Orthobiologics is a broad term used to define substances and materials used to aid in the healing of musculoskeletal injuries in the operative and nonoperative setting. Although the field of orthobiologics is not new, the bulk of advances have occurred within the past 20 years, and innovation continues to progress at a rapid pace, particularly within the foot and ankle.
ankle subspecialty where several clinical pathologies present unique opportunities for biological augmentation. The aim of this article is to outline the current state of orthoregenerative approaches for foot and ankle pathology via three broad categories of bone-based, cartilage-based, as well as blood/stem cell and injectable modalities. Despite physical and mechanistic differences between the categories, there is significant interplay and combinations of each that can be used to treat a spectrum of pathology.

**Bone-Based Therapies**

**Autograft**

Bone-based biologic therapies for foot and ankle conditions are comprised primarily of various grafting options. The gold standard bone grafting material is cancellous or cortical autograft, depending on the procedural need. In foot and ankle procedures, autograft is commonly harvested from the iliac crest, proximal tibia, and/or calcaneus, with the amount of available graft decreasing in that order. Despite multiple inherent benefits, autograft is not without its drawbacks in the form of limited supply. A significant complication rate of up to 8.6% is reported in the literature. One recent review has advocated for use of lower extremity autograft harvests as opposed to the iliac crest due to potentially lower complication rates. For cases in which autograft is either not an option or is insufficient, allograft and various synthetic bone graft substitutes can be employed.

**Allograft**

There is no shortage of allograft bone grafting options available, which exist in various forms. Cortical bone graft is harvested from cadavers and is generally used to provide structural support, often needed after acute traumatic injuries or to supplement osteotomy or fusion procedures about the ankle. Depending on the preservation technique used, the graft can vary in mechanical integrity and osteogenic/osteinductive potential. Fresh-frozen grafts retain the most structural integrity due to less formation of free radicals. Freeze-dried grafts are a more cost-effective option that also have the advantage of storage at room temperature, a disadvantage is the reduced mechanical strength. Prior studies have shown effective incorporation and host remodeling of these structural allografts.

Cancellous allografts come in various shapes and sizes (typically in the form of “chips”) and are primarily used to fill bony voids and assist with fusion, but in areas where structural integrity is not necessary. These grafts are primarily osteoconductive. The high-level literature comparing autologous and allogenic bone grafting in foot and ankle procedures is sparse; despite this, a single level II systematic review by Müller et al. included 928 hindfoot arthrodeses and osteotomies with equivalent fusion rates between structural allografts and autografts. However, the authors caution on the quality of the individual studies included. The final, most widely used grafting option in the allograft family is demineralized bone matrix (DBM), which is a highly processed allograft combined with various growth factors. Similar to other allograft options, the osteogenic and osteoinductive capacity of the specific DBM is based on the specific preparation technique. As a result of the highly processed nature of DBM, manufacturers have the ability to provide it in various forms, including powder or putty, thereby fitting a wide spectrum of clinical needs.

**Synthetic Bone Graft Substitutes**

In cases where autograft or allograft is unavailable, bone graft substitutes can be applied to provide an osteoconductive environment. Favoring for their widespread availability, reasonable cost, flexibility in preparation and form, and minimal risk profile, bone graft substitutes are commonly used. The primary benefits of bone graft substitutes are the elimination of risks associated with autograft harvester and the theoretical concerns of disease transmission or culture beliefs associated with allograft. The mechanism of bone graft substitutes relies primarily on providing a scaffold into which native osteoprogenitor cells can migrate and begin to form new bony growth while also being resorbed over time as the patient’s bone fills the space previously occupied by the graft. The three primary synthetic bone graft substitute options that are widely available are calcium sulfate (CS), calcium phosphate (CP), and tricalcium phosphate (TCP). Other less frequently used materials, such as bioactive glasses and polymers, are also available.

