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Review

Surgical treatment of cartilage lesions in the knee: A narrative review

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ABSTRACT

Purpose: The treatment of cartilage injury is challenging owing to its low self-healing capacity. Here we describe a literature review of the current diagnostic methods, surgical treatment options, and techniques for knee cartilage injuries, including possible future treatments and augmentations.

Methods: Studies describing surgical techniques for knee cartilage injuries were searched and arbitrarily selected in PubMed. Possible future treatments and augmentations, growth factors, and cell-based treatments are also discussed.

Results: Surgical options for cartilage injury, such as microfracture, osteochondral autografts or allografts, and autologous chondrocyte implantation, are well-established methods with overall satisfactory short- and long-term outcomes. However, the limitations and disadvantages of these treatments, such as repair with fibrous cartilage, donor site morbidity, and two-step surgery, have raised concerns. Various surgical treatments or augmentations have been developed to overcome these limitations, including autologous matrix-induced chondrogenesis, bone marrow aspirate concentrate, particulate chondrocyte implantation, and particulate juvenile allograft chondrocytes, and promising short-to mid-term results have been reported. Additionally, numerous studies are underway on the augmentation of biological healing including growth factor and stem cell therapies.

Conclusions: Although treating cartilage injuries remains challenging, advancements have been made. It is advisable for surgeons and clinicians to update their surgical techniques and knowledge of cartilage repair and regeneration to better treat patients with knee cartilage injuries.

1. Introduction

Articular cartilage is an avascular tissue that is largely composed of abundant extracellular matrix with a low cellular density. Owing to its avascularity and low cellularity, articular cartilage has low self-healing capacity. In addition, the dense three-dimensional composition of extracellular matrix obstructs stem cell migration and prevents cartilage regeneration. Therefore, once the cartilage is injured, it is progressively lost, eventually resulting in joint osteoarthritis (OA).

Articular cartilage injuries are occasionally associated with knee injury. Articular cartilage injury is observed in 34–62% of knees during arthroscopy; however, the prevalence of cartilage injuries may vary depending on the definition and evaluation method [1–3]. In a systematic review, full-thickness cartilage defects were detected in 36% of athletes, although 14% of athletes had no obvious symptoms [4]. For the treatment of knee cartilage injuries, conservative treatment, such as non-steroidal anti-inflammatory drugs (NSAIDS) and intra-articular hyaluronic acid or steroid injections, can be provided to patients with mild symptoms and relatively small lesions. However, surgical treatment is often necessary in many cases owing to its low healing potential, and the optimal surgical treatment should be chosen based on the injury and patient background. Over the past decades, the surgical management of cartilaginous injuries has evolved. Therefore, it is important for surgeons and clinicians to update their knowledge of cartilage repair and regeneration as well as their surgical techniques.

This study aimed to review relevant literature and describe the current diagnostic methods, surgical treatment options, and techniques for knee cartilage injuries. In addition, possible future treatment options are discussed.

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2. Methods

The current study aimed to summarize and conduct a narrative review of the current surgical treatments for cartilage injuries. Studies describing surgical techniques for knee cartilage injuries were searched in PubMed and arbitrarily selected, primarily based on the current treatment concept. Since this was not a systematic review, it did not completely cover all related papers with strict inclusion criteria. The basic search strategy was to include reports on clinical outcomes regarding mainly traumatic rather than osteoarthritic cartilage injuries although some reports possibly include both conditions. For relatively established treatments, review papers, representative clinical studies, and reports were selected to cover the overall outcomes of each treatment. For possible future treatments and augmentations, topics related to growth factors and stem cells were selected. The selected papers were reviewed and included by the authors.

3. Basic science

Articular cartilage is composed of four highly structured zones: superficial, intermediate, deep, and calcified zones. In the superficial or tangential zone, type II collagen fibers are oriented tangentially to the surface and provide resistance to shear stress. In the middle or transitional zone, shear forces from the superficial layer transition to compressional forces in the cartilage. In the deep or radial zone, collagen fibers are attached vertically into the tidemark, and the load is distributed to resist compression. The calcified zone contains the tidemark, which is a basophilic line that demarcates the boundary between noncalcified and calcified cartilage. The subchondral and cancellous bones are located deep in the calcified zone. The chondrocyte phenotype varies across zones, from tangentially layered spindle cells in the superficial zone to round cells arranged in columns in the deep zones (Fig. 1). However, chondrocytes occupy only 2% of articular cartilage volume and are responsible for extracellular matrix (ECM) synthesis, turnover, and remodeling [5]. Chondrocytes are surrounded by abundant ECM, which is composed of a cross-linked network of type II collagen, proteoglycans, several other important collagens (VI, IX, X, XI, etc.), and non-collagenous proteins [6,7].

In cartilage injuries, owing to the lack of blood vessels and cells that can repair significant tissue defects, there is little to no self-repairing capacity [8,9]. Unlike injuries limited to cartilage, hemorrhage and fibrin clot formation occur in osteochondral injuries, activating the inflammatory response. This response induces growth factors and cytokines, including transforming growth factor (TGF-β) and PDGF, and stimulates vascular invasion and migration of undifferentiated cells into defects. Some mesenchymal cells differentiate into chondrocytes that synthesize ECM. The defect is filled with hyaline-like cartilage, which typically has a composition and structure intermediate between hyaline cartilage and fibrocartilage. However, because of the inferior mechanical properties of this repaired tissue, most deteriorate within a year or less, depending on the size and location of the cartilage lesions [9]. Therefore, treatment of cartilage injuries remains challenging.

