


Long-Term Evaluation of Autologous Chondrocyte Implantation: Minimum 7-Year Follow-Up

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Abstract

Purpose: The purpose of this study was to report the clinical outcomes of autologous chondrocyte implantation (ACI) procedures performed by a single orthopedic surgeon at a minimum of 7 years follow-up. **Methods:** A retrospective review of prospectively collected data was performed on 29 patients who underwent ACI of the knee between the years of 1998 and 2003. Prospective data were collected to assess changes in standardized outcome measures preoperatively and 2, 4, and 7 years postoperatively. All patients enrolled in the study were also recruited to undergo physical examination when possible. **Results:** The final cohort consisted of 29 patients with a mean final follow-up time of 8.40 years (range = 7.14–10.88 years). Comparing preoperative scores to 7-year postoperative values, the mean International Knee Documentation Committee (IKDC) score improved from 39.80 to 59.24 ($P < 0.001$), mean Tegner-Lysholm score increased from 48.07 to 74.17 ($P < 0.001$), SF-12 physical score improved from 40.38 to 48.66 ($P < 0.001$), and SF-12 mental score improved from 44.14 to 48.98 ($P < 0.05$). Significant improvement occurred in Knee Injury and Osteoarthritis Outcome Score (KOOS) pain (56.03 to 80.36), symptoms (54.19 to 74.75), activities of daily living (72.01 to 85.90), sports (23.34 to 55.34), and quality of life (24.56 to 56.03) ($P < 0.001$). In addition, 7-year postoperative scores were at or near levels seen at 2 years (mean = 2.16; range = 0.94–4.03 years) and 4 years (mean = 4.43; range = 2.16–5.88 years) postoperatively, reflecting durable improvement. Subjectively, on a scale of 1 to 10 (10 being completely satisfied), the mean postoperative satisfaction rate was 8.14. Additionally, 88.9% of the patients would elect to have this surgery again if the same problem was to occur in the contralateral joint. **Conclusions:** The results of ACI in patients who present with symptomatic, full-thickness chondral defects remain durable at a minimum of 7-year follow-up with persistent, high levels of patient satisfaction. **Level of Evidence:** Case series; Level of evidence, IV.

Keywords

outcome measures, articular cartilage, chondrocytes, knee, autologous chondrocyte implantation

Introduction

Full-thickness articular cartilage lesions can result from traumatic injuries and high-impact joint loading or may occur insidiously. These lesions often lead to debilitating pain, progressive osteoarthritis, and decreased functional capacity.^{1–3} Such lesions can be extremely common, with some studies reporting a prevalence of 5% to 11% in patients undergoing diagnostic knee arthroscopy.^{4–6} Due to the inherent poor healing capacity of chondral tissue, these injuries often require a surgical intervention. These procedures have been classified as palliative, reparative, and restorative, where palliative procedures include debridement and lavage, reparative include microfracture and autologous chondrocyte implantation (ACI), and restorative include osteochondral allograft and autograft implantation.⁷

ACI has been studied extensively to measure clinical efficacy and patient satisfaction, especially in the short and intermediate term.^{8–10} As a result, this research has led to the acceptance of ACI as a reparative technique for patients with contained, full-thickness focal chondral lesions greater than 2 cm².^{11,12} In addition to subjective improvement, histological assessments of the repaired defect site in patients treated with ACI exhibit formation of hyaline-like cartilage,

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tissue with better biomechanical properties as compared to fibrocartilage that results after microfracture.^{13,14} However, data on the long-term efficacy of this procedure are limited in the literature.

The purpose of this study was to report clinical outcomes from 29 patients following an ACI procedure performed by a single surgeon (senior author) at a single medical center with a minimum of 7 years follow-up. Effectiveness of ACI was determined by comparing validated outcome scores and correlating subjective data with available physical examination data. We propose that ACI is an efficacious procedure that provides long-term pain relief, improved functional ability, and greater quality of life for patients presenting with full-thickness focal chondral defects.

Methods

Patient Preoperative Assessment

All patients were retrospectively selected for this study. Each of the enrolled patients underwent an ACI and at the time of surgery signed an institutional review board–approved informed consent form allowing storage of preoperative subjective and objective data. The postsurgical data at a minimum of 7 years were collected in order to compare preoperative to postoperative outcomes. Special considerations were made for patients presenting with alignment and stability deficiencies. Thus, concomitant procedures such as osteotomy, cruciate ligament reconstruction, or other techniques were performed at the time of surgery.

Subjective evaluations were performed using validated knee survey analyses of the SF-12 Physical Component Summary and Mental Component Summary (PCS and MCS, respectively), Lysholm, International Knee Documentation Committee (IKDC), and Knee Injury and Osteoarthritis Outcome Score (KOOS). A thorough physical examination was also performed on all patients prior to the procedure, including assessment of range of motion, pain, effusion, and stability.

