Biologic Options for Articular Cartilage Wear (Platelet-Rich Plasma, Stem Cells, Bone Marrow Aspirate Concentrate)

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KEYWORDS

- Articular cartilage • Platelet-rich plasma • Stem cells
- Bone marrow aspirate concentrate

KEY POINTS

- Biological treatments for articular cartilage repair have gained in popularity in the past decade.
- Advantages of these therapies include minimal invasiveness, improved healing time, and faster recovery.
- Biological therapies for cartilage repair include platelet-rich plasma, bone marrow aspirate concentrate, and cell-based therapies.
- These methods have the added benefit of containing growth factors and/or stem cells that aid in recovery and regeneration.
- The purpose of this article was to review the current cartilage treatment options and the existing literature on outcomes, complications, and safety profile of these products for use in the knee and hip joints.

INTRODUCTION

Articular cartilage damage is a serious clinical and economic burden for the orthopedic community and the public health system. The most common forms that affect articular cartilage include focal chondral lesions and early osteoarthritis (OA). Recently, identifying and treating cases of early OA has become an important

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concern, because many patients with painful OA already have extensive structural disease that may preclude treatment with nonoperative modalities. Isolated chondral lesions are also a prevalent pathology seen by orthopedic surgeons. These lesions have been reported in up to 57.3% of all patients undergoing knee arthroscopy, with Outerbridge grade 3 or 4 lesions found in 5.2% of all patients with a diagnosed cartilage lesion.[1] In those undergoing knee arthroscopy for meniscal pathology, 32% of patients in their 20s have been shown to have Outerbridge changes to the articular surfaces of the knee joint.[2]

Procedures available for articular cartilage repair are constantly evolving and in recent years, the focus has shifted from surgical procedures to that of biological interventions. Biological therapies provide a less-invasive and less-expensive alternative to surgery, and therefore represent a potential attractive option for patients with articular cartilage lesions or early OA. The purpose of this article was to review the current cartilage treatment options and the existing literature on outcomes, complications, and safety profile of these biologic products for use in the knee and hip joints.

PLATELET-RICH PLASMA

The use of platelet-rich plasma (PRP) has gained significant attention throughout the orthopedic community in recent years.[3] PRP refers to autologous blood that has been centrifuged to produce a higher concentration of platelets than average.[4,5] A number of studies have attempted to determine the optimal concentration of platelets for purposes of musculoskeletal healing.[6–8] Recently, Fleming and colleagues[6] evaluated the effect of PRP supplementation on graft healing following anterior cruciate ligament (ACL) reconstruction in minipigs using either 1 × (n = 10), 3 × (n = 10), or 5 × (n = 10) PRP concentrations. Interestingly, only the 1 × platelet concentration improved healing over traditional ACL reconstruction. Similarly, Yoshida and colleagues[7] found that, after suspending porcine ACL fibroblasts in various platelet concentrations of PRP, 1 × PRP significantly outperformed 5 × PRP in terms of type I and type III collagen gene expression, apoptosis prevention, and cell metabolism stimulation. Weibrich and colleagues[8] found that an intermediate concentration of platelets (2–6×) resulted in optimal peri-implant bone regeneration in rabbits.

Various formulations of PRP exist. In addition to controlling the concentration of platelets, the white blood cell concentration also may be controlled, with leukocyte-rich PRP (LR-PRP) and leukocyte-poor PRP (LP-PRP) both being used in the literature. No randomized or prospective clinical studies have been performed to compare outcomes between LR-PRP versus LP-PRP,[4] although a recent meta-analysis found improved functional outcome scores with LP-PRP for the treatment of knee OA in comparison with hyaluronic acid (HA) and placebo.[9] A number of randomized clinical trials have demonstrated a positive effect of LP-PRP on OA in comparison with placebo[10] or HA.[11,12] On the other hand, 2 randomized clinical trials have demonstrated no significant difference in outcomes between LR-PRP and HA for the treatment of OA.[13,14] Based on these studies, more consistent literature exists regarding LP-PRP for intra-articular usage.

