Outcomes of Autologous Chondrocyte Implantation in a Diverse Patient Population

Allison G. McNickle,* MS, Daniel R. L'Heureux,* Adam B. Yanke,* MD,
and Brian J. Cole,*†‡ MD, MBA
*From the *Department of Orthopaedic Surgery and †Rush Cartilage Restoration Center, Rush University Medical Center, Chicago, Illinois*

Background: Autologous chondrocyte implantation is indicated as a second-line treatment of large, irregularly shaped chondral defects after failure of first-line surgical intervention. This study examines the clinical results of a patient cohort undergoing autologous chondrocyte implantation and elucidates factors associated with subjective improvement after implantation.

Hypothesis: Autologous chondrocyte implantation will result in long-term functional and symptomatic improvement.

Study Design: Case series; Level of evidence, 4.

Methods: The cohort included 137 subjects (140 knees) who underwent autologous chondrocyte implantation of the knee. Mean defect size per patient was 5.2 ± 3.5 cm^2 (range, 0.8-26.6 cm^2). Patients averaged 30.3 ± 9.1 years of age (range, 13.9-49.9 years) and were followed for 4.3 ± 1.8 years (range, 2.0-9.7 years). Outcomes were assessed via clinical assessment and established outcome scales, including the Lysholm scale, International Knee Documentation Committee scale, and Short Form-12.

Results: A significant improvement after surgery was observed in all outcome assessments including the Lysholm (41-69; $P < .001$) and International Knee Documentation Committee (34-64; $P < .001$) scales. Subjectively, 75% of patients indicated they were completely or mostly satisfied with the outcome and 83% would have the procedure again. Preoperatively, 32% of patients had a Tegner score of 6 or greater, compared with 82% before injury and 65% at most recent follow-up. Multivariate analysis identified age ($P < .021$) and receiving workers' compensation ($P < .018$) as independent predictors of follow-up Lysholm score. Twenty-one patients (16%) required debridement of the autologous chondrocyte implantation site secondary to persistent symptoms, whereas 9 knees (6.4%) clinically failed and underwent a revision procedure.

Conclusion: Autologous chondrocyte implantation is a viable treatment option for chondral defects of the knee, resulting in durable functional and symptomatic improvement. Age and workers' compensation status are independent predictors of outcome.

Keywords: knee; autologous chondrocyte implantation; cartilage; outcome

Focal cartilage injuries of the knee are common and are suggested to increase the risk of progressive osteoarthritis.[19] A review of 31 516 knee arthroscopies noted a 63% prevalence of chondral lesions, with 19.2% having grade IV chondromalacia.[5] These defects may cause pain, swelling, mechanical symptoms, and functional impairment. Given the poor intrinsic ability of cartilage to heal, surgical intervention is often necessary for symptomatic relief. Published surgical algorithms[4,11] progress toward more aggressive intervention based on defect geometry and patient activity level. First-line treatments—including debridement, microfracture, or osteochondral autograft transplantation—provide adequate relief for low-demand patients with small lesions (<4 cm^2).[12,32] Patients with large defects and athletes frequently fail these modalities, necessitating a second surgical intervention including chondrocyte implantation or osteochondral allograft transplantation.[9,12,23,33]

Autologous chondrocyte implantation (ACI) provides a method of resurfacing large or irregular chondral defects without the morbidity and risk of osteochondral grafting. Potential sequelae of ACI include periosteal site morbidity as well as risks associated with the preliminary cartilage biopsy and subsequent procedures attributable to graft hypertrophy.[35] The presence of autogenous chondrocytes within the repair construct enhances the formation of hyaline-like cartilage, which is superior, both in biomechanics and durability, to the fibrocartilaginous fill of microfracture.[13,27] Despite the potential for hyaline-like tissue, authors have demonstrated that ACI repairs still contain a significant percentage of fibrocartilage.[16,17] Regardless of tissue composition, the first 100 patients

‡Address correspondence to Brian J. Cole, MD, MBA, 1725 West Harrison St, Suite 1063, Chicago, IL 60612 (e-mail: bcole@rushortho.com).

One or more authors have declared a potential conflict of interest: Brian J. Cole has received consulting fees from Genzyme. The other authors have no potential conflict to declare.

