CLINICAL COMMENTARY

Treatment of Articular Cartilage Defects of the Knee With Autologous Chondrocyte Implantation

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Damage to the articular cartilage in the knee has long been thought to be a precipitating event leading to accelerated onset of osteoarthritis. Although the true natural history of full thickness chondral defects in the knee has yet to be defined and the clinical course may be unpredictable, it is nonetheless recognized that articular cartilage lesions are often associated with continued patient symptoms and followed by degenerative changes typical of osteoarthritis (16, 34,35). The inability of the articular cartilage to heal traumatic defects with a similar quality tissue has been appreciated by physicians since the time of Hippocrates. The deficiency of human articular cartilage repair was succinctly noted by Hunter in the 18th century when he stated, "Ulcerated cartilage is a troublesome thing; once destroyed, it is not repaired" (30). In the 20th century, surgeons began utilizing various techniques to attempt to stimulate the damaged joint surfaces into a repair mechanism. The advent of the arthroscope not only led to a greater appreciation of the extent of cartilage lesions associated with various mechanisms of knee injury but also provided the avenue for further attempts at treatment trying to alter the otherwise often dismal natural history of full thickness chondral defects of the knee. It

The treatment of focal full thickness articular defects in the knee has continued to present a challenge, with no traditional treatment method providing consistent acceptable long-term clinical results. Patients with significant chondral defects frequently have persistent joint line pain, swelling, and catching in the knee. In contrast to marrow stimulation treatment techniques, such as abrasion arthroplasty, drilling, or microfracture which populate the defect with pluripotential stem cells, the use of cultured autologous chondrocytes fills the defect with cells of a committed pathway to develop hyaline-like cartilage. This hyaline-like cartilage more closely recreates the wear characteristics and durability of normal hyaline cartilage than the fibrous or fibrocartilage repair tissue formed by pluripotential stem cells. The purpose of this paper is to review the efficacy of available treatment options as well as the basic science rationale, indications, technique, postoperative rehabilitation, and clinical results of using cultured autologous chondrocytes in the treatment of focal full thickness chondral defects of the knee.

Key Words: articular cartilage surgery, knee joint disease, autologous chondrocyte, cell transplantation

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is these full thickness defects down to the subchondral bone which invariably progress in size and often lead to early osteoarthritis. Despite numerous different techniques aimed at repair, no method has been able to create the characteristics of normal hyaline cartilage which can withstand the demands placed on the chondral surfaces within the knee (9,16,18,33, 34,50). Because of the deficiencies of various traditional repair techniques, research has focused on new ways to create a more durable repair tissue that more closely approximates hyaline cartilage able to alter the otherwise downward spiral leading to early onset osteoarthritis.

Since the early work of Pirdie and Insall, who combined open joint debridement with stimulation of the subchondral bone to treat osteoarthritis of the knee, numerous techniques were developed using arthroscopic methods (31,54). As with many other procedures, the use of arthroscopic techniques reduced the morbidity of treatment methods for cartilage repair and allowed for early detection of chondral defects of the knee. The work of Noyes et al (44), Casteleyn et al (12), and Dehaven (17) independently documented the incidence of articular cartilage lesions associated with acute hemarthroses of the knee. They found an

incidence of between 6 and 20% of chondral damage in these patients. Chondral lesions were particularly associated with the type of injury mechanisms producing anterior cruciate ligament tears. The natural history of these chondral defects was found to lead to a higher incidence of persistent symptoms, such as pain, catching, and swelling, particularly in patients continuing with impact loading activities (35,44). More recently, Curl et al have noted chondral lesions present in 63% of 31,516 knee arthroscopies performed by 136 surgeons between June 1991 and October 1995 (15). The average age of the patients with chondral lesions was 43 years. The prevalence of chondral injury in this series noted 41% of grade III (partial thickness involvement greater than 50% of the depth of cartilage) and 19.2% of grade IV (full thickness involvement down to exposed bone) lesions. The most common sites were the medial femoral condyle and patella. Because of the significant incidence and clinical problems of cartilage lesions, there has been much interest focused on new treatments for articular cartilage defects.

Current Treatment Methods

The most basic of current arthroscopic techniques to treat articular cartilage damage in the knee is lavage and debridement. The initial clinical benefits of "washing out" the loose cartilage fragments, catabolic enzymes, and loose bodies and removing flaps of damaged cartilage have been demonstrated since the wide-spread use of the arthroscope became available in the early 1980s (16,34). Jackson et al showed that up to 88% experienced some initial improvement following this procedure although, by 3 years, only 68% still maintained improvement (32). Baumgartner et al showed 52% of 44 patients with osteoarthritis were initially improved after arthroscopic debridement; however, only 40% still

had benefit at 33 months (4). Other studies by Bert and Maschka (5), Timoney et al (60), and Rand (55) have demonstrated good results in up to 66% of patients in up to a 5-year follow-up. Hubbard has shown that arthroscopic debridement was superior to lavage alone when assessing Lysholm scores over 5 years following the procedures (29,37). Gibson et al (24) showed little clinical benefit from arthroscopic lavage and debridement in patients with osteoarthritis, especially in those with exposed bone-on-bone contact. Longer-term follow-up for debridement and/or lavage of predominantly partial thickness articular cartilage lesions greater than 1 cm in young adults has been reported by Messner and Maletius (39). They noted 21 of 28 patients demonstrated continued functional improvement at a 14-year follow-up on Lysholm score, but 16 patients demonstrated joint space narrowing or other signs of early arthritis (39).

