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# Cartilage Repair: What Works in Young Arthritic Knees

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## Abstract

**Background:** Cartilage repair is one of the most challenging treatments due to the specificity, complex structure and biomechanical behavior of the cartilage tissue. Chondral injuries and damage have several clinical implications and can lead to patients' daily and sports limitations or restrictions, along with future degeneration.There are various cartilage surgical techniques described for cartilage repair and further research has been made to improve orthobiological assessment for those conditions. In this review article we aim for an updated overview of what can works in young arthritic knees.

**Keywords:** Cartilage, Chondral, orthobiological, arthritic knees.

## Introduction

Historically, it was thought that the articular cartilage was an inert structure that would not respond to harm or injuries. However, nowadays we know that the articular cartilage is a metabolically active structure with biomechanical properties able to maintain a viable and integral articular surface.

Articular cartilage injuries in load-bearing joints such as the knee are observed with increasing frequency and result from significant joint stresses associated with pivoting, mechanical stress loading and high-impact sports activities. Injuries to the articular cartilage remain difficult to diagnose, but advances in magnetic resonance imaging (MRI) and arthroscopy allow us to determine the real impact and frequency of these injuries.

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Articular cartilage is a thin layer of connective tissue that consists of structural macromolecules. Its principal function is to provide a smooth lubricated surface for articulation and to facilitate transmission of loads with a low frictional coefficient. Articular cartilage is an avascular structure, devoid of blood vessels, lymphatics, and nerves, and is subject to harsh bio-mechanical environment. The pain associated with cartilage damage is believed to be due to irritation of surrounding structures, subchondral bone and intra-articular effusion leading to functional limitation. Similarly, articular cartilage has limited self-repair ability due to low mitotic activity and very few specialized cells, creating a fibrous tissue (fibrocartilage). Fibrocartilage is less effective than mature hyaline cartilage at supporting the biomechanical requirements of the knee, leading to short or midterm early articular degeneration. Clinical symptoms of articular cartilage injury consist of recurrent pain and swelling in the knee joint. Frequently, cartilage injuries are incidental findings on MRI or during arthroscopy. A thorough history and physical exam are necessary to identify symptomatic injuries and treat them appropriately. Treatment of articular cartilage lesions in the knee remains a challenge for the practising orthopaedic surgeons. A wide range of surgical techniques are available depending on the type, size, and depth of the chondral injury, anatomical site and load area. The various techniques available for surgical intervention and surgeon experience/preference makes it difficult to compare the surgical outcomes.

Nevertheless, some characteristics have been identified as risk factors for cartilage repair failure, such as: age greater than 30 years old, obesity (BMI greater than 30), smokers, sedentary lifestyle, inflammatory arthritis, meniscal disease, ligament instability, knee malalignment, cartilage defect extension and longer interval from symptoms onset until surgery [1-4]. The location of the injury is also an important parameter regarding treatment and results. Medial femoral condyle injuries have shown consistently better results than lateral femoral condyle injuries. Microfracture treatment on the femoral condyle shows better clinical outcomes after 36 months compared to other locations, patella or tibial plateau

