Orthobiologics for Cartilage Repair

Yusuf N. Mufti, BS, Jared P. Sachs, MS, Andrew S. Bi, MD, Adam B. Yanke, MD, PhD, Brian J. Cole, MD, MBA*

KEYWORDS

• Orthobiologics • Cartilage repair • Cartilage regeneration
• Mesenchymal stromal cells • Mesenchymal signaling cells • Platelet-rich plasma
• Bone marrow aspirate

KEY POINTS

- Orthobiologics, such as platelet-rich plasma and concentrated bone marrow aspirate, are increasingly used to augment cartilage repair procedures.
- Platelet-rich plasma, concentrated bone marrow aspirate, adipose tissue, and human umbilical cord blood have all shown promise as practical sources for mesenchymal signaling cells and growth factors crucial in cartilage repair.
- Existing cartilage repair technology has shown relatively positive results with additional orthobiologic augmentation.
- Cartilage repair technologies involving matrix-induced autologous chondrocyte implantation, osteochondral grafts, and artificial scaffolds have shown positive results.

OVERVIEW

Orthobiologics are substances derived from biological sources and are increasingly used in cartilage repair. Mesenchymal signaling cells (MSCs) play a crucial role in cartilage regeneration, but face challenges in clinical application. Platelet-rich plasma (PRP), concentrated bone marrow aspirate (cBMA), adipose tissue, and human umbilical cord blood have all demonstrated potential as sources for MSCs and growth factors necessary for cartilage repair. Existing cartilage repair techniques have shown good outcomes with additional orthobiologic augmentation. Emerging techniques involving third-generation and fourth-generation matrix-induced autologous chondrocyte implantation, decellularized or cryopreserved osteochondral grafts, and artificial scaffolds have demonstrated promising results long-term with cartilage repair procedures.

Cartilage Restoration Center, Department of Orthopaedic Surgery, Midwest Orthopaedics at Rush, Chicago, IL, USA
* Corresponding author. 1611 West Harrison Street, Suite 300, Chicago, IL 60612.
E-mail address: brian.cole@rushortho.com

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BACKGROUND

Articular cartilage provides a low friction surface and load distribution allowing the knee joint to withstand a wide variety of weight-bearing movements for daily function. Focal articular defects commonly occur secondary to trauma, degenerative disease, or other etiologies.[1] These lesions pose a significant challenge since cartilage has extremely limited regenerative capacity due to its aneural and avascular properties.[2]

A wide range of treatment options exists for cartilage defects, ranging from nonoperative modalities, such as physical therapy and injections, to surgical procedures, such as microfracture, matrix-induced autologous chondrocyte implantation/autologous chondrocyte implantation (MACI/ACI), osteochondral grafts, and scaffold implantation.[3] Orthobiologics are substances derived from a biologic source (human, animal, microorganism, and so forth) that interact with the body's own cells and tissues to stimulate a healing response. These substances can be administered as injections alone or be used to augment surgical cartilage repair procedures.[4] The purpose of this review is to highlight modern cartilage repair techniques and summarize the literature on orthobiologics in isolation or as an augmentation to cartilage repair.

Mesenchymal "Stem" Cells

Stem cells have the ability of self-renewal and the ability to differentiate along multiple lineages, with pluripotent stem cells meeting both criteria. Mesenchymal stem cells are multipotent stromal cells capable of differentiating into cell types of mesodermal origin, which includes muscle, fat, bone, and cartilage.[5] The initialism MSC, for mesenchymal stem cell, has attracted controversy since its inception, as several studies have demonstrated that true multipotent mesenchymal stem cells are present in minute concentrations (0.001%–0.01%),[6] and that "MSC" therapy may, in fact, be beneficial primarily due to a high concentration of growth factors and anti-inflammatory cytokines, such as vascular endothelial growth factor, platelet-derived growth factor (PDGF), bone morphogenic protein (BMP), transforming growth factor-beta (TGF-β), and interleukin-1 receptor antagonist (IL-1RA), as well as an ability to recruit autologous multipotent stem cells.[7] As a result, a growing number of authorities have suggested the name "mesenchymal signaling cells" instead, and we will refer to MSCs as mesenchymal signaling cells in this review unless otherwise specified.[8] This moniker more accurately reflects the fact that the healing ability of MSCs lie more in their paracrine immunomodulatory and trophic effects rather than their multipotency or pluripotency.[9]