In an attempt to improve on the results of debridement and lavage and, particularly, the longevity of treatment, repair mechanisms were directed toward marrow stimulation to provide blood elements to form a fibrin clot in the defect leading to differentiation into a fibrocartilage repair. Different methods to accomplish this stimulation include arthroscopic abrasion, drilling, and microfracture (5,9,16,33,34,56). Each of these techniques includes debridement of damaged articular cartilage remnants and any fibrous tissue within the defect back to the demarcation of surrounding more healthy cartilage to allow the clot to bind to the edges of the normal remaining cartilage. Abrasion arthroplasty is performed by abrading the surface of the exposed subchondral bone with an arthroscopic burr to create a bleeding bony surface. Arthroscopic drilling relies on multiple drill holes through the exposed subchondral bone to provide access to the marrow blood elements and formation of a

clot in the defect. The microfracture technique achieves access to the vascularity of the bone by creating small holes with the use of sharp awl-shaped picks which penetrate the subchondral bone and propagate small microfractures around the holes, thereby increasing access to the marrow blood supply (56).

Each of these techniques relies on some degree of violation of the subchondral bone to provide access to the vascular channels of the bone to bring blood elements to the surface of the defect. The essential cells provided by the marrow blood are mesenchymal stem cells which are pluripotential in nature and can differentiate into cartilage, fibrous tissue, or bone according to the biologic and mechanical environment in the knee. Results of various studies reporting biopsy of the reparative tissue indicate predominantly fibrous tissue and/or fibrocartilage (18,33,34, 50). Unfortunately, these types of repair tissue do not exhibit the wear characteristics of hyaline cartilage. The repair tissue becomes unable to withstand the load demands of the knee and again breaks down, leading to recurrence of symptoms and progression of the size of the defect. The clinical results of these various arthroscopic techniques to produce marrow stimulation in the base of full thickness chondral defects as a method of stimulating the growth of fibrous or fibrocartilage repair tissue have been reflective of the poor wear characteristics and inadequate durability. Factors associated with poorer results include defects larger than 1 cm and increased impact loading activity (16). Numerous reports document that results with these methods steadily deteriorate over a relatively short period postoperatively (4,5,18, 22,24,34,50,55).

Johnson, in the most extensive report on the results of abrasion arthroplasty, noted poor results in an older population of almost 400 patients with an average age of 60 years (33). Postoperatively, 66% of patients

continued to have pain, and only 12% were without symptoms. Virtually all the patients had restriction in activity levels. In separate studies, Friedman et al, Bert and Maschka, and Rand all demonstrate only 50–60% satisfactory results at a 3- to 5-year follow-up using arthroscopic abrasion arthroplasty, with better results occurring in younger patients (5,22,55). Rodrigo et al reported on the benefit of continuous passive motion after using the microfracture technique, noting that 45% of patients in the noncontinuous passive motion group showed no improvement, whereas, in the group using continuous passive motion for 8 weeks postoperatively, only 15% failed to show improvement (56). The results of second-look arthroscopy showed a significant improvement in the quality of the repair tissue in the continuous passive motion group vs. the noncontinuous passive motion group when grading by appearance of the tissue. Because of the inconsistent results and overall high rate of recurrent symptoms and inability to progress in functional activities, other methods of articular cartilage repair have continued to be sought.

Biologic Repair With Autologous Tissue

In an attempt to improve the results of patients with full thickness chondral defects, Homminga et al (27) used autologous perichondrial grafts obtained from rib cartilage to repair grades III and IV chondral defects in the knees of 25 patients. The perichondral grafts were cut to fit the shape of the defect and held in place with fibrin glue. Arthroscopic assessment at almost 1 year postoperatively showed the defects had completely filled with cartilage-like tissue in 90% of the defects. The patients showed marked functional improvement as measured by Hospital for Special Surgery knee scores,

and 18 of 25 patients were essentially symptom-free at 1 year. However, with over 80 patients treated and followed for up to 8 years, 20% of the grafts had developed endochondral ossification with bone forming at the repair site, and 60% of the patients had failed this treatment (28). A similar experience with late endochondral ossification and delamination of the perichondral grafts has been noted by Minas, leading to failure of 6–10 grafts at 4 years (41).

O'Driscoll et al studied the effects on rabbits using periosteum to resurface articular cartilage defects (47), then later expanded the use of this technique in humans (46). O'Driscoll has reported on the use of autologous periosteal grafts for the treatment of chondral defects of the knee in 23 patients using debridement of the bone defect to a bleeding surface and suturing the periosteum to the base of the defect with the cambium layer toward the joint (46). Of 15 patients followed clinically, there were nine satisfactory results and six unsatisfactory results due to graft failure (46). The procedure was not recommended for general use until further research was available. Angermann and Riegels-Nielsen reported 80% of 14 young patients with femoral condyle osteochondritis dissecans were pain-free while walking and 64% were pain-free while running 1 year after undergoing periosteal transplantation over the osteochondritis dessicans defects (1). However, by an 8-year follow-up, 75% of patients had a poor or fair outcome, and over 50% of patients had progressed to osteoarthritis (2). Hoikka et al used autologous periosteal grafts and subchondral drilling to treat 13 patients with full thickness chondral defects of the patella (26). At 4 years, eight patients were rated as good, four as fair, and one as a failure. Nine of these patients were later followed at 9 years, and 64% had developed worse pain (59). Biopsies in six of eight patients failed to demonstrate hyaline-like repair tissue (59).

