TREATMENT OF FULL-THICKNESS CHONDRAL DEFECTS WITH AUTOLOGOUS CHONDROCYTE IMPLANTATION

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Introduction

With the introduction of new treatment methods for cartilage repair over the past ten to fifteen years, a corresponding interest has developed in gaining a better understanding of the scope of the clinical problem and classification of cartilage injuries. While understanding of the natural history of cartilage injuries in the knee remains elusive, this interest has nonetheless elucidated the scope, complexity, and diversity of cartilage injuries. Certainly all cartilage defects do not produce the same degree of clinical symptoms, progress at the same rate toward osteoarthritis or require the same uniform treatment. Consideration must be given to the size, depth of involvement, location and number of the defects. Additionally, individual patient parameters such as age, body mass, activity demands and perhaps most importantly, the condition of the remainder of the knee all influence treatment decision making. We have learned that failure to address any co-pathologies of the knee such as mechanical malalignment, ligamentous instability, or deficient meniscal function will expose any cartilage repair process to a continued overload environment and often doom the clinical outcome. Therefore, not all cartilaginous injuries require the same treatment, and treatment must be tailored to the individual patient and cartilage lesion.

As with any new and innovative treatment methods, there have been constant refinements in technique, indications and clinical expectations for these recent advances in cartilage repair. The new techniques of cellular repair with autologous chondrocyte implantation as well as tissue transfer with osteochondral autografts and allografts have continued to evolve with further scrutiny toward optimizing the results
from these treatment methods. While no treatment option is universally ideal for all full-thickness cartilage defects, the goal remains a repair that can restore the normal surface congruity of the joint, control the patients’ symptoms, maintain the characteristics to withstand the intra-articular forces of the knee over time and prevent the progression of focal chondral injuries to diffuse osteoarthritis. These newer treatment methods continue to be evaluated as to their consistency and reproducibility of outcomes, durability of repair, and cost effectiveness.

The technique of Autologous Chondrocyte Implantation (ACI), first reported by Peterson, Brittberg and colleagues in 1994 has found a major role in the treatment of large full-thickness chondral injuries. In this technique, a small biopsy of healthy chondral tissue is obtained arthroscopically when the lesion is identified and then undergoes in-vitro chondrocyte cell culture returning a 12-fold increase in the number of cells available for implantation into the defect at the second stage of the procedure. The principle behind using autologous chondrocytes is to produce a repair tissue that more closely resembles the morphologic characteristics of hyaline cartilage, therefore better able to restore the durability and natural function of the knee joint. As experience around the world has grown and the durability of the repair tissue has been demonstrated with good clinical outcomes seen beyond a decade post-operatively, indications and confidence in the technique have expanded to include treatments for more complex knee pathologies in combination with large articular cartilage defects.
Indications for Autologous Chondrocyte Implantation:

The predominant indication for Autologous Chondrocyte Implantation is symptomatic, large full-thickness chondral lesions located on the femoral condyles or the trochlear groove, including Osteochondritis Dissecans (OCD) in patients from adolescent age to the fifties. It is also important that patients are willing and able to comply with the post-operative rehabilitation protocol. ACI is not indicated as a treatment option for severe osteoarthritis, as defined by the presence of bipolar bone on bone lesions. If a large lesion is present on the reciprocal surface (kissing lesions) with exposed bone, greater than a grade III chondromalacia, the opposing surface is typically not suitable for this technique. This is particularly true when secondary bony deformity exists as a result of the arthritic process. There are however, exceptions to this general rule, namely trochlea and patellar defects or femoral condyle lesions with small tibial lesions in the milieu of an absent meniscus. In these special cases, which usually occur in younger patients, options exist for resurfacing both defects and correcting the underlying knee pathologies.

Results of treatment of isolated chondral injuries of the patella and tibia with ACI have not been as consistent as treating those of the femoral condyles and trochlea. However, with greater experience in the understanding of the importance of patellar alignment, the results of patellar ACI have improved. The indications for ACI treatment of the tibia include a traumatic substantial sized defect in a younger patient. Degenerative lesions on the tibia are rarely indicated for this technique of chondral resurfacing. ACI is contraindicated in active inflammatory arthritis or infection. Prerequisites for a successful outcome with ACI also include appropriate bony alignment, ligamentous stability, meniscal function, adequate motion and muscle
strength and compliance, in addition to a focal chondral injury in a knee without significant bony arthritic changes.

**Patient Selection and Pre-Operative Evaluation:**

As experience with biologic resurfacing of cartilage injuries has grown, it is apparent that the assessment of the condition of the overall knee is as important as the assessment of the chondral defect itself. The presence of coexisting knee pathology such as ongoing ligamentous instability, bony malalignment, or complete meniscal deficiency will prevent an environment conducive for cartilage repair.\(^8,9\) Any abnormalities in these factors must be addressed prior to or concomitant with treatment of the cartilage defect with ACI. Failure to recognize and treat these co-existing factors will result in poorer patient outcomes or complete failure of the resurfacing procedure.