Patient Selection

Using our surgical database, we identified a potential 119 patients who underwent an ACI procedure between 1998 and 2003. Of these 119 patients, 57 patients presented with sufficient preoperative information. From this cohort, 18 patients were excluded due to unreliable contact information. This left 39 patients who were contacted for participation and scheduling at a minimum 7-year postoperative visit.

Of the 39 patients, it was determined that 3 patients had complications arising from their implantation procedure and required a revision procedure within the follow-up

period of this study. Having undergone a revision procedure, these patients were deemed as “failures”, and the data collected from these patients are presented separately as it would not reflect the postoperative outcome of the ACI but rather that of the revision procedure.

Considering exclusion criteria, a total of 36 patients qualified for the study. Of the 36 patients, 29 (80.56%) agreed to participate in the subjective assessment. All 29 patients were also recruited to undergo physical examination of their affected knee in order to compare subjective outcome measures with objective data. Sixteen patients (55% of cohort) agreed to participate in physical examination and presented to the office for examination. The remaining patients chose not to participate in the second phase due to time or travel constraints (**Fig. 1**).

Subjective Outcomes Assessment

Outcome evaluations were performed subjectively using validated knee survey analyses of the SF-12 PCS and MCS, Tegner-Lysholm, IKDC, and KOOS at 2, 4, and at least 7 years postoperatively.¹⁵⁻¹⁷ All patients were also asked to rate their overall satisfaction with the procedure on a scale of 0 to 10 (with 0 being extremely unsatisfied and 10 being extremely satisfied) and whether they would undergo the same procedure on the contralateral side if they were to have the same problem in the future. All subjective information was obtained using a composite of these measures assembled into one standardized survey, identical to the survey used in the preoperative evaluation.^{18,19}

Objective Outcomes Assessment

In addition to the subjective questionnaires, all patients were also recruited to undergo physical examination of their affected knee. A subset of 16 patients agreed to participate in the objective part of the study and presented to the office for examination. Each patient underwent a full bilateral knee examination assessing pain, range of motion, crepitus, alignment, patella tracking, ligament stability, and meniscal stability.

Statistical Evaluation

Descriptive statistics were calculated according to standard methods when appropriate to determine mean, standard deviation, frequency, and range. Clinical outcome scores were analyzed by determining the mean value of each statistical measure at all 4 time periods for the entire patient cohort. These averages were plotted in order to establish data trends over time from preoperatively to 7 years postoperatively. The preoperative scores and 7-year postoperative scores were then compared against each other in a 2-tailed *t* test to determine clinically significant increases. Statistical significance was set at $P < 0.05$.

