Management of Focal Cartilage Defects in the Knee

Is ACI the Answer?

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Abstract

Injuries to the articular cartilage of the knee are common. They alter the normal distribution of weightbearing forces and predispose patients to the development of degenerative joint disease. The management of focal chondral lesions continues to be problematic for the treating orthopaedic surgeon. Although many treatment options are currently available, none fulfill the criteria for an ideal repair solution: a hyaline repair tissue that completely fills the defect and integrates well with the surrounding normal cartilage. Autologous chondrocyte implantation (ACI) is a relatively new cell-based treatment method for full-thickness cartilage injuries that in recent years has increased in popularity, with early studies showing promising results. The current article reviews the nature of cartilage lesions in the knee and the treatment modalities utilized in their management, focusing on the role ACI plays in the surgical treatment of these complex injuries.

More than 250 years ago, in a paper presented to the Royal Medical Society, Scottish physician William Hunter stated that "from Hippocrates to the present age, it is universally accepted that an ulcerated cartilage is a troublesome problem and once destroyed, it never repairs."[1] Even today, with our rapidly evolving basic science knowledge and improved technology, articular cartilage injuries continue to be problematic for the treating orthopaedic surgeon. Patients with full-thickness cartilage defects typically present with vague symptoms of knee pain and intermittent swelling episodes. These defects are significant, as they can produce an altered distribution of weightbearing forces and possibly lead to the premature development of degenerative arthritis.

Cartilage injury in the knee is an underestimated problem among orthopaedic surgery patients. Recent reviews of consecutive knee arthroscopies have demonstrated an incidence of chondral defects ranging from 60% to 65%, irrespective of the surgical indication.[1-4] Hjelle and colleagues showed in a prospective evaluation of 1000 consecutive cases that chondral or osteochondral lesions were present in 61% of their cases.[4] Nineteen percent of patients in this series had focal defects with a mean size of 2.1 cm^2. The authors reported that when isolated cartilage injuries were present, their most common site was on the medial femoral condyle (58%). In a similar series of 993 arthroscopic cases, Aroen and coworkers also reported a high prevalence of cartilage injury in a general sports medicine patient population.[2] Despite the fact that the majority of these procedures were performed for meniscal pathology, articular cartilage defects were found in 66% of cases. Focal defects were observed to be present in 20% of patients, with the medial femoral condyle most often affected. Overall, a localized International Cartilage Repair Society (ICRS) grade III or IV lesion was found in 11% of patients, with 55% of these defects at least 2 cm^2 in size.

Basic Science of Articular Cartilage

The hyaline cartilage of the articular surface is an aneural, avascular, and alymphatic tissue with a limited intrinsic healing potential.[5] Water makes up 65% to 80% of the wet

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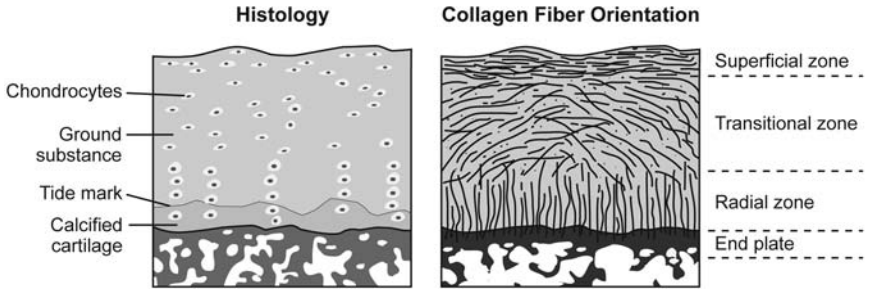

Figure 1 Ultrastructure of articular cartilage. The composition, structure, and function of the components of articular cartilage varies depending on the depth from the joint surface.

weight of articular cartilage, allowing for the load-dependent deformation and viscoelasticity important for normal weight bearing joint function. Ten to 20% of the wet weight of cartilage is attributable to collagen, predominantly type II collagen, forming the principal component of the macrofibrillar structural network and providing tensile strength to the tissue. Proteoglycans make up another 10% to 20% of the wet weight. These protein-polysaccharide molecules are secreted into the extracellular matrix by chondrocytes, where they are primarily responsible for the compressive strength of the tissue. Chondrocytes make up only 1% to 5% of the volume of articular cartilage and are spread sparsely throughout the extracellular matrix where they synthesize matrix components and regulate the tissue's metabolic activity.

