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Long-term Outcomes of Autologous Chondrocyte Implantation in Adolescent Patients

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Background: Treating symptomatic articular cartilage lesions is challenging, especially in adolescent patients, because of longer life expectancies and higher levels of functional activity. For this population, long-term outcomes after autologous chondrocyte implantation (ACI) remain to be determined.

Purpose: To evaluate long-term outcomes in adolescents after ACI using survival analyses, validated outcome questionnaires, and standard radiographs.

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

Methods: We performed a review of prospectively collected data from patients who underwent ACI between 1996 and 2013. We evaluated 27 patients aged <18 years old (29 knees; mean age, 15.9 years) who were treated by a single surgeon for symptomatic, full-thickness articular cartilage lesions over a mean 9.6-year follow-up (median, 13 years; range, 2-19 years). A mean of 1.5 lesions per knee were treated over a mean total surface area of 6.2 cm^2 (range, 2.0-23.4 cm^2) per knee. Survival analysis was performed using the Kaplan-Meier method, with graft failure as the end point. The modified Cincinnati Knee Rating Scale, Western Ontario and McMaster Universities Osteoarthritis Index, visual analog scale, and Short Form 36 scores were used to evaluate clinical outcomes. Patients also self-reported knee function and satisfaction. Standard radiographs were evaluated using Kellgren-Lawrence grades.

Results: Both 5- and 10-year survival rates were 89%. All clinical scores improved significantly postoperatively. A total of 96% of patients rated knee function as better after surgery, and all patients indicated that they would undergo the same surgery again. Approximately 90% rated knee-specific outcomes as good or excellent and were satisfied with the procedure. At last follow-up, 12 of 26 successful knees were radiographically assessed (mean, 5.6 years postoperatively), with no significant osteoarthritis progression. Three knees were considered failures, which were managed by autologous bone grafting or osteochondral autologous transplantation. Twenty knees required subsequent surgical procedures. These were primarily associated with periosteum and were arthroscopically performed.

Conclusion: ACI resulted in satisfactory survival rates and significant improvements in function, pain, and mental health for adolescent patients over a long-term follow-up. ACI was associated with very high satisfaction postoperatively, despite the subsequent procedure rate being relatively high primarily because of the use of periosteum. If periosteum is used, this rate should be a consideration when discussing ACI with patients and their parents.

Keywords: autologous chondrocyte implantation; pediatric; adolescent; articular; cartilage; repair

Articular cartilage injuries in the knee joint are relatively common and have the potential to progress to osteoarthritis (OA).[7] The treatment of articular cartilage injuries presents a challenge to orthopaedic surgeons, especially in adolescent patients because of the extent of their life expectancy and high level of functional activity.

The 2 most common cartilage lesions in young patients are traumatic cartilage lesions and osteochondritis dissecans (OCD). Although the incidence of symptomatic, high-grade chondral injuries is poorly understood, it has been reported that between 5% and 10% of active young patients with hemarthrosis of the knee after a traumatic event will have a focal chondral injury.[1,53] Similarly,

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OCD, which is an acquired, idiopathic, focal lesion of the subchondral bone, is also common in young patients and can progress to involve the overlying articular cartilage. OCD is most commonly observed in athletically active young children and adolescents, occurring in approximately 15 to 29 per 100,000 patients.[20,28,31] When nonoperative treatments fail, surgical intervention is required. Surgical procedures in clinical application include debridement,[21] bone marrow stimulation,[22,60] autologous bone grafting,[23] osteochondral autograft transplant,[19] osteochondral allograft transplant,[15] autologous chondrocyte implantation (ACI),[5,55] and the ACI "sandwich" technique.[24,39,54,61,62]

Controversy continues to exist regarding the optimal treatment for articular cartilage lesions. Since the first report on ACI by Brittberg et al[5] in 1994, several studies have shown effective and durable long-term outcomes associated with ACI for the treatment of articular cartilage lesions.[43,49,51] However, there have been few studies regarding the use of ACI in adolescent patients.[33,37,44] Additionally, studies have failed to identify long-term results associated with ACI in adolescent patients, despite the fact that these patients constitute the group to which concerns regarding durability and long-term outcomes are most relevant. Therefore, the purpose of this study was to evaluate long-term clinical outcomes of ACI in adolescent patients using validated outcome questionnaires and standard radiographs. We hypothesized that ACI would provide ideal functional outcomes and survival rates over a long-term follow-up.

