Evidence-Based Approach to Orthobiologics for Osteoarthritis and Other Joint Disorders

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KEYWORDS

• Osteoarthritis • Orthobiologics • Cartilage

KEY POINTS

- Osteoarthritis and cartilage lesions are a major cause of functional limitations and the goal of biological treatment is to preserve the native joint to delay the onset of OA.
- Biological cell-based cartilage restoration treatment addresses the need for the long-term viability of repaired tissue.
- The treatment of full-thickness cartilage lesions in the knee using a hyaluronic acid-based scaffold with activated bone marrow aspirate concentrate has good to excellent clinical outcomes at long-term follow-up.

INTRODUCTION

Osteoarthritis (OA) is one of the most common joint diseases; characterized mainly by joint pain and functional impairment, owing to articular cartilage degeneration, subchondral bone remodeling, and synovial inflammation.[1] OA affects 7% of the global population and is one the highest cause of years lived with disability worldwide,[2] making it an important problem to solve for the orthopedic surgeon.

Control of the tissue healing is not only limited to the optimization of the biomechanical environment, but also to other coexisting factors such as diabetes, smoking, hypercholesterolemia, or local factors (poor vascularity, tissue degeneration, cell death, and so forth) which can further impair this healing.[3] Over more than 30 years, the orthopedic community has explored ways to use the biologic response of the connective tissues to optimize the healing process. These have resulted in cell-based, cytokine-based, and scaffold-based therapies. This book chapter intends to provide a review of the current status of biological therapies for cartilage injuries and OA in orthopedics.

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Bone Marrow Stimulation Techniques

Bone marrow stimulation techniques refer to methods using bleeding from subchondral marrow space and further formation of a fibrin clot, which functions as a scaffold for subchondral stem cell migration and consequent formation of fibrocartilage. In general full-thickness cartilage lesion of a surface area < 1 cm^2, without subchondral bone lesions is usually considered an indication for a bone marrow stimulation technique as an isolated procedure.[4] Although, one should be aware that these recommendations should be carefully considered for every patient individually.

Microfracture is probably the most commonly known and used procedure owing to availability, simplicity, and low cost.[5–7] The surgical procedure is fairly uncomplicated; however, there are crucial steps surgeon should be aware of. Firstly, cartilage lesion borders should be thoroughly prepared, loose cartilage should be removed and borders made perpendicular to the subchondral bone. Then using a small diameter chondral awl (1 mm) holes are made and at this point it is vital to maintain the awl perpendicular to the surface not to damage the subchondral plate. Finally, saline pressure is reduced to visualize the release of fat droplets and bleeding that will later form a clot on the defect.[6–9] Studies have shown that this fibrocartilage matrix consists mainly of type I collagen and other noncollagenous proteins, making this tissue more delicate and less elastic, with inferior mechanical properties than normal articular cartilage.[10,11] Newly formed tissue may progressively deteriorate and long-term results of microfracture may not be satisfactory in every patient. In our study, 67 patients treated with microfracture owing to full-thickness cartilage lesions were prospectively followed up for 10 years.[5] All patients reported outcomes increased significantly at 2 years but deteriorated in the long term. Interestingly, patients with smaller lesions ($\leq$400 mm^2) and younger patients ($\leq$30 years) demonstrated significantly improved results in knee injury and osteoarthritis outcome score (KOOS), visual analog scale (VAS), and Marx scores. This suggests that when applied in young patients with smaller lesions, microfracture can offer good clinical outcomes at short-term follow-up. It should be stressed that microfracture may damage the subchondral bone and lead to the formation of microcysts that may accelerate the deterioration of the cartilage and compromise the articular surface for future procedures.[12]

Autologous Matrix-Induced Chondrogenesis (AMIC) is based on the same concept as microfracture but aided with a porcine collagen scaffold.[13] Indications include focal chondral or osteochondral defects with Outerbridge classification grade 3 to 4 with a defect size of approximately 1.0–8.0 $cm^{2,}$ and patient age of 18 to 55 year old.[3] Scaffold is added after microfractures are conducted to cover the defect and to allow the ingrowth of mesenchymal stem cells (MSCs) from the subchondral bone. AMIC has several advantages, such as no donor site morbidity, the possibility of arthroscopic approach, and low cost compared with autologous chondrocyte implantation (ACI). Good clinical results of AMIC in midterm follow-ups have been described.[14] However, the reliability of these results is limited because of the dwindling number of patients available for the final follow-up evaluation.

