Nr 2024;14 (2):239-246

Orthobiologics Injection Therapies in the Treatment of Muscle and Tendon Disorders in Athletes: Fact or Fake?

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DOI:
10.32098/mltj.02.2024.02

LEVEL OF EVIDENCE: 7

SUMMARY

Muscle and tendon injuries encompass a wide range of conditions, including both acute and chronic ailments, and are common among athletes, representing a significant cause of injuries in various sports. Frequently affected areas include the hamstrings, quadriceps, gastrocnemius, and hip flexors. Concurrently, tendinopathy presents a complex clinical challenge, affecting a majority of athletes due to high load demands and repetitive movements, with its incidence in sports practice increasing over the last decades to account for up to 30% of all injuries. The substantial costs, both in terms of time away from competition and financial loss, have spurred growing scientific interest in therapies that can enhance the healing process of these injuries. In this context, innovative orthobiologic approaches, particularly platelet-rich plasma (PRP) and mesenchymal stem cells (MSCs), have been explored for their potential to facilitate the return-to-play phase and reduce the risk of reinjury by modulating inflammation and promoting tissue regeneration. This narrative review aims to summarize the current evidence regarding the role of orthobiologics in the management of sports-related muscle and tendon injuries.

KEY WORDS

Orthobiologics; mesenchymal stem cell; PRP; athletes; tendinopathy; muscle injuries; sport medicine.

INTRODUCTION

Muscle and tendon injuries are common causes of morbidity in athletes, manifesting as acute traumatic episodes and chronic conditions (1). Such injuries are prominent among athletes in sports like soccer and basketball (2). According to the classification by the Italian Society of Muscles, Ligaments, and Tendons (ISMuLT) based on the mechanism of onset, muscle injuries can be divided into direct and indirect categories, which are further classified as non-structural and structural. Direct injuries result from the application of an external force, such as a direct trauma, while indirect injuries are caused by overstretching beyond the viscoelastic limits of the muscle. Indirect structural muscle injuries, commonly referred to as "muscle tears", are frequently encountered in clinical practice (3). Among professional soccer players, muscle injuries account for more than 30% of all injuries, leading to significant time away from matches (4). Certain muscle groups, including the hamstrings, quadriceps, gastrocnemius, and adductors, are more susceptible to strains, often during eccentric contractions. In cases of re-injury, the return-to-sport time is typically longer than after the first episode. Generally, the incidence of muscle injuries increases with age, especially in the case of calf muscle injuries (5), and with certain health conditions, such as COVID-19 (6).

Tendinopathy represents a heterogeneous clinical condition affecting athletes due to high load demands and repetitive mechanical exposure, leading to a persistently failed healing response. This failure results in the progressive accumulation of matrix damage and micro-ruptures of collagen fibrils in tendons. The incidence of tendinopathies in sports has been rising over the last decades, representing up to 30% of all sports-related injuries, with a specific anatomical distribution. Achilles tendinopathy, for instance, affects up to 30% of runners, predominantly those who are middle-aged, often untrained, and engage in activities sporadically (7, 8), while sudden ruptures are more common in younger individuals (9). Overuse injuries in the pelvis and hip tendon structures, such as greater trochanter pain syndrome, proximal hamstring tendinopathy, or groin pain, are prevalent; patellar tendinopathy, or jumper's knee, primarily affects volleyball and basketball players (10, 11). Lateral elbow tendinopathies and plantar fasciopathy are significantly more common in sports like tennis and running (12).

The considerable time out of competition and financial losses associated with muscle and tendon lesions have spurred interest in therapies that can aid the healing process. Methods aimed at improving the biological aspects of tissue healing, particularly the use of "orthobiologic" agents like platelet-rich plasma (PRP) and bone marrow-derived cells, have gained popularity in the treatment of tendinopathies and soft tissue pathologies in athletes (13, 14). Despite the increasing use of these regenerative therapies, evidence supporting orthobiologics remains mixed, and reports on their formulations are highly variable. This highlights the necessity for standardized production methods and more rigorous studies.