Calcium phosphate primarily comes in cement form and has been used since the mid-1990s. With the ability to conform to almost any shape, a slow integration profile of up to 2 years postimplantation, and mechanical properties superior to cancellous bone, CP provides a flexibility in application that is not available in autograft or allograft options. Conversely, the brittle nature of CP cement has been shown in a meta-analysis on skull reconstruction to have a high complication rate of up to 13% with its use, with 9% considered a major complication. Calcium sulfate was next to gain U.S. Food and Drug Administration (FDA) approval in the mid-1990s. CS has similar advantages to CP in that it is plentiful, does not elicit a strong host response, and is versatile in application. Unlike CP, CS is resorbed much quicker (up to one month postimplantation) and cannot be used in cases where early weight-bearing and mobilization through the graft is necessary. Moreover, too rapid resorption may lead
to nonunion if the host has not produced enough bone extracellular matrix.

TCP is a grafting substitute similar in physical properties to cancellous bone and is, thus, used commonly in cases where structural support is required. Studies have shown TCP to be safe, with minimal host reaction, and is generally incorporated anywhere between 6 and 8 months after implantation. Noninferiority studies focusing on the use of TCP in reconstructive efforts reveal a similar fusion rate when compared to autograft. In the foot and ankle specifically, TCP use was studied retrospectively as part of calcaneal fracture ORIF in 74 patients by Jiang et al., who found that the mean Böhler angle reduced by only 4° at one-year postoperatively, with similar changes in the angle of Gissane, combined with over 90% of patients reporting good or excellent results on the Maryland foot score. Similar positive results have been reported in smaller case series focusing on TCP use in foot and ankle trauma, arthrodesis, and oncology cases.

Bioactive glasses offer an additional option outside of the more widely used calcium-based substitutes. Bioactive glass is an osteoconductive material that, when combined with body fluids, forms a gel-like calcium phosphate layer that, within a few hours, will further reconstitute into a hydroxyapatite layer that closely resembles native bone and promotes attachment of local tissues. The resorptive time frame of the bioactive glass depends on composition, but can be as soon as 6 months postimplantation for silica-based options. The primary drawback of bioactive glasses is their mechanical properties, as they tend to be brittle and exhibit inferior biomechanical strength properties in comparison to calcium-based substitutes. The outcomes after use of bioactive glasses have been studied in foot and ankle arthrodesis in combination with other additives, including bone marrow aspirate (BMA). Shi et al. studied hindfoot arthrodesis using bioactive glass and BMA in 48 joints about the hindfoot in 29 patients, resulting in a union rate comparable to autograft and other graft substitute options. Additional studies in the foot and ankle tumor and infection literature cite similar positive outcomes with the use of bioglass and present the material as a safe and effective option in the appropriate clinical setting.

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**Fig 1.** (A) Arthroscopic view of talar cartilage lesion. (B) Full-thickness cartilage lesion after debridement. (C) Microfracture of lesion. (D) Application of particulated juvenile cartilage to lesion.
Proteins

BMP

Bone morphogenic proteins, or BMPs, are growth factors within a subclass of the transforming growth factor family known to have osteogenic potential.\textsuperscript{30} There are currently only two forms of BMPs available on the market, those being recombinant human (rh) forms: rhBMP-2 and rh-BMP-7, with rhBMP-2 being the more widely used.\textsuperscript{30} Despite the narrow FDA indications for use, including lumbar spine fusions and open tibial fractures, rhBMP-2 has been studied in the foot and ankle as well, with promising results.\textsuperscript{31} The highest-level study was performed by Fourman et al., who performed a retrospective case-control study on the off-label use of rhBMP-2 in ankle arthrodesis using Ilizarov technique within a subset of 82 medically complex patients with comorbidities that predispose to difficulty healing. They found a significantly higher union rate of 93\% in the rhBMP-2 group vs. only 53\% in the control group, less time in the frame (124 vs 161 days), and more bridging on CT scans (48\% vs 32\%).\textsuperscript{32} Similarly high fusion and union rates were reported by Bibbo et al., with rhBMP-2 adjunct use in hindfoot arthrodesis at 96\%, and by Rearick et al. in an assortment of foot and ankle procedures at 92\%.\textsuperscript{33,34}