4. Clinical features and evaluation

4.1. Location

According to a systematic review of cartilage defects in 931 athletes, cartilage defects were observed in the medial (n = 207, 22.2%) and lateral (n = 96, 10.3%) femoral condyles, patellae (n = 209, 22.4%), and trochlea (n = 118, 12.7%). In a review of 217 soccer players, cartilage defects were most frequently located in the medial (n = 103, 47.5%), lateral femoral condyles (n = 54, 24.9%), and trochlea (n = 20, 9%) [10].

4.2. Clinical examination

Pain is commonly the main symptom in patients with knee cartilage injury, although its location remains unclear. Therefore, clinicians should carefully assess when and how the pain occurs. Some patients complain of catching or crepitus. Joint effusion is often associated with cartilage injury and is a good indicator of unstable cartilage lesions.

The biomechanical conditions of the knee joint, such as knee laxity, alignment, and patellar tracking, should also be evaluated for patellofemoral (PF) cartilage injuries.

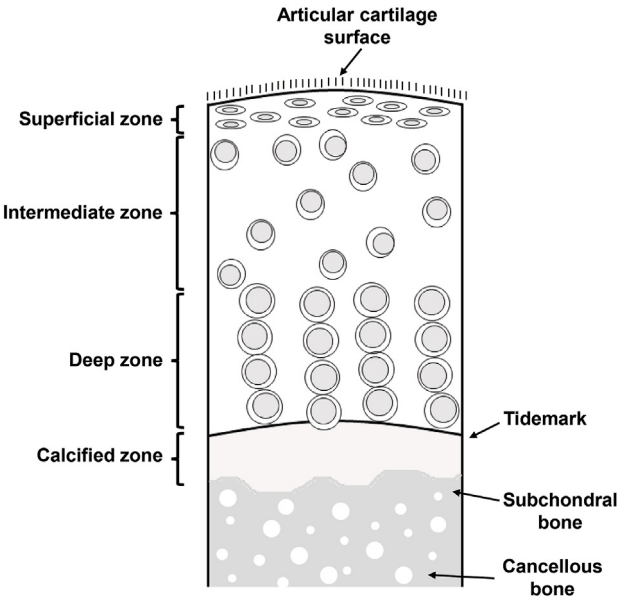

Fig. 1. Structure of articular cartilage.

4.3. Radiographic and magnetic resonance imaging evaluations

Standard standing anteroposterior and lateral and Rosenberg and long leg view radiographs are necessary to evaluate joint space narrowing, OA condition, and whole leg alignment. Axial view radiographs are necessary to evaluate patellar position and the presence of PF OA. If an osteochondral defect is suspected, computed tomography (CT) is recommended to precisely assess the location and size of the defect.

Magnetic resonance imaging (MRI) was used to evaluate cartilage injury. Meniscal condition needs to be carefully assessed using MRI. For an optimal cartilage repair environment, concomitant surgeries, such as ligament reconstruction, osteotomy, and patella-stabilizing surgeries, should be considered. For a large meniscal defect in the same compartment as the cartilage injury, a meniscal allograft may be required. Since allografts are not available in some countries, osteotomies can be performed to reduce loading on the repair site; however, long-term outcomes remain a concern. If any significant pathological condition is not addressed when repairing cartilage, it may adversely affect repair outcomes. Krych et al. retrospectively examined failed primary cartilage repair surgeries and found that the reasons for failure were untreated malalignment ($\geq 5^\circ$ of mechanical axis deviation) (56%), graft failure (27%), untreated meniscal deficiency (19%), and untreated instability (5%) [11].

The condition of the subchondral bone should be evaluated. Severe subchondral bone marrow edema after a prior marrow stimulation technique is a predictor of autologous chondrocyte implantation (ACI) graft failure [12]. Therefore, management of subchondral bone lesions may be necessary. Osteochondral plug transplantation is a treatment option for cartilage defects and osteonecrosis. If the defect is large, ACI combined with the sandwich technique is a viable option [13].

4.4. Imaging for evaluation of cartilage injury

MRI is the standard imaging method for diagnosis and subsequent postoperative monitoring. It is used to evaluate the morphological status

of cartilage defects, including the size and location of the defect, subchondral bone edema, and postoperative tissue repair [14].

4.4.1. Pre-surgery

For preoperative evaluation, MRI sequences, such as proton-density-weighted images and T2-weighted images, clearly depict the cartilage as an intermediate-signal intensity structure, in contrast to the hyperintense synovial fluid. Various fat suppression modes have also been used to evaluate bone marrow abnormalities, such as edema or subchondral cysts [15].

4.4.2. Post-surgery

Magnetic resonance observation of cartilage repair tissue (MOCART) is the most common scoring system used to evaluate cartilage repair tissue postoperatively. The score contains nine variables: the degree of defect repair and filling of the defect, integration into the border zone, surface of the repaired tissue, repaired tissue structure, repaired tissue signal intensity (on T2 fast-spin echo and T2 fat-suppression), subchondral lamina, subchondral bone, adhesions, and synovitis. T2 fast-spin echo is useful because of the high contrast between the cartilage and the adjacent synovial fluid for the detection of surface defects. Marlovits et al. reported that defect filling, subchondral bone, and repaired tissue structures had the best correlation with the visual analog scale (VAS) and KOOS [16]. Defect filling and subchondral bone are positively correlated with patient-related outcomes, including Lysholm and International Knee Documentation Committee (IKDC) scores [17]. The Henderson classification system is also frequently used to evaluate repaired sites. It consists of four variables: degree of defect filling, cartilage signal intensity, subchondral bone edema, and joint effusion. Several studies have also shown its correlation with clinical scores, such as ICRS and modified Cincinnati scores [18–20]. Both scoring systems were originally developed to evaluate the repair status after ACI but may be used to compare the outcomes of different surgical repair techniques [21].