MSCs are present in various tissues in the body, but their concentration is very low, making sufficient extraction and processing challenging, which has led to the development of expansion techniques through cell cultures. However, in vitro culturing of stem cells is subject to Food and Drug Administration (FDA) regulatory denial in the United States, precluding cell expansion from being clinically feasible, whereas these therapies are more often utilized in European countries.[10–12]

Platelet-rich Plasma

PRP is a substance derived from a sample of the patient's own blood. Using centrifugation, blood can be divided into its constituents, separating and concentrating platelets, which contains a high concentration of growth factors that can stimulate cell reproduction and trigger healing in the treated area.[13]

PRP can be further classified as either leukocyte-rich PRP (LR-PRP) or leukocyte-poor PRP (LP-PRP) based on the concentration of white blood cells (WBCs) in the solution. Controversy exists over the comparative efficacy of both formulations.

Leukocytes can have proinflammatory effects, and therefore, the presence of WBCs may enhance the initial inflammatory response necessary for healing but may also prolong inflammation in the affected tissue, hindering the long-term healing response.[14] Recent studies in our laboratory have demonstrated reduced retear rates in rotator cuff surgery and increased cartilage volume and improved clinical outcomes in mild osteoarthritis of the knee with LP-PRP.[15,16]

The use of PRP in cartilage repair has shown positive results. PRP promotes chondrogenic differentiation and enhanced cartilage repair in vitro, with increased proteoglycan and collagen deposition within 6 months to 1 year following injections, and benefits have been demonstrated in clinical in vivo studies, as well.[15,17–19] Meta-analyses on the subject have found improved clinical outcomes with PRP injections alone and in conjunction with other procedures when compared to controls.[20] PRP injections reduce inflammatory markers such as tumor necrosis factor-α, IL-1, and IL-6, and improve the histology of cartilage and synovium.[21,22] PRP also increases the proliferation, migration, and chondrogenic differentiation of mesenchymal stem cells.

Concentrated Bone Marrow Aspirate

cBMA, known as "BMAC" colloquially from the brand naming of Harvest Technologies Corporation (Plymouth, MA), is a preparation of autologous bone marrow aspirate, processed in a centrifuge to concentrate regenerative factors, such as platelets, growth factors, BMPs, IL-1RA, and perhaps most importantly, MSCs.[23] cBMA has been demonstrated to have the highest concentrations of IL-1RA and lowest concentrations of proinflammatory cytokines, such as matrix metalloproteinases, with equivalent levels of TGF-β and PDGFs compared to LP-PRP or LR-PRP.[24,25] Older studies have demonstrated higher percentages of MSCs with posterior iliac crest harvesting compared to anterior crest or other sites, and multiple smaller volume harvests compared to a single, large volume aspirate.[26–28] Due to the aforementioned difficulties of MSC culturing in the United States, cBMA represents a more economical way to concentrate and deliver MSCs in clinical settings.[10] cBMA can be utilized in patients with focal chondral defects, as well as degenerative joint disease, and in isolation or as augmentation of concomitant procedures. A 2018 meta-analysis published by Cotter and colleagues[29] examining basic science, animal studies, and clinical outcomes in cBMA found positive results on all fronts. Animal models showed superior cartilage quality with the application of cBMA both macroscopically and histologically. Additionally, clinical studies have found significant improvement in patient-reported outcomes (PROs) as both a standalone and adjuvant treatment, with Cavinatto and colleagues[23] demonstrating improved short-term and midterm functional and pain scores in clinical studies on cBMA injection in focal chondral lesions. However, they found the results of animal studies to be more equivocal and ultimately concluded that current studies on the use of cBMA in cartilage repair were of low scientific rigor.