Another option which has recently stimulated considerable interest is osteochondral autografts (6,38). In this procedure, cylindrical osteochondral plugs are harvested from areas of normal cartilage on non-weight-bearing surfaces about the intercondylar notch or the anterior superior lateral femoral condyle and then transferred to matching holes made in the base of the chondral defect. Matsusue et al (38) first described treatment of a 15-mm defect of the medial femoral condyle using three 5-mm autologous osteochondral plugs. Arthroscopy at 2 years postoperatively showed good healing of the transferred plugs. Yamashita et al (63) demonstrated that osteochondral transfers retained the viability of the hyaline tissue and had fibrocartilage filling the borders between the graft and articular cartilage. Bobic treated 12 patients with anterior cruciate ligament deficiency and chondral defects ranging in size from 10 to 22 mm with three to five autologous osteochondral plugs (6). Ten of 12 patients were reported as excellent at 1-year follow-up. This technique appears promising for smaller defects less than 2 cm^2 in size, although no longer term follow-up is presently available. Osteochondral allografts have also been used to treat massive osteochondral defects or osteochondritis dissecans of the femoral condyles with fresh or frozen tissue. Results of up to 80% success rates have been reported by Garrett (23), Convery et al (13), and Zukor and Gross (64) for defects which frequently have accompanying large areas of bone loss.

Autologous Chondrocyte Implantation

Based on encouraging results in animal studies in a rabbit model performed both at the Hospital for Joint Disease in New York and later at the University of Gothenburg in Sweden, Brittberg et al and Grande et al re-

fined a technique to culture autologous chondrocytes from a small sample of human patients' own normal articular cartilage (7,8,25). In 1987, human clinical trials were begun to treat full thickness chondral defects in the knee with a periosteal graft and autologous chondrocytes (7).

The recommended indications for this treatment have evolved to include patients with focal full thickness chondral defects of the femoral condyles, trochlea, and osteochondritis dissecans. Relative indications are for patellar, tibial, or multiple defects and are evaluated by surgeons based on the available treatment options for each clinical situation. The prerequisites for this technique require appropriate biomechanical alignment, ligamentous stability, and range of motion. Patients with abnormal biomechanical alignment such as a varus knee may require corrective high tibial osteotomy to alleviate the abnormal force concentration within the involved knee compartment (14, 42,52). Patients with patellar tracking abnormalities would require realignment of the extensor mechanism prior to or in conjunction with autologous chondrocyte implantation for a patellar or trochlea defect. Anterior-cruciate-ligament-deficient patients likewise require ligament reconstruction in conjunction with autologous chondrocyte implantation for femoral condyle defects. It should be cautioned, however, that patients with longstanding ligamentous deficiency or biomechanical abnormalities are more likely to have greater degrees of coexisting degenerative changes and, therefore, may not be suitable candidates for this reason. The same is true with patients who have longstanding changes following a distant total meniscectomy. For patients with inflammatory arthritis and moderate to severe degenerative joint disease, autologous chondrocyte implantation is not recommended. This procedure is not intended as a treatment for osteoarthritis; rather, the goal of the treatment is to prevent a symptomatic cartilage defect from possibly progressing to advanced degenerative arthritis while providing longer term relief of patient symptoms and allowing them to return to physical activities (42,52,53).

Surgical Procedure

At the time of arthroscopic assessment of the joint, either as an evaluation of the degree of suspected articular damage or when an articular defect is found in conjunction with some other intra-articular pathology such as an anterior cruciate ligament or meniscal tear, a chondral biopsy is obtained for autologous chondrocyte tissue culture. The biopsy is obtained from the outer edge of the superior medial or lateral femoral condyle or the inner edge of the lateral femoral condyle at the intercondylar notch. Two to three fill-thickness samples of healthy articular cartilage are necessary for culture, weighing 200–300 mg or about the volume of a pencil eraser. The biopsy specimen is then placed in the biopsy vial and sent to a commercial facility (Genzyme Tissue Repair, Cambridge, MA), where the culture process occurs, leading to a 10- to 12-fold increase in the number of viable autologous chondrocytes. This process usually takes about 3 weeks, although the process can be safely temporarily suspended for months if necessary until the patient is ready for implantation. At the time of implantation, the cells are delivered to the surgeon in a vial containing about .3–.4 cc of medium with 12 million autologous chondrocytes.

At the implantation procedure, an arthrotomy is necessary to gain exposure to the site of the chondral defect. This can usually be accomplished with a limited exposure depending on the location of the defect. Any other planned procedures are also accomplished in conjunction with the implantation. Anterior cruciate ligament reconstruction, patellofemoral realignment, and even me-niscal transplant can be accomplished at the time of autologous chondrocyte implantation. The chondral defect is first debrided circumferentially back to a healthy rim of surrounding normal cartilage (Figure 1A and B). Any fibrous tissue or remaining damaged cartilage is removed from the base of the defect with a curette, with careful attention to avoid violating the subchondral bone in order to keep the bone from bleeding. Any punctate bleeding that might occur is controlled with compression sponges impregnated with epinephrine or thrombin. Once the defect has been debrided and conveniently shaped, it is carefully measured for sizing of the periosteal patch.

