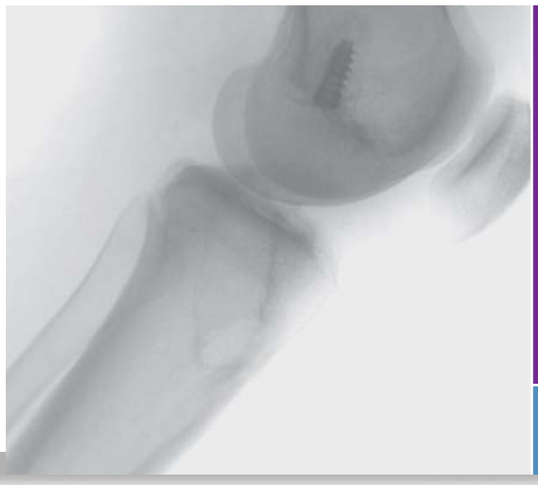


AUTOLOGOUS CHONDROCYTE IMPLANTATION

59

J. WINSLOW ALFORD, MD, BRIAN J. COLE, MD, MBA

HISTORY OF THE TECHNIQUE

Historically, the initial treatment of chondral injury included arthroscopic debridement to smooth the surface and remove debris that might promote an inflammatory response. Reparative techniques such as marrow stimulation offer another option that involves penetration of the subchondral bone to stimulate bleeding and recruitment of pluripotent mesenchymal marrow stem cells that differentiate and form fibrocartilage.[1] Restorative options used to replace the damaged cartilage include osteochondral autograft and allograft transplantation. Finally, autologous chondrocyte implantation (ACI), the subject of this chapter, involves the biologic replacement of articular cartilage. First reported clinically by Brittberg et al.[2] in 1994 and subsequently by several other authors,[3–5] ACI has become an acceptable treatment option in appropriately indicated patients with symptomatic chondral defects.

The procedure involves an arthroscopically performed biopsy of articular cartilage followed by implantation of cultured chondrocytes beneath a periosteal patch. At this juncture, ACI is considered a first-generation technology and advances in biologic carriers, cell-seeded scaffolds, and single-stage biological techniques are sure to replace ACI within the next 5 to 10 years depending upon regulatory pathways. Although the vast majority of the clinical experience with these technologies is with the treatment of chondral injuries of the knee, our experience is beginning to include other weight-bearing diarthrodial joints as well.

Preclinical Experience

In the 1980s, several groups reported the results of ACI performed in rabbit articular cartilage defects.[6,7] In shallow defects, an average of 82% of the surface area of the defect was covered by reformed cartilage. More recently, Brittberg et al.[8] placed periosteal patches on rabbit patellar defects with and without implanting chondrocytes. After 1 year, the periosteal grafts with chondrocytes had resulted in an average repair area of 87% of the total area of the defect compared to 31% in the animals treated without chondrocytes. In addition, the tissue produced by the chondrocytes and periosteal flap had a hyalinelike appearance compared to a fibrous appearance in the group without chondrocytes.

In contrast, Breinan et al.[9] found no difference at 12 or 18 months in coverage area or histologic appearance of defects repaired with either empty periosteal patches or chondrocyte-filled patches. In this study, a substantial number of defects involved violation of the subchondral bone, resulting in the creation and evaluation of osteochondral defects. Since this work, the importance of avoiding violation of the subchondral bone and antecedent bleeding has been implicated as a key feature of the ACI procedure. With respect to the longevity of the chondrocytes, studies monitoring the fate of labeled chondrocytes have demonstrated that implanted chondrocytes contribute to the formation of repair tissue and are integrated into surrounding normal articular cartilage up to 18 months following implantation.[10]

INDICATIONS AND CONTRAINDICATIONS

Overview

Traumatic focal chondral lesions are rarely found in isolation. A thorough evaluation of the involved extremity is essential. Assessment of associated ligament injuries, menis-

cal deficiency, and coexisting mechanical axis malalignment [mb1] or patellofemoral maltracking must be identified with a strategy for correction incorporated into the overall surgical plan and postoperative rehabilitation.

Patient evaluation and identification of candidates for ACI treatment remain challenging. This is in part due to the fact that the natural history of commonly found asymptomatic lesions is unclear. In general, incidentally discovered articular cartilage lesions are well tolerated and rarely become symptomatic.[11] It is generally accepted that a symptomatic cartilage lesion that fails to respond to conservative care or initial arthroscopic measures is likely to persist or worsen without treatment.[12–14] Alternatively, the likelihood of a cartilage lesion detected incidentally on magnetic resonance imaging (MRI) or at arthroscopy becoming symptomatic depends on its location, depth, geographic configuration, the physical demands of the patient, subjective pain tolerances, and the presence of co-morbidities. Added to the unpredictable nature of the incidental lesion, the tendency for articular cartilage to respond to injury with a disordered and often incomplete repair response is likely to be related to the variability of symptoms that patients demonstrate following cartilage injury.[1,2,15]

Obtaining a history of the mechanism of injury, the onset and pattern of symptoms, prior treatments and the response to these treatments, as well as a thorough review of previous operative reports, arthroscopic images, and video is an important part of the initial patient evaluation. For example, Peterson et al.[16] demonstrated that the typical patient indicated for ACI had an average of 2.1 previous treatments. The senior author (BJC) has had a similar experience in more than 120 ACI procedures, and we have learned that direct verbal or written communication with the most recent treating physician is extremely useful.