Adipose-derived Stem Cells

Adipose tissue, like bone marrow, is derived from embryonic mesoderm and can be harvested to concentrate MSCs. Compared to cBMA, studies have demonstrated that adipose-derived stem cells (ADSCs) can be isolated in much greater concentrations from similar volume aspirates with reduced harvest morbidity given the common subcutaneous donor sites of the abdomen or buttocks.[30] Moreso than any other orthobiologic, there has been minimal scientific regulation of terminology used and processing methodology reporting in the literature. ADSCs can be harvested by surgical excision, Coleman's technique of a hollow blunt-tipped cannula, or even arthroscopic shavers.[31,32] They are then processed either by gravity separation, Coleman fat

centrifugation, microfragmented adipose tissue (MFAT) mechanical techniques (ie, Lipogems, Milan, Italy, Tulip, San Diego, CA, or Puregraft, Solana Beach, CA), enzymatic separation via collagenase, which produces a stromal vascular fraction (SVF), which is not approved by the FDA, and true ADSC isolation followed by cell expansion in vitro.[32] Clearly, with the number of acronyms (ADSCs, MFAT, and SVF) and harvest techniques, which have been demonstrated to affect ADSC yield, accurate reporting of harvest and processing techniques are essential when publishing on the use of adipose tissue for MSCs.

Available research on ADSCs in orthopedic conditions is lacking in quantity. In a 2023 review, Kunze and colleagues[33] analyzed available animal and clinical studies on ADSCs. They found that studies in animal models have shown that ADSCs improve healing and histologic appearance of injury sites and increase concentration of growth factors. The limited clinical studies in human subjects have shown pain improvement for rotator cuff and Achilles tendinopathies, improvements in pain and function in osteoarthritis, and improved cartilage regeneration in focal defects. However, the available evidence is low, as many of the studies lack an adequate control group.

As it pertains to cartilage repair, a 2015 study by Kim and colleagues[34] found significant improvement and PROs following arthroscopic debridement and ADSC injection in knees with full-thickness cartilage defects in 55 patients. A 2014 study by the same author examined chondral lesions of the talus compared arthroscopic injection of SVF-containing ADSCs with marrow stimulation alone. All functional outcomes were superior in the ADSC group at mean 22 months follow-up.[35]

Amniotic-derived Treatments and Formulations

Research into amniotic-derived formulations, such as from the amniotic membrane, amniotic fluid, and umbilical cord has attracted a great deal of interest within recent years. Amniotic products have been shown to be a robust source of MSCs.[36] Preclinical and early clinical data have shown promising results for ligamentous and tendinous injury, degenerative joint disease, and focal cartilage defects.[37–40] In 2016, Vines and colleagues[41] found a general improvement in all PROs after the injection of human amniotic suspension allograft into the knee of 6 patients with severe osteoarthritis.

Of note, human umbilical cord-derived mesenchymal signaling cells (hUCB-MSCs) are isolated from umbilical cord blood. Since umbilical cord blood is usually harvested immediately after birth, this can be done without any harm to the mother and is less invasive as compared to collecting cBMA.[42] Umbilical cord blood has been shown to be a reliable source of MSCs with high potential for cartilage regeneration.[43] The proliferation rate and expansion capacity of hUCB-MSCs is significantly higher when compared to bone-marrow derived MSCs,[44] and data and long-term safety in high-grade cartilage defects have been similarly positive.[45] In 2021, Lee and colleagues[46] found that hUCB-MSCs were more effective than cBMA for cartilage regeneration in medial unicompartmental OA in patients undergoing high tibial osteotomy (HTO). Similarly, Park and colleagues[44] in a 2023 meta-analysis of 7 studies and 499 patients, comparing hUCB-MSCs to cBMA in patients undergoing HTO, found improved clinical outcomes in both treatments in the osteoarthritic knee. They also found that hUCB-MSCs were more effective in articular cartilage regeneration as compared to cBMA, with higher International Cartilage Regeneration & Joint Preservation Society Cartilage Repair Assessment (ICRS)-CRA grades on second look arthroscopy. Notably, these substances are regulated similar to a drug that is not available in the United States outside of clinical FDA trials.

Recent literature has demonstrated positive outcomes with long-term studies using hUCB-MSCs. One multicenter randomized clinical trial (RCT) in Korea found that hUCB-MSCs resulted in improvements in pain, function, and cartilage ICRS grades at up to 5 years follow-up compared to microfracture in the treatment of large, full-thickness cartilage defects.[47] hUCB-MSCs currently remain the subject of several clinical trials (ie, NCT01041001 and NCT01626677), both in the United States and abroad.