The composition, ultrastructure, and function of articular cartilage varies depending on the depth from the joint surface (Fig. 1).[5] The superficial zone is the thinnest layer, composed of flattened ellipsoid shaped cells, with a high collagen and low proteoglycan content. Collagen fibers in the superficial zone are arranged parallel to the surface, providing tensile and shear strength to the tissue. The transitional zone has a lower cell density with spheroid shaped cells present, abundant extracellular matrix, and large diameter collagen fibers arranged in a random pattern. The deeper radial zone has the lowest cell density, the highest proteoglycan content, and the largest diameter collagen fibers oriented perpendicular to the surface, contributing to the compressive strength of the tissue with joint loading. Finally, the calcified cartilage zone, the region just below the tidemark, has few cells with low metabolic activity. The unique characteristic of the calcified cartilage zone is the production of type X collagen, which helps anchor the tissue to the underlying subchondral bone

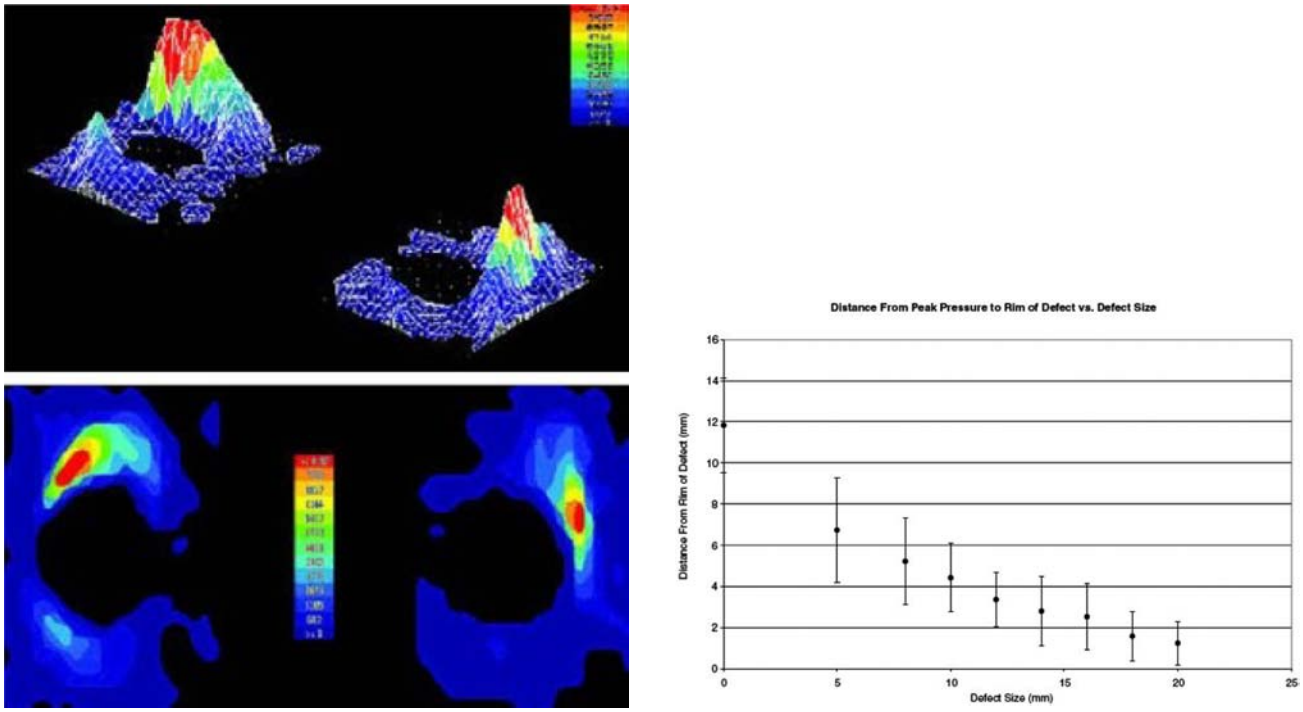

Figure 2 Impact of full-thickness chondral defects on load distribution in cadaveric knees. In defects greater than 1 cm in size, stress from applied loads concentrates on the defect rim (Left). The larger the defect, the greater the stress concentration at the defect edge (Right). (Reproduced from: Guettler JH, Demetropoulos CK, Yank KH, Jurist KA. Osteochondral defects in the human knee: influence of defect size on cartilage rim stress and load redistribution to surrounding cartilage. Am J Sports Med. 2004. 32(6):1451-8). © 2004 American Orthopaedic Society for Sports Medicine. With permission.)

Table 1 Outerbridge Classification of Chondral Injury

Grade 0	Normal appearing cartilage
Grade 1	Softening/swelling of the cartilage
Grade 2	Fragmentation/fissuring < ½ inch in diameter
Grade 3	Fragmentation/fissuring > ½ inch in diameter
Grade 4	Cartilage erosion down to subchondral bone

Table 2 International Cartilage Repair Society (ICRS) Classification

Grade 0	Normal appearing cartilage
Grade 1	Soft (a) or superficial fissure (b)
Grade 2	Defect < 50% of the cartilage thickness
Grade 3	Defect > 50% of the cartilage thickness
Grade 4	Defect extends to or into the subchondral bone

while acting as a shock absorber during activity.

The unique composition and structure of articular cartilage allows it to function as a low friction gliding surface, while evenly distributing applied loads, thereby minimizing peak pressures experienced by the underlying subchondral bone. Under normal circumstances, articular cartilage is a relatively wear resistant tissue. However, in the presence of a full-thickness chondral defect, there is an alteration in the distribution of weightbearing joint forces.[6] When defects occur in the cartilaginous surface, there is a concentration of stresses at the defect rim and on the opposing articular surface. The decreased contact area and the edge loading that results increases peak stresses experienced in the adjacent cartilage. This can lead to degenerative changes, including chondrocyte apoptosis, changes in the composition of the extracellular matrix (decreased proteoglycan content and increased water content), and overall altered mechanical properties. Using digital pressure sensors placed on the articular surface, Guettler and associates[6] evaluated the impact of full-thickness defects on load distributions in human cadaveric knees. The investigators found that for defects greater than 10 millimeters in diameter stress from applied loads concentrated on the defect rim. The larger the defect, the higher the peak stresses seen on the adjacent cartilage and the greater the concentration at the defect rim (Fig. 2).