A thorough history provides the first evaluation step in assessing patient suitability for ACI. Additionally, it is important to confirm that symptoms are indeed coming from the chondral injury. This is particularly relevant to patients that have undergone prior repair techniques such as marrow stimulation for the cartilage defect. Perhaps the repair has been adequate and further symptoms are from incomplete rehabilitation of the patellofemoral joint with corresponding anterior knee complaints and not symptoms from a previously treated femoral condyle lesion. Typically patients with condyle lesions will have pain with weight-bearing or increased loading circumstances, complaints of catching or partial locking, recurrent swelling and have point tenderness in the area of the defect. The presence of a trochlea or patellar lesion will have similar findings, but with aggravation of pain complaints with stairs, getting in and out of a chair or car and
anterior knee pain. Patellar subluxation symptoms are often present as well.

Additional information is often available on patients with known articular cartilage lesions through previous operative reports, previous studies and intra-operative video photographs of prior procedures. Taking advantage of any available information will help in determining the suitability of the defect for ACI.

Physical examination includes motion assessment, basic ligamentous exam, provocative meniscal tests, and patellar tracking tests. Additionally, careful palpation of each compartment and accessible chondral surface will give further clues as to potential sources of the patients’ complaints. While examination gives a good indication of involved compartment and the presence or absence of other knee pathology, additional testing with appropriate radiographs and MRI will be necessary. These studies will aid in confirming the clinical exam.

In order to adequately evaluate a patient for ACI, it is essential that weight bearing AP and 45° PA and patellar alignment radiographs be obtained.\textsuperscript{8,13,31} This allows initial assessment of the alignment of the tibio-femoral and patellofemoral portions of the joint and gives an indication of any underlying bone involvement associated with the defect from OCD or a traumatic osteochondral defect. A long leg limb alignment view to assess the mechanical axis is used to definitively determine the potential need for realignment osteotomy. (Figure1) MRI can then be used to assess both the ligament and meniscal status as well as defining the degree of subchondral bone involvement.\textsuperscript{29} Increased signal and edema in the subchondral bone of a chronic nature may indicate persistent overload of the involved compartment making realignment a more likely adjunct to
cartilage resurfacing. Bone loss of greater than 7-8 mm in depth requires bone grafting prior to or at the time of cell implantation.

The most definitive step in assessing the suitability of a chondral lesion for ACI comes at the time of arthroscopic evaluation. The size, location, and depth of the defect, the status of the surrounding articular cartilage and underlying bone as well as the status of the opposing chondral surfaces are all evaluated. Containment of the defect is also assessed. In other words, does the bordering rim of healthy articular cartilage fully surround the defect or do the margins of the defect fade into the intercondylar notch or perimeter of the condyle or trochlea. This assessment is important as it may indicate special techniques will be necessary to secure the periosteal patch to hold the autologous chondrocytes during implantation. The basic questions to answer when assessing the cartilage status is: will the joint be improved with resurfacing of the defect or is the degenerative process too advanced diffusely within the joint with multiple involved bipolar surfaces in which case ACI or any other biologic resurfacing procedure will be inadequate in improving the patient’s symptoms. The ideal chondral lesion to repair with autologous chondrocyte implantation is a full thickness defect surrounded by healthy, normal appearing cartilage in an otherwise healthy knee. Any deviation from the ideal may require specific variations in technique or concomitant procedures to address additional pathology. In general, the defects treated by this technique are larger than 2 cm² and the average size in the authors’ series has been well over 5 cm². Arthroscopic assessment also gives an opportunity for exam under anesthesia to confirm ligament stability and allows evaluation of the meniscal function and patellofemoral tracking.
Surgical Technique

Chondral Biopsy

The surgical technique for autologous chondrocyte implantation requires two stages, one to obtain a chondral biopsy for growing the autologous chondrocytes and another for implantation of the cells within the chondral defect. The essential steps include an initial chondral biopsy for autologous chondrocyte cell culture obtained at the time of arthroscopic assessment. The biopsy is obtained from the superior peripheral edges of the lateral or medial femoral condyles superior to the sulcus terminalis or from the inner edge of the intercondylar notch. We have found an arthroscopic gouge to be the easiest tool to use to obtain several small slivers of healthy chondral tissue for the biopsy. The total volume needed is roughly equivalent to the size if a pencil eraser and is typically three or four slivers measuring about 5 x 10 mm with the thickness of the healthy articular cartilage. After the biopsy fragments are removed from the knee with arthroscopic graspers, they are placed in the biopsy medium/shipping vial in sterile fashion and forwarded for cell culture. The ACI procedure is then performed at a second stage consisting of arthrotomy, defect preparation, periosteal procurement, fixation of the periosteal tissue, securing a watertight seal with fibrin glue, implanting the chondrocytes and wound closure.\(^ {4,8,9,19,22,25}\) The time between the biopsy and the implantation can be as short as 3 to 6 weeks or can wait months until the optimal time as determined by the patient and surgeon.

Surgical Exposure

The amount of exposure necessary for the implant procedure arthrotomy is determined by the size and location of the defect. A midline incision is generally recommended, followed by a medial or lateral para-patellar arthrotomy, exposing the corresponding
chondral injury. As with any surgical procedure, it is essential that the full extent of the defect is exposed facilitating all the technical aspects of the implantation. Inadequate exposure can lead to the incomplete securing of the periosteal patch to the defect, possibly resulting in cell leakage or graft delamination. Multiple, complex or hard to reach chondral injuries often require a larger midline incision with a medial parapatellar arthrotomy and eversion of the patella. When performing a concomitant patellar realignment procedure, we have detached the tubercle and turned the tubercle and patella proximally giving wide exposure to the knee. (Figure 2) The tubercle is then reattached with cortical screws in the realigned position after the cell implantation.

