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REVIEW

Biologic therapies for foot and ankle injuries

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ABSTRACT

Introduction: The use of orthobiologics as supplemental treatment for foot and ankle pathologies have increased in the past decades. They have been used to improve the healing of bone and soft tissue injuries. There have been several studies that examined the use of biologics for knee and hip pathologies but the foot and ankle construct has unique features that must be considered.

Areas covered: The biologics for foot and ankle injuries that are covered in this review are platelet-rich plasma (PRP), stem cells, growth factors, hyaluronic acid, bone grafts, bone substitutes, and scaffolds. These modalities are used in the treatment of pathologies related to tendon and soft tissue as well as cartilage.

Expert opinion: The utilization of biological adjuncts for improved repair and regeneration of ankle injuries represents a promising future in our efforts to address difficult clinical problems. The application of concentrated bone marrow and PRP each represents the most widely studied and commonly used injection therapies with early clinical studies demonstrating promising results, research is also being done using other potential therapies such as stem cells and growth factors; further investigation and outcome data are still needed.

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Foot and ankle; BMAC; stem cells; PRP; tendons; cartilage

1. Introduction

There are a number of risk factors including patient-specific medical and social factors that cause delayed healing and result in poor clinical outcomes in the management of foot and ankle pathologies. Effective rehabilitation is crucial for the proper management of such injuries. Over the past few decades, the use of biologic adjuncts to aid healing has been steadily gaining popularity.[1] Biologics adjunct therapies, specifically orthobiologics, are biological substances that can be used to improve the healing of skeletal and soft tissue injuries; the substances include platelet-rich plasma, stem cells, growth factors, hyaluronic acid, bone grafts, bone substitutes, and scaffolds (Figure 1).[1,2], Orthobiologics provide foot and ankle clinicians several options to supplement operative and nonoperative treatments.

While there have been a number of studies that examined the use of biologics in the hip and knee joints, the foot and ankle construct has unique features that must be considered in regard to how biologics affect it. The cartilage of the ankle is thinner than both the knee and hip[3]. Chondrocytes of the talus tend to be single cells arranged in a horizontal orientation; whereas in the knee, they are in closer proximity and in a 'string and cluster' pattern. Ankle chondrocytes are more resistant to pro-inflammatory mediators such as IL-1β and more responsive to anabolic markers as compared to the knee[4]. The purpose of this expert opinion is to review the use of orthobiologics in foot and ankle injuries, most recent developments, and future applications.

1.1. PRP

Platelet-rich plasma (PRP) is at the forefront of treatment options for both acute and chronic musculoskeletal pathologies (Table 1) including cartilage and tendon injuries like Achilles tendon injuries (Figure 2). Derived from autologous blood, PRP is composed of a concentrated volume of platelets containing over 1,500 growth factors/cytokines in the alpha-granules[5]. These growth factors and cytokines secreted by concentrated platelets (PLTs) in PRP affect local inflammatory reactions, recruitment and proliferation of stem cells, cell adhesion, and angiogenesis [6]. In particular, PRP is a known anti-inflammatory treatment that acts as a reservoir of growth factors, and, because PRP is autologous, it is devoid of cross-reactivity, immune reactions, and possible risk of disease transmission. Thus, PRP is considered to be an excellent biologic for the treatment of musculoskeletal injuries, specifically tendon injuries, with the global market value estimated to grow to 647 USD million by 2025 [7,8].

Concentrated PLTs increase the amounts of multiple growth factors released to a localized injury site, which, in turn, augment the healing process in injured tissues. The anti-inflammatory effects of PRP are well-known as evidenced

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Article highlights box

- A breadth of orthobiologics has emerged to improve the healing of foot and ankle injuries?
- Current clinical therapies are platelet-rich plasma, stem cells, growth factors, hyaluronic acid, bone grafts, bone substitutes, and scaffolds, of which PRP and stem cells are at the forefront due to their autologous nature.
- PRP therapy is an attractive and popular option for the treatment of injured tendon, plantar fascitis, and cartilage injuries especially when combined with other repair enhancing factors. capability.
- Bone marrow aspirate concentrate has utility in Achilles tendinopathies and other pathologies due to its efficacy in controlling inflammation, reducing fibrosis, and cell recruitment.
- Scaffold based treatments have been used in cartilage related pathologies and have resulted in lower pain scores compared to controls. Platelet-derived growth factorshave been shown to recruit inflammatory cells and stimulate angiogenesis in human trials.

through *in vitro* and *in vivo* studies. For example, PRP treatment of tendon cells *in vitro* induced the release of hepatocyte growth factor (HGF) from PLTs, which is a major anti-inflammatory growth factor[9]. Injection of PRP or HGF into wounded mouse Achilles tendons *in vivo* decreased PGE_2 production in the tendinous tissues. Injection of platelet-poor plasma (PPP) however, did not reduce PGE_2 levels in the wounded tendons[10]. The injection of the HGF antibody inhibited the effects of PRP and HGF. Furthermore, injection of PRP or HGF also decreased COX-1 and COX-2 proteins. These results indicate that PRP exerts anti-inflammatory effects on injured tendons through HGF[10]. This is true in human chondrocytes, where HGF is shown to disrupt NF-κB transactivation activity, which is important for the anti-inflammatory effect of PRP for treating articular cartilage injuries[10]. In addition, PRP, in the form of PRP-clot releasate (PRCR), promoted differentiation of tendon stem/progenitor cells (TSCs) into active tenocytes exhibiting high proliferation rates and collagen production capability. PRCR treatment of TSCs did not induce the expression of non-tenocyte-related genes (PPARγ, Sox-9, and Runx-2) suggesting the safety of PRP treatment for tendon injuries[11].

1.2. Application of PRP in Tendon and Other Soft Tissues

Due to the widely reported efficacy in preclinical studies, there has been an increase in the use of PRP in prospective clinical trials, particularly for the treatment of tendinopathy[12]. Clinical trials in the past decade demonstrated that injections of PRP are efficacious for the treatment of tendinopathy [13–-13–16]. Specifically, numerous clinical studies on patellar tendinopathy using PRP with a follow-up of 6 months – 2 years showed promising positive effects [14,15,17–23]. For example, in 46 patellar tendinopathy patients, PRP administration offered a superior clinical outcome compared to extracorporeal shock wave therapy according to VISA-P (Victorian Institute of Sports Assessment – Patellar Tendon) and VAS (Visual Analogue Score) pain scores[14]. In another study, the PRP group combined with exercise recorded a superior outcome in terms of VISA-P score with respect to the control group at 3 months; however, by 6 months results were comparable between PRP and control groups. Thus, this study showed that PRP acted mainly by accelerating the *early* phases of tissue repair and remodeling [15], and that the positive benefits of PRP dissipated over time.

Another clinical study has also shown that intratendinous injection of PRP resulted in a significant functional increase and pain reduction, and 80% of patients were able to go back to sports activity on average of 4 months after treatment[17]. A single PRP injection also resulted in satisfactory results with improved tendinous structure revealed by MRI at 24 months [18]. When two PRP injections were administered three weeks apart in the patellar tendon, a reduction in the hypoechoic areas in the majority of tendons, improvement in fibrillar echotexture, and reduced hypervascularity were reported at 6-month evaluation[19]. Significant improvement in VAS and VISA-P pain scores were reported in patients who received a single injection of PRP with 18 months follow up[20].

Many clinical trials combined PRP treatment with a physical therapy/exercise program, based on the paradigm that moderate exercise can facilitate and enhance healing and repair of the tendon. A physical therapy program in the form of exercise after PRP injection improved pain scores in patellar tendinopathy patients in the degenerative state after 26 weeks[24]. Therefore, the combination treatment is considered to be promising for patients in the late/degenerative phase of patellar tendinopathy. A few other studies also reported similar

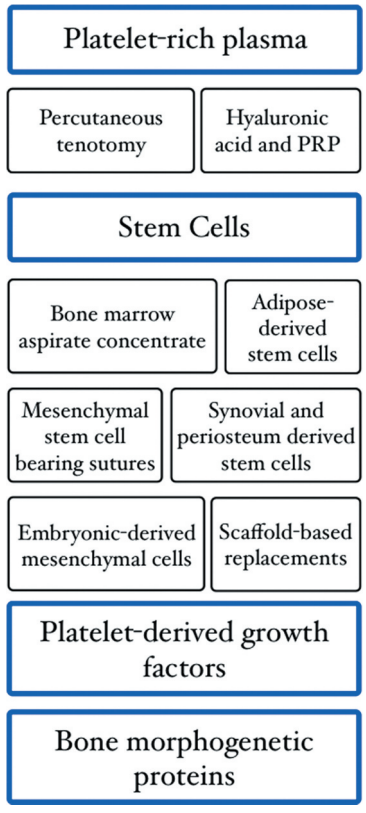

Figure 1. Current biologics for the treatment of foot and ankle pathologies.

Table 1. PLTs are the major component of PRP that enhance tissue healing and repair.