MICROFRACTURE AND ORTHOBIOLOGICS

Microfracture aims to stimulate the body's intrinsic healing process via creation of channels through the subchondral bone, allowing marrow MSCs to differentiate in to "cartilage-like" cells.[48] This technique is easy to perform arthroscopically, does not require any additional expenses, and produces a mix of type I and II collagen. This fibrocartilage is generally of inferior quality as compared to native hyaline cartilage. Initial outcomes are typically good, but studies looking at long-term follow-up have found that improvements tend to fade after 2 years.[49]

A number of studies have highlighted the effect of orthobiologic augmentation in microfracture. In a 2022 study looking at a rabbit model, Kinoshita and colleagues[50] found that microfracture augmented with a platelet-rich fibrin (PRF) matrix yielded significantly better macroscopic cartilage grade at 6 month follow-up as compared to microfracture alone. Looking at clinical outcomes, a meta-analysis by Boffa and colleagues[51] in 2020 found that PRP provided a statistical improvement in PROs in microfracture of the knee and ankle, but this improvement was not clinically significant. They ultimately concluded that there was a paucity of high level research on the clinical effects of PRP on microfracture.

The research on MSC augmentation of microfracture is similarly equivocal. In 2020, Jin and colleagues[52] found no significant difference in clinical outcomes between cBMA-augmented microfracture and microfracture alone in patients with osteoarthritis, but they did find improved cartilage repair quality in the augmented group. Macroscopic and histologic analysis of the results of cBMA-augmented microfracture has shown positive results, with one case series demonstrating "almost normal" hyaline-like or fibrocartilaginous cartilage at 12 months.[53] Looking at ADSC augmentation, in a 2016 prospective randomized trial with 2 year follow-up, Koh and colleagues[54] found that compared with microfracture alone, microfracture with ADSCs provided improvements radiologically and in PROs at long-term follow-up in 80 patients with a single ICRS grade III/IV symptomatic cartilage lesion 3 cm^2 or larger.

Microfracture can also be augmented with a collagen matrix to stabilize the clot and concentrate marrow MSCs, termed autologous matrix-induced chondrogenesis (AMIC).[55] AMIC is thought to counteract the long-term deterioration of outcomes in microfracture alone. In a 2024 RCT, Volz and colleagues[55] demonstrated in 47 patients with 10 year follow-up, sustained improvement in AMIC up to 5 years with improved MRI defect fill, while the microfracture group had progressive deterioration in clinical outcomes and MRI findings after 2 years. Kim and colleagues[56] found similar greater improvement in International Knee Documentation Committee (IKDC) scores and MRI findings with AMIC compared to microfracture alone in a meta-analysis with minimum 2 year follow-up.

CELL-BASED CHONDRAL SURFACE REPAIR TECHNIQUES AND ORTHOBIOLOGICS

Autologous Chondrocyte Implantation

Chondral surface repair techniques have significantly advanced in recent years. ACI involves harvesting and culturing the patient's own chondrocytes for reimplantation

in a chondral defect in a 2 stage procedure. First-generation ACI techniques involved implantation of chondrocytes injected into a cartilage defect and covered with a sutured periosteal flap.[57] Second-generation ACI utilized a porcine collagen membrane to cover the defect (Chondro-Gide Geistlich, Wolhusen, Switzerland), which helped in reducing the complications associated with periosteal patch, such as overgrowth.[58]

Third-generation Matrix-induced Autologous Chondrocyte Implantation

Third-generation ACI eliminated the need for patches altogether. MACI (Vericel, Cambridge, MA) seeds laboratory-expanded chondrocytes directly onto a type I or III collagen membrane, and then attaching this membrane directly to subchondral bone with fibrin glue.[59] While MACI still requires a first stage surgery for cartilage biopsy, recent techniques have demonstrated feasibility of minimally invasive in-office techniques using nanoarthroscopy.[60] In 2024, Ebert and colleagues[59] found sustained improvements in PROs, no significant degradation in radiological outcomes, and 89% graft survival at 10 year follow-up. Notably, patients with tibiofemoral defects had significantly better outcomes than those with patellofemoral lesions. Multiple RCTs have evaluated ACI/MACI compared to other techniques, such as microfracture (**Table 1**).[61–66] RCTs comparing first-generation ACI found no superiority, whereas RCTs comparing MACI found superior outcomes compared to microfracture.