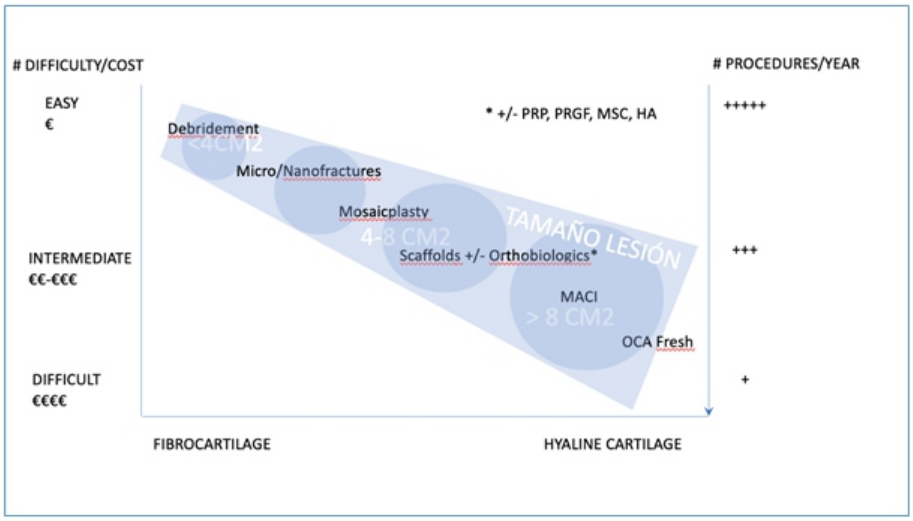


**Figure 1:** Treatment of osteochondral injuries algorithm depending on the size of the injury, type of repair, cost and number of procedures per year. ACI: Autologous Chondrocyte Implantation; MACI: Matrix Induced Autologous Chondrocyte Implantation; OCA: Osteochondral Allograft.

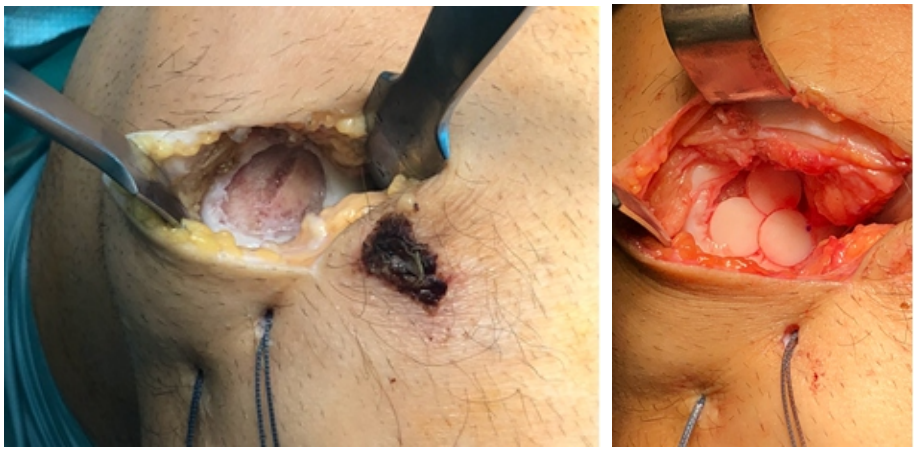

**Figure 2: A.** Grade IV chondral defect in the lateral femoral condyle. The sutures belong to an outside-in meniscal repair of the lateral meniscus. **B.** Final construction using three 8 mm osteochondral cylinders impacted in the injured recipient area. The donor area of the cylinders corresponds to the super external region of the femoral trochlea.

[5,6].

There are several proposed treatment algorithms for treatment of osteochondral lesions (Figure 1).

Current development and increasing combination of new biological cell therapies, including growth factors, scaffolds, matrix and tissues or cartilage preparations, makes it very difficult to assess the long-term effectiveness of each of these techniques and will not be explained in full detail in this article (Table 1).

## 2. Treatment options for chondral lesions

Numerous techniques have been described for the repair of damaged cartilage tissue. The main surgical techniques are listed below and will be summarized throughout the article: arthroscopic debridement (chondroplasty), bone marrow stimulation techniques (microfractures and nanofractures), osteochondral autograft transplantation (mosaicplasty), ACI (autologous chondrocyte implantation) and MACI (Matrix-induced autologous chondrocyte implantation), fresh osteochondral allografts (OCA). Also, biological therapies (PRP– platelet-rich plasma, mesenchymal cells, autologous particulate cartilage) associated with stabilizing matrix or scaffolds (collagen membranes, fibrin gel, PRP clot and others) are in the midst of a steady expansion and development.

Comparative studies with longer follow-up are needed regarding the more recent techniques versus most commonly used procedures at present.