Autologous Cartilage Use

In acute lesions use of autologous cartilage is an optimal alternative to repair a cartilage defect. It is described that covering an acute cartilage defect with minced fragments from a large piece of cartilage achieves good clinical results.[15] Authors retrieved a large chondral fragment and minced it into multiple small ones (<1 x 1 $\times$ 1 mm) with a scalpel. First, the cartilage defect is debrided and drilled into the subchondral bone using a 1.4 mm K-wire. Then, minced cartilage fragments are placed

into the defect and attached using fibrin glue. This concept has been known since 1980s. The procedure using minced cartilage was modified and combined with various materials to become Cartilage Autograft Implantation System (CAIS).[16] A comparative study looking at different minced cartilage sizes showed that cartilage paste (smaller cartilage size) demonstrated significantly increased extracellular matrix production in contrast with other groups.[17] Consequently, the optimum degree of cartilage fragmentation should always be considered. Stone and colleagues recently reported a 10- to 23-year long-term results in 74 patients treated with Articular Cartilage Paste Graft, the biopsies of the repaired tissue revealed that 14 (48.3%) contained hyaline-like cartilage, 24 (82.8%) fibrocartilage with GAG, 10 (34.5%) fibrocartilage without GAG, and 3 (10.3%)fibrous tissue.[18]

Osteochondral Autograft Transplantation

Osteochondral Autograft Transfer System (OATS) is performed in a single-stage procedure, arthroscopically or through arthrotomy. Cylindrical plugs are harvested from donor sites in nonarticulating regions within the joint. Its main advantage is that it recreates the osteochondral unit in cartilage lesions with damaged subchondral bone, like OCD lesions. This technique is one of the few that has the benefit of restoring the hyaline cartilage. OATS is usually used for lesions smaller than 2 cm^2. One up to 3 osteochondral plugs of varying sizes are harvested and then transferred to the affected area. Authors of a 17-year prospective multicentric study performed in 383 patients found good to excellent results in 91% of femoral mosaicplasty, 86% of tibial, and 74% of patellofemoral mosaicplasty. Interestingly, patellofemoral pain associated with graft harvest was observed in only 5% of cases.[19] Congruent, gliding surfaces of the transplants and satisfactory fibrocartilage coverage of donor sites were seen in second-look arthroscopies. A significant drawback of this procedure is difficult to recreate the anatomic curvature of the articular surface. Wu and colleagues have shown that osteochondral plugs protruding 1 mm resulted in significantly increased contact pressures.[20] Furthermore, treatment using the OAT technique is limited by the availability of autologous tissue, as donor site morbidity is an essential concern if multiple grafts are used.

Autologous Chondrocyte Implantation

ACI consists of 2 steps; first, a piece of healthy cartilage is obtained from a non–weight-bearing area and subsequently expanded in vitro. The second step is grafting of the chondrocyte suspension into the defect.[21] Four generations of ACI have been introduced through the years. First generation, developed by Lars Peterson,[22] consists of infusion of the chondrocyte suspension under periosteal flap. In the second generation, the chondrocyte suspension is injected under a collagen membrane. The third generation also known as matrix-induced autologous chondrocyte implantation (MACI), involves the infusion of the expanded chondrocytes into a scaffold which is further implanted in the cartilage defect. The most recent fourth generation is a one-step procedure with chondrocyte isolation through biopsies and direct implantation. Long-term results with ACI first-generation technique are available with good term results at 20 years follow-up.[23] Some studies report significantly better functional outcomes in patients who underwent second-generation ACI compared with patients with first-generation ACI.[24,25] On the other hand, when comparing MACI against second or first-generation techniques, overall clinical results have not proved superiority with the latest technique.[26]

ACI in comparison with bone marrow stimulating techniques such as microfracture has shown to be superior over time owing to longer-lasting effects. Although the final

tissue is still fibrocartilage, it has better quality and is more "hyaline-like" in contrast with the one provided by the microfracture procedure.[27,28] However, when compared with other cell membrane techniques such as the one-step procedure hyaluronic acid combined with bone marrow aspirate, outcomes have not shown statistically significant difference (41).