Autologous Chondrocyte Implantation, Matrix-induced Autologous Chondrocyte Implantation, and Additional Orthobiologics

A number of studies have compared ACI and MACI with orthobiologics. For example, a 2015 study by Gobbi and colleagues[67] found similar clinical and radiographic outcomes when comparing MACI with cBMA injection alone for large patellofemoral chondral lesions at a minimum 3 year follow-up. In a 2017 study, Jeyakumar and colleagues[68] found that PRP increased human chondrocyte proliferation and redifferentiation in vitro, concluding that PRP could increase the efficacy of ACI and MACI, at least in terms of culture expansion. Similarly, in 2016 Wu and colleagues[69] found that chondrocytes grown in SVF had higher proliferation compared to adipose stem cells. Additionally, when implanted in a mouse model, constructs of SVF and chondrocytes resulted in more cartilage matrix formation than ASC and chondrocytes. Conversely, in a 2022 study, Kato and colleagues[70] investigated the effect of PRP on the outcomes of ACI in a rabbit model. They found that adding PRP appeared to have deleterious effects on ACI, demonstrating a smaller area of cartilage regeneration when compared to ACI alone. PRP appeared to interfere with the engraftment and maturation of regenerated cartilage in this study.

"Fourth-generation" Autologous Chondrocyte Implantation

Europe, in particular, has continued to advance ACI techniques, developing so-called fourth-generation ACI that can be implanted arthroscopically. Among these is Spherox (CO.DON GmbH, Leipzig, Germany), which cultivates chondrocytes into microscopic "spheroids" approximately 600 μm in diameter, which are then implanted into the cartilage defect arthroscopically.[71] In 2019, Niemeyer and colleagues[72] found spheroid ACI to be noninferior to microfracture, with superiority in some PROs and better cartilage repair quality. In another phase III clinical trial in 2021, Hoburg and colleagues[73,74] found similar results when evaluating spheroid ACI against microfracture and additionally found fewer treatment failures at 3 year follow-up, which was corroborated by a recent RCT with 5 year follow-up. Another fourth-generation ACI is Novocart Inject Plus (TETEC AG, Reutlingen, Germany), a hydrogel-based ACI, which mixes the culture-expanded autologous chondrocytes with a polyethylene glycol cross-linking gel that

Table 1
Randomized control trials comparing varying generations of autologous chondrocyte implantation to microfracture

Year Study References	ACI Generation	Comparator	Follow-up	Findings
Knutsen et al,[61] 2007	First generation	Microfracture	5 y	No significant difference between ACI and microfracture in ICRS, Lysholm, Tegner, SF-36, and radiographic progression of osteoarthritis (by Kellgren–Lawrence grade); both treatments had positive results in 77% of patients
Knutsen et al,[62] 2016	First generation	Microfracture	15 y	No significant difference in long-term failure (defined as reoperation) or ICRS, Lysholm, Tegner, SF-36, and radiographic progression of osteoarthritis (by Kellgren–Lawrence grade)
Saris et al,[63] 2009	Second generation	Microfracture	3 y	Significantly better Knee Injury and Osteoarthritis Outcome Score (KOOS) and lower failure rates, no difference in Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) in ACI group
Saris et al.[64] 2014	Third generation (MACI)	Microfracture	2 y	Significantly better KOOS (all subscores), similar cartilage histology and fewer failures and adverse events in MACI group
Brittberg et al,[65] 2018	Third generation (MACI)	Microfracture	5 y	Significantly higher KOOS, no difference in defect filling by MRI
Ibarra et al,[66] 2021	Third generation (MACI)	Microfracture	6 y	Superior improvements in KOOS (all subscores except symptoms) higher cartilage grade by ICRS, MRI (MOCART), better defect filling, and lower failure rate

is arthroscopically injected into the defect.[75] At 24 months follow-up, this technique demonstrated superior outcomes when compared to microfracture.[76]

OFF-THE-SHELF PARTICULATED/MINCED/MICRONIZED AUTOLOGOUS OR ALLOGRAFT CARTILAGE OPTIONS

A potential drawback of ACI and MACI is that the procedure requires 2 surgeries, which significantly increases both cost and patient morbidity. One review of 46 patients found only 12 (26.1%) of patients actually underwent the second-stage cartilage restoration procedure.[77] The development of particulated, micronized, or minced cartilage products has emerged as a promising, off-the-shelf solution to this issue.