## 3. Articular cartilage repair techniques

### 3.1. Arthroscopic debridement (Chondroplasty)

The main goal of arthroscopic debridement is to soften and regularize the articular surface. This involves smoothing off the edges of the torn cartilage, eliminating small chondral fibrillary flaps and avoiding joint inflammation, chondral damage extension or loose bodies.

Chondroplasty can be performed mechanically (using a motorized shaver) or thermally (radiofrequency device), both through arthroscopy. This technique should be performed in small and superficial injuries (Outerbridge grade ≤2) [8] (Table 2), with caution to avoid damaging healthy cartilage. It is important to switch working portals for better visualization from different angles in order to obtain a smooth surface.

### 3.2. Bone marrow stimulation techniques (Microfractures)

Microfracture is a bone marrow stimulating procedure, which creates subchondral perforation in the bone, allowing pluripotent mesenchymal stem cells to migrate from the marrow into the chondral defect and form fibrocartilaginous tissue. The fibrocartilaginous tissue, abundant in type I collagen, is a fragile substitute for the mature hyaline cartilage, abundant in type II collagen [9]. Unlike hyaline cartilage, fibrocartilage does not have the

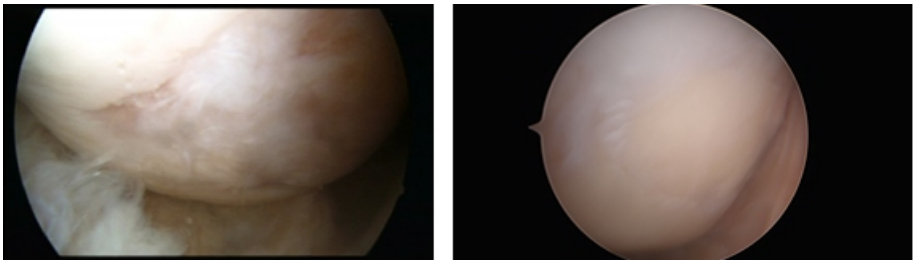

**Figure 3: A.** Left knee arthroscopic view of grade IV osteochondral injury in the lateral femoral condyle. **B.** Second look of the same patient (during hardware removal of a lateral femoral plate used for Varus producing lateral wedge opening osteotomy), 1 year postoperative after mosaicplasty, three 8 mm plugs.

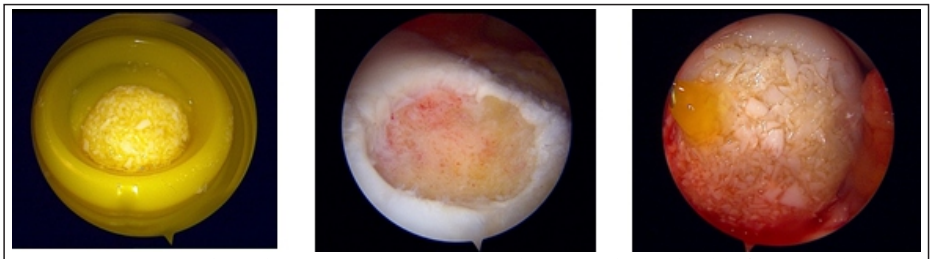

**Figure 4: A.** Minced autologous cartilage mixed with PRP in the back table forming a biologic mesh. **B.** Grade IV chondral defect in the lateral femoral condyle, arthroscopic view using the camera after mini-open approach, lateral parapatellar arthrotomy. **C.** Arthroscopic view using the camera after mini-open; grade IV chondral defect in the lateral femoral condyle filled with scaffold containing the particulated cartilage chips mixed with PRP.

