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SPORTS & ARTHROSCOPY

Current trends in the treatment of focal cartilage lesions: a comprehensive review

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- Focal cartilage lesions refer to localized damage or defects in the cartilage covering joint surfaces, often resulting from trauma, wear and tear or underlying joint conditions. These lesions can lead to pain, impaired joint function and, if left untreated, may contribute to the development of degenerative joint diseases.
- Challenges in treatment of focal cartilage lesion are mainly due to limited intrinsic healing capacity, difficulty in early detection of lesions and variability in symptoms make timely intervention tricky.
- Conservative treatments varies from addressing symptoms using physical therapy, corticosteroid injections and viscosupplementation, to regenerative attempts such as in platelet-rich plasma and mesenchymal stem cells therapy. These modalities provide a limited duration of improvement and are commonly used to delay more aggressive treatment.
- Traditional surgery options are mainly summed up by microfractures (MFX) for smaller lesions, osteochondral autograft transfer, osteochondral allograft transfer (OCA) and autologous matrix-induced chondrogenesis for moderate-to-large lesions. Cellular approaches encompass autologous chondrocyte implantation (ACI), which involve targeted transplantation of chondrocytes.
- Current research is concentrating on cell-based surgical approaches utilizing advanced biomaterials for both scaffold and scaffold-free implants. While gene therapy and tissue engineering approaches aim to optimize chondrocyte proliferation and differentiation for improved quality of the transplanted biomaterial and patient's outcomes.

Keywords: focal chondral lesions; osteochondral autograft/allograft transfer; autologous matrix-induced chondrogenesis; autologous chondrocyte implantation; cell-based surgical treatment

Introduction

Recent history of articular cartilage treatment

In 1743, the renowned anatomist John Hunter stated a negative notice, which remained principal statement in cartilage repair for the coming 200 years, which is: 'cartilage injury is a troublesome thing and once injured is seldom repaired' (1).

In the middle of the 20th century, a few popular procedures, such as the pioneering work of Pridie on subchondral drilling in 1959 (2) and Johnson on abrasion arthroplasty in 1986, were developed (3) and have been in practice since then. J Richard Steadman developed in the early 80s the microfracture concept and he carried out the technique refining using horses

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EFORT Open Reviews (2025) **10** 203–212
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as an animal model (4). The main disadvantage of these techniques was that they resulted in largely undesirable fibrous to fibrocartilaginous tissue (5).

Motivated by the fact that the total joint replacement is not suitable for young individuals, the physician William Green and collaborators in 1977 performed seminal experiments using decalcified bone as scaffold for cell transplantation and rabbit as animal models to investigate the reparative potential of autologous and homologous chondrocyte transplantation (6). The team concluded that articular chondrocytes exhibited several intrinsic properties, making them a key to repair the cartilage tissue. Green's work is considered 'revolutionary' and it marked the birth of the field of tissue engineering.

Between 1977 and 1994, researchers carried out many preclinical trials *in vitro* and in animals. When introducing new treatment option into clinical settings, suitable animal models are pivotal in closing the gap between *in vitro* experiments and the in-human clinical trials (7).

The result of the first autologous chondrocyte transplantation (ACI) using a periosteal flap for an in-human clinical trial was published in 1994 by Brittberg and colleagues (8).

Etiologies of focal cartilage lesions

Focal lesions in the articular cartilage are mainly caused by trauma to the joint and represent major risk factor for rapid cartilage degeneration leading to symptomatic osteoarthritis (9). There are often ligamentous or meniscal deficiencies associated (10).

Osteochondritis dissecans is a different entity of articular cartilage lesion, most commonly found in young adults with high athletic activities (11). It is more of a subchondral bone disease with aseptic necrosis of the subchondral bone lamina and detachment of the overlaying cartilage (12).

Epidemiology

Articular cartilage injuries are observed in 60–66% of knees undergoing arthroscopy, with a median patient age ranging from 30 to 39 years (13, 14). Focal full-thickness chondral defects have a prevalence ranging from 4.2–6.2% among all patients undergoing knee arthroscopy, and they may affect up to 36% of athletes (15).

These focal articular cartilage defects can significantly impact patients' lives and have been demonstrated to impair quality of life to a degree comparable to individuals with severe osteoarthritis (16).