There is some debate as to the effects of PRP at the cellular layer. Although some investigators believe that the effects of PRP are due mainly to its anti-inflammatory effects, rather than changing the progression of OA,[15] there is evidence that it promotes chondrogenic differentiation in vitro and leads to enhanced cartilage repair in animal models.[16]

In a randomized clinical trial of patients with Kellgren-Lawrence (K-L) grade II to IV knee OA undergoing knee arthroscopy, Duif and colleagues[17] reported short-term

improvement in patients receiving intra-articular injections of PRP during surgery compared with a control group. Patients in the intervention group demonstrated significantly better visual analog scale (VAS) pain scores ($P = .008$), Lysholm scores ($P = .033$), and SF-36 physical component summary scores ($P = .027$) at 6-month follow-up. However, no difference was found between intervention and control groups at 12-month follow-up in terms of pain and SF-36 scores.

In another randomized clinical trial of 192 patients with unilateral knee OA (K-L grade 0 to III), Filardo and colleagues[13] compared outcomes of 3 weekly intra-articular injections of LR-PRP versus HA. At 12-month follow-up, patients in both groups demonstrated significant improvement compared with pretreatment in terms of the subjective International Knee Documentation Committee (IKDC) and Tegner scores. However, no significant intergroup difference was demonstrated in IKDC, Tegner, Knee Injury and Osteoarthritis Outcome Scores (KOOS), or EuroQol visual analog scale (EQ-VAS) at 2-month, 6-month, or 12-month follow-up.

Fewer studies have investigated the effects of PRP on hip OA, although recently Dallari and colleagues[18] performed a randomized controlled trial on 111 patients to compare the efficacy of autologous PRP, HA, and a combination of both for the treatment of hip OA. Patients and health care providers were not blinded to the treatments used, although the data collectors and analysts were blinded. Patients received 3 intra-articular ultrasound-guided injections 1 week apart during outpatient surgery, although the types of surgical procedures were not mentioned. In addition, the leukocyte concentration of the PRP formulations was not mentioned. Patients were assessed at 2, 6, and 12 months after treatment. The PRP group demonstrated lower VAS pain scores at all follow-up times and significantly better Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores at the 2-month and 6-month follow-up periods.

Battaglia and colleagues[19] also performed a nonblinded, randomized trial comparing ultrasound-guided PRP versus HA injections for hip OA in 100 consecutive patients. Patients underwent 3 injections every 2 weeks of 5 mL autologous PRP or 2 mL HA. The PRP samples were obtained through a double-spin technique to create a sixfold platelet count. Using the Harris Hip Score (HHS) and VAS, patients in both groups demonstrated significant improvements between 1-month and 3-month follow-up. Although patients showed progressive worsening of symptoms between 6-month and 12-month follow-up, scores were still significantly improved compared with baseline ($P<.0005$). No significant differences were found between the PRP and HA groups.

In terms of focal chondral defects, limited studies in animal models have demonstrated successful results with intra-articular injections of PRP[20] and autologous conditioned plasma (ACP)[21] and the use of an autologous platelet-enriched fibrin scaffold,[22] although similar studies have not been published with human subjects. However, PRP has shown promising results in conjunction with the surgical treatment of knee[17] or hip OA[18] or as a nonoperative treatment modality for these pathologies[19] (**Table 1**). Overall, PRP for knee OA has demonstrated short-term improvement in pain and function.[16] As indications for PRP continue to expand, it will become increasingly important for future studies to state specific methodologies used in the preparation of PRP to recognize ideal preparation techniques and the ideal number of PRP injections for each pathology.[4]

Intra-articular PRP injections have shown promising results in the treatment of knee and hip OA at short-term follow-up periods up to 12 months following injection. However, the long-term effects of these treatments are still unknown, and their results in comparison to injections of HA (viscosupplementation) are also undetermined.