**Table 1: Main surgical techniques for chondral and osteochondral injuries according to size of the injury.**

| | ≤ 2cm$^2$ | ≥ 2cm$^2$ |
|---|---|---|
| **Chondral injury** | Debridement +/- microfractures | ACI/MACI |
| **Osteochondral injury** | Mosaicplasty – Osteochondral Autograft Transplantation | Fresh Osteochondral allograft (OCA) |

same strength and resiliency of cartilage normally found in a joint and could lead to early deterioration in young symptomatic patients [8]. Microfracture is still the most extended cartilage procedure because it is cost effective, technically not complicated, has a low rate of morbidity and is effective in the short term [9]. The results of microfracture technique have shown good results in the short- to mid-term. However, it has been criticized for the damage produced at the level of the subchondral bone causing bone edema, subchondral cysts, and osteophytes.

More recent studies such as Eldracher et al. [9] recommend the use of "nanofractures," perforations in the subchondral bone of 1 mm diameter, allowing for deeper perforation into subchondral bone with less trabecular fragmentation and compaction when compared with microfracture. It results in better restoration of the normal subchondral bone architecture at 6 months.

These bone marrow stimulation techniques should be used in small injuries (<2 cm$^2$), with intact subchondral plaque and preferably in young patients. Both, micro and nanofractures techniques can be performed arthroscopically; it starts by producing a debridement with a curette or a shaver of the remaining calcified cartilage layer over the defective area. Subsequently, the perforations are performed using an angled awl with a separation of 3–4 mm (4 mm depth drilling for microfractures and 5–10 mm depth drilling for nanofractures) using a 1.5 mm diameter Kirchner wire.

Some authors recommend the use of collagen membranes [11] or scaffolds with natural polymers such as fibrin or chitosan to prevent blood clot loss, as it can disappear with arthroscopic washing or with the synovial fluid after surgery. The use of chitosan has been shown to produce higher quality repair tissue at 5 years follow-up when compared to isolated microfractures [12].

### 3.3. Autologous chondral grafts (Mosaicplasty)

Autologous chondral mosaicplasty involves harvesting and transferring one or several healthy osteochondral plugs from a non-weight-bearing area of the femur (lateral trochlea or intercondylar notch) and transplanting them in the region of chondral or osteochondral defect, such as the femoral condyles. The plug size is usually 6 to 10 mm in diameter and it is impacted press-fit using specific instrumentation (13) (Figure 2). The main indication for mosaicplasty is small, deep (≤ 2 cm2) and damaged osteochondral area affecting the subchondral bone (e.g., osteochondritis dissecans). In mosaicplasty the defects can be filled immediately with mature hyaline cartilage, as well as primary bone integration (subchondral bone repair) with faster healing than microfracture technique (14).

This mosaicplasty technique is a cost-effective, minimally invasive, single stage procedure which can be done by arthroscopy or mini-open. It allows for quick recovery and early mobilization, which improves range-of-motion and minimizes stiffness. However, this is a technically challenging procedure and donor site morbidity after mosaicplasty

**Table 2. The Outerbridge classification is a grading system for joint cartilage breakdown. It is divided into four grades by MRI, typically using fat-saturated proton density sequences. This grading system was originally devised for arthroscopy, initially**

| | CHARACTERISTICS |
|---|---|
| GRADE 0 | • MRI: Homogenous and smooth delineation<br>• Arthroscopy: uniform thickness and intact surface<br>• Macroscopy: Normal cartilage |
| GRADE I | • MRI: Focal areas of hyperintensity with normal contour<br>• Arthroscopy: softening or swelling of cartilage<br>• Macroscopy: Focal thickening |
| GRADE II | • MRI: Blister-like swelling/fraying of articular cartilage extending to surface<br>• Arthroscopy: fragmentation and fissuring within soft areas of articular cartilage<br>• Macroscopy: Superficial defect(s), less than 50% |
| GRADE III | • MRI: Partial-thickness cartilage loss with focal ulceration<br>• Arthroscopy: partial thickness cartilage loss with fibrillation ("crab-meat appearance")<br>• Macroscopy: Deep defect(s) more than 50% |
| GRADE IV | • MRI: Exposed subchondral bone<br>• Arthroscopy: cartilage destruction with exposed subchondral bone<br>• Macroscopy: Full thickness defect(s) |

