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Autologous Chondrocyte Implantation

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Summary

Currently, autologous chondrocyte implantation (ACI) is ideally indicated for symptomatic ICRS grade III–IV lesions greater than 2 cm^2 along the femoral condyle or trochlear regions. High-demand patients between the ages of 15 to 55 years of age with excellent motivation and compliance potential should be chosen. Lars Peterson assessed his first 101 patients at intermediate to long-term follow-up. Good to excellent clinical results were seen in 92% of the isolated femoral condylar lesions, while these results decreased to 67% in patients with multiple lesions. Osteochondritis dissecans lesions demostrated 89% good-to-excellent results, and in contrast to the initial series patellar lesions did relatively well with 65% good-to-excellent results. Histologic analysis of the matrix in 37 biopsy specimens assessing for type II collagen showed a correlation between hyaline-like repair tissue and good-to-excellent clinical results. Scott Gillogly evaluated 112 patients with 139 defects treated with the ACI procedure over a 5-year period of time. Average size of the defect was 5.7 cm^2 with over 60% of patients having failed at least one prior procedure. According to the clinician evaluation portion of the Modified Cincinnati Scale 93% demonstrated good-to-excellent outcomes, while the patient evaluation portion demonstrated 89% good-to-excellent outcomes. This chapter will describe the technique of ACI first reported by the senior author (LP) in 1994, as well as additional methods to deal with the various complex problems that can arise during these demanding procedures. A further review of the current literature supporting this techique as well as those studies that compare ACI to other accepted treatment options will be undertaken as well. In addition, we will review and discuss developing literature supporting current use of various matrices in combination with autologous chondrocytes to treat this difficult patient population.

Key Words: Articular cartilage; chondrocyte; implantation; subchondral bone; collagen; scaffold.

INTRODUCTION

Injuries to joint surfaces can result from acute high-impact or repetitive shear and torsional loads to the superficial zone of the articular cartilage architecture. Two studies using direct arthroscopic visualization have shown that the overall incidence of isolated, focal articular cartilage defects is around 5%. While retrospectively reviewing more than 31,000 arthroscopic procedures, Curl et al. demonstrated a 63% incidence of chondral lesions, with an average of 2.7 lesions per knee *(1)*. With increasing age, this percentage and the number of individuals with multiple defects gradually rose. Using the modified Outerbridge classification system, they found grade IV lesions in 20% of the patients, but only 5% of individuals in this category were younger than 40 yr. Three of four people in this younger population had solitary lesions.

Interestingly, in a prospective study undertaken by Hjelle and colleagues, chondral or osteochondral lesions were found in 61% of the patients, and focal defects were found in 19%

From: *Cartilage Repair Strategies*
Edited by: Riley J. Williams © Humana Press Inc., Totowa, NJ

of the patients; these percentages were similar to those found in the retrospective analysis *(2)*. In this prospective assessment, the mean defect size was 2.1 cm^2. A single, well-defined International Cartilage Repair Society (ICRS) grade III or IV defect (at least 1 cm^2) in a patient younger than 40, 45, or 50 yr old accounted for 5.3, 6.1, and 7.1% of all arthroscopies, respectively. The incidence of articular lesions secondary to work-related and sporting activities has been reported to be as high as 22–50% in other studies *(3,4)*. Such injuries alone or in combination with ligamentous instability, meniscal pathology, or mechanical malalignment can be quite debilitating for patients.

Although it is difficult to predict the long-term effects of cartilage defects in the multiply injured knee, it is certain that pain, loss of motion, effusions, and eventual joint degeneration can result from untreated cartilage injuries. Several recent studies have demonstrated that symptomatic, isolated traumatic articular defects benefit from surgical intervention *(5–8)*. The most appropriate technique to treat these lesions has been controversial, but increasing clinical experience backed by critical outcome measures has demonstrated that implantation of autologous chondrocytes with or without a scaffold is an effective means to correct the underlying pathology by creating a hyalinelike repair tissue.

This chapter describes the technique of autologous chondrocyte implantation (ACI) first reported by the senior author in 1994 and reviews the current literature supporting this technique as well as those studies that compare ACI to other accepted treatment options *(9)*. Furthermore, we review and discuss developing literature supporting current use of various matrices used in combination with autologous chondrocytes to treat this difficult patient population.

CLINICAL PROBLEM

Articular cartilage is an avascular, aneural tissue that protects the subchondral bone from compressive axial and shear forces. In particular, the limited vascularity in comparison to other mesenchymal tissues creates a poor environment for spontaneous repair in response to injuries to the cartilage surface. Chondrocytes also have limited migratory ability, and as a result the surrounding normal cartilage cells do not fill the defect.

Henry Mankin reported on a transient but insufficient response to injury demonstrated by the chondrocyte *(10)*. These cells will increase mitotic activity as well as glycosaminoglycan and collagen production but only for a short period of time and to a limited degree. Normal articular cartilage also has relatively low cell numbers existing in isolated cell lacunae within the extracellular matrix, further decreasing the healing potential following injury. These factors in combination with the continued use of the extremity by the individual produce repetitive compressive and shear forces, creating an extremely poor environment for spontaneous repair.

When trauma extends through the subchondral bone, creating active bleeding, there is exposure to multipotential mesenchymal stem cells, leading to fibrocartilage formation; unfortunately, this tissue lacks the biomechanical properties required to protect the underlying subchondral bone plate, especially in the high-demand patient *(11,12)*. In addition, as the size of the defect increases, the surrounding normal articular cartilage no longer protects the subchondral bone at the base of the lesion (Fig. 1). Exposure of the subchondral bone to repetitive axial and shear forces leads to progressive pain and disability, especially in a high-demand patient.

As a result of the clinical problem, several techniques have been used to improve the repair potential by implanting other cell or tissue phenotypes that have chondrogenic potential

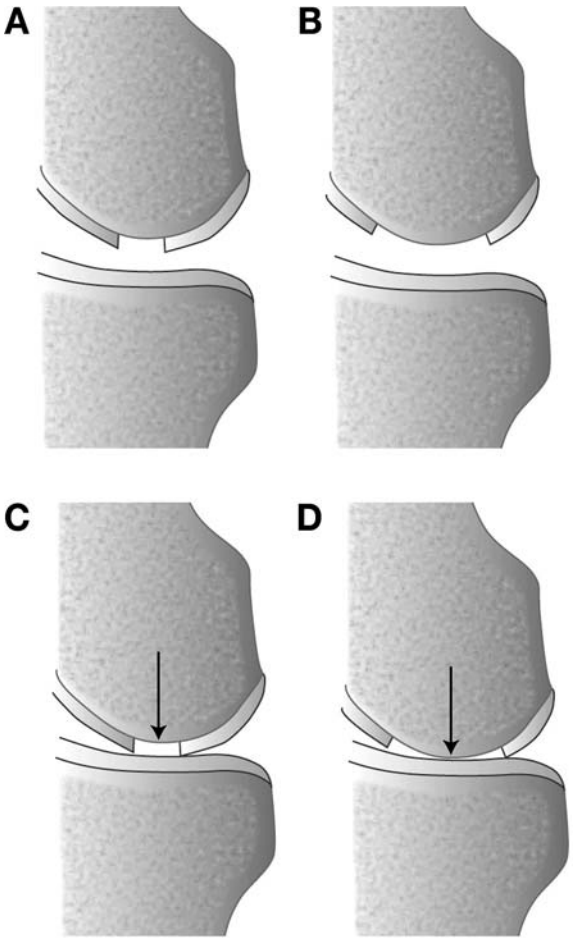

Fig. 1. Schematic representation: loading of focal femoral condyle defects. Small lesions (depicted on the left) are well contained and protect the tibial surface during activity and movement of the joint. Larger lesions, as depicted on the right, expose the subchondral bone and margins of the lesion to the tibial articular surface. Increased cartilage wear rates result along with mechanical symptoms and pain *(68)*.

(13–19). Using a rabbit model, Grande et al. first reported the successful repair of full-thickness cartilage defects through the implantation of cultured articular chondrocytes *(20)*. Based on these promising results, the technique was first used on humans in 1987 and was termed *autologous chondrocyte transplantation*. Currently, in the United States and most of Europe it is referred to as the autologous chondrocyte implantation (ACI) procedure.

Indications

Currently, ACI is ideally indicated for symptomatic ICRS grade III-IV lesions along the femoral condyle or trochlear regions *(21,22)*. High-demand patients between the ages of 15 and 55 yr with excellent motivation and compliance potential should be chosen. Failure of a previous biologic reconstructive procedure such as mosaicplasty or microfracture in a high-demand patient is not an uncommon scenario. In lesions less than 2 cm^2, it is appropriate to

use the aforementioned biological procedures as a first-line option. However, in the symptomatic patient with a lesion size greater than 2 cm^2 and up to 12 cm^2, ACI is a viable option. Bone involvement is not a contraindication, but with bony involvement deeper than 6–8 mm, staged or concomitant autologous bone grafting should be undertaken.

Although the senior author (L. P.) has extensive experience and success with ACI in some high-demand patients with reciprocal or "kissing" lesions, this is currently a contraindication for the technique *(23,24)*. However, when no other treatment options are possible in young, high-demand patients, ACI could be tried as a salvage procedure. Surgeons are increasingly using the ACI procedure to repair patellar lesions. Although the initial results in this region were not as successful, the concomitant use of tibial tubercle osteotomy and anteromedialization has significantly improved patient outcomes *(9,25)*.

Preoperative Assessment

In identifying appropriate candidates for the ACI procedure, all factors that could compromise successful healing of the implant should be recognized and corrected in a staged or concomitant manner. Key factors to consider in evaluating patients are physiological age, desired postoperative activity level, etiology, postoperative compliance potential, and social factors such as worker's compensation claims, postoperative work conditions, and allowed time off from work.

Physical examination should focus on gait status, knee alignment, and body mass index (BMI). Weight reduction should be an integral component of the preoperative program, thus limiting postoperative stress to the healing lesion. Knee range of motion is documented and compared to the opposite side; losses of extension or flexion greater than 2–3° in comparison to the opposite side must be addressed. Any preoperative deficits should be corrected with a combination of physical therapy, dynamic splinting, and arthroscopic debridement with manipulation. Medial and lateral femoral chondral, trochlear groove, and patellar facets are palpated for tenderness and correlated with patient complaints.

While performing the arthroscopic biopsy and during chondrocyte implantation, the surgeon should keep this preoperative evaluation in mind as it is not uncommon to have isolated regions of ICRS grade II change along the articular surface; if asymptomatic or nontender during the initial evaluation, these regions should be ignored. Patellofemoral crepitus should be assessed for location and quality (i.e., coarse or fine); further, provocative maneuvers such as the patellar grind test should be performed and correlated again with symptoms. Associated ligamentous disruption and meniscal pathology should be recognized and addressed in staged or concomitant fashion as well.