The burden of chronic disease accounts for over a million years of healthy life lost for middle-aged and older population (17). Such alarming numbers in the face of an aging population worldwide should be used to work toward improving disease prevention and treatment modalities. Disability-adjusted life years (DALYs) trends changes should continue to be monitored to optimize patient reported outcomes and quality of life.

Treatments

Cartilage lesions treatment as an unmet medical need

The avascular and unenervated qualities of the articular cartilage might be responsible for the poor auto repair and healing of this tissue (18) (Fig. 1). In addition, this makes it hard for most graft material to integrate with the native cartilage and/or the subchondral bone.

Treatment aims to alleviate symptoms, restore activity and prevent further damage, focusing on the patient's best interests. The current treatment modalities vary from conservative to minimally invasive surgery, to osteotomy and to joint replacement or fusion.

Conservative treatment improves symptoms, but it is not curative (19). The use of analgesics and oral chondroprotectors remains limited in their efficacy. Intraarticular injections with corticosteroids (CSs), viscosupplementation or platelet-rich plasma (PRP) are commonly used to delay more aggressive treatment (19, 20). Lifestyle modifications and auxiliary methods might be proposed, including weight loss, activity modifications, crutches use, bracing and physical therapy. However, there has been no solid evidence of structural improvement with such modalities (21).

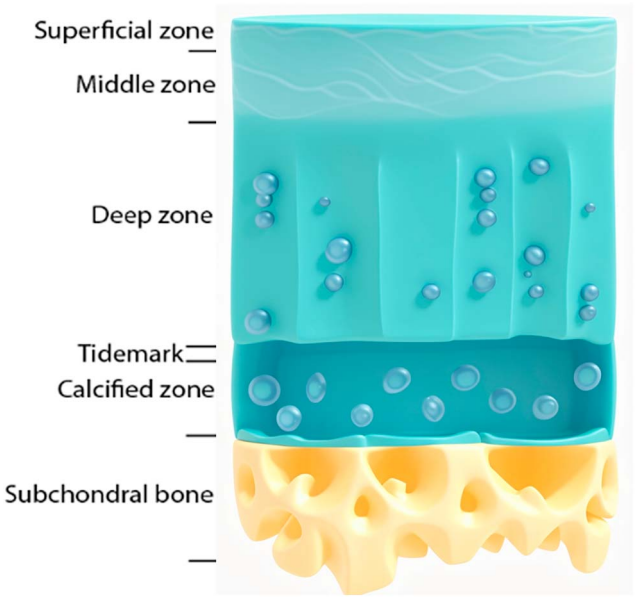

Figure 1

Hyaline cartilage cross-section showing cartilage layers and tissue organization.

EFORT Open Reviews (2025) **10** 203–212
https://doi.org/10.1530/EOR-2024-0083

Surgical options for focal chondral lesions aim to promote healing and alleviate symptoms. Many different options are being used, such as microfractures (MFX), chondral abrasion, osteochondral autograft transfer (OAT), osteochondral allograft transplantation (OCA) and autologous chondrocyte implantation with or without associated membrane (ACI/MACI).

The selection of surgical intervention depends on factors such as lesion size, location and patient characteristics, aiming to restore joint function and mitigate long-term joint degeneration. In addition, global treatment of articular cartilage lesions is shaped by cultural, economic and religious influences. Economic factors may prioritize cost-effective options, while surgeon training and cultural norms can also impact decisions. Religious constraints may affect particular tissue type usage in specific populations (22, 23).

Fundamental research over the past 30 years tried tirelessly to recreate the structural and biomechanical features of hyaline cartilage through tissue engineering and cell modulation. The main idea was to offer a long-lasting solution for the patient, which is the repair of the chondral defects, and this has been extensively studied around the world (24, 25, 26). However, to date, available cartilage regeneration techniques only produce fibrocartilage or fibrohyaline cartilage with poor integrative capacities and higher friability, which is less than optimal as fibrocartilage does not have the same physical and chemical properties as the native articular cartilage and is less resistant to axial and sheer forces that subject the joint; thus, it tends to delaminate after two years (27, 28). Regenerating cartilage through cell culture remains challenging, particularly with respect to sourcing cells, their availability, chondrogenic capabilities and the lasting viability of the graft, following implantation at the injury site (24, 29, 30).

Conservative treatments

CS injections

Intraarticular CS injections are frequently administered before referral to secondary care in an attempt to manage symptoms and postpone surgery. While these injections seem to alleviate pain in patients for a short period, they come with side effects and do not provide sustained symptomatic relief beyond six weeks (31, 32). This will have no effect on structural damage.