5. Surgical treatments

5.1. Debridement/chondroplasty

Arthroscopic debridement is a technique used to remove loose cartilage flaps that cause mechanical symptoms and effusion to a stable end [22]. The goal of this technique is to relieve mechanical symptoms and inflammation and prevent cartilage lesion progression due to mechanical stress on an unstable flap. The advantages of this surgery are immediate weight bearing and a short recovery period because of its minimal invasiveness. It is a relatively inexpensive procedure that does not require remarkable preoperative planning or a staged procedure, similar to other cartilage repair procedures. However, a limitation of surgical debridement is that it cannot restore normal articular cartilage congruency because it only treats mechanical symptoms caused by the loosened cartilage flap.

5.2. Fixation of unstable osteochondral fragments or loose bodies

Unstable osteochondral fragments or loose bodies are occasionally observed in cases of PF instability or osteochondritis dissecans. If viable cartilage and bone are present in these osteochondral fragments, fixation of the fragments to the donor site should be considered. Cartilage fixation is ideal because it uses one's own cartilage, can be performed in a single step, and is inexpensive. Unfortunately, in the case of long-standing loose bodies, the cartilage may be of poor quality, resorbed, or enlarged, and may be difficult to fix to the donor site. Bioabsorbable pins and screws are often used to fix fragments with good clinical outcomes [23–25]. In addition, techniques using suture bridge fixation have been described [26,27]; however, the outcomes of this technique have yet to be reported.

5.3. Microfracture

Microfracture is a technique that was introduced in the 1980s to treat articular cartilage defects in the knee by accessing bone marrow cells deep within the subchondral surface to allow healing of total cartilage defects [28]. Microfractures are the treatment of choice for cartilage lesions <2 cm^2 with a surrounding margin of healthy cartilage [22]. Systematic reviews have shown clear improvements in knee function 24 months after microfracture; however, no conclusions regarding durability or treatment failure have been drawn after >5 years [29,30]. At an average follow-up of 7 years, 80% of patients rated improvement after microfracture, with patients aged <35 years showing the greatest improvement [31]. Microfracture treatment of full-thickness articular cartilage defects (3.4 ± 2.1 cm^2) was performed in those with a symptom duration of 43.4 ± 68.0 months. The failure rates ranged from 11 to 27% within 5 years, and from 6 to 32% at 10 years. Microfractures provide good function and pain relief in the mid-term, followed by mostly satisfactory clinical outcomes [32].

5.4. Osteochondral autograft transplantation/mosaicplasty

Osteochondral autograft transplantation (OAT) involves harvesting an osteochondral plug from the non-weight-bearing surface of the knee (usually the peripheral surface of the medial or lateral trochlea or intercondylar notch) and transferring it to a weight-bearing chondral lesion. The plug size is typically 6–10 mm; for larger defects, multiple plugs can be used (Fig. 2). Riboh et al. performed a meta-analysis showing that OAT most consistently reproduces hyaline-like tissue at the recipient site when compared with ACI and microfractures [33]. In addition, OAT showed a lower reoperation rate than microfractures [34]. The randomized controlled trial by Solheim et al. demonstrated that OAT resulted in a better clinical outcome than microfracture at short, medium, and long term (minimum 15 years) in articular cartilage defects from 2 to 5 cm^2 [35]Furthermore, in a large systematic review, Jones et al. found that the minimum clinically important difference (MCID) values for IKDC, Lysholm, and VAS pain scores were maintained for >10 years, demonstrating the durability of this surgical technique when patients were carefully selected [36]. Although OAT is best suited for relatively small cartilage lesions, a previous study showed that the postoperative outcomes of patients who underwent OAT for large osteonecrosis lesions

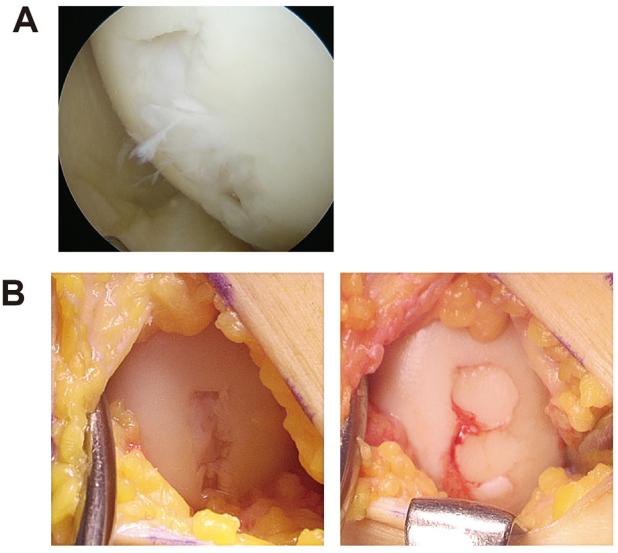

Fig. 2. A case of autologous osteochondral plug transplantation. (A) An arthroscopic view showing a cartilage injury in the medial femoral condyle. (B) Macroscopic view of the cartilage injury site. (C) Two osteochondral plugs with a diameter of 8 mm were transplanted into the defect.

