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Cell-based chondral restoration

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Abstract As our patients become more physically active at all ages, the incidence of injuries to articular cartilage is increasing and is causing patients significant pain and disability at a younger age. The intrinsic healing response of articular cartilage is poor, because of its limited vascular supply and capacity for chondrocyte division. Nonsurgical management for the focal cartilage lesion is successful in the majority of patients. Those patients that fail conservative management may be candidates for a cartilage reparative or reconstructive procedure. The type of treatment available depends on a multitude of lesion-specific and patient-specific variables. First-line therapies for isolated cartilage lesions have demonstrated good clinical results in the correct patient but typically repair cartilage with fibrocartilage, which has inferior stiffness, inferior resilience, and poorer wear characteristics. Advances in cell-based cartilage restoration have provided the surgeon a means to address focal cartilage lesions utilizing mesenchymal stem cells, chondrocytes, and biomimetic scaffolds to restore hyaline cartilage.

Keywords Hyaline · Cartilage · Chondrocyte · Matrix · Scaffold

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Introduction

Due to the increase in physical activity among patients of all ages, injury to articular cartilage is increasing causing significant pain and disability. One study of 31,516 knee arthroscopies found that 63 % of patients had chondral injury [1]. Another review of 993 knee arthroscopies of patients with a mean age of 35 years old, found an 11 % incidence of full thickness cartilage lesions that could have benefited from surgical treatment [2]. Even though we do not know what factors lead asymptomatic cartilage lesions to eventually become symptomatic, we do know that chondral lesions further degenerate within the knee over time [3, 4].

The intrinsic healing response of articular cartilage is poor, because of its limited vascular supply and capacity for chondrocyte division and migration [5]. Superficial damage will injure chondrocytes, limit their metabolic capacity for repair, and lead to decreased proteoglycan concentration, increased hydration, and altered fibrillar organization of collagen [6, 7]. This leads to increased force transmission to the damaged cartilage causing damage to the neighboring healthy cartilage. This vicious cycle is thought to contribute to the progression of partial-thickness articular cartilage injuries to full-thickness injuries and eventually diffuse osteoarthritis [8, 9].

A defect that penetrates the subchondral plate has a higher capacity to heal with a normal healing response beginning with hematoma formation, stem cell migration, and synthesis of type 1 cartilage [10]. Once the subchondral plate has been violated, an influx of marrow contents including inflammatory cells, undifferentiated mesenchymal cells, cytokines, and growth factors bathe the injured area and stimulate cartilage formation [11]. However, the resultant repair typically resembles fibrocartilage instead of hyaline cartilage, which has inferior stiffness, inferior resilience, and poorer wear characteristics [12].

Nonsurgical management of articular cartilage injury consisting of rest, analgesics to control pain, and anti-inflammatory medications has remained largely the same over many decades. There is little to no evidence in the literature supporting corticosteroid or viscosupplementation injections in the setting of focal cartilage lesions. Failure of a trial of nonoperative treatment for 4–6 months is an indication for surgery to address the focal cartilage defect. However, surgical treatment of chondral injuries continues to evolve, and there are many techniques currently at the surgeon's disposal. Autologous chondrocyte implantation is one of these techniques that are currently being refined to restore the more durable hyaline cartilage.

Evaluation of chondral injuries

Most patients will present with pain in the affected joint and not always recall a specific injury. A patient who recalls a single injury or series of injuries is likely to have incurred a focal chondral or osteochondral lesion, whereas an atraumatic injury is likely a degenerative chondral lesion or diffuse osteoarthritis. A thorough exam should be performed assessing gait, limb alignment, range of motion, presence of an effusion, and ligamentous stability at the time of initial presentation.

Initial evaluation should include radiographs. Radiographic examination not only may show the specific osteochondral defect, it may also show associated pathology such as osteophytes, joint space narrowing, fractures, or signs of ligamentous injury which may affect treatment options. MRI can assist with preoperative planning to determine the size and location of the lesion and can better access the other compartments and soft tissue components of the knee.