**Defect Debridement**

During debridement of the defect all damaged and unhealthy appearing cartilage and fibrocartilage is removed using small curettes leaving exposed subchondral bone with a rim of stable cartilage around the circumference of the defect. Failure to debride the calcified zone of cartilage inhibits the integration of the repair tissue to the subchondral bone. Any thinned, fissured or damaged surrounding cartilage needs to be debrided to an edge leaving healthy firm articular cartilage. This provides a stable non-mobile edge to affix the periosteal patch and decreases the risk of micro-motion of the patch during rehabilitation with incumbent increased risk of graft delamination or periosteal hypertrophy. During debridement, the subchondral bone should not be violated. Penetration of the subchondral bone leading to bleeding potentially introduces stem cells and fibroblasts into the defect that can compromise the quality of the repair tissue. If bleeding in the defect is encountered, hemostasis should be obtained for any bleeding bone. Techniques to control any bleeding bone include using compression over the area with epinephrine soaked neuro-patties with a dilute 1 to 1,000 epinephrine and
saline solution. Thrombin spray or temporary gel-foam may also be utilized. Fibrin glue may be applied to the bleeding area and then compressed with a neuro-patty or in refractory punctate bleeding from the bone, electrocautery with a needle point bovie, set at a low setting of five to eight watts can be the final step for controlling bleeding. In some cases an internal or intra-lesional intra-articular osteophytes in the subchondral bone may be encountered during debridement of the defect. These can be the result of penetration of the sub-chondral bone either from injury or prior surgical procedures, such as drilling or microfracture and are more common in chronic lesions. These bony prominences can be addressed by gently tapping them back into the subchondral bone plate with a smooth, non-corrugated bone tamp. Attempts to excise or curette the osteophytes will otherwise lead to excessive bleeding within the defect. The goal of adequate debridement of the defect is to have a dry defect with clean subchondral bone and a healthy surrounding cartilage border at the periphery. Defect dimensions can then be measured using a sterile ruler to determine the size of the defect. The best method for obtaining the correct size for the periosteal graft is to create a template from the sterile paper that comes with surgical gloves. A template can be made by placing a slightly larger size piece of the paper over the defect and outlining the defect with a marking pen. The template is then cut around the pen markings oversizing by 1 to 1.5 mm around the circumference. The purpose of slightly oversizing the template is to account for the fact that the periosteum has a tendency to shrink slightly after harvest.

Periosteal Harvest

The next step is to obtain a periosteal graft to be transferred to the defect and secured to contain the cells. The periosteum harvest is from the proximal medial tibia, two fingerbreadths distal to the pes anserinus and medial collateral ligament insertion on the
subcutaneous border. A separate incision is made just anterior to the posterior border of the tibia. The periosteum is easily accessible at this location, using blunt dissection down through the overlying subcutaneous fat. All fat and fascia layers should be removed from the periosteum using both sharp and blunt dissection with a moist sponge. Leaving the thin fascia layer or fat on the periosteum is one of the most common mistakes made with harvesting the periosteal graft.\textsuperscript{5} The template is then placed over the exposed periosteum and a 15 blade used to sharply demarcate the periosteal graft and a sharp curved periosteal elevator is used to gently dissect the periosteum from the bone. Smooth forceps can be used on the leading edge of the periosteum to provide countertraction for subperiosteal dissection. Obesity, inactivity, smoking, and increased age may lead to atrophy of the periosteum.\textsuperscript{24,28} In the event that the proximal medial tibia periosteum is thin and inadequate, an alternate site for periosteal procurement is the distal femur. Rather than use the distal femoral periosteum, just proximal to medial and lateral femoral condyle articular surfaces, we have found the periosteum on the metaphyseal flare of the femur to be closer to typical tibial periosteum and not as overly thick as the more distal femoral periosteum. This can easily be exposed by a limited sub-vastus approach, lifting the vastus medialis anteriorly to expose this second source of periosteum. Regardless of which periosteal harvest site is used, the final graft should be a clean contiguous layer without holes or excessive fat or fascia on its outer surface. Although the medial femoral metaphysis serve as a good backup source, usually the proximal tibia serves as the best and most consistent source for periosteal graft harvest.