METHODS

Patient Demographics

The study was approved by our institutional review board, and informed consent was obtained from all patients at the time they were entered into the database (usually at the time of the index surgery). Between March 1996 and October 2013, a total of 27 patients aged <18 years old were treated with ACI for symptomatic, full-thickness chondral defects. A single surgeon performed all procedures. Of this cohort, all 27 patients (29 knees) were included in the analysis, as all had successfully completed more than 2 years of follow-up by the time of data analysis.

Patient Evaluation

Patients who underwent ACI were evaluated prospectively. Indications for surgery included ≥1 full-thickness articular cartilage lesion of the knee, with symptoms matching the defect location. Surgery was only indicated in patients who were resistant to nonoperative therapies, including physical therapy and injectable therapies. Patients were evaluated through a physical examination, radiography, magnetic resonance imaging (MRI), and arthroscopic surgery before treatment with ACI was considered. Contraindications to treatment included inflammatory joint disease, unresolved or recent septic arthritis, metabolic or crystal disorders, or deficient soft tissue coverage. Tibiofemoral malalignment <2° to 3° from the neutral mechanical axis into the involved compartment was corrected with concomitant osteotomy. Osteochondral lesions deeper than 6 to 8 mm were addressed with concomitant bone grafting. Additionally, meniscal deficiencies were addressed with meniscal allograft transplantation. Consequently, the presence of tibiofemoral malalignment, deep osteochondral lesions, or meniscal deficiencies were not considered as contraindications for surgery. A philosophy of a single "biological reconstruction" managing the background factors of the cartilage injury was followed.

TABLE 1
Concomitant Procedures (N = 29 Knees)[a]

Procedure	n
TTO alone	10
Sandwich technique alone	4
TTO with sandwich technique	2
DFO alone	2
Combined DFO and TTO with meniscal allograft transplantation	2
Combined DFO and TTO with medial collateral ligament repair	1
HTO alone	1
No concomitant procedure	7

[a]DFO, distal femoral osteotomy; HTO, high tibial osteotomy; TTO, tibial tubercle osteotomy.

Presurgical Planning and Surgical Technique

ACI was performed as described in detail previously.[26,40] Briefly, after an arthroscopic cartilage biopsy was performed during the initial surgery, chondrocytes were cultured, cryopreserved, and then thawed and recultured for definitive implantation after insurance approval. Secondary surgery was then performed for implantation with arthrotomy. For surgeries performed before May 2007, periosteum was harvested from the proximal tibia or distal femur (16 knees). After May 2007, a bilayer type I/III collagen membrane, derived from porcine peritoneum and skin (Bio-Gide; Geistlich), was used (13 knees) in place of autologous periosteum. Periosteum or a collagen membrane was placed on the cartilage defect and secured with multiple 6-0 Vicryl sutures (Ethicon). The suture line was waterproofed with fibrin glue (Tisseel; Baxter), and autologous chondrocytes were injected underneath the membrane.

Articular comorbidities (background factors), such as malalignment and patellar maltracking, were corrected at the time of surgery. Tibiofemoral malalignment <2° to 3° was corrected via osteotomy of the tibia or femur, with correction of the mechanical axis to neutral or 0°. Concomitant procedures are shown in Table 1. Six knees underwent surgery using the "sandwich technique,"[24,39,54,61,62] which involves the use of an autologous bone graft for the subchondral bone defect, and ACI for the overlying cartilage defect. Patellofemoral maltracking was addressed with anteromedialization with tibial tubercle osteotomy to centralize patellar tracking[13,41] and proximal soft tissue balancing (lateral

☐1 ☐2 POOR ☐3 ☐4 Fair ☐5 ☐6 Good ☐7 ☐8 Very Good ☐9 ☐10 Excellent	
Poor (1-2)	I have significant limitations that affect activities of daily living.
Fair (3-4)	I have moderate limitations that affect activities of daily living. No sports possible.
Good (5-6)	I have some limitations with sports but I can participate; I compensate.
Very Good (7-8)	I have only a few limitations with sports.
Excellent (9-10)	I am able to do whatever I wish (any sport) with no problem.