The American Journal of Sports Medicine, Vol. X, No. X
DOI: 10.1177/0363546509332258

undergoing ACI demonstrated decreased symptoms and a return to activities, with good to excellent results in 92% of isolated femoral condyle defects and 89% of osteochondritis dissecans lesions.[29] Further studies have established the viability of ACI for patellofemoral lesions and in combination with meniscus transplantation.[7,8,11,20,31]

This study evaluates the outcomes of autologous chondrocyte implantation for a large single-surgeon cohort and answers the following questions: What was the overall subjective, sports, and clinical function of these patients at follow-up? What factors are predictive of improvement after ACI? What are the reoperation and failure rates of ACI in this cohort?

MATERIALS AND METHODS

Patient Selection

The study protocol was approved by the institutional review board of the medical center. Between December 1997 and May 2005, patients receiving ACI for chondral defects of the knee were prospectively enrolled into the study. These patients were indicated for ACI attributable to symptomatic, full-thickness defects of the patella, trochlea, or femoral condyles that were refractory to prior treatment (microfracture, debridement, or osteochondral autograft transplantation).

Operative Technique

Autologous chondrocyte implantation was performed as described by Peterson et al.[28] Indications for ACI included symptomatic, full-thickness (grade IV) cartilage lesions of the femoral condyle, trochlea, or patella. Contraindications were significant subchondral bone loss, multicompartment osteoarthritis, inflammatory joint disease, and unwillingness to comply with postoperative rehabilitation. Briefly, a 100- to 200-mg biopsy sample of cartilage was harvested from the intercondylar notch during a diagnostic arthroscopy and shipped to Genzyme (Cambridge, Massachusetts) for processing. Chondrocytes were extracted from the extracellular matrix and expanded in culture to a final concentration of 2 to 3×10^7 cells per milliliter. At implantation, the defect was identified and curetted down to subchondral bone with vertical side walls. The greatest width in 2 orthogonal planes was measured and used to determine lesion area. The largest defect was considered to be the primary site for chondrocyte implantation. A periosteal patch was harvested from the anteromedial tibial diaphysis and trimmed to match the inside dimensions of the defect. The patch was sutured to the periphery using interrupted 6-0 Vicryl (Ethicon, Somerville, New Jersey) and sealed with fibrin glue (Baxter, Deerfield, Illinois) to ensure water tightness. Chondrocytes were resuspended and implanted into the chamber with an angiocatheter.

Opening wedge high tibial osteotomy or distal femoral osteotomy was indicated for greater than 10° of uncorrected varus or valgus alignment, respectively, especially in patients with peripheral condylar lesions and early wear of the ipsilateral tibial plateau. Alignment was determined with double-stance, long-leg mechanical axis and lateral radiographs. Concurrent anteromedialization was used to offload the repair in cases of distal lateral patellar or lateral trochlear lesions. Patients with central to medial lesions on the patella or trochlea were contraindicated for an alignment procedure. Preoperative radiographic assessment of patellar alignment included Merchant (shallow flexion angle axial) and Rosenberg (weightbearing posteroanterior) views.

A meniscal allograft transplantation was indicated in patients with symptomatic (pain, activity-related swelling) prior total or subtotal meniscectomy ipsilateral to the articular cartilage lesion that would compromise the mechanics of the ACI. Concurrent meniscus transplantation was accomplished with a bridge-in-slot technique with interference screw fixation and peripheral suturing. Concurrent ligament reconstructions were avoided because of the increased risk of stiffness.

Postoperative Rehabilitation

Patients were placed in a hinged knee brace limited to full extension without weightbearing for the first 2 weeks. Continuous passive motion was initiated on the first postoperative day (0°-30°, 1 cycle per minute) in 2-hour increments for 6 to 8 hours per day. The objective was to obtain 90° of flexion by week 4 for condylar constructs and weeks 6 to 8 for implantations to the trochlea or patella. Incremental return to full weightbearing occurred between 6 and 12 weeks. Closed kinetic chain exercises were initiated at 4 to 6 months with a return to high-impact activities at 16 months if pain-free.

Clinical Assessment

Preoperatively, patients received a baseline survey and underwent knee examination (including range of motion via goniometer and quadriceps circumference), which was repeated postoperatively at 6 months and thereafter annually. The survey included the following outcome scales: Noyes, Tegner, Lysholm, International Knee Documentation Committee (IKDC), Knee Injury and Osteoarthritis Outcome Score (KOOS), and Short Form-12 (SF-12). The KOOS score is subdivided and scored in 5 categories: Pain, Other Disease-specific Symptoms, Activities of Daily Living Function (ADL), Sport and Recreation Function, and Knee-related Quality of Life (QOL).