Achilles Tendinopathy	One-year follow-up of platelet-rich plasma treatment in chronic Achilles tendinopathy: a double-blind randomized placebo-controlled trial.	de Jonge et al., Am J Sports Med, 2011
	Ultrasound-Guided Injection Therapy of Achilles Tendinopathy With Platelet-Rich Plasma or Saline: A Randomized, Blinded, Placebo-Controlled Trial.	Krogh et al., Am J Sports Med, 2016
	Platelet-rich plasma injection for chronic Achilles tendinopathy: a randomized controlled trial.	de Vos et al., JAMA, 2010
	Effect of High-Volume Injection, Platelet-Rich Plasma, and Sham Treatment in Chronic Midportion Achilles Tendinopathy: A Randomized Double-Blinded Prospective Study.	Boesen et al., Am J Sports Med, 2017
	Achilles tendinopathy management: A pilot randomized controlled trial comparing platelet-rich plasma injection with an eccentric loading programme.	Kearney RS et al. Bone Joint Res. 2013
	Platelet rich plasma treatment for chronic Achilles tendinosis	Monto RR Foot Ankle Int. 2012 May
	Can platelet-rich plasma have a role in Achilles tendon surgical repair?	De Carli A et al. Knee Surg Sports Traumatol Arthrosc. 2016 Jul
	Autologous platelets have no effect on the healing of human Achilles tendon ruptures: a randomized single-blind study.	Schepull T et al. Am J Sports Med. 2011
Plantar Fasciitis	Comparison of Plantar Fasciitis Injected With Platelet-Rich Plasma vs Corticosteroids.	Jain SK et al. Foot Ankle Int. 2018 Jul
	Plantar Fasciitis – A Comparison of Treatment with Intralesional Steroids versus Platelet-Rich Plasma. A Randomized, Blinded Study	Acosta-Olivo C et al. J Am Podiatr Med Assoc. 2017 Nov
	Beneficial effects of platelet-rich plasma on improvement of pain severity and physical disability in patients with plantar fasciitis: A randomized trial.	Vahdatpour B et al. Adv Biomed Res. 2016
Osteochondral lesions of the talus	Clinical outcomes of platelet rich plasma (PRP) as an adjunct to microfracture surgery in osteochondral lesions of the talus.	Guney A et al. Knee Surg Sports Traumatol Arthrosc. 2015 Aug
	Microfracture for osteochondral lesions of the ankle: outcome analysis and outcome predictors of 105 cases.	Chuckpaiwong B et al. Arthroscopy. 2008 Jan
	Osteochondral lesion of the talus: is there a critical defect size for poor outcome?	Choi WJ et al. Am J Sports Med. 2009 Oct
	Clinical Effects of Platelet-Rich Plasma and Hyaluronic Acid as an Additional Therapy for Talar Osteochondral Lesions Treated with Microfracture Surgery: A Prospective Randomized Clinical Trial.	Görmeli G et al. Foot Ankle Int. 2015 Aug
	Platelet-rich plasma or hyaluronate in the management of osteochondral lesions of the talus.	Mei-Dan O et al. Am J Sports Med. 2012 Mar
Ankle Osteoarthritis	Conservative Treatment of Ankle Osteoarthritis: Can Platelet-Rich Plasma Effectively Postpone Surgery?	Repetto I et al. J Foot Ankle Surg. 2017
	Safety and Efficacy of Intra-articular Injection of Platelet-Rich Plasma in Patients With Ankle Osteoarthritis	Fukawa T et al.Foot Ankle Int. 2017

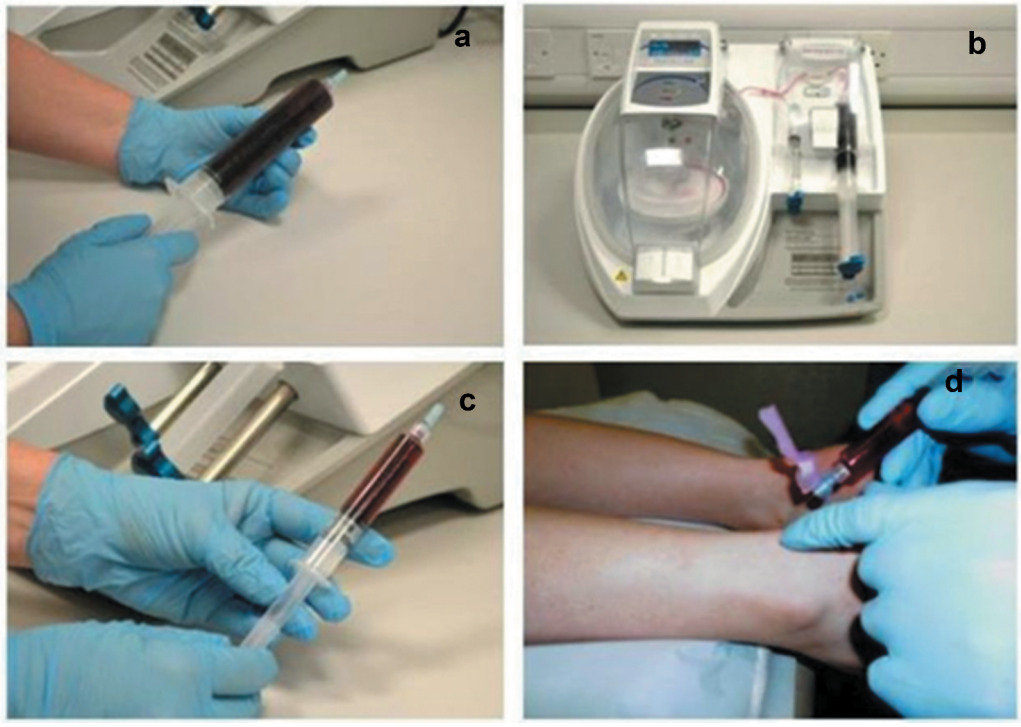

Figure 2. (A) A whole blood sample is taken. (B) A Platelet Separator System is used to produce PRP. (C) The resulting PRP is collected in a syringe for injection into the Achilles tendon rupture gap. (D) The injection is delivered in the tendon rupture gap.[2]

positive outcomes in PRP clinical trials of patellar tendinopathy [21–23,25]. Clinical trials using PRP for Achilles tendinopathy also demonstrated positive clinical outcomes [26–31]. In summary, PRP can enhance healing and repair of tendinopathic tendons, but clinical studies with PRP are largely inconsistent in methodology.

The efficacy of PRP treatment for tendinopathy is highly controversial with conflicting claims regarding reduced pain and improved healing and function in clinical trials [32–36]. Despite reasonable preclinical evidence to support the use of PRP to improve tendon healing, there is no clinical consensus to support its routine use of PRP to enhance healing. Recent studies state several factors that may affect the efficacy of PRP. First, there are huge variabilities in PRP methodologies/preparations by multiple commercial systems despite common principles such as collecting peripheral blood mixed with anticoagulant followed by centrifugation. The adopted parameters differ in time, centrifugal force, plasma fractions collected, and type and concentration of agonist used in PRP activation. The combination of these parameters results in different cellular and molecular compositions of PRP. Comparison of growth factors and platelet concentration from commercial PRP separation systems demonstrate extensive variations[37]. Leucocyte content in PRP is one of the major factors that may affect the PRP efficacy. Neutrophils, the most predominant leukocyte, are detrimental to tissues as they release various proteinases and proinflammatory cytokines[38]. Leucocyte-rich PRP (LR-PRP) induces pro-inflammatory and catabolic responses of tendon cells [39], causing tendon inflammation that can impair the repair of injured tendons [5,40]. Compared with leukocyte-poor PRP (LP- PRP), LR-PRP caused a significantly greater acute inflammatory response at 5 days after injection into a rabbit patellar tendon[40]. Although LR-PRP contains more growth factors, it also contains more inflammatory mediators such as IL-1β[41]. Leukocyte and erythrocyte concentrations of PRP formulations differentially affect the production of inflammatory mediators[42]. Treatment of synovial cells with LR-PRP and red blood cells resulted in significant cell death and elevated proinflammatory mediator production (IL-1β, IL-6, TNF-α, interferon-λ).

Other potential issues remain in the efficacy of PRP that is associated with patient-related factors such as age, patient activity level, treatment history, and post-recovery plan that may or may not include physical therapy[43]. Another major issue is that most clinical studies on PRP are limited by poor design, small subject numbers, and highly variable and subjective outcome measures of pain which prevent definitive conclusions regarding the effectiveness of this treatment. The use of appropriate controls, adequate sample size, stringent inclusion/exclusion criteria, and long-term follow up are some factors that need to address to properly assess the efficacy of trials [36,44].

Another potential issue that may affect the efficacy of PRP for tendinopathy treatment is the disease stage of tendinopathy. In addition to tendon inflammation, tendinopathy at late stages is manifested by extensive degenerative changes (lipid accumulation, mucoid degeneration, and tissue calcification)[45]. Previously we have shown that PRP can induce differentiation of TSCs into tenocytes that enhance repair, however, it is unable to reverse the aberrant differentiation of TSCs into non-tendinous tissues [46]. The repair will not progress unless the non-tendinous tissues are appropriately

debrided before PRP administration so that PRP can recruit TSCs and help induce differentiation to tenocytes to participate in repair. Therefore, late-stage tendinopathy patients should receive debridement using percutaneous ultrasound tenotomy (PUT) to remove these non-tendinous tissues so that injection of P-PRP can enhance healing and repair of the tendinopathic tendon. Ultrasound-guided percutaneous needle tenotomy followed by PRP injection for the treatment of chronic, recalcitrant tendinopathy was shown to be a safe and relatively effective treatment[47].

For non-operative management of plantar fasciitis, previous studies have shown PRP injection as a viable, safe alternative as compared to placebo or corticosteroid (CS) injection [48–50]. Many of the studies demonstrated good long-term results – improved long-term pain relief and function no complications; whereas, short-term results were better with CS injection, but there was a significant drop-off effect [51–54]. However, corticosteroid injections carry the risk of deleterious effects on collagen and plantar fascia rupture [55,56].In 2019, unlike all previous studies, a double-blind multicenter randomized control trial (RCT) demonstrated the superiority of PRP in reducing pain and increasing function compared to CS injection[57].

1.3. Application of PRP in Cartilage and Osseous Repair

PRP has exhibited effectiveness in osseous healing, specifically the treatment of osteochondral lesions of the talus (OLTs) and calcaneal fractures. A preclinical animal (rabbit) model demonstrated that OLTs treated with PRP had improved histological scoring with improved integration of the osteochondral graft at the bone-cartilage interface, and increased hyaline-like cartilage[58]. Another study that used a rat tendon graft-bone tunnel interface model showed that when PRP alone is used, there was no cartilage-like tissue and minimum collagen 1 and 2 staining[59]. This same study examined the effects of a biocompound, kartogenin with PRP, and found abundant proteoglycans signifying cartilage formation at the interface. Also, the pull-out strength of the kartogenin/PRP vs the PRP group was higher. Clinical studies have demonstrated the potential of PRP adjunct to microfracture of OLT with improved outcomes compared to surgical repair alone or hyaluronic acid (HA) [60–62]. Despite this, long-term, level 1 randomized trials are needed to determine the optimal combination of PRP components (platelets, leukocytes, erythrocytes, etc.) and maximal efficacious platelet concentration. In the management of calcaneal fractures, those treated with allograft in conjunction with PRP had similar American Orthopedic Foot & Ankle Society (AOFAS) score and radiographic parameters compared to autograft alone, and both exhibited better results than allograft alone[1].