(>4 cm^2) were comparable to those of patients who underwent OAT for small osteonecrosis lesions (≤4 cm^2) [37].

5.5. Osteochondral allograft transplantation

Osteochondral allograft transplantation (OCA) is an effective treatment for a variety of cartilage lesions [38–40].

In particular, they are useful in young, healthy patients with large and deep osteochondral lesions >2 cm^2, both in primary and revision settings [41]. Levy et al. reported the outcomes of 122 patients (129 knees) who underwent OCA of the femoral condyle, with revision surgery or conversion to arthroplasty defined as graft failure [42]; survival rates were 82% at 10 years, 74% at 15 years, and 66% at 20 years. Patients aged >30 years at the time of surgery or those who had undergone two or more previous operations were more likely to experience graft failure.

Despite its utility in the treatment of large osteochondral lesions, it is limited by its availability, waiting time, and high cost of obtaining fresh OCA.

5.6. Autologous chondrocyte implantation

5.6.1. First and second generation ACI

ACI is effective for small to large cartilage defects and is particularly useful in the treatment of large cartilage defects. Articular cartilage fragments were harvested during the first surgery. Chondrocytes were isolated from cartilage fragments, grown in culture, and implanted into the cartilage defect during the second surgery. In the first generation of ACI, autologous periosteal patches taken from the proximal tibia were used to cover the cartilage defect, and a cell suspension was injected beneath the periosteum [43]. In a series of more than 200 patients treated with ACI for larger lesions (mean defect size, 8.4 ± 5.5 cm^2), ACI provided durable results with a 71% survival rate at 10 years and improved function in 75% of patients [44].

Although good clinical outcomes after first-generation ACI have been reported, periosteal hypertrophy is a common complication [45]. In second-generation ACI, the periosteal patch was replaced with porcine type I/III collagen membrane, which has proven to be safer, more cost-effective, and with fewer graft hypertrophies than that seen with periosteal patch use [46,47].

5.6.2. Matrix-induced autologous chondrocyte implantation

In third-generation ACI, chondrocytes are cultured either directly or in a matrix after monolayer expansion. Matrix chondrocytes were attached to the cartilage defect with fibrin glue or bioabsorbable sutures and without collagenous flap coverage. Owing to its simplicity, matrix-based chondrocyte implantation has become popular, with reportedly favorable outcomes [48–53]. A recent systematic review comparing the outcomes of third-generation ACI with those of microfractures for the treatment of focal knee cartilage defects showed significantly superior outcomes with lower failure rates after third-generation ACI [54].

In Japan, an atelocollagen-associated ACI (JACC; Japan Tissue Engineering Co., Ltd., Aichi, Japan) was developed [54] and is currently the only approved ACI technique. In the ACI technique using JACC, cultured chondrocytes in atelocollagen were implanted into the cartilage defect and covered by the periosteum or type I/III collagen membrane (Chodro-Gide, Geistlich Pharma AG, Wolhusen, Switzerland) (Fig. 3). Good short- and mid-term clinical outcomes with second-look arthroscopy and MRI evaluation have been reported in atelocollagen-associated ACI [55–59].

Several arthroscopic ACI techniques have been developed to simplify and reduce the invasiveness of the procedure. The Chondrosphere® (co.don AG, Teltow/Berlin, Germany) is a type of matrix-associated chondrocyte implantation shaped into spheroids. The 3D-cultured chondrocytes in spheroids can be implanted into cartilage defects without any coverage or glue. Good short- and mid-term outcomes after treatment with chondrospheres have been reported [60,61]. Chondron® (Sewon Cellontech Co., Ltd., Seoul, South Korea) is a gel-type ACI that can be arthroscopically implanted. Choi et al. first reported good outcomes after Chondron implantation via arthrotomy in 98 patients [62]. Yoon et al. recently reported good outcomes of arthroscopic Chodron® implantation with second-look observation and histological assessment [63].

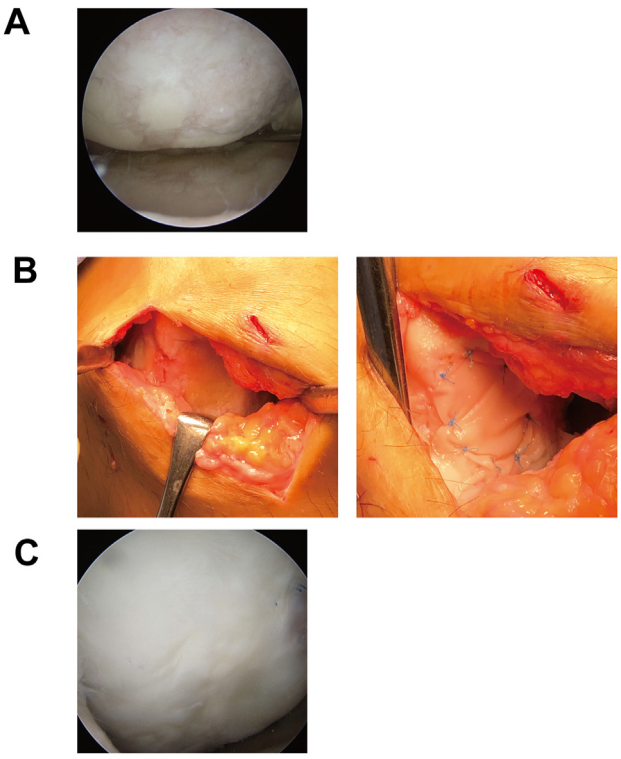

Fig. 3. A case of autologous chondrocyte implantation (ACI). (A) An arthroscopic view at the time of cartilage harvest showing the cartilage injury site in the lateral femoral condyle. (B) Intraoperative image showing 5 cm^2 cartilage lesion (left). ACI using JACC™ was performed. The ACI was covered with type I/III collagen membrane (ChodroGuide™) (right). (C) Second-look arthroscopy showed a well-repaired injury site with complete coverage and integration with surrounding cartilage.