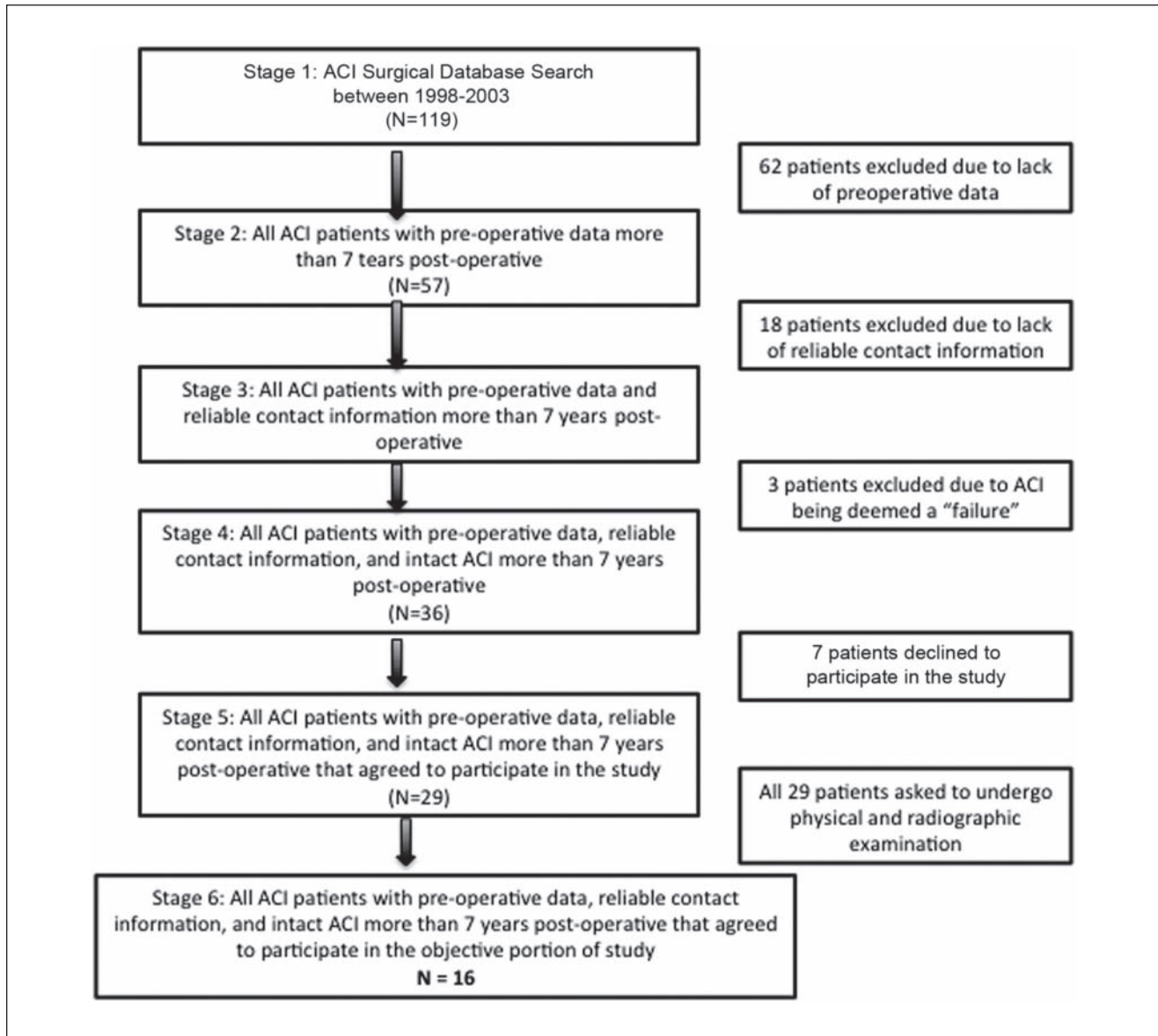


Figure 1. Patient selection flowchart.

Preselected subgroup analysis was also completed to uncover significant differences in 7-year postoperative clinical outcomes across different subpopulations within the cohort by analyzing specific variables that have all been hypothesized to affect ACI outcomes in earlier literature.²⁰⁻²² The effects of age, gender, body mass index (BMI), lesion size, lesion location, and presence or absence of concomitant knee procedures on the 7-year postoperative subjective outcome scores were assessed. Averages for each subjective outcome score were calculated for each subgroup in the 7-year postoperative state, and multivariate analysis using the Mann-Whitney *U* test of significance was conducted. Cohorts that displayed statistically significant differences in 7-year postoperative scores were further

examined by comparing preoperative to 7-year postoperative scores using a 2-tailed *t* test. All multivariate data were generated through SPSS for Windows version 17.0 (SPSS Inc., Chicago, IL).

Surgical Procedure

The ACI procedure has been described at length in previous publications.^{1,7,9,11} This procedure is indicated after failure of first-line treatment for patients with symptomatic, well-contained, full-thickness (Outerbridge grade IV with less than 6-8 mm of subchondral bone loss) chondral lesions (especially patellofemoral lesions) larger than 2 cm² on the femur (condyle and trochlea) and off-label use for the