1.4. Hyaluronic acid and PRP

Hyaluronic acid (HA) is a glycosaminoglycan located within the synovial fluid that has nociceptive properties that may play a role in osteoarthritis treatment. It has also been found to promote cartilage regeneration through increased chondrocyte proliferation, synthesis of proteoglycans, and prevents the production of deleterious proinflammatory cytokines and metalloproteinases[63]. For these reasons, it is primarily used to target diseases that affect articular cartilage, such as OLTs and OA of the ankle [60,62,64–68]. HA supplementation has demonstrated potential chondroprotective and regenerative effects in animal models (rabbits and sheep), enhancing gross and histological filling of defects [65,66]. Specifically, in the treatment of OLT, three recent studies demonstrated improved outcomes when microfracture treatment was supplemented HA compared to microfracture alone [60,67,68]. An RCT has demonstrated that when three consecutive intraarticular injections were administered of either HA or PRP, both were effective in reducing pain and improving function at 6 months[62]. However, PRP led to a significantly better outcome. A subsequent study showed when a single dose PRP injection was compared with a multidose HA injection as an adjunct to OLT microfracture surgery, both PRP and HA were found to improve outcomes. PRP, similar to the previous study, was recommended to be superior, however, given that it demonstrated comparable effects with just a single dose[60].

1.5. Future Applications

Several factors are combined with PRP to enhance the repair of injured tissues. For example, kartogenin was combined with PRP to enhance the repair of tendon-to-bone injuries by promoting the formation of the fibrocartilage transition zone [59,69]. Incorporation of PRP into scaffolds based on natural, synthetic, and composite materials are potentially advantageous for tissue regeneration[70]. The most common biomaterials for scaffolds are collagen, chitosan, gelatin, alginate, hyaluronic acid, polyethylene glycol, polycaprolactone (PCL), polyglycolide, and poly(DL-lactide-co-glycolide) (PLGA)[71]. These methods allow the mobilization of a number of highly-concentrated bioactive factors, creating an optimized micro-environment, and impacting upon tissue regeneration [72,73]. The application of collagen-PRP hydrogel has been studied in detail for anterior cruciate ligament (ACL) repair[74].

In summary, repair of injured tendons, plantar fascia, and cartilage is a prolonged process, and it frequently results in improperly healed tissue, i.e. the quality of such tissue is poor at the structural, mechanical, functional levels. The concept of PRP therapy is attractive and popular because it makes use of autologous blood product that produces very few side effects, if any, unlike the injection of corticosteroids or other drug treatments; it is also noninvasive. However, a rigorous and systematic approach should be undertaken to effectively address the inconsistencies in PRP efficacy rather than a "one-size-fits-all' approach. Clinical studies suggest that PRP efficacy largely depends on the specific indication; therefore, when aiming at a realistic clinical option, 'indications, indications, indications' should be

the catchphrase. In addition, PRP alone may not be effective in healing all tissues and tissues at different stages of the disease. A combination approach utilizing tissue engineering methods or tissue debridement in conjunction with PRP (e.g. PUT prior to PRP) appears to be necessary to achieve efficient and positive outcomes.

2. Stem cells

2.1. Tendon and soft tissue

2.1.1. Bone marrow aspirate concentrate (BMAC)

BMAC has utility in Achilles tendinopathies due to its efficacy in controlling inflammation, reducing fibrosis, and cell recruitment (including tenocytes and MSCs) [75,76]. *An in vitro* study demonstrated increased cell proliferation when used in conjunction with a scaffold[77]. An *in vivo* study reported that BMAC augmentation of open repair of sport-related Achilles tendon ruptures resulted in a 92% return to sport with no re-ruptures[78]. However, this was a retrospective, single-center study with no controls.

2.1.2. Adipose-derived stem cells

There have been few studies evaluating the use of adipose-derived stem cells (ADSCs) in Achilles tendon pathologies. A clinical trial described the use of ADSCs to treat non-insertional Achilles tendinopathy compared to PRP injection. 44 patients were included in the study, 23 in the PRP group and 21 in the ABSCs group, there were a total of 28 tendons treated in each group. Patients were assessed preoperatively and 15,30,60,120 and 180 days postoperatively using VAS pain scale, VISA-A and AOFAS Ankle-Hindfoot Score. The study found that both treatment groups had improved outcomes from pre-op to post-op but the ABSCs group had significantly better results at 15 and 30 day postop as compared to the PRP group. However, there were no differences in clinical outcomes scores at the later post op time marks. The ADSC group obtained earlier significant results; therefore, the authors suggested that this should be taken into consideration to early return to play or daily activities[79]. However, this is novel and must be further investigated with higher-level studies. A 2011 animal study using rabbit ADSCs showed increased fibrillar linearity and continuity by histological evaluation compared to control groups indicating improved structural and mechanical properties[80]. Another animal study that compared ADSCs and GDF5 (Growth/differentiation factor 5) for use in Achilles tendon injury showed higher collagen fiber organization and increased tendon biomechanics in the ADSCs treatment group compared to GDF5[81].

2.1.3. Human amnionic tissue

Amnionic membrane has been shown to be a readily available source of multipotent stem cells and growth factors such as EGF (epidermal growth factor), FGF (fibroblast growth factor) and PDGF (platelet-derived growth factor) [82,83]. This membrane is the innermost layer of the placenta, collection of this tissue poses no risk [82] to mother and fetus and has been used in various clinical applications for a number of years, notably for wound healing. [84–86]

Zelen et al conducted an RCT that evaluated patients with plantar fasciitis. These patients were either treated with a single injection of dehydrated human amnionic membrane/chorionic membrane or a saline placebo. After an 8 week course, the treatment group reported statistically significant improvement in AOFAS hindfoot scores compared with control group (5)[83]. These results were supported by Werber et al; 44 patients that were unresponsive to multiple standard therapies for at least 6 months were given one treatment of a cryopreserved amnionic membrane injection around the plantar fascia and/or the Achilles paratenon. Over 12 weeks, the average VAS score decreased from 8.1 to 1.5 for plantar fasciitis and from 8.2 to 2.3 for Achilles tendinosis (7) [87]. Another study that compared amnionic membrane to traditional corticosteroid injection in a 23 patient RCT showed no significant difference between treatment groups in regards to foot pain scores[88].

Animal studies have shown mixed results with the use of amnionic membranes for treatment in tendon repair. McQuilling et al showed that augmenting Achilles tendon repair with amnionic membrane in a rat model resulted in a 0% re-rupture rate at 4 weeks compared to 20% of controls. The treatment group also showed increased cell migration[89]. In another rat model, Kueckelhaus et al examined the use of amnion derived cytokine solution in carboxy-methyl cellulose gel for Achilles tendon ruptures. Tendons were repaired with a Kessler suture in the control group vs an amnionic membrane augmented suture in the treatment group. Tissues were harvested at 1,2,4,6 and 8 weeks: at the 2 and 4 week mark, the treatment group had greater tensile strength and yield strength but at 8 weeks post repair, the control group had improved strength[90]. A Turkish study using a rat model showed that amnionic membrane did not add anything to the early healing process of ruptured Achilles tendons. [91]

2.1.4. Mesenchymal stem cells and MSC-bearing suture

There have also been some studies that have evaluated the efficacy of MSC-bearing sutures in rat models [92,93]. When suture was externally coated with bone marrow-derived stem cell, the MSC plus suture group demonstrated statistically greater structural strength in early healing (7 and 10 days), but not in later stages (14 and 28 days)[93]. There was also no macroscopic difference observed between groups[93]. Another study compared conventional repair, conventional repair with local injection of MSCs, and suture loaded with MSCs within the core[92]. The failure strength was higher in both groups that were augmented with MSCs compared to suture alone; however, unlike the loaded suture group, the local injections of MSCs demonstrated a significant decrease in ultimate failure at 28 days compared with 14[92].

Gissi et. Al. showed that extracellular vesicles (EVs) that are released by MSCs are mediators of its paracrine effects. Two core molecules that expressed from these EVs are Pro-collagen A2 and Matrix Metallopeptidase 14, both of which are important in tendon remodeling. In this study, both low and high

doses of BMSC-EVs were injected into a rat Achilles tendon injury model produced optimal realignment of tendon fibers as compared to the control group. [94]

2.1.5. Scaffold-based replacement

The ideal scaffold for Achilles tendon repair should promote natural and fast bridging of the tendon defect and also organized collagen-rich tissue[76]. An animal study researching rat Achilles tendons using polyhydroxyalkanoates, specifically poly-3-hydroxybutyrate-co-3-hydroxyhexanoate (PHBHHx) as a scaffold for tendon repair demonstrated that the PHBHHx scaffold was mechanically and histologically superior compared to controls (tendon repair without scaffold)[95]. Decellularized tendon tissue has also been used as a scaffold, which maintains the native structural characteristic including the majority of the proteoglycans and growth factors[96]. In a rat model, decellularized tendon demonstrated enhancement of mechanical properties; also, decellularized porcine tendon has been shown to be re-cellularized with human tenocytes [97,98].

2.2. Cartilage

2.2.1. Embryonic stem cells (ESCs)

ESCs are pluripotent stem cells with unlimited self-renewal and the ability to differentiate into all three primary germ layers: endoderm, mesoderm, and ectoderm[64]. The use of ESCs for cartilage repair is still relatively new. There have been a few studies conducted to evaluate the ability of ESCs to repair osteochondral defects. Studies have induced ESCs *in vitro* to form mesenchymal stem cells (MSCs) including chondrocytes [99,100] and demonstrated the potential for cartilage regeneration evidenced by improved histologic scoring and upregulation of chondrogenic genes [64,101]. Grogan et al. have shown some promise with a study that demonstrated proof of concept through the repair of in vivo repair of rabbit osteochondral injuries using ESCs[102]. Although promising, the use of ESCs for clinical management is not clear. In addition to lack of evidence, there are concerns about tumorigenicity and ethical concerns due to their derivation from early-stage preimplantation embryos.