The etiology of chondral lesions is variable and includes blunt trauma, focal wear, or chronic conditions (i.e., osteochondritis dissecans). Variable etiology and associated biology are further affected by prior treatments rendered, functional expectations of the patient, and unique patient personality characteristics. For these reasons, identifying candidates for ACI remains challenging. For a specific patient at a particular point in time there may be several reasonable treatment options. A central tenant of cartilage restoration is that a selected treatment must not "burn bridges" but rather allow for further treatments should they prove necessary. It is essential to avoid "linear reasoning" when evaluating a particular patient. There are often several potential etiologies that lead to patient complaints of knee pain, and, thus, incidental defects must not be inappropriately labeled as responsible for a patient's symptoms.

In addition to lesion characteristics, an evaluation of the relative severity of commonly occurring co-morbidities such as ligament and meniscal insufficiency and malalignment of the patellofemoral or tibiofemoral joints must also occur. This coexisting pathology must be addressed in conjunction with the articular cartilage pathology or in an appropriately staged fashion. Left untreated, coexisting pathology remains a contraindication to ACI. Ligament reconstruction, corrective osteotomies, or meniscal transplants are frequently required in addition to an ACI procedure. A comprehensive plan to address all features of the patient's joint pathology must be devised and discussed at length with the patient before proceeding. Treating co-morbidities greatly enhances a patient's possibility of achieving a good outcome by providing a symbiosis of two or more mutually beneficial procedures. The decision to perform multiple procedures concomitantly or in a staged manner requires the judgment of an experienced articular cartilage surgeon.

Imaging

Radiographic evaluation should include standing anterior to posterior, non–weight-bearing 45-degree flexion lateral, patellar skyline (i.e., Merchant), 45-degree flexion posterior-anterior (PA) weight bearing, full-length alignment views. The PA weight bearing 45-degree (tunnel or Rosenberg) view is essential because it brings the posterior femoral condyle into a tangential position relative to the tibial plateau and x-ray beam. A normal appearing joint in a standing AP x-ray may reveal severe articular cartilage loss in the region of the posterior femoral condyle when viewed with the knee in 45 degrees of flexion.

Recent advancements in cartilage-specific MRI technology permit precise diagnosis and measurement of articular cartilage pathology. High-resolution fast spin echo sequencing techniques provide a high level of accuracy in predicting defect location, size, and depth.[17] Techniques using fat saturation in T2 protocols or fat suppression in T1 protocols combined with ionic gadolinium diethylene triamine pentaacetic acid (Gd-DTPA) contrast allow for inferences of biomechanical and biochemical changes involved in matrix degradation and formation.[18,19] Improvements in MRI technology allow for a more accurate preoperative determination of lesion characteristics and also may allow for the postoperative assessment of actual glycosaminoglycan content and an assessment of the overall biochemical quality of the healing tissue.

Animal studies investigating the utility of ultrasound technology in the evaluation of articular surfaces were modeled to evaluate degenerative lesions, and the reliability of ultrasound for the evaluation of focal chondral lesions is unproven at this time.[20] Nuclear medicine studies are of limited value due to the nonspecific nature of the information it provides. However, in the presence of osteochondritis dissecans (OCD), a completely different pathophysiology exists and a bone scan can provide information about biologic activity and healing potential.

Arthroscopy

An examination under anesthesia will allow for an assessment of co-morbidities that may need to be addressed. A

thorough arthroscopic evaluation is valuable to determine the location, topical geography, surface area, and depth of a defect in addition to providing a formal assessment of comorbidities such as the condition of the opposing articular surface, ligament and meniscus status, and an evaluation for other unsuspected defects. Grading of articular cartilage lesions depends on direct visual assessment and has inter- and intraobserver variability. In addition to the rating systems of Outerbridge,[21] Insall,[22] Baur,[23] and Noyes and Stabler,[24] which are frequently cited in the literature, the International Cartilage Repair Society (ICRS) has offered a grading system to be used as a universal language when surgeons are communicating about cartilage lesions.[25] Verbal or written grading of articular surfaces should specify which grading system is being used and should be accompanied by a written and diagrammatic description of the lesion.

If the lesion is located in the patellofemoral joint, careful arthroscopic analysis of patellofemoral tracking and mechanical alignment is important because a combined anteromedialization of the tibial tubercle is generally recommended in conjunction with ACI of the patellofemoral joint.