Classification of Cartilage Injuries

To guide management decisions and understand the prognosis of articular cartilage lesions, the treating orthopaedic surgeon needs the ability to classify these injuries when present. In 1961, Outerbridge[7] classified cartilage abnormalities present at the time of knee arthrotomy. In this frequently used classification system (Table 1), grade 1 changes include evidence of softening or swelling of the cartilage surface. Grade 2 changes include fragmentation and fissuring less than 0.5 inch in size, while grade 3 describes lesions that are greater than 0.5 inch in diameter. Outerbridge grade 4 lesions have erosion of cartilage to subchondral bone.

With increasing interest in cartilage injuries and repair techniques, the International Cartilage Repair Society (ICRS) developed its own classification system to more accurately describe chondral defects and to allow for uniformity in research reporting (Table 2). ICRS grade 1 lesions include those that demonstrate softening (a) or those with superficial fissures present (b). Grade 2 injuries describe defects that have a depth less than 50% of the tissue thickness. Defects that have a depth greater than 50% of the tissue thickness are designated as grade 3, while ICRS grade 4 lesions are those that are full thickness, extending to or through the subchondral bone plate.

Treatment Options

For the symptomatic patient with a full-thickness cartilage injury who has failed a trial of nonoperative treatment, including nonsteroidal anti-inflammatory medications (NSAIDs) and physical therapy, surgical intervention may be necessary. An ideal surgical treatment method would allow for regeneration of a hyaline repair tissue, completely filling the chondral defect while integrating with the surrounding normal cartilage tissue. The repair tissue would be long lasting and have normal mechanical properties. The current surgical treatment options utilized by sports medicine specialists in the management of chondral defects include lavage and shaving chondroplasty, marrow stimulation procedures (microfracture and subchondral abrasion), osteochondral grafting techniques (mosaicplasty and the osteochondral autograft transfer system [OATS]), and cell-based repair methods (autologous chondrocyte implantation).

Lavage and Shaving Chondroplasty

Evaluating the efficacy of lavage and debridement, Hubbard compared simple lavage with shaving chondroplasty in 76 patients with focal grade 3 and 4 lesions of the medial femoral condyle.[8] Although debridement provided symptom relief in 80% of patients at 1-year follow-up, the results deteriorated at 5 years, with only 59% of patients reporting pain free knee function. While this was significantly better than the outcomes seen with lavage alone (20% pain free at 1 year and 11% pain free at 5 years), Hubbard concluded that while lavage and debridement may provide temporary

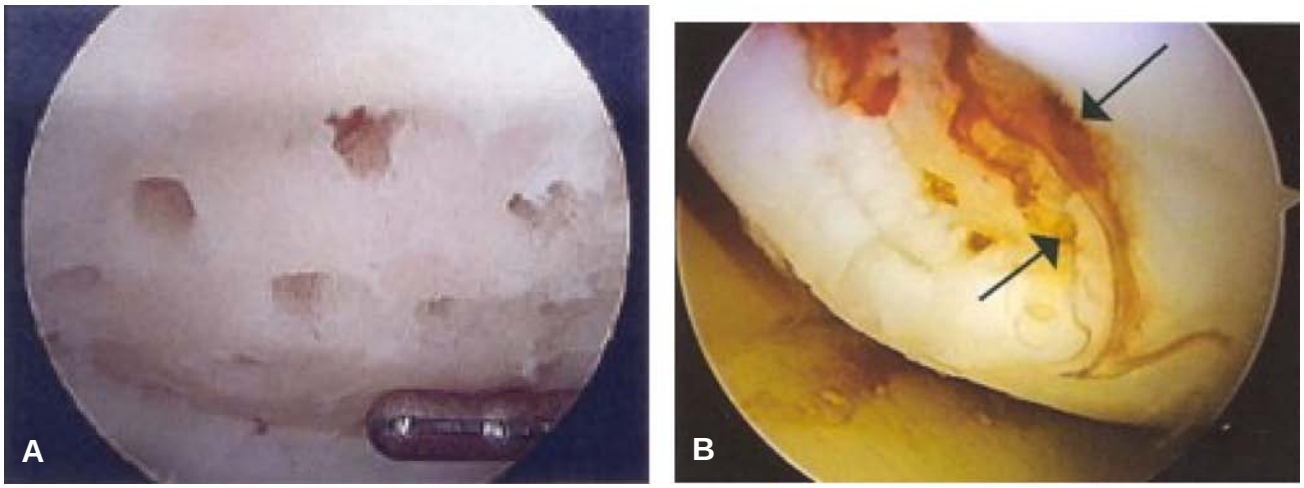

Figure 3 Marrow stimulation technique. Penetration of the subchondral bone plate with microfracture (**A**) leads to bleeding and subsequent fibrin clot formation within the chondral defect (**B**). Marrow derived mesenchymal cells migrate into the clot and allow for the formation of a fibrocartilaginous repair tissue.

symptomatic relief, it does not address the primary pathology present.