Therefore, this narrative review seeks to summarize the current scientific evidence on the management of muscle injuries and tendinopathies using various emerging orthobiologic approaches, with a special focus on cell therapy and PRP (**figure 1**).

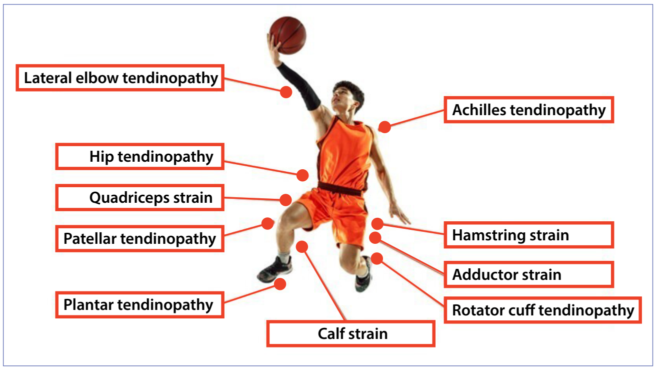

Figure 1. Orthobiologics' most frequent clinical targets in sports medicine.

FORMULATION OF ORTHOBIOLOGICS INJECTION THERAPIES

Cell therapies offer a broad range of strategies for tissue healing, with stem cells playing a pivotal role due to their ability to self-renew and differentiate into various cell types depending on their biological environment (15). Mesenchymal stem cells (MSCs), for example, can differentiate into adipocytes, chondrocytes, and osteoblasts. Furthermore, MSCs are capable of producing numerous molecules, including growth factors, cytokines, and chemokines, which are essential in healing processes such as immunomodulation, anti-apoptosis, and neo-angiogenesis (16). MSCs are primarily derived from bone marrow (with the distal femur and proximal humerus being common sites), but they can also be isolated from other tissues such as adipose, skin, and synovial fluid (17, 18). Cell therapies can be categorized into culture-expanded undifferentiated and differentiated cells, culture-expanded differentiated cells, and minimally manipulated heterogeneous native cells. Populations of culture-expanded MSCs and laboratory-purified cell lines may offer higher potency (19). However, the complexity of cell expansion and the regulatory and legal considerations may limit their practical application in clinical settings. Conversely, minimally manipulated cells do not require expansion, allowing physicians to prepare and utilize them directly for tendon tissue regeneration. Ongoing research aims to optimize the harvesting, processing, and delivery techniques of stem cells for treating athletes' injuries (20).

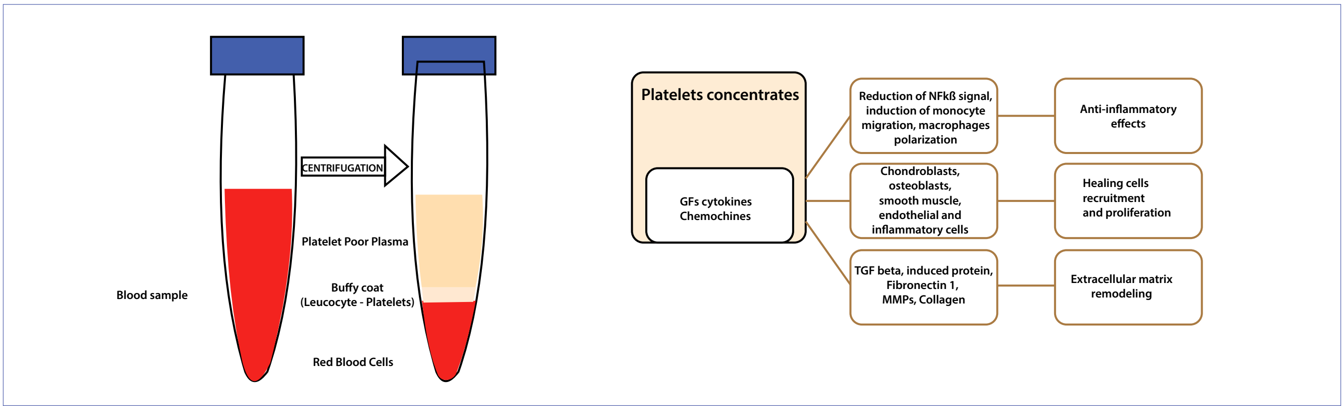

Figure 2. Blood sample manipulation through centrifugation to extract PRP.