The periosteum is obtained through a small separate incision over the anteromedial tibia just distal to the insertion of the pes tendons. The periosteum from the proximal tibia and distal femur have been shown to be chondrogenic and provide a paracrine effect to chondrocyte growth, as well as providing a water-tight seal to contain the cells as they attach to the subchondral bone and populate the defect. The periosteal patch is harvested slightly oversized and then placed over the defect with the cambium layer down to the bone and secured in place to the surrounding normal cartilage with multiple interrupted 6–0 absorbable sutures. The suture line around the periosteum is then further sealed with fibrin glue made from the patient's own cryoprecipitate mixed with thrombin and calcium chloride. A small opening at the superior portion of the defect is left open to allow for injection of the cells.

The patient's autologous chondrocytes are then aspirated from the vial into a tuberculin syringe and injected with an 18-gauge plastic angiocath into the defect, ensuring complete fill of the defect with the cells. The small remaining opening is then closed with one or two final sutures and sealed with fibrin glue, complet-

ing the implantation. The arthrotomy incision and wound are then closed routinely.

Rehabilitation Overview

The goal of rehabilitation is to return the patient to the optimal level of function through a well-controlled gradual and progressive rehabilitation program which emphasizes full motion, progressive weight-bearing, controlled exercises while protecting and promoting the maturation of the implanted autologous chondrocytes. As the repair tissue matures, the rehabilitation process advances with appropriate exercises to condition the lower extremity for strength, flexibility, and proprioception, leading to a return to aerobic and sports activities.

Joint motion and continuous passive motion play an important role in the healing of articular cartilage. It is combined with traditional modalities, including biofeedback, electrical stimulation, and cryotherapy during the immediate postoperative period. Peterson utilized continuous passive motion during the first 48 hours following the autologous chondrocyte implantation procedure and has continued to use this regimen in over 500 patients (53). The adverse effects of immobilization on both the macroscopic and microscopic appearance of articular cartilage are extensively documented and would severely hamper the successful growth and maturation of the autologous chondrocytes (3,19–21,40,51,61,62).

Stress and strain play a very important role in the synthesis and organization of cells in all types of tissues. In general, if there is a decrease in stress applied to the tissues, there is a corresponding decrease in the cell synthetic function and decreased organization of the tissue matrix. Increases in stress can lead to increased cell synthetic function and increased matrix organization, provided the stress is below the level that causes tissue damage (10). Thus, the goal of the rehabilitation program is to provide the stimulus for cartilage healing without overstressing the repair tissue, which may result in cartilage damage.

The use of continuous passive motion to assist in the treatment of articular cartilage defects has been studied extensively. In the rabbit model, continuous passive motion has been shown to improve the healing of full thickness cartilage defects treated by various marrow stimulation techniques, such as drilling or abrasion (36,47,48,58). Furthermore, continuous passive motion has been
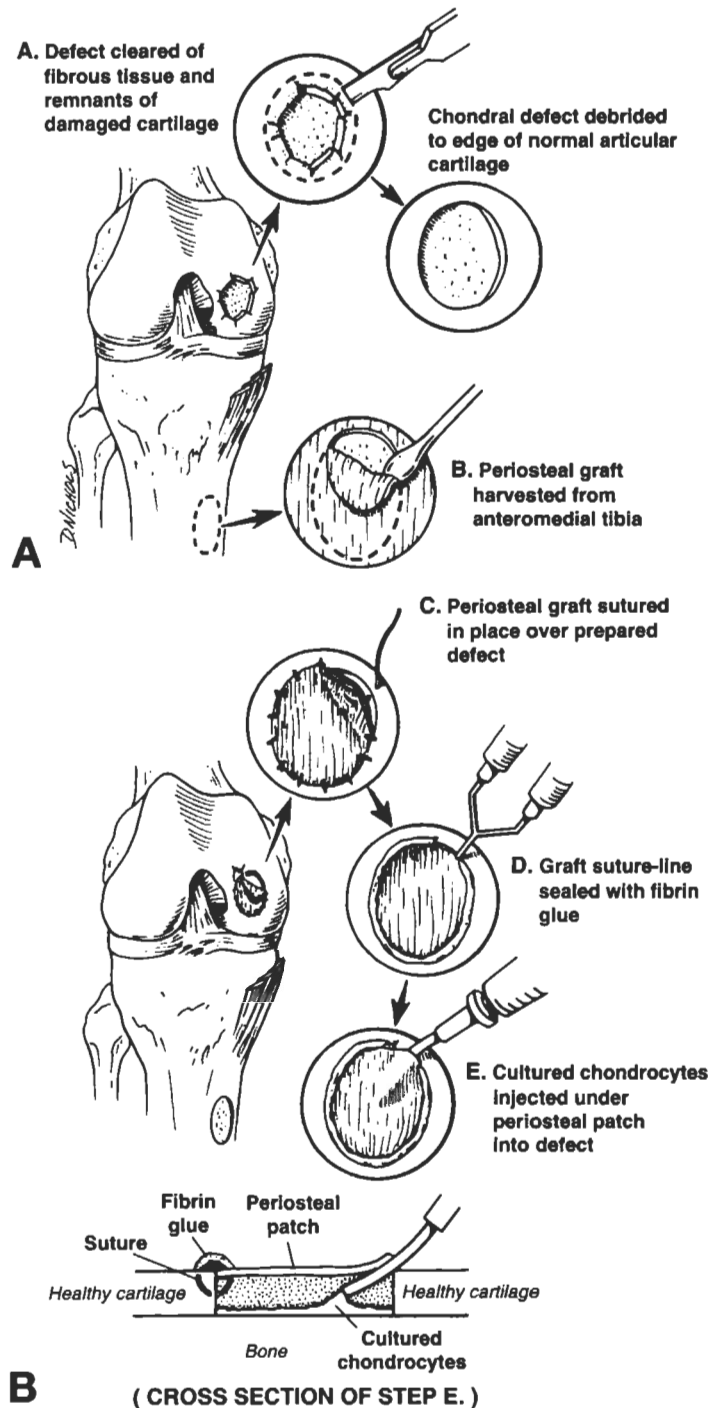

FIGURE 1. A, B) Autologous chondrocyte implantation procedure as described in text.