PDGF

PDGF is an autologous product contained within the alpha granules of platelets and acts via chemotaxis to attract various inflammatory and regenerative cells to the site of injection, thereby, theoretically promoting healing. Multiple randomized controlled studies have been conducted to study the use of PDGF in foot and ankle fusion in comparison to the gold standard of autograft, with each study showing nonequivalence and a reduction in the side effects associated with autograft use.\textsuperscript{35-37}

Cartilage Based Therapies

Cartilage is a particular area of interest in the setting of orthobiologics owing to the lack of natural regenerative capacity. A number of orthoregenerative approaches to cartilage restoration in the ankle over the years, with variable levels of documented success. The first line of surgical treatment for a symptomatic osteochondral lesion of the ankle is a form of debridement with or without a bone marrow stimulation procedure (e.g., microfracture, drilling). While bone marrow stimulation has historically shown success as a minimally invasive, effective treatment option, more recent literature has demonstrated inferior outcomes over longer-term follow up, particularly with larger lesions and lesions located at the talus shoulder.\textsuperscript{38-41}

Several revision or salvage options exist for use in the setting of failed primary or revision procedures for osteochondral lesions of the ankle, including numerous different scaffold-based techniques. Autologous chondrocyte implantation (ACI) is one such option that has been used since the 1980s and involves a biopsy with subsequent lab growth of patient-specific cartilage cells that are later implanted back into the defect.\textsuperscript{42} In the first generation of ACI, the cells were placed in liquid form and covered with a periosteal cap, which was notable for postoperative pain at the donor site and an incidence of periosteal hypertrophy that was substantial.\textsuperscript{43,44} Second-generation ACI techniques addressed these concerns by using a collagen cap instead of a periosteal graft. Giannini et al. reported on their experience in eight patients with the first-generation technique on the talus and found reparative cartilage tissue in all patients on second-look arthroscopy, with resolution of pain.\textsuperscript{45} In a sample of 10 year follow-up patients, 70\% reported excellent results, 20\% good, and 10\% fair, with no complications, which are similar to results found by Whittaker et al. with 4 years follow up, that reported 90\% of patients as pleased or extremely pleased with their outcome.\textsuperscript{46,47} Subsequently, third-generation ACI techniques were developed with a biodegradable porcine matrix loaded with harvested chondrocytes. This became known as matrix-induced autologous chondrocyte implantation (MACI) and has been approved for use in the knee in the United States, but not in the ankle and still requires a second procedure after the index harvest. Despite the innovation, the issue of overgrowth still remains in the latest generation of ACL.\textsuperscript{48}

Combining microfracture and autologous chondrocyte implantation procedures, autologous matrix-induced chondrogenesis (e.g., AMIC) involves a 1-step process of bone marrow stimulation or abrasionplasty and subsequent application of a porcine based type I/III collagen membrane.\textsuperscript{49} These techniques have become known as ‘enhanced bone marrow stimulation’ techniques. One recent consensus by Rothrauff et al. suggested that this procedure can be used for lesions >1 cm\textsuperscript{2} in both primary and revision scenarios and can be accompanied with bone grafting if needed.\textsuperscript{50} Matrix-augmented BMS provides the advantage of a 1-stage procedure, in which autologous cells are endogenously recruited into the defect site. Although several scaffolds are available, the scientific evidence is highest for the use of a collagen I/III membrane.\textsuperscript{51} Usuelli studied 20 patients who underwent the AMIC procedure for types III and IV talar lesions and found improvements in PROs (American Orthopedic Foot and Ankle Society, visual analog scale [VAS], 12-Item Short Form Health Survey) and magnetic resonance observation of cartilage repair tissue (MOCART) at up to 24 months post-op.\textsuperscript{52} Similarly, Weigelt followed a cohort of 33 patient who underwent AMIC for talar lesions at an average of 4.7 years post-op.
Matrix-associated stem cell transplantation (MAST) is a modification of the technique that attempts to use a higher concentration of stem cells into the microfracture defect. As part of this technique, aspirate is taken from the iliac crest, centrifuged, and impregnated into a similar Type I/III collagen matrix as in traditional matrix-augmented BMS. The remaining steps are similar with bone marrow stimulation of the lesion and subsequent covering with the matrix. Results after a 2-year follow-up by Richter et al. on 26 chondral lesions treated with MAST found a significant improvement in VAS foot and ankle to 94.5 and 89% of patients returning to sports. Richter later reported on 130 patients with 2-year follow-up and 100 patients with 5-year follow-up and found similar positive results, with the 2-year cohort VAS-FA improving significantly to 87.5 on average and the 5-year cohort improving to 84.4 on average. Particulated juvenile cartilage allograft transplantation (PJCAT) is an additional technique in the realm of orthoregenerative procedures, in which fresh juvenile cartilage allograft tissue is embedded within the native extracellular matrix and is fixed with fibrin adhesive inside the lesion. The cartilage allograft is obtained from donors from newborn to 13 years old, but primarily from donors less than 2 years of age. This procedure has gained popularity due to its relative simplicity in execution, being single-stage with no donor site morbidity, and a minimal chance of immunological reaction, as cartilage tissue is considered immune privileged compared to other allogenic materials. Conversely, downsides of PJCAT include the relative scarcity of juvenile donor cartilage and potential for disease transmission. Several clinical studies have been reported in the talus, with mixed results. Figure 1 shows the use of PJCAT in the treatment of a large talar cartilage lesion.