\textit{Securing Periosteal Graft}
The periosteal graft is then aligned over the defect in the orientation matching the template with the cambium layer of the periosteum facing the defect. The periosteum is next sutured to the cartilage rim with multiple 6-0 vicryl interrupted sutures spaced every 2-3 mm. The knots should be tied on the periosteal side, not on the surface of the cartilage, thus minimizing any friction or toggling that could cause loosening of the knots. Securing the periosteum works best if several sutures are placed superiorly and then inferiorly to ensure proper tension on the graft to create a drum-like effect recreating the contour of the site as well as ensuring that the graft will fully cover the defect. Also, ensure the graft will cover medial to lateral as well. Typically as the “corners” are secured, it becomes apparent that there is some redundancy of the graft which can be trimmed with sharp scissors to keep appropriate tension on the graft. Having several different needle choices that are available with these small sutures is helpful for the variation in cartilage thickness present in most knees. While a smaller needle with a shorter radius of curvature works best around thick normal cartilage, a thin needle with a greater radius of curvature allows a longer pass through thinner cartilage and therefore holds the suture better than a shorter pass. Once all the sutures are in place with only a small opening remaining, the watertight integrity of the graft can be tested using an 18-gauge catheter attached to a saline-filled tuberculin syringe placed deep to the periosteum through the small opening. By slowly filling the defect with saline, any leakage can easily be seen around the perimeter of the repair site and any additional sutures can be placed as necessary. Next the suture line at the periosteal graft—defect interface is sealed with fibrin glue using any of the commercial preparations of fibrin glue available in most operating rooms to assure a watertight seal of the chondral edges and the periosteum by acting as a rapidly setting sealant.
Implantation of Autologous Chondrocytes

The autologous chondrocytes are then sterilely aspirated from their shipping vial into a sterile tuberculin syringe using an 18-gauge plastic angiocatheter and injected under the periosteal graft into the defect. Each vial contains about ten to twelve million chondrocytes, and provides more than adequate cells for defects up to 10 cm\textsuperscript{2}. The injection site is then closed with one or two additional sutures and sealed with fibrin glue. (Figure 3) At this point the ACI is complete and all retractors are removed from the knee, and the knee should be brought into full extension, insuring that there is no contact with any opposing surface during the maneuver. Any further wound hemostasis or irrigation is then done making sure that there is no inadvertent contact with the graft and no deep suction is used. Any concomitant procedures should be completed prior to implanting the chondrocytes no additional manipulation of the joint should follow the implantation. The arthrotomy and wound is then closed in a layered fashion, and a soft sterile dressing and knee immobilizer applied to the knee. A drain is not routinely used due to the potential for damage to the graft by contact or from the suction effect of the drain. The postoperative course and rehabilitation will be covered in a later section.

Complex Defects

Uncontained Chondral Lesions

In cases where the defect is not fully contained by a rim of healthy cartilage, special techniques may be necessary to secure the periosteum and still establish a watertight seal. Locations where defects not infrequently involve at least one uncontained border include those extending to the intercondylar notch, such as OCD defects of the medial femoral condyle, the proximal margin of the patella, the lateral margin of trochlear defects from patellar dislocations, and the posterior lateral femoral condyle in lateral
OCD. If a synovial fringe of tissue exists and is still well attached to the margin of the bone, the periosteum can be attached securely to the synovium. More frequently, there is no appropriate soft tissue for fixation and only bone surface remains at the margin. In these cases, absorbable micro-anchors loaded with 5-0 absorbable suture and the smallest free needle available work very well in securing the periosteum directly to the bone in the uncontained portion of the defect. Usually 3 to 4 anchors are utilized, and should be placed first and then each sequential suture is brought through the periosteum in a vertical mattress fashion. The periosteum tends to bunch up when using this method so we tend to oversize the periosteum a little more for uncontained lesions. We have never seen an anchor pull out, either intraoperatively or post-operative. Following securing the periosteum at the uncontained portion of the defect, the remaining periosteum is sutured and the suture line sealed with fibrin glue.

Multiple Chondral Lesions

Despite more extensive involvement in knees with multiple chondral lesions, good to excellent outcomes are still very possible.²³ Provided the remaining knee is free of significant bony arthritic changes, and coexisting knee pathology conditions are corrected, excellent outcomes with ACI, comparable to smaller lesions, can be achieved. The main factors to consider when undertaking multiple lesions treated with ACI are extensile exposure, insuring that multiple vials of cells will be available, and a plan to obtain sufficient periosteum. In general it is feasible to obtain two typical sized grafts from the usual proximal tibia site. Both templates should be placed on the periosteum to achieve the best orientation and utilization of available periosteum before cutting the grafts. (Figure 4) If there has been previous surgery at the tibia and there is concern about adequate periosteum, we have used the contralateral tibia in several
cases. The distal femur as described above under periosteal harvest should also be used when necessary for multiple defects.

**Massive Chondral Lesions**

A massive chondral defect is defined as a lesion greater than 8 cm². We have used ACI on defects over 20 cm² with outcomes similar to more usual sized defects. Provided that the knee is non-arthritic and coexisting pathologic conditions are addressed, excellent outcomes can be expected with treating massive chondral defects with ACI. One significant difference however, is the time required for healing of the maturing repair tissue. It will take longer for maturation and therefore the rehabilitation process is controlled accordingly. We have also used an unloader brace during the first 6 months post-operative in cases where an osteotomy was not necessary. Special planning is again required for periosteum harvest similar to the techniques used for multiple defects. These massive sized chondral lesions are also more likely to have uncontained cartilage borders and the technique of securing the periosteum with micro-anchors is frequently used. As a general rule, one vial of cells contains approximately ten to twelve million autologous cultured chondrocytes, and should be used for each 8 to 10 cm² of a defect. Therefore at least two vials of cells need be available for massive defects. Additionally, in order to insure uniform disbursement of the cells, we will inject the cells with one vial of cells at the midpoint of the defect and another at the superior aspect of the defect closing each injection site sequentially with additional sutures and fibrin glue.
Co-Pathology and Concomitant Procedures