Statistical Analysis

Descriptive statistics were performed according to standard methods, including frequencies, means, standard deviations, and ranges when appropriate. Patient data sets included the scores on the previously listed scales at 2 time points: preoperatively and at most recent follow-up. Score improvement of the study population was calculated using a paired t test. A factor analysis of patient age, body mass index (BMI), defect area, and time to follow-up was conducted using Pearson correlation with post hoc t testing.

TABLE 1
Baseline Characteristics of the Cohort Receiving Autologous Chondrocyte Implantation[a]

	Overall	OCD	WC
n (%)	140	22 (16)	35 (26)
Patient age, mean ± SD (range)	30.3 ± 9.1 (13.9-49.9)	23.5 ± 6.5 (14.9-36.7)	36.2 ± 6.6 (22.0-47.9)
Gender, n (%)			
Male	79 (58)	15 (68)	20 (57)
Female	58 (42)	7 (32)	15 (43)
Body mass index, kg/m^2, mean ± SD (range)	26.5 ± 4.8 (18.9-40)	24.8 ± 3.8 (19.7-35.2)	28.7 ± 5.5 (19.6-41.0)
Number of defects, n (%)			
1	111 (79)	19 (86)	22 (63)
2	24 (17)	3 (14)	9 (26)
3+	5 (4)	0	4 (11)
Primary defect location, n (%)			
Lateral femoral condyle	24 (17)	8 (36)	4 (11)
Medial femoral condyle	62 (44)	10 (45)	14 (40)
Patella	41 (29)	1 (5)	12 (34)
Trochlea	13 (9)	3 (14)	5 (14)
Single defect area, cm^2, mean ± SD (range)	4.1 ± 2.3 (0.5-16.2)	5.2 ± 2.0 (2.6-11.4)	4.0 ± 2.3 (1.3-10.6)
Total defect area, cm^2, mean ± SD (range)	5.2 ± 3.5 (0.8-26.6)	5.7 ± 2.9 (2.5-16.2)	5.3 ± 3.7 (1.3-18.6)

[a]OCD, patients diagnosed with osteochondritis dissecans lesions, WC, patients receiving workers' compensation.

Changes in knee and overall function were assessed with the Lysholm and SF-12 scores (most recent follow-up minus preoperative values). Multivariate analysis was conducted to determine independent predictors of improvement in Lysholm score. Statistical significance was set at $P < .05$. Statistics were performed using GraphPad Software (San Diego, California) and SPSS version 15.0 (SPSS Science Inc, Chicago, Illinois).

RESULTS

Between December 1997 and May 2005, 137 patients (3 bilateral, 140 knees) receiving ACI to chondral defects of the knee were prospectively enrolled. The average patient age was 30.3 ± 9.1 years (range, 13.9-49.9 years), and the group contained 79 men and 58 women. Patients had an average BMI of 26.5 ± 4.8 kg/m^2 (range, 18.9-41.0 kg/m^2) (Table 1). Thirty-five patients (25%), mean age 36.2 ± 6.6 years (range, 22.0-47.9 years), were receiving workers' compensation at the time of surgery. ACI was used to treat osteochondritis dissecans (OCD) in 22 patients (16%). Mean patient age with OCD was 23.5 ± 6.5 years (range, 14.9-36.7 years).

Operative Technique

Because of the 2-staged nature of the procedure, at minimum, a diagnostic arthroscopy/cartilage debridement/cartilage biopsy was performed on all patients before chondrocyte implantation. Many patients had multiple procedures before ACI (range, 1-6). In many cases, first-line cartilage restoration was done concurrent to the biopsy, including microfracture (43%), chondroplasty (4%), and osteochondral autograft transplantation (3%). Patient histories were also positive for meniscal (18%), alignment (8%), and ligament (10%) procedures (Table 2).

Of the 140 knees, 24 (17%) had 2 defects, 4 (3%) had 3 defects, and 1 had 4 defects concurrently repaired with ACI. Three patients (2%) with multisite implantations had reciprocal lesions of the patella and trochlea. The average size of a single defect was 4.1 ± 2.3 cm^2 with a total area per patient of 5.2 ± 3.5 cm^2. ACI was chosen for small defects when an osteochondral autograft transfer system (OATS) plug would be difficult to place (central trochlea, patella) or when a larger defect was being treated with ACI and an associated lesion was found and simultaneously treated with ACI. Seventy-one patients (51%) had concomitant procedures, most frequently alignment (n = 48) or meniscal procedures (n = 16).