The disadvantages of ACI include the need for two-stage surgery and open arthrotomy, high cost, and indications for knees with OA conditions.

5.7. Micronized cartilage extracellular matrix

The micronized cartilage ECM, commercially known as BioCartilage® (Arthrex Inc., Naples, FL, USA), contains an allogenic ECM that is native to the cartilaginous environment and includes type II collagen, proteoglycans, and cartilaginous growth factors [64]. It is usually used to augment marrow stimulation techniques (MST), such as microfractures and drilling. After MST, BioCartilage® is usually applied with platelet-rich plasma (PRP) or bone marrow aspirate concentrate (BMAC) to the prepared cartilage defect and sealed with fibrin glue. Open or arthroscopic surgery can also be performed. BioCartilage® ECM elements promote MST-released mesenchymal cells to differentiate along chondral lineage, resulting in new hyaline cartilage formation. An animal study using an equine cartilage injury model showed that treating cartilage defects using microfracture and BioCartilage® improved the outcomes compared with using microfracture alone. A histological evaluation showed more collagen type II in the repaired site of the BioCartilage® group than in the control microfracture group; however, none of the repaired cartilage was restored to the same structure or collagen type II expression as normal hyaline cartilage [65]. A multicenter prospective

study of 48 patients who underwent microfracture augmentation with BioCartilage® for the treatment of cartilage defects demonstrated significantly improved patient-reported outcomes (PROs) at the 2-year follow-up visit. Of the 48 patients, 90% achieved MCID and 85% achieved an acceptable symptomatic state at the 2-year follow-up visit [66]. Another prospective study showed significant improvements in several PROs at 2-year follow-up, with 90% of the patients returning to their pre-injury level of work 1 year postoperatively [67]. However, no long-term clinical data are currently available.

5.8. Autologous matrix-induced chondrogenesis

Autologous matrix-induced chondrogenesis (AMIC) is an MST based technique. A type I/III porcine collagen- or hyaluronan-based membrane was placed over the defect after MST. The membrane acts as a scaffold to retain bone marrow elements within cartilage defects [68]. The membrane was fixed with absorbable sutures or fibrin glue and minimal arthrotomy was required (Fig. 4).

In a randomized control trial (RCT) comparing AMIC with microfracture alone, the AMIC group showed significantly better clinical outcomes and cartilage defect filling than the microfracture group at 2- and 5-year follow-up [69]. Another RCT comparing AMIC and ACI showed that there was no significant difference in clinical outcomes at the 2-year follow-up [70]. A meta-analysis conducted by Kim et al. showed that the mean improvement in the IKDC subjective score was significantly greater in the AMIC group than in the microfracture group at 2-year follow-up. The MOCART score was also higher in the AMIC group than in the microfracture group [71]. Another systematic review demonstrated that compared with microfractures, AMIC showed lower VAS scores, greater IKDC scores, and lower revision rates [72]. Karpinski et al. reported that there were no differences in the PROs between patients who received AMIC and those who received microfracture alone at the 2-year follow-up, whereas, the Cincinatti score was significantly decreased in the microfracture group compared to the AMIC group at the 5-year follow-up [73].

The primary limitations of MST-based treatments are their limited size, violation of the subchondral bone plate, and dependency on bone marrow-derived cells for cartilage repair. Its advantages are that it is not associated with donor site morbidity, is performed in a one-step procedure, unlike most cell-based treatments, and is cost effective. AMIC could be promoted as an effective augmentation for microfractures and as a low-cost alternative to ACI.

5.9. Bone marrow aspirate concentrate implantation

Bone marrow aspirate concentrate (BMAC) is the concentration of mesenchymal progenitor cells, growth factors, and cytokines in autologous bone marrow harvested from the patient's iliac crest, distal femur, proximal tibia, or calcaneus. BMAC is prepared according to each system's protocol and is applied to cartilage defects; it may be combined with AMIC [74,75]. There are several studies showing that BMAC combined with biological scaffolds enhanced maturation of the cartilage [76,77]. A systematic review by Cavinatto et al. concluded that BMAC treatment, used either as the main treatment or as a biological supplement, leads to improved short- and mid-term outcomes [78]. However, currently available evidence regarding BMAC use is preliminary. Therefore, high-quality studies are necessary to understand the efficacy of BMAC in cartilage repair.