**Table 3: Advantages and disadvantages of OCA vs MACI techniques used for the treatment of chondral defects ≥ 2 cm².**

| | OCA | MACI |
|---|---|---|
| ADVANTAGES | • Mature hyaline cartilage<br>• Immediate structural support<br>• Bone to bone healing | • Availability<br>• Patellar defects<br>• Uncontained defects |
| DISADVANTAGES | • Donors availability<br>• Logistics and cost | • Osteochondral defects<br>• Two-staged procedure<br>• Complex cellular processing<br>• High cost<br>• Long recovery |

is an issue (15) that can lead to an onset of joint pain or patellofemoral impairment over time in some patients. Another disadvantage is that the donor site areas are filled with fibrous tissue, which has inferior biomechanical properties compared to hyaline mature cartilage (16). The best results of mosaicplasty are obtained on the femoral condyles compared to the tibial plateau or the patella (17) (Figure 3).

### 3.4. Regenerative biological therapies

### ACI/MACI)

The Autologous Chondrocyte Implantation (ACI) technique is mainly indicated in ≥ 2 cm² injuries, well aligned knees of young and active individuals and aim to provide the potential for hyaline cartilage generation. The ACI technique takes place in two stages. The first procedure is performed arthroscopically to harvest between 200 and 300 milligrams cartilage from a "non-essential" area, the intercondylar notch or the superior ridge of the medial or lateral condyles. The chondrocytes are isolated from the matrix and are grown in vitro in a laboratory for approximatively four to six weeks. The second-stage operation is an open procedure in which the chondrocytes are implanted on the damaged area. If the later application of the cells is on a matrix that adheres to the subchondral bone, the procedure is called Matrix-Induced Autologous Chondrocyte Implantation (MACI). The matrix can then be sutured to healthy cartilage or sealed with fibrin (18).

The MACI technique has the advantage of preserving the subchondral bone and generating hyaline cartilage (does not repair subchondral bone).

Disadvantages of MACI technique is the cost of MACI scaffold, two stage procedure, and prolonged rehabilitation, between 12 and 18 months, given slower graft maturation process. In case of deep osteochondral injuries, Brittberg et al. (19) proposed the ACI "sandwich" technique: a procedure that requires impaction bone grafting of the lesion and two collagen membranes to separately secure the bone graft and cultured chondrocytes. The first type I/III collagen bilayer membrane is positioned over the bone graft and secured to the defect with fibrin glue and sutures. A second membrane is then sutured to the articular surface overlying the first collagen membrane, and the chondrocytes are injected between the two membranes. Another new surgical technique is the high-density autologous chondrocyte implantation (HD-ACI), with an increase in the cell density (5 million cells per cm2) when compared to MACI (1 million cells per cm2), which could potentially improve the defect fill (18).

Rehabilitation should be progressive and dependant on the stability of our repair. Recent studies have shown that patients undergoing MACI may experience the same improvement regardless of the rehabilitation protocol as long as they

adhere to 6 weeks of progressive weight-bearing. No differences were seen in failure rates when compared to more conservative protocols of 8 to 12 weeks until full weight-bearing without protection (20).

### 3.5. Fresh osteochondral allograft (OCA)

Fresh OCA is based on mosaicplasty principles (the term "OAT" can involve both techniques: osteochondral autograft or allograft transfer), but differs in the use of allograft tissue, with the advantage of not adding morbidity for the patient as it is not an autologous (own) tissue. The term "OAT" can involve both techniques: osteochondral autograft or allograft augmentation. Fresh osteochondral allografts are reserved for osteochondral injuries greater than 2 $cm^2$ because of the difficulty to obtain these grafts.

Fresh OCA can be obtained from deceased donors and harvested from weight-bearing areas and anatomical zones identical to the injury location matching shape, size, depth and curvature.