Marrow Stimulation Procedures

The principle behind marrow stimulation procedures is that penetration of the subchondral bone plate leads to bleeding and fibrin clot formation within the chondral defect (Fig. 3). Pluripotent, marrow-derived mesenchymal cells migrate into the clot and allow formation of a fibrocartilaginous repair tissue. This tissue provides a more congruous joint surface, leading to symptomatic improvement in the majority of published reports. However, the resultant fibrocartilaginous repair tissue present following marrow stimulation techniques is composed of predominantly type 1 collagen, with poor wear characteristics and an associated deterioration of clinical results over time.[9-11,14] The inferior biochemical and biomechanical properties of fibrocartilage have led many investigators to question its durability and longevity, with most believing that its presence will predispose the patient to the development of future degenerative joint disease.

Steadman and colleagues[9] reviewed the outcome of microfracture in 72 patients younger than 45 years old with isolated, full-thickness chondral defects. The authors reported that at 7 years of follow-up, 80% of the patients in the study were "improved." Multivariate analysis demonstrated that age was a predictor of functional improvement, with younger patients having better outcomes at each follow-up time point. The treated lesions in this study were relatively small (2.7 cm^2), and no histologic evaluation of the repair tissue was performed. In a prospective evaluation of 85 patients with full-thickness lesions managed with microfracture, Kreutz and colleagues[10] found that patients younger than 40 years old had significantly better outcomes than those older than 40, demonstrating higher ICRS and Cincinnati knee scores and postoperative MRI with evidence of better defect fill.[10] Importantly, the investigators demonstrated a decline in clinical results between 18 and 36 months following the procedure, which was especially pronounced in the patients from the over 40 years treatment group.

Osteochondral Grafting Techniques

The goal of osteochondral grafting techniques is complete reconstruction of the normal architecture of the cartilaginous surface. This is accomplished by taking autologous osteochondral plugs from non-weightbearing regions of the knee to fill full-thickness defects (Fig. 4). Mosaicplasty and OATS have shown good results for the treatment of small and medium size defects (ranging from 1 to 4 cm^2), but their applicability is limited by defect size, available donor site surface area, donor site morbidity, and difficulties achieving optimal surface congruence. The advantages of osteochondral grafting procedures include being a one-stage technique and chondral defect fill with hyaline cartilaginous tissue. The graft retains its normal histologic appearance and shows consistent integration at the implantation site secondary to bony healing. The main drawback noted with OATS and mosaicplasty is the persistent gap that remains between defect edges and the graft following implantation, often filling with fibrous tissue (Fig. 5). This lack of integration with the adjacent area cartilage leads to persistent alteration in load distribution, potentially leaving the patient open to the development of future degenerative changes.

Hangody and Fules[11] reviewed 831 mosaicplasty cases performed over a 10-year period and found that for full-thickness femoral condyle defects the procedure led to good to excellent results in 92% of cases. Three percent of patients in this series reported donor site symptoms. Eighty-three patients underwent second-look arthroscopy,