Radiographic Assessment

The initial radiographic workup should include a postero-anterior (PA) weight-bearing view (Rosenberg) to assess for medial or lateral compartment narrowing, particularly in the postmenisectomized knee *(26)*. Bilateral Merchant views to assess for medial and lateral facet wear as well as patellar subluxation and tilt are important *(27)*. When patella alta or baja is suspected, bilateral supine lateral views at 30° flexion should be obtained and appropriate measurements made. Finally, bilateral long-leg standing films (hip to ankle) should be obtained to determine the mechanical axis and potential sites of increased load to the repair site *(28)*.

A direct side-to-side comparison should be performed on all views. This will delineate subtle narrowing in comparison to the opposite side; demonstrated asymmetries should not be ignored but addressed to unload the affected compartment and create an optimal environment

for the short- and long-term survival of the repair tissue produced by the sensitive chondrocytes that are implanted.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has quickly proven its worth as a reliable, noninvasive method of diagnosing osteochondral injuries. Controversy remains regarding the sensitivity and the specificity of MRI in detecting isolated chondral injuries. In 1998, Potter et al. used cartilage-sensitive pulse sequencing in detecting defects in the articular surface and reported high sensitivity and specificity for chondral pathology with minimal interobserver variability *(29)*. They concluded that MRI was an accurate and reproducible imaging modality for the diagnosis of chondral lesions in the knee.

Friemert et al. reported a sensitivity of 33–53% and specificity of 98–99% in detecting advanced articular cartilage lesions by MRI when compared directly with diagnostic arthroscopy *(30)*. Palosaari et al. found an even higher sensitivity of 80–96% when diagnosing cartilaginous lesions by MRI *(31)*. Again, findings should be correlated with clinical symptoms.

Arthroscopic Assessment and Biopsy

Arthroscopic assessment should be performed with the above workup in mind. Areas of ICRS grade III–IV change are noted and sized and the reciprocal surface visualized for degree of damage as well. If the patient is deemed an appropriate candidate for chondrocyte implantation, then a biopsy should be obtained. A preoperative discussion with the patient about the ACI procedure and the typical postoperative course is extremely helpful in determining whether a biopsy should be taken. We warn against taking unnecessary biopsies or taking cartilage immediately following other biologic reconstructive procedures, such as microfracture. These other reconstructive procedures typically need 6–12 mo to demonstrate clinical efficacy. A premature biopsy can place an unnecessary burden on the patient-surgeon relationship, forcing surgery before the procedure has had a chance to work. In addition, unused biopsies place an additional burden on the extensive resources required to process the specimen.

Biopsies are ideally taken from the superomedial edge of the femoral trochlea, but if pathology extends into this region or if there is concern about the patellofemoral articulation, the superolateral trochlear edge can be used. An additional site for biopsy is the lateral aspect of the intercondylar notch, the area of typical notchplasty used during anterior cruciate ligament surgery (Fig. 2A–C). The typical biopsy specimen is 200–300 mg total weight and should include the entire cartilage surface along with a small portion of the underlying subchondral bone. This amount of cartilage should contain approx 200,000–300,000 cells and will fill the bottom portion of the specimen container.

Studies of cartilage obtained from femoral osteophytes and debrided cartilage have demonstrated continued type II collagen production and molecular activity associated with normal articular chondrocyte phenotype *(32,33)*. Despite these findings, current recommendations are that these "abnormal" sources of cartilage should not be used to obtain the cells needed for implantation. This also applies to patients with osteochondritis dissecans (OCD) lesions. The surgeon should resist the temptation to use cartilage from the discarded OCD fragment.

Once the biopsy has been performed, cells are maintained at 4°C until processing occurs, as demonstrated in Fig. 3. Isolated defects up to 3 cm^2 can be treated with one vial allowing full coverage of the defect base with a confluent cell population. With multiple lesions and areas approaching greater than 6 cm^2, more than one vial will be required; lesion size should be taken into account when ordering cells prior to implantation.

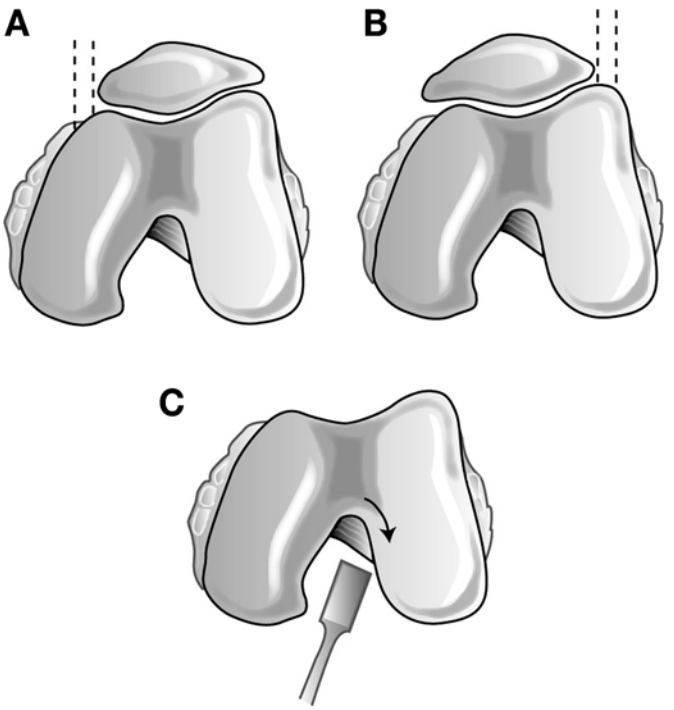

Fig. 2. Appropriate cartilage biopsy sites: (**A**) superior medial trochlear ridge; (**B**) uncovered lateral superior ridge; (**C**) lateral intercondylar notch. All sites should be sharply incised prior to harvest to avoid gouge slippage *(24)*.

SURGICAL TECHNIQUE

Exposure

Typically, a midline skin incision is utilized to facilitate exposure during any future operative interventions. However, previous surgical incisions should be taken into consideration as well as lesion location. When possible, based on defect size and location relative to the knee flexion zone, implantation can be performed through a medially or laterally based miniarthrotomy, sparing quadriceps weakness and intra-articular adhesions postoperatively. Alternatively, a subvastus approach can be used, particularly for medial femoral condyle lesions, as the exposure allows the surgeon to subluxate the patella laterally during knee flexion. Anterior dissection along the tibial plateau surface should be performed carefully, avoiding damage to the anterior horns and central body of the menisci. When treating tibial plateau lesions, it is necessary to reflect the meniscus through a takedown of the intermensical ligament and anterior meniscal horn of the involved compartment as described in ref. *24*. When performing a concomitant tibial tubercle osteotomy, slight lateral placement of the incision can avoid injury to the infrapatellar branch of the lesser saphenous nerve. Other concomitant procedures as well as planned periosteal graft harvest sites should also be considered prior to incision. The arthrotomy should, however, always be adjusted to allow an optimal surgical approach to the defect.

Defect Preparation

Once visualized, the lesion should be carefully debrided back to normal vertical articular cartilage margins (Fig. 4A–C). All fibrillated and partially delaminated cartilage should be

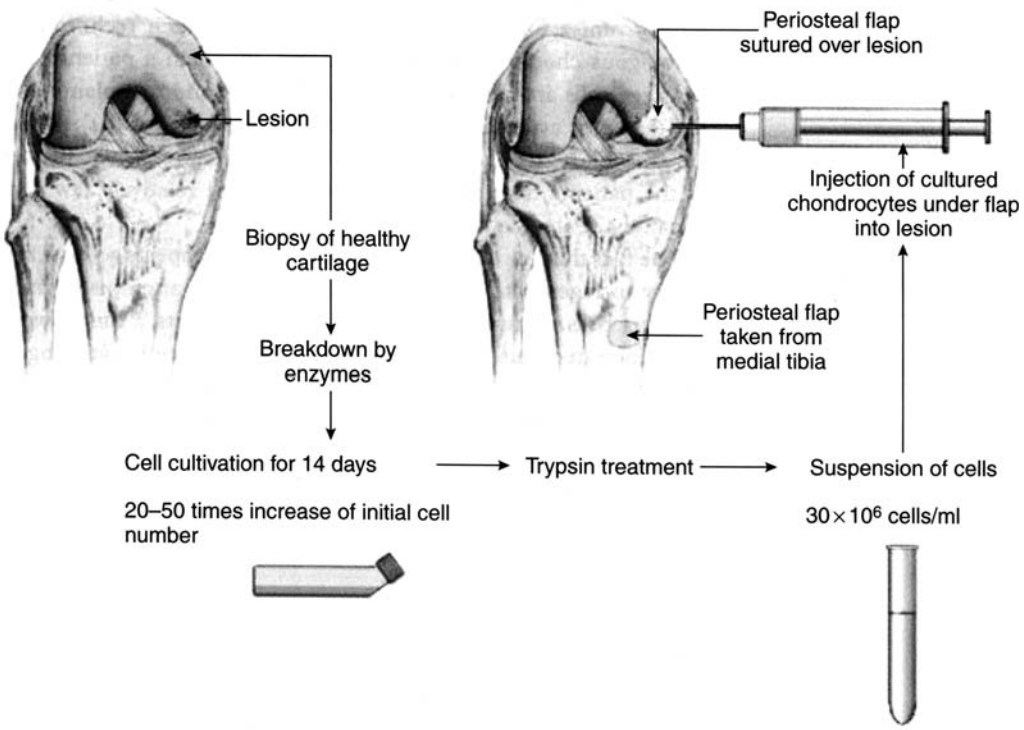

Fig. 3. Schematic drawing of cartilage biopsy preparation and autologous chondrocyte implantation (From ref. *69*. By permission of Oxford University Press).

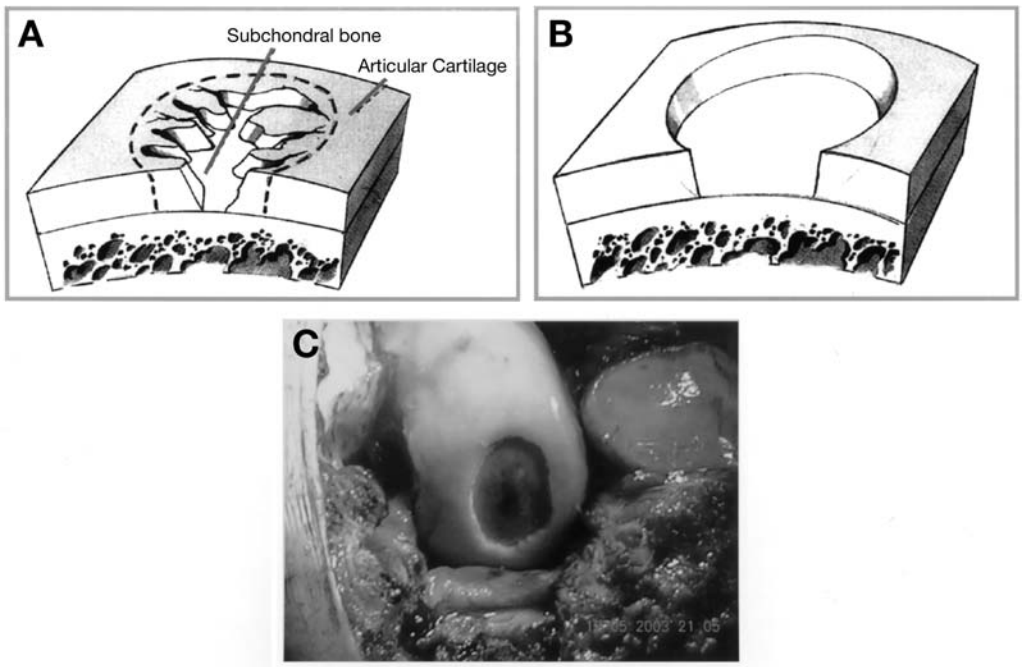

Fig. 4. Schematic drawing of defect preparation: (**A**) fibrillated cartilage lesion; (**B**) debridement to healthy cartilage margins with smooth vertical borders created on completion; (**C**) isolated cartilage lesion following debridement.