Indications

The overall assumption is that identified defects are at least in part responsible for the patient's signs and symptoms at the time of clinical evaluation. Smaller acute defects (i.e., less than 3 cm^2) are typically treated initially with other modalities, whereby ACI is employed when these treatments fail to improve upon the patient's clinical presentation following adequate time for recovery and response. ACI is ideal for symptomatic, unipolar, full thickness, or nearly full thickness chondral or shallow osteochondral defects. Commonly, patients have failed previous treatments. Occasionally, larger symptomatic lesions in high demand patients are indicated for ACI as a first line treatment. ACI is traditionally indicated for treatment of focal defects in the knee, but its off-label use has recently been expanded to include the treatment of chondral defects in the ankle, shoulder, elbow, wrist, and hip.[26–30] In the knee, off-label usage for the patella and tibia has also met with success rates that parallel the femoral condyle and trochlea. Bipolar lesions (greater than grade II changes on the opposing surface) are a relative contraindication to ACI. As already discussed, malalignment, ligament instability, and meniscus deficiency are not considered contraindications to ACI as long as they are addressed concomitantly or in a staged fashion.

Patellofemoral lesions are commonly treated with simultaneously performed anteromedialization of the tibial tubercle. It is important to determine the desired ratio of anteriorization to medialization required from the distal realignment as this will determine the angle of the tubercle osteotomy performed at the time of implantation.

OCD is not a contraindication for ACI provided that bone loss is less than 6 to 8 mm. Greater degrees of bone loss are corrected with bone grafting in a single- or two-stage procedure. A "sandwich technique" where the cells are injected between two opposing layers of periosteum placed over a bone graft to re-establish the subchondral bed has been utilized in a single stage, but the senior author (BJC) prefers to first graft the lesion and biopsy at that time only to return if necessary to perform the ACI procedure no sooner than 6 months following the index treatment.

SURGICAL TECHNIQUES

Stage I

Prior to biopsy, we make every effort to obtain insurance approval for both phases of the ACI procedure. We rarely will biopsy a patient without the explicit intention to definitively treat the defect with ACI. The first stage involves an arthroscopic evaluation of the focal chodral lesion to assess containment, depth, and potential bone loss **(Fig. 59-1)**. A biopsy of normal hyaline cartilage is obtained from either the superomedial edge of the trochlea,[31] or our preferred site, the lateral side of the intercondylar notch (i.e., where bone is removed for an ACL notchplasty) using a curved bone-graft harvesting gouge **(Fig. 59-2)**. If the biopsy is obtained from the trochlear ridge, it is recommended that a ring curette be used to allow for visualization of the biopsy process. The total volume of the biopsy should be approximately 200 to 300 mg preferably in three "Tic-Tac-sized" fragments. It is preferable to penetrate to the subchondral bone to ensure that the deep chondrocytes are included in the biopsy. The prepared shipping container has a collection vial that is clearly

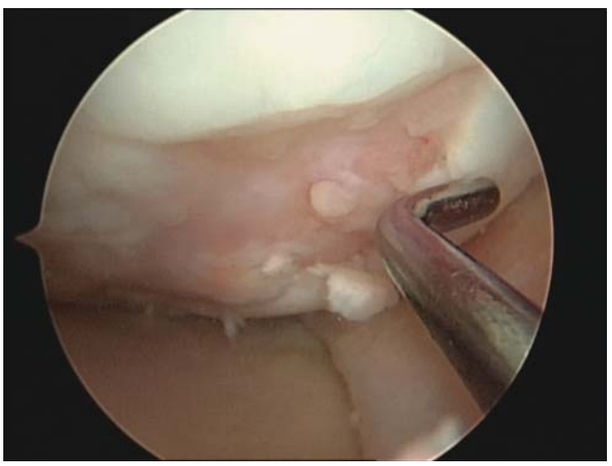


Fig. 59.1. An arthroscopic evaluation of focal chondral lesion provides direct measurement and assessment of lesion containment and potential bone loss.

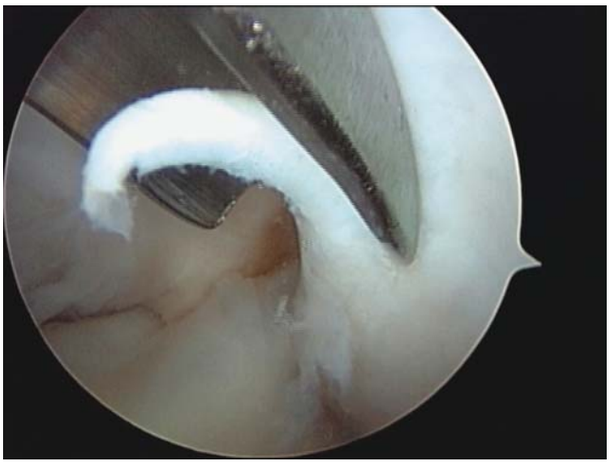


Fig. 59.2. An arthroscopic biopsy of articular cartilage cells is taken from the non–weight-bearing portion of lateral femoral condyle in a left knee.

marked to indicate adequate biopsy volume **(Fig. 59-3)**. As when performing an ACL notchplasty, it is important not to violate the weight-bearing articular cartilage. The biopsy is sent to Genzyme Biosurgery Corp (Cambridge, Mass) for processing and cellular expansion.