ACI has proven to offer a durable solution in the treatment of large full-thickness cartilage lesions. However, the need for 2 surgical interventions, the excessive cost for chondrocyte culture, and comparable results compared with one-step biological scaffolds remain the ACI technique's major drawbacks.

Cartilage Allografts

Fresh osteochondral allograft is used mostly in lesions whereby mosaicplasty cannot be performed. The benefits of using allografts include the flexibility of graft sizing and the possibility to treat the entire lesion with a single transplanted plug and no donor site morbidity. Improved patient-reported outcomes can be expected after OCA transplantation, with a survival rate of 78.7% at 10 years, with worse results in cases of patellar lesions and bipolar lesions. Some drawbacks include lower chondrocyte viability owing to storage and processing and potential immunogenic response concerns.[29]

Cell-Based Chondral Scaffolds

Cell-based Chondral Scaffold Allografts consist of hyaline cartilage chondrocytes in a malleable scaffold that can be formed to fill the defect. Because of their "one-time" biological approach, compared with MACI, they are an interesting and accessible alternative to treat cartilage. In general, they have shown good short-term results without significant problems concerning tolerability. Still, there is not enough evidence regarding long-term results. Chondrocytes in human tissue allograft, consisting of juvenile viable hyaline cartilage pieces (DeNovo NT Natural Tissue Graft) have proven to have increased metabolic and proliferative activity when compared with adult chondrocytes,[30] with a proper filling of the defect shown on MRI in addition to good clinical results at over 2-years follow-up.[31] Intriguingly, cells in a cryopreserved viable chondral allograft (Cartiform) shown to stay viable, up to 70%, at 2-years follow-up.[32] An additional option is dehydrated micronized allogeneic cartilage scaffold (BioCartilage) combined with platelet-rich plasma and fibrin glue, although the research on short or long-term outcomes is limited.[33]

Hyaluronic Acid Scaffold with Bone Marrow Aspirate Concentrate Augmentation

HA-BMAC scaffold, developed 30 years ago, allowed the treatment of larger cartilage defects in a one-step surgery. This procedure provided good long-term results and proved its superiority to microfracture owing to continued effect up to 15 years compared with the 2 to 3 years with microfracture. Additionally, it can be used in the case of multiple compartment and extensive lesions or in older patients.[28,34–38] The senior authors' selected technique is a one-stage cartilage repair with a three-dimensional hyaluronic acid-based scaffold (Hyalofast) paired with activated bone marrow aspirate concentrate (HA-BMAC). Compared with 2-step MACI, the clinical outcomes have not shown a significant difference. Additionally, the study showed that there was no relationship between the clinical outcome and the number of Colony Forming Units (CFU) found in bone marrow aspirate, therefore, supporting the rationale of the one-stage treatment.[37]

Every procedure should be preceded with a careful examination under anesthesia to confirm or exclude any limitations in range of motion or ligamentous instability.

The procedure is conducted through a small arthrotomy or arthroscopic depending on the lesion's extent and location. Loose cartilage is removed, stable vertical walls are created around the periphery of the defect with special chondrectomy. Then the calcified cartilage layer must be thoroughly removed without damaging the subchondral plate (**Fig. 1**). The defects are sized with aluminum foil templates and then a matching hyaluronic acid-based scaffold is used to cover the defect. Bone marrow is harvested from the iliac crest and centrifuged to acquire a concentrated bone marrow which is later combined with Batroxobin (Plateltexact-Plateltex S.R.O. Bratislava, SK) to produce a clot. The hyaluronic acid-based scaffold and clot from activated bone marrow aspirate concentrate are blended to create a biologically active construct for cartilage repair (HA-BMAC, **Fig. 2**). The HA-BMAC is positioned on the lesion and secured with fibrin glue. Afterward, the knee is cycled to confirm stability.[39] A technique that is another variation of this procedure was described by Sadlik and colleagues, in which a morselized bone graft is used to fill the lesion and then covered with hyaluronic acid scaffold embedded with BMAC.[40]