A 2021 meta-analysis of randomized-controlled trials by Donovan *et al.* demonstrated that CS injections did not provide superior symptom relief compared to other injectables, including placebo, at 3 months and beyond (33).

Viscosupplementation

Viscosupplementation, a therapeutic approach involving the injection of hyaluronic acid (HA) into affected joints, aims to replenish the natural viscoelastic properties of synovial fluid and have anti-inflammatory properties (34). Safali *et al.* recently conducted a study involving 128 patients, which showed that a triple low-dose injection (30 mg) of HA is more effective in improving WOMAC, VAS and Lequesne Index scores than a single high-dose injection (60 mg) (35).

Contraindications for HA injection mirror those of other injection therapies, with typically mild, local and transient adverse events. Viscosupplementation proves effective for pain reduction and enhanced functionality (36).

PRP

PRP is a concentrated form of platelets obtained through centrifugation of whole blood. It has a higher platelet concentration compared to regular whole blood and contains various growth factors. PRP has been shown to reduce inflammation, enhance angiogenesis and stimulate the proliferation and differentiation of chondrocytes by releasing a plethora of cytokines, chemokines and growth factors. These properties contribute to the healing process of bone and cartilage injuries (37, 38). In a meta-analysis of 34 randomized-controlled trials, Filardo *et al.* in 2021 showed that PRP injections are more effective than CS and HA injections, with significant benefits after 6–12 months, although the improvement remains partial and based on a low level of evidence (39).

Mesenchymal stem cells (MSCs)

The use of MSCs for articular cartilage repair noted a remarkable increase. However, before them being accepted as a cell source, it is necessary to identify bioactive components that enable them to trigger orderly and durable cartilage tissue repair.

MSCs used for cartilage repair are classified on the type and differentiation stage of cells present in the graft as follows: cell preparation containing i) unprocessed naive MSCs together with contaminant cells present in the native tissues, ii) processed naive MSCs, iii) expanded MSCs, and iv) differentiated MSCs after chondrogenic culture (40).

Wide variety of cell sources based on the use of stem and progenitor cells are considered to produce chondrocytes. MSCs originating from bone marrow, umbilical cord blood, adipose tissue or synovial membrane are used due to their immunomodulatory properties.

Efficacy has been demonstrated in repairing cartilage damage. However, the evidence regarding the effectiveness of intraarticular MSCs on both clinical outcomes and cartilage repair is still limited. While high-quality studies support the potential of MSC therapy, further refinement of the methodology is necessary to justify its routine clinical use (41).

In a recent randomized-controlled trial involving 69 patients, Saw *et al.* investigated the effects of

EFORT Open Reviews (2025) **10** 203–212
https://doi.org/10.1530/EOR-2024-0083

arthroscopic marrow stimulation with subchondral drilling into large chondral defects of the knee, followed by postoperative intraarticular injections of MSCs combined with HA. The study found that this treatment approach is safe and results in significant improvements in both clinical and radiological scores when compared to the combination of HA injections and physiotherapy (42).

Traditional surgical approaches

Bone marrow stimulation by microfracture (MFX)

In the 1990s, Steadman introduced microfracture (MFX), which remains the most performed technique for cartilage repair due to its technical simplicity and minimal patient morbidity (43).

MFXs are created by perforating the subchondral bone at the chondral lesion site to allow releasing MSCs (Fig. 2). Under this stimulation, MSCs will differentiate and generate locally new tissue to repair the induced perforations. Microfracture is considered the standard treatment for focal lesions smaller than 2 cm^2 (44). MFX has proved its efficacy in elevating patient's symptoms with good clinical outcome for a period time of 2 years in average, and up to 5 years in some cases (44). However, after this period, clinical results decline significantly. However, microfracture technique can only generate fibrocartilage, which lacks long-term stability (45). Others brought to light the importance of drilling diameter in this technique and its impact on bone and cartilage healing. Zedde *et al.* showed in an animal study in 2016 that the use of smaller-diameter (known as nanofractures) and deeper subchondral bone perforation for MSC stimulation is an effective technique with less trabecular fragmentation and compaction when compared to MFX (46). In a recent meta-analysis of 14 randomized-controlled trials, Abraamyan *et al.* demonstrated that cell-based surgical treatments, such as autologous chondrocyte implantation (ACI) and matrix-assisted autologous chondrocyte implantation (MACI), resulted in statistically and clinically significant improvements in the Knee Injury and Osteoarthritis Outcome Score (KOOS) sport scores compared to MFX (47).