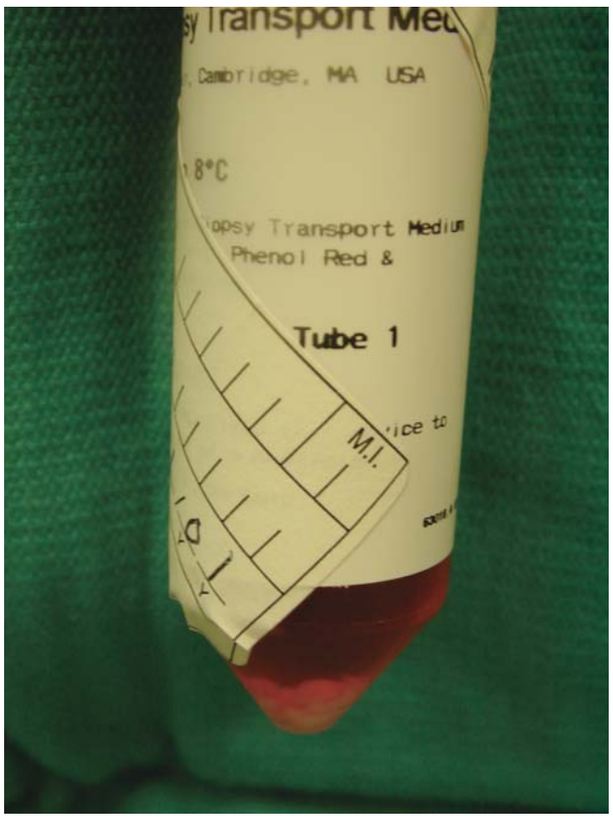


Fig. 59.3. Prepared shipping vial, demonstrating proper collection to assess adequate biopsy volume.

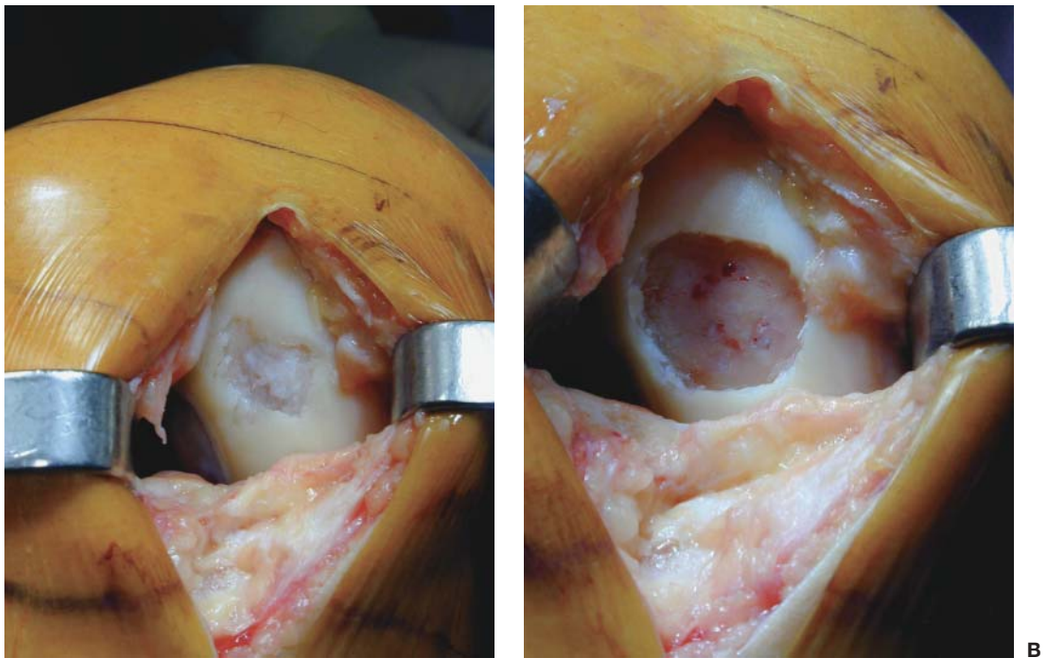
Stage II

The second stage of the procedure is cell implantation, which takes place between 1 and 18 months following the biopsy. A tourniquet is typically used until after the defect is prepared and the periosteal patch is harvested. The surgical exposure depends upon defect location. Patellofemoral (PF) lesions are approached through a midline incision allowing a simultaneously performed tibial tubercle osteotomy. We prefer to access PF lesions through a lateral retinacular release without formally everting the patella 180 degrees. We also avoid disruption of the fat pad and dissection around the patellar tendon to reduce complications related to postoperative stiffness. The tibial tubercle osteotomy does afford some increased patellar mobility facilitating access to the defect, but we intentionally avoid complete elevation and "flipping" of the tibial tubercle to minimize trauma to the fat pad and patellar tendon.