Good results with autologous chondrocyte implantation, like any method of cartilage repair, should not be expected if coexisting knee pathology is not addressed. As we have developed a greater understanding of the clinical presentation of articular cartilage lesions, it is apparent that there are typically multiple factors that contribute to intra-articular knee problems. It is therefore predictable that there will often be co-existing knee pathology accompanying large chondral defects. Regardless of whether or not any co-existing knee pathology contributed to or occurred simultaneous with the chondral injury, the presence of continued knee pathology is clearly detrimental to restoring articular cartilage function and durability. The maturation of the repair tissue can be severely altered or inhibited in a compromised environment. When ACI is used to repair articular cartilage defects in the presence of co-existing pathology, it is essential that the intra-articular environment of the knee be restored to as close to normal as is possible. As discussed in the patient selection portion of this chapter, aggressive evaluation and diagnosis needs to be accompanied by definitive treatment of the co-existing knee pathology. This can be accomplished as a staged procedure or concomitant with ACI. Biomechanical malalignment, mal-tracking, meniscal deficiency, and ligamentous insufficiency are examples of an altered intra-articular environment, that can lead to shear stresses, excessive friction and abnormal compressive loads across the injured chondral surface. Therefore, it is critical that associated knee pathology, including mechanical malalignment (both of the tibio-femoral joint as well as the patellofemoral articulation), ligamentous instability, and meniscal deficiency be corrected prior to or in conjunction with the cells being implanted. (Figure 5) Another issue to be assessed is the degree of underlying bone damage to the subchondral bone, especially in OCD lesions or traumatic osteochondral injuries. Failure to
recognize coexistent knee pathology prior to autologous chondrocyte implantation will dramatically reduce the chances of a good outcome.\textsuperscript{8,23,27}

When deficiencies are present in any of these areas, treatment needs to be planned to maximize the recovery of the patient while still addressing the various co-pathologies. Many factors, such as the degree or severity of the deficiency, total number of problems, age of the patient, and their ability to comply with post-operative restrictions go into determining the best approach to each individual patient situation. In the author’s experience, performing only one additional procedure at the same time as the ACI is preferred. This would include performing an ACL reconstruction or osteotomy or meniscal transplantation or anteromedialization of the tibial tubercle in addition to the ACI.\textsuperscript{7, 8} However, when more extensive co-existing knee pathology exists to where three or more definitive reconstructive procedures may be indicated, staging seems more prudent. This is intended to cut down on the effect of cumulative potential complications.\textsuperscript{10, 11} While there is no absolute answer as to when to include a concomitant procedure versus staging the author has not found an increased risk of complications when combining ACI with one additional procedure. Of the initial 200 patients undergoing ACI, 55\% underwent a concomitant procedure, in order of frequency, anteromedialization of the tibial tubercle, ACL reconstruction, HTO, and meniscal transplant. An additional 12\% underwent a staged procedure, usually bone grafting of an osteochondral defect or HTO.\textsuperscript{8}

\textit{Tibio-femoral malalignment}

Biomechanical mal-alignment is typically addressed at the time of ACI. The type and location of the osteotomy depends on the type and degree of deformity. The traditional
recommendations for osteotomy correction of knee malalignment calls for over-correcting the deformity to shift the mechanical axis into to the opposite compartment.\textsuperscript{15,32} While that may be appropriate for treatment of osteoarthrosis, the purpose of osteotomy associated with cartilage resurfacing is to decrease the forces in the overloaded compartment and balance the forces across the joint. As many of these patients are younger in age, they would not tolerate over-correction which they view as a deformity. We have found in more appropriate to aim at shifting the mechanical axis to the 50\% mark in the middle of the tibial spines. We have increasingly used medial opening wedge high tibial osteotomy either with plate fixation or external fixation with medial hemicallotasis for overload of the medial compartment. For overload of the lateral compartment we use either a lateral opening tibial HTO with fibular osteotomy or for bigger corrections or bone deformity on the lateral femoral condyle from OCD we use lateral opening distal femoral osteotomy with a locking plate. We favor a closing wedge tibia osteotomy in patients who are smokers, while the medial hemicallotasis technique is better suited for staged ACI procedures. If the osteotomy is done concomitantly with ACI, the suturing of the periosteum and implantation of the cells are completed after the osteotomy.

**Ligamentous Insufficiency**

Persistent ligamentous insufficiency produces excessive shear forces across the chondral surfaces in the knee. Even subtle laxity or giving way of the knee can result in unacceptable forces across the maturing cells resulting in damage the maturing repair tissue produced by autologous chondrocyte implantation. Anterior cruciate ligament (ACL) tears have been the most common ligamentous injury we have seen with full thickness chondral injuries.\textsuperscript{8} PCL reconstruction also can accompany ACI. Typically
performed concomitantly, ACL reconstruction should be completed prior to proceeding with ACI. The ligament reconstruction should be performed in standard fashion with whatever technique and graft are desired by the surgeon and patient. Arthroscopic ACL reconstruction should be completed prior to proceeding with the arthrotomy for the autologous chondrocyte implantation. In cases where exposure may be a problem such as very posterior condylar or any tibial defect, it may be beneficial to wait for final fixation of the tibial side of the ACL graft until the ACI procedure is completed. No specific accommodation to the ACL rehabilitation protocols are needed because the ACI rehabilitation program is more limiting and is the overriding guidance post-operatively.