Arthroscopy is the most accurate way to access the location, size, depth, shape, and stability of articular cartilage. Currently, the most used classification system for describing chondral injuries was initially described by Dr. Outerbridge [13], which was designed to describe chondromalacia of the patella. This system classifies chondral injury in four grades: grade 1, softening and swelling of the cartilage; grade 2, partial thickness fragmentation and fissuring of the cartilage in an area less than 1.5 cm in diameter; grade 3, full thickness fracturing and fissuring involving greater than 1.5 cm in diameter of cartilage; and grade 4, erosion of cartilage down to bone.

Recently, the International Cartilage Repair Society (ICRS) introduced a universal grading system that offers a more precise description of the damaged cartilage [14, 15]. In this system, grade 1 is normal, grade 1a has some mild softening or fibrillations, and grade 2 has more involvement but still less than 1/2 the cartilage depth. Grade 3 lesions involve more than 1/2 the cartilage depth and include subgroups a, b, c, and d with increasing severity of damage (3a, 50 % cartilage thickness damage; 3b, damage to calcified cartilage; 3c, exposed subchondral bone; and 3d, full-thickness delamination). A grade 4 lesion is an osteochondral lesion violating the subchondral plate (4a, superficial, and 4b, deep bony involvement).

Chondral injuries cannot be treated in a vacuum. Concomitant ligamentous insufficiency, mechanical malalignment, patellar maltracking, and dysfunctional menisci must be addressed to maximize patient outcomes and provide a suitable environment for the cartilage restorative procedure [5, 16]. Failure to do so may overload the restored cartilage, as the concomitant pathology did to the native cartilage, leading to surgical failure even when the biology may have otherwise been successful. Even a partial meniscectomy leads to increased tibiofemoral contact pressures [17], and concomitant meniscal repair or in more severe cases allograft transplantation should be considered, as opposed to meniscectomy, as these patients have shown equivalent or superior results when compared to patients undergoing cartilage restoration procedures alone [18, 19].

Cultured autologous chondrocyte implantation

Autologous chondrocyte implantation (ACI) is a technique, developed by Dr. Lars Peterson and coworkers in Sweden during the 1980s, that attempts to repair the damaged chondral tissue by replacing it with viable autogenous chondrocytes [20]. As originally described, this is done in two separate procedures. The first stage involves an arthroscopic evaluation of the focal chondral lesion to assess containment, depth, and potential bone loss. During the first stage, biopsy of normal hyaline cartilage is performed from a nonweight-bearing region of the knee. The typical harvest sites include the lateral trochlea near the sulcus terminalis, the intercondylar notch, and the medial trochlea [21, 22]. The total volume of the biopsy should be approximately 200 to 300 mg, preferably in three "Tic-Tac-sized" fragments [1A]. This tissue is then sent to a lab to be enzymatically treated to release the chondrocytes, which are subsequently expanded in culture for a period of 2–4 weeks to create more than 10 million cells from only the few hundred thousand cells originally in the biopsy.

The second stage of the procedure is cell implantation, which typically takes place between 6 weeks and 18 months after the biopsy, and is done through an arthrotomy. The surgical exposure depends on defect location. Patellofemoral lesions are approached through a midline incision, allowing a simultaneously performed tibial tubercle osteotomy, and femoral condyle lesions are addressed through limited parapatellar arthrotomies. Circular- or oval-shaped prepared defects are biomechanically more stable [23] (Fig. 1b). The diseased cartilage is debrided down to the subchondral layer, leaving healthy surrounding hyaline cartilage to form stable vertical walls shouldering the lesion. Care must be taken not to penetrate the subchondral bone, and the site should be packed with thrombin-soaked gauze to prevent bleeding into the area of repair, which could impede chondrocyte growth. Additionally, preoperative imaging and initial arthroscopy should provide the