Femoral condyle lesions are addressed through limited ipsilateral parapatellar arthrotomies. For medial defects, we use a limited subvastus medialis approach, which has, in our experience, reduced the magnitude of postoperative pain allowing earlier and more complete return of motion. Lateral defects are approached through a limited lateral retinacular release. We then utilize a separate 3-cm incision beneath the pes anserine tendon insertion to harvest the periosteal patch. These recent modifications have allowed us to perform the majority of our ACI procedures on an outpatient basis.

Defect preparation involves removing the loose cartilage flaps and leaving healthy surrounding hyaline cartilage to form stable vertical walls shouldering the lesion. Circular or oval-shaped prepared defects are biomechanically more stable.[31] A no. 15 scalpel and sharp ring curettes are used to incise the defect border to, but not through, the level of the subchondral bone **(Fig. 59-4A,B)**. Hemostasis is controlled with the use of neuropatties soaked with a dilute 1:1,000 epinephrine solution.

The periosteal patch is harvested through a 3-cm incision on the proximal medial tibia, 2 fingerbreadths distal to the pes anserine tendon attachments. More distal and anteromedial locations tend to provide the best source for the periosteal patch. If a simultaneous tibial tubercle osteotomy is performed, we use a single extensile incision and harvest the periosteum prior to performing the osteotomy. Superficial subcutaneous fat is carefully removed with sharp dissection from the periosteum on the anteromedial tibia to avoid inadvertent penetration. Smokers tend to have poor quality periosteum and obese patients have a larger amount of adherent adipose tissue to separate from the periosteum, which will require extra care. In addition, older patients tend to have very thin periosteum. A patch that is at least 2 mm larger than the defect is harvested to account for slight shrinkage following detachment. The patch edges are scored to bone with a no. 15 scalpel on three sides, leaving it attached proximally, and elevated with a sharp curved periosteal elevator beginning distally and



A B

Fig. 59.4. Defect before **(A)** and after **(B)** preparation.

moving toward the inferior edge of the pes and overlying sartorius fascia **(Fig. 59-5)**. The character of the periosteum will change as the sartorius fascia fibers are encountered. It is recommended that the fat and small blood vessels found on the periosteum be dissected off after the periosteum is safely elevated from the bone, but before detaching the final proximal edge. The outer surface is marked to distinguish it from the inner cambium layer. Additional sources for periosteum, if necessary, are the distal femur, which is thicker and more vascular than the periosteum on the proximal tibia, or the contralateral leg, which carries the disadvantage of a second surgical site. In extreme cases, two periosteal patches may be sewn together, taking care to minimize suture bulk at the seam.

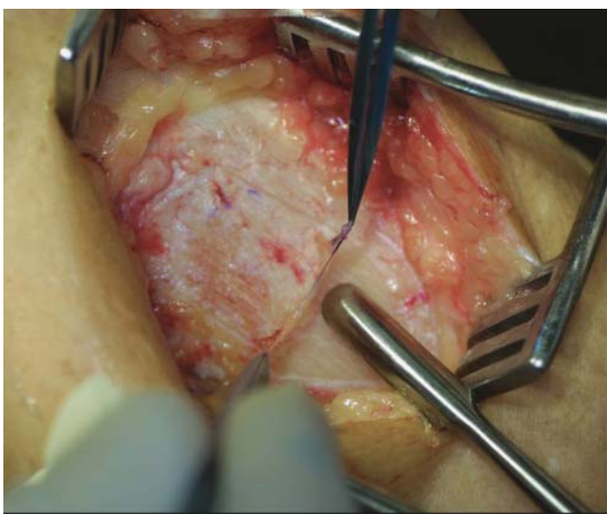


Fig. 59.5. Periosteal harvest from anteriomedial tibia, using curved-tipped elevator to minimize risk of penetrating periosteum during harvest.

The tourniquet is then deflated and meticulous hemostasis is obtained. The patch is then sewn onto the cartilage with the cambium layer facing the defect. The periosteum is secured with a 6-0 absorbable Vicryl suture on a P-1 cutting needle. The suture should be coated in sterile glycerin or mineral oil to prevent adherence to the surgical gloves, periosteum, and articular cartilage, allowing smooth suture passage without tissue tearing. The suture is passed through the patch edge first and then through the surrounding articular cartilage. The needle should enter the cartilage perpendicular to the inside wall of the defect at a depth of 2 mm below the articular surface and exit the articular surface 3 to 4 mm from the edge of the defect. The goal is to anchor the periosteum flush with the surrounding articular cartilage surface. One strategy is to first secure the four corners of the defect and then fill in the gaps with sutures every 3 mm, leaving one 4- to 6-mm gap to perform water tightness testing and injection of the cells. The location of this "gap" region should be selected to allow for easy syringe and catheter orientation. The patch should be taught over the defect to create a potential space to accept the cell suspension. In the trochlear groove, however, overtightening will cause a loss of concavity and result in a prominence, which can impinge on the patella. If small holes are inadvertently created in the periosteum patch, they may be carefully

repaired with a single 6-0 Vicryl suture. If the surrounding cartilage is unable to hold suture, microanchors loaded with absorbable suture may be used or if at the edge of an articular surface, small bone tunnels may be created with a 0.45 K-wire to pass transosseous sutures. Uncontained osteochondritis dissecans is typically on the lateral edge of the medial condyle and extending into the notch. Grafting these lesions may require that patch sutures be placed into the synovium surrounding the posterior cruciate ligament.