**Meniscal Deficiency**

The determination of when a partial meniscectomy leads to a loss of meniscal function equivalent to a total meniscectomy is not easily made. The posterior third of the menisci are more important than the anterior third in terms of function. Also, the peripheral fibers of the menisci providing the hoop stress function are particularly essential. Volume of lost meniscus alone is not the only criterion in determining deficient meniscal function as even a relatively small appearing radial tear of the meniscus can dramatically diminish the function. Meniscus transplantation should be considered in knees that have had a total meniscectomy performed in the same compartment as the chondral injury. A meniscal allograft will help to reduce the concentrated forces in the involved compartment and help protect the newly formed repair tissue. The exact indications still are unclear. We tend to favor meniscal transplantation in younger patients and adolescents with complete absent menisci and certainly if early tibial articular wear is present. The older patients with longstanding
meniscectomy may be better served with osteotomy. It is interesting to note that of all the patients reported from the extensive Swedish series with its high percentage of good and excellent results at long term follow-up, no patients underwent meniscal transplantation as that procedure is unavailable in that country. One could logically conclude that meniscal transplantation is the least essential component to a successful clinical outcome. Once again the decision on whether to perform meniscal transplantation as a staged procedure or concomitantly with autologous chondrocyte implantation depends on surgeon and patient preference. If there is any question, staging the two procedures seems more prudent. When performed concomitantly, the meniscal transplantation should be performed first, using the surgeon’s standard technique, followed by completion of the ACI. Clinical experience in this area is limited; however, Gersoff has preliminarily reported on ten patients that have had concomitant meniscal allograft transplantation and ACI with 80% success at 2 year follow-up.  

Patellofemoral Malalignment
Abnormal patellar tracking is not only the likely source of the patellar or trochlear injuries, but also would preclude an environment conducive for the maturation of the implanted chondrocytes into the ideal hyaline-like repair tissue. In addition to the concerns of lateral maltracking of the patella, the concept of decreasing the patellofemoral contact forces also is desirable. Depending on the degree of lateral maltracking, the amount of medialization can be adjusted accordingly. The anteromedialization of the tibial tubercle as described by Fulkerson offers the option of adjusting the degree of medialization while still elevating the tubercle anteriorly. In some cases without lateral maltracking, anterior transfer of the tibial tubercle alone may be sufficient to reduce the contact pressure of the patellofemoral articulation.
In the vast majority of cases of patellar or trochlear chondral injuries, a distal patellar realignment procedure should be performed in combination with ACI. In our series of 92 patella and/or trochlea ACI procedures, 94% (88/94 patients) underwent concomitant anteromedialization of the tibial tubercle. While the patellar realignment can be performed with the initial arthroscopy, we have found it more prudent to almost always combine the distal realignment with the ACI for patellar or trochlear defects allowing the tubercle to be turned up proximally giving extensile exposure as noted above. Regardless of whether the surgeon elects a concomitant realignment or a staged procedure, patellofemoral alignment, tracking and load distribution need to be optimized at the time of ACI, providing the chondrocytes the optimal environment for maturation.\textsuperscript{13}

**Bone Deficiency**

One situation that routinely requires staging is the treatment of bone deficiency. In cases where the bony deficiency of the defect exceeds 7–8 mm in depth, a separate staged bone grafting procedure is performed. With further experience, the initial technique of open bone grafting has been replaced with an arthroscopic technique. After arthroscopic debridement of any necrotic bone in the base of the defect, autologous bone is harvested from the proximal tibia or distal femur through a cortical window and then a core harvest instrument from an osteochondral graft set. The harvest sites are back filled with off the shelf bone graft plugs. The autologous bone is then interspersed with allograft paste and inserted into the debrided bony defect through an 8-10 mm canula, impacted, and sealed with fibrin glue. Fluid inflow to the knee is turned off during the arthroscopic grafting, impaction, and fibrin glue application. The ACI procedure can then be performed at least 4 to 6 months later after the bone graft has incorporated. Bone grafting allows restoration of the level of the subchondral bone.
and gives a healthy base for the chondrocytes to attach and grow.\(^5\) (Figure 6)

Additionally, it minimizes the amount of hyaline-like repair tissue that must be regenerated in the defect speeding up ultimate maturation. Staged bone grafting is usually done at the time of arthroscopic evaluation and chondral biopsy.