Outcome Assessment

Completed survey data sets were available on 122 patients (87%), and mean follow-up was 4.3 ± 1.8 years after ACI. Statistically significant improvement ($P < .01$) was noted on all outcome scales, including the Lysholm (41-69, $P < .001$), the IKDC (34-64, $P < .001$), all 5 subscores of the KOOS scale, and both SF-12 components (Figure 1). Preoperatively, 32% of patients had a Tegner score of 6 or greater, compared with 82% before injury and 65% at most recent follow-up (Table 3). Overall, 27 patients (22%) regained their preinjury activity level and 81 (66%) improved their Tegner score compared with preoperative levels. Subjectively, 35% of patients were completely satisfied with the procedure, 41% mostly satisfied, 20% somewhat satisfied, and 5% unsatisfied. Eighty-three percent of patients responded that they would have the surgery again.

TABLE 2
Concurrent and Previous Surgical Procedures to the Ipsilateral Knee[a]

	Previous	Concurrent
Cartilage		
Debridement	140 (100)	1 (1)
Microfracture	60 (43)	2 (1)
Chondroplasty	5 (4)	0
Osteochondral autograft	4 (3)	4 (3)
Meniscus		
Meniscectomy	20 (14)	1 (1)
Meniscus repair	4 (3)	0
Meniscus transplant	2 (1)	15 (11)
Alignment		
Distal realignment	3 (2)	35 (25)
Lateral release	9 (6)	6 (4)
High tibial osteotomy	0	5 (4)
Distal femoral osteotomy	0	2 (1)
Ligament		
ACL reconstruction	7 (5)	0
Other	7 (5)	0

[a]Data reported as number of patients (percentage). ACL, anterior cruciate ligament.

Increasing age was associated with less improvement in Lysholm scores at most recent follow-up ($P < .030$, $r = -.20$). Little association of BMI ($P < .292$, $r = 0.10$), defect area ($P < .439$, $r = -.07$), and time to follow-up ($P < .437$, $r = -.07$) with improvement in Lysholm score was observed. Multivariate analysis demonstrated 2 independent predictors of Lysholm outcome score improvement: age ($P < .021$) and workers' compensation status ($P < .018$). Gender, previous microfracture, concurrent alignment procedure, and lesion characteristics (OCD cause, location, and number) were not predictive of outcome (Table 4). Indeed, the workers' compensation cohort had a lower mean follow-up Lysholm score (55 ± 25) than the remainder of the cohort (73 ± 19).

Clinical Examination

Seventy patients returned for a follow-up knee examination beyond 2 years, at an average of 42 months (range, 24-86 months) after implantation. Objective range of motion was full in all patients with extension to 0° ± 1° (range, –2° to 5°) and flexion of 132° ± 6° (range, 120°-140°). Fifty-two patients underwent radiographs at follow-up, with 38 (73%) demonstrating joint space preservation and normal appearance. The remainder had evidence of interval (since preoperative imaging) degenerative changes: 7 (13%) had mild osteoarthritic changes, 4 (8%) had joint space narrowing, and 3 (6%) had flattening of the femoral condyle. Despite radiographic changes, these patients had decreased symptoms compared with their preoperative state.

Reoperation

Twenty-one knees (15%) had debridement of the ACI site secondary to periosteal hypertrophy or partial patch delamination. Reoperation occurred at an average of 27 months after the implantation (range, 5-73 months), most frequently attributable to mechanical symptoms. A second debridement was performed in 5 patients at a mean of 37 months (range, 17-79 months) after the first debridement. Nine knees (6.4%) had clinical failure of the ACI and underwent a revision—2 reimplantations, 4 osteochondral allografts, and 3 total knee replacements (1 bilateral)—at a mean of 43 months (range, 26-62 months) after implantation. Patient demographics of the cohorts undergoing reoperation and revision were not statistically different than the demographics of the overall study population (Table 5).

DISCUSSION

This study evaluated the clinical outcomes of ACI in a large patient cohort, which demonstrated a reduction of symptoms and increased function. One third of the patients were greater than 5 years out from ACI and had continuing improvement from their preoperative state. Because this was a single center-single surgeon investigation, consistency was maintained throughout the treatment algorithm and follow-up care. The size of this cohort permitted a multivariate analysis of outcome to further delineate the factors associated with prognosis for ACI in a diverse patient population.