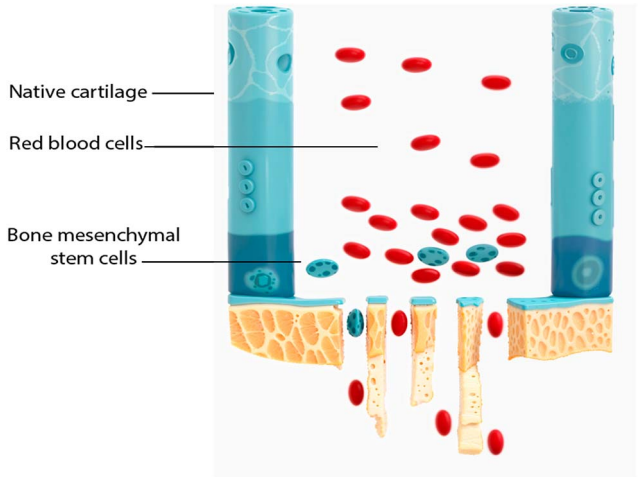

Figure 2

Microfractures.

OAT

This one-stage surgical technique is performed by transferring cylindric osteochondral autografts from a low weight-bearing area of the joint toward the lesion site (48).

It is best described as robbing Peter to pay Paul as donor site morbidity varies based on the harvest size and number. However, it remains commonly used especially for grafting lesions up to 3 cm^2. An important aspect to respect is the curvature and thickness restoration of the recipient site to be able to obtain good distribution of stresses (49). In a study of 142 patients, Ollat *et al.* reported that this technique is reliable, yielding significantly improved functional scores, high patient satisfaction and a complication rate of 13% at a minimum 5-year follow-up (50). Similarly, in a study of 152 patients, Emre *et al.* demonstrated excellent results in restoring joint function, with no complications observed during a short-term follow-up of 18 months (51).

Autologous minced cartilage repair

This technique is another one-stage surgical procedure. In this procedure, small amounts of cartilage are harvested from a non-weight-bearing area of the joint and minced into tiny fragments. These minced cartilage fragments are then transferred to the lesion site. Autologous minced cartilage repair is suitable for small-to-moderate cartilage lesions (<2–3 cm^2) (42). It differs from OAT in that it involves transferring minced cartilage instead of cylindrical osteochondral autografts. At 12 and 24 months, clinical outcomes showed nearly comparable results to commonly used cartilage repair techniques, such as ACI, MACI and MFX. This method appears to be a promising alternative to standard ACI/MACI, especially in cases where these procedures are not available (49). Runer *et al.* also demonstrated that 34 consecutive patients treated with a one-stage autologous minced cartilage repair had good postoperative outcomes and low reoperation rates after a minimum 5-year follow-up (52).

Osteochondral allograft transfer (OCA)

Coming from a deceased donor, these grafts offer the largest surface possible to treat large (>2–3 cm^2), full thickness (grade III or IV) chondral or osteochondral lesions as a primary surgical management (53).

However, as the graft needs to be relatively fresh, less than 28 days, the availability and the suitability of it with the recipient might be a challenge. Even though OCA might

EFORT Open Reviews (2025) **10** 203–212
https://doi.org/10.1530/EOR-2024-0083

have osteointegration in the host joint, cartilage lateral integration remains lacking (54). The use of OCA has increased in recent years, as medium- and long-term studies have demonstrated good outcomes and graft survivorship. In a systematic review of 19 studies, Familiari *et al.* reported a 5-year survival rate of 86.7% (range: 64.1–100.0%) and a 10-year survival rate of 78.7% (range: 39.0–93.0%) (55).

Autologous matrix-induced chondrogenesis (AMIC®)

AMIC® is a combined method that incorporates marrow stimulation and the addition of a solid acellular type I/III collagen membrane into cartilage defects following microfracture treatment. It is important to distinguish AMIC® from MACI, which stands for 'matrix-induced ACI' (56). One randomized-controlled study showed promising results with long-term pain relief using AMIC® and AMIC®+ (Augmented AMIC® with bone marrow aspirate concentrate) and that they are effective treatments for focal chondral lesions, with beneficial effect lasting up to 9 years (57). Volz *et al.* in 2017 showed that AMIC® is an effective cartilage repair procedure in the knee, with significantly better results than the MFX at 5 years (58). A network meta-analysis by Migliorini *et al.* in 2021, encompassing 36 studies, demonstrated that AMIC achieved better Lysholm and Tegner scores, along with the lowest failure rates, compared to other surgical techniques (MFX, OAT, ACI and MACI) at a median follow-up of 36 months (55).