Table 1
Clinical studies on biological treatments for knee and hip articular cartilage lesions

Treatment	Study	Indication	Maximum Follow-Up, mo	Outcome Measures
PRP	Filardo et al,[13] 2015	Knee OA	12	IKDC, KOOS, EQ-VAS, Tegner score
	Duif et al,[17] 2015	Knee OA	12	VAS pain, Lysholm score, SF-36
	Dallari et al,[18] 2016	Hip OA	12	HHS, VAS, WOMAC
	Battaglia et al,[19] 2013	Hip OA	12	HHS, VAS
BMAC	Kim et al,[24] 2014	Knee OA	12	VAS pain, IKDC, SF-36, KOOS, Lysholm
	Hauser & Orlofsky,[25] 2013	Hip, knee, or ankle OA	6 wk	Pain, stiffness, range of motion, crepitus, ability to exercise
	Gobbi et al,[27] 2011	Knee chondral lesions	24	VAS, IKDC, KOOS, Lysholm, Marx, SF-36, Tegner
	Gobbi et al,[28] 2016	Knee chondral lesions	48	MRI, KOOS, IKDC, VAS, Tegner
MSCs	Emadedin et al,[42] 2015	Knee, ankle, or hip OA	30	Walking distance, VAS, WOMAC score
	Pers et al,[43] 2016	Knee OA	6	Safety, WOMAC
	Soler et al,[44] 2016	Knee OA	48	VAS, HAQ, SF-36, Lequesne functional index, WOMAC
	Kim et al,[45] 2015	Knee OA	28	IKDC, Tegner score, ICRS grade

Abbreviations: BMAC, bone marrow aspirate concentrate; EQ-VAS, EuroQol visual analog scale; HAQ, health assessment questionnaire; HHS, Harris Hip Score; ICRS, International Cartilage Repair Society; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; MSCs, mesenchymal stem cells; OA, osteoarthritis; PRP, platelet-rich plasma; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

Furthermore, the effects of PRP injections on focal chondral defects in human subjects has not been demonstrated.

BONE MARROW ASPIRATE CONCENTRATE

Bone marrow aspirate concentrate (BMAC) has experienced a rise in popularity because it is one of the few US Food and Drug Administration (FDA)-approved methods for delivering stem cells.[23] BMAC is most often formulated from iliac or tibial bone marrow, which is extracted and mixed with anticoagulants and batroxobin enzyme, although other methods of activation have been reported.[23–25] The quality of the bone marrow aspirate can be improved by aspirating at multiple locations with a small syringe. Hernigou and colleagues[26] found that, when aspirating bone marrow from the iliac crest, progenitor cell concentrations were on average 300% higher using a 10-mL syringe compared with a 50-mL syringe ($P<.01$). The bone marrow extraction procedure typically has minimal interference with daily activities, with 3 hours of bed rest immediately after the procedure and restrictions on extreme exercise for 6 weeks postoperatively.[24] The most commonly reported side effects are joint pain and swelling.[23]

The concentration of stem cells in BMAC is relatively low (0.001% to 0.01% of mononuclear cells following centrifugation). In addition to stem cells, BMAC contains growth factors that may assist in the regeneration and preservation of cartilage, and have been shown to have anti-inflammatory and anabolic effects on the injected tissue (**Table 2**).[23] The growth factors present in BMAC include platelet-derived growth factor, transforming growth factor-beta (TGF-β), and bone morphogenetic protein (BMP)-2 and BMP-7.[23]

In a case series of 41 patients (75 knees) with knee OA (K-L grades I to IV), Kim and colleagues[24] evaluated outcomes of BMAC injection with adipose tissue. At 12-month follow-up, VAS pain score, IKDC, SF-36, KOOS, and Lysholm scores increased among the group compared with preoperative scores, although statistical significance was not mentioned in this study. A significant association was found between higher K-L grade and inferior outcomes at follow-up. Overall, joint swelling (92%) and pain (41%) were the most common side effects experienced by patients.