Lately, the use of local cartilage cells from the defect has been discussed in the treatment of cartilage defects to overcome the scarcity of juvenile cartilage. Cartilage from the defect site contains still viable cells. The cells are minced and mixed with fibrin and PRP. For stabilization, the minced cartilage is covered with a scaffold (e.g., AMIC membrane). First studies on the knee reported a safe application. However, the cellular outgrowth from adult cartilage tissue was largely absent in an in vitro model. Regarding the ankle, so far, there are no clinical studies available to assess the value of this technique finally.

**Blood-Based/Injectable Preparations**

Injectable preparations of orthobiologics are increasingly popular in orthopaedics and have been studied in a variety of applications in foot and ankle surgery ranging from osteoarthritis (OA) to numerous soft tissue applications. Many of these products are derived from the patient’s own blood or tissue and are, therefore, considered safe options for most patients. Evidence derived from animal models has been extensively used for regenerative purposes, with positive results and set the foundation for clinical testing of blood-based products. Importantly, the findings of these animal models served to propel various specialties to perform investigations that provided encouraging results. This discussion is not meant to be exhaustive; instead, it merely highlights the most prominent current products and their applications in foot and ankle pathology.

![Fig 2](image-url) (A) Diseased peroneus brevis tendon. (B) Injection of concentrated bone marrow aspirate (CBMA) into tubularized brevis tendon. (C) Continuation of tubularization of tendon. (D) Completed tubularization of tendon with CBMA embedded.
Platelet-rich-plasma, or PRP, was first noted among hematologists in the 1970s and used for transfusions, with subsequent expansion into other medical specialties in the following years. PRP has become a popular option in musculoskeletal care based on the mechanism of providing a localized injection of growth factors and regenerative signaling molecules to a site of injury, theoretically prompting a host healing response and has been used extensively to treat the spectrum of foot and ankle pathologies. There has been discussion on various techniques of PRP that contain a higher or lower concentration of leukocytes, termed leukocyte-rich or poor PRP, and how this may affect healing. There is some evidence suggesting that leukocyte-rich preparations may elicit too robust of a host inflammatory response that could result in increased scar formation and pain. Regarding outcomes, PRP has been studied extensively in foot and ankle-based trials, of varying quality, with mixed results. Multiple level I studies have been performed on PRP for noninsertional Achilles’ tendinopathy, with inconsistent evidence supporting its use over placebo. For treatment of OA, Repetto et al. reviewed 20 patients with symptomatic ankle OA, who received weekly PRP injections and reported a significant improvement in pain, function, and satisfaction at an average follow-up of 17.7 months. Similarly, Fukawa et al. reported on 20 patients with ankle OA who received biweekly injections and found a significant improvement in pain and function up to 6 months postinjection with maximum benefit at 3 months. Building on the momentum of PRP, other blood-based preparations are in the process of clinical trial testing, including mixtures of preparations in the search of synergistic activity. One such investigation involved the use of a platelet-poor plasma (PPP) biomatrix loaded with MSC, which was studied in regenerative endodontic procedures with good clinical results at 12-month follow-up. Building on these data, a current clinical trial is under way to evaluate both the safety and efficacy of this preparation for use in osteochondral lesions of the talus (ClinicalTrials.gov Identifier: NCT03905824).