Cell-based surgical treatment

The major challenge of tissue engineering methods to treat cartilage defect is to produce a hyaline cartilage tissue or a tissue with similar histological and biomechanical characteristics as the articular cartilage, with the capacity to integrate into the native environment (subchondral bone and surrounding cartilage). However, the available methods lead mainly to fibrocartilage tissue.

Autologous chondrocytes implantation (ACI)

Cellular therapy based on autologous chondrocytes implantation has emerged as the most promising therapeutic option for restoring hyaline cartilage and represents more durable solution (5). ACI has been used for over 20 years and it has been constantly evolving. Despite remarkable advances in tissue engineering, the produced cartilage tissues obtained from mature chondrocyte do not possess the characteristics of native cartilage (25). They are made-up of more fibrocartilaginous extracellular matrix, which differs histologically and biomechanically from hyaline cartilage. These grafts can hardly be produced from the cells from patients over 55 years old (5). Recently, Colombini *et al.*, in a systematic review, demonstrated the mid- and-long-term effectiveness of ACI and matrix-assisted autologous chondrocyte implantation (MACI) in treating knee cartilage defects in the presence of osteoarthritis, with an improvement up to 11 years with ACI and up to 15 years with MACI, with a failure rate of about 10% up to 11 years (59).

In brief, the first ACI generation involves an *in vivo* regeneration of cartilage after cell transplantation. These autologous chondrocytes were cultured in a monolayer fashion and transplanted under a periosteal patch (8). This technique fell out of favor due to hypertrophic tissue regeneration due to the abundance of collagen X in the periosteum.

The second generation uses a similar culture method; however, it uses a different external scaffold (porcine or synthetic collagen membrane) to support hyaline matrix production by the chondrocytes (Fig. 3). The use of second-generation ACI results in superior long-term clinical outcomes compared to first-generation ACI (60).

The third-generation ACI (matrix-autologous chondrocyte implantation or MACI) improved the *in vitro* cartilage production using suspension of chondrocytes culture in a collagen scaffold (Fig. 4). This method targeted larger cartilage lesion (>3 cm^2). Whereas several products have been developed using third-generation ACI, none of them offers long-term solution to treat cartilage damage, especially when regarding the lateral integration with the surrounding cartilage and graft delamination. In most analyses, the incremental cost-effectiveness ratios for ACI compared with MFX appear to be within a range usually considered acceptable. A recent study showed that third-generation ACI achieves good-to-excellent clinical outcomes after 2 years in the majority of 21 treated patients, with a failure rate of 19% (61). It is particularly effective for athletic patients compared to non-athletic

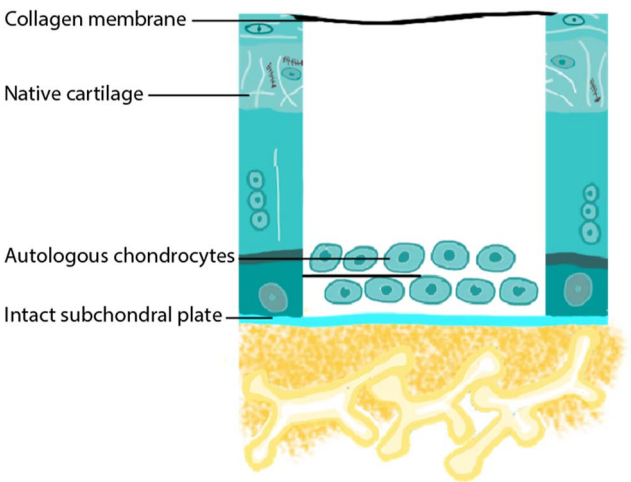

Figure 3

Second-generation ACI.