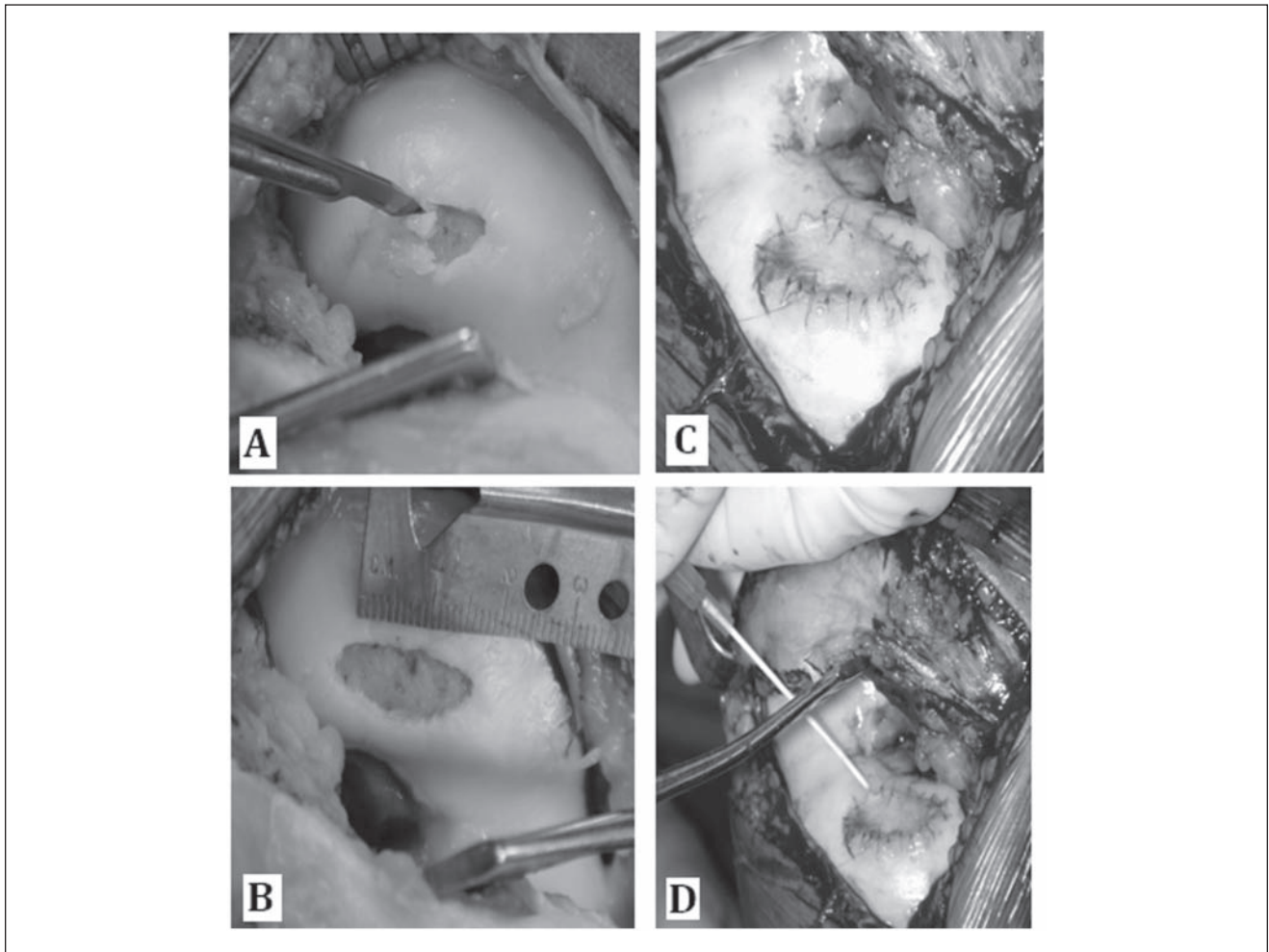


Figure 2. Surgical procedure of autologous chondrocyte implantation (ACI). (A) Exposed chondral defect and debridement. (B) Prepared chondral defect with vertical walls established. (C) Periosteal patch sutured over defect site. (D) Injection of expanded chondrocytes under patch.

patella.^{2,7,11} ACI can also be employed as a second-line treatment option after failed arthroscopic debridement or marrow stimulation techniques.¹¹

ACI is a 2-stage surgical procedure. During the first stage, an arthroscopic procedure was performed to assess the extent of the chondral defect. The lesion size, site, and grade; concomitant lesions; and the need for concomitant procedures were also assessed at the time of this arthroscopy. A 200- to 300-mg cartilage biopsy was taken from a nonweightbearing site in the knee, and this specimen was sent to a cell culturing facility (Carticel, Genzyme Biosurgery, Cambridge, MA) for chondrocyte expansion to a final concentration of 2 to 3×10^7 chondrocytes/mL.¹⁸

With completion of chondrocyte expansion, a process that takes 4 to 6 weeks, each patient underwent the second stage where an open arthrotomy was performed to expose the defect site. Once visible, the lesion site was debrided using a No. 15 scalpel and a ring curette to remove damaged cartilage and form a surrounding vertical wall of hyaline

cartilage. The creation of a vertical wall lesion is essential in order to allow for suturing of the periosteum patch, obtained from the proximal medial tibia, and to allow the surrounding cartilage to distribute load more effectively. (Note: Current ACI protocol can involve off-label use of a collagen I/III bilayer membrane patch to reduce the surgical adverse event ratio.²³⁻²⁵) The periosteal patch was harvested using a periosteal elevator as previously described by Gomoll *et al.*,²⁴ and the obtained patch was appropriately sized to cover the lesion site. The sized patch was sutured over the lesion site using 6-0 Vicryl sutures (polyglactin; Ethicon Inc., Somerville, NJ, USA) spaced 2 to 3 mm apart, leaving a small opening at the top to allow for injection of the cultured chondrocytes under the patch. Fibrin glue was applied around the sutured regions to ensure a watertight seal. Cells were suspended into a syringe and injected underneath the patch. Once the chondrocytes were injected, the small opening was closed using sutures and fibrin glue. Once completed, the arthrotomy was closed in layers (Fig. 2).

Table 1. Average Preoperative and Final Subjective Outcome Scores for All Patients ($n = 29$)

Knee rating system	Preoperative	Postoperative	Percentage change	P value
SF-12 physical	40.38	48.66	20.50	0.000131
SF-12 mental	44.14	48.98	10.94	0.019610
Tegner-Lysholm	48.07	74.17	54.30	0.000001
IKDC	39.80	59.24	48.84	0.000001
KOOS pain	56.03	80.36	43.42	0.000001
KOOS symptoms	54.19	74.75	37.95	0.000016
KOOS ADL	72.01	85.90	19.30	0.000183
KOOS sports	23.34	55.34	137.08	0.000005
KOOS QOL	24.56	56.03	128.13	0.000008
Overall satisfaction		8.14		
% would have surgery again		88.89%		

Note: SF-12 = Short-Form 12; IKDC = International Knee Documentation Committee; KOOS = Knee Injury and Osteoarthritis Outcome Score; ADL = activities of daily living; QOL = quality of life.