2.2.2. Mesenchymal stem cells (MSCs)

MSCs have also been used for cartilage repair; unlike ESCs, MSCs are a multipotent and derived from adult tissue which avoids the ethical concerns associated with ESCs. MSCs are found in the bone marrow and other tissue, and thought to be responsible for physiologic growth, wound healing, and cell replenishment after daily turnover. Grogan et al. have demonstrated that infrapatellar fat pad mesenchymal stem cells contained high levels of chondrogenic genes and integrated with the surrounding osteoarthritic host cartilage in their study [102]. A clinical trial showed statistically significant improvement at 12 months when allogeneic MSCs were mixed with recycled autologous cartilage-derived cells to treat cartilage defects in the knee in symptomatic cartilage defect patients. [103]

Bone marrow stem cells are the most common source of MSCs. BMAC is optimal in clinical settings because it can be easily accessed from a patient's iliac crest during surgery, and it is widely available. In addition to MSCs, a successful harvest of BMAC also contains hematopoietic stem cells (HSCs), platelets that contain growth factors, bone morphogenetic proteins (BMPs), and other progenitor cells [104,105]. Its use is increasing in popularity for conservative treatment and as an operative supplement of foot and ankle pathologies, with strong evidence in animal investigations supporting its use to aid bone healing[106]. Early clinical studies have suggested that these findings can be translated to the repair of human OLTs as shown in Figure 3, including improved clinical outcome sores and radiographic findings [58,99,107],[109][108],, particularly as an adjunct in surgical treatment[109]. It should be noted that these findings may be limited by defect size; large lesions (> 109 mm2) and lesions with subchondral cysts predicted unsatisfactory results[110]. Studies have been shown to use similar marrow harvesting and processing

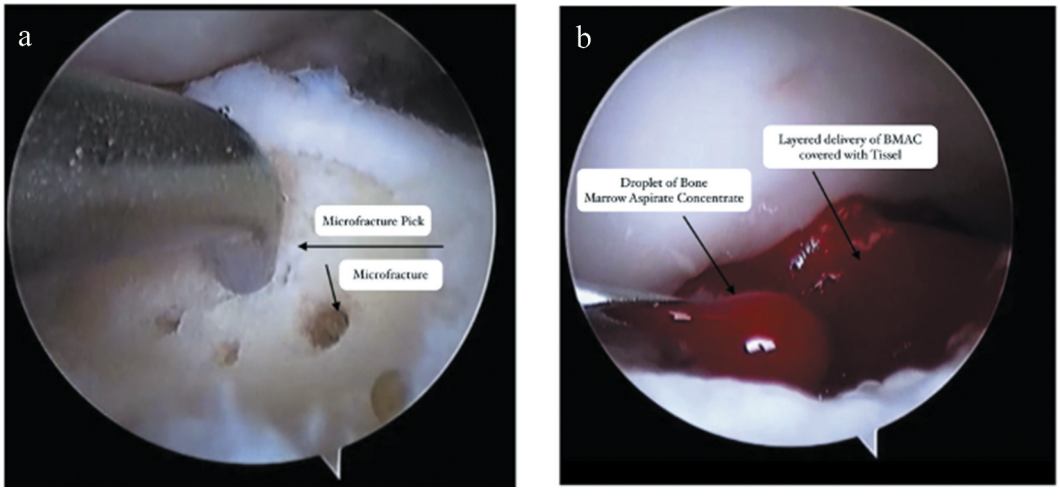

Figure 3. (A)The microfracture pick is inserted into the prepared lesion. (B) BMAC and Tisseel fibrin glue are layered in a controlled fashion.[114].

techniques in OLT repairs. Approximately 60 ml of bone marrow is harvested from the ipsilateral iliac crest. Two studies used the posterior iliac crest and two others used the anterior iliac crest. They then used a commercial BMAC centrifuge system and had a yield of 3 to 6 ml of BMAC [58,108,111,112].Pierini et al. found that in a 22 patient study that compared harvesting from the anterior vs. posterior crest, that there was no difference in viability, phenotype, and differentiation potential however, the posterior crest yielded on average 60% more MSCs than the anterior[113].

MSCs can also be obtained from adipose tissue, synovial lineages, and periosteum-derived cells. MSCs have the potential to differentiate into chondrocytes, and, *in vitro*, cartilage from ADSCs have high total collagen count with relatively lower levels of type II collagen. They have demonstrated improved clinical and MRI outcome scores when combined with marrow stimulation compared to marrow stimulation alone[115]. A study showed that autologous human ADSCs may have beneficial outcomes at 96 weeks[116] another study showed similar results at 6 months. [117] Shimozono et al. conducted a recent study that showed that autologous micronized adipose tissue injections could be used as augment therapy in patients undergoing arthroscopic debridement for advanced stage post traumatic osteoarthritis of the ankle. The small (19 ankles) sample of patients reported improved Foot and Ankle Outcome Scores and VAS after an average 14 months of follow-up although one third of patients stated they were unsatisfied with the procedure[118]. Kim et al. looked at 65 patients older than 50 years old with OLTs. 37 ankles had isolated marrow stimulation and 31 ankles had marrow stimulation in addition to ADSCs injection. Both groups had significantly improved VAS and AOFAS scores but the group that underwent ADSC injection had significantly better scores than the group with just marrow stimulation. Another key finding was that lesions that were 109 mm or greater and/or had subchondral cysts had significant unsatisfactory clinical outcomes in the group that just went under stimulation vs. the group that had stimulation and ADSC injection did not have these outcomes [110,119].

A benign tumor of the synovial membrane, synovial chondromatosis, generated interest among researchers to investigate its use in cartilage regeneration. *In vitro*, these cells demonstrate high chondrocyte potential than the more common MSC sources. Periosteum-derived stem cells are very novel but have chondroprogenitor cells and dual lineage (bone and hyaline cartilage) potential.

Application of MSCs as adjunct treatment is promising in cartilage restoration and regeneration, but further studies are needed to better characterize their induction potential with regards to optimal outcomes via the vehicle of bioactive matrices. [120]Of necessary consideration is the regulatory guidelines that govern the use of MSCs in a clinical matter. These guidelines are in place to prevent inadequate handling or processing that may damage or contaminate cells or tissues and to strive to ensure clinical safety[121]. For example, in the USA, clinical studies involving MSCs are categorized under the investigational new drug (IND) protocol by the FDA. Part of the protocol requires precise details of the studies plans and goals as well as details on preparation and testing of the therapeutic cell product. [122]

It should be noted that, theoretically fresh allografts are the gold standard for cartilage repair. Its promise is not without its significant limitations, however[123]. These include graft availability, viability and differences in processing and storage techniques. One animal study showed that grafts stored for 21 days and over and then transplanted into non-human primates had severe degenerative changes compared to grafts that were stored for less than 21 days. Further research and trials are needed to access different storage of grafts to analyze the impact on viability. [124]

2.2.3. Scaffold-based replacement

A scaffold is a structure created to mimic a physiologic environment suitable for cell growth and differentiation. There are various types of scaffolds used to treat foot and ankle pathologies: including autologous chondrocyte implantation (ACI), matrix-induced autologous chondrocyte implantation (MACI), autologous matrix-induced chondrogenesis (AMIC), and matrix-induced stem cell transplantation (MAST). ACI and MACI are two-stage scaffolds that require donor site morbidity; cartilage is taken from healthy tissue, cultured, and then re-implanted at the site of the injury [125,126]. Studies demonstrate that these treatments have potential in OLT treatment, reporting increased AOFAS scores postoperatively. AMIC and MAST are single-stage scaffolds that do not require cells to be cultured [111,127–130]. The literature on AIMC demonstrates that it can reduce pain post-operatively in patients with OLTs [111,127,128,131]. MAST and cell-free scaffolds have also shown to improve clinical scores post-operatively [129,130,132].

2.2.4. Human amnionic tissue

There have been few human studies on amniotic membranes and cartilage defects. Anderson and Swayzee studied the use of amniotic membrane allograft during ankle arthroscopy/microfracture for talar dome lesions less than 2 cm. This was a nonblinded study of 101 patients of which 54 were part of the treatment group. Compared to control group, the treatment group had significantly improved VAS scores at 24 months and American College of Foot and Ankle Surgeons score (ACFAS) at 3, 12, and 24 months[133].An animal study that examined rat tibia fracture that were treated with human amniotic fluid (HAF) vs saline control. After a 5-week treatment period, there was significantly better histological and radiographic bone healing[134].

3. Growth factors and bone morphogenetic proteins

Growth factors are proteins that stimulate the growth and development of tissue. They have several functions that include cartilage growth and extracellular matrix synthesis, which have the potential to augment cartilage repair and healing.

3.1. Platelet-derived growth factors (PDGFs) and Fibroblast growth factors (FGF)

PDGFs is a family of growth factors released from platelets and macrophages in response to tissue injury. A series of growth factors form from the disulfide-linked dimers including PDGF-AA, AB, BB, CC, and DD[135]. PDGF-BB, the most potent of the isoforms, has been shown to recruit inflammatory cells and stimulate angiogenesis [136,137]. The use of rhPDGF-BB has been approved for ankle and hindfoot fusions in the United States, Canada, New Zealand, and Australia. It is also under review in Europe. There have been several clinical studies that demonstrate the use of recombinant PDGF (rhPDGF-BB) in foot and ankle injuries, specifically surgery. A multicenter, prospective clinical trial assessed the safety and efficacy of recombinant human rhPDGF-BB[138]. They demonstrated that there was 75% and 88% union at 16-weeks and 59-weeks respectively. Although there was no control group was utilized, this study did not demonstrate any uncommon safety or adverse events that were not previously stated in literature [136,139,140]; this suggests acceptable effectiveness. When compared to autologous bone graft, the patient who received rhPDGF-BB showed statistically significant equivalence with fewer complications[141]. Daniels et al showed in another study that used a 5:1 randomized rhPDGF-BB combined with a beta-tricalcium phosphate collagen matrix (number of patients = 63) to autographs (n = 12) model that at 24 weeks post op the treatment group had a computer tomography approved fusion rate of 84% compared to the control group which had 65%. These results improved to 91% and 78%, respectively[142]. Concerns have been raised about the increased incidence of cancer associated with topical PDGF administration, but there have been no associations with surgical application in the foot and ankle surgery to date[143].

