel. Tissue Eng. 2007;13(5):1103–12.
84. Betancourt J, Murrell W. Leukocyte-poor platelet-rich plasma to treat degenerative meniscal tear: a case report. J Clin Orthop Traum. 2016;7:106–9.
85. Blanke F, Vavken P, Haenle M, von Wehren L, Pagenstert G, Majewski M. Percutaneous injections of platelet rich plasma for treatment of intrasubstance meniscal lesions. Musc Ligam Tend J. 2015;5(3):162.
86. Everhart JS, Cavendish PA, Eikenberry A, Magnussen RA, Kaeding CC, Flanigan DC. Platelet-rich plasma reduces failure risk for isolated meniscal repairs but provides no benefit for meniscal repairs with anterior cruciate ligament reconstruction. Am J Sports Med. 2019;47(8):1789–96.
87. Dai WL, Zhang H, Lin ZM, Shi ZJ, Wang J. Efficacy of platelet-rich plasma in arthroscopic repair for discoid lateral meniscus tears. BMC Musculoskelet Disord. 2019;20(1):113.
88. Kemmochi M, Sasaki S, Takahashi M, Nishimura T, Aizawa C, Kikuchi J. The use of platelet-rich fibrin with platelet-rich plasma support meniscal repair surgery. J Orthop. 2018;15(2):711–20.
89. van Trommel MF, Simonian PT, Potter HG, Wickiewicz TL. Arthroscopic meniscal repair with fibrin clot of complete radial tears of the lateral meniscus in the avascular zone. Arthroscopy. 1998;14(4):360–5.
90. Ra HJ, Ha JK, Jang SH, Lee DW, Kim JG. Arthroscopic inside-out repair of complete radial tears of the meniscus with a fibrin clot. Knee Surg Sports Traumatol Arthrosc. 2013;21(9):2126–30.
91. Koch M, Hammer S, Fuellerer J, et al. Bone marrow aspirate concentrate for the treatment of avascular meniscus tears in a one-step procedure-evaluation of an in vivo model. Int J Mol Sci. 2019;20(5):1120.
92. Piontek T, Ciemniewska-Gorzela K, Naczk J, et al. Complex meniscus tears treated with collagen matrix wrapping and bone marrow blood injection: a 2-year clinical follow-up. Cartilage. 2016;7(2):123–39.