Water tightness testing is performed with a nonantibiotic saline-filled tuberculin syringe and 18-guage catheter. The patched cavity must be watertight to ensure cell containment and to prevent cell cavity contamination from postoperative hemarthrosis. After the saline is injected for the water tightness test, it should be removed completely. Additional sutures are placed at leakage locations and, after gently drying the cartilage surrounding the patch, the edges of the patch are sealed with fibrin glue (Tisseel, Baxter Healthcare Corp, Glendale, Calif) and a second water tightness test is performed as previously described. Do not prime the fibrin glue syringe needle prior to injection because the needle bore will clog, requiring tip replacement.

The chondrocytes are delivered and stored in vials that should remain upright at all times. Meticulous attention to sterile technique is paramount during this step as the vial's exterior is not sterile. The vials are held vertical without disturbing the pellet of cells in the bottom of the vial. The lid is removed, and the top is thoroughly sterilized with ethanol alcohol. An 18-gauge angio-catheter is inserted into the vial and advanced so the tip is submerged in the fluid, but above the pellet of cells in the bottom of the vial. The metal trochar is withdrawn, leaving the plastic catheter in the vial. Next, a 3-cc syringe is attached to the external portion of the catheter and only the fluid is aspirated into the syringe, leaving the pellet of cells behind **(Fig. 59-6)**. This fluid is gently injected back into the vial atraumatically, suspending the cells in the fluid. This process is methodically repeated until a homogeneous suspension is achieved. The entire contents of the vial are then drawn into the syringe. The syringe and catheter are carefully withdrawn from the vial while maintaining negative pressure in the syringe to prevent inadvertent escape of the chondrocyte suspension. The catheter tip is then discarded and replaced with a fresh sterile angio-catheter tip for implantation.

To implant the cells into the prepared defect, the catheter is placed through the opening at the top of the defect and advanced to the distal end. The cells are slowly injected into the bed of the defect with a side-to-side motion for even dispersal while the catheter is slowly withdrawn. The opening is then closed with additional sutures and sealed with fibrin glue **(Fig. 59-7)**.

Fig. 59.6. Angio-catheter tip is submerged in fluid while the vial containing chondrocytes is held vertical. Meticulous attention to sterile technique during this step is paramount.

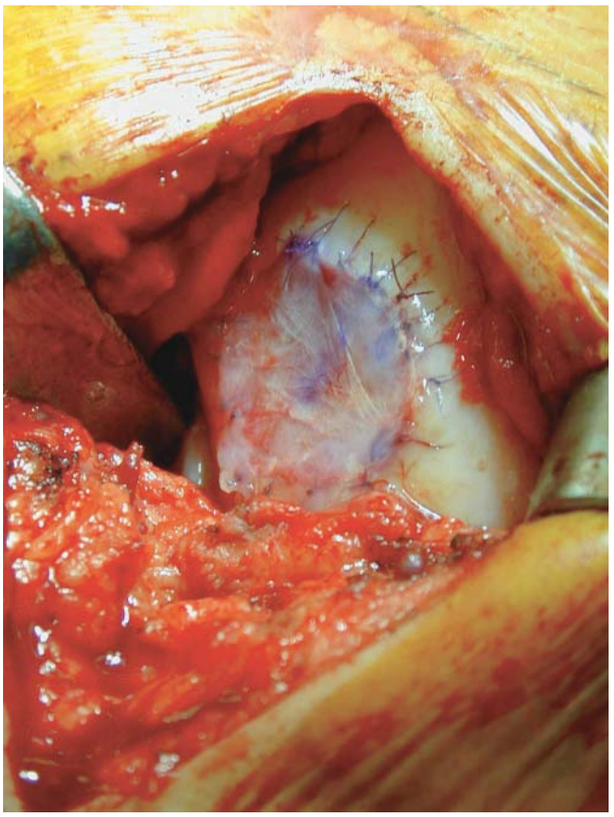


Fig. 59.7. After cell implantation, the sutured periosteal patch is sealed with fibrin glue.

TECHNICAL ALTERNATIVES AND PITFALLS

Most defects are easily accessible on the weight-bearing surface of the femoral condyle through a standard parapatellar arthrotomy. However, far posterior condylar lesions or focal cartilage defects of the tibial plateau may require additional strategies for exposure, including an open submeniscal [mb2] approach or even en block osteotomy of the collateral ligaments, which are repaired with interference screws at the completion of the procedure.