Another newer technique is the so-called sandwich bone grafting technique that allows single stage bone grafting of a bony defect in combination with ACI. In this procedure, the defect is exposed with an arthrotomy as described above and the base of the defect debrided of necrotic bone. Bone graft is then obtained either from the iliac crest or from the distal femur or proximal tibia as described above. We have favored taking local bone from around the knee and back filling the donor site rather than expose the patient to the morbidity of an iliac crest harvest. The bone graft is then impacted into the defect up to the level of the subchondral bone. A template is then made of sterile glove paper of the size of the base of the defect and a first periosteal graft is harvested corresponding to the template. This first periosteal graft is then placed in the defect with the cambium side up toward the joint and secured with sutures either into the base of the rim of articular cartilage or with absorbable suture anchors into the bone. Fibrin glue then seal the deep perimeter separating the blood and marrow elements from the defect. Another template is then made for the size of the articular cartilage defect identical to the routine ACI procedure. This is the used to harvest a second periosteal graft which is secured to the chondral surface with the cambium side down toward the defect, again in an identical fashion to the basic ACI procure. The cells are then injected below the outer layer of periosteum thus “sandwiching” the cells between the two layers of periosteum both with their cambium layers facing the cells. The bone graft then consolidates concurrent to the chondrocytes maturing. This procedure is technically
very demanding. Advancement of weight bearing and loading exercises are typically delayed after this procedure.

Rehabilitation Following ACI

Rehabilitation following ACI is based on the maturation process of the chondrocytes, the size of the defect, and the location of the defect. The concept of a slow gradual maturation of the repair tissue is crucial to understanding the rehabilitation following ACI. The biologic nature of the hyaline-like repair tissue must be both protected and stimulated to allow the maturation and remodeling of the tissue. Premature overload of the repair tissue will increase the likelihood of failure. There are three basic phases associated with this healing process, the proliferative phase, the matrix production phase, and the maturation phase. Each successive phase can accommodate greater degrees of load allowing the addition of sequential weightbearing, exercise and impact. Fully mature repair tissue which might take 12 to 24 months, shows stiffness very close to the surrounding articular cartilage. During the initial phase of rehabilitation, the critical elements are motion, to help with cellular orientation and the prevention of adhesions, protection of the graft from mechanical overload, and strengthening exercises to allow for a functional gait. Continuous passive motion is started 6-12 hours after surgery. Initial touch weight bearing is usually progressed to full weightbearing after 4 to 6 weeks post-operatively. Addition of further exercises should be based upon the size, location and amount of containment of the lesion by normal surrounding cartilage. The knee is gradually loaded with increased strengthening exercises after 3 months and various impact loading activities after 6 months. The patella and trochlea are protected from open chain exercises and shear loading for at least the first 3
months. Following these principles during the repair maturation continuum will provide an optimum environment for the tissue to grow and mature.\textsuperscript{8,9,25} The addition of concomitant procedures does not require any change to the rehabilitation principles as the ACI program remains the rate limiting step while still satisfying the rehabilitation principles of early motion and progressive joint loading.

**Clinical Results**

ACI has been performed for over a decade in the United States and Europe and almost two decade in Sweden. Peterson et al. have reported a retrospective analysis on the first 100 patients treated with ACI, with follow-up ranging between 2 to 9 years.\textsuperscript{25} Twenty three of 25 (92\%) patients with isolated femoral condyle chondral lesions had successful outcomes, while 16 of 18 (89\%) patients with osteochondral defects had good to excellent results. Multiple rating scales, including the Modified Cincinnati, Tegner, Lysholm scores were used to assess the clinical and functional outcomes. Additionally, they reported a 96\% durability of good to excellent results initially at 2 year follow-up with 30 of 31 patients maintaining those results at 7.5 year follow-up.\textsuperscript{25} The overall clinical outcomes remained constant (80\% good to excellent results at 2 years, and 78\% at 7.5 years) and second look arthroscopies did not show signs of tissue breakdown. Additionally, experience has grown rapidly in the US and Europe, further documenting and defining the clinical applicability of this technique.\textsuperscript{1,2,8,14,18,23,25,26,30}

Other international centers with at least 2-year follow-up have reported comparable outcomes to the Swedish series. Spalding from the United Kingdom and Bahuard from France, both reported good to excellent clinical outcome of 75 and 84\% respectively with military personnel, showing that the majority of these patients were able to return to
active military duty.\textsuperscript{1} Further series from Norway and the UK show similar clinical results and also show histologic data on biopsies with 75\% of the specimens showing hyaline like repair tissue.\textsuperscript{14,30} Bentley and colleagues reported on a prospective randomized study comparing ACI and mosaicplasty found that 88\% excellent and good results with ACI versus 69\% in the mosaicplasty group at 19 months follow-up. One year second look arthroscopies showed 82\% excellent and good repairs in the ACI group versus only 34\% in the mosaicplasty group.\textsuperscript{2} Horas and associates reported on forty patients randomly assigned to ACI or mosaicplasty for chondral injuries. At two years, both group had improved pain although the ACI group lagged behind the mosaicplasty group on Lysholm scores. Histologically, the ACI group showed fibrocartilage superficially and hyaline-like repair tissue closer to the subchondral bone.\textsuperscript{16} Knutsen et al reported a randomized controlled study of forty patients treated with microfracture and forty patients treated with ACI at four centers with two year follow-up. Both methods showed acceptable outcomes at this early follow-up and there were no significant differences on macroscopic appearance or histologic findings.\textsuperscript{17}