The in vivo effects of FGF on tendon wound healing have been contradictory. Studies have showed that there was an absence of increase healing when BMSCs that were transected with Basic FGF was transplanted in a rat Achilles tendon model while a model studying rat rotator cuff tendons that had a directed administration of Basis FGF showed increased strength and higher histological scores [144–147]. Usman et al. reported that FGF2, type 1 collagen and VEGF were upregulated when MicroRNA (miR) – 210 was injected into to injured rat Achilles tendons. miR-210 has been reported to increase angiogenesis and thus increase tissue repair. In this study two groups of rats, a control and treatment, underwent Achilles tendon transection and then repaired with suture. The control group was injected with nonfunctional dsRNA and the treatment with miR-210. At 2 and 6 weeks the treatment group had larger diameter collagen fibers than the control group[148].

3.2. Bone morphogenetic proteins (BMPs)

Bone morphogenetic proteins (BMPs) are the key modulators of pluripotent mesenchymal stem cells and osteoprogenitor cells during osseous healing. Currently, recombinant BMP-2 (rhBMP) is FDA approved for open tibia fractures and lumbar interbody fusions. In the foot and ankle, BMPs are used for arthrodesis off-label, in addition to delayed and nonunion. Studies have reported increased overall union rates with rhBMP-2, but these studies have been underpowered or retrospective [149–152]. rhBMP-2 has demonstrated increased efficacy when compared to autograft [138,153–155]. BMP-7 is also used off-label for foot arthrodesis. Data has shown some promise but much more work needs to be done.

It has been shown on an in vitro level that BMP was able to induce bone formation within tendon, which is not beneficial for tendon healing. [144,156] It was then discovered that the overexpression of the molecule Smad8 will have the effect of inhibiting the osteogenic pathway of BMP and promote the tenogenic route. This was seen in a in vivo Achilles tendon partial defect model where the engineered cells were able to induce tendon regeneration that could be seen on MRI[157].

4. Conclusion

The use of orthobiologics in the foot and ankle injuries is relatively novel and continues to evolve. Biologic adjunct therapies stimulate soft tissue and bone healing. The use of these materials has been studied in other areas of orthopedics and can be applied to foot and ankle treatment as long as there is continued focus on their unique physiologic and anatomic features. The autologous nature of BMAC and PRP provides a superb safety profile with nominal donor site morbidity. PRP and BMAC promote tissue healing by delivering high concentrations of autologous growth factors, stem cells, and platelets [58,107].[109][108], PRP has demonstrated some benefit in tendon and ligament injuries in the foot and ankle, while BMAC has demonstrated improved outcomes in OLTs and boney injuries [58,107,158].[109][108], Scaffolds provide structural support that mimics the physiologic environment ideal for cell growth and migration. Bone allografts have been used in foot and ankle arthrodesis, but they have been associated with increased infection rates[158]. ACI, MACI, AMIC, and MAST have all demonstrated an ability to improve outcomes; however, ACI and MACI have increased morbidity because these methods require two procedures [125–130]. BMP and HA are commonly used in spine and knee arthritis respectively but have been gaining momentum for use in foot and ankle. In the ankle, HA has been shown to mitigate pain and improve patient outcomes. BMP has been used as an adjunct for foot and ankle arthrodesis with some reported outcomes superior to autograft [138,153–155]. Though there is a plethora of biologic therapies available for foot and ankle care, more studies are needed to evaluate and standardize use for treatment.

5. Expert opinion

The utilization of biological adjuncts for the improved repair and regeneration of ankle injuries represents a promising

future in our efforts to address difficult clinical problems. Challenges and opportunities concerning the biologic shortcomings of current reparative and replacement strategies for foot and ankle pathologies still remain. Although in vitro findings suggest good focal points for translation to clinical applications in humans, cell-based therapies remain in their relative infancy. Recent advances have shown that progenitor cells from most tissue types including adipose, periosteum, and synovium provide excellent sources of renewable stem cells. The application of concentrated bone marrow and PRP each represents the most widely studied and commonly used injection therapies with early clinical studies demonstrating promising results, but long-term application and investigation still needed. Overall growth factors, cell therapies, and biocompatible scaffolds could ultimately lead to better healing and regeneration. Future research through regenerative bioengineering will lead the way forward. There is a clear need for high-level evidence for the use of biologic adjunct therapies in foot and ankle injuries. Though BMAC and PRP are autologous, there is a great variation for each preparation. It is true that all PRP preparations are not equal. Further research is necessary to delineate the optimal preparations for different treatment targets, whether that may be for the purposes of Achilles tendinopathy, OLT, or other foot and ankle pathologies. The more tailored and specific the concentration and preparations are for each individual condition, the more advantageous the results may be. The consideration of the stage of the disease processes also needs to be taken into account in specific PRP formulations. The modalities that are reviewed in this study may also be successful when combined in a comprehensive plan and not just as monotherapies. Further studies need to examine the efficacy of dual therapies of stem cells and PRP for example. BMAC and PRP composition should be quantified to truly evaluate the outcomes associated with these treatments moving forward. Over the years, there have been multiple classification systems created for PRP, none of which have gained a footing in the literature. With regard to growth factors, further research is needed to examine the effects of gradual release growth factor treatments that correlate with the gradual nature of wound healing. Stem cell therapies are popular in the basic science research realm but further work needs to be done to account for insufficient data from in vitro assays, animal models, and clinical studies. This data along with more refined definitions of stem cells are needed to develop a safety profile and support needed for the use in more human trials. The important undertone of the future of biologics in the treatment of foot and ankle pathologies is that one size does not fit all – different cell formulations, dosing schedules, and culturing parameters will likely be required based on the tissue being treated and the desired biological target. More work has to be done to understand why some therapies work for some indications and not for others and for protocols to be standardized to optimal treatments. As healthcare continues to move toward value-based, it is important to consider what value these modalities may bring to treatment and patient outcomes.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Wei LC, Lei GH, Sheng PY, et al. Efficacy of platelet-rich plasma combined with allograft bone in the management of displaced intra-articular calcaneal fractures: a prospective cohort study. J Orthop Res. 2012;30(10):1570–1576.
   - **Important trial by Wei et al. on the efficacy of PRP augmented with allografts.**
2. Zhao E, Carney D, Chambers M, et al. The role of biologic in foot and ankle trauma-a review of the literature. Curr Rev Musculoskelet Med. 2018;11(3):495–502.
3. Shepherd DE, Seedhom BB. Thickness of human articular cartilage in joints of the lower limb. Ann Rheum Dis. 1999;58(1):27–34.
4. Kraeutler MJ, Kaenkumchorn T, Pascual-Garrido C, et al. Peculiarities in Ankle Cartilage. Cartilage. 2017;8(1):12–18.
5. Boswell SG, Schnabel LV, Mohammed HO, et al. Increasing platelet concentrations in leukocyte-reduced platelet-rich plasma decrease collagen gene synthesis in tendons. Am J Sports Med. 2014;42(1):42–49.
6. Hall MP, Band PA, Meislin RJ, et al. Platelet-rich plasma: current concepts and application in sports medicine. J Am Acad Orthop Surg. 2009;17(10):602–608.
7. Report. Platelet rich plasma (PRP) market analysis by product (pure, leukocyte-rich, leukocyte-rich fibrin), by application (orthopedics, cosmetic surgery, ophthalmic surgery, neurosurgery), and segment forecasts, 2014–2025. 2017.
8. Global $647 Million Platelet Rich Plasma (PRP) Market Analysis 2014-2017 & Forecasts to 2025. 2018. [cited 2020 Jun 08]. Available from: https://www.prnewswire.com/news-releases/global-647-million-platelet-rich-plasma-prp-market-analysis-2014-2017–forecasts-to-2025-300489825.html.
9. Alsousou J, Keene DJ, Hulley PA, et al. Platelet rich plasma in achilles tendon healing 2 (PATH-2) trial: protocol for a multicentre, participant and assessor-blinded, parallel-group randomised clinical trial comparing platelet-rich plasma (PRP) injection versus placebo injection for Achilles tendon rupture. BMJ Open. 2017;7(11):e018135.
10. Zhang J, Middleton KK, Fu FH, et al. HGF mediates the anti-inflammatory effects of PRP on injured tendons. PloS One. 2013;8(6):e67303.
11. Bendinelli P, Matteucci E, Dogliotti G, et al. Molecular basis of anti-inflammatory action of platelet-rich plasma on human chondrocytes: mechanisms of NF-kappaB inhibition via HGF. J Cell Physiol. 2010;225(3):757–766.
12. Zhang J, Wang JH. Platelet-rich plasma releasate promotes differentiation of tendon stem cells into active tenocytes. Am J Sports Med. 2010;38(12):2477–2486.
13. Scott A, LaPrade RF, Harmon KG, et al. Platelet-Rich Plasma for Patellar Tendinopathy: A Randomized Controlled Trial of Leukocyte-Rich PRP or Leukocyte-Poor PRP Versus Saline. Am J Sports Med. 2019;47(7):1654–1661.