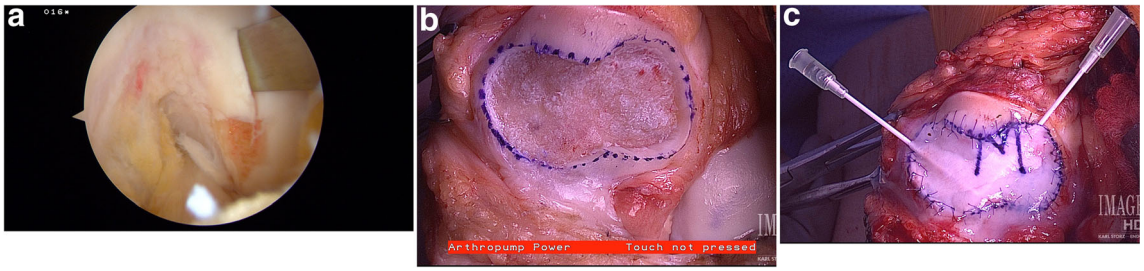

Fig. 1 **a** Arthroscopic photograph of a chondral harvest of a nonweight-bearing portion of the femoral condyle. **b** Prepared lesion of the patella articular surface. **c** Patellar lesion that has been prepared with autologous chondrocyte implantation using collagen membrane (C-ACI) technique and ready for chondrocyte implantation

surgeon with evidence of subchondral endplate disruption, and if the depth of the lesion is >8 mm, then it is recommended to perform bone grafting of the lesion at the time of ACI or in a staged fashion. According to the original description, the cultured cells are then implanted under an autologous periosteal patch taken from the proximal medial tibial cortex using a separate incision. This periosteal patch is then secured with a 6–0 vicryl suture on a cutting needle, and a watertight seal is created with fibrin glue. Prior to sealing the top of the patch and injecting the chondrocytes, a water–seal test should be first performed by completely drying the surgical site and injecting a small volume of sterile saline. There should be a complete containment of the saline without leaking. In cases where the cartilage lesion is located near the edge of the articular surface, the periosteal patch repair may be augmented with a small suture anchor or bone tunnels in order to contain the injected chondrocytes. This original description of ACI is now known as first-generation technique or periosteum-based autologous chondrocyte implementation (P-ACI).

Limitations of the periosteal patch (such as periosteal hypertrophy, periosteum suturing, calcification, delamination, intra-articular adhesions, another surgery to harvest the periosteum, and patch integrity in older patients) have led to the development of synthetic substitutes [24•]. Second-generation ACI substitutes the periosteum with a membrane containing type I/III collagen [25] (Fig. 1c). The advantages of second-generation ACI are the availability of the biopatch, usability, decreased risk of patch hypertrophy, and decreased surgical time. Third-generation ACI uses biomimetic membranes or scaffolds that are seeded with the harvested chondrocytes prior to implantation [26]. The scaffolds have a nanofiber architecture that maximizes the potential for chondrocyte ingrowth and maintenance of the extracellular matrix. These surgical techniques are also called autologous chondrocyte implantation using collagen membrane (C-ACI) and membrane-associated autologous chondrocyte implantation (M-ACI), respectively.

Results of autologous chondrocyte implantation

Cultured autologous chondrocyte implantation has also shown to improve pain and function in patients with second-look biopsies showing hyaline-like cartilage [27–29, 30•]. Good results have also been reported at 85 % on patellar lesions as long as an anteromedialization tibial tubercle osteotomy was done concurrently [31]. While there has been evidence that autologous cultured chondrocyte implantation has a higher failure rate and worse clinical outcome following a failed microfracture procedure [32, 33], other investigators have shown clinical improvement following marrow-stimulating procedures [34]. Ideally, cultured chondrocyte implementation is used on focal unipolar defect measuring 2–10 cm^2 with minimal subchondral bone loss.

Dr. Peterson et al. [27] reported 10–20-year follow-up (mean 12.8 years) on 224 patients who underwent ACI for cartilage lesions measuring about 5.3 cm^2. Seventy-four percent of these patients reported their status as better or the same, and 92 % of patients were satisfied and would have ACI again. They also noted an increase in all functional knee scores (Lysholm, Tegner–Wallgren, Brittberg–Peterson, modified Cincinnati (Noyes), and Knee Injury and Osteoarthritis Outcome Score (KOOS)) compared to their preoperative values. In the USA, Dr. Minas et al. [30•] reported a 10-year outcome data (mean follow-up of 12 years) on 210 patients who had received ACI for lesions with a mean surface area of 8.4 cm^2. He reported a 25 % (53 patients) failure rate of the graft at 10 years with 19 of these patients going on to arthroplasty, 27 getting a revision ACI procedure, and 7 declining further treatment. Seventy-five percent of his patients had an increase of function, and he reported increases in all of the function knee scores compared to their preoperative values. He also reported that a previous marrow-stimulating procedure and lesions larger than 15 cm in patients were predictors for failure in his cohort.