Minas has reported results on 235 patients treated with autologous chondrocyte implantation, and has had an 87\% success rate over a six-year period.\textsuperscript{23} The majority of his patients had complex lesions with coexistent knee pathology or salvage patients with early degenerative changes, such as osteophytes or some joint space narrowing. Minas has also noted that salvage patients with early degenerative changes do not obtain as high of activity scores after ACI; however, they have the highest patient-satisfaction ratings, perhaps because they were stating at very difficult baseline levels.\textsuperscript{22,23}
The author’s clinical results with the initial 112 patients treated with ACI have shown a 91% good to excellent success rate over a five year period. Of the 54 patients with a two-year or greater follow-up, significant improvements from the baseline scores were noted in each of the assessment tools utilized (Modified Cincinnati Rating Scale {MCRS}, Knee Society Clinical Rating, and Sports Score) with a consistent progression over time. The average clinician and patient evaluations of overall knee function showed significant improvement from baseline, and showed an improvement on an annual basis. The baseline scores for clinician and patients were scores of 3.9. The 24-month follow-up showed improvement in knee function with a significant increase (p<.001) in average score to 8.3 and 7.9. At 36, 48 and 60 months, the clinician and patient scores continued to show improvement over baseline without decline in function over time. Additional subgroup analysis has showed no statistical difference in outcomes for gender, size of the defect, location of the defect on the femur, isolated versus multiple defects or ACI with concomitant procedure or alone. There was however a statistical difference, with better results with lesions treated within one year from injury or onset of symptoms than in chronic defects present for greater than one year.10, 11

The Cartilage Registry Report, an international multi-center observational assessment of patients treated with ACI, has revealed that 78% of all defects treated with ACI had improvement by patient assessment, while 81% of isolated femoral condyle defects had improved. Clinician evaluations have shown a 79% improvement for all lesions and an 85% improvement in femoral condyle lesions. The most common adverse event reported with ACI is intra-articular adhesions (2%). The next most common adverse events include detachment/delamination less than 1%.18
Conclusion

Autologous chondrocyte implantation is a reproducible treatment option for large full thickness symptomatic chondral injuries with appropriate knowledge of technique and patient selection. It provides a cellular repair which offers a high percentage of good to excellent clinical results over a long follow-up period. It is applicable over a wide range of chondral injuries from simple to more complex lesions. It is essential that the intraarticular environment be as close to normal as possible for successful cartilage repair. Co-existing knee pathology must be aggressively treated. ACI does have a prolonged postoperative rehabilitation course necessitated by the biologic nature of the repair and patients must be able to comply with the rehabilitation and temporary restrictions required for a successful outcome.

The next generation of cellular repair for cartilage defects is optimistic. Newer techniques such as embedding the autologous cells in a biologic matrix, augmenting their maturation with growth factors and other forms of cell regulation are some of the options currently being investigated. Matrix ACI implantation without the need for a periosteal patch has already been performed at some centers in Europe. With further basic science and clinical research the reproducibility, ease of surgical delivery of the autologous cells, and results can only be anticipated to improve.
References


Figure 1a.
Figure 1: a, b) This long limb alignment film demonstrates the mechanical axis shifted to the lateral compartment, well lateral to the lateral tibial spine in a patient with a lateral femoral condyle full-thickness chondral defect. c) Realignment with lateral opening distal femoral osteotomy performed concomitantly with ACI treatment of the lateral femoral condyle defect.
Figure 2: The tibial tubercle has been detached and turned proximally allowing excellent exposure for ACI of the trochlea and patellar defects (arrows). Anteromedialization of the tibial tubercle is typically combined with ACI of the trochlea or patella.

Figure 3: a) This lateral femoral condyle defect has been debrided down to subchondral bone insuring the removal of the calcified cartilage layer. The edges of the surrounding cartilage are distinct and the lesion is well contained. b) Final appearance of the defect after the peristemeum has been secured, sealed with fibrin glue and the cells injected under the periosteum.
Figure 4: Multiple periosteal grafts can be harvested from the proximal tibia through a separate incision on the posteromedial margin of the proximal tibia just distal to the pes tendons. Note how the templates are laid out prior to cutting the grafts to insure maximizing all available periosteum.
Figure 5: a) Arthroscopic view of medial compartment in a 39 year old female with chronic ACL deficiency after failed reconstruction. Note the absent medial meniscus and medial femoral condyle full-thickness chondral defect. The patient underwent multiple procedures in two stages to include revision ACL reconstruction with patellar tendon allograft, medial opening high tibial osteotomy, medial meniscal allograft transplantation, and ACI of the medial femoral condyle massive full-thickness chondral defect that was partially uncontained. b) Radiograph showing the medial opening HTO, ACL fixation and metallic micro suture anchors for the uncontained portion of the ACI. c, d) MFC defect at the time of ACI. e) Final arthroscopic view 24 months after completion of all stages of this complex knee reconstruction showing intact medical meniscus transplantation and excellent resurfacing of the MFC defect with ACI.
Figure 6: OCD defect of the lateral femoral condyle with bone loss greater than 8 mm. treated with staged arthroscopic bone grafting a) Arthroscopic debridement of the necrotic bone in the base of the defect. b) Arthroscopic Autologous cancellous bone graft impacted into the defect and sealed with fibrin glue after the inflow is turned off. c) During ACI after 6 months to allow healing of the graft, the defect shows healed bone in the base up the level of the subchondral bone. d) Periosteum in place and cells being injected under the periosteal graft.