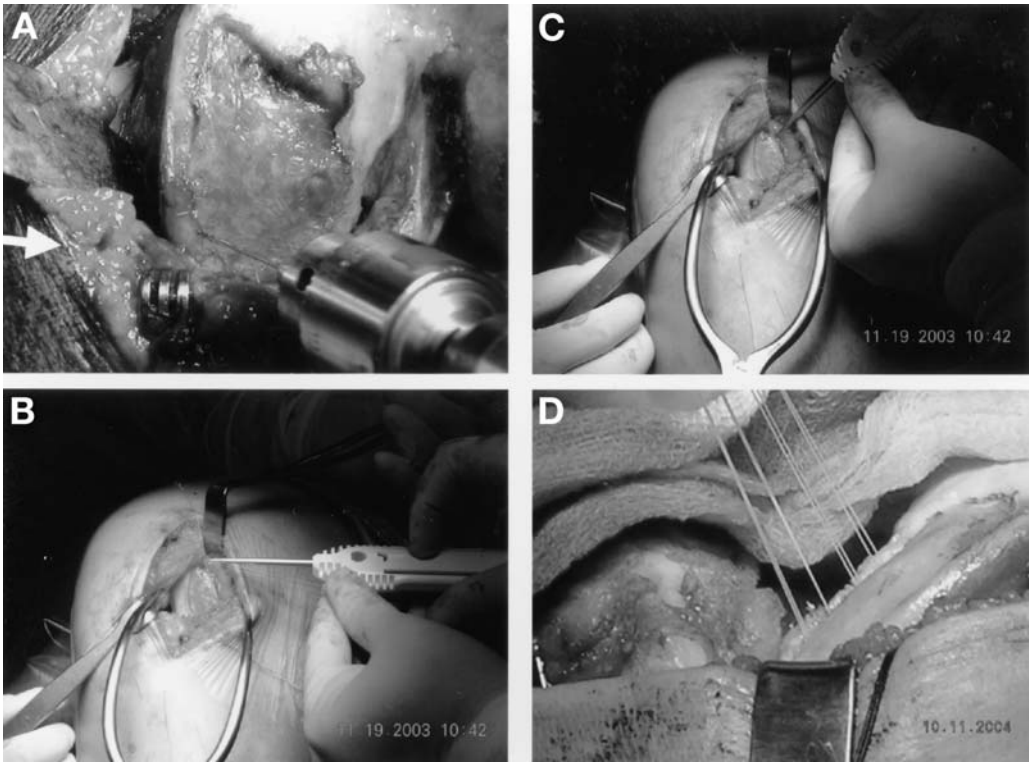

Fig. 5. (**A**) A no. 5 Keith needle used as drill bit in poorly contained lesion creating bony tunnel for later suture placement. (**B**) Microfix anchor (Mitek Inc., Raynham, MA). (**C**) Following use of the Microfix drill bit and replacement of the nonabsorbable suture with 5-0 vicryl suture, the anchor is implanted. (**D**) Application of several anchors along poorly contained border of lesion.

removed. The margins of the lesion are first demarcated with a no. 15 blade, and the damaged cartilage is then removed, typically with a ring-shaped curette, avoiding breakage through the subchondral bone plate. This prevents intraoperative bleeding into the defect, limiting exposure to the different cellular phenotypes present in human blood.

Minimally chondromalacic areas (i.e., ICRS grade I and early grade II) along the border of the lesion are left alone when appropriate suture fixation is possible. When debridement necessitates extension into poorly contained regions, the bone edge should be prepared for later suture fixation of the periosteal graft. This can be performed with the use of a no. 5 Keith needle acting as a drill bit to create a bone tunnel for later suture placement (Fig. 5A). Alternatively, small suture anchors have become commercially available (Microfix, Mitek Inc., Raynham, MA). Prior to placement, the anchors must be reloaded with a 5-0 or 6-0 vicryl suture. These anchors are ideal for poorly contained regions such as the intercondylar notch or peripheral aspect of the femoral condyle or areas such as the posterior edge of a lesion located in the 70–90° flexion zone, where it is difficult to place sutures appropriately (Fig. 5B,C). With extension into the intercondylar notch, interrupted and running suture techniques can be utilized to supplement graft fixation. As in all areas of orthopedic surgery, strong fixation of the periosteal graft to the defect is critical to prevent future graft delamination and to allow early motion of the joint.

In many instances, intralesional osteophytes or sclerotic bone regions are encountered following removal of the calcified cartilage layer or fibrocartilage. Smaller intralesional osteophytes could carefully be tapped down or curetted down to the subchondral bone level. Although it is ideal to avoid exposure to the cancellous bone, a high-speed burr should be used to remove the protuberant bone region and sclerotic bone layer. If carefully performed, a thin layer of subchondral bone should remain to serve as an appropriate viable bed for chondrocyte attachment.

Following debridement, the tourniquet, if used, should be deflated, and in those areas where bone bleeding is visualized, adequate hemostasis should be obtained. First attempts at hemostasis should involve the use of neuropatties soaked in a 1:1000 epinephrine-normal saline mixture. The patty is applied, and pressure is maintained during periosteal graft harvest. For continued bleeding, thrombin spray has been helpful. An alternative method that also works involves placing a drop of fibrin glue (Tiseel, Baxter Healthcare Corp., Glendale, CA) over the bleeding spot and compressing for a minute with a fingertip. Finally, if sites of excessive bleeding are experienced, particularly when previous bone procedures such as microfracture have been performed, a needle-tip bovie cautery unit on a low setting (20–25 coagulation setting) should be used judiciously.

As mentioned, in cases of bone deficiency deeper than 6–8 mm such as osteochondral fracture, OCD, or failed osteochondral grafting procedures, concomitant or staged bone grafting should be performed *(24)*. If performed in a staged manner, bone grafting should be performed up to the level of the subchondral bone plate. Prior to bone grafting, it is important to remove all sclerotic bone; in OCD cases in particular, drilling through the bed following debridement allows appropriate blood flow into the defect, ensuring subsequent bone graft incorporation (Fig. 6A–D). Fibrin glue, sutures, or resorbable membranes such the Restore® patch (Depuy, Raynham, MA) can be used to maintain the bone graft in place. Continuous passive motion is used postoperatively with touch-down to 25% partial weight bearing for 4 wk. Patients are then allowed to resume full weight bearing, but chondrocyte implantation is not undertaken until 6–9 mo following bone grafting to allow for appropriate reconstitution of a subchondral bone plate (Fig. 7A,B).

Alternatively, the sandwich technique as described in ref. *34* can be used. Using a high-speed burr, the sclerotic bone bed is removed down to bleeding cancellous bone, and the base is drilled as previously described. Following bone grafting to the level of the subchondral bone plate, a periosteal flap the size of the bony defect is harvested and anchored in place with the cambium layer facing up to the defect and the fibrous layer facing the bone graft. Leaving a small ridge of healthy subchondral bone can help in stabilizing this initial periosteal flap. We have successfully used Microfix anchors to help in anchori144ng the first periosteal flap (Fig. 8A–G). Fibrin glue should be injected between the periosteal flap and the bone graft to richly fill the interval. After the fibrin glue is injected for 3 min, the bone graft and periosteal cover should be compressed with a dry sponge to help fixation of the flap to the bone graft as well stabilize the bleeding. A second periosteal flap is then applied as later described in Graft Fixation following.

Periosteal Graft Harvest

Defect size should be measured with a sterile ruler to determine appropriate graft size. Alternatively, a paper template of the defect site can be created by placing it directly over the site and using a typical skin marker, tracing the defect on the paper with sequential dots. One additional technique is to use a sterile knife blade package as an aluminum template to press directly into the defect, creating an imprint of the lesion. The paper or aluminum template is created by cutting around the edge of the dots or imprint. The template should be 2 mm larger

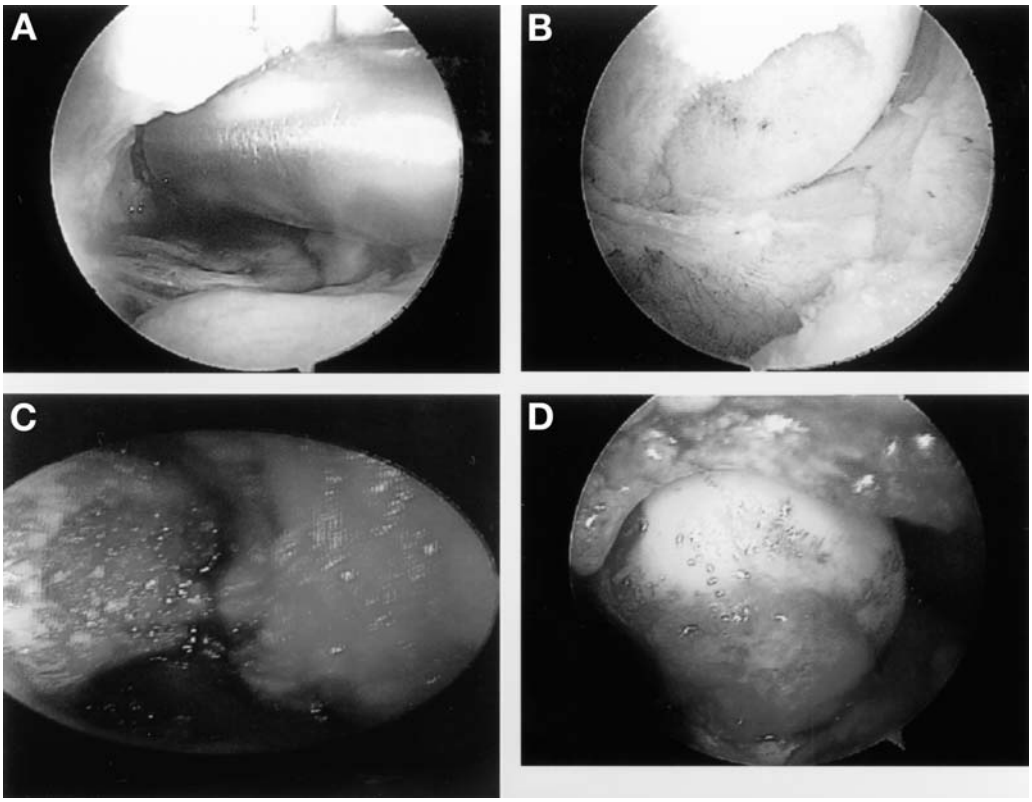

Fig. 6. (**A**) Debridement of osteochondritis dissecans lesion to bleeding healthy bone. (**B**) Drilled base of lesion to create bleeding. (**C**) Autologous bone graft applied arthroscopically to defect. (**D**) Fibrin glue applied over defect to maintain bone graft in place and avoid extravasation into surrounding tissues.

than the actual defect when treating the femoral condyle or tibial plateau surfaces. When grafting the trochlear groove or patellar surfaces, a template 3 mm larger than the actual lesion should be created to take into account the concave and convex surfaces, respectively *(24)*.