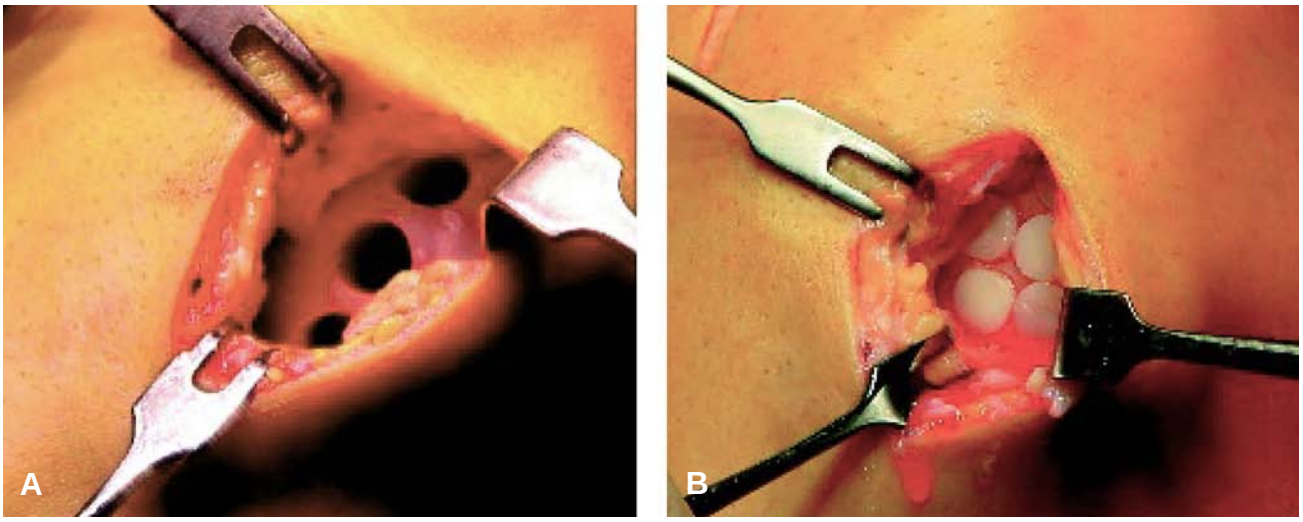

Figure 4 Osteochondral grafting techniques. Autologous osteochondral plugs are harvested from non-weightbearing regions (**A**) to fill full thickness defects on the femoral condyle (**B**). (Reproduced from: Hangody L, Füles P. Autologous osteochondral mosaicplasty for the treatment of full-thickness defects of weight-bearing joints: ten years of experimental and clinical experience. J Bone Joint Surg Am. 2003;85(Suppl 2):25-32. © 2003 The Journal of Bone and Joint Surgery, Inc. With permission.)

which showed a high percentage of graft survival (83%), grossly congruent joint surfaces, and donor sites that had filled in with fibrocartilage tissue. Jakob and colleagues[12] found similar good results in their series of 52 cases treated with autologous osteochondral grafting, with 88% of patients satisfied with their outcome at a mean follow-up of 37 months. Four cases in this series required reoperation secondary to graft failure. In a prospective review of 37 young athletes with grade 4 chondral defects treated with mosaicplasty, Marcacci and coworkers[13] reported that at 2 years of follow-up 78% of patients had good to excellent results. The investigators found that young age and the presence of concomitant procedures, such as ligamentous reconstructions, were factors that contributed to a good outcome. They also found that the larger the defect, the poorer the outcome following mosaicplasty. Overall, 73% of patients in this series were able to return to athletics at their pre-injury level and were satisfied with their functional outcome following surgery.

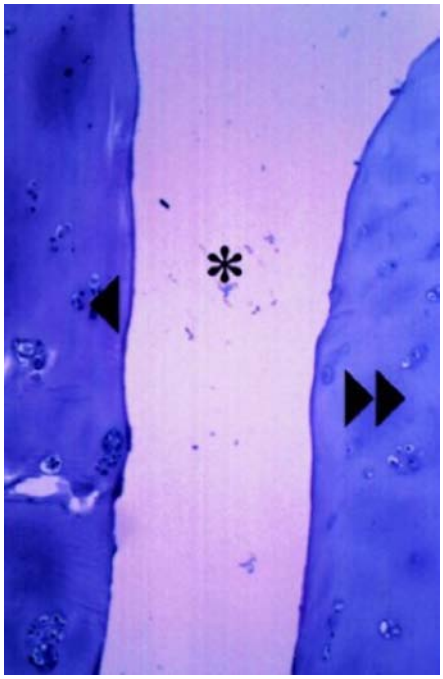

Figure 5 Persistent gap remaining between the defect edges and the implanted graft. Lack of integration with the adjacent area cartilage leads to persistent alteration in load distribution. (Reproduced from: Horas U, Pelinkovic D, Herr G, et al. Autologous chondrocyte implantation and osteochondral cylinder transplantation in cartilage repair of the knee joint: a prospective, comparative trial. J Bone Joint Surg Am. 2003. 85185-92. © 2003 The Journal of Bone and Joint Surgery, Inc. With permission.)

Autologous Chondrocyte Implantation (ACI)

Autologous chondrocyte implantation was first described, in 1994, by Brittberg and colleagues.[14] At the present time, autologous chondrocyte implantation is a two stage procedure. The procedure starts with an arthroscopic biopsy of healthy chondral tissue with in-vitro culture expansion followed by chondrocyte implantation as a second surgical procedure. The main principle behind the technique is that implantation of chondrocytes will produce a repair tissue that most closely replicates the composition and function of normal hyaline cartilage, restoring the durability and function of the joint articular surface.

Indications for ACI include symptomatic, large, full-thickness chondral lesions located on the femoral condyles or the trochlear groove. Recent studies have shown that results for patellar and tibial lesions are not as consistent. ACI is typically reserved for younger patients with indications including normal bony align-