Postoperative Rehabilitation

Exact rehabilitation protocol differed slightly on a patient-specific basis depending on lesion location. Patients were generally nonweightbearing for the first 2 weeks, with progression to partial weightbearing for weeks 2 to 8 and full weightbearing at 8 weeks. Continuous passive motion was used in 2-hour blocks for 6 to 8 hours per day for the first 3 weeks (0° - 30° : 1 cycle/minute), with range of motion increasing 5° to 10° daily, reaching 120° range of motion by 8 weeks and full range of motion at 12 weeks. Closed chain exercises were started at 4 weeks postoperatively, with patients progressing to treadmill exercise at 12 weeks. Ultimately, high-impact exercise began at 12 months if the patient was pain free.

Results

Patient and Defect Characteristics

In this cohort of 29 patients, 36 lesions were repaired using the ACI technique. Fourteen (38.88%) patients underwent an ACI of the right knee, while 15 (41.66%) underwent ACI of the left knee. All lesions were Outerbridge grade IV,^{26,27} with a mean lesion size of 3.50 cm^2 (standard deviation = 1.91; range = 0.0224 - 7.50 cm^2). Of the lesion locations that could be localized, the distribution was as follows: 15 medial femoral condyle, 9 femoral trochlea, 5 lateral femoral condyle, 1 patella, and 6 unspecified (lesion locations were not recorded on operative notes). Of this population, 13 (44.83%) were male, and 16 (55.17%) were female, with a mean final follow-up time of 8.40 years (range = 7.14-10.88 years). The mean age at preoperative examination was 30.7 years (range = 14.4-49.6 years), the mean age at time of surgery was 32.0 years (range = 14.9-49.9 years), and the mean age at postoperative examination

was 40.36 years (range = 22.5-58.5 years). Average BMI at the time of arthroscopic harvest operation was reported at 27.09 kg/m^2 (standard deviation = 7.05; range = 17.93 - 52.22 kg/m^2), and one patient was classified as workers' compensation status.

Subjective Clinical Outcomes

As a single cohort, the 29 patients who completed the 7-year follow-up surveys reported statistically significant improvements from preoperative to follow-up values in all scoring scales: SF-12 PCS, SF-12 MCS, Tegner-Lysholm, IKDC, and all 5 KOOS categories (pain, symptom, activities of daily living, sports, quality of life). The mean IKDC score improved from 39.80 to 59.24 ($P < 0.05$). The mean Tegner-Lysholm score showed an increase from 48.07 to 74.17 ($P < 0.05$). SF-12 PCS and MCS scores improved from 40.38 to 48.66 ($P < 0.001$) and from 44.14 to 48.98 ($P < 0.05$), respectively. Values for all 5 KOOS subcategories significantly improved from baseline to follow-up: pain (56.03 to 80.36), symptoms (54.19 to 74.75), activities of daily living (72.01 to 85.90), sports (23.34 to 55.34), and quality of life (24.56 to 56.03) ($P < 0.05$) (**Table 1**; **Fig. 3**).

The mean satisfaction score was 8.14 (of 10), and 88.89% of the patients would elect to have this surgery again if they had the same problem on the opposite knee (**Fig. 4**).

Patient outcomes were also measured postoperatively at 2 and 4 years to establish trends in outcome measures over time. The average follow-up time at the 2-year postoperative mark was 2.16 years (range = 0.94-4.03 years), and the average follow-up time at the 4-year postoperative mark was 4.43 years (range = 2.16-5.88 years). According to the data gathered, which are presented in **Table 2**, all measures exhibit durable increases in the 2-, 4-, and 7-year postoperative states when compared to the preoperative state.