Few randomized controlled trials comparing the various cartilage restoration procedures exist; however, there are a few comparing ACI to microfracture, each reporting differing results. Knutsen et al. [35] compared microfracture to ACI with histology ranging from fibrous to hyaline-like in both groups with no correlation with clinical outcome at 5 years. On the other hand, Saris et al. [36] reported superior histology of biopsies of a chondrocyte-cell-based technology compared to microfracture at 5 years, with those patients implanted with

the chondrocyte-cell-based technology procedure demonstrating superior outcomes. Criticisms of the Knutsen series included inadequate numbers for statistical power and lack of subset analysis of smaller versus larger lesions.

Second- and third-generation ACIs have also shown promising restoration of hyaline-like cartilage and similar results while mitigating the limitations of P-ACI [37–39] (Table 1). First, Gomoll et al. [19] reported the results of 300 consecutive patients who underwent P-ACI to the results of the next 100 consecutive patients who underwent C-ACI for failure rates and reoperation rates due to graft hypertrophy. They saw a decrease from 23 to 5 % in reoperation rates due to graft hypertrophy after switching to C-ACI with no significant difference in failure rates. Gooding et al. [40] reported the 2-year results of P-ACI (33 patients) compared with those of C-ACI (35 patients) in a randomized controlled study. The mean age

Table 1 Table summarizing the current available literature for autologous chondrocyte implantation technique (ACI)

Author, year	Type of study	Technique evaluated	Follow-up	Subjective results	Objective results
Peterson et al. 2010 [27]	Case series	ACI (224 patients)	12.8 years	74 % reported same or better than before surgery 92 % were satisfied and would do again	Significant increase in Lysholm, Tegner, Brittberg–Peterson, and KOOS scores
Minas et al. 2014 [30•]	Prospective cohort	ACI (210 patients)	12 years	75 % reported improved function 71 % did not need another surgery	Improved modified Cincinnati, WOMAC, KSS, SF-36 scores
Knutsen et al. 2007 [35]	Randomized controlled trial	ACI (40 patients) versus Microfracture (40 patients)	5 years	Both techniques had a success rate of 77 %	No difference in histological quality on second look biopsies 33 % of patients in both groups had radiographic findings of OA
Saris et al. 2011 [36]	Randomized controlled trial	ACI (51 patients) versus Microfracture (61 patients)	5 years	7 failures in ACI and 10 failures in MF	Better increases in KOOS scores are noted in the ACI group, especially if onset of the symptoms was less than 3 years
Gomoll et al. 2009 [19]	Retrospective cohort	P-ACI (300 patients) versus C-ACI (100 patients)	1 year		P-ACI had 2.3 % failure rate and 25.7 % reoperation rate due to graft hypertrophy C-ACI had 4 % failure rate and 5 % reoperation rate due to graft hypertrophy
Gooding et al. 2006 [40]	Randomized controlled trial	P-ACI (33 patients) versus C-ACI (35 patients)	2 years	P-ACI had 67 % good to excellent results C-ACI had 74 % good to excellent results	Second look arthroscopies showed similar results 36.4 % in P-ACI group required shaving for graft hypertrophy
Bartlett et al. 2005 [39]	Randomized controlled trial	C-ACI (44 patients) versus M-ACI (47 patients)	1 year		Comparable increases in modified Cincinnati and CRS scores. Comparable graft hypertrophy and reoperation rates. Both techniques had hyaline-like cartilage on second-look biopsies
Zeifang et al. 2010 [41]	Randomized controlled trial	P-ACI (10 patients) versus M-ACI (11 patients)	2 years		No differences in IKDC, SF-36, and Tegner scores between groups. Lysholm score were significantly better in the P-ACI group. MOCART scores on postoperative MRI were significantly better in P-ACI group
Niethammer et al. 2015 [42•]	Retrospective cohort	M-ACI (143 patients)	2 years		Revision rate was 23.4 % for symptomatic bone marrow edema (8.3 %, n=3), arthrofibrosis (22.2 %, n=8), and partial graft cartilage deficiency (47.2 %, n=17)