Phase I: Protective Phase (Weeks 0–6)
Goals:
 Protect healing tissue from load and shear forces
 Restoration of full passive knee extension
 Gradual improvement of knee flexion
 Regaining quadriceps control
Brace:
 Locked at 0° during weight-bearing activities
 Sleep in locked brace for 2–4 weeks
Weight bearing:
 Nonweight bearing for 2 weeks, progress to toe touch weight bearing (approximately 20–30 lbs) for
  4 weeks
 Toe touch weight bearing (approximately 1/4 body weight) at week 5
Range of motion (ROM):
 Immediate motion exercise
 Continuous passive motion after 4–12 hours (0–40°), 4–12 hours per day for 2–3 weeks
 Progress continuous passive motion ROM as tolerated 5–10° per day
 Patellar mobilization
 Passive knee flexion ROM 2–3 × daily
 Knee flexion ROM goal is 90° by 2 weeks
 Knee flexion ROM goal is 105° by 4 weeks and 120° by 6 weeks
 Stretch hamstrings, calf, and quadriceps
Stretching program:
 Ankle pump using rubber tubing
 Multiangle isometrics (co-contractions quadriceps and hamstrings)
 Active knee extension 90–40° (no resistance)
 Straight leg raises (four directions)
 Stationary bicycle when ROM allows
 Biofeedback and electrical muscle stimulation as needed
 Isometric leg press at week 4 (multiangle)
Functional activities:
 Gradual return to daily activities
 If symptoms occur, patient should reduce activities to reduce pain and inflammation
 Extended standing should be avoided
Phase II: Transition Phase (Weeks 6–12)
Goals:
 Gradually increase ROM
 Gradual improvement in quadriceps strength and endurance
 Gradual increase in functional activities
Criteria to Progress to Phase II
 1. Full passive knee extension
 2. Knee flexion to 115–120°
 3. Minimal pain and swelling
Brace:
 Discontinue brace at 4–6 weeks
Weight bearing:
 Progress weight bearing as tolerated
 Half of body weight with crutches at 6 weeks
 Progress to full weight bearing 8–9 weeks
 Discontinue crutches at 8–9 weeks
Range of motion:
 Gradual increase in ROM
 Maintain full passive knee extension
 Progress knee flexion to 120–125°
 Continue patellar and soft tissue mobilization as needed
 Continue stretching program
Strengthening exercises:
 Initiate minisquats 0–45°
 Closed kinetic chain exercises (leg press)
 Toe-calf raises
 Open kinetic chain knee extension (passive resistance exercises) 1 lb per week
 Stationary bicycle (gradually increase time)   *Continued*

TABLE 1. *Rehabilitation program following autologous chondrocyte implantation procedure.*

shown to increase cell proliferation and the total amount of type II collagen when used in rabbits treated with periosteal grafts placed over cartilage defects (43,47,49). Conversely, immobilization after the periosteal grafting has been shown to inhibit chondrogenesis (57). Continuous passive motion also plays a role in ensuring the distribution of synovial fluid necessary for articular cartilage nutrition to the remainder of the joint (36,57). Another as yet not fully understood mechanism thought to be derived from continuous passive motion is that of modulation of the chondrocyte precursors, prechondrocytes, to develop and initiate matrix production necessary for type II cartilage (7,36). There is no definitive answer as to the optimal time that continuous passive motion needs to be used. Continuous passive motion used 8 hours/day appears to be as effective as 24 hours/day and is certainly better tolerated by patients. Peterson (52,53) and Brittberg et al (7) advocated using continuous passive motion for the first 48 hours after surgery and have reported over 90% good and excellent results for isolated femoral condyle lesions. Perhaps the initial effect on the prechondrocytes shortly after implantation is the most important mechanism for autologous chondrocyte implantation. Further use of continuous passive motion may benefit the patient in achieving motion, diminishing adhesions, and reducing pain.