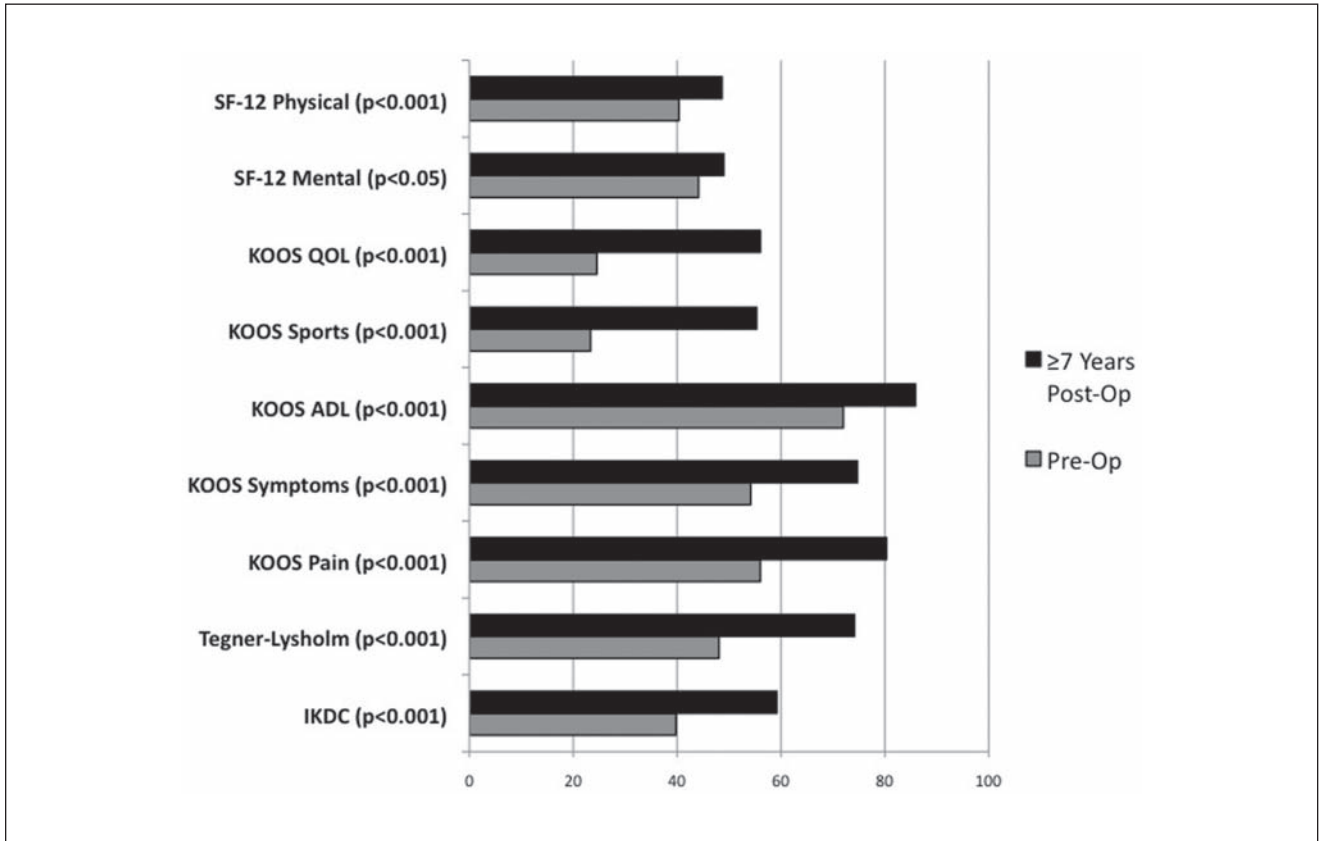


Figure 3. Average preoperative subjective outcomes versus average postoperative subjective outcomes. SF = Short-Form Health Survey; KOOS = Knee Injury Osteoarthritis Outcome Score; ADL = activities of daily living; QOL = quality of life; IKDC = International Knee Documentation Committee.

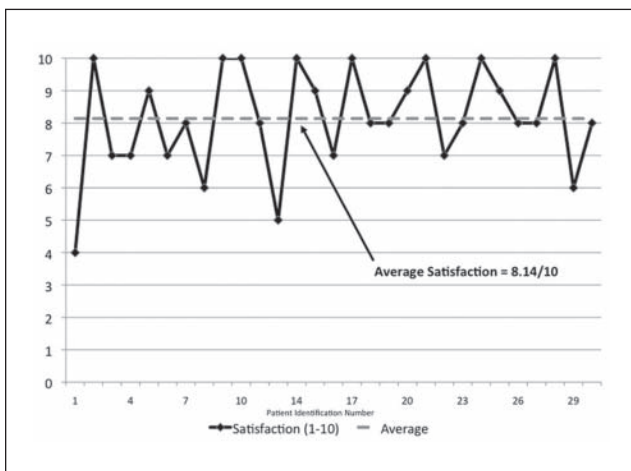


Figure 4. Patient satisfaction on a scale of 1 to 10. Every patient in the 29-patient cohort is represented by a single data point. Dotted gray line denotes the average satisfaction of 8.14 of 10.

Subgroup Analysis

As described earlier, patients were divided into subgroups that have been hypothesized to affect the outcomes of chondrocyte implantation, such as age, gender, BMI classification,

lesion size, lesion location, and presence or absence of previous/concomitant knee procedures.²¹ Seven-year post-operative outcome scores were averaged for each subgroup and compared in multivariate analysis in order to examine differences in patient satisfaction and clinical outcome for different subpopulations.

Analysis of data within our 29-patient cohort demonstrated relevant trends in variation with respect to BMI and concomitant meniscal transplantation procedure but was underpowered to detect statistical significance. A slight trend showed improved outcomes following concomitant meniscal transplantation and worse outcomes with high BMI (meniscal transplantation, *n* = 5; BMI, *n* = 4). However, these subgroups were very small, preventing the production of conclusions.