EFORT Open Reviews (2025) **10** 203–212
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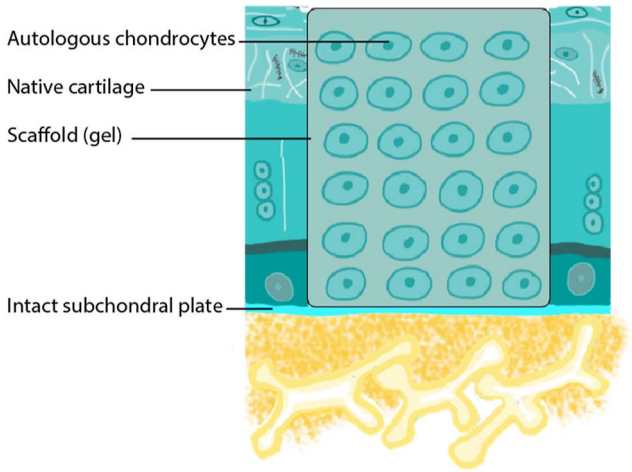

Figure 4

Third-generation ACI (matrix-induced ACI, 'MACI').

ones. Research is needed into long-term results of new forms of ACI (62).

The fourth-generation ACI involves one-stage procedures, where one type of different cell lines with potential of chondrogenesis is implanted in various ways (Fig. 5). This may include direct isolation of chondrocytes mixed with autologous or allogeneic MSCs seeded in a matrix (59).

Therapies using chondrocytes extracted from patient's cartilage have two main limitations, which are the quantity and the quality of the extracted cells. First, a significant amount of cartilage (usually 100–200 mg of cartilage) needs to be harvested to obtain a sufficient population of chondrocytes for cell expansion. This might increase the risk of secondary lesions for the patients even in a non-weight-bearing area. Second, cell culture expansion is necessary, especially to treat large lesions, but extensive expansion leads to chondrocyte differentiation into fibroblast-like cells, hence, producing mostly a fibrocartilage tissue (63). This has been shown to be particularly challenging among patients older than 55 years. Third, cell differentiation to produce hyaline cartilage with the ability to integrate in the native environment is difficult to achieve. Most of the produced cartilage tissue is not of hyaline nature and is not able to fully integrate in the existing environment.

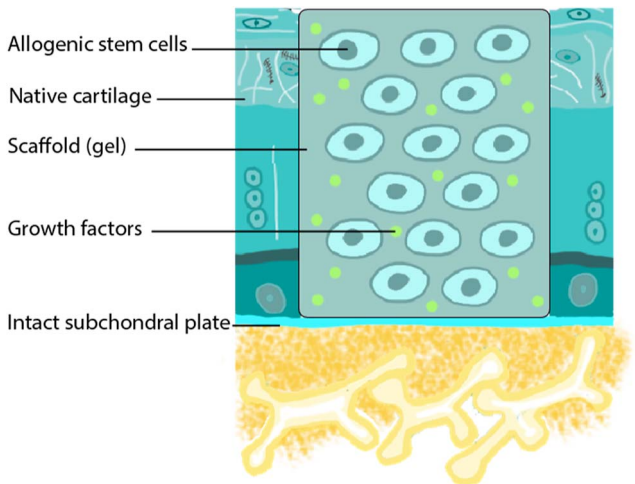

Figure 5

Fourth-generation ACI.

Future therapy

To overcome the limited numbers of harvested cells, researchers have proposed collecting cartilage from the nasal septum cartilage. However, the risk remains high in creating secondary complications, such as septal perforation or infection. Chondrocytes extracted from nasal cartilage have been shown to be more efficient to produce hyaline cartilage than knee chondrocytes (64). However, after extensive cell amplification, chondrocytes tend to dedifferentiate into fibroblast-like cells, producing fibrocartilage tissue with less or no expression of collagen II specific of hyaline cartilage but enriched in collagen type I, specific of fibrocartilage. The biomechanical properties are different according to the composition of the cartilage tissue (9, 45, 65).

A remarkable advancement in autologous chondrocyte implantation is matrix-associated ACI with spheroids. Chondrocytes undergo monolayer expansion, followed by three-dimensional culture to form self-adhesive spheroids with their extracellular matrix. Unlike other ACI methods, this approach eliminates the need for exogenous matrix, glue or sutures. Moreover, it allows for arthroscopic or minimally invasive application. Studies with follow-ups ranging from 1 to 5 years have shown promising results for ACI with spheroids (66). However, this method needs a large cartilage harvest and up to 500 mL of patient's blood for culture medium. In addition, it remains limited in the number of expanded chondrocytes before losing their chondrogenesis abilities.