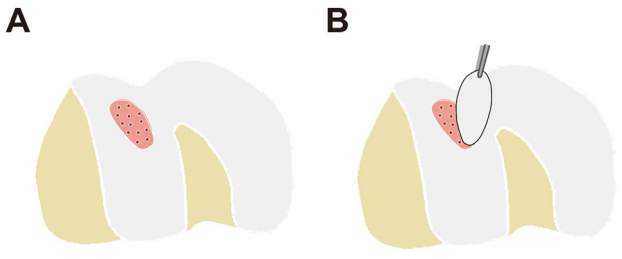

Fig. 4. A graphic image showing the concept of autologous matrix-induced chondrogenesis (AMIC). (A) First, microfracture is performed to stimulate cartilage repair after debridement. (B) Subsequently, the injured site is covered with type I/III collagen membrane to enhance cartilage regeneration.

5.10. Particulated juvenile allograft cartilage

Particulated juvenile allograft cartilage (PJAC) is hyaline cartilage obtained from young donors. Once juvenile cartilage is obtained, the cells are viable for up to 45 days. Immature articular cartilages have a significantly higher cell density, metabolic activity, and proliferation rate than those of mature articular cartilage and can produce greater amounts of ECM [79]. Either open or arthroscopic surgery can be performed when using PJAC. After the standard preparation of the cartilage defect, fibrin glue is added to the base of the defect, and PJAC is added and gently pressed. PJAC is indicated for ICRS 3–4 cartilage defects with a size of 1–6 cm^2 after debridement [80]. PJAC easily matches the contour, making it a suitable treatment option for PF cartilage lesions [22,81–83]. It is contraindicated for uncontained lesions or lesions with subchondral bone insufficiency [84].

Currently, only one PJAC product (DeNovo NT Natural Tissue Graft; Zimmer Inc., Warsaw, IN, USA) is commercially available. The product is prepared from femoral condyles of juvenile cadavers <13 years of age. Juvenile cartilage is technically considered as other allografts, such as OAC and bone-patellar-bone allograft [85]. It has been a commercially available in the United States since 2007 and several case series have been reported: A case series of 15 knees with patellar cartilage lesions treated with PJAC using DeNovo NT showed improved clinical outcomes, and 80% of the cases had an at least 90% defect coverage. However, five patients (33%) had graft hypertrophy, of which two required arthroscopic debridement [86]. Another series of PF cartilage lesions treated with PJAC showed improved 2-year clinical results [87]. However, no long-term results or high-quality RCT have been published to date. The advantage of PJAC over ACI is that it can be a one-stage surgery; however, it is expensive, and there is a limited supply of juvenile donor cartilage.

5.11. Particulated autologous cartilage implantation

The concept of particulated autologous cartilage implantation (PACI) is very similar to that of PJAC; it uses particulate cartilage obtained during surgery. Approximately 200–300 mg of cartilage without subchondral bone is harvested from the intercondylar notch or medial/lateral femoral trochlear ridge [88]. The harvested cartilage was fragmented into pieces that were smaller than 1 mm on the back table [89]. The cartilage defects are filled with fragmented cartilage using fibrin glue, as in PJAC. It is covered with a synthetic or collagen/hyaluronan-based membrane and fixed to the surrounding cartilage using absorbable sutures [90].

A case series of 27 patients with knee chondral lesions treated with PACI showed improved pain and functional outcomes [91]. A comparative study between OAT and PACI showed no significant difference between the two groups at the 2-year follow-up. However, the PACI group had more failures than the OAT group (25% vs. 0%) [92]. It is relatively inexpensive compared to ACI and could be a good alternative for those unable to bear medical costs or in countries with limited access to allografts. Further RCT trials assessing long-term results are required.

The cited studies for surgical treatments are listed in Table 1.

6. Others

Although a variety of surgical treatments for cartilage injury have been developed, potential morbidity associated with autologous tissue and cells and limited allogeneic tissue quantity have been raised as concerns. Therefore, the biological augmentation of cartilage

Table 1
Summary of reports of surgical treatments of cartilage injuries.