**Concentrated Bone Marrow Aspirate**

Concentrated bone marrow aspirate (CBMA) is another autologous product obtained by aspiration of marrow, typically from the iliac crest, tibia, or calcaneus, with subsequent centrifugation via one of several commercially available systems into its final concentrated form. CBMA contains similar platelet counts when compared to PRP but different cellular and cytokine compositions, including significantly increased interleukin-1 receptor antagonist protein in CBMA by comparison to PRP. CBMA may be a useful adjunct in both cartilage and bone procedures. Currently, the bulk of the literature on CBMA use in foot and ankle is limited to retrospective studies. CBMA has been used to augment percutaneous Jones fracture fixation in multiple studies with union rates between 92.5% and 100% in athletes. It has also been investigated in the treatment of osteochondral lesions of the talus as an adjunct to microfracture in several studies, including a cohort followed by Vannini et al. at a mean of 10 years postop that showed sustained improvements in multiple PRO measures at this late time period. Figure 2 shows one example use of CBMA as part of a peroneal brevis tendon repair.

**Hyaluronic Acid**

Hyaluronic acid injections have been popularized as an alternative to corticosteroid with the theorized benefit of prolonged treatment effect. However, despite the theoretical benefits of HA of providing an arthritic joint with the proteoglycans and glycosaminoglycans that are lacking, the literature in treating ankle arthritis has not supported its use. DeGroot et al. performed a randomized, double-blinded, placebo-controlled study to study the efficacy of HA injection compared to normal saline and found no difference in outcomes at 12 weeks, which is in line with the literature as a whole.

**Cell-Based Therapy**

The most controversial, and widely misunderstood, class of injectable biologics currently available are the stem cell-based therapies. The most commonly used "stem cell" (stromal cell) therapy in foot and ankle is mesenchymal stem cell allografts from donor tissue. Used for its osteogenic, osteoconductive, and osteoinductive potential, allogenic mesenchymal stem cell preparations have been popularized in fusion procedures to assist in the formation of new bone, particularly in the revision setting. Studies have shown positive results in achieving fusion with the cellular bone grafts, particularly in patients with comorbidities associated with difficulty healing. Along similar lines, the use of adipose tissue derivatives has been a source of recent investigation with adipose tissue-derived stem cells micronized adipose tissue injections being a few of the examples. There is currently a lack of level 1 evidence to support the use of these adipose tissue-derived preparations; however, some smaller case series have shown promise for further investigation for its use in osteoarthritis, tendinopathy, and osteochondral lesions. The use of various stem cell preparations is a rapidly evolving field with new, well-designed studies being conducted across orthopedic subspecialties that will continue to refine the proper use of these adjuncts.

**Conclusions**

The use of biologics in orthopedics is a rapidly expanding and evolving landscape, particularly within the subspecialty of the foot and ankle. Although it is difficult to compartmentalize such a broad field into a tidy framework, organizing the biologics into cartilage,
bone, and blood/injectable-based therapies is one way to make sense of the plethora of current information available. While biologics are widely considered safe, studies on the efficacy, indications for use, and proper formulation are forthcoming as the role of biologics continues to expand.

References

34. Rearick T, Charlton TP, Thordarson D. Effectiveness and complications associated with recombinant human bone morphogenetic protein-2 augmentation of foot and ankle.


64. Salzmann GM, Ossendorff R, Gilat R, Cole BJ. Autologous minced cartilage implantation for treatment of chondral...