Figure 1. Modified Cincinnati Knee Rating Scale for overall condition.

release, vastus medialis obliquus advancement) as necessary to centralize the extensor mechanism.

Postoperative Course

Postoperatively, patients were instructed to use a continuous passive motion machine for 6 to 8 hours daily for 6 weeks. Patients remained nonweightbearing for 6 to 8 weeks, with gradual progression to full weightbearing by 10 to 12 weeks. Patients were permitted to return to most activities of daily living after 3 months and to nonimpact functional activities including the use of a stationary bicycle, treadmill walking, and progression to an elliptical trainer and swimming, without cutting movements, after 4 to 5 months. After 12 months, inline jogging was permitted if there was no swelling or pain evident. Pivoting activities were permitted from 14 to 18 months postoperatively. The postoperative recovery protocol was individually adjusted according to defect location, concurrent procedures, degree of graft maturation, and previous activity level.[42]

Definition of Failure

Failure was defined as persistent or recurrent symptoms in conjunction with MRI evidence of graft delamination or surgical removal of >25% of the graft area, repeat ACI, or additional surgical treatment violating the subchondral bone, such as microfracture or autologous bone grafting.

Radiographic Evaluation

Radiographs were taken to identify whether the distal femoral physis was open or closed at the time of the index surgery. Standing, long axial alignment radiographs; anteroposterior, posteroanterior (Rosenberg), and lateral radiographs of the tibiofemoral joint; and weightbearing skyline views of the patellofemoral joint were scored according to the Kellgren-Lawrence (K-L) grading system[25] to evaluate the progression of OA before and after the index surgery.

Survival Analysis and Clinical Outcome Evaluation

The survival rate was evaluated with the Kaplan-Meier method, with failure of the graft as the end point measure. Patients were evaluated with a range of functional scores, including the modified Cincinnati Knee Rating Scale,[6,36] Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC),[2] visual analog scale (VAS), and Short Form 36 (SF-36).[4] The original Cincinnati Knee Rating Scale was based on a 0-to-100 continuous scale,[52] whereas the modified Cincinnati Knee Rating Scale uses a 1-to-10 categorized scale, with a 2-point change being considered clinically meaningful (Figure 1).[6,36] Patients also answered questions regarding self-rated knee function and satisfaction with the procedure. Scores were gathered preoperatively and at yearly intervals postoperatively during consultations or via a mailed questionnaire. A subanalysis was performed according to patient sex, cartilage defect size (<6 cm^2 vs >6 cm^2), number of cartilage lesions (single vs multiple), status of the distal femoral physis (open vs closed), type of injury (traumatic vs OCD), and presence of concomitant osteotomy.

Statistical Analysis

Kaplan-Meier curves were used for survival analyses. The Wilcoxon signed-rank test was used to compare differences in functional scores (obtained from the modified Cincinnati Knee Rating Scale, VAS, WOMAC, and SF-36) between the 2 time points (preoperatively and at last follow-up). Mann-Whitney *U* tests were used to compare the improvement in scores between the different groups. The level of significance was set a priori at $P < .05$. All statistical analyses were performed with Stata (version 13; StataCorp LP).

RESULTS

Patient Cohort

The mean patient age was 15.9 years at the time of the index surgery (range, 13-17 years) and consisted of 14 female and 13 male patients. Patients were followed up for a mean of 9.6 years (median, 13 years; range, 2-19 years) after surgery. A total of 19 patients underwent follow-up to 5 years, 15 of whom were still undergoing follow-up at 10 years. The mean number of treated lesions per knee was 1.5 (range, 1-5), with a mean total surface area of 6.2 cm^2 (range, 2.0-23.4 cm^2) per knee. Diagnoses included traumatic chondral injuries (n = 18; 62%) and OCD (n = 11; 38%). A total of 21 knees presented with single lesions, while 8 knees exhibited multiple lesions. Bipolar lesions

TABLE 2
Patient Demographics (N = 27 Patients, 29 Knees)[a]