ACI is considered a second-line treatment for Outerbridge grade IV defects of the knee: especially large or irregular lesions with minimal subchondral bone involvement. Comparison of ACI with other cartilage treatments has yielded conflicting results. Several reports suggest that ACI provides results superior to debridement, microfracture, and osteochondral autografting, especially in cases of prior failed treatment.[1,3,9] Conversely, recent randomized trials reveal no difference in clinical outcomes compared with mosaicplasty or microfracture.[6,16,17] First-line intervention had failed to provide relief in these patients; thus, they were indicated for ACI. Unlike Knutsen's studies in which microfracture and ACI were performed at the same stage of the treatment algorithm, this study investigated ACI as a revision to microfracture.[16,17] Within the population of failed marrow-stimulating techniques (42%), ACI proved to be a viable revision option for symptomatic relief and improvement of function. Importantly, a history of microfracture did not adversely affect subjective outcomes. In this treatment algorithm, the use of ACI is warranted and provides the option for osteochondral allograft revision.

Historically, chondral defects of the patella and trochlea are difficult because of the irregular surface architecture. ACI, because of the custom nature of the construct, has been used successfully within the patellofemoral joint. Improvement in Lysholm, IKDC, and Cincinnati scores as well as good to excellent results in 70% of patients are reported in patellofemoral ACI.[7,20,25] The results of this cohort are comparable, even in the few cases of bipolar "kissing" lesions. Concurrent alignment procedures were performed to off-load the repair site, which potentially contributed to the successful outcomes. However, neither defect location nor concurrent alignment procedure was an independent predictor of improvement in Lysholm score.

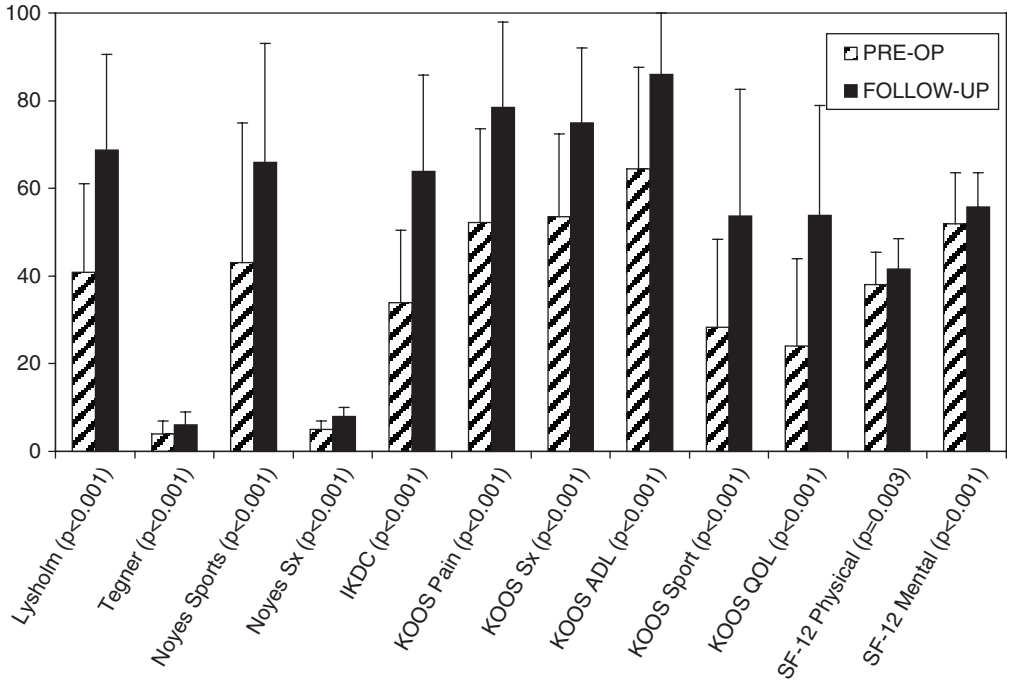

Figure 1. Comparison of outcome scores before and after ACI. *P* values were derived from a paired *t* test of preoperative and most recent follow-up scores. Sx, symptoms; ADL, activities of daily living; QOL, knee-related quality of life; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; SF-12, Short Form-12.

TABLE 3
Tegner Sport Score for Patients Receiving Autologous Chondrocyte Implantation[a]

Score	Preinjury	Preoperative	Current
≤5	22 (18)	83 (68)	43 (35)
6	1 (1)	15 (12)	23 (19)
7	5 (4)	3 (2)	14 (11)
8	16 (13)	2 (2)	8 (7)
9	17 (14)	14 (11)	26 (21)
10	61 (50)	5 (4)	8 (7)

[a]Data presented as number of patients (percentage).