Rehabilitation Program

The postoperative protocol is accompanied by the use of immediate cryotherapy, elevation, compression, and continuous passive motion. The knee is immobilized in a standard postoperative dial-lock brace locked at 0° for functional activities. With nonweight-bearing activities, the brace may be unlocked for comfort, and motion is encouraged. Active ankle pumping should also be en-

Treadmill walking program
Balance and proprioception drills
Initiate front and lateral step-ups
Continue use of biofeedback and electrical muscle stimulation as needed
Functional activities:
    As pain and swelling (symptoms) diminish, the patient's functional activities may be gradually
        increased
    Gradually increase standing and walking
Phase III: Maturation Phase (Weeks 12–26)
Goals:
    Improve muscular strength and endurance
    Increase functional activities
Criteria to Progress to Phase III
    1. Full range of motion
    2. Acceptable strength level
        • hamstrings within 10% of contralateral leg
        • quadriceps within 10–20% of contralateral leg
    3. Balance testing within 30% of contralateral leg
    4. Able to walk 2 miles or bike for 30 minutes
    5. 50 lateral step-ups (8″ height)
Range of motion:
    Patient should exhibit 125–135° of flexion
Exercise program:
    Leg press (0–90°)
    Bilateral squats (0–60°)
    Unilateral step-ups progressing from 2 to 8″
    Forward lunges
    Walking program
    Open kinetic chain knee extension (0–90°)
    Bicycle
    Stairmaster
    Swimming
    NordicTrack®
Functional activities:
    As patient improves, increase walking (distance, cadence, incline, etc.)
    Light running can be initiated toward end of phase
Phase IV: Functional Activities Phase (Weeks 26–52)
Goals:
    Gradual return to full unrestricted functional activities
Criteria to Progress to Phase IV
    1. Full nonpainful ROM
    2. Strength within 90% of contralateral extremity
    3. Balance and/or stability within 75% of contralateral extremity
    4. No pain, inflammation, or swelling
Exercises:
    Progress resistance as tolerated
    Progress agility and balance drills
    Impact loading program should be specialized to the patient's demands
    Progress sports programs depending on patient variable
Functional activities:
    Patient may return to various sports activities as his/her progression in rehabilitation and cartilage
        healing allows.
    Generally, low impact sports such as skating, rollerblading, and cycling are permitted at about 6
        months. Higher impact sports such as jogging, running, and aerobics may be performed at 8–9
        months. High impact sports such as tennis, basketball, and baseball are allowed at 12 months.

TABLE 1. *Continued from previous page.*

couraged in the first week after surgery to help reduce lower extremity swelling. Until biking or swimming can be safely performed for cardiovascular training, an upper body ergometer should be utilized.

The rehabilitation program is outlined in Table 1. The rate of progression may vary based on the patient's defect size, location, and concomitant procedures. Additionally, the patient's response to the surgery will also determine the rate of progression. The rehabilitation specialist must consider all of these factors when designing the postoperative program.

Through a well-controlled rehabilitation program, patients undergoing autologous chondrocyte implantation will optimally achieve the goals of the procedure to alleviate symptoms and return to a higher functional level of participation. The above outlined program allows for overcoming the effects of surgery, controlling swelling and inflammation, advancing motion with gradual return of weight bearing, and progressive strengthening and agility training corresponding to the known maturation process of implanted autologous chondrocytes in an environment that encourages healing of articular cartilage without overloading the repair tissue. It is stressed that this program is a guide that needs to be modified for the specific needs of each patient's situation.

Clinical Results With Autologous Chondrocyte Implantation

Brittberg et al (7) reported on the first 23 patients with full-thickness chondral defects, 16 with femoral condyle and seven with patellar defects. The results in 14 of 16 femoral condyle patients (87%) were graded as excellent and good at the 39-month follow-up. Second-look arthroscopy and biopsy demonstrated formation of new cartilage that was similar to surrounding normal cartilage and had an abundance of type II collagen and metachromatic staining of the matrix. Results were less satisfactory in treatment of defects of the patella. Although five of seven patients were improved, only two were good or excellent. The group with patellar lesions did not undergo realignment procedures (7).

Encouraged by these promising initial results, the treatment was ex-

Site of Defect	Number of Patients	Follow-Up (Years): Range = 2–10 years	Excellent and Good Results
Femoral condyle, isolated	57	4.0	90%
Osteochondritis dissecans	32	3.9	84%
Femoral condyle with any ACL reconstruction	27	4.3	74%
(Only primary ACL reconstruction)			(85%)

ACL = Anterior cruciate ligament.

TABLE 2. Autologous chondrocyte implantation: Overall clinical assessment of consecutive patients (53).

panded to include over 500 patients by 1997. Peterson reported on 219 consecutive patients with an average 4-year follow-up (range = 2–10 years) treated with autologous chondrocyte implantation for isolated femoral condyle defects, femoral condyle osteochondritis dessicans, and for femoral condyle defects with anterior cruciate ligament reconstruction, which indicated consistently good to excellent results (53) (Table 2). The majority of these patients had under-gone prior attempts at repair of their chondral defects using either arthroscopic debridement and/or marrow stimulation techniques with failed results. The clinical results were evaluated by multiple methods of clinical testing to include the Modified Cincinnati, Tegner, Lysholm, VAS (visual analog scale), and the Brittberg scales, all of which indicated a statistically significant improvement (37,45, 52,53). Of 19 biopsy specimens, 14 demonstrated hyaline-like tissue with type II collagen and five with fibrous tissue. There was a correlation of hyaline-like repair tissue with good and excellent clinical results as well as fibrous tissue with fair and poor results (52). Furthermore, a computerized arthroscopic probe was used on 10 femoral condyle repair sites to measure stiffness. The measurements indicated 3.08 Newtons of stiffness at control sites of healthy cartilage, 2.77 Newtons for hyaline-like repair tissue, and only 1.23 Newtons in areas of fibrous tissue. The more normal mechanical stiffness of hyaline-like repair tissue appears to also correlate with better clinical outcome (52). These findings of the histology and mechanical stiffness correlating with clinical outcomes confirm the conclusions and rationale for clinical failure of other methods of cartilage repair, which lead to fibrocartilage or fibrous repair tissue (18). The more hyaline-like the repair tissue, the better durability and wear characteristics it will exhibit. Dzioba in 1988 hypothesized that patients would have the best results when the repair tissue more closely resembles the structure of hyaline cartilage rather than the fibrocartilage or fibrous tissue he found in biopsies of patients undergoing arthroscopic drilling (18).