	Value
Age at surgery, y, mean ± SD (range)	15.9 ± 1.3 (13-17)
Sex, male/female, n	13/14
Side, right/left knee, n	14/15
BMI, kg/m^2, mean ± SD (range)	24.7 ± 5.2 (17.1-37.7)
Follow-up, y, mean ± SD (range)	9.6 ± 6.2 (2-19)
Preoperative duration of symptoms, n	
<1 y	6
>1 y	23
Duration of symptoms, y, mean (range)	3.3 (0.25-13)
Cartilage lesions, n	
1	21
2	5
3	1
4	1
5	1
Open physes, n	9
Lesion type, n	
Traumatic	18
OCD	11
No. of defects per knee, mean ± SD (range)	1.5 ± 1.0 (1-5)
Total defect surface area per knee at index surgery, cm^2, mean ± SD (range)	6.2 ± 4.3 (2.0-23.4)
Defect location, n	
Lateral femoral condyle	10
Medial femoral condyle	8
Trochlea	6
Patella	10
Lateral tibial plateau	5
Medial tibial plateau	1
Patients with bipolar lesion, n	4 (5 lesions)
Bipolar lesion, patellofemoral/lateral/patellofemoral and medial, n	2/1/1

[a]BMI, body mass index; OCD, osteochondritis dissecans.

were present in 4 patients (5 lesions), including the patellofemoral compartment in 2, lateral compartment in 1, and both patellofemoral and medial compartment in 1 (Table 2). Preoperative radiographs were available to review in all knees; of these radiographs, open growth plates at the time of the index surgery were observed in 9 knees. A total of 22 knees had undergone at least 1 previous surgery (Table 3). One patient with prior incision drainage for septic arthritis underwent ACI at 2 years after the drainage procedure. A sterile knee was determined preoperatively by a normal peripheral white blood cell count, erythrocyte sedimentation rate, and C-reactive protein level as well as aspiration of the knee with negative culture results. Intraoperatively, cultures were taken and found to remain sterile. Three patients (3 knees) were considered to have failed results. These patients were included in the clinical outcome evaluation before failure occurred. However, they were excluded from the results of the radiographic evaluation because they underwent revision surgery during the follow-up period. Revision surgery included autologous bone grafting and osteochondral autologous transplantation (OAT).

TABLE 3
Previous Procedures

Procedure	n
Abrasion/drilling/microfracture	8
Debridement	8
Fragment reattachment/removal	5
Meniscal repair/meniscectomy	2
Internal fixation	2
Bone grafting	2
Diagnostic arthroscopic surgery	1
Debridement for septic arthritis	1
Open incision and drainage	1
Meniscal allograft transplantation	1
Anterior cruciate ligament reconstruction	1
None	7

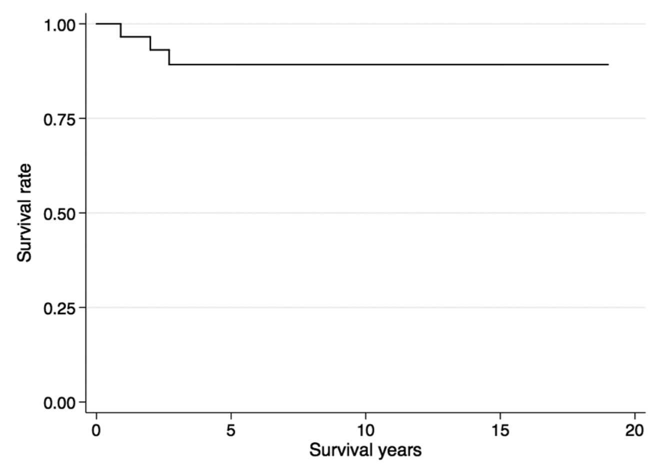

Figure 2. Kaplan-Meier survival curve. The end point was defined as graft failure.

Survival Analysis

Among knees undergoing ACI, survival was 89% (95% CI, 70%-96%) at both 5 and 10 years (Figure 2).