Platelet-rich plasma (PRP) is among the most utilized orthobiologic therapies in athletes, playing a crucial role in the healing and regenerative processes of injuries. PRP, containing platelets, inflammatory cells, and a rich array of proteins such as platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), epithelial growth factor (EGF), and adhesion molecules (21), promotes cell recruitment, proliferation, and neo-angiogenesis at the injury site (**figure 2**). PRP is derived from the patient's own blood, which is centrifuged to separate platelets and leukocytes from erythrocytes (22), and then concentrated (almost 4 times). However, significant variability exists in preparation methods, including the absolute number of platelets, the presence of leukocytes, and the activation techniques. This variability allows PRP to be further categorized based on its cellular composition, most notably into leukocyte-rich PRP and leukocyte-poor PRP. The biology of the individual patient also plays a crucial role in these differences. PRP has gained increasing interest in recent decades due to its relatively low cost and minimally invasive application (23). Nonetheless, the lack of standardization challenges the generation of robust scientific data, thus hindering the development of evidence-based treatment protocols (24).

ORTHOBIOLOGICS IN MUSCLE INJURY: RATIONALE AND CLINICAL EVIDENCE

The absence of high-quality studies makes it challenging to draw definitive conclusions about the efficacy and safety of MSC therapy for human muscle injuries. However, preclinical evaluations suggesting that the local injection of autologous PRP might reduce the recovery time for muscle injuries have led to its increased use in clinical practice, primarily for sports-related injuries (25). Theoretically, PRP's effectiveness in promoting muscle injury healing is attributed to its high concentration of paracrine healing and growth factors, which enhance muscle regeneration and myogenesis, besides regulating inflammation response and pain control. Moreover, several clinical studies have demonstrated the benefits of PRP applications in the muscle healing process, achieving a significantly faster return to play (25-28). PRP reduced the time to return to sports after acute muscle injuries in athletes compared with a control group in the study by Rossi *et al.* (25). Delos *et al.* (26) reported that injured athletes could recover in half the usual time with ultrasound-guided PRP injections.

Nonetheless, some recent high-quality studies have cast doubt on these benefits (27, 28). A meta-analysis by Grassi *et al.* (29), which included six randomized clinical trials involving 374 patients, investigated the effects of PRP compared to placebo injections or physical therapy in acute muscle injuries. The generalization of the results was challenging due to the variability in PRP protocols and the heterogeneity of muscle injury types, showing no clear advantage of PRP injections in terms of clinical outcomes, time to return to sport, and recurrence rates. There were also controversies regarding subjective pain evaluation and muscle strength.

In 2017, Sheth *et al.* (30) conducted a meta-analysis comparing PRP injection, physiotherapy, and placebo injection in athletes with acute grade I or II muscle strains. The primary outcome was the time to return to sport; the secondary outcome was the reinjury rate with a minimum follow-up of 6 months. A specific subgroup analysis was also performed to assess the efficacy of PRP in treating hamstring muscle strains (grade I/II) alone. This analysis included five randomized controlled trials and analyzed 268 patients. The outcomes indicated a significant reduction in the time to return to sport for the PRP group compared to the control group. However, the subgroup analysis showed no difference between PRP and the control group in the time to return to activity. Moreover, no significant difference was observed in the secondary outcome at 6 months of follow-up. The authors concluded that PRP could offer an earlier return to sport for patients with grade I/II muscle strains without an increased risk of reinjury at follow-up. Nonetheless, specifically for patients with grade I/II hamstring muscle strains alone, no significant difference was noted. The high heterogeneity of the results does not provide clear evidence for the use of PRP in muscle injuries (31).