Objective Clinical Outcomes

Of the 16 patients who returned for a physical examination, 8 patients reported no pain on postoperative examination. Of the remaining 8 patients who reported some level of pain or tenderness in the postoperative physical examination, the mean satisfaction level was 7.88 of 10, and all 8 patients (100%) stated they would have the same procedure

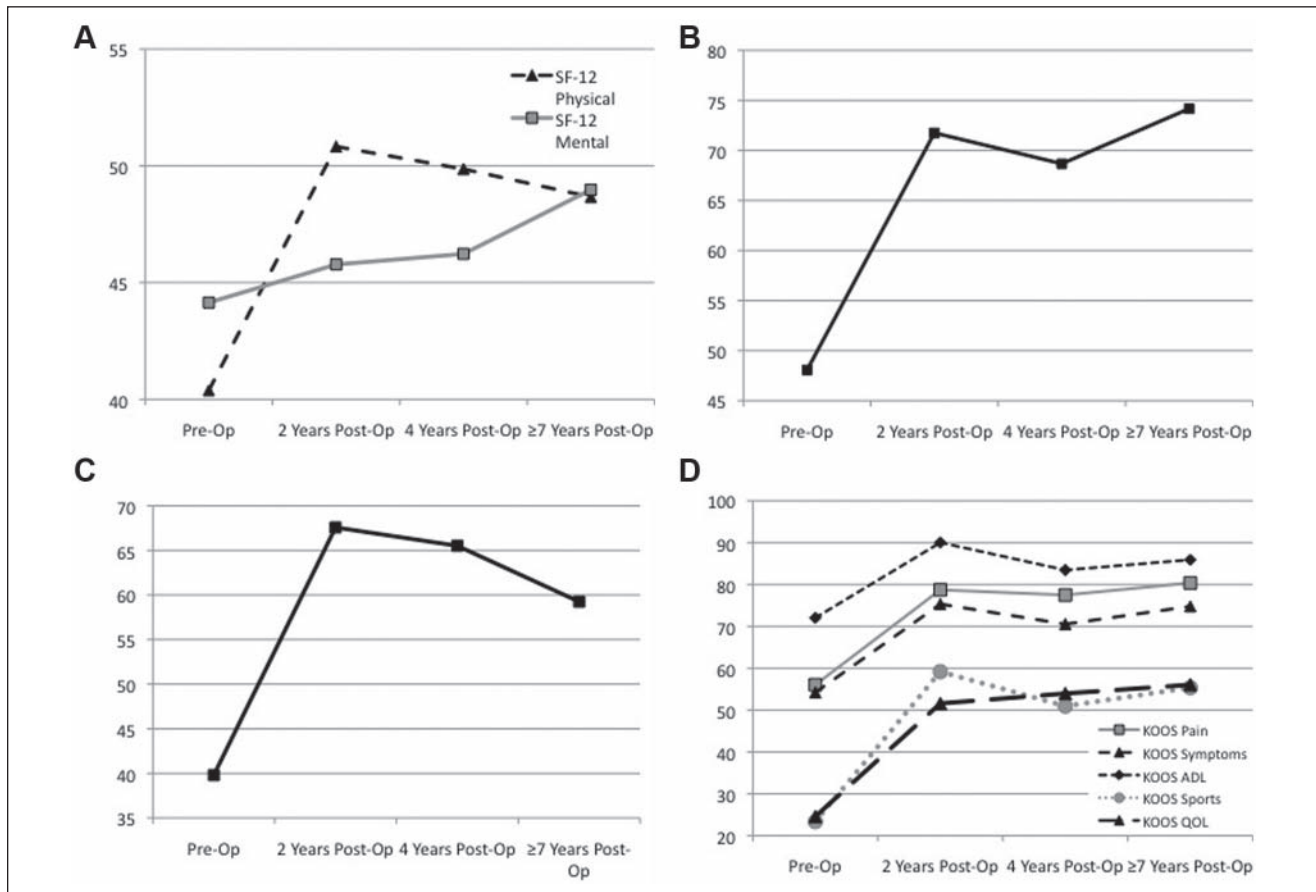


Figure 5. Mean subjective outcome scores preoperatively and 2, 4, and 7 years postoperatively arranged by subjective outcome measure for the 29-patient cohort. These graphs clearly exhibit statistical trends, indicating large increases in subjective satisfaction from preoperatively to 2 years postoperatively. As illustrated by the graph, these subjective improvements remain durable at 4 and 7 years postoperatively for nearly all measures, with only a slight decline in International Knee Documentation Committee (IKDC) scores. (A) Short Form-12 (SF-12) outcome trends. (B) Lysholm trends. (C) IKDC trends. (D) Knee Injury and Osteoarthritis Outcome Scores (KOOS) trends. ADL = activities of daily living; QOL = quality of life.

again, which indicated that pain and functional level were improved compared to the preoperative state.