ACI has traditionally been applied to treat relatively shallow lesions of articular cartilage without involvement of the subchondral bone. For osteochondral defects of more than 8 to 10 mm in depth, bone grafting is recommended. The bone graft may be performed at the time of biopsy, and the implantation may be delayed to allow for bone graft consolidation. Alternatively, the "sandwich technique" has been utilized to replace bone and resurface the defect in a single step. A complete description of the procedure is reported elsewhere.[32] With that technique, the bone defect is filled with bone graft, periosteum is sutured on top of the bone graft at the level of the subchondral bone plate, a second layer of periosteum is placed over the cartilage defect, and the chondrocytes are then placed between the layers of periosteum. The result is a cancellous grafted bone defect covered by two layers of watertight periosteal patches with the cambium layers facing each other and into the cavity filled with autologous chondrocytes.

It is commonly believed that for all of these techniques, realignment osteotomy should be performed as an adjunct procedure if the lesion is in a compartment under more than physiological compression.[33] Outcome data clearly indicate that poorer results are expected if mechanical axis or patellofemoral joint malalignment is left uncorrected at the time of the cartilage restoration procedure.[33]

Patellofemoral joint realignment with a tibial tubercle osteotomy is a familiar procedure and has been in the mainstream of orthopedics for decades.[34] We recommend that any cartilage restoration procedure performed on the PF joint be combined with a distal realignment procedure that anteriorizes the patella to unload the newly resurfaced PF joint. Any associated PF maltracking or instability must be appreciated preoperatively and corrected at the time of the distal realignment. Whether performing the distal realignment to anteriorize the patella and unload the PF joint or to medialize it to correct lateral instability associated with a pathologic Q angle, the surgeon must be intimately familiar with each patient's PF mechanics to choose the proper osteotomy angle. Flatter angles will medialize more than anteriorize, and steeper angles will provide more anteriorization than medialization. A lateral release should be performed in addition to the distal realignment. There are commercially available surgical instruments to make the procedure technically easier to perform with precision (Tracker AMZ guide, Mitek, Norwood, Mass).

A high tibial osteotomy is required when performing a cartilage restoration procedure in the medial compartment of a varus knee. Many of these patients are relatively young and do not desire or tolerate large cosmetic changes in their lower extremity alignment. Unlike standard high tibial osteotomy for isolated medial compartment osteoarthritis, in which the aim is to correct the mechanical axis laterally to 62% of the width of the tibial plateau in the lateral compartment,[35] high tibial osteotomies combined with cartilage restoration in the medial compartment should correct the mechanical axis to neutral or just beyond. Because of its simplicity and reduced morbidity, we prefer an opening medial osteotomy to create a valgus correction rather than the traditional closing lateral osteotomy. Commercially available instrumentation (Arthrex, Inc, Naples, Fla) allows for a technically simple, rapidly performed osteotomy with precision and rigid fixation. Similarly, laterally based defects in a valgus knee are corrected with a simultaneously performed opening wedge distal femoral osteotomy.

When performing a corrective osteotomy combined with a cartilage restoration procedure, it is critical to establish a preoperative plan that allows for a stepwise incorporation of both procedures. For example, when performing an ACI of the PF joint with a combined distal realignment, the periosteal patch must be harvested from the anteromedial tibia prior to making the osteotomy of the tubercle through that area. Articular cartilage lesion preparation, graft suturing, and cell implantation require subluxation or eversion of the patella and should be performed prior to establishing rigid fixation of the tubercle osteotomy distally.

Uncorrected ligamentous instability is a contraindication to ACI. Methods of ligament reconstruction are well established and will not be reviewed here. When performing an ACL reconstruction in the setting of an ACI, periosteal patch harvest would occur before hamstring harvest or tibial drilling. If treating patellar or trochlear defect with ACI and distal realignment, hamstring autograft or patellar tendon allograft would be required as the osteotomized tibial tubercle insertion would be unavailable as an ACL graft source.

In complex cases, a guideline of two procedures per operation and staging subsequent procedures should be followed. When staging procedures, osteotomies should be performed first with a 4- to 6-month healing interval to allow for complete bone healing and remodeling. Subsequent hardware removal should be incorporated into the overall surgical plan.

REHABILITATION

The rehabilitation protocol for ACI in the knee is based on the three phases of the natural maturation process of the graft.[36–38] The proliferative phase occurs soon after the cells are implanted, followed by the matrix production phase during which the tissue becomes incorporated and integrated into the host. To assist cellular orientation and to prevent

adhesions, early continuous passive motion is crucial and begins at least 6 hours after the procedure is completed and continues for up to 6 weeks at 6 hours per day. The graft must be protected from mechanical shear, and closed chain strengthening exercises are initiated to allow for a functional gait. Patients are allowed passive motion and touch down weight bearing until 4 to 6 weeks when progression to full weight bearing is allowed. Weigh bearing in extension for PF lesions theoretically could be permitted early in the process, but we remain concerned about the potential for sustaining a tibial fracture through the tibial tubercle osteotomy site. The third phase is the maturation phase, which results in graft stiffness that more closely resembles the surrounding articular cartilage. During this extended phase, various impact-loading activities are phased in with increased strength work. Concomitant procedures do not generally change the rehabilitation protocol.