Functional Outcomes and Patient Satisfaction

In all 29 knees, patients demonstrated significant improvements for all functional scores (Table 4). Furthermore, we performed a subanalysis to evaluate differences between specific groups according to sex, number of cartilage lesions, size of the lesions, status of the physis, and whether combined osteotomy was performed. The only significant differences noted were an improvement in the VAS score for female patients and the mental component summary (MCS) of the SF-36 for the open distal physis group.

At the latest follow-up, most patients exhibited satisfaction with the procedure and rated the results of the surgery as good to excellent. With the exception of only 1 patient, all patients reported that their knee was better than before surgery, and all patients suggested that they

TABLE 4
Preoperative and Final Follow-up Clinical Outcomes[a]

Outcome Measure	Preoperative	Final Follow-up	*P* Value
Modified Cincinnati Knee Rating Scale	3.7 ± 1.6	6.8 ± 1.4	<.001
VAS	6.5 ± 1.5	3.0 ± 1.7	<.001
WOMAC			
Total	46.5 ± 15.3	18.6 ± 10.8	<.001
Pain	10.4 ± 3.4	4.4 ± 2.3	<.001
Stiffness	4.7 ± 1.7	2.0 ± 1.5	<.001
Function	31.4 ± 11.8	12.1 ± 8.0	<.001
SF-36			
PCS	35.6 ± 6.0	50.5 ± 6.4	<.001
MCS	47.0 ± 6.6	53.2 ± 6.2	<.001

[a]Data are reported as mean ± SD. MCS, mental component summary; PCS, physical component summary; SF-36, Short Form 36; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

TABLE 5
Satisfaction With the Procedure at Final Follow-up (N = 29 Knees)

Question	n
Compared with before surgery, how would you rate the operated joint now?	
Better	28
About the same	0
Worse	1
What is your overall satisfaction level with the joint surgery?	
Satisfied	26
Neutral	3
Dissatisfied	0
If you could go back in time and make the decision again, would you choose to undergo your joint surgery?	
Yes	29
Uncertain	0
No	0
How would you rate the results of your joint surgery?	
Good/excellent	27
Fair	2
Poor	0

would choose to undergo this procedure again if they could go back in time (Table 5).

Radiographic Outcomes

Of 26 successful knees, 12 were available for radiographic evaluation at a mean of 5.6 ± 3.0 years (range, 2-11 years) postoperatively. There was no significant difference in the level of OA, based on K-L grading, before and after surgery (0.3 ± 0.5 preoperatively and 0.4 ± 0.5 postoperatively; P = .16). Of the 12 knees evaluated, the K-L grade exhibited no increase in 10, while the remaining 2 knees had a 1-point increase (Table 6).

Of the 3 knees exhibiting failure, 2 were available for radiographic evaluation. Based on K-L grading, an increase of 1 and 2 points was observed postoperatively at 3 and 11.5 years, respectively.

Subsequent Surgical Procedures

A total of 20 knees required 29 subsequent surgical procedures. The most common requirements for subsequent surgery were related to the periosteum-covered ACI graft (n = 10), including 5 for periosteal hypertrophy, 3 for periosteal delamination, and 2 for partial graft delamination (Table 7). Non–graft-related reasons for subsequent surgery included arthrofibrosis in 7 knees, painful hardware in 3, arthroscopic assessment in 2, distal femoral osteotomy in 1, removal of a loose body in 1, partial meniscectomy in 1, and compartment syndrome in 1. Overall, 79% of subsequent surgical procedures were performed arthroscopically. Four patients (5 bipolar lesions) required a mean of 1.2 subsequent surgical procedures; in these 4 patients, subsequent surgery was effective, with no failure observed. Three of the 20 knees requiring subsequent surgery proceeded to become failures.