Particulated juvenile articular cartilage (PJAC) is a promising solution for the treatment of focal chondral defects that provides an off-the-shelf option. Denovo NT (Zimmer Biomet, Warsaw, IN) involves harvesting highly regenerative cartilage from donors under the age of 13 years, processing them into fragments, and applying them to the defect with fibrin glue.[78] Clinical studies have demonstrated significant improvements in pain, function, and radiographic outcomes at 2 year follow-up.[79] This technique has also been demonstrated to be more cost-effective than MACI in the treatment of patellar chondral defects in a 2022 study by LeBrun and colleagues.[80] PJAC can also be augmented with orthobiologics, as Alcaide-Ruggiero and colleagues[81] demonstrated improved macroscopic appearance, histologic structure and chondrocyte repair in a sheep model when comparing PJAC with PRP when compared to particulate cartilage alone.

Minced Autologous Cartilage

AutoCart (Arthrex, Naples, FL) is a single-step autologous minced cartilage procedure. This involves harvesting chondrocytes during surgery from a non–weight-bearing portion of the knee (such as the notch or lateral trochlear ridge) using an arthroscopic shaver, which minces the cartilage during harvest. This can then be reimplanted in the same surgery and adhered to the chondral defect using fibrin glue. A 2023 case series of 34 patients with 5 year follow-up demonstrated satisfactory increases in PROs with only 1 patient in the study cohort developing postoperative complication that required revision surgery.[82] In a 2019 case series analyzing this technique, Massen and colleagues[83] found significant increases in PROs at 2 year follow-up. In a 2022 case series, Wodzig and colleagues[84] found good cartilage repair scores measured by MRI at 2 year follow-up.

Micronized Allograft Cartilage Extracellular Matrix

A relatively novel off-the-shelf development is a micronized allograft cartilage extracellular matrix (ECM), BioCartilage (Arthrex Inc, Naples, FL). This ECM can be applied as a scaffold over articular defect microfracture or subchondral bone stimulation and can also be augmented with PRP or MSCs.[85] BioCartilage theoretically supports the migration and attachment of cells, which is thought to improve the quality of repair tissue and prolong functional outcomes when compared to traditional microfracture alone and, in addition, can be implanted arthroscopically.[86] Several studies have examined BioCartilage augmented with orthobiologics, with positive results (**Table 2**[85,87–90]). Examining both animal and clinical studies, BioCartilage augmented with orthobiologics has been shown to be an effective method of cartilage repair, demonstrating positive outcomes functionally and radiographically. However, there are no studies that compare BioCartilage augmented with orthobiologics against BioCartilage alone, making it difficult to draw definitive conclusions.

Table 2
Studies investigating biocartilage with additional orthobiologic augmentation

Year Study Reference	Orthobiologic	Follow-up	Findings
Fortier et al,[87] 2016; Cole et al,[88] 2015	BioCartilage with PRP	13 mo	Superior ICRS and histologic cartilage grade compared with microfracture in an equine model
Brusalis et al,[89] 2020	BioCartilage with PRP	2 y	Increased chondral filling on MRI and significant increases in all patient-reported outcomes (IKDC, KOOS Jr. Marx Activity Rating Scale, SF-12)
Castrodad et al,[90] 2021	BioCartilage with cBMA vs chondroplasty alone	2 y	Significant improvements in postoperative outcomes (visual analog scale for pain; University of California, Los Angeles activity scores; Knee Outcome Survey Activities of Daily Living, and Sports subscores) in patients with grade 3–4 focal cartilage defects compared to chondroplasty alone
Cole et al,[85] 2021	BioCartilage with PRP	2 y	Low complication rate in 48 patients, with 90% achieving a minimal clinically important difference for IKDC and all KOOS subscores

A final off-the-shelf option for the treatment of focal articular defects is viable cartilage allograft. CartiMax (CONMED, Utica, NY) is a cryopreserved viable cartilage allograft putty. Cartilage flakes from donor tissue are mixed with a lyophilized ECM, forming a putty that can be molded and applied to the chondral defect at the time of initial surgery.[91] In a 2024 case series of 27 patients treated with CartiMax for focal chondral defects, Desai and colleagues[92] found significant increases on all outcome scores, with MRI and arthroscopy showing successful graft integration and repair at 2 year follow-up.