This technique requires only one stage surgery, unlike ACI/MACI, and it has the advantage of providing immediate living hyaline cartilage and a faster bone to bone integration. The graft must be kept fresh in serum at 4º C for maximum 15 to 28 days after extraction. Cryopreserved allografts at -80º have few viable cells, which affects the recovery of cartilaginous morphology and are therefore not suitable for this technique. Challenges associated with OCA transplantation include allograft storage and size matching, tissue availability, the possibility of immunologic graft response, and a demanding surgical technique. Limited tissue availability of donors and grafts makes the procedure more expensive (21). Sports reintegration takes 9 to 12 months, especially when there are other associated injuries to repair, but overall the time for return-to-sports is less than ACI/MACI. Fresh OCA can be used for osteochondral defects in unusual locations, such as the femoral trochlea or the patella, but there are locations in which this technique is more difficult to apply, such as the tibial plateau (21).

Multiple studies with fresh OCA show good results in the long term, especially for femoral condyle and trochlea, osteochondritis dissecans and patients younger than 50 years old. The worst results are reported in lesions > 8 cm2, at the level of the patella and tibia, in bipolar lesions, in diffused arthropathy or in fracture´s sequelae (22, 23). (Table 3).

### 3.6. Platelet-rich plasma (PRP) coated mesh

The biological mesh shares similarities with ACI/MACI and OCA techniques, but it has inherent advantages: doesn´t require two surgeries and it remains fresh for the surgery since preparation. This relatively new technique is recommended for full-thickness chondral defects with 1.2 x 0.5 to 2.5 x 2 cm and has been tested in both knee and ankle.

This procedure consists of a combination of arthroscopy and mini-open arthrotomy. The samples of healthy hyaline cartilage from defect edges are obtained using a curette. Care is taken to create a perpendicular or vertical rim on the cartilage defect, so that it may better contain the autologous matrix. The cartilage samples are minced in the back table, cartilage chips were mixed with PRP, which then acted as a framework or scaffold containing all the signalling molecules (Figure 4).

The liquid-to-gel composition of the PRP are rich in growth factors and cytokines which are important in promoting bone healing. The free signalling molecules initiate the signalling cascade of their transduction pathways leading to expansion, viability and proliferation of many cell types, including chondrocytes, synoviocytes and tenocytes. (24).

In 2015 a study (24) reported the outcomes two cases of patients with knee osteochondral lesions (KOL) treated with one-step surgical procedure consisting of an autologous-based matrix composed of healthy hyaline cartilage chips, mixed plasma poor-rich in platelets clot, and intra-articular injection of plasma rich in growth factors (PRGF). The authors reported return to playing soccer at preinjury level, excellent knee function, and excellent defect filling with cartilage of similar signal and absence of significant bone edema on MRI. Most importantly, a second-look arthroscopy evidenced a surprisingly similar appearance and consistency on palpation of the newly formed cartilage compared to surrounding healthy articular cartilage (24). To assess the cartilage repair, a subsequent study analysed patient with full-thickness cartilage defect (8 mm diameter) undergoing this novel cartilage restoration surgical technique. The novel treatment enhanced chondrogenesis and regenerated hyaline cartilage at 6 months with nearly normal macroscopic ICRS assessment.

Complete integration to border zone in macro and microscopic evaluation was observed. Histological analysis showed equivalent structure to mature cartilage tissue in the defect and a collagen expression pattern in the newly formed cartilage similar to that found in adjacent healthy articular cartilage. This novel autologous-made matrix provided excellent clinical, functional, and MRI-based (cartilage repair quality and quantity) outcomes in young, active individuals with full-thickness cartilage or osteochondral defects (25).

This procedure seems an excellent alternative for cartilage injuries, as it can be performed in very active, young individuals. It can be performed as a single stage surgery, is cost effective, has no intolerance or rejection reactions, and

has shown histological and immunohistochemical similarities to healthy articular cartilage in animal studies (25).