Several sites are available for periosteal graft harvest. The first option for harvest should be the proximal medial tibial diaphysis distal to the pes anserinus insertion or below the semitendinosis tendon insertion point. This site typically has robust but thin enough periosteum, making it ideal for implantation. Normal periosteum is a thin membrane several cell layers thick and consisting of an outer fibrogenic layer and an inner osteogenic cambium layer. In the proximal tibia, an incision is made through the subcutaneous fat and the thin fascial layer. Care should be taken to remove all overlying fascial and fatty layers prior to removal from the bone surface. This is typically best performed using sharp scissor dissection to reveal an underlying white, shiny periosteum. Attempts at periosteal debridement following harvest can cause "buttonholing" through the graft surface with resultant sites of cell leakage on implantation. No electrocautery device should be used around the periosteum prior to harvest. This will injure the periosteum and could kill the sensitive cells in the cambium layer.

Secondary sites of graft harvest include the femoral metaphyseal-diaphyseal region. During large arthrotomies, this portion of the femur is easily visualized with appropriate

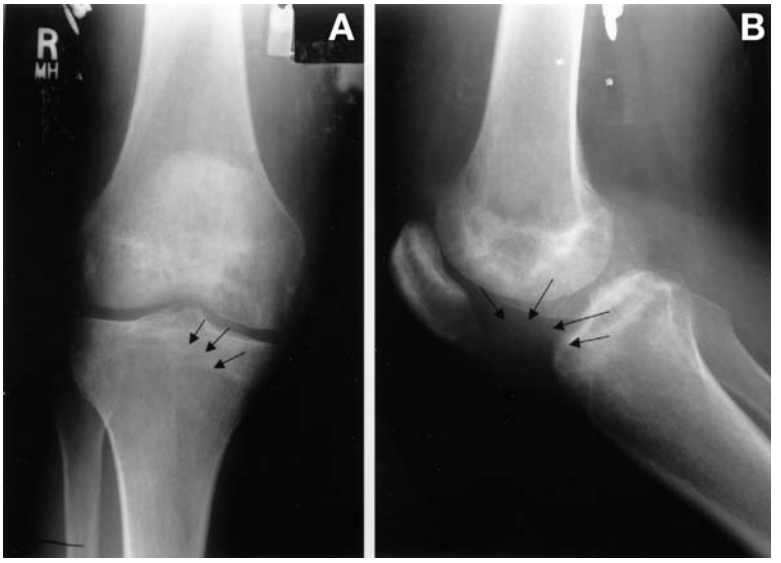

Fig. 7. (**A**) Postoperative anterior-posterior view 4 mo following bone graft application to defect. Notice reconstitution of subchondral bone contour following continuous passive motion machine treatment and non-weight-bearing status for 4 wk. (**B**) Lateral view demonstrating normal subchondral contour.

retraction of the quadriceps musculature. Periosteal graft harvest from this location requires carefully incision of the overlying synovium to expose the underlying periosteum. The synovium should be placed back into its normal anatomic location following graft harvest from the femur to prevent postoperative scarring. The femoral periosteum is typically thicker. This may theoretically inhibit synovial fluid diffusion and cell nutrition during the initial growth phase. Thicker periosteum may also predispose to increased rates of periosteal overgrowth. Finally, the required soft tissue dissection in the suprapatellar region can lead to bleeding and an increased incidence of postoperative intra-articular adhesions. Because of these factors, femoral periosteum should be used only as a second-line, not primary, source of periosteal graft during ACI. All periosteum should be maintained in a moist environment and, in cases of multiple lesions, labeled to prevent any confusion during graft implantation.

Resorbable membrane substitutes have become commercially available. Two examples are Chondrogide® (Geistlich Biomaterials, Wolhusen, Switzerland) and Restore® (Depuy, Raynham, MA). Haddo et al. reported on 31 patients in whom chondrogide was used in place of periosteum *(35)*. Assessment included arthroscopic second looks at 1 yr and clinical outcome evaluations at 1 and 2 yr after the second stage of the procedure. They reported no evidence of periosteal graft hypertrophy and satisfactory clinical outcomes at 2 yr. One of us (D. G. J.) has used the Restore patch as a substitute for periosteum in 30 cases as well as in cases requiring autologous bone grafting. At short-term follow-up (1–2 yr), there have been no adverse events or effects on clinical outcome (unpublished data, June 2005). Bartlett et al. reported similar results *(36)*.

When there is limited periosteum, for example because of scarring, damage from graft harvesting, poor tissue quality because of age or disuse atrophy, and in revision cases or cases with

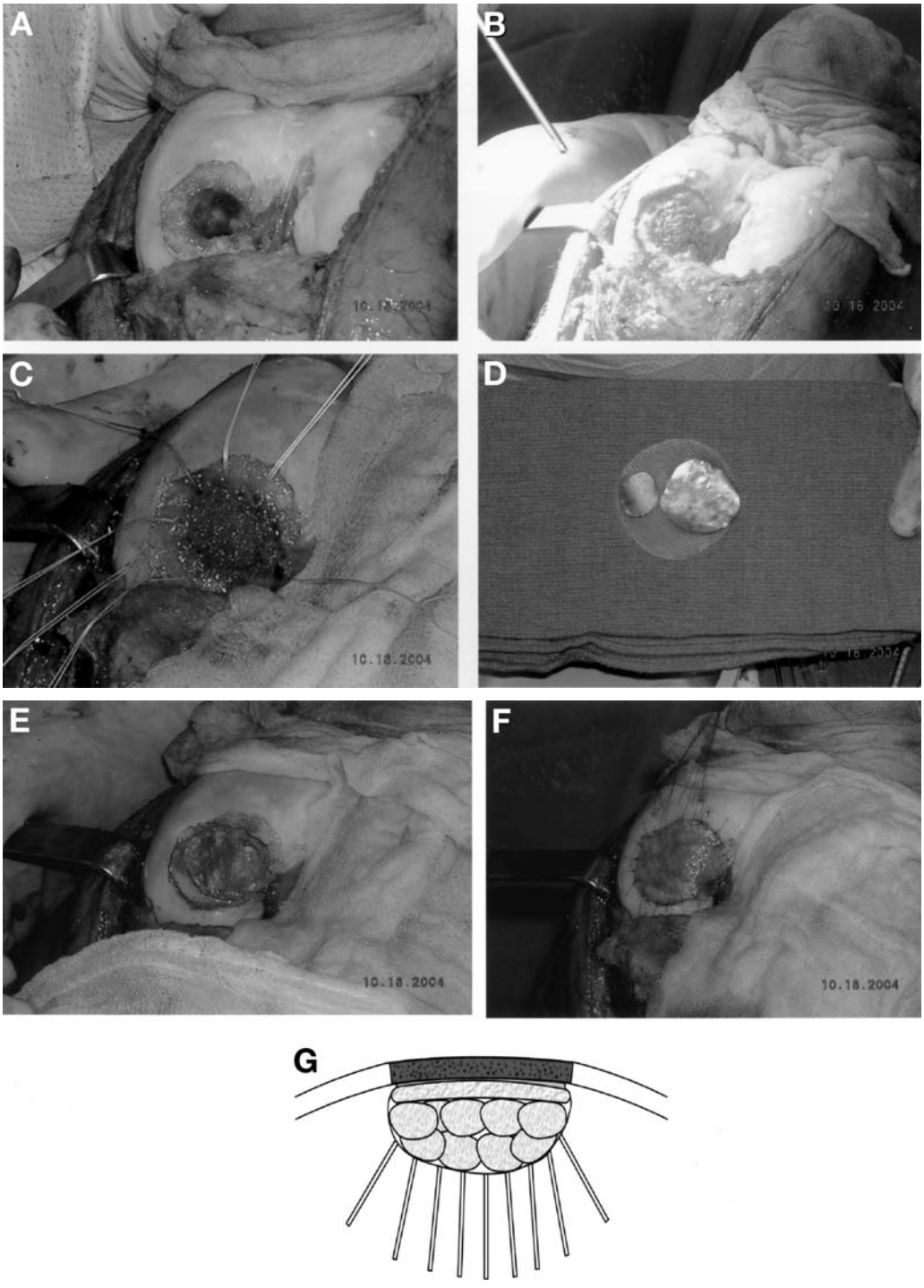

Fig. 8. (**A**) Bone lesion following debridement of sclerotic bone and drilling of base of lesion. Notice shelf of normal subchondral bone around bony defect. (**B**) Bone graft application up to but not over subchondral bone height. (**C**) Application of Microfix anchors around bone defect periphery. (**D**) Restore patch (Depuy Orthopaedics Inc., Warsaw, IN) with aluminum templates over graft prior to preparation

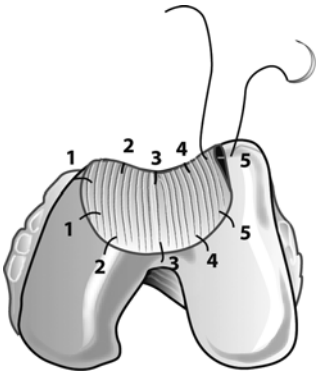

Fig. 9. Trochlear defect: It is important to create the normal trochlear configuration. The template must be oversize by approx 3 mm. The periosteal patch is then sutured sequentially from medial to lateral as denoted by numbers 1–5, taking care to re-create the normal convex surface, thus avoiding postoperative overload to the repair site *(24)*.

large surface areas, these membranes can provide an alternate source of membrane. The use of resorbable membranes as a defect cover to replace the traditional autologous periosteum has been termed the collagen-associated autologous chondrocyte implantation (CACI) procedure. Published results from the CACI procedure are discussed in more detail later in the chapter *(37)*.

Graft Fixation

The periosteal graft is fixed with 6-0 vicryl suture using a P-1 cutting needle. Ideally, the suture should be dyed to ease visualization when sewing against the normal white articular cartilage surface. Sterile mineral oil should coat the suture prior to passage through the periosteum, particularly to prevent binding between the suture-periosteal interface. The needle is first passed through the superficial surface of the periosteum approx 2 mm from the graft edge and then into the cartilage margin, entering the vertical border perpendicular to the inside wall of the defect. The needle should enter the cartilage approx 2 mm from the surface and extend peripherally, exiting the defect 4 mm from the edge of the defect (Fig. 6).