• **Recent trial on different types of PRP for use on patellar tendinopathy.**

14. Peerbooms JC, Sluimer J, Bruijn DJ, et al. Positive effect of an autologous platelet concentrate in lateral epicondylitis in a double-blind randomized controlled trial: platelet-rich plasma versus corticosteroid injection with a 1-year follow-up. Am J Sports Med. 2010;38(2):255–262.
15. Vetrano M, Castorina A, Vulpiani MC, et al. Platelet-rich plasma versus focused shock waves in the treatment of jumper's knee in athletes. Am J Sports Med. 2013;41(4):795–803.
16. Dragoo JL, Wasterlain AS, Braun HJ, et al. Platelet-rich plasma as a treatment for patellar tendinopathy: a double-blind, randomized controlled trial. Am J Sports Med. 2014;42(3):610–618.
17. Le ADK, Enweze L, DeBaun MR, et al. Current Clinical Recommendations for Use of Platelet-Rich Plasma. Curr Rev Musculoskelet Med. 2018;11(4):624–634.
18. Kon E, Filardo G, Delcogliano M, et al. Platelet-rich plasma: new clinical application: a pilot study for treatment of jumper's knee. Injury. 2009;40(6):598–603.
19. Volpi P, Quaglia A, Schoenhuber H, et al. Growth factors in the management of sport-induced tendinopathies: results after 24 months from treatment. A pilot study. J Sports Med Phys Fitness. 2010;50(4):494–500.
20. Ferrero G, Fabbro E, Orlandi D, et al. Ultrasound-guided injection of platelet-rich plasma in chronic Achilles and patellar tendinopathy. J Ultrasound. 2012;15(4):260–266.
21. Gosens T, Den Oudsten BL, Fievez E. Pain and activity levels before and after platelet-rich plasma injection treatment of patellar tendinopathy: a prospective cohort study and the influence of previous treatments. Int Orthop. 2012;36(9):1941–1946.
22. Dallaudiere B, Pesquer L, Meyer P, et al. Intratendinous injection of platelet-rich plasma under US guidance to treat tendinopathy: a long-term pilot study. J Vasc Interv Radiol. 2014;25(5):717–723.
23. Kaux JF, Croisier JL, Bruyere O, et al. One injection of platelet-rich plasma associated to a submaximal eccentric protocol to treat chronic jumper's knee. J Sports Med Phys Fitness. 2015;55(9):953–961.
24. Charousset C, Zaoui A, Bellaiche L, et al. Are multiple platelet-rich plasma injections useful for treatment of chronic patellar tendinopathy in athletes? A prospective study. Am J Sports Med. 2014;42(4):906–911.
25. van Ark M, van den Akker-scheek I, Meijer LT, et al. An exercise-based physical therapy program for patients with patellar tendinopathy after platelet-rich plasma injection. Phys Ther Sport. 2013;14(2):124–130.
26. Mautner K, Colberg RE, Malanga G, et al. Outcomes after ultrasound-guided platelet-rich plasma injections for chronic tendinopathy: a multicenter, retrospective review. Pm R. 2013;5(3):169–175.
27. Gaweda K, Tarczynska M, Krzyzanowski W. Treatment of Achilles tendinopathy with platelet-rich plasma. Int J Sports Med. 2010;31(8):577–583.
28. Owens RF Jr., Ginnetti J, Conti SF, et al. Clinical and magnetic resonance imaging outcomes following platelet rich plasma injection for chronic midsubstance Achilles tendinopathy. Foot Ankle Int. 2011;32(11):1032–1039.
29. Monto RR. Platelet rich plasma treatment for chronic Achilles tendinosis. Foot Ankle Int. 2012;33(5):379–385.
30. Deans VM, Miller A, Ramos J. A prospective series of patients with chronic Achilles tendinopathy treated with autologous-conditioned plasma injections combined with exercise and therapeutic ultrasonography. J Foot Ankle Surg. 2012;51(6):706–710.
31. Filardo G, Kon E, Di Matteo B, et al. Platelet-rich plasma injections for the treatment of refractory Achilles tendinopathy: results at 4 years. Blood Transfus. 2014;12(4):533–540.
32. Murawski CD, Smyth NA, Newman H, et al. A single platelet-rich plasma injection for chronic midsubstance achilles tendinopathy: a retrospective preliminary analysis. Foot Ankle Spec. 2014;7(5):372–376.
33. de Vos RJ, Weir A, van Schie HT, et al. Platelet-rich plasma injection for chronic Achilles tendinopathy: a randomized controlled trial. JAMA. 2010;303(2):144–149.
34. Castricini R, Longo UG, De Benedetto M, et al. Platelet-rich plasma augmentation for arthroscopic rotator cuff repair: a randomized controlled trial. Am J Sports Med. 2011;39(2):258–265.
35. de Jonge S, de Vos RJ, Weir A, et al. One-year follow-up of platelet-rich plasma treatment in chronic Achilles tendinopathy: a double-blind randomized placebo-controlled trial. Am J Sports Med. 2011;39(8):1623–1629.

•• **Important double blind study on PRP in Achilles tendinopathy.**

36. Kon E, Filardo G, Di Martino A, et al. Platelet-rich plasma (PRP) to treat sports injuries: evidence to support its use. Knee Surg Sports Traumatol Arthrosc. 2011;19(4):516–527.
37. Andia I, Martin JI, Maffulli N. Advances with platelet rich plasma therapies for tendon regeneration. Expert Opin Biol Ther. 2018;18(4):389-398..
38. Castillo TN, Pouliot MA, Kim HJ, et al. Comparison of growth factor and platelet concentration from commercial platelet-rich plasma separation systems. Am J Sports Med. 2011;39(2):266–271.
39. Anitua E, Sanchez M, Nurden AT, et al. Autologous fibrin matrices: a potential source of biological mediators that modulate tendon cell activities. J Biomed Mater Res A. 2006;77(2):285–293.
40. Zhou Y, Zhang J, Wu H, et al. The differential effects of leukocyte-containing and pure platelet-rich plasma (PRP) on tendon stem/progenitor cells - implications of PRP application for the clinical treatment of tendon injuries. Stem Cell Res Ther. 2015;6:173.
41. Dragoo JL, Braun HJ, Durham JL, et al. Comparison of the acute inflammatory response of two commercial platelet-rich plasma systems in healthy rabbit tendons. Am J Sports Med. 2012;40(6):1274–1281.
42. 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):2135–2140.
43. Braun HJ, Kim HJ, Chu CR, et al. 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):1204–1210.
44. Wang JH. Can PRP effectively treat injured tendons? Muscles Ligaments Tendons J. 2014;4(1):35–37.
45. Abate M, Di Gregorio P, Schiavone C, et al. Platelet rich plasma in tendinopathies: how to explain the failure. Int J Immunopathol Pharmacol. 2012;25(2):325–334.
46. Kannus P, Jozsa L. Histopathological changes preceding spontaneous rupture of a tendon. A controlled study of 891 patients. J Bone Joint Surg Am. 1991;73(10):1507–1525.
47. Zhang J, Wang JH. PRP treatment effects on degenerative tendinopathy - an in vitro model study. Muscles Ligaments Tendons J. 2014;4(1):10–17.
48. Finnoff JT, Fowler SP, Lai JK, et al. Treatment of chronic tendinopathy with ultrasound-guided needle tenotomy and platelet-rich plasma injection. Pm R. 2011;3(10):900–911.
49. Monto RR. Platelet-rich plasma and plantar fasciitis. Sports Med Arthrosc Rev. 2013;21(4):220–224.
50. Monto RR. Platelet-rich plasma efficacy versus corticosteroid injection treatment for chronic severe plantar fasciitis. Foot Ankle Int. 2014;35(4):313–318.
51. Aksahin E, Dogruyol D, Yuksel HY, et al. The comparison of the effect of corticosteroids and platelet-rich plasma (PRP) for the treatment of plantar fasciitis. Arch Orthop Trauma Surg. 2012;132(6):781–785.