ORTHOBIOLOGICS IN TENDINOPATHIES: RATIONALE AND CLINICAL EVIDENCE

The pathogenesis of tendinopathy is multifactorial and complex, beginning with repetitive tendon overload leading to structural microscopic damage. The tendon's poor intrinsic healing ability, insufficient blood supply, and lack of adequate recovery time may result in a gradual accumulation of matrix damage (32). Consequently, tendon tissue cannot efficiently repair itself, leading to the formation of fibrous and scar tissues, which can cause adhesions. To treat chronic tendinopathy in its degenerative phase, it's crucial to restore the tendon's reparative capacity by modulating inflammation, thereby curbing degeneration and reinforcing the pro-resolving system.

MSC therapy, administered through cell injection, is suggested to exert an immunomodulatory effect that can steer the inflammatory environment towards healing the injured tendon. The ability of stem cells to reduce inflammatory status and promote cellular response proliferation can be harnessed to modulate the degenerative tendon environment, making this cell therapy a promising approach to treating these injuries (33). Recent data have clearly shown that stem cells present in tendon connective tissue are capable of self-regeneration and multipotential differentiation. It is, therefore, critical to thoroughly investigate their potential to develop new biological therapeutic strategies for tendinopathies. Human tendon-derived stem cells (hTDSCs) have potential future applications in various scientific fields, such as sports medicine and rehabilitation, because these cells can be enhanced in vitro and then injected into the patient's tendon. Moreover, TDSCs can be directly stimulated in the tendon using specific supplements/drugs and cytokines/chemokines (34).

Studies evaluating MSC therapy for tendon healing have demonstrated a promising significant effect size for pain and functional scores, as well as structural healing (35). Some studies have reported superior radiological and clinical outcomes for cell therapy in tendon disease, while others have noted faster healing rates (36). Specifically, Hernigou *et al*. (37) showed that patients who received a bone marrow adipose cell injection into their rotator cuff tears experienced faster healing, improved repair quality, and fewer relapses than those in the control group (38).

PRP is a therapeutic option for chronic tendon injuries in athletes, with many studies showing positive outcomes on tendon healing (39). One preclinical study demonstrated that PRP, when locally injected into the Achilles tendon of rats, increased tendon stiffness and strength by about 30% after just seven days, compared to controls (40). Additional findings have highlighted enhanced growth factor release and increased immunoreactivity of collagen I/III when PRP was percutaneously injected into the rat patellar tendon during the early phases of tendon healing (41). Furthermore, the osteoinductive efficacy of PRP in tendon-to-bone healing was analyzed in a sheep infraspinatus repair model through histology and MRI scans, reporting fibrocartilage and new bone formation at the lesion site (42). Scientific data on the use of PRP in human Achilles, patellar, wrist, and supraspinatus tendons have been published but are largely limited to case reports, lacking high methodological quality. The most beneficial results have been observed in chronic patellar tendinopathy, gluteus medius tendinopathy (43), and lateral epicondylitis (44), with promising outcomes for the rotator cuff, while no benefit has been reported for Achilles tendinopathy (45-47).

WHAT'S THE EVIDENCE?

Sports injuries involving tendons and muscles are common, and their conservative treatment often fails to produce lasting and decisive outcomes (47, 48). In this context, orthobiologic injection therapies emerge as a highly innovative and compelling treatment option. Injecting MSC and PRP into muscles and tendons has the dual effect of modulating the inflammatory cascade underlying tissue damage through the secretion of neoangiogenic and anti-inflammatory factors and promoting tissue repair through the release of specific growth factors. These injections are now considered relatively safe, with serious adverse events being rare. However, the results reported in this review are sparse and conflicting, suggesting that sports physicians should carefully weigh the existing evidence against the clinical situation and patient preferences, especially when considering orthobiologics with limited clinical evidence (49).

Regarding muscle injuries, PRP injections have not shown a protective effect against reinjury risk, and no significant differences have been found between PRP and placebo injections or rehabilitation in speeding up the return to sport after injury. As for the use of MSCs in muscle injuries, the literature currently lacks sufficient data to provide scientific evidence and recommendations, despite their proven efficacy in promoting immunomodulation and cell regeneration.