TABLE 4
Multivariate Analysis of Independent Factors Affecting Improvement in Lysholm Scores[a]

Variable	*P* Value
Age	.021
Gender	.940
Body mass index	.320
Receiving workers' compensation	.018
Diagnosed osteochondritis dissecans	.059
Number of defects	.263
Defect location	.405
Previous microfracture	.947

[a]Model R^2 = .138.

ACI is used to treat osteochondritis dissecans defects of the knee that have failed open reduction–internal fixation and have minimal subchondral bone loss.[26] Outcomes of the 20 patients with OCD are comparable with previous studies that report good to excellent results in approximately 90% of OCD patients.[28,29] OCD patients, as a subset, had higher follow-up scores than the remainder of the cohort; however, diagnosed OCD was not a significant independent predictor of outcome score improvement. More likely, the younger mean age of the OCD cohort is the confounding and contributing factor to higher score levels.

The patients receiving workers' compensation demonstrated significantly lower scores at both preoperative and follow-up assessment. A similar trend of lower subjective outcome scores has been observed in workers' compensation patients undergoing rotator cuff repair and arthroplasty.[22,24] Yates[36] demonstrated a mean modified Cincinnati score of 7.2 and 80% excellent or good results in 10 patients followed to 4 years. Our cohort of 35 workers' compensation patients had a mean Cincinnati score of 6.4 and 68% good to excellent results at a mean of 4.1 years after surgery. Not surprisingly, workers' compensation was determined to be an independent predictor of improvement in Lysholm scores postoperatively.

Reoperation is a common sequela of ACI with an incidence of 15% to 30%.[7,9,14,17,21,25] Periosteal hypertrophy and delamination, which account for 22.1% and 17.7%, respectively, of the adverse events reported to the US Food and Drug Administration, frequently require ACI site

TABLE 5
Characteristics of Patients Requiring Reoperation

	Debridement	Revision
n (%)	21 (15)	9 (6)
Patient age, mean ± SD (range)	31.0 ± 10.4 (16.0-48.2)	36.6 ± 9.5 (24.1-51.7)
Gender, n (%)		
Male	11 (52)	4 (44)
Female	10 (48)	5 (56)
Body mass index, kg/m^2, mean ± SD (range)	25.3 ± 4.5 (18.9-34.7)	19.8 ± 6.9 (19.8-38.9)
Number of defects, n (%)		
1	16 (76)	7 (78)
2	4 (19)	1 (11)
3+	1 (5)	1 (11)
Reoperation defect location, n (%)		
Lateral femoral condyle	1 (5)	1 (11)
Medial femoral condyle	11 (52)	7 (78)
Patella	2 (10)	0
Trochlea	7 (33)	1 (11)
Single defect area, cm^2, mean ± SD (range)	4.4 ± 2.4 (0.75-8.8)	4.8 ± 2.8 (2.3-10.0)
Total defect area, cm^2, mean ± SD (range)	5.2 ± 3.0 (0.75-12.5)	6.9 ± 7.7 (2.3-26.6)

debridement.[35] In this cohort receiving ACI with periosteal patch, 16% required debridement for relief of mechanical symptoms. Recently developed treatments, including collagen-covered autologous chondrocyte implantation and matrix-induced autologous chondrocyte implantation, avoid the use of periosteum, thus eliminating the most symptomatic component of the repair. Early European studies of these techniques report a frequency of debridement less than 10%.[2,10,30,34]

ACI failure occurs in 4% to 22% of patients depending on defect traits and duration of follow-up.[7,9,21,25,27-29] The rate of failure increases with time from surgery and age. A continuing study of single condylar defects reported 5% failure at 2 years, which increased to 22.5% at 5 years.[16,17] One comparison of ACI by patient age demonstrated good to excellent results in 85.7% of patients younger than 20 years compared with 55.9% older than 40 years.[18] Osteoarthritis models suggest that older chondrocytes have decreased synthetic capabilities and lower response to growth factors.[15] The present population had an incidence of failure at 6%; 5 of the 7 patients in whom ACI failed were older than 40 years. Retrospectively, these patients were probably not the best candidates for ACI in light of chondrocyte quality and willingness to comply with the intensive rehabilitation regimen.