### 3.7. Bone Marrow Aspirate Concentrate (BMAC) therapy

Bone marrow aspirate concentrate (BMAC) therapy can be applied to treat several osteo-articular pathologies. BMAC is a concentrate of mesenchymal stem cells (MSC) obtained from a patient's own bone marrow. BMAC are obtained through density gradient centrifugation of bone marrow aspirate harvested from both posterior iliac crests (26). MSC are multipotent cells that exhibit self-renewal abilities and capacity to differentiate into chondrocytes, adipocytes, and osteocytes. Recent experimental results point towards paracrine effects as the underlying mechanism of action behind MSC (27). Additionally, BMAC contains hematopoietic stem cells, platelets, growth factors, cytokines and chemokines (28). Growth factors also initiate stem cell migration to the injury site. Moreover, BMAC possess anti-inflammatory and angiogenic trophic effects enhancing cartilage repair.

Therapeutic capabilities of BMAC have been traditionally related to concentration of MSC defined as total stromal progenitor counts per volume unit (CFU-F/mL) with previously clinically effective doses of 1500 to 9000 CFU-F/mL (29). Cugat et. al reported 3000 CFU-F/mL consistently regardless of BM volume used (60mL, 90mL or 120 mL). Another parameter associated with BMAC's healing potential is the number of CFU-F per total nucleated cells which ranges from 25 to 39 CFU-F/ 106 TNC. In the same study by Cugat et al. they noticed processing 60 mL of BM resulted in statistically significant lower total cellular doses in BMAC than those found when processing 90 to 120 mL; however, increasing BM processed from 90 to 120 mL did not statistically change the total cellular doses in BMAC (30).

The use of BMAC in arthroscopic treatment represents an improvement on the currently available techniques for cartilage repair as a single-stage procedure. The intra-articular application has resulted in pain reduction, functional impairment and/or tissue regeneration as demonstrated by many studies. Centeno et. al published a randomized cross-over trial of high-dose BMAC injected versus physical therapy showing excellent results compared with control (31). Gobbi et al. reported BMAC with one step implantation of mesenchymal stem cell can be a viable alternative in the treatment of grade IV chondral lesions of the knee (32). Repair of chondral injury using a hyaluronic acid-based scaffold with activated BMAC (HA-BMAC) provided better clinical outcomes and more durable cartilage repair at medium-term follow-up when compared with microfracture. Repair of full-thickness cartilage injury in the knee with a HA-BMAC provided good to excellent clinical outcomes at long-term follow-up in the treatment of small to large lesions. Assessment of clinical effectiveness of BMAC based on available published literature shows that the evidence is highest for knee osteoarthritis with level II evidence based on relevant systematic reviews, randomized controlled trials, and nonrandomized studies. There is level III evidence for knee cartilage conditions (33).

## 4. Conclusions and future directions

Most of the aforementioned cartilage restoration or repair techniques have shown clinical improvements in the symptomatology of the patients in the short to mid-term. Long-term results are less promising for many of these procedures given the difficulty of conducting long-term randomised comparative studies. There is not enough published evidence in literature to choose one technique over another for all situations and injuries.

The treatment goal is to choose the most appropriate technique for each individual patient: a treatment "a la carte". In athletes, especially in professional athletes, it is necessary to take into account the time of return-to-competitive sports for each technique and not to over-treat these injuries. The repair of focal cartilage injuries requires an accurate diagnosis and a surgical technique indication proportional to the injury and symptoms, and should be adapted to each athlete.

The future of cartilage repair must be based on an accurate diagnosis and more precise imaging modalities that will allow for an early diagnosis and treatment follow-up. Cell therapy and tissue engineering, as well as 3D printing of cells and matrix, will play a very important role in the forthcoming years. A current challenge is finding mechanical and biological solutions that mimic the native cartilage and adapt to the joint environment, while avoiding early degradation.

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