A simple instrument tying technique is used, with each throw placed parallel to the defect wall edge. This localizes the knot over the periosteum rather than placing the knot on the articular surface, where it could be exposed to shear forces, damaging fixation. During initial suture placement, all four quadrants of the graft should be tied first to stabilize the graft and then further sutures placed at 3-mm increments around the lesion to produce a watertight seal. An exception to this method of suture placement (four quadrants first) is during trochlear ACI. In this case, sutures are first placed along the medial margin and sequentially placed from medial to lateral, producing a convex surface to allow for appropriate patellar tracking (Fig. 9). Similarly, contour of the graft should be considered with patellar ACI,

Fig. 8. *(Continued)* for suture fixation. (**E**) Suture fixation of Restore patch to bone defect. (**F**) Final suture fixation of larger Restore patch and application of cells using the "sandwich" technique. (**G**) Schematic of sandwich technique; drilling base of lesion, application of bone graft, placement of bottom periosteal patch (cambium layer facing up), followed by cells and then top periosteal patch (cambium layer facing down).

especially in the centrally based patellar lesion; the normal convexity of the patella should be considered as well as height of graft placement along the defect. The significant shear forces in this area can lead to catching at the leading and trailing edges of the defect with knee motion *(24)*.

It is important to leave one region along the lesion open to allow for cell implantation. However, to prevent cell extrusion after implantation, place the sutures in the standard fashion but do not tie them immediately. Once cells are implanted simply instrument tie the sutures at that time. In large, particularly long defects, the contour of the femur may not allow placement of the angiocatheter utilized in cell implantation far enough into the defect. This can limit the ability to create an even cell suspension at the base of the lesion. In these cases, leaving a more posterior, distal second site of cell implantation is helpful. Cells are implanted in this site first and sutures tied. Cells are then implanted into the more anterior proximal site secondarily.

Prior to cell implantation, the repair should be assessed to determine whether a watertight seal has been created. Normal saline without antibiotics should be placed into the planned area of cell implantation with a 1.5-in. 18-gage angiocatheter and tuberculin syringe. The intra-articular portion of the knee is dried, and sites of leakage are noted. Further sutures are placed into the site, and testing is performed again. Only after a watertight seal has been verified should the wound edges be further sealed with fibrin glue.

Autologous fibrin glue is formed by taking the cryoprecipitate from 1 unit of the patient's whole blood and combining it with a mixture of bovine thrombin and calcium chloride. An excellent alternative to this cumbersome technique is to use the commercially available fibrin glue called Tisseel. It is important to limit the amount of Tisseel or fibrin glue placed into the joint as this has the potential to increase postoperative fibrous adhesions. Further, the senior author, using an in vivo rabbit model, demonstrated the potential deleterious effects of Tisseel on chondrocyte migration and healing potential *(38)*. As a result, care should be taken to limit the amount of Tisseel applied and to avoid its exposure to the chondrocytes.

Chondrocyte Implantation

Once a watertight seal has been created, cell implantation is undertaken. Cells, provided by Genzyme Biosurgery Corporation (Cambridge, MA), arrive in a small vial and should be maintained at 4°C until implantation. The typical concentration is 12 million cells/0.4 mL medium. One vial should cover a lesion of approx 6 cm^2. Cells are gently placed into suspension using the angiocatheter previously described and then injected into the defect. Sutures are tied, and fibrin glue or Tisseel is applied to the site of implantation.

POSTOPERATIVE REHABILITATION

Cartilage maturation occurs through several phases (Table 1). This process must be considered during the critical rehabilitation process following surgery. The first phase in cartilage metabolism, termed the *proliferative phase*, occurs during the first 6 wk when initial partial weight bearing is allowed (15–20 kg or 30–40 pounds). During the immediate postoperative period, cells are allowed to adhere to the subchondral bone plate, avoiding motion for at least 6–12 h. Continuous passive motion is initiated at this time to provide a chondrogenic stimulus as demonstrated by O'Driscoll and Salter *(14)*. Typically, this is performed during the first 4 wk for approx 6–8 h/d.

Table 1
ACI Time-Course Healing

Stage	*Time*	*Tissue*
Proliferation	0–6 wk	Soft, primitive repair tissue
Transition	7 wk–6 mo	Expansion of matrix puttylike consistency
Remodeling	6–18 mo (changes can occur for up to 3 yr)	Matrix remodeling, tissue stiffens to normal hardness

A soft, primitive repair tissue forms during this initial phase. The second phase, termed the *transition phase*, occurs during the ensuing 4–5 mo, usually ending at approx 6 mo postoperatively. This phase is characterized by expansion of the matrix released by the chondrocytes into a puttylike consistency. Weight bearing is continued progressively, increasing to full weight bearing within 12 wk after surgery. Important factors to consider at this time are the size and location of the lesion. Well-contained lesions have some degree of protection from the surrounding native cartilage, and load bearing can be initiated as early as 4 wk postoperatively (Fig. 10A,B). Conversely, poorly contained lesions require longer periods of protection. Full weight bearing in these large lesions should not occur until after about 8–14 wk (Fig. 10C,D). Patients with multiple lesions should progress more slowly as well. If there is subtle varus or valgus malalignment in the medial- or lateral-based lesions, respectively, then an unloader brace should be considered on initiation of weight bearing. Significant malalignment issues should be addressed with a concomitant or staged osteotomy as stated.

Isolated patellofemoral lesions can be protected during weight bearing if the knee is maintained in full extension during gait. A postoperative hinged immobilizer locked in extension during ambulation can achieve this goal, allowing weight bearing during the initial 6 wk. Patellofemoral lesions are susceptible to the high shear forces that occur across the implantation site; as a result, open-chain exercises should be avoided during the first 4–6 mo. The continuous passive motion machine is initiated at the same time, but progression to greater than 90° flexion should occur more slowly than with a femoral chondral lesion.

The final phase in maturation, termed the *matrix remodeling phase*, is characterized by progressive hardening of the cartilage tissue to the hard, firm quality of adjacent native cartilage. This process begins at approx 6 mo and occurs over the ensuing 6–12 mo. Although patients are allowed to resume regular activities at this time, further graft maturation can continue for up to 3 yr following implantation. Factors that affect this process are size, location, physiological age, and final activity level. Patients will have some continued symptoms along the implant site as the activity level is increased during this critical period. However, as graft maturation occurs, allowing greater protection of the subchondral bone, preoperative symptoms should resolve slowly. Preoperative patient education of this biologic process, particularly the expected length of time to recovery, is critical. This prevents the patient from exposing the graft to potentially traumatic forces during the initial phases of cartilage maturation.

POSTOPERATIVE IMAGING/EVALUATION

As our ability to assess articular cartilage, repair tissue quality, and degree of fill of defects by MRI improves, this tool becomes an increasingly important source of information that can

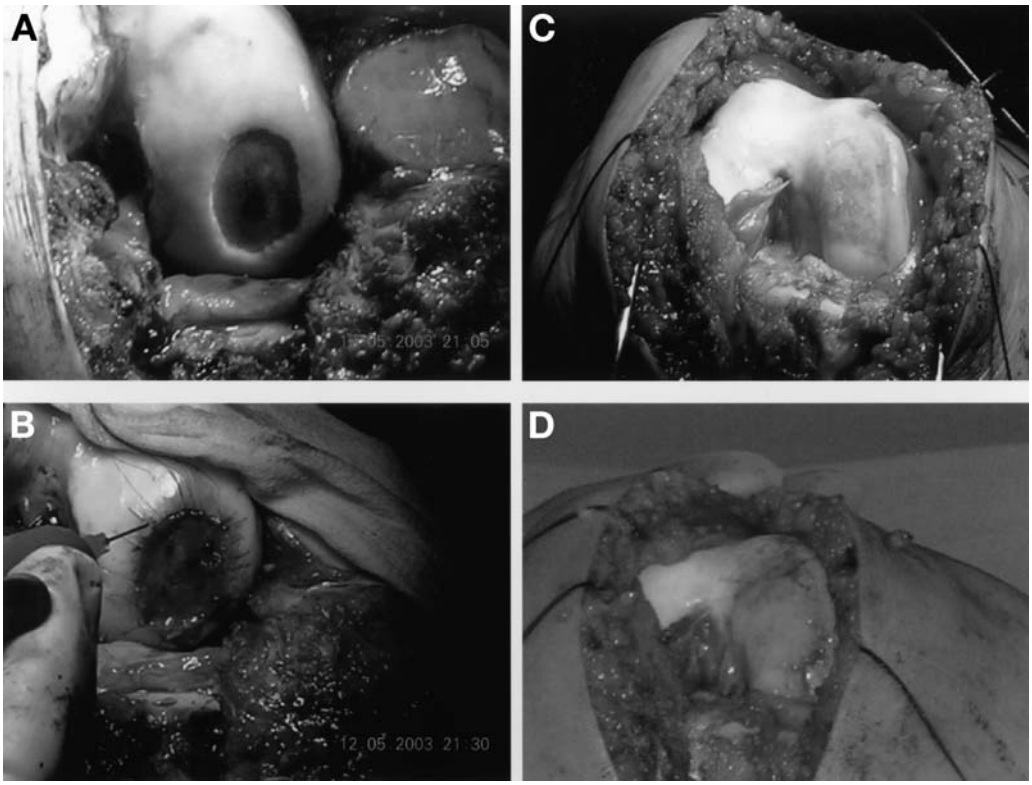

Fig. 10. (**A**) Well-contained lesion with normal articular cartilage borders. (**B**) Following implantation, the repair site is protected from damage, and a more aggressive rehabilitation program can be initiated. (**C**) Poorly contained lesion with limited normal articular cartilage margins. (**D**) Following implantation, the repair site is not well protected by the surrounding cartilage, and a slower rehabilitation program should be initiated with full weight bearing after 8–10 wk.

be used by the surgeon to help progress patients following biologic reconstructive procedures *(39,40)*. Henderson et al. reviewed the 2-yr treatment outcome of ACI in 53 patients (72 lesions) through clinical evaluation, MRI, second-look arthroscopy, and concomitant biopsy. MRI studies demonstrated 75.3% of defects with at least 50% defect fill, 46.3% with near-normal signal, 68.1% with mild to no effusion, and 66.7% with mild to no underlying bone marrow edema at 3 mo *(39)*. These values improved to 94.2, 86.9, 91.3, and 88.4% at 12 mo, respectively. At 24 mo, further improvements to 97, 97, 95.6, and 92.6%, respectively, were observed. Improvement in clinical outcome correlated well with information obtained from second-look arthroscopy and core biopsies as compared with MRI findings at 12 mo *(41)*.

Watrin-Pinzano et al. evaluated the ability of T_2 mapping on an 8.5-T imager to characterize morphologically and quantitatively spontaneous repair of rat patellar cartilage defects *(42)*. T_2 mapping was able morphologically to identify three types of repair tissue observed macroscopically and histologically: total, partial, and hypertrophic. Total and partial repair tissues were characterized by global T_2 values almost similar to controls, whereas hypertrophic repair tissues were characterized by T_2 global values higher than controls. They concluded that T_2 mapping with MRI was a noninvasive technique that could be used in clinical longitudinal studies of articular cartilage repair.