A new scaffold-free product (Cartibeads), currently in clinical trials, result from a novel culture method of mature chondrocytes in both two-dimensional and three-dimensional conditions. This standardized protocol produces high-quality hyaline cartilage tissue from dedifferentiated chondrocytes, requiring only a small biopsy (~30 mg) from a non-weight-bearing zone of the affected joint. Through a patented three-step process, Cartibeads reverse dedifferentiation and redifferentiate chondrocytes, regardless of patient age or osteoarthritic status. They treat focal chondral lesions by completing missing surface areas and integrating into surrounding tissue, offering a promising solution with reduced site morbidity (67).

EFORT Open Reviews (2025) **10** 203–212
https://doi.org/10.1530/EOR-2024-0083

Biodegradable cartilage biomimetic hydrogels also show promise for treating cartilage lesions and tissue engineering by delivering cells *in vivo*. Noteworthy advantages include injectable delivery, controlled *in situ* polymerization, mechanical support and the potential for incorporating chondrogenic cells. Preclinical studies in various animal models have demonstrated excellent outcomes in osteochondral

Table 1 Summary of most used surgical strategies, indications, advantages and disadvantages.

Strategy	Target patients	Advantages	Disadvantages
Traditional surgical approaches			
Microfracture (MFX)	•Moderate symptoms •Small lesions (1.5 cm^2) •Grade III, IV	•Low cost •One stage	•Not for deep lesions (>10 mm) •Fibrocartilage with a tendency to degenerate over time •Less impact than Pridie drilling on biomechanics of underlying subchondral bone
Mosaicplasty	•Moderate symptoms •Moderate lesions (2–3 cm^2)	•One stage •No graft rejection	•Donor site morbidity •Joint surface congruency
Osteochondral allograft	•Moderate symptoms •Large lesions > 3 cm^2 •Grade III, IV	•One stage	•Fresh graft <28 days •Graft acceptance
AMIC	•Moderate symptoms •Moderate-to-large lesions (>2 cm^2)	•One stage •Readily available	•Fibrocartilage
Tissue engineering			
ACI			
ACI (I) – first generation	•Moderate symptoms •Moderate-to-large lesions (2–4 cm^2) •Grade III, IV	•Inexpensive	•Two stages •Two incisions •Hypertrophic graft effect •Periosteal patch needs suturing or gluing
ACI (II) – second generation	Same as ACI (I)	•One incision	•Tow stages •Collagen I/III membrane needs suturing or gluing •Expensive
ACI (III) – third generation/MACI	Same as ACI (I)	•One incision •No need for patches •Better control to cells distribution •Better management for osteochondral defects	•Two stages •Chondrocytes limited expansion capacity •Collecting more cell resources may damage the articular cartilage
ACI (IV)– fourth generation	Large lesions	•One stage	•Cell source availability •Fibrocartilage
Advanced transplantation techniques			
Nose-to-knee	•Moderate symptoms •Moderate-to-large lesions (2–4 cm^2)	•Better control of cells distribution •Fibrohyaline cartilage	•Nasal septum cartilage harvest
Spherox	•Moderate symptoms •Moderate-to-large lesions (2–4 cm^2)	•No need for patches •Better control of cells distribution	•Large cartilage harvest •Fibrohyaline cartilage •Little lateral integration •Maximal age 55 yo
Cartibeads	•Moderate symptoms •Moderate-to-large lesions (2–11 cm^2)	•Small cartilage harvest •Hyaline cartilage •No maximal age limits •Lateral and subchondral integration •No need for patches •Better control of cells distribution	•Two stages •Expensive •In clinical trial phase

AMIC, autologous matrix-induced chondrogenesis; ACI, autologous chondrocytes implantation; MACI, matrix-induced ACI.

EFORT Open Reviews (2025) **10** 203–212
https://doi.org/10.1530/EOR-2024-0083

defect repair, although human experience remains limited (68).

Table 1 is a summary of the above discussed therapies highlighting the advantages and limitations of each them, (Table 1).

Conclusion

Focal cartilage lesions represent a complex clinical scenario, necessitating a multifaceted approach involving both surgical and nonsurgical interventions. The massive variation of treatment methods indicates a real lack of a gold standard and predictable outcome. The ongoing pursuit of innovative therapies underscores the commitment to improving patient outcomes and addressing the challenges associated with these lesions. The future of these treatments will privilege a one-stage surgery with the least invasive methods and demonstrated long-term effect, all while optimizing therapy costs.

ICMJE Statement of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the work reported.

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