52. Lopez-Gavito E, Gomez-Carlin LA, Parra-Tellez P, et al. Platelet-rich plasma for managing calcaneus tendon tendinopathy and plantar fasciitis. Acta Ortop Mex. 2011;25(6):380–385.
53. Martinelli N, Marinozzi A, Carni S, et al. Platelet-rich plasma injections for chronic plantar fasciitis. Int Orthop. 2013;37(5):839–842.
54. Ragab EM, Othman AM. Platelets rich plasma for treatment of chronic plantar fasciitis. Arch Orthop Trauma Surg. 2012;132(8):1065–1070.
55. Kalaci A, Cakici H, Hapa O, et al. Treatment of plantar fasciitis using four different local injection modalities: a randomized prospective clinical trial. J Am Podiatr Med Assoc. 2009;99(2):108–113.
56. Acevedo JI, Beskin JL. Complications of plantar fascia rupture associated with corticosteroid injection. Foot Ankle Int. 1998;19(2):91–97.
57. Cohen IK, Diegelmann RF, Johnson ML. Effect of corticosteroids on collagen synthesis. Surgery. 1977;82(1):15–20.
58. Peerbooms JC, Lodder P, den Oudsten BL, et al. Positive effect of platelet-rich plasma on pain in plantar fasciitis: a double-blind multicenter randomized controlled trial. Am J Sports Med. 2019;47(13):3238–3246.
•• **Recent multicenter trail on the use of PRP for plantar fasciitis.**
59. Hannon CP, Ross KA, Murawski CD, et al. Arthroscopic bone marrow stimulation and concentrated bone marrow aspirate for osteochondral lesions of the talus: a case-control study of functional and magnetic resonance observation of cartilage repair tissue outcomes. Arthroscopy. 2016;32(2):339–347.
60. Zhou Y, Zhang J, Yang J, et al. Kartogenin with PRP promotes the formation of fibrocartilage zone in the tendon-bone interface. J Tissue Eng Regen Med. 2017;11(12):3445–3456.
61. Gormeli G, Gormeli CA, Ataoglu B, et al. PRP injections are more effective than single injections and hyaluronic acid in knees with early osteoarthritis: a randomized, double-blind, placebo-controlled trial. Knee Surg Sports Traumatol Arthrosc. 2017;25(3):958–965.
62. Guney A, Akar M, Karaman I, et al. Clinical outcomes of platelet rich plasma (PRP) as an adjunct to microfracture surgery in osteochondral lesions of the talus. Knee Surg Sports Traumatol Arthrosc. 2015;23(8):2384–2389.
63. Mei-Dan O, Carmont MR, Laver L, et al. Platelet-rich plasma or hyaluronate in the management of osteochondral lesions of the talus. Am J Sports Med. 2012;40(3):534–541.
64. Kawasaki K, Ochi M, Uchio Y, et al. Hyaluronic acid enhances proliferation and chondroitin sulfate synthesis in cultured chondrocytes embedded in collagen gels. J Cell Physiol. 1999;179(2):142–148.
65. Pilichi S, Rocca S, Pool RR, et al. Treatment with embryonic stem-like cells into osteochondral defects in sheep femoral condyles. BMC Vet Res. 2014;10:301.
66. Kaplan LD, Lu Y, Snitzer J, et al. The effect of early hyaluronic acid delivery on the development of an acute articular cartilage lesion in a sheep model. Am J Sports Med. 2009;37(12):2323–2327.
67. Strauss E, Schachter A, Frenkel S, et al. The efficacy of intra-articular hyaluronan injection after the microfracture technique for the treatment of articular cartilage lesions. Am J Sports Med. 2009;37(4):720–726.
68. Shang XL, Tao HY, Chen SY, et al. Clinical and MRI outcomes of HA injection following arthroscopic microfracture for osteochondral lesions of the talus. Knee Surg Sports Traumatol Arthrosc. 2016;24(4):1243–1249.
69. Doral MN, Bilge O, Batmaz G, et al. Treatment of osteochondral lesions of the talus with microfracture technique and postoperative hyaluronan injection. Knee Surg Sports Traumatol Arthrosc. 2012;20(7):1398–1403.
70. Zhang J, Yuan T, Zheng N, et al. The combined use of kartogenin and platelet-rich plasma promotes fibrocartilage formation in the wounded rat Achilles tendon entheses. Bone Joint Res. 2017;6(4):231–244.
71. Walden G, Liao X, Donell S, et al. Biological, and biomaterials perspective into tendon injuries and regeneration. Tissue Eng Part B Rev. 2017;23(1):44–58.
72. Kuo CK, Marturano JE, Tuan RS. Novel strategies in tendon and ligament tissue engineering: advanced biomaterials and regeneration motifs. Sports Med Arthrosc Rehabil Ther Technol. 2010;2:20.
73. Zhang X, Wang J, Ren M, et al. A novel collagen/platelet-rich plasma (COL/PRP) scaffold: preparation and growth factor release analysis. Cell Tissue Bank. 2016;17(2):327–334.
74. Fang D, Jin P, Huang Q, et al. Platelet-rich plasma promotes the regeneration of cartilage engineered by mesenchymal stem cells and collagen hydrogel via the TGF-beta/SMAD signaling pathway. J Cell Physiol. 2019. DOI:10.1002/jcp.28211
75. Vavken P, Murray MM. The potential for primary repair of the ACL. Sports Med Arthrosc Rev. 2011;19(1):44–49.
76. Imam MA, Holton J, Horriat S, et al. A systematic review of the concept and clinical applications of bone marrow aspirate concentrate in tendon pathology. Sicot J. 2017;3:58.
77. Indino C, D'Ambrosi R, Usuelli FG. Biologics in the treatment of achilles tendon pathologies. Foot Ankle Clin. 2019;24(3):471–493.
78. Broese M, Toma I, Haasper C, et al. Seeding a human tendon matrix with bone marrow aspirates compared to previously isolated hBMSCs–an in vitro study. Technol Health Care. 2011;19(6):469–479.
79. Stein BE, Stroh DA, Schon LC. Outcomes of acute Achilles tendon rupture repair with bone marrow aspirate concentrate augmentation. Int Orthop. 2015;39(5):901–905.
80. Usuelli FG, Grassi M, Maccario C, et al. Intratendinous adipose-derived stromal vascular fraction (SVF) injection provides a safe, efficacious treatment for Achilles tendinopathy: results of a randomized controlled clinical trial at a 6-month follow-up. Knee Surg Sports Traumatol Arthrosc. 2018;26(7):2000–2010.
81. Behfar M, Sarrafzadeh-Rezaei F, Hobbenaghi R, et al. Adipose-derived stromal vascular fraction improves tendon healing in rabbits. Chin J Traumatol. 2011;14(6):329–335.
82. de Aro AA, Carneiro GD, Teodoro LFR, et al. Injured achilles tendons treated with adipose-derived stem cells transplantation and GDF-5. Cells. 2018;7(9):127.
83. Heckmann N, Auran R, Mirzayan R. Application of amniotic tissue in orthopedic surgery. Am J Orthop (Belle Mead NJ). 2016;45(7):E421–e425.
84. Zelen CM, Poka A, Andrews J. Prospective, randomized, blinded, comparative study of injectable micronized dehydrated amniotic/chorionic membrane allograft for plantar fasciitis–a feasibility study. Foot Ankle Int. 2013;34(10):1332–1339.
• **Important study on the use of amniotic membrane allograft for plantar fasciitis.**
85. Adly OA, Moghazy AM, Abbas AH, et al. Assessment of amniotic and polyurethane membrane dressings in the treatment of burns. Burns. 2010;36(5):703–710.
86. Eslani M, Baradaran-Rafii A, Cheung AY, et al. Amniotic membrane transplantation in acute severe ocular chemical injury: a randomized clinical trial. Am J Ophthalmol. 2019;199:209–215.
87. Caruso M, Evangelista M, Parolini O. Human term placental cells: phenotype, properties and new avenues in regenerative medicine. Int J Mol Cell Med. 2012;1(2):64–74.
88. Werber B. Amniotic tissues for the treatment of chronic plantar fasciosis and achilles tendinosis. J Sports Med (Hindawi Publ Corp). 2015;2015:219896.
89. Hanselman AE, Tidwell JE, Santrock RD. Cryopreserved human amniotic membrane injection for plantar fasciitis: a randomized, controlled, double-blind pilot study. Foot Ankle Int. 2015;36(2):151–158.
90. McQuilling JP, Sanders M, Poland L, et al. Dehydrated amnion/chorion improves achilles tendon repair in a diabetic animal model. Wounds. 2019;31(1):19–25.
91. Kueckelhaus M, Philip J, Kamel RA, et al. Sustained release of amnion-derived cellular cytokine solution facilitates achilles tendon healing in rats. Eplasty. 2014;14:e29.

92. Coban I, Satoğlu IS, Gültekin A, et al. Effects of human amniotic fluid and membrane in the treatment of Achilles tendon ruptures in locally corticosteroid-induced Achilles tendinosis: an experimental study on rats. Foot Ankle Surg. 2009;15(1):22–27.
93. Adams SB Jr., Thorpe MA, Parks BG, et al. Stem cell-bearing suture improves Achilles tendon healing in a rat model. Foot Ankle Int. 2014;35(3):293–299.
94. Yao J, Woon CY, Behn A, et al. The effect of suture coated with mesenchymal stem cells and bioactive substrate on tendon repair strength in a rat model. J Hand Surg Am. 2012;37 (8):1639–1645.
95. Gissi C, Radeghieri A, Antonetti Lamorgese Passeri C. Extracellular vesicles from rat-bone-marrow mesenchymal stromal/stem cells improve tendon repair in rat Achilles tendon injury model in dose-dependent manner: A pilot study. PloS One. 2020;15(3): e0229914.
96. Webb WR, Dale TP, Lomas AJ, et al. The application of poly(3--hydroxybutyrate-co-3-hydroxyhexanoate) scaffolds for tendon repair in the rat model. Biomaterials. 2013;34(28):6683–6694.
97. Ning LJ, Zhang Y, Chen XH, et al. Preparation and characterization of decellularized tendon slices for tendon tissue engineering. J Biomed Mater Res A. 2012;100(6):1448–1456.
98. Farnebo S, Woon CY, Bronstein JA, et al. Decellularized tendon-bone composite grafts for extremity reconstruction: an experimental study. Plast Reconstr Surg. 2014;133(1):79–89.
99. Lohan A, Stoll C, Albrecht M, et al. Human hamstring tenocytes survive when seeded into a decellularized porcine Achilles tendon extracellular matrix. Connect Tissue Res. 2013;54(4–5):305–312.
100. Kimbrel EA, Kouris NA, Yavanian GJ, et al. Mesenchymal stem cell population derived from human pluripotent stem cells displays potent immunomodulatory and therapeutic properties. Stem Cells Dev. 2014;23(14):1611–1624.
101. Toh WS, Lee EH, Cao T. Potential of human embryonic stem cells in cartilage tissue engineering and regenerative medicine. Stem Cell Rev Rep. 2011;7(3):544–559.
102. Cheng A, Kapacee Z, Peng J, et al. Cartilage repair using human embryonic stem cell-derived chondroprogenitors. Stem Cells Transl Med. 2014;3(11):1287–1294.
103. Grogan SP, Dorthé EW, Glembotski NE, et al. Cartilage tissue engineering combining microspheroid building blocks and microneedle arrays. Connect Tissue Res. 2020;61(2):229–243.
104. de Windt TS, Vonk LA, ICM S-C, et al. Allogeneic mesenchymal stem cells stimulate cartilage regeneration and are safe for single-stage cartilage repair in humans upon mixture with recycled autologous chondrons. Stem Cells. 2017;35(1):256–264.
105. Cottom JM, Plemmons BS. Bone marrow aspirate concentrate and its uses in the foot and ankle. Clin Podiatr Med Surg. 2018;35 (1):19–26.
•Important review article on the uses of BMAC for foot and ankle pathlogies
106. Harford JS, Dekker TJ, Adams SB. Bone marrow aspirate concentrate for bone healing in foot and ankle surgery. Foot Ankle Clin. 2016;21(4):839–845.
107. Fortier LA, Potter HG, Rickey EJ, et al. Concentrated bone marrow aspirate improves full-thickness cartilage repair compared with microfracture in the equine model. J Bone Joint Surg Am. 2010;92(10):1927–1937.
108. Buda R, Vannini F, Cavallo M, et al. One-step bone marrow-derived cell transplantation in talarosteochondral lesions: mid-term results. Joints. 2013;1(3):102–107.
109. Kennedy JG, Murawski CD. The treatment of osteochondral lesions of the talus with autologous osteochondral transplantation and bone marrow aspirate concentrate: surgical technique. Cartilage. 2011;2(4):327–336.
110. Yasui Y, Ross AW, Kennedy JG, et al. Concentrated bone marrow aspirate in surgical treatment for osteochondral lesions of the talus. Foot Ankle Clin. 2016;21(4):869–884.
111. Kim YS, Park EH, Kim YC, et al. Clinical outcomes of mesenchymal stem cell injection with arthroscopic treatment in older patients with osteochondral lesions of the talus. Am J Sports Med. 2013;41 (5):1090–1099.
112. Giannini S, Buda R, Battaglia M, et al. One-step repair in talar osteochondral lesions: 4-year clinical results and t2-mapping capability in outcome prediction. Am J Sports Med. 2013;41 (3):511–518.
113. Giannini S, Buda R, Vannini F, et al. One-step bone marrow-derived cell transplantation in talar osteochondral lesions. Clin Orthop Relat Res. 2009;467(12):3307–3320.
114. Pierini M, Di Bella C, Dozza B, et al. The posterior iliac crest outperforms the anterior iliac crest when obtaining mesenchymal stem cells from bone marrow. J Bone Joint Surg Am. 2013;95 (12):1101–1107.
115. Murphy EP, Fenelon C, McGoldrick NP, et al. Bone marrow aspirate concentrate and microfracture technique for talar osteochondral lesions of the ankle. Arthrosc Tech. 2018;7(4):e391–e396.
116. Kim YS, Lee HJ, Choi YJ, et al. Does an injection of a stromal vascular fraction containing adipose-derived mesenchymal stem cells influence the outcomes of marrow stimulation in osteochondral lesions of the talus? A clinical and magnetic resonance imaging study. Am J Sports Med. 2014;42(10):2424–2434.
117. Song Y, Du H, Dai C, et al. Human adipose-derived mesenchymal stem cells for osteoarthritis: a pilot study with long-term follow-up and repeated injections. Regen Med. 2018;13(3):295–307.
118. Peretti G, Ulivi M, de Girolamo L, et al. Evaluation of the use of autologous micro-fragmented adipose tissue in the treatment of knee osteoarthritis: preliminary results of a randomized controlled trial. J Biol Regul Homeost Agents. 2018;32:193–199.
119. Shimozono Y, Dankert JF, Kennedy JG. Arthroscopic debridement and autologous micronized adipose tissue injection in the treatment of advanced-stage posttraumatic osteoarthritis of the ankle. Cartilage. 2020;1947603520946364. DOI:10.1177/1947603520946364
120. Usuelli FG, D'Ambrosi R, Maccario C, et al. Adipose-derived stem cells in orthopaedic pathologies. Br Med Bull. 2017;124(1):31–54.
121. Ho-Shui-Ling A, Bolander J, Rustom LE, et al. Bone regeneration strategies: engineered scaffolds, bioactive molecules and stem cells current stage and future perspectives. Biomaterials. 2018;180:143–162.
122. Liras A. Future research and therapeutic applications of human stem cells: general, regulatory, and bioethical aspects. J Transl Med. 2010;8:131.
123. Gee A. Mesenchymal stem-cell therapy in a regulated environment. Cytotherapy. 2001;3(5):397–398.
124. Temple HT, Malinin TI. Orthobiologics in the Foot and Ankle. Foot Ankle Clin. 2016;21(4):809–823.
125. Malinin T, Temple HT, Buck BE. Transplantation of osteochondral allografts after cold storage. J Bone Joint Surg Am. 2006;88 (4):762–770.
126. Kwak SK, Kern BS, Ferkel RD, et al. Autologous chondrocyte implantation of the ankle: 2- to 10-year results. Am J Sports Med. 2014;42 (9):2156–2164.
127. Giannini S, Buda R, Ruffilli A, et al. Arthroscopic autologous chondrocyte implantation in the ankle joint. Knee Surg Sports Traumatol Arthrosc. 2014;22(6):1311–1319.
128. Albano D, Martinelli N, Bianchi A, et al. Clinical and imaging outcome of osteochondral lesions of the talus treated using autologous matrix-induced chondrogenesis technique with a biomimetic scaffold. BMC Musculoskelet Disord. 2017;18(1):306.
129. D'Ambrosi R, Maccario C, Serra N, et al. Osteochondral lesions of the talus and autologous matrix-induced chondrogenesis: is age a negative predictor outcome? Arthroscopy. 2017;33(2):428–435.
130. Richter M, Zech S. Matrix-associated stem cell transplantation (MAST) in chondral defects of foot and ankle is effective. Foot Ankle Surg. 2013;19(2):84–90.