Failures

A total of 3 knees had failures within the study interval. The mean time to failure after the index surgery was 1.9 years (range, 0.9-2.7 years). The first patient, with OCD in the lateral femoral condyle (LFC), exhibited failure at 2 years after the index surgery because of delamination of the graft; before the failure, the patient had returned to all activities without significant discomfort. Autologous cancellous chip bone grafting without chondrocyte implantation[23] was performed with removal of the sclerotic bone, and the patient was able to return to all activities. The second patient with OCD in the LFC exhibited failure at 11 months after surgery. Notably, the patient reported no pain, but joint effusion was observed after surgery. Because of delamination of the graft, the patient underwent revision surgery, during which autologous cancellous chip bone grafting without chondrocyte implantation[23] was performed to restore the subchondral bone and promote repair of the fibrocartilage surface. The third patient, with chondral lesions of the medial femoral condyle (MFC) and trochlea, was observed to have moderate genu varum but refused to undergo primary realignment. He

TABLE 6
Radiographic Evaluation After ACI[a]

Knee	Age, y	Sex	Size of Cartilage Lesion, cm^2	Site of Cartilage Lesion	Concurrent Surgery	K-L Grade, Preoperative/Postoperative	Radiographic Follow-up Time, y
1	13	Male	3.25	LTP	None	0/1	7.5
2	14	Male	2.38	LTP	None	0/0	7.0
3	15	Female	3	Patella	TTO	0/0	7.8
4	16	Female	6.6	LFC	TTO	0/1	9.2
5	16	Male	4	Trochlea	Sandwich	0/0	2
6	16	Female	3.96	LFC	TTO	1/1	2.5
7	16	Female	6	LFC, LTP	TTO, DFO, MAT	0/0	6.3
8	17	Female	2	LTP	DFO	1/1	11
9	17	Male	10	MFC	Sandwich	0/0	4.7
10	17	Female	3.75	Patella	TTO	0/0	4.3
11	17	Male	7	LFC	None	0/0	3.0
12	17	Male	8.11	MFC, LFC, patella	TTO	1/1	2.2

[a]ACI, autologous chondrocyte implantation; DFO, distal femoral osteotomy; K-L, Kellgren-Lawrence; LFC, lateral femoral condyle; LTP, lateral tibial plateau; MAT, meniscal allograft transplantation; MFC, medial femoral condyle; TTO, tibial tubercle osteotomy.

TABLE 7
Subsequent Surgical Procedures Related and Unrelated to the ACI Graft (Periosteum vs Bio-Gide)[a]

	Related to ACI Graft		Unrelated to ACI Graft	
	n	Timing Postoperatively, mo	n	Timing Postoperatively, mo
Periosteum (16 knees)	10	17.1 (5.7-35.5)	8	29.0 (2.1-76.1)
Bio-Gide (13 knees)	3	19.8 (12.3-27.6)	8	14.3 (0.1-50.5)
Total	13	16.9	16	21.6

[a]Postoperative timing of subsequent procedures is reported as mean (range). ACI, autologous chondrocyte implantation.

returned to high-impact activities after ACI of the MFC and trochlea but complained of recurrent symptoms with athletic activities. Consequently, the patient underwent high tibial osteotomy and OAT for the MFC lesion at 2.7 years postoperatively. All patients underwent autologous biological reconstruction for graft failure and did not require an allograft or prosthesis and continue to do well.

DISCUSSION

In this review of a prospectively collected data set, we analyzed data from 27 patients (29 knees) aged <18 years who underwent ACI for symptomatic articular cartilage lesions of the knee joint. Our results showed an 89% survival rate at both 5 and 10 years postoperatively and significant improvement in all clinical outcomes. Importantly, long-term patient satisfaction was encouraging, with very high satisfaction observed at a mean of 9.6 years postoperatively. Additionally, our results demonstrated that ACI might prevent the progression to OA in 12 of 29 knees that had follow-up repeat radiographs (with a minimum of 2 years postoperatively), with no significant changes in K-L grading noted on the radiological evaluation at a mean of 5.6 years postoperatively. As far as we are aware, this study is the longest follow-up study of cartilage repair in an adolescent population treated with ACI. Those patients who had primary failures of their ACI were managed by joint-preserving autologous reconstruction, which is critical in this young population for whom prosthetic arthroplasty is not an option.