	Author	Study design	Number of patients	Area of lesion	Level of evidence
Microfracture	Mithoefer K et al. (2009) [29]	Systematic review	NA	NA	IV
	Goyal D et al. (2013) [30]	Systematic review	NA	NA	II
	Steadman JR et al. (2003) [31]	Case series	68	2.8 (0.2–10) cm^2	IV
	Orth P et al. (2020) [32]	Systematic review	NA	NA	IV
Osteochondral autograft transplantation	Riboh JC et al. (2017) [33]	Meta-analysis	NA	NA	I
	Solheim E et al. (2020) [34]	Cohort study OAT vs MFx	203 OAT: 84 MFx: 119	OAT: 4.8 ± 2.9 cm^2 vs MFx: 3.0 ± 1.1 cm^2	III
	Solheim E et al. (2018) [35]	RCT OAT vs MFx	40 OAT: 20 MFx: 20	OAT: 3.4 ± 0.9 cm^2 vs MFx: 3.6 ± 0.8 cm^2	I
	Jones KJ et al. (2019) [36]	Systematic review	NA	NA	IV
	Yabumoto H et al. (2019) [37]	Cohort study OAT using the eyeglass technique vs OAT using standard technique	29 Eyeglass: 18 Standard: 11	6.89 (4.2–11.3) cm^2 vs 2.3 (1.1–3.6) cm^2	III
Osteochondral allograft transplantation	Briggs DT et al. (2015) [38]	Case series	61	NA	IV
	Chahal J et al. (2013) [39]	Systematic review	NA	NA	IV
	Familiari F et al. (2018) [40]	Systematic review	NA	NA	IV
	Riff AJ et al. (2020) [41]	Cohort study OCA vs ACI	359 Primary OCA: 79 Secondary OCA: 88 Primary ACI: 100 Secondary ACI: 92	NA Primary OCA: 5.0 cm^2 Secondary OCA: 4.0 cm^2 Primary ACI: 4.0 cm^2 Secondary ACI: 4.2 cm^2	III
	Levy YD et al. (2013) [42]	Case series	129	NA	IV
Autologous chondrocyte implantation	Brittberg M et al. (1994) [43]	Case series	23	3.1 (1.6–6.5) cm^2	IV
	Minas T et al. (2014) [44]	Case series	210	8.4 ± 5.5 cm^2	IV
	Peterson L et al. (2000) [45]	Case series	101	4.2 (1.3–8.0) cm^2	IV
	Gooding CR et al. (2006) [46]	RCT ACI with periosteal cover (ACI-P) vs ACI with type I/III collagen (ACI-C)	68 ACI-P: 33 ACI-C: 35	4.5 cm^2	I
	Schneider U et al. (2011) [48]	Case series	116	5.4 ± 2.4 cm^2	IV
	Ebert JR et al. (2017) [49]	Case series	31	2.5 (1.0–5.0) cm^2	IV
	Matsushita T et al. (2022) [50]	Case series	9	4.1 (2.0–4.5) cm^2	IV
	Niemeyer P et al. (2019) [51]	Cohort study MACI vs MFx	6425 MACI: 152 MFx: 6273	NA	III
	Schuette HB et al. (2017) [52]	Systematic review	NA	NA	IV
	Dhillon J et al. (2022) [53]	Systematic review	NA	NA	II
	Brittberg M et al. (2018) [54]	RCT MACI vs MFx	128 MACI: 65 MFx: 63	MACI: 5.1 ± 3.0 cm^2 MFx: 4.9 ± 2.0 cm^2	I
	Ochi et al. (2002) [55]	Case series	28	2.9 (2.0–16.0) cm^2	IV
	Adachi et al. (2014) [56]	Case series	73	3.6 (2.0–16.0) cm^2	IV
	Tohyam H et al. (2009) [57]	Case series	27	3.2 (1.2–9.4) cm^2	IV
	Takazawa K et al. (2012) [58]	Case series	14	3.8 (0.6–11.3) cm^2	IV
	Siebold R et al. (2018) [61]	Case series	30	6.0 ± 3.1 cm^2	IV
	Choi NY et al. (2010) [62]	Case series	98	5.2 ± 2.7 cm^2	IV
	Yoon TH et al. (2020) [63]	Case series	10	2.9 ± 1.2 cm^2	IV
Micronized cartilage extracellular matrix	Sew D et al. (2018) [64]	Systematic review	NA	NA	IV
	Cole BJ et al. (2011) [66]	Case series	48	2.4 ± 1.4 cm^2	IV
	Brusalis CM et al. (2020) [67]	Case series	10	2.4 (0.7–5.0) cm^2	IV
Autologous matrix-induced chondrogenesis	Volts M et al. (2017) [69]	RCT AMIC vs MFx	30 AMIC: 17 MFx: 13	3.6 (2.1–6.6) cm^2	II
	Fossum V et al. (2019) [70]	RCT ACI vs AMIC	41 ACI:21 AMIC: 20	ACI: 4.9 ± 4.4 cm^2 AMIC: 5.2 ± 2.4 cm^2	II
	Kim JH et al. (2020) [71]	Systematic review	NA	NA	IV
	Milgliorini F et al. (2022) [72]	Systematic review	NA	NA	IV
	Karpinski K et al. (2021) [73]	Systematic review	NA	NA	I
Bone marrow aspirate concentrate implantation	Gobbi A et al. (2016) [74]	Cohort study BMAC vs MFx	50 BMAC: 25 MFx: 25	BMAC: 6.5 cm^2 MFx: 4.5 cm^2	II
	Gobbi A et al. (2015) [75]	Cohort study BMAC vs MACI	37 BMAC: 18 MACI: 19	BMAC: 10.4 ± 6.0 cm^2 MACI: 9.7 ± 6.1 cm^2	II
	Enea D et al. (2015) [76]	Case series	9	2.5 ± 0.4 cm^2	IV
	Krych AJ et al. (2016) [77]	Cohort study	46 Control scaffold: 11 Scaffold + PRP: 23 Scaffold + BMAC: 12	Control: 3.3 (2.2–5.3) cm^2 PRP: 3.9 (1.5–6.0) cm^2	III

(*continued on next page*)

Table 1 (*continued*)

	Author	Study design	Number of patients	Area of lesion	Level of evidence
				BMAC: 3.6 (2.0–6.0) cm^2	
	Canvinatto L et al. (2019) [78]	Systematic review	NA	NA	IV
Particulated juvenile allograft cartilage	Farr J et al. (2014) [81]	Case series	25	2.7 ± 0.8 cm^2	IV
	Grawe B et al. (2017) [82]	Case series	45	2.0 (0.04–5) cm^2	IV
	Dawkins BJ et al. (2022) [83]	Case series	36	2.0 (1.0–7.0) cm^2	IV
	Tompkins M et al. (2013) [86]	Case series	15	NA	IV
	Wang T et al. (2018) [87]	Case series	30	2.1 ± 1.2 cm^2	IV
Particulated autologous cartilage implantation	Christensen BB et al. (2021) [89]	Case series	8	3.1 (1.5–4.7) cm^2	IV
	Cole BJ et al. (2011) [90]	RCT	29	PACI: 2.8 ± 0.2 cm^2	II
		PACI vs MFx	PACI: 20 MFx: 9	MFx: 3.5 ± 0.12 cm^2	
	Massen FK et al. (2019) [91]	Case series	27	3.1 ± 1.6 cm^2	IV
	Di Martino A et al. (2021) [92]	Cohort study	27	PACI: 2.6 ± 1.0 cm^2	III
		PACI vs OAT	PACI: 12 OAT: 15	OAT: 2.2 ± 1.0 cm^2	