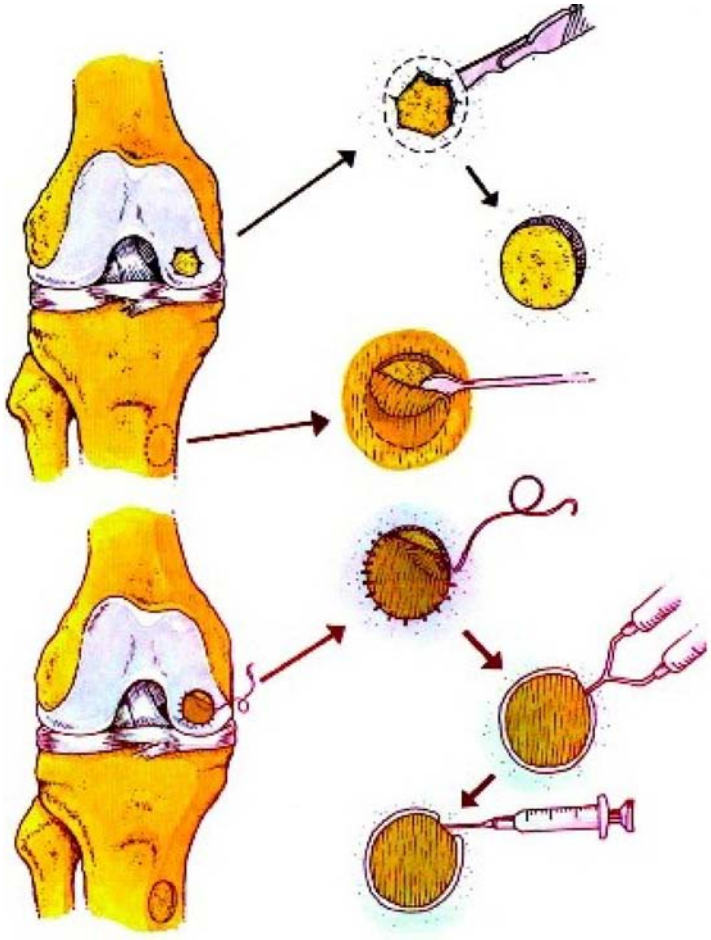

Figure 6. Schematic of autologous chondrocyte implantation (ACI) technique. (Illustration courtesy of and copyright © 2011 Jón Karlsson, MD, PhD, Professor of Orthopaedics and Sports Traumatology, Göteborg University Göteborg, Sweden. With permission. Illustrator: Annette Dahlström. Source: Brittberg M, Peterson L, Sjgren-Jansson E, et al. Articular cartilage engineering with autologous chondrocyte transplantation. J Bone Joint Surg Am. 2003;85(Suppl 3):109-15. Originally published in Karlsson J (ed): Knäledens Sjukdomar och Skador. Södertälje, Sweden: Astra Läkemedel, 2000, p. 70.)

ment, ligamentous stability, intact menisci, normal knee range of motion, and the ability to comply with a relatively rigorous postoperative rehabilitation program. If normal alignment or ligamentous stability is not present, concomitant procedures may be necessary in order to optimize the outcome of the cartilage repair. ACI is contraindicated in patients with inflammatory arthritides, a history of septic arthritis, and those with advanced degenerative changes, such as significant lesions on the opposing articular surface.

ACI Surgical Technique

The surgical technique starts with an arthroscopic evaluation of the lesion, noting its location and size, in addition to the condition of the opposing articular surface. Using a curette or gouge, a chondral biopsy is taken from either the superior peripheral edges of the medial or lateral femoral condyle or from the edges of the intercondylar notch. Ideally, 3 to 4 slivers, 5 x 10 millimeters in size are harvested, yielding 200 to 300 milligrams of healthy cartilage tissue. The specimens are then shipped to the lab where the chondrocytes are enzymatically isolated from the extracellular matrix and cultured in monolayer for 3 to 4 weeks. This increases the volume of cells available for implantation 30-fold, for a yield of approximately 12 million viable chondrocytes. The time between the first and second stages of the procedure typically range from 6 weeks to 6 months.

The surgical approach for the implantation step of the procedure depends on the size and location of the defect with either a medial or lateral parapatellar arthrotomy used. The defect is prepared into a circular or oval shape by debriding all damaged and unstable tissue down to subchondral bone with a rim of stable healthy cartilage. The walls of the defect are kept as vertical as possible to allow for suture fixation of the graft. Care is taken to avoid penetration of the subchondral bone plate, as this would stimulate a fibrous response similar to that seen with the microfracture procedure. Next, a periosteal flap that will cover the cartilage defect is harvested from the proximal medial tibia, 2 to 3 centimeters distal to the pes anserinus insertion (the medial distal femur is an alternate donor site). All overlying fat and fascial tissue is removed and an appropriately sized flap, typically oversized by 2 mm, is cut sharply with the tissue carefully elevated from the bony surface.

With the cambium, or inner layer, of the periosteal flap facing the defect, it is secured to the surrounding cartilage

using 6-0 vicryl suture, with the sutures spaced 2 to 3 millimeters apart. The suture fixation is started at the corners of the flap to allow for appropriate tensioning and a small opening is left superiorly for the injection of the cultured chondrocytes. Fibrin glue is applied to fill the gaps between the sutures, creating a water tight pouch, which is checked with a trial saline injection. With the periosteal pouch prepared, the cultured chondrocyte suspension is aspirated from the shipping vial into a tuberculin syringe with an 18-gauge angiocatheter. The cells are then injected into the defect, focusing on an even distribution within the periosteal pouch. The superior opening is then closed with 6-0 vicryl suture and is sealed with fibrin glue (Fig. 6).

Postoperative Rehabilitation

In the immediate postoperative period, patients are kept non-weightbearing in a functional or unloader brace. Early range of motion is encouraged, with 6 to 8 hours of continuous passive motion (CPM) recommended daily. Protocols for rehabilitation following autologous chondrocyte implantation vary considerably in the orthopaedic literature. Most authors divide postoperative therapy into five phases over a 1-year period, with early rehabilitation tailored to protect the healing graft. The three main components to ACI rehabilitation include protected and progressive weightbearing, restoration of knee range of motion, and enhancement of muscle control and strengthening.