OUTCOMES AND FUTURE DIRECTIONS

It is estimated that ACI has been performed on 10,000 patients worldwide.[33] Micheli et al.[39] reported on 50 patients who were followed for a minimum 36 months and demonstrated a significant improvement of 5 points on the Modified Cincinnati scale measuring overall knee function (10-point scale). Eighty-four percent had an improvement in their condition, 2% were unchanged, and 13% deteriorated. One third of these patients had failed a previous marrow stimulation procedure. Peterson et al.[40] published his results on 94 patients with 2- to 9-year follow-up. The results varied considerably based upon defect location. The results of ACI when treating the patella initially were 62% good to excellent. However, later in the series, simultaneously performed tibial tubercle osteotomy was performed and results improved to 85% good and excellent. Twenty-four out of the 25 isolated femoral condyle lesions were graded as having good to excellent results with a 92% success rate. In the OCD group, 16 of 18 patients were rated good to excellent representing an 89% success rate. The majority of follow-up biopsies revealed hyalinelike tissue that demonstrated type II collagen on immunohistochemical staining. In 10% to 15% of cases, the biopsy site demonstrated an exaggerated healing response in the notch, resulting in discomfort and catching that may occur between 3 and 9 months. This routinely responded well to simple arthroscopic debridement.

To study the long-term durability of ACI, Brittberg et al.[32] followed 61 patients for a mean of 7.4 years after ACI. Good or excellent results were found in 81% at 2 years, and 83% at 5- to 11-year evaluation. The total failure rate was 16%, all of which occurred in the first 2 years. In this series, patients with the longer outcome were early patients who underwent ACI before full maturation of the surgical technique. As all failures occurred before 2 years, this study illustrates the durability of results at 2 years.

To compare microfracture to ACI, Knutsen et al.[41] randomized 80 patients with focal chondral defects in nonarthritic knees to receive either ACI or microfracture. At 2 years, arthroscopic evaluation, biopsy, and clinical evaluation, using Tegner, Lysholm, ICRS, and SF-36, demonstrates significant improvement in both groups, with significant difference between groups, favoring microfracture. In this series, both groups of patients were allowed immediate partial weight bearing (up to 50 lb), which may be disruptive for the fragile ACI patch. In addition, multiple surgeons were included in the study, all of whom included their early ACI patients for comparison. Longer term results will be needed from this study to determine the ability of microfracture to endure, given historical questions of its durability.

Horas et al.[42] compared ACI to osteochondral autograft transplantation at 2 years in 40 patients with a single femoral condyle chondral defect. Both treatments decreased symptoms, but the improvement provided by ACI lagged behind that provided by the osteochondral autograft transplant. Histologically, the ACI tissue was primarily fibrocartilage, whereas the osteochondral transplants retained their hyaline character. There was a persistent gap and lack of integration between the bone plugs and the surrounding articular cartilage. This study had a small number of patients in each group, a relatively short follow-up, and no control group.

To compare mosaicplasty to ACI, Bently et al.[43] randomized 100 patients with an average age of 31.3 with isolated traumatic focal chondral defects to receive ACI or mosaicplasty. Modified Cincinnati scores and clinical assessment measures rated good to excellent results in 88% of ACI patients and only 69% of the mosaicplasty patients. Arthroscopy at 1 year demonstrated 82% healing among ACI patients, but only 34% healing among mosaicplasty patients. This is the only prospective, randomized controlled comparison of ACI and mosaicplasty, and it appears to demonstrate the superiority of ACI over small-plug autologous mosaicplasty.

In the future, techniques utilizing minimally invasive implantation will spare the patient the morbidity of an open arthrotomy. All arthroscopic techniques have been reported, but are not currently implemented in the United States.[44] The technique is based on implanting a 2-mm thick polymer fleece, preloaded with autologous chondrocytes in a fibrin gel, that is anchored to the condyle arthroscopically. Lee has implemented in vitro culturing of a chondrocyte-laden scaffold prior to implantation. In a canine model, he evaluated full thickness focal chondral defects without bone involvement 15 weeks after implantation of an autologous articular chondrocyte-laden type-II collagen scaffold that had been cultured in vitro prior to implantation.[45] In these cultured scaffolds, the reparative tissue formed from the scaffolds filled 88% $\pm$ 6% of the cross-sectional area of the original defect, with hyaline cartilage accounting for 42% $\pm$ 10% (range, 7% to 67%) of the defect area. Further work is necessary to identify the specific culture and cell density parameters needed to maximize this advantage of in vitro scaffold culture prior to final implantation compared to the

results of noncultured implantation.[46,47] In the future, allogeneic sources of cells or single-stage biologic techniques may offer the added advantage of eliminating the need for biopsy prior to implantation. As ACI technology becomes more mainstream and techniques improve, it will likely be used more routinely to treat other joint surfaces as well as the knee.

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