Brown et al. evaluated 180 MRI examinations in 112 patients who had cartilage-resurfacing procedures, including 86 microfractures and 35 ACI, at a mean of 15 and 13 mo after surgery, respectively *(43)*. ACI-treated defects showed consistently better fill at all times compared with microfracture, but there was graft hypertrophy in 63% of ACI surgeries. By contrast, the repair cartilage over the microfracture was depressed with respect to native cartilage and had a propensity for bone development and loss of adjacent cartilage with progressive follow-up.

Stefan Marlovits and colleagues used a surface phased array coil over the knee on a 1-T MRI scanner to obtain high-resolution images in 45 patients treated with three different techniques for cartilage repair (microfracture, autologous osteochondral transplantation, and ACI) *(44)*. Patients were analyzed 6 and 12 mo after the procedure, and pertinent variables were defined to describe the repair tissue. Nine pertinent variables were described: the degree of filling of the defect, the integration to the border zone, the description of the surface and structure, the signal intensity, the status of the subchondral lamina and subchondral bone, the appearance of adhesions, and the presence of synovitis.

It becomes clear that MRI is a useful tool to assess cartilage repair, and as our imaging techniques improve and our grading systems based on these images are refined, this will become an important clinical tool to evaluate the repair tissue, which will help in determining postoperative rehabilitation and the appropriate time for the patient to return to higher impact activities.

Schneider et al., as part of a prospective clinical pilot study, evaluated 17 patients at 6 wk as well as 3, 6, and 12 mo after ACI. A synovial analysis was performed, and molecular markers for bone and cartilage metabolism were determined. A number of parameters, including deoxypyridinolin, matrix metalloproteinase 1 and 3, as well as proteoglycan levels were analyzed. The levels were referenced to the total protein concentration of the synovial fluid, and analyses were compared with clinical parameters (Larson score) and MRI examinations. The most notable marker was deoxypyridinolin, which increased continuously between surgery and wk 12 and then disappeared after the repair process was complete 1 yr after surgery. All molecular markers for cartilage degradation increased initially after surgery and dropped off below the original levels 3–6 mo later *(45)*. This is a potential adjunct to MRI that is minimally invasive and less expensive. Further studies to define the appropriate markers that correlate with clinical outcome are required prior to recommending widespread use of this method.

Arthroscopic assessment remains the gold standard for postoperative evaluation as it allows direct visualization of the repair site; in conjunction with histomorphologic biopsy assessment and probe analysis, this method provides the most thorough postoperative information *(46)*. Arthroscopic probe indentation stiffness testing is increasingly used to evaluate clinical outcomes *(47)*. Vasara et al. arthroscopically evaluated 30 patients following ACI, and indentation stiffness was measured and clinical evaluations performed. Stiffness of the repair tissue improved to 62% (mean 2.04 ± 0.83 N, mean ± standard deviation) of adjacent cartilage (3.58 ± 1.04 N). In 6 patients, the normalized stiffness was at least 80%, suggesting hyalinelike repair; indentation stiffness of the OCD lesion repairs (1.45 ± 0.46 N; $n = 7$) was less than that of the non-OCD lesion repair sites (2.37 ± 0.72 N; $n = 19$). Gadolinium-enhanced MRI of the cartilage during follow-up of 4 patients suggested proteoglycan replenishment. The authors concluded that low stiffness values may indicate incomplete maturation or predominantly fibrous repair; increasing stiffness in comparison to the adjacent cartilage correlated with improved clinical outcomes.

LITERATURE REVIEW/CLINICAL OUTCOMES

In a landmark article, the senior author (L. P.) published his initial experience with ACI in 1994 *(9)*. Twenty-three patients were treated in this initial series, with 14 of 16 patients who

were implanted along the distal femur obtaining good-to-excellent results. Only 2 of 7 patients who were implanted in the patellar region obtained promising results. Second-look biopsies were obtained, and hyalinelike cartilage was demonstrated in 11 of 15 distal femoral lesions; only 1 of 7 patellar lesions demonstrated hyalinelike repair tissue. Biopsy results correlated well with clinical outcome, demonstrating a direct correlation between hyalinelike repair tissue and good-to-excellent function 2 yr following the surgery.

This same experience was further evaluated during the intermediate- to long-term period (2–9 yr), and this initial trend continued, as well as a clear demonstration of a significant learning curve that occurs as the surgeon gains experience with the procedure *(25)*. In this study, graft failure occurred in 7 patients, with 4 occurring in the first 23 patients but only 3 occurring in the next 78 patients. Clinical, arthroscopic, and histologic results from the first 101 patients treated using this technique were reported in this study. Patient- and physician-derived clinical rating scales were used as well as arthroscopic assessment of cartilage fill, integration, and surface hardness. Biopsies were obtained, and standard histochemical techniques were utilized in the assessment. Ninety-four patients of this initial group underwent reevaluation. Good-to-excellent clinical results were seen in 92% of the isolated femoral condylar lesions; these results decreased to 67% in patients with multiple lesions. OCD lesions also did well (89% good-to-excellent results). In contrast to the initial series, patellar lesions did relatively well, with 65% good-to-excellent results. Strict attention to patellofemoral tracking and malalignment issues were important; concomitant tibial tubercle advancement and trochleoplasty procedures protected the patellofemoral implant during postoperative rehabilitation, accounting for the improved clinical results in this area in comparison to the initial series. Patients who underwent femoral condylar implantation with concomitant anterior cruciate ligament reconstruction demonstrated 75% good-to-excellent results. Periosteal overgrowth, as demonstrated by arthroscopy, was identified in 26 patients, but only 7 were symptomatic and resolved after arthroscopic trimming. Histologic analysis of the matrix in 37 biopsy specimens assessing for type II collagen showed a correlation between hyalinelike repair tissue and good-to-excellent clinical results.

Using this same group of patients, arthroscopic evaluation was performed on a subset of patients treated for isolated cartilage defects on the femoral condyle or the patella *(46)*. Sixty-one patients with a mean follow-up of 7.4 yr (range 5–11) were assessed for durability by comparing the clinical status at long-term follow-up with that found 2 yr after transplantation. Of 61 patients, 50 had good or excellent clinical results at 2 yr, increasing to 51 of 61 good or excellent results at 5–11 yr. Hyalinelike repair tissue was demonstrated in 8 of 12 biopsies as characterized by Safranin O staining and homogeneous appearance under polarized light. Three fibrous and eight hyaline biopsy specimens stained positive to aggrecan and to cartilage oligomeric matrix protein. Hyalinelike specimens stained positive for type II collagen; fibrous specimens stained positive for type I collagen.

An electromechanical indentation probe was used to assess the grafted areas from 11 patients during a second-look arthroscopy procedure (mean follow-up 54.3 mo; range 33–84 mo); 8 patients demonstrated stiffness measurements that were 90% or more in comparison to normal cartilage measurements. The mean stiffness of grafted areas with hyalinelike repair tissue, as determined by histologic assessment, was 3.0 ± 1.1 N. By contrast, the mean stiffness of grafted areas with fibrous tissue was 1.5 ± 0.35 N. Again, good or excellent clinical outcomes were directly correlated with the demonstration of a hyalinelike repair tissue at the implanted site; fibrous fill correlated with poorer clinical outcomes. More important,

durability of the repair tissue was clearly demonstrated with results at 9 yr that were equal to or better than the initial 2-yr results.

Genzyme Tissue Repair (Cambridge, MA) initiated an international registry assessing the clinical effectiveness of the ACI procedure. Data from this registry were used to evaluate the first 50 patients treated in the United States *(22)*. Mean age was 36 yr, and mean defect size was 4.2 cm^2, with minimum 3-yr follow-up. Seventy-eight percent had undergone previous articular cartilage repair procedures on the affected knee during the previous 5 yr. Failed marrow stimulation technique had occurred in 18% of the patients. Outcome was measured with the modified Cincinnati Knee Rating system, with graft failure defined as replacement or removal of the graft because of mechanical symptoms or pain. Statistically significant median improvement in the clinician-based portion of the evaluation was 4; the patient-based portion of the evaluation increased by 5 points ($p < 0.001$). Previous treatment with marrow stimulation techniques or the size of defect did not have an impact on the results with ACI. Three patients had graft failure, and Kaplan-Meier-estimated freedom from graft failure was 94% at 36 mo postoperatively (95% CI = 88–100%).

Using this same registry, the first 76 patients treated in the United States were evaluated 6 yr following implantation *(48)*. Mean age remained at 36 yr, with 57 patients having single lesions with a mean size of 4.4 cm^2. Nineteen patients had multiple lesions with a mean total surface area of 10.8 cm^2. Nine treatment failures occurred, with 7 occurring within the first 24 mo following the procedure. Including these failed patients, overall condition scores improved from 3.1 preoperatively to 6.0 at 6-yr follow-up ($p < 0.001$). Pain and swelling scores improved 2.7 and 2.6 points from baseline to follow-up, respectively.

Scott Gillogly evaluated 112 patients with 139 defects treated with the ACI procedure over a 5-yr period of time *(49–51)*. Average size of the defect was 5.7 cm^2, with over 60% of patients having failed at least one prior procedure. Of the patients, 22 had multiple defects. Forty-two patients had patellofemoral lesions (27 trochlea, 15 patella). Outcomes were measured using the Modified Cincinnati Rating Scale, Sports Score, and Knee Society Rating Scale. There were three clinical failures, and three patients were lost to follow-up. Average follow-up was 43 mo, with a range from 24 to 65 mo. Using the clinician evaluation portion of the Modified Cincinnati scale, 93% demonstrated good-to-excellent outcomes; the patient evaluation portion demonstrated 89% good-to-excellent outcomes. Importantly, no deterioration in outcomes occurred during the 2- to 5-yr follow-up period. Worker's compensation claims had no effect on clinical outcomes.

Two other studies have assessed ACI in the worker's compensation sector. Seidner and Zaslav assessed direct medical and nonmedical costs as well as return-to-work status in patients undergoing ACI who used the same claims system for a single worker's compensation insurer *(52)*. In comparison to a matched control group, 24 patients treated with ACI (mean age 35 yr) were followed to claim closure. Occupations ranged from light- to heavy-demand work status. In the ACI group, total medical costs averaged $90,235 per patient, and average indemnity costs were $64,704; overall, 71% returned to work. By comparison, the control group had total medical costs averaging $80,407 ($p < 0.001$) and indemnity costs averaging $89,226 ($p < 0.001$); overall, 83% returned to work in this group, which was not statistically different from the ACI group ($p = 0.24$). They concluded that ACI results in similar return to work at an average cost savings of $15,000/patient in comparison to the controls.

James Yates performed a prospective longitudinal study in 24 worker's compensation patients with lesions greater than 2 cm^2 (mean lesion size was 4.7 cm^2, range 2–10 cm^2) *(8)*. Five lesions were on the patella; the remaining 19 lesions were on the distal femur. The

Modified Cincinnati Knee Rating scale was used with clinician and patient evaluations. Overall clinical scores improved from a mean of 3.2 at baseline to 6.8 at 1 yr after the operation. Good-to-excellent results were demonstrated in 78% of the patients. In patients with greater than 1-yr follow-up, 63% returned to unrestricted work status at a mean of 7 mo, with an additional 22% returning to modified work status.