OSTEOCHONDRAL GRAFTS AND ORTHOBIOLOGICS

Osteochondral grafts are powerful options to replace focal chondral or osteochondral defects. These can either be autografts harvested from non–weight-bearing portions of articular cartilage or an allograft donor. Osteochondral autograft transfer system (OATS) are generally more appropriate for smaller lesions, whereas osteochondral allografts (OCAs) are better for larger lesions to match the defect size and shape.[93] A 2023 meta-analysis of RCTs comparing OATS with microfracture found quicker return to preinjury activity level and superior PROs for the OATS group.[94] OCA data have similarly found superior PROs, return to sport, and sustained improvement compared to microfracture.[95]

Osteochondral Autograft Transfer System and Orthobiologics

Several studies have looked specifically at additional orthobiologic augmentation in osteochondral grafts. Maruyama and colleagues[96] compared cartilage quality in OATS alone, OATS augmented with PRF, and OATS augmented with PRP in a rabbit model. They found that cartilage quality in OATS with PRF was superior to OATS in isolation or augmented with PRP. Microscopically, the PRF group healed with hyaline-like cartilage, whereas the other 2 groups healed with fibrocartilage. In humans, augmentation of OATS with PRP has been demonstrated to be a procedure that is safe and effective for the treatment of full-thickness cartilage defects.[97] However, there is a lack of comparative research on the clinical efficacy of PRP augmentation of OATS, with no RCTs comparing OATS with or without PRP or other orthobiologics to date.

Osteochondral Allografts and Orthobiologics

OCAs augmented with orthobiologics have been the subject of more translational and comparative studies with varying results. Stoker and colleagues[98] treated canine OCAs with cBMA or PRP, culturing and analyzing cell growth and osteogenic protein release. They found that cBMA-treated grafts showed superior cellular penetration and protein release, with very little effects observed in PRP-treated OCAs. In human studies, Wang and colleagues[99] found that OCAs augmented with cBMA was not associated with improvements in osseus integration, cystic changes, or any other indicator of improved cartilage healing when compared to OCA alone on MRIs 6 months postoperatively. In a similar study also conducted in 2019, Ackermann and colleagues[100] found that OCA augmented with cBMA did not result in superior imaging when compared to OCA alone when analyzed using the comprehensive Osteochondral Allograft MRI Scoring System at 6 months follow-up (**Fig. 1**).

Conversely, Oladeji and colleagues[101] compared 22 patients who underwent OCA with cBMA augmentation to 14 patients who underwent OCA without and found that cBMA-augmented OCAs demonstrated significantly higher levels of graft integration and less graft sclerosis at 6 month follow-up on imaging studies. Additionally, in the only RCT

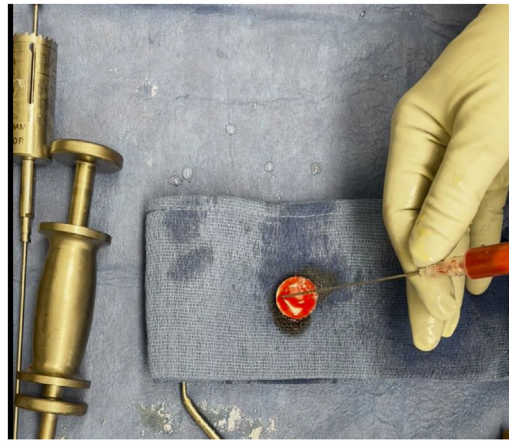

Fig. 1. Intraoperative image of osteochondral allograft soaked in cBMA.

conducted on cBMA augmentation of OCA grafts (NCT04739930), initial findings by Yanke and colleagues[102] demonstrated that, compared with controls, cBMA soaked OCA grafts demonstrated significantly superior Western Ontario and McMaster Universities Arthritis Index (WOMAC) and Patient-Reported Outcomes Measurement Information System (PROMIS) pain scores 1 year postoperatively, as well as fewer cystic changes. Ultimately, there remains a dearth of high-quality RCTs examining OCA augmentation with additional orthobiologics.