BMAC may also be used to treat subchondral bone pathologies. Joint cartilage and subchondral bone function as a unit and over the last few years a debate on the part of subchondral bone purpose has been going on. Bone marrow lesions (BMLs) are focal defects in the subchondral bone and can be diagnosed by magnetic resonance imaging (MRI). The number of pathologies of ischemic, mechanical, and reactive background can be responsible for the formation of these lesions. When evaluating a patient with BML it is vital to assess whether the lesion is reversible and irreversible.[41] Subchondroplasty (SCP) Procedure (Zimmer Biomet) is used to treat bone marrow lesions via the implantation of a bone substitute. A variation of this procedure that uses a biological approach is Osteo-Core-Plasty (Marrow Cellution). This minimally invasive subchondral bone augmentation procedure offers both biological (Bone Marrow) and mechanical (Autologous Bone Core) components to improve the osteochondral unit and boost natural regeneration. This procedure may also be used in the treatment of insufficiency fractures, subchondral cysts, and avascular necrosis[a,.[42]

This method is made of 2 parts, the first being the aspiration of bone marrow and the collection of the bone core grafts. The second involves the application of the material to the defect. Bone marrow is aspirated from the iliac crest, the trocar is advanced into the medullary space and the material is aspirated with a syringe. It is recommended to change the trocar direction throughout aspiration to obtain bone marrow aspirate

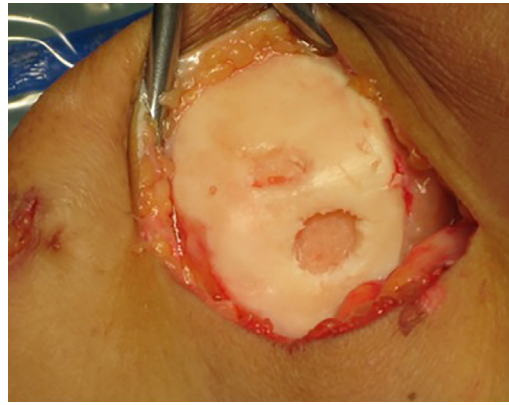

Fig. 1. A hyaluronic acid based scaffold combined with activated BMAC forming a sticky clot ready to be implanted in the prepared lesion site.

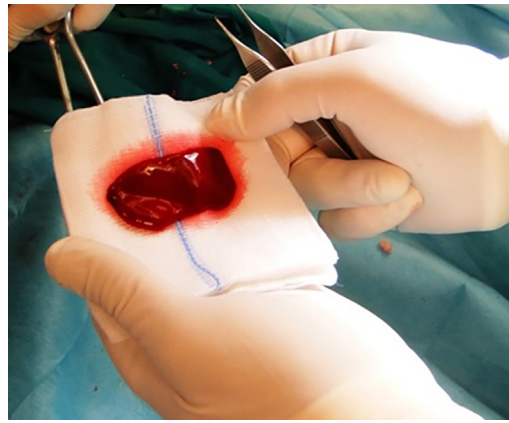

Fig. 2. Two cartilage lesions on the patella. The lesions have been prepared for HA-BMAC implantation, the loose cartilage has been removed and borders of the lesion made perpendicular to the subchondral bone.

(BMA) from various places. After the collection of the BMA, bone cores can be harvested from the same entry point. The application may be conducted arthroscopically or through an open approach, both require fluoroscopic assistance. Necrotic Tissue Zone is identified under fluoroscopy on AP and lateral images. In an open technique, the lesion is debrided, and necrotic bone underneath is removed. In an arthroscopic technique, a K-wire is introduced to the target zone from outside the joint and a cannulated drill bit is inserted over the K-Wire. Then Bone Core Graft is delivered to the necrotic zone with Extraction/Delivery Tool in both open and arthroscopic approaches. The bone core graft is pushed with a probe to the target point. Lastly, aspirated BMA is injected into the necrotic site or in the case of an open procedure the BMA Saturated Matrix Scaffold Membrane is used.[43,44]

Although there are systems available that use centrifugation to obtain a concentrated product, the recent data show that there is no for this step. Brozovich and colleagues used flow cytometry to detect MSCs, colony-forming units (CFUs), and cytokine profiling and found a lower concentration of CFUs in BMAC. They concluded that significantly lower CFUs in BMAC may result in a lower potency of MSCs compared with BMA.[42] Bone marrow aspirate with the aforementioned system was demonstrated to include a sufficiently high CFU-fs/mL and CD34+/mL and therefore not require centrifugation. Additionally, the level of CFU-fs/mL was significantly higher in comparison to BMAC in side-by-side evaluation from the same patient. In OsteoCore plasty, there is no need for centrifugation and the surgeon can precisely apply the aspirate to the target zone.[45]

Biological Treatment in Osteoarthritis

Even though there is a variety of techniques to treat chondral lesions sometimes the onset of OA is inevitable. OA has such a big influence on patients' quality of life it is, therefore, crucial to understand which therapy offers the most. A variety of conservative therapies are available, both drugs and physical therapy, still they usually fail to provide long-term relief. That is why biological therapies have been earning more and more attention.