Minas evaluated the health economics of the ACI procedure *(53)*. He prospectively examined the efficacy of treatment and quality of life in 44 patients undergoing the procedure and calculated the average cost per additional quality-adjusted life year. At 12-mo follow-up, ACI treatment showed improvement in patient function as measured by both the Knee Society score (114.02–140.67, $p < 0.001$) and the Western Ontario and McMaster Universities Osteoarthritis Index (35.30–23.82, $p < 0.05$). Quality of life was measured by the Short Form-36 Physical Component Summary and improved from 33.32 prior to biopsy to 41.48 ($p < 0.05$) 12 mo after implantation. Improvement on all three outcomes measures occurred during the following 12–24 mo. As a result of these findings, an estimated cost per additional quality-adjusted life year was $6791. He concluded that ACI improved quality of life in patients and was a cost-effective treatment for cartilage lesions.

Comparative Assessments

Several comparative studies have been reported assessing ACI directly with other biologic reconstructive procedures. Horas et al. compared ACI to osteochondral cylinder transplantation (OCT) in a prospective, single-center study investigating 2-yr outcomes in 40 patients *(6)*. Mean lesion size was 3.86 cm^2, and mean age was 31.4 yr in the ACI group. Mean lesion size was 3.63 cm^2, and mean age was 35.4 yr in the OCT group. Of 20 patients in the ACI group, 7 had undergone previous abrasion arthroplasty. In the OCT group, 2 patients had undergone abrasion arthroplasty, and 2 had undergone microfracture.

Recovery after ACI was slower than with OCT at 6 mo as assessed by Lysholm score; both groups demonstrated substantial improvement at 2 yr as assessed by the Meyers score and Tegner activity score. The one treatment failure in the study occurred in the ACI group but represented the only patellofemoral patient in either group. This patient had a large (5.6 cm^2) patellofemoral lesion, and failure was considered a result of poor rehabilitation. Histomorphologic assessment was performed on 7 biopsies in 6 ACI patients, with 2 biopsies coming from the patellofemoral patient; 5 biopsies were obtained from the OCT group.

In all ACI cases except for the one failure, gross evaluation demonstrated a complete, mechanically stable resurfacing of the defect. Biopsies from the ACI group demonstrated predominant areas of fibrocartilage with localized areas of hyalinelike regenerative tissue close to the subchondral bone. In the OCT group, all biopsies demonstrated hyaline articular cartilage that was histomorphologically similar to the surrounding cartilage. All OCT specimens demonstrated a persistent interface between the transplant and the surrounding cartilage, however.

One significant limitation of the study is the small number of patients in each treatment group, raising questions regarding the effect of the learning curve associated with the ACI procedure in particular. This study also had relatively short-term follow-up. With longer follow-up, the durability of the repair in both groups would be better delineated. Further, the one treatment failure in the ACI group was in the trochlear groove, with a surface area much larger than the other defects treated, placing this patient at higher risk for delamination or poor clinical outcome.

In a similar prospective, randomized study of ACI and mosaicplasty, Bentley et al. assessed 100 consecutive patients (mean age 31.3 yr and defect size 4.66 cm^2) *(5)*. Mean duration of

symptoms prior to operative repair was 7.2 yr, and mean number of previous operative procedures, excluding arthroscopy, was 1.5 yr. Mean follow-up was 19 mo. Fifty-eight patients underwent ACI; 42 patients underwent microfracture. Using modified Cincinnati and Stanmore functional rating systems as well as objective clinical assessment, excellent or good results were seen in 88% of the ACI patients compared to 69% after mosaicplasty. Lesions were assessed based on the ICRS grading system using arthroscopic evaluation at 1 yr. Grade I–II appearance was demonstrated in 31 of 37 ACI patients (84%) compared with only 8 of 23 patients treated with microfracture (35%). They noted that 50% of the ACI patients demonstrated a soft consistency on probe assessment at 1 yr. Biopsies were obtained for 19 ACI patients at 1 yr, 3 from patellar lesions and 16 from femoral condylar lesions. Seven patients' biopsies demonstrated hyalinelike cartilage as assessed by Safranin O staining, polarized light, and S100 protein immunostaining. Seven patients demonstrated a mix of hyalinelike and fibrocartilaginous regions; 5 patients' biopsies demonstrated a fibrocartilagenous appearance that was well bonded to the subchondral bone. One patient biopsy had a mixed appearance; the patient was rebiopsied at 2 yr, and the lesions had converted to hyalinelike cartilage consistent with the maturation process. There were 7 poor results in the mosaicplasty group, demonstrating poor graft incorporation in the interface in 4, graft disintegration in 3, and exposed subchondral bone at the margin in 1.

Two studies have assessed ACI in comparison to the Steadman microfracture technique *(54)*. In a prospective, concurrently controlled study, Anderson et al. compared the two techniques with 23 patients in each group *(55)*. Defects less than 2 cm^2 as well as patellar and tibial lesions were excluded. No differences were noted in overall defect area, body mass index, number of prior procedures, or baseline scores. A worker's compensation claim was filed in 39% of the ACI group as opposed to 14% of the microfracture group. Mean improvements in overall condition score from baseline was 3.1 in the ACI group as opposed to 1.3 in the microfracture group. Two ACI and 6 microfracture patients met the study criteria for treatment failure. When treatment failures were excluded from each group, ACI patients had a mean improvement of 4.7 in overall condition score, and microfracture patients improved by 2.8. This difference was statistically significant ($p = 0.023$).

In a separate study, Knutsen et al. evaluated 80 patients, each with a single symptomatic cartilage defect of the femoral condyle, who were treated with either ACI or microfracture (40 per group) *(56)*. ICRS, Lysholm, Short Form-36 (SF-36), and Tegner standardized scoring systems were used to evaluate patients, with an independent observer performing follow-up assessments at 12 and 24 mo. Arthroscopic biopsy was performed 2 yr postoperatively; histological evaluation was performed by a pathologist and a clinical scientist, with both evaluators blinded to each patient's operative treatment. At 2 yr, both groups had significant clinical improvement. However, by SF-36 physical component score, improvements in the microfracture group were significantly better than in the ACI group ($p = 0.004$). Two failures occurred in the ACI group; one occurred in the microfracture group. Eighty-four percent of patients underwent arthroscopic biopsy. Hyalinelike tissue was seen in 72% of specimens evaluated in the ACI group; 25% demonstrated a mixed hyaline-fibrocartilage appearance. Only 3% demonstrated true fibrocartilage in the ACI group. In the microfracture group, 40% demonstrated hyalinelike tissue, and 29% demonstrated a mixed hyaline-fibrocartilage appearance. Fibrocartilage was demonstrated in 31% of specimens from the microfracture group. No correlation between histologic appearance and clinical outcome was demonstrated in this study.

One important question following a critical review of this study *(56)* is whether the ACI procedure would have been used as a first-line treatment in many of these patients. Baseline

Table 2
Lesion Size and Operative Treatment Recommended

Recommended treatment	*Lesion size*
Microfracture	1–2.5 cm^2 Well-shouldered, protected edges
Osteochondral autograft	1–2.5 cm^2 Grafts need to be perpendicular and flush to surface
Autologous chondrocyte	>2 cm^2 Background factors need to be addressed; compliant with rehab
Osteochondral allografts	>4 cm^2 Large lesion uncontained involving significant bony loss

scores in the ACI group were higher than baseline scores in the microfracture group. Currently, the ACI procedure necessitates a concomitant arthrotomy with associated morbidity as opposed to the microfracture technique. Based on the reported sizes of the defects, many of these patients might have been more appropriately treated with a less-invasive option. At this time, for isolated lesions less than 2 cm^2, most surgeons would probably consider use of the microfracture or the mosaicplasty procedure first and use the ACI procedure for treatment failures after at least 1 yr has been allowed for healing *(57,58)* (Table 2).

Further, the multicenter nature of the study raises concerns about the learning curve associated with the ACI procedure and how this may have affected treatment outcomes in the ACI group. Critical biostatistical assessment using comparative study designs suggests that a minimum of 120 patients would be needed in each study arm to determine clear superiority of one technique over the other. Thus, as the authors concluded *(56)*, each technique demonstrated clinical efficacy with statistically significant improvements in function at short-term follow-up in both groups. As there were demonstrated histologic differences in appearance between the two techniques, it will be interesting to see the clinical results with return to normal activities at the intermediate and long-term follow-up time-points.

Matrix-Supported Autologous Chondrocyte Implantation

With the introduction of the ACI procedure, the significant regenerative potential of cultured chondrocytes was recognized. Simultaneously, interest in possible carriers and matrices that would potentially expedite the maturation process arose. In 1994, Hendrickson et al. used fibrin as a vehicle for the implantation of articular chondrocytes into 12-mm full-thickness defects in horses *(59)*. The chondrocytes, isolated from a 9-d-old foal, were mixed 1:1 with fibrinogen and thrombin and injected into 12-mm circular defects on the lateral trochlea of the distal femur of eight normal horses. Similar defects created in the contralateral knee were left empty and served as the controls. Statistically significant ($p < 0.05$) increases in type II collagen (61.2% grafted, 25.1% control) as well as aggrecan levels (58.8 µg/mg grafted, 27.4 µg/mg control; $p < 0.05$) were noted in the grafted tissue at 8 mo.

Lee et al. isolated chondrocytes from adult canine knees; cells were expanded in number in monolayer for 3 wk, seeded into porous type II collagen scaffolds, and cultured for an

additional 4 wk in vitro *(60)*. The populated scaffolds were then implanted into chondral defects in the trochlear groove of the opposite knee joint. The reparative tissue filled 88 ± 6% (mean ± standard error of the mean; range 70–100%) of the cross-sectional area of the original defect, with hyaline cartilage accounting for 42 ± 10% (range 7–67%) of defect area. These values were greater than those reported previously for untreated defects and defects implanted with a type II collagen scaffold seeded with autologous chondrocytes within 12 h prior to implantation *(61)*.

Based on these preliminary studies and the promise of decreased surgical time and morbidity, Hyalograft® C (Fidia Biopolymers Inc; Abano Terme, Italy) was introduced. This innovative tissue-engineering approach uses a three-dimensional hyaluronan-based scaffold entirely made of HYAFF 11, a benzyl ester of hyaluronic acid with 20-μm fibers. Autologous chondrocytes are grown under laboratory conditions on the scaffold prior to implantation into knee cartilage defects. Pavesio et al. reported on a cohort of 67 patients treated with Hyalograft C with a mean follow-up of 17.5 mo following implantation. Patients were evaluated arthroscopically and histologically. Subjective evaluation of patients' knee conditions demonstrated 97% improvement; quality-of-life assessment demonstrated 94% improvement. Surgeons' knee functional testing produced best scores in 87% of the patients; arthroscopic evaluation of cartilage repair revealed 96.7% biologically acceptable results, and histological assessment of the grafted site demonstrated hyalinelike tissue in a majority of specimens.