In the case of tendinopathies related to sports injuries, *in vitro* and *in vivo* data suggest that tendon MSCs contribute

to tendon-regenerative processes. This capacity is crucial in redirecting tendon repair from profibrotic degeneration to tissue regeneration. However, future research on cellular therapies must implement standardized methods in clinical practice to explore tenogenic differentiation phases more comprehensively.
Moreover, less is known about the potential benefits of combining MSCs with biomaterials to improve muscle and tendon tissue regeneration while optimizing functional tissue activity. Regarding tendon injuries, the lack of sufficient scientific evidence precludes the provision of clinical recommendations.
Table I summarizes the 2020 National Basketball Association (NBA) consensus statement recommendations on the use of orthobiologics (50). Similarly, the National Football Association (NFA) has expressed concerns over the lack of scientific support for these therapies, cautioning against their routine recommendation due to potential health risks for athletes from indiscriminate use of orthobiologics (51).

CONCLUSIONS

At present, there is limited scientific evidence to support the routine use of orthobiologic injections in sports medicine. Clinical trials need to be designed, conducted, and reported with higher quality to substantiate the use of MSCs and PRP in managing muscle and tendon injuries. Further research, particularly on human subjects, is required to develop more data and perform risk/benefit analyses, especially concerning athletic sports injuries. Given the high functional demands of this population, it is prudent to exercise caution when employing MSCs/PRP in rehabilitation pathways, adhering to rigorous guidelines both in preparation (**table II**) (52) and clinical practice (**table III**) (44, 53).

Table I. NBA Orthobiologics Consensus Statement Recommendations

Injury	Recommendations
Muscle injuries	Not routinely recommended
Patellar tendinopathy	Leukocyte-poor PRP injection as an adjunct to first-line conservative treatment and/or when conservative treatment fail Cell-based therapy not recommended
Achilles tendinopathy	Not routinely recommended
Plantar fasciopathy	PRP injection as an adjunct to first-line conservative treatment and/or when conservative treatment fail Cell-based therapy not recommended

PRP: platelet-rich plasma.

Table II. Important variables to be considered when preparing orthobiologics.

Variables for consideration	PRP	MSCs
Starting volume	Whole blood sample	60 mL bone marrow
Final volume injected		6 mL
Collection site		Iliac crest
Type of anticoagulant used	Acid citrate dextrose solution A, calcium citrate, citric acid, citrate phosphate dextrose, sodium citrate	
Method of separation and processing machine used	Centrifugation	
Setting of the machine used	Number of spin cycles, duration of spin cycles, spin rate and/or G force	
Desired concentration of platelets for clinical indication	Leukocyte rich *vs* leukocyte poor	
Platelet-activation method	$CaCl_2$, thrombin, dry needling, calcium gluconate, tissue factor	
Use of buffer	$NaHCO_3$	
Initial nucleated cell count		4.7×10^6 cells/mL
Final nucleated cell count		24.9×10^6 cells/mL
Final composition	Leukocyte, erythrocyte and platelets	
Final volume	3-5 mL	
Time for preparation to use	1 hour	

Table III. The rigorous and structured approach to follow when using orthobiologics in clinical practice.

Approaches
Always consider firstly therapies less invasive, safer, with higher scientific evidence and more cost-effective
Avoid patients' motivation as a therapy choice
Never be influenced by commercial motivations
The regenerative medicine therapy should be delivered following research and manufacturer recommendation
Prefer image-guided procedures
Keep always continuing to study and to update about injection procedures
The patient's informed consent must be always obtained
Musculoskeletal-specific Patient-Reported Outcome Measures are useful in the clinical management of patients

FUNDINGS

None.

DATA AVAILABILITY

Data are available under reasonable request to the corresponding author.

CONTRIBUTIONS

AV, SP: conceptualization. RG, DT, FS: methodology. FV, AC, AF, LB: writing – original draft. AD, MV, IB: writing – review & editing. FS, SP, MZ, AF: supervision.

ACKNOWLEDGMENTS

Figure 1 is an adapted image by master1305 freely downloadable from Freepik.

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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