In a small case series of 7 patients with hip, knee, or ankle OA, Hauser and Orlofsky[25] performed intra-articular injections (mean 4.1 injections per patient) with unfractionated whole bone marrow in combination with hyperosmotic dextrose. At a minimum 6-week follow-up, 5 of 7 patients noted complete relief or strong functional improvement. Based on a VAS from 0 (complete relief) to 10 (maximum limitation), average pain intensity scores improved from 6.2 preoperatively to 0.07 at follow-up ($P = .002$). Likewise, joint stiffness improved from 7.0 to 0.7 ($P = .002$). No adverse events were noted.

In terms of focal chondral defects, Gobbi and colleagues[27] performed a prospective case series of 15 patients with grade IV knee chondral lesions undergoing operative

Table 2
Biological therapy comparison

Treatment	PRP	BMAC	Stem Cells
Invasiveness	Minimal	Moderate	Moderate
Presence of stem cells	None	Minimal	High
Presence of growth factors	High	High	None

Abbreviations: BMAC, bone marrow aspirate concentrate; PRP, platelet-rich plasma.

transplantation with BMAC covered with a collagen I/III matrix (Chondro-Gide; Geistlich, Wolhusen, Switzerland). The average lesion size was 9.2 cm^2 and 6 of 15 patients had multiple chondral lesions. At a final follow-up of 24 months, patients showed significant improvement ($P<.005$) in VAS, IKDC, KOOS, Lysholm, Marx, SF-36, and Tegner scores compared with preoperative scores. In 3 patients who underwent a second-look arthroscopy with concomitant biopsy at 2-year follow-up, hyaline-like histologic findings were found for all samples. Furthermore, no adverse events were reported in this study.

Gobbi and colleagues[28] also performed a prospective cohort study in patients with International Cartilage Repair Society (ICRS) grade IV chondral lesions in the knee. Patients were treated operatively with a hyaluronan-based scaffold (Hyalofast; Anika Therapeutics Inc, Bedford, MA) soaked in BMAC. A study group of patients older than 45 years (n = 20) was compared with a control group younger than 45 years (n = 20). At a final follow-up of 4 years, the following outcome scores significantly improved for both groups: all KOOS subscores, Tegner score, and subjective IKDC (all $P<.001$). Results in the study group were affected by lesion size, with a significantly better subjective IKDC score ($P = .006$) and a trend toward a significantly better KOOS pain score ($P = .086$) in patients with lesions smaller than 8 cm^2 compared with larger than 8 cm^2 at final follow-up. Based on MRI, greater than 50% filling of the defect was observed in 81% and 71% of patients in the study and control groups, respectively, at final follow-up. Overall, 2 patients experienced persistent subchondral bone edema, but otherwise no major adverse reactions were reported.

Few studies have reported outcomes of BMAC for knee or hip cartilage defects, although the outcomes in these studies are good to excellent overall.[23] Patients with mild OA and smaller focal chondral defects have been shown to benefit more from BMAC than those with severe OA (as assessed by the K-L scale) and larger defects. As with PRP, long-term outcomes have not yet been reported by multiple studies.

STEM CELLS (CONNECTIVE TISSUE PROGENITORS)

Connective tissue progenitors (CTPs) are defined as proliferative cells capable of differentiating into various connective tissue phenotypes.[29] Thus, the term CTP not only encapsulates pluripotent stem cells but also progenitors derived from stem cells that may be at various stages of cellular commitment.