RCT: randomized control study. N/A: Not applicable. MFx; microfracture. MACI: matrix-induced chondrocyte implantation. AMIC; Autologous matrix-induced chondrogenesis. BMAC: Bone marrow aspirate concentrate implantation. PACI: Particulated autologous cartilage implantation. The area of lesion was expressed as mean ± standard deviation or mean (range).

regeneration and tissue engineering approaches have been explored.

6.1. Growth factor

Based on the results of basic research, growth factors, such as bone morphogenetic protein (BMP), TGF-β, fibroblast growth factor (FGF), and insulin-like growth factor (IGF) are considered promising anabolic molecules that can stimulate cell growth, enhance chondrogenesis, and recruit cells to augment or repair cartilage defects. Among growth factors, TGF-β1 and FGF-18 have been tested in clinical settings for the treatment of knee OA. Lee et al. reported the results of phase II clinical trials of genetically engineered allogeneic human chondrocytes expressing TGF-β1 (TissueGene-C; Kolon TissueGene Inc., Rockville, MD, USA) for Kellgren-Lawrence grade 2 knee OA. They reported significant improvements in IKDC scores and reduced cartilage damage progression in the TGF-β1 group compared with the placebo group [93]. Hochberg et al. reported the 2-year results of a multicenter RCT examining the efficacy of intra-articular recombinant human FGF-18 injections (Sprifermin; EMD Serono Inc., Rockland, MA, UAS; subsidiary of Merck KGaA, Germany) for the treatment of Kellgren-Lawrence grades 2–3 knee OA. They reported a significant improvement in the total femorotibial joint cartilage thickness, with a slight increase after 2 years compared with the control group, where a slight decrease was observed. However, the clinical outcomes were not significantly different between the two groups [94].

PRP, which contains a variety of growth factors, has shown promise as a possible solution for promoting cartilage healing, improving clinical function, and decreasing pain associated with cartilage lesions and OA [95–97]. A recent review by Liang et al. reported that PRP has a positive effect on cartilage repair and joint function in the treatment of cartilage injuries. However, they also noted that a lack of standardization and wide inconsistency in PRP preparation make it difficult to draw a definitive conclusion regarding the efficacy of PRP in cartilage repair [98]. An RCT showed that intra-articular PRP injection did not show any superiority over placebo in terms of clinical symptoms and joint structure in patients with mild to moderate knee OA [99]. Further research is necessary to determine the efficacy of PRP for cartilage repair.

6.2. Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are an alternative source of cells for cartilage repair. MSCs can be obtained from the bone marrow, adipose tissue, and synovium. Since MSC use can avoid the sacrifice of normal cartilage tissue, its transplantation may have advantages over conventional ACI. Although MSCs can differentiate into chondrocytes, this ability is lost after expansion. Studies have revealed that transplanted MSCs constituting the repaired cartilage in vivo are scarce; therefore, the transplanted MSC effect is considered trophic, in which MSC-secreted factors stimulate host cells to repair the tissue [100,101]. Clinical studies on arthroscopic synovial stem cell transplantation are currently underway [102].

6.3. Human embryonic and human-induced pluripotent stem cells

Human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs) share characteristics, such as pluripotency and self-renewal. As both hESCs and hiPSCs can be expanded almost infinitely owing to their self-renewal capacity, a large number of chondrocytes can be prepared from a small tissue sample. Protocols for hiPSC differentiation into chondrocytes have been developed, and it may be possible to generate sufficient chondrocytes and hyaline cartilaginous tissue for cartilage repair at the experimental level [103,104]. However, several issues, including tumorigenesis and high costs, must be resolved before translating these experimental findings into a clinical setting.

7. Summary and conclusions

Surgical cartilage repair options, such as microfractures, OAT, and ACI, have been established, with reportedly satisfactory short-to long-term outcomes. However, the limitations and disadvantages of traditional surgical treatments, such as repair with fibrous cartilage, donor site morbidity, and two-step surgery, have raised concerns. Various surgical treatments and augmentations have been developed to overcome the limitations of traditional surgical treatments, including MACI, BMAC, PACI, and PJAC. In addition, numerous studies on cartilage repair techniques and the augmentation of biological healing are underway. To improve the outcomes of cartilage injury treatment, understanding the basics of the cartilage repair process and choosing an appropriate treatment option are important. Therefore, surgeons and clinicians should regularly update their surgical techniques and knowledge regarding cartilage repair and regeneration.

Authors' contributions

TaM designed the study. TaM and TT wrote the manuscript's initial draft. KO and SS contributed to the analysis and interpretation of data and assisted in the preparation of the manuscript. KaN, KoN, and YH contributed to the data interpretation and critically reviewed the manuscript. All authors contributed to the writing of the final draft of the manuscript. All authors have read and approved the final manuscript draft for submission.

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Declaration of competing interest

The authors declare no competing interests.

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