Although this study was able to assess the outcomes of a large cohort of patients treated with ACI, its retrospective design has several limitations. No control or comparison group was followed, and these patients were not randomized into treatment groups. Additionally, there were no set protocols for consistent reimaging or second-look arthroscopy. For the majority of patients, these options were only pursued with ongoing symptoms. Although the overall cohort size was large, several of the subsets (eg, lesion location and concurrent procedures) were sufficiently small so as to underpower the multivariate analysis of their effects.

CONCLUSION

Autologous chondrocyte implantation is a viable option in the treatment of cartilage defects after the failure of primary measures (debridement, chondroplasty, or microfracture). Improvements in function and symptoms are observed to nearly 10 years, attesting to the long-term durability of the repair. Predictive factors in the outcome of ACI include increasing patient age and workers' compensation status. All patients, especially those of advanced age, should maintain a realistic expectation for overall improvement and the potential need for reoperation or revision.

ACKNOWLEDGMENT

Dr Brian Cole is a consultant for Genzyme Biosurgery, Inc (Cambridge, Massachusetts), manufacturer of Carticel.

REFERENCES

1. Bachmann G, Basad E, Lommel D, Steinmeyer J. MRI in the follow-up of matrix-supported autologous chondrocyte transplantation (MACI) and microfracture. *Radiologe.* 2004;44:773-782.
2. Bartlett W, Skinner JA, Gooding CR, et al. Autologous chondrocyte implantation versus matrix-induced autologous chondrocyte implantation for osteochondral defects of the knee: a prospective, randomised study. *J Bone Joint Surg Br.* 2005;87:640-645.
3. Bentley G, Biant LC, Carrington RW, et al. A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee. *J Bone Joint Surg Br.* 2003;85:223-230.
4. Cole BJ, Lee SJ. Complex knee reconstruction: articular cartilage treatment options. *Arthroscopy.* 2003;19(suppl 1):1-10.
5. Curl WW, Krome J, Gordon ES, Rushing J, Smith BP, Poehling GG. Cartilage injuries: a review of 31,516 knee arthroscopies. *Arthroscopy.* 1997;13:456-460.
6. Dozin B, Malpeli M, Cancedda R, et al. Comparative evaluation of autologous chondrocyte implantation and mosaicplasty: a multicentered randomized clinical trial. *Clin J Sport Med.* 2005;15:220-226.
7. Farr J. Autologous chondrocyte implantation improves patellofemoral cartilage treatment outcomes. *Clin Orthop Relat Res.* 2007;463:187-194.
8. Farr J, Rawal A, Marberry KM. Concomitant meniscal allograft transplantation and autologous chondrocyte implantation: minimum 2-year follow-up. *Am J Sports Med.* 2007;35:1459-1466.
9. Fu FH, Zurakowski D, Browne JE, et al. Autologous chondrocyte implantation versus debridement for treatment of full-thickness chondral defects of the knee: an observational cohort study with 3-year follow-up. *Am J Sports Med.* 2005;33:1658-1666.
10. Gobbi A, Kon E, Berruto M, Francisco R, Filardo G, Marcacci M. Patellofemoral full-thickness chondral defects treated with Hyalograft-C: a clinical, arthroscopic, and histologic review. *Am J Sports Med.* 2006;34:1763-1773.
11. Gomoll AH, Minas T, Farr J, Cole BJ. Treatment of chondral defects in the patellofemoral joint. *J Knee Surg.* 2006;19:285-295.
12. Gudas R, Stankevicius E, Monastyreckiene E, Pranys D, Kalesinskas RJ. Osteochondral autologous transplantation versus microfracture for the treatment of articular cartilage defects in the knee joint in athletes. *Knee Surg Sports Traumatol Arthrosc.* 2006;14:834-842.