Stem cells are defined as undifferentiated cells that are capable of proliferation, regeneration, self-maintenance, and replication.[30] Human embryonic stem cells (hESCs), induced pluripotent stem cells (iPSCs), and mesenchymal stem cells (MSCs) have all been used for treatment of OA.[15] Due to their accessibility, MSCs are the most popular stem cell option for articular cartilage repair.[31] Furthermore, it is more difficult to ensure homogeneity in cell division with iPSCs or hESCs than with MSCs.[32] MSCs are present in a range of tissue types, have anti-inflammatory effects, can be harvested in large quantities, and are shown to produce proteins conducive to cartilage regeneration.[33] In 2006, the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy defined the following minimal criteria for a human cell to be classified as an MSC: (1) the ability to adhere to plastic when maintained in standard culture conditions; (2) expression of CD105, CD73, and CD90; (3) lack of expression of CD45, CD34, CD14, or CD11b, CD79alpha, or CD19 and HLA-DR surface molecules; and (4) the ability to differentiate to osteoblasts, adipocytes, and chondroblasts in vitro.[34] Without meeting these criteria, the term MSC should not be used.

Chang and colleagues[31] suggested that MSCs also have anti-inflammatory elements, as preclinical trials in small mammals observed an anti-inflammatory response. Because of their easy accessibility and minimal morbidity caused during harvest, adipose-derived stem cells (ASCs) result in a high yield of stem cells and have gained recent attraction for this reason.[35] Furthermore, the growth properties of ASCs are superior to bone marrow–derived MSCs (BMSCs).[35] ASCs may be obtained either through liposuction aspirates or from the infrapatellar fat pad.[36] When cultured with appropriate growth factors (TGF-β, BMP-2, BMP-6, BMP-7), ASCs may differentiate into chondrocytes in vitro or in vivo.[37]

BMSCs are popular because of ease of collection (the procedure is minimally invasive) and the extensive laboratory characterization of these cells.[36,38] However, the cell yield is low following bone marrow aspiration, and therefore these stem cells often must be isolated and expanded in cell culture before clinical use. Common extraction sites are the iliac crest, the tibia, and the femur.[31] MSCs may differ between anatomic regions of the same tissue type in terms of yield and characteristics.[5] In the case of BMSCs, bone marrow is aspirated 3 weeks before the transplantation is set to occur. The aspirated cells are then cultured in a monolayer for expansion. Several factors can be used to induce these cells to differentiate into host mesenchymal tissue, including cartilage and bone. The cells can then be cultured in scaffolds to transplant into the affected joint. Synovial-derived MSCs have the most promising chondrogenic ability, but little literature exists exploring this topic.[31]

There are 2 methods of incorporation of MSCs into articular cartilage: (1) surgical implantation by embedding the cells in a scaffold, and (2) intra-articular injections.[38] Several animal models have been used to test the effects of matrix-assisted or scaffold-assisted MSC transplantation,[39,40] as well as intra-articular injection of MSCs[41] for the treatment of focal chondral defects, with overall successful results in terms of macroscopic and histologic observations. However, similar studies have not been conducted in human subjects with isolated cartilage defects.

In a case series of 18 patients with knee, ankle, or hip OA, Emadedin and colleagues[42] evaluated the effect of 1 intra-articular injection of approximately 5×10^5 cells/kg body weight of BMSCs. At a final follow-up of 30 months' posttransplantation, no serious adverse events were reported. Furthermore, no changes were observed in liver function, hematology, or biochemistry analyses. Walking distance, VAS for pain, and WOMAC scores all improved from baseline to final follow-up. In terms of imaging outcomes, reduced subchondral bone edema was appreciated in 3 of 6 patients with knee OA and 4 of 6 patients with ankle OA at 6-month follow-up. Articular cartilage repair was visualized with MRI in 3 of 5 patients with hip OA.

Results of a phase I clinical trial were recently published on the use of ASCs for the treatment of knee OA.[43] A consecutive series of 18 patients with severe knee OA were treated with a single intra-articular injection of autologous ASCs. To determine a potential dose-response relationship, patients were separated into 3 groups of 6 patients each: low dose (2×10^6 cells), medium dose (10×10^6 cells), and high dose (50×10^6 cells). At 6-month follow-up, no serious adverse events were reported, and even patients in the low-dose group experienced significant improvements in pain levels and function compared with baseline.