Peterson has further reported on the clinical durability of the repair tissue (53). Thirty-one patients with good and excellent results at 2 years postautologous chondrocyte implantation were again reevaluated an average of 7.4 years postoperatively (range = 5–10 years). Thirty of 31 patients maintained good and excellent results at long-term follow-up, indicating a 96% clinical durability of the repair (53).

The procedure of autologous chondrocyte implantation has been performed in the United States since 1995. The demographic information, defect description, and clinical parameters have been carefully monitored by a Registry Advisory Board for each patient undergoing the procedure outside of Sweden (11). The
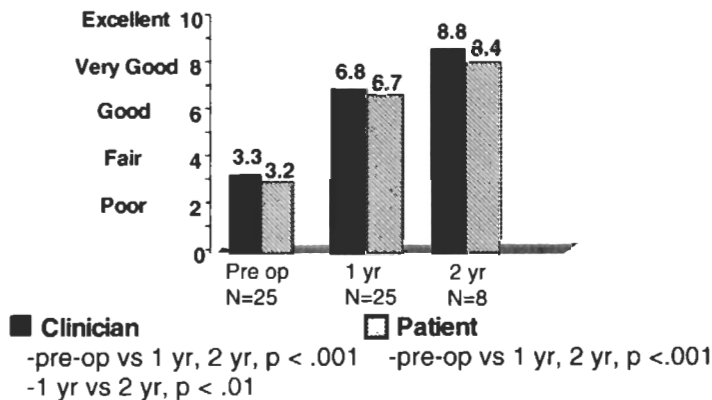

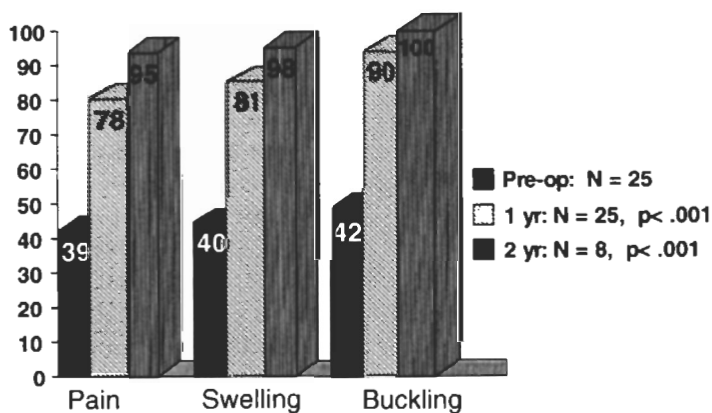**FIGURE 2.** Modified Cincinnati rating scale, preoperatively vs. 1 and 2 years follow-up.

FIGURE 3. Symptom rating scale for pain, effusion, and giving way; preoperatively vs. 1 and 2 years follow-up.
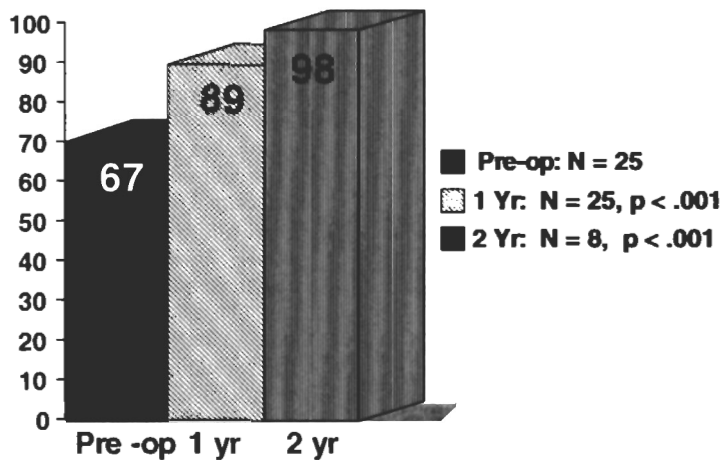
FIGURE 4. *Knee Society clinical rating system, preoperatively vs. 1 and 2 years follow-up.*

Cartilage Repair Registry periodic report from June 1997 documents results on 191 patients with 6 months and 84 patients with 1-year follow-up (9). The results indicate an improvement at 1 year on clinician evaluation, improved from a baseline mean of 3.2–6.9 ($p < 0.001$), and on patient evaluation, improved from a baseline mean of 3.1–6.5 ($p < 0.001$) at follow-up, using the modified Cincinnati Knee Rating System. There was also a significant increase ($p < 0.001$) of the 12-month scores over the 6-month scores for both clinician and patient evaluations. Respectively, the patient and clinician evaluations at 1 year were improved in 85% and 80% of knees. Additionally, the ratings for joint line pain, swelling, stiffness, catching, and locking were all

significantly reduced (9). There were 3.3% of patients with arthrofibrosis and adhesions, which required arthroscopic lysis and release.