The results of our study were consistent with those of previous studies that have shown significant clinical improvements in adolescent patients after ACI. However, the majority of the literature is limited to intermediate-term follow-up durations without postoperative radiological evaluations. For example, Micheli et al[37] reported that 28 of 32 patients with articular cartilage defects of the distal femoral condyle showed significant clinical improvement at an average of 4.3 years postoperatively. Mithöfer et al[47] observed that 96% of adolescent athletes reported good or excellent clinical results at an average of 3.9 years postoperatively. Similarly, Macmull et al[33] reported that 84% of pediatric and adolescent patients achieved excellent or good clinical results at an average of 5.5 years postoperatively. Our observations were comparable with these studies but were obtained over a much longer follow-up period. Moreover, the radiographic evaluation indicated that ACI might be effective in preventing OA progression, although larger sample sizes will be necessary to accurately assess and validate this observation. Conversely, the rate of knees requiring subsequent surgery in our study was higher (69%) than in previous studies (up to 20%). The relatively high rate of subsequent surgery noted in this study is likely because of the use of periosteum in treating multiple large defects. However, it is difficult to directly compare these results, as our study was performed over a substantially longer follow-up period and included patients with larger lesions; a longer, chronic preoperative symptomatic presentation; higher rates of multiple, bipolar, and patellofemoral lesions; and greater rates of concurrent procedures. It is possible that the rate of concurrent procedures in this study is related to our surgical preference for addressing background factors, such as malalignment and maltracking, as a means of biologically reconstructing an environment in which optimal clinical outcomes can be achieved. Despite a relatively high rate of subsequent surgical procedures, all patients noted that they would choose to undergo this procedure again, and approximately 90% of patients were satisfied with the procedure at the last follow-up. It is possible that the high rate of satisfaction, despite the high rate of subsequent surgery, is related to the use of arthroscopic surgery in the majority of secondary procedures, which generally has short operative times, has low surgical morbidity, has a relatively low cost, and requires only a limited amount of time before the patient can return to daily activities. Notably, most of the subsequent surgical procedures that were related to grafts were associated with periosteal hypertrophy and had a quick resolution of symptoms from graft hypertrophy. Given the fact that the type I/III collagen membrane exhibited a lower reoperation rate than the periosteum patch,[14] future studies should examine the use of collagen membranes with respect to reoperative rates in a similar population with a larger sample size.

Several studies have shown that ACI provides effective and durable long-term outcomes in the general population. Compared with results from a previous study using the same indications and procedure for ACI in the general population,[43] the survivorship rate noted in adolescent patients in this study was superior. This finding may be explained by previous basic research regarding the difference in cell quality and response to growth factors between pediatric and adult patients. Schmal et al[57] have previously noted an age-specific difference in chondrocytes that may account for the differences in survivorship noted when comparing this study to the literature. In the Schmal et al[57] study, a correlation analysis in all patients younger than 30 years revealed statistically significant associations between age and aggrecan or collagen type II (Col-2) expression after incubation in alginate beads. In addition to this observation, a different study demonstrated that Col-2 and CD44 expression, as well as cell viability before implantation, are related to clinical outcomes after ACI.[50] Therefore, when considered together, these studies suggest that improved survivorship in our study population can be explained by the relatively high quality of implanted chondrocytes, especially with respect to Col-2 expression. Additionally, the healing potential of our study population should be noted. A number of studies have shown that anabolic growth factors are integral to regulating the synthetic activity of chondrocytes. With aging, however, the response of chondrocytes to growth factors, such as insulin-like growth factor 1 (IGF-1),[32,34,35] osteogenic protein 1 (OP-1), bone morphogenetic protein 7 (BMP-7),[10] or transforming growth factor β (TGF-β), decreases.[3,56] Therefore, stronger responses to anabolic growth factors in pediatric and adolescent patients may be advantageous in the cartilage repair process.

When examining differences in clinical outcome measures, no significant differences were noted according to sex, cartilage defect size (<6 cm^2 vs >6 cm^2), number of cartilage lesions (single vs multiple), status of the distal femoral physis (open vs closed), type of injury (traumatic vs OCD), or presence of combined osteotomy. Significant differences were, however, noted according to female sex and the presence of open physes, with improvements in the VAS score and MCS, respectively. On closer examination of the data, however, female patients exhibited a significantly higher VAS score preoperatively than male patients; this may be responsible for the VAS score observed postoperatively. Similarly, the open physis group had a significantly lower MCS preoperatively, which again facilitated larger improvement in the MCS postoperatively. Notably, the observations regarding physeal status were in agreement with those of a previous study,[47] which suggested that skeletal maturity, as defined by the closure of the epiphyses at approximately 15 years of age, is not always consistent with cartilage maturity and healing potential. Recent research by Schmal et al[57] suggests that the age border between juveniles and adults, with respect to cartilage maturity, is approximately 20 years old.