Marcacci et al. reported on a retrospective cohort, multicenter study investigating the subjective symptomatic, functional, and health-related quality-of-life outcomes of patients treated with Hyalograft C. A cohort of 141 patients with follow-up assessments ranging from 2 to 5 yr (average 38 mo) demonstrated that 91.5% of patients improved according to the International Knee Documentation Committee (IKDC) subjective evaluation, 76% had no pain as assessed by a visual analog scale, and 88% of patients had no mobility problems based on quality-of-life assessment. Surgeon evaluations revealed 95.7% of the patients had normal or nearly normal findings in the treated knee; Arthroscopic assessment of the cartilage repair demonstrated normal or nearly normal findings in 96.4% of the knees evaluated. Histological assessment of 21 second-look biopsies demonstrated hyalinelike tissue in 12 specimens, mixed hyaline and fibrocartilaginous findings were demonstrated in 5 specimens, and 4 cases demonstrated fibrocartilaginous findings. Interestingly, no fixation was used in 57.4% of cases, with the other cases using sutures or fibrin glue. A limited number of complications were recorded as well, with the authors concluding that Hyalograft C is a potentially safe and effective therapeutic option for the treatment of articular cartilage lesions. At the 2004 International Cartilage Repair Society, Marcacci reported on 88 patients treated arthroscopically with the Hyalograft C implant using no fixation. Computed tomographic and MRI evaluations were performed on all patients at 6, 12, and 24 mo, with no complications reported. Average preoperative IKDC scores were 41 and increased to 76 at 24-mo follow-up *(62)*.

Marlovits and coworkers reported on 16 patients with full-thickness, weight-bearing chondral defects of the femoral condyle *(63)*. All patients were treated with a three-dimensional collagen type I–III membrane seeded with cultured autologous chondrocytes (Fig. 11A,B). Fibrin glue was used with no periosteal cover or further surgical fixation. All patients were prospectively assessed using high-resolution MRI to determine the early postoperative attachment rate (range 22–47 d) after scaffold implantation. Implants were completely attached in 14 of 16 patients (87.5%), and full coverage was demonstrated in these patients as well. One patient had a partial detachment, and a patient had a complete detachment of the graft. At 24-mo

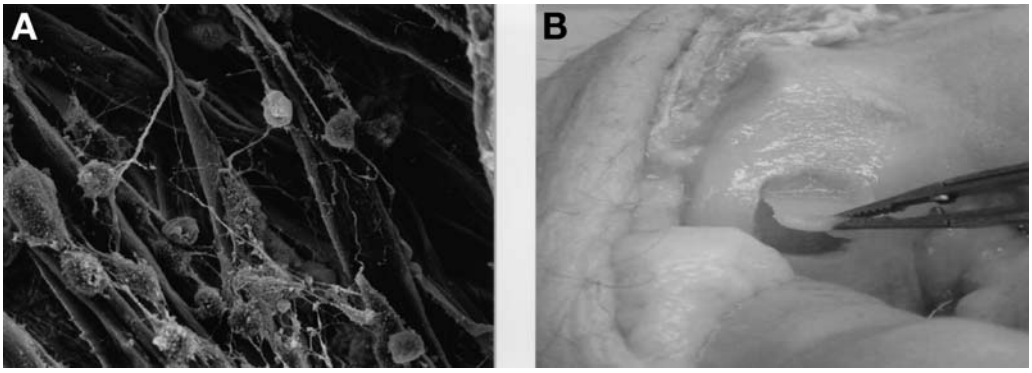

Fig. 11. (A) Electron microscopy of type I/III collagen scaffold seeded with articular chondrocytes. **(B)** Matrix on implantation into cartilage defect.

follow-up, significant improvements in IKDC, knee injury and osteoarthritis outcome, Lysholm, and modified Cincinnati scores were demonstrated in a majority of patients as well.

The term matrix-induced autologous chondrocyte implantation (MACI) has been used to describe procedures that specifically use a scaffold in addition to the autologous chondrocytes. Bartlett et al. performed a prospective, randomized study comparing the CACI procedure using a porcine-derived type I/III collagen cover to the MACI procedure using a bilayer of type I/III collagen *(37)*. Symptomatic chondral defects of the knee were evaluated in 91 patients, with 44 patients receiving the CACI procedure and 47 patients receiving the MACI procedure. Mean modified Cincinnati knee score at 1 yr increased by 17.6 in the CACI group and 19.6 in the MACI group ($p = 0.32$); good-to-excellent ICRS scores were demonstrated in 79.2% of CACI patients, and 66.6% of MACI patients had good-to-excellent results. Hyalinelike cartilage or hyalinelike cartilage with fibrocartilagenous regions were found in the biopsies of 43.9% of the CACI and 36.4% of the MACI grafts after 1 yr. Minimal graft hypertrophy and reoperation rates were noted in both groups. The authors concluded that the MACI procedure was technically attractive, but further long-term studies would be required before the technique is widely adopted.

CONCLUSIONS

The numerous matrices available in Europe and initial clinical reports associated with these devices are encouraging. The MACI procedure offers the benefit of sutureless fixation, minimally invasive or arthroscopic implantation, and fewer postoperative adhesions. The framework for future tissue engineering advances has clearly been laid. Several studies have demonstrated that articular chondrocytes, mesenchymal cells, and other cell phenotypes can be modulated by a variety of means to create hyalinelike articular cartilage.

Smith et al. exposed high-density primary cultures of bovine chondrocytes to hydrostatic pressure applied intermittently at 1 Hz or constantly for 4 h in serum-free medium or in medium containing 1% fetal bovine serum *(64)*. In serum-free medium, intermittent pressure increased aggrecan messenger ribonucleic acid (mRNA) signal by 14%, and constant pressure decreased type II collagen mRNA signal by 16% ($p < 0.05$). In the presence of 1% fetal bovine serum, intermittent pressure increased aggrecan and type II collagen mRNA signals by 31% ($p < 0.01$) and 36% ($p < 0.001$), respectively, whereas constant pressure had no effect on either

mRNA. Intermittent and constant pressure stimulated glycosaminoglycan synthesis 65% ($p < 0.001$) and 32% ($p < 0.05$), respectively. These results were reproduced using human articular chondrocytes, simultaneously demonstrating that the duration and magnitude of applied IHP differentially altered chondrocyte matrix protein expression and anabolism *(65)*.

Nawata et al. used muscle-derived mesenchymal cells from postcoital rat embryos that were then propagated in vitro in monolayer culture for 10 d and packed within diffusion chambers together with type I collagen (CI) and 0, 1, or 10 µg rHuBMP-2; cells were implanted into abdominal subfascial pockets of adult rats *(66)*. Tissue pellets generated in the chamber 5 wk after implantation were transplanted into a full-thickness cartilage defect made in the patellar groove of the same strain of adult rat. In the presence of 10 µg recombinant bone morphogenic protein-2 (rHuBMP-2), muscle-derived mesenchymal cells expressed type II collagen (CII) messenger RNA at 4 d after transplantation, and a mature cartilage mass was formed 5 wk after transplantation in the diffusion chamber. Cartilage was not formed in the presence of 1 µg rHuBMP-2 or in the absence of rHuBMP-2. Defects receiving cartilage engineered with 10 µg rHuBMP-2 were repaired and restored to normal morphologic condition within 6 mo after transplantation.

Zhou et al. used bone marrow-derived stromal cells (BMSCs) in a porcine knee joint model to test this cell phenotype's ability to repair articular osteochondral defects in a minimal weight-bearing area of porcine knee joints *(67)*. BMSCs were cultured, in vitro expanded, and induced with dexamethasone (group A) or with dexamethasone and transforming growth factor-β1 (TGF-β1) (group B). Cells were seeded on a construct of polyglycolic acid (PGA) and polylactic acid (PLA) and co-cultured for 1 wk before implantation. Four osteochondral defects (8-mm diameter, 5 mm deep) were created in each animal on both sides. The defects were repaired with dexamethasone-induced BMSC-PGA/PLA construct in group A, with dexamethasone and TGF-β1-induced BMSC-PGA/PLA construct in group B, with PGA/PLA construct alone (group C), or left untreated (group D) as controls.

Stronger expression of type II collagen and aggrecan were observed in BMSCs induced with both dexamethasone and TGF-β1 *(67)*. At 3- and 6-mo time-points, gross observation and histologic evaluation showed that a majority of defects in group A were repaired by fibrocartilage and cancellous bone with an irregular surface. However, most of group B defects were completely repaired by engineered hyaline cartilage and cancellous bone. No repair tissue or fibrous tissue was observed in groups C and D. The compressive moduli of repaired cartilage in groups A and B reached 30.37 and 43.82% of normal values at 3 mo and 62.69 and 80.27% at 6 mo, respectively; further, high levels of GAG contents in engineered cartilage of group A (78.03% of normal contents) and group B (no statistical difference from normal contents) were noted. Confocal microscopy revealed the presence of green fluorescent protein-labeled cells in engineered cartilage lacuna and repair of underlying cancellous bone. The authors concluded that implanted BMSCs can differentiate into either chondrocytes or osteoblasts at different local environments and repair a complex articular defect with both engineered cartilage and bone. TGF-β1 and dexamethasone in vitro induction promoted chondrogenic differentiation of BMSCs and improved the results of repairing articular defects.

The above studies demonstrate that cells of variable phenotypes can be modulated, and under appropriate conditions mature hyalinelike or normal articular cartilage is regenerated. Certainly, in light of the results with the MACI procedure, the in vitro manipulation and subsequent implantation of maturing cartilage constructs will be attempted.

Our experience with the traditional ACI technique using autologous chondrocytes with an autologous periosteal patch has been quite promising as well. In a majority of these patients, prior operative interventions had failed, or the total surface area of involvement was too extensive for less-versatile techniques. At this time, when the lesion size is less than 2 cm^2, minimally invasive procedures such as the microfracture or mosaicplasty techniques should be considered. However, for lesions greater than or equal to 2 cm^2 or when there are multiple lesions, the surgeon should consider the ACI procedure (Table 2). Critical evaluation of the biologic repair process has clearly demonstrated a reproducible sequence of events that occur as the tissue matures. If preoperative attention is given to those potential factors that could delay or prevent this process, failures can be avoided and the desired outcomes achieved.

Potential long-term benefits of the ACI procedure include durable repair tissue that can function in a manner similar to normal hyaline cartilage, withstanding the high shear and compressive loads applied during daily and sporting activities. The senior author has clearly demonstrated results in patients up to 11 yr following the ACI procedure that are equal to or better than those demonstrated at the initial 2-yr time-point. Further, as delineated in this chapter in the review of literature, second-look biopsies that demonstrated hyalinelike or mixed hyaline-fibrocartilaginous tissue reacted to indentation probe assessment in a manner similar to the adjacent host cartilage, suggesting a more normal response to physiologic loads; in line with these findings, a direct correlation between hyalinelike biopsies and better clinical results has been demonstrated in several studies as well.

The future of biologic regeneration and tissue engineering of articular cartilage to heal defects looks promising, and with further modifications in the techniques, arthroscopic or minimally invasive repair of these defects will be obtained, and successful return of patients to normal activity will be achieved on a regular basis.

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