In phase 1, during the first 4 weeks post-procedure, the goals of therapy are to protect the healing tissue from loading and shear forces, to prevent the formation of adhesions, and to restore full passive knee extension while regaining quadriceps control. Most surgeons keep their patients in a functional brace while allowing partial weightbearing. The modalities typically used during this early phase of therapy include CPM, cryotherapy, and patellar mobilization techniques. From 4 weeks to 8 weeks following ACI (phase 2), weightbearing is progressed, with the goal of full weightbearing at 8 weeks. During this phase, patients are started on active range of motion exercises and modalities such as hydrotherapy are effective. In phase 3, the brace is discontinued, and the patients start light resistance and balance training in an effort to regain full, active knee range of motion with normal proprioception and quadriceps function. Between 3 and 4 months post-procedure (phase 4), patients work on increasing their strength and stamina in anticipation of returning to athletic activity. After the 6 months (phase 5), most surgeons allow their patients to resume low impact athletic activity, while a full return to contact sports is often delayed until 1 year following the procedure.

Outcomes Following ACI

Brittberg and associates[15] reported 2- to10-year outcomes on 244 patients with large grade 3 and 4 chondral defects. They found that at a mean follow-up of 4 years, 90% of patients treated for femoral condylar lesions had good to excellent results. A portion of this cohort was followed for a mean of 7.4 years postoperatively, and their results were found to be stable at this longer term time point, with 84% of the overall cohort having good to excellent results.[16] The investigators demonstrated continued improvement in the patients' Cincinnati knee score and Tegner activity score between 2 years and their final follow-up. Based on their data, the authors concluded that if ACI is successful, a long lasting, durable repair is achieved. Second-look arthroscopy performed at a mean of 54 months showed that 75% of cases had hyaline-like repair tissue present, while the remainder had a mix of hyaline and fibrocartilage. Importantly, the majority of specimens in this series had evidence of a fibrous periosteal remnant present. In a multi-center prospective study in the United States, Browne and colleagues[17] evaluated the outcomes of ACI in a group of patients with large chondral defects, with 70% of patients having failed at least 1 prior cartilage repair. The investigators found that at 5 years of follow-up, significant improvements were seen with respect to pain, swelling, and overall function; this led them to conclude that ACI was an effective treatment for large defects that have failed prior attempts at restoration.

The initial success reported with ACI for younger athletic patients led some authors to try and expand its indications to include older patients with symptomatic chondral lesions. Rosenberger and coworkers[18] prospectively evaluated a cohort of 56 patients older than 45 years and found that at a mean follow-up of 4.7 years, 72% rated their outcome as good or excellent, and 81% would choose the procedure again if necessary. However, 43% of patients in this series (24 cases) required additional arthroscopic procedures for periosteal-related problems and adhesions that had developed post-op. A similar high reoperation rate was reported by Henderson and associates[19] in their series of 170 cases in which 97 patients required an additional procedure; 74% of the reoperations in this series performed within 2 years of the index procedure were related to hypertrophy of the periosteal flap. Patients in this series who required reoperation following ACI, whether it was for the treatment of postoperative periosteal hypertrophy or for other reasons, had significantly worse knee functional scores at 4.5 years of follow-up compared to those who did not require an additional procedure.

Fu and colleagues[20] retrospectively compared the outcomes following ACI with that seen after debridement in 96 patients followed for 3 years postoperatively. At the time of final follow-up, 81% of patients from the ACI treatment group had at least 5 points of improvement in their Cincinnati knee score compared to a 2-point improvement seen in 60% of patients managed with debridement. Patients in the ACI group had significantly less knee pain and fewer swelling episodes but reported more subsequent procedures compared to those in the debridement group.

In a comparison of ACI and microfracture, Knutsen and coworkers[21] performed a randomized control trial, including 80 patients who presented with symptomatic, full-thickness chondral defects. At 2 years of follow-up, both treatment groups showed improvement and the authors noted only subtle differences between the two treatment options with respect to the postoperative Lysholm knee score and visual analog pain score. Overall, the younger patients tended to fare better, and while patients with small defects treated with microfracture had better outcomes than those with large defects, no size effect was reported for those managed with ACI. Histologic exam at second-look arthroscopy showed no significant difference between the treatment groups. However, the reoperation rate was significantly higher in the ACI cohort, with 10 patients undergoing additional procedures secondary to graft hypertrophy. Based on their findings, the investigators recommended microfracture as the first line treatment for smaller, focal defects, while reserving ACI for larger defects and for patients in whom microfracture failed to improve their symptoms or knee function.