In another phase I-II clinical trial, Soler and colleagues[44] recently reported on 15 patients with knee OA (K-L grade II or III) who were treated with a single intra-articular injection of a mean 40.9×10^6 autologous BMSCs. At a follow-up of 12 months, 1 serious adverse event had been reported, a ruptured ovarian cyst, which was likely not related to the stem cell therapy. Compared with baseline, VAS pain score, the

Lequesne functional index, and the WOMAC score significantly improved at the 12-month follow-up (all $P = .001$). Furthermore, each of the following WOMAC subscales significantly improved between baseline and 12-month follow-up: pain ($P = .008$), stiffness ($P = .01$), and functionality ($P = .001$). Thirteen of the 15 patients were followed until 4 years' postinjection and assessed with the VAS, which revealed a further reduction in pain from the 12-month follow-up. Finally, MRI T2 mapping was performed to assess cartilage quality, with a steadily decreasing value observed from preinjection to 12-month follow-up, indicative of cartilage regeneration.

In a retrospective cohort study of patients undergoing arthroscopic procedures for knee OA, Kim and colleagues[45] compared outcomes of MSC injections in combination with PRP (n = 20) versus a matched pair of patients who underwent MSC implantation on a fibrin glue scaffold (n = 20). At a mean follow-up of 28.6 months, IKDC and Tegner activity scores significantly improved in both groups compared with preoperatively, with a significantly higher IKDC score in the implantation group. Although preliminary outcomes of cartilage treatment by BMSCs in the knee show no tumor growth or infection, long-term safety of stem cell therapy for articular cartilage therapy has yet to be proven.[38]

MSCs are an attractive option for patients with articular cartilage damage, as MSCs may differentiate into chondrocytes in the appropriate environment. Currently, published outcomes are mostly limited to phase I-II clinical trials, with their primary goal focused on the assessment of safety and tolerability of MSC transplantation. Further research is necessary to determine optimal harvest location, culture methods, cell concentration, and transplantation method. Although the intra-articular transplantation of MSCs has not been associated with severe adverse events, long-term follow-up is necessary before this therapy can be definitively considered safe and effective.

DISCUSSION

As awareness increases throughout the orthopedic community of the importance of treating early osteoarthritis and focal chondral defects, newer treatment modalities have been used in an attempt to prevent or delay progression to late-stage OA. Although successful surgical procedures exist, particularly for the treatment of isolated articular cartilage lesions, biological therapies carry the advantages of being less invasive and less expensive. Based on this review, few studies have reported outcomes of these treatment options in the management of knee and hip articular cartilage damage, although generally positive outcomes have been reported in these studies.

Although many of the studies discussed in this review have focused on the use of singular treatment methods, some of these options can and have been used in conjunction with each other. PRP has been used to augment BMAC therapy, although it is still unknown if these treatments result in a synergistic effect.[23]

There are a number of variables within each of the biological treatment options discussed in this review. As a result of the variability that exists within each of these treatment options, further research is necessary (1) to establish benchmarks for preparation and formulation of each biological therapy, and (2) to make comparisons between different biological options. For example, the viability and efficacy of BMAC or stem cell therapy likely is affected by harvest location, cell concentration, donor sex,[46,47] donor age,[47,48] and donor health.[49] Likewise, the effectiveness of PRP likely depends on leukocyte concentration.[9]

More research is necessary for all biological options described in this review to draw any definitive conclusions, especially in the realm of long-term effects. Most studies in

the current literature include patients with knee OA, with few published studies demonstrating outcomes in patients with hip OA. BMAC appears as a promising option at present, as it is FDA-approved and has the benefits of including both stem cells and growth factors.[23] Although all biological options provide a viable alternative to surgery for patients, the long-term effects of these modalities are yet to be determined.

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