Failures

A separate group of three patients that underwent 4 implantations were deemed failures as they experienced no or minimal benefit from the ACI, with recurrent episodes of pain, requiring further surgical intervention. The mean time to failure was 3.75 years (range: 1.46 to 5.12 years). Of this small population of 3 patients, all reported workers' compensation status. Two of the 3 patients were female. Mean lesion size for these failures was 2.73 cm² (minimum standard deviation = 0.55 cm²), and all 3 patients had a BMI <30 kg/m². All failures occurred on the femoral condyle, with 3 occurring medially and 1 laterally. All 3 patients failed a microfracture procedure that was performed prior to the ACI, and 1 patient underwent a concomitant anteromedialization with ACI. Two failures were revised to osteochondral allograft, and the patient with

bilateral ACI failures was indicated for bilateral total knee arthroplasty.

Discussion

In this study, we retrospectively investigated the clinical durability of ACI of the knee for 29 patients at a minimum of 7 years. There were noted trends of improvement in clinical outcome scores as well as patient satisfaction and recovery at 7 years as compared to preoperative data. Objective clinical data gathered at the time of the final physical examination support reported subjective outcomes. Furthermore, data collected at 2- and 4-year follow-up intervals demonstrated similar trends in positive subjective outcome measures as the data collected at 7 years when compared to the preoperative state, suggesting the durability of the ACI procedure. These sustained increases in clinical outcome scores show that ACI is viable up to 7 years postoperatively. The trends for each statistical measure are shown in **Figure 5 (Table 2)**.

Table 2. Mean Subjective Outcome Score Durability (n = 29)

Knee rating system	Preoperative	2 years postoperative	4 years postoperative	7 years postoperative	P value preoperatively v. 7 years postoperatively
SF-12 physical	40.38	50.82	49.86	48.66	<0.001
SF-12 mental	44.14	45.77	46.23	48.98	<0.05
Tegner-Lysholm	48.07	71.75	68.67	74.17	<0.001
IKDC	39.8	67.57	65.51	59.24	<0.001
KOOS pain	56.03	78.7	77.47	80.36	<0.001
KOOS symptoms	54.19	75.3	70.5	74.75	<0.001
KOOS ADL	72.01	90.01	83.44	85.9	<0.001
KOOS sports	23.34	59.17	50.93	55.34	<0.001
KOOS QOL	24.56	51.56	53.94	56.03	<0.001

Note: SF-12 = Short-Form 12; IKDC = International Knee Documentation Committee; KOOS = Knee Injury and Osteoarthritis Outcome Score; ADL = activities of daily living; QOL = quality of life.

Although often chosen as a second-line treatment, patient objective findings provide further support in that the value of ACI in a clinical setting can offer satisfactory clinical results. Based on these findings, we feel that ACI is a viable treatment option for patients with symptomatic full-thickness cartilage lesions and can reduce pain, increase range of motion, and improve patient function in the long term. This is consistent with previously reported results over the short and intermediate term.^{3,18,19,20,28}

This study and cohort are unique in that all procedures were performed by a single surgeon (senior author) at an individual medical center, thus minimizing the confounding variables associated with surgical technique and rehabilitation protocols inherent in a multicenter study. Even though the ACI procedure has become fairly standardized over the years, the procedure remains technically challenging due to periosteal harvest and cell implantation. This fact is illustrated by a recent study by Moseley *et al.*,²⁸ in which the 72-patient cohort was taken from 35 different medical centers, with 21 of the 72 patients (29% of the patient population) representing the first ACI case ever completed by the surgeon. By analyzing clinical data from a single surgeon cohort, this study avoided confounding variables introduced due to surgical differences, increasing the power of the evidence presented in our study.

Our present study limitations include a small patient population, limiting the statistical power of this study. Our final cohort of 36 patients included 7 patients who chose not to participate in the study for unknown reasons. According to the study by Kim *et al.*,²⁹ it is reasonable to question whether these patients did not participate because of poor ACI outcomes. For that reason, much consideration was given in assessing these 7 patients in the “failure” category, more accurately reflecting the negative outcomes within our cohort. However, as none of these patients required further surgical intervention beyond ACI repair, they did not fit the failure criteria for this study.

Due to the small cohort of our study, no statistical significance can be concluded on the long-term reliability of the ACI. Instead, the data provided in this cohort study represent trends seen in the subjective outcome scores over time. In examining the trends as opposed to the actual statistics, one can see that ACI led to drastic increases in subjective outcome scores in the short term, with little decline as the cohort progressed further into the postoperative period. The durability seen in the trends serves as evidence that ACI repair may provide a long-term treatment option with little decline in patient satisfaction over time. Although we feel outcome trends would likely resemble those of a larger sample, further studies are needed to enhance the statistical power of the data. In addition, the lack of a control group limits the power of the evidence presented; due to the nature of the intervention, it was difficult to generate this group.

The results of ACI in patients who present with symptomatic, full-thickness chondral defects remain durable at a minimum 7-year follow-up with persistent, high levels of patient satisfaction.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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