The most commonly used injectable is hyaluronic acid (HA), but studies have shown that PRP is more efficient both in short-or long-term pain and functional recovery.[46]

PRP contains a large number of growth factors and proteins stored in the alpha granules of platelets which were found to have regenerative and analgesic effect.[47,48] Additionally, studies have shown that platelet-rich plasma (PRP) has an anti-inflammatory effect and counteracts catabolic processes within the joint.[49–51] Injections of PRP can be conducted separately or in cycles of 3 injections, which is the authors preferred method. PRP is obtained from patients' peripheral blood, which is centrifuged in a special processing kit. The PRP is injected into the joint after careful disinfection of the needle entry point. Peak beneficial effect is observed at 6 months after the cycle of injections, but it may last up to 2 years.[52] A meta-analysis of randomized controlled trials using PRP in the treatment of knee OA has shown that statistically significant beneficial effect over placebo is seen at 6 and 12 months.[53] Interestingly a recent study has shown that there are no significant differences between leukocyte rich and leukocyte poor plasma in the treatment of knee AO.[54]

Treatment of joints other than knee has much fewer data to present. In hip for example, the results are promising, offering a short-term relief of symptoms and better outcome than HA injections[55,56] On the contrary, in carpometacarpal OA, better results were observed with HA injections compared with PRP and in ankle OA no significant improvement of pain and function was found when PRP was compared with placebo.[57,58]

Although satisfactory results can be achieved with PRP research on more efficient treatment has been going on for a few years. An autologous microfragmented adipose tissue (MFAT) in contrast to peripheral blood has 25,000 times more reparative cells.[59] MFAT is obtained from adipose tissue from abdominal or supragluteal region with a special lipoaspirate cannula. Lipoaspirate is transferred to the Lipogems device a low-pressure cylindrical system, to get fluid with a concentration of pericytes and MScs. This product is then applied to the joint through an injection or during arthroscopy. Promising results have been shown in literature.[60–62] Moreover, a study comparing leukocyte poor PRP combined with HA and MFAT has shown statistically significant difference favoring AMAT for Tegner and KOOS symptoms at 6 months and Tegner at 12 months of follow-up.62 However, one should be aware that this is a more invasive procedure than a PRP injection.

SUMMARY

OA is a raising burden and many possibilities to treat cartilage lesions and early OA have been reported. To treat cartilage defects, cell therapies using chondrocytes, MSCs, and other cell sources have been used. To obtain the best cartilage quality, these cartilage preserving/regenerating techniques combined with alignment correction osteotomy will give the best results. The biology of the articular cartilage must be fully explained before cartilage repair technologies can advance further. Collecting evidence of experimental studies on cartilage repair and early OA treatment will enable us to develop a clinical use of novel techniques for biological healing. Therefore, the use of the most appropriate line of treatment and proper patient selection is key to improving results.

CLINICS CARE POINTS

Pearls

- Adequate and thorough exposure to the cartilage lesion is crucial and may be problematic in the patellofemoral compartment. Use traction as needed to get a comfortable working space.

- If dimensions of the cartilage defect are difficult to measure, use an aluminum foil (or similar material) template to assist with accurate scaffold size matching.
- The hyaluronic acid-based scaffold is symmetric; after creating the HA-BMAC graft, implantation may proceed with either side placed against the subchondral bone.

Pitfalls

- Arthroscopic cartilage repair should proceed only in cases whereby the entirety of the defect can be appreciated and treated in a minimally invasive manner; repair should be performed in an open manner otherwise.
- Confirm secure graft seating within the cartilage defect by cycling the knee under arthroscopic visualization; failure to do so may increase the risk of graft delamination in the postoperative period.

DISCLOSURE

The Authors have nothing to disclose.

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