OFF-THE-SHELF DECELLULARIZED AND VIABLE CELL OSTEOCHONDRAL ALLOGRAFT OPTIONS

Although a powerful tool for the treatment of focal articular defects, OCA requires cold-preserved cartilage from donors that can have a high financial cost, narrow window for implantation once available, and limited availability, particularly with increased matching criteria specific.[103] Several solutions were developed to address the need for off-the shelf OCA plugs.

Decellularized OCAs are one such example. Chondrofix (Zimmer Biomet, Warsaw, Indiana) involves taking a harvested OCA through a multistep process involving lipid extraction, viral inactivation, and radiation sterilization to create an acellular graft that retains the mechanical properties of a fresh OCA graft, albeit at the cost of cellularity. In a 2017 study Johnson and colleagues[104] found a 2 year graft survivorship of only 61%, with the authors ultimately concluding that such an implant should be used with great caution. Another study evaluating a similar decellularized implant found a failure rate of 72% within the first 2 years of implantation.[105] As such, the authors of this study do not recommend the use of decellularized, frozen OCAs.

Cryopreserved viable OCAs were developed in response to the failure of decellularized, frozen OCAs. Cryopreservation of OCAs theoretically allows for the preservation of chondrocytes and chondrogenic growth factors. These grafts can be stored for up to 2 years while preserving their biological activity, increasing surgeon flexibility without sacrificing outcomes.[106] Cartiform (Arthrex, Naples, FL) and ProChondrix CR (Stryker, Kalamazoo, MI) are 2 examples of cryopreserved viable OCAs that have shown some promise. In a series of 12 patients with unipolar patellofemoral cartilage defects, Cartiform was found to have improved PROs and imaging findings at

2 year follow-up but had a 21% reoperation rate.[106] ProChondrix is a thin, laser-etched, cryopreserved allograft that is flexible enough to be contoured to challenging cartilage defects. In 2022, Mehta and colleagues[107] found improvements in all PROs with a failure rate of 11.1% at an average of 30 month follow-up.

Artificial scaffolds have attracted recent interest. Agili-C, developed by CartiHeal (recently acquired by Smith and Nephew, London, UK), is a crystalline osteoconductive aragonite osteochondral scaffold that has been recently approved by the US FDA. A 2023 RCT analyzing 251 patients found superior PROs and radiographic indicators at 2 year follow-up in patients with knee chondral defects 1 to 7 cm^2 in area when compared to microfracture and arthroscopic debridement.[108] In 2024, de Caro and colleagues[91] demonstrated continued significant clinical improvement and MRI findings at 5 year follow-up, with only 1 failure in the 12 patients analyzed.

SUMMARY

A wide range of treatment modalities exists for the repair of focal articular defects, from minimally invasive procedures involving orthobiologic injectables alone to arthroscopic, off-the-shelf, or readily available surgical techniques, such as microfracture with or without orthobiologics and BioCartilage to more invasive, complex repair techniques, such as MACI or OCAs, with or without orthobiologic augmentation. The algorithm remains nuanced without significant evidence-based decision-making, with a variety of noncomparative cohort studies or case series demonstrating clinical improvement with a single-arm treatment at short-term follow-up. Orthobiologics, whether used alone or in conjunction with existing cartilage repair procedures, have shown generally positive results with minimal additional risk. However, while these biologics may offer benefits in cartilage regeneration, their overall impact and long-term outcomes are still under investigation and cost-effectiveness studies remain to be seen. There exists a clear need for studies investigating orthobiologics in isolation, and as an augment for cartilage repair surgical techniques. In an ideal world, there would be a high-quality RCT for every orthobiologic injection compared to placebo, corticosteroid, or hyaluronic acid injections, and for every cartilage repair surgical technique with and without augmentation of each orthobiologic.

CLINICS CARE POINTS

- Sources of orthobiologics in cartilage repair include Platelet-rich plasma, concentrated bone marrow aspirate, adipose tissue, and human umbilical cord blood.
- Cartilage repair technology has shown positive results with orthobiologic augmentation.
- Use of orthobiologics is recommended for cartilage repair procedures.

DISCLOSURE

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