131. Kanatli U, Eren A, Eren TK, et al. Single-step arthroscopic repair with cell-free polymer-based scaffold in osteochondral lesions of the talus: clinical and radiological results. Arthroscopy. 2017;33(9):1718–1726.
132. Valderrabano V, Miska M, Leumann A, et al. Reconstruction of osteochondral lesions of the talus with autologous spongiosa grafts and autologous matrix-induced chondrogenesis. Am J Sports Med. 2013;41(3):519–527.
133. Kaipel M, Schreiner M, Kellner R, et al. Beneficial clinical effects but limited tissue quality following osteochondral repair with a cell-free multilayered nano-composite scaffold in the talus. Foot Ankle Surg. 2017;23(4):302–306.
134. Anderson J, Swayzee Z. The use of human amniotic allograft on osteochondritis dissecans of the talar dome: a comparison with and without allografts in arthroscopically treated ankles. Surg Sci. 2015;06:412–417.
135. Sarı E, Yalçınozan M, Polat B, et al. The effects of cryopreserved human amniotic membrane on fracture healing: animal study. Acta Orthop Traumatol Turc. 2019;53(6):485–489.
136. Alvarez RH, Kantarjian HM, Cortes JE. Biology of platelet-derived growth factor and its involvement in disease. Mayo Clin Proc. 2006;81(9):1241–1257.
137. Easley ME, Trnka HJ, Schon LC, et al. Isolated subtalar arthrodesis. J Bone Joint Surg Am. 2000;82(5):613–624.
138. Hollinger JO, Hart CE, Hirsch SN, et al. Recombinant human platelet-derived growth factor: biology and clinical applications. J Bone Joint Surg Am. 2008;90(Suppl 1):48–54.
139. Daniels T, DiGiovanni C, Lau JT, et al. Prospective clinical pilot trial in a single cohort group of rhPDGF in foot arthrodeses. Foot Ankle Int. 2010;31(6):473–479.
140. Frey C, Halikus NM, Vu-Rose T, et al. A review of ankle arthrodesis: predisposing factors to nonunion. Foot Ankle Int. 1994;15(11):581–584.
141. Haddad SL, Coetzee JC, Estok R, et al. Intermediate and long-term outcomes of total ankle arthroplasty and ankle arthrodesis. A systematic review of the literature. J Bone Joint Surg Am. 2007;89(9):1899–1905.
142. DiGiovanni CW, Lin SS, Baumhauer JF, et al. Recombinant human platelet-derived growth factor-BB and beta-tricalcium phosphate (rhPDGF-BB/beta-TCP): an alternative to autogenous bone graft. J Bone Joint Surg Am. 2013;95(13):1184–1192.
143. Daniels TR, Younger AS, Penner MJ, et al. Prospective randomized controlled trial of hindfoot and ankle fusions treated with rhPDGF-BB in combination with a β-TCP-collagen matrix. Foot Ankle Int. 2015;36(7):739–748.
144. Lin SS, Montemurro NJ, Krell ES. Orthobiologics in Foot and Ankle Surgery. J Am Acad Orthop Surg. 2016;24(2):113–122.
145. Citeroni MR, Ciardulli MC, Russo V, et al. In Vitro Innovation of Tendon Tissue Engineering Strategies. Int J Mol Sci. 2020;21:18.
146. Kraus TM, Imhoff FB, Reinert J, et al. Stem cells and bFGF in tendon healing: effects of lentiviral gene transfer and long-term follow-up in a rat Achilles tendon defect model. BMC Musculoskelet Disord. 2016;17:148.
147. Kraus TM, Imhoff FB, Wexel G, et al. Stem cells and basic fibroblast growth factor failed to improve tendon healing: an in vivo study using lentiviral gene transfer in a rat model. J Bone Joint Surg Am. 2014;96(9):761–769.
148. Tokunaga T, Shukunami C, Okamoto N, et al. FGF-2 stimulates the growth of tenogenic progenitor cells to facilitate the generation of tenomodulin-positive tenocytes in a rat rotator cuff healing model. Am J Sports Med. 2015;43(10):2411–2422.
149. Usman MA, Nakasa T, Shoji T, et al. The effect of administration of double stranded MicroRNA-210 on acceleration of Achilles tendon healing in a rat model. J Orthop Sci. 2015;20(3):538–546.
150. Bibbo C, Anderson RB, Davis WH. Complications of midfoot and hindfoot arthrodesis. Clin Orthop Relat Res. 2001;391:45–58. DOI:10.1097/00003086-200110000-00007
151. Coughlin MJ, Grimes JS, Traughber PD, et al. Comparison of radiographs and CT scans in the prospective evaluation of the fusion of hindfoot arthrodesis. Foot Ankle Int. 2006;27(10):780–787.
152. Fourman MS, Borst EW, Bogner E, et al. Recombinant human BMP-2 increases the incidence and rate of healing in complex ankle arthrodesis. Clin Orthop Relat Res. 2014;472(2):732–739.
153. DeVries JG, Nguyen M, Berlet GC, et al. The effect of recombinant bone morphogenetic protein-2 in revision tibiotalocalcaneal arthrodesis: utilization of the retrograde arthrodesis intramedullary nail database. J Foot Ankle Surg. 2012;51(4):426–432.
154. Hreha J, Krell ES, Bibbo C. Role of recombinant human bone morphogenetic protein-2 on hindfoot arthrodesis. Foot Ankle Clin. 2016;21(4):793–802.
155. Daniels TR, Anderson J, Swords MP, et al. Recombinant human platelet-derived growth factor BB in combination with a beta-tricalcium phosphate (rhPDGF-BB/beta-TCP)-collagen matrix as an alternative to autograft. Foot Ankle Int. 2019;40(9):1068–1078.
156. Anderson JJ, Boone JJ, Hansen M, et al. Ankle arthrodesis fusion rates for mesenchymal stem cell bone allograft versus proximal tibia autograft. J Foot Ankle Surg. 2014;53(6):683–686.
157. Schneider M, Angele P, TAH J, et al. Rescue plan for Achilles: therapeutics steering the fate and functions of stem cells in tendon wound healing. Adv Drug Deliv Rev. 2018;129:352–375.
158. Hoffmann A, Pelled G, Turgeman G, et al. Neotendon formation induced by manipulation of the Smad8 signalling pathway in mesenchymal stem cells. J Clin Invest. 2006;116(4):940–952.