The author's (SDG) own experience with 53 defects in 41 knees undergoing autologous chondrocyte implantation also appears promising. The average size of the defects was 5.74 cm^2, indicating very large-sized lesions. The average age was 36.2 years and ranged from 14 to 52 years of age. There were 25 males and 16 females. Twenty-nine of the 41 patients had undergone a total of 50 previous surgeries directed at their chondral injuries which had failed to provide relief of symptoms. The medial femoral condyle was the most frequent defect site with 27, followed by the lateral femoral condyle (12),

trochlea (7) and patella (6), and one of the lateral tibial plateau. Six patients had osteochondritis dissecans of a femoral condyle, four on the medial condyle and two on the lateral condyle. Nineteen patients underwent concomitant procedures at the time of the implantation for anterior cruciate ligament reconstruction (7), anteromedialization of the tibial tubercle (12), high tibial osteotomy (1), and meniscal transplant (1). Of 25 patients with over 1-year follow-up (range = 12–36 months), 22 (88%) patients show significant improvement and rate as good, very good, or excellent using the Knee Society and Modified Cincinnati rating scales (45). The average clinician and patient evaluations of overall knee scores significantly improved from a baseline of 3.3 and 3.2, respectively, to 6.8 and 6.7 at 1 year ($p < .001$) and 8.8 and 8.4 at 2 years postoperatively ($p < .001$). There was a statistically significant improvement ($p < .01$) in clinician evaluation between the 1- and 2-year follow-up, indicating continued clinical improvement in some patients for up to 24 months after autologous chondrocyte implantation (Figure 2). Patient-reported pain improved from 3.9 to 7.8 at 1 year and 9.5 ($p < .001$) at 2-year follow-up, and swelling improved from 4.25 to 8.1 at 1 year and 9.8 ($p < .001$) at 2 years (Figure 3). The Knee Society clinical rating scale jumped from a score of 67 to 89 at 1 year and 98 at 2 years, both statistically significant ($p < .001$) (Figure 4). The sports score, which takes into account not only level of sports activity but also frequency and duration of activity, significantly improved from a preoperative score of 38–66 at 1 year and 88 at 2 years (both $p < .001$) (Figure 5). One patient underwent debridement for hypertrophy of the repair cartilage at 6 months, and two patients undergoing concomitant procedures required arthroscopic lysis of adhesions for decreased motion at 5 and 6 months postoperatively.
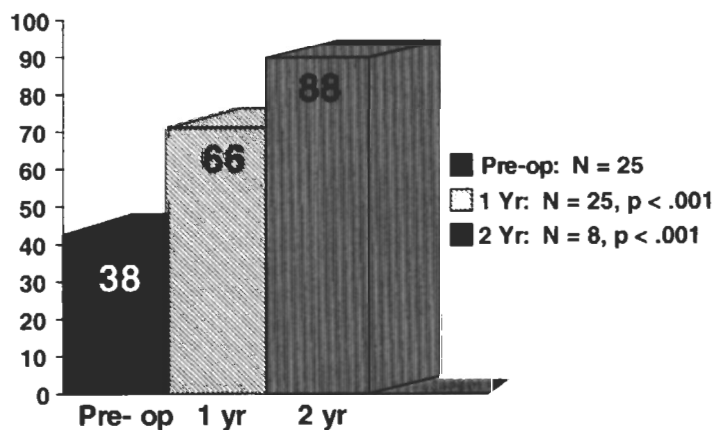

FIGURE 5. *Sports score based on level of fitness activity and frequency of participation, preoperatively vs. 1 and 2 years follow-up.*

Minas and Nehrer have recently reported on their early experience with autologous chondrocyte implantation in 50 patients (42). They have noted a gradual time-related improvement in patient-reported symptoms. By 12 months, there is a 90% improvement, and, by 18 months, there is near complete resolution of the preoperative pain. This was felt to be reflective of the repair tissue maturation over time and corresponds to the findings at second-look arthroscopy from an indentable softer tissue at 3–6 months to a firm nonindentable tissue at 18 months. These findings parallel the Swedish experience as well as the author's (7,52,53).

These early good to excellent clinical results noted in the Cartilage Repair Registry and by Minas and Nehrer and the author mirror the early results noted in the Swedish group of patients that have continued to demonstrate good and excellent results up to and over 10 years, with an average of 4 years follow-up (11,42,52,53).

CONCLUSIONS

Full thickness chondral defects of the knee are a relatively frequent finding in patients less than 50 years of age and do not spontaneously heal with similar quality hyaline tissue. These defects are often associated with continued patient symptoms and can lead to progressive onset of early osteoarthritis, although the exact incidence is unknown. The treatment of these defects by the traditional methods of marrow stimulation, which provide access to the bone-blood supply by penetrating the subchondral bone to provide mesenchymal stem cells within the fibrin clot, have demonstrated mixed early results and only fair to poor long-term results. The goal of achieving hyaline-like repair tissue, which would provide better wear characteristics and durability, is seldom achieved with these treatment techniques. Autologous chondrocyte implantation, on

the other hand, by providing chondrocytes committed to forming type II cartilage, appears to provide hyaline-like repair tissue, with corresponding improvement in the histologic, biomechanical, and durability characteristics as reflected by better clinical outcomes in up to 90% of patients with femoral condyle defects with an average of 4-year follow-up and up to 10 years postoperatively (53). The renewed interest by the medical field and the recent interest by the public underscore the scope of the clinical problems of cartilage defects in the knee in an active population and will undoubtedly lead to further refinements and developments, ultimately providing even better results for this difficult clinical problem. JOSPT

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