13. Henderson I, Lavigne P, Valenzuela H, Oakes B. Autologous chondrocyte implantation: superior biologic properties of hyaline cartilage repairs. *Clin Orthop Relat Res.* 2007;455:253-261.
14. Henderson I, Tuy B, Oakes B. Reoperation after autologous chondrocyte implantation: indications and findings. *J Bone Joint Surg Br.* 2004;86:205-211.
15. Horton WE Jr, Bennion P, Yang L. Cellular, molecular, and matrix changes in cartilage during aging and osteoarthritis. *J Musculoskelet Neuronal Interact.* 2006;6:379-381.
16. Knutsen G, Drogset JO, Engebretsen L, et al. A randomized trial comparing autologous chondrocyte implantation with microfracture: findings at five years. *J Bone Joint Surg Am.* 2007;89:2105-2112.
17. Knutsen G, Engebretsen L, Ludvigsen TC, et al. Autologous chondrocyte implantation compared with microfracture in the knee: a randomized trial. *J Bone Joint Surg Am.* 2004;86:455-464.
18. Krishnan SP, Skinner JA, Bartlett W, et al. Who is the ideal candidate for autologous chondrocyte implantation? *J Bone Joint Surg Br.* 2006;88:61-64.
19. Lefkoe TP, Trafton PG, Ehrlich MG, et al. An experimental model of femoral condylar defect leading to osteoarthrosis. *J Orthop Trauma.* 1993;7:458-467.
20. Mandelbaum B, Browne JE, Fu F, et al. Treatment outcomes of autologous chondrocyte implantation for full-thickness articular cartilage defects of the trochlea. *Am J Sports Med.* 2007;35:915-921.
21. Minas T. Autologous chondrocyte implantation for focal chondral defects of the knee. *Clin Orthop Relat Res.* 2001;(391 suppl): S349-S361.
22. Misamore GW, Ziegler DW, Rushton JL II. Repair of the rotator cuff: a comparison of results in two populations of patients. *J Bone Joint Surg Am.* 1995;77:1335-1339.
23. Mithoefer K, Williams RJ III, Warren RF, Wickiewicz TL, Marx RG. High-impact athletics after knee articular cartilage repair: a prospective evaluation of the microfracture technique. *Am J Sports Med.* 2006;34:1413-1418.
24. Mont MA, Mayerson JA, Krackow KA, Hungerford DS. Total knee arthroplasty in patients receiving workers' compensation. *J Bone Joint Surg Am.* 1998;80:1285-1290.
25. Niemeyer P, Steinwachs M, Erggelet C, et al. Autologous chondrocyte implantation for the treatment of retropatellar cartilage defects: clinical results referred to defect localisation. *Arch Orthop Trauma Surg.* 2008;128:1223-1231.
26. Ong B, Sekiya J, Harner C. Primary repair of osteochondritis dissecans in the knee. In: Miller MD, Cole BJ, eds. *Textbook of Arthroscopy.* Philadelphia, PA: Saunders; 2004:581-592.
27. Peterson L, Brittberg M, Kiviranta I, Akerlund EL, Lindahl A. Autologous chondrocyte transplantation: biomechanics and long-term durability. *Am J Sports Med.* 2002;30:2-12.
28. Peterson L, Minas T, Brittberg M, Lindahl A. Treatment of osteochondritis dissecans of the knee with autologous chondrocyte transplantation: results at two to ten years. *J Bone Joint Surg Am.* 2003;85(suppl 2):17-24.
29. Peterson L, Minas T, Brittberg M, Nilsson A, Sjogren-Jansson E, Lindahl A. Two- to 9-year outcome after autologous chondrocyte transplantation of the knee. *Clin Orthop Relat Res.* 2000;374:212-234.
30. Robertson WB, Fick D, Wood DJ, Linklater JM, Zheng MH, Ackland TR. MRI and clinical evaluation of collagen-covered autologous chondrocyte implantation (CACI) at two years. *Knee.* 2007;14:117-127.
31. Rue JP, Yanke AB, Busam ML, McNickle AG, Cole BJ. Prospective evaluation of concurrent meniscus transplantation and articular cartilage repair: minimum 2-year follow-up. *Am J Sports Med.* 2008;36:1770-1778.
32. Steadman JR, Briggs KK, Rodrigo JJ, Kocher MS, Gill TJ, Rodkey WG. Outcomes of microfracture for traumatic chondral defects of the knee: average 11-year follow-up. *Arthroscopy.* 2003;19:477-484.
33. Steadman JR, Miller BS, Karas SG, Schlegel TF, Briggs KK, Hawkins RJ. The microfracture technique in the treatment of full-thickness chondral lesions of the knee in National Football League players. *J Knee Surg.* 2003;16:83-86.
34. Steinwachs M, Kreuz PC. Autologous chondrocyte implantation in chondral defects of the knee with a type I/III collagen membrane: a prospective study with a 3-year follow-up. *Arthroscopy.* 2007;23:381-387.
35. Wood JJ, Malek MA, Frassica FJ, et al. Autologous cultured chondrocytes: adverse events reported to the United States Food and Drug Administration. *J Bone Joint Surg Am.* 2006;88:503-507.
36. Yates JW Jr. The effectiveness of autologous chondrocyte implantation for treatment of full-thickness articular cartilage lesions in workers' compensation patients. *Orthopedics.* 2003;26:295-300; discussion 300-301.