Alternative procedures for articular cartilage lesions have previously been examined according to clinical outcomes, with varying results. Steadman et al[59] examined outcomes of microfracture treatment in patients aged 12 to 18 years, with an average follow-up of 5.8 years. They reported increased activity and excellent function based on the Lysholm score and Tegner activity scale. However, the mean size of lesions in their study was substantially smaller (mean size of MFC/LFC: 177/188 mm^2; mean size of patellofemoral: 209 mm^2) than in our study (mean size of MFC/LFC: 427/606 mm^2; mean size of patellofemoral: 379 mm^2). Moreover, further long-term research is required, as a number of other studies have shown that results from microfracture deteriorate over time in both physically active adults and immature children.[16,29,46] Gudas et al[17] performed a prospective randomized study of arthroscopic mosaic-type OAT against microfracture for the treatment of OCD (2-4 cm^2) of the femoral condyle in children aged 12 to 18 years, with an average of 4.2 years of follow-up. Their results showed significant superiority of OAT over microfracture; however, both procedures were associated with significant clinical improvement when compared with the preoperative evaluation. A total of 83% of patients in the OAT group reported excellent or good results, compared with 63% in the microfracture group, at 4.2 years postoperatively. A long-term follow-up study remains necessary to determine the durability of OAT and the disability of the harvest site in this population. In addition, the outcomes associated with OAT for larger lesions remain unknown. Recently, Murphy et al[48] reported the results of osteochondral allograft transplantation in pediatric patients. Similar to the results observed in this study, they noted a survivorship rate of 93% at 5 years and 90% at 10 years and improvement in clinical outcomes at an average of 8.4 years postoperatively. However, it should be noted that the majority of lesions included in the study by Murphy et al[48] were single lesions of the femoral condyle, and a recent systematic review by Chahal et al[9] has suggested that osteochondral allografts for patellofemoral lesions are associated with poorer results than those for tibiofemoral lesions. This inferiority is probably caused by the anatomic complexity of the patellofemoral joint. Even considering the greater rate of patellofemoral lesions in our study, our results are comparable with those of Murphy et al.[48] Further investigation, with a larger patient cohort and more specific control of the lesion size and location, will facilitate stronger recommendations regarding the optimal treatment in this population.

Additionally, it is necessary to consider the costs and morbidity associated with ACI. ACI requires a significantly longer postoperative period for recovery than do microfracture and OAT (up to 18 months).[18] However, it should be noted that several studies have shown that improvements in pain and functional scores after ACI have better longevity than other techniques, especially in athlete populations, which are likely to constitute the best representation of adolescent populations with respect to relative activity levels.[8,12,27,58] Moreover, it has been noted that ACI is a more expensive procedure than other cartilage repair procedures. However, the long-term cost-effectiveness of ACI has been described in several studies.[11,30,38]

A number of limitations must be noted in this study. First, there was no control or alternative treatment group. Ideally, a randomized controlled study should be conducted; however, the inclusion of patients younger than 18 years in controlled trials is not routinely recommended because of the legal and practical implications related to the consent process and the ethical treatment of minors.[45] Second, a limited number of failures made it difficult to determine the predictors of failure. A more rigorous subanalysis would be possible with a larger patient cohort. Finally, it was not possible to obtain radiographs from all patients at the last follow-up.

CONCLUSION

Our study has demonstrated that ACI for the treatment of chondral and osteochondral lesions in adolescent patients provides reliable clinical outcomes with significant improvements in function, pain, and mental health. Furthermore, over a mean 9.6-year follow-up, the graft survival rate was 89% at 5 and 10 years, indicating favorable durability. Very high patient satisfaction rates were noted over the long-term follow-up; however, the rate of subsequent surgical procedures was relatively high primarily because of the use of periosteum, which should be a primary concern when discussing ACI for articular cartilage lesions with patients and their parents.

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