Bentley and colleagues[22] compared ACI and mosaicplasty in a prospective randomized controlled trial, including 100 patients with large, full-thickness cartilage lesions. At 19 months of follow-up, the investigators reported good to excellent results in 88% of patients treated with ACI compared to 69% of patients managed with mosaicplasty. Second-look arthroscopy performed at 1 year following the index procedure demonstrated that 84% of the ACI cases had good to excellent repair tissue based on the ICRS score compared with 34% of those treated with mosaicplasty. Biopsies of 19 patients in the ACI group were taken at the time of the second-look arthroscopy, and 74% of cases had evidence of hyaline-like repair tissue present. Predominance of fibrocartilage was seen in 26% of cases, which the authors attributed to potential undetected penetration of the subchondral bone plate during the time of defect preparation. In a similar comparison of ACI and the OATS procedure, Horas[23] randomized 40 patients with a mean defect size of 3.75 cm^2. Identical postoperative protocols were utilized, and both groups showed significant improvement over 2 years of follow-up. However, the functional improvement seen in the ACI group consistently lagged behind that seen in the OATS group throughout the follow-up course. Six patients in the ACI group underwent second-look arthroscopy and had biopsies of the repair tissue taken. Histologic analysis demonstrated that the defect was completely filled, and the repair tissue had integrated well with the surrounding normal cartilage. However, the repair tissue was found to be highly cellular and irregular in appearance. Staining showed that the tissue was predominantly fibrocartilage with only focal areas of type II collagen present deep within the repaired defect. Second-look performed on eight patients from the OATS cohort showed macroscopically viable cartilage with no evidence of degeneration and a gross appearance similar to the surrounding normal tissue. Histologic evaluation showed that while the implanted plugs retained a hyaline appearance and composition and had good bony integration at their bases, gaps between the plug and the native tissue remained. Based on their clinical and histologic findings, the authors concluded that while both treatment options were effective, they advocated OATS over ACI for lesions smaller than 4 cm^2 in size.

Second and Third Generation ACI Techniques

Secondary to the reports of complications associated with the periosteal patch leading to high reoperation rates, recent modifications to the ACI technique have been developed. Second generation ACI utilizes a specialized bilayer collagen membrane instead of the periosteal flap to cover the implanted chondrocytes within the treated chondral defect. The collagen membrane has a compact layer to prevent diffusion of the cells out of the pouch and an inner porous layer to encourage cell invasion and attachment. This adaptation avoids the second incision needed in the classic ACI technique and theoretically reduces the potential for postoperative periosteal hypertrophy.

Haddo and associates[24] evaluated the outcomes following second generation ACI in a series of 31 patients and found at second-look arthroscopy that good to excellent integration was seen in 72% of cases. More importantly, the collagen membrane was found to have completely resorbed in every case with no evidence of graft hypertrophy noted. In a prospective randomized trial comparing first and second generation ACI techniques, Gooding and colleagues[25] showed that 74% of collagen covered cases had good to excellent results compared to 67% of periosteal flap covered cases.[6] While 36% of the periosteal flap covered cases required reoperation for symptomatic graft hypertrophy, none of the collagen covered cases required an additional operative procedure.

Recently, a third generation of ACI has been introduced using three-dimensional scaffolds to act as carriers for the implanted chondrocytes. This matrix induced ACI (MACI), contains the chondrocytes within the defect and supports the maintenance of a chondrocyte phenotype without requiring a periosteal or collagen flap for defect coverage. Marlovits and coworkers[26] used high resolution MRI to evaluate early graft incorporation following MACI in 16 patients treated for full-thickness cartilage lesions. The authors found that 87.5% of patients in this series had evidence of complete defect coverage and graft incorporation at approximately 1 month post-procedure. In a prospective randomized controlled trial comparing collagen-covered ACI with MACI in 91 patients, Bartlett and associates[27] showed both treatments resulted in clinical improvement at 1 year of follow-up. Evaluation at the time of second-look arthroscopy demonstrated 74% of cases with good to excellent repair tissue in the second generation ACI

patients compared to 67% good to excellent results in the third generation ACI treatment group. Interestingly, graft hypertrophy still occurred, even with the modifications to the ACI surgical technique, leading to a 9% incidence of reoperation in both groups.

Conclusion and Summary

Full-thickness chondral defects remain a significant challenge to the treating orthopaedic surgeon secondary to the limited healing potential that is intrinsic to the tissue. While many treatment options exist, variable outcomes for each technique have been reported in the orthopaedic surgery literature. Each treatment brings its own advantages and disadvantages, and to date none has fulfilled the criteria for an ideal management solution. In recent years, ACI has increased in popularity, and early studies show promising results. Although the benefits of a cell based technique that results in a hyaline repair tissue with good integration at the defects is attractive, the problems associated with the current forms of ACI have kept it from being convincingly better than other available cartilage repair methods. Autologous chondrocyte implantation has been shown to be a good option for the management of both medium sized and large chondral defects. As the technology and technique evolves, it may become the first line treatment method, but for now it remains as one of a few tools for managing this difficult pathology.

Future directions include the development of a single stage ACI technique, which has been initiated with the CAIS system (Depuy Mitek, Raynham, Massachusetts). With this system, the harvested cartilage tissue biopsies are morselized and dispersed onto a three-dimensional scaffold at the time of the index procedure. A recent pilot study demonstrated this technique to be effective, with patients' reporting significant improvement from their baseline and postoperative MRI showing good graft incorporation.[28] Other possibilities include advances in gene therapy to allow genetically modified chondrocytes to be implanted into the chondral defects, implantation of osteochondral allografts, and the use of partial surface replacement implants.

Disclosure Statement

None of the authors have a financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

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