ACI autologous chondrocyte implantation, *KOOS* Knee Injury and Osteoarthritis Outcome Score, *P-ACI* periosteum-based autologous chondrocyte implementation, *C-ACI* collagen membrane autologous chondrocyte implantation, *M-ACI* membrane-associated autologous chondrocyte implantation, *MOCART* magnetic resonance observation of cartilage repair tissue, *CRS* cincinnati rating system, *IKDC* international knee documentation committee, *KSS* knee society score, *OA* osteoarthritis, *SF-36* short form 36, *MF* Microfracture, *WOMAC* Western Ontario and McMaster Universities Arthritis Index

of the patients was 30.5 years, and the mean lesion size was 4.54 cm^2. They did not show any statistical difference in results between the two groups; however, a significant number of patients required a subsequent arthroscopy and periosteal shaving in the P-ACI group.

M-ACI was developed to mitigate some of the disadvantages of P-ACI and C-ACI, namely, unequal distribution of cells in the chamber, delamination, and suturing of the membrane to surrounding cartilage. A collagen I/III matrix is infused with the harvested chondrocytes and implanted as a unit, with early reported results comparable to previous generations of ACI, although inconclusive. Bartlett et al. [39] preformed a randomized, prospective trial comparing C-ACI (44 patients; mean age, 33.7 years) to M-ACI (47 patients; mean age, 33.4 years) with a mean lesion size of 6 cm^2 and a mean follow-up period of 1 year. He reported improvement in all clinical scores with both the techniques, and histologic assessments showed no significant difference between the groups. Zeifang et al. [41] compared full-thickness cartilage lesions treated with either P-ACI or M-ACI techniques in 21 patients with a mean defect size of 4.1 cm^2 on the femoral condyle. At 2 years, they found similar IKDC, Tegner, and SF-36 scores; however, the Lysholm and Gillquist scores were significantly lower in the M-ACI group. On MRI examination, the M-ACI group had significantly lower magnetic resonance observation of cartilage repair tissue (MOCART) scores. Recently, a revision rate of 23 % has been reported in M-ACI within the first 2 years for arthrofibrosis, symptomatic bone marrow edema, and partial graft cartilage deficiency [42•]. Also, many of these patients have graft hypertrophy within the first 2 years with an unknown clinical significance [43•].

Because these techniques are relatively new, there are only a few short-term follow-up studies with small patient cohorts, and predominance of young patients with medium-sized defects. More studies are needed with larger sample sizes and longer follow-up going forward with these newer techniques to demonstrate improved outcomes compared to first-generation ACI. In our practice, we perform C-ACI using a noncrossed-linked type I/III collagen porcine collagen patch (Bio-Gide® Geistlich). This patch is commonly used in oral-maxillary facial procedures and has a natural bilayer with a smooth layer that is placed facing the joint and a dense porous layer that acts as a guide for chondrocyte attachment. The patch can be easily handled by the surgeon and has resiliency ideal for suture placement. There are several commercially available collagen membrane patches, some of which utilize bovine collagen. The ideal patch should have acceptable biodegradation time (Bio-Gide 4–6 weeks), high vascularization and ingrowth, and limited potential for foreign body reaction. Patch overgrowth has not been an issue utilizing this commercially available collagen patch.

In our active duty military patient population, it is critical to select the appropriate patient for success of the procedure and return to full duty. In addition to the aforementioned indications and contraindications, one of the most important factors leading to success is selecting a patient who can be cooperative with weight-bearing restrictions and for a long rehabilitation protocol (12–18 months). Surgeons should be aware that all generations of ACI are considered experimental in the patellofemoral joint and on the talus. C-ACI and M-ACI are also considered experimental due to the lack of conclusive evidence of improved outcomes over first-generation ACI.

Conclusion

Significant chondral injury is a major clinical challenge to bring relief and increased function to patients. There are many surgical options available to treat this difficult condition, and many of these techniques are continuing to be developed and refined. It is imperative for a provider treating these conditions to keep up on current literature. Cell-based therapies, including ACI, offer promising and attractive treatment options for patients with the isolated cartilage lesion or as salvage procedures for other failed treatments. Further randomized controlled studies to investigate the long-term outcomes of these procedures are needed to help guide treatment in this continually evolving field of cartilage reconstruction.

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Compliance with Ethics Guidelines

Conflict of Interest Dr. Giuliani and Dr. Pickett have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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