Autologous Chondrocyte Implantation Improves Knee-Specific Functional Outcomes and Health-Related Quality of Life in Adolescent Patients

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Autologous Chondrocyte Implantation Improves Knee-Specific Functional Outcomes and Health-Related Quality of Life in Adolescent Patients

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Background: Existing studies of autologous chondrocyte implantation (ACI) in adolescent patients have primarily reported outcomes that have not been validated for cartilage repair and have failed to include measures of general health or health-related quality of life.

Purpose: This study assesses validated knee-specific functional outcomes and health-related quality of life after ACI in adolescent patients.

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

Methods: Patients younger than 18 years who underwent ACI between 1999 and 2011 with a minimum 2-year clinical follow-up were identified from a prospectively collected database. A total of 37 patients were included in the analysis. Patient demographic data and pre- and postoperative functional outcomes scores were collected and chondral lesion characteristics were assessed. Primary outcome measures were the International Knee Documentation Committee (IKDC) subjective score and the Knee Injury and Osteoarthritis Outcome Score–Quality of Life (KOOS-QOL) subscore; secondary outcome measures were Short Form–12 (SF-12) and other KOOS subscores. In subgroup analyses, we assessed whether primary outcome results differed based on lesion location, concurrent meniscal allograft transplantation (MAT), and subsequent surgery after ACI.

Results: Study patients had a mean 4.6 ± 2.4 years of follow-up, a mean age of 16.7 ± 1.5 years, and a mean lesion size of 4.0 ± 2.2 cm². The IKDC subjective score improved from 34.9 preoperatively to 64.6 postoperatively (mean improvement, 29.7 points [95% CI, 20.7 to 38.7 points]; P < .001) and the KOOS-QOL subscore improved from 24.3 to 55.3 (mean improvement, 31.0 points [95% CI, 21.3 to 40.7 points]; P < .001) at final follow-up. All other KOOS subscales and the SF-12 physical component score also showed significant improvements (P < .008 in all cases), whereas the SF-12 mental component score showed no improvement (P = .464). There was a 37.8% rate of subsequent surgery after ACI (most commonly, chondral debridement [54%], meniscectomy [11%], microfracture [9%], and loose body removal [9%]). Subgroup analysis showed no effect of lesion location, concurrent MAT, or subsequent surgery on improvement in IKDC subjective scores and KOOS-QOL subscores (P > .05 in all cases).

Conclusion: ACI is an effective treatment for adolescent patients with symptomatic, large chondral lesions, resulting in significant improvements in knee-specific functional outcome scores and health-related quality of life scores. Although patients must be cautioned on the relatively high reoperation rate (37.8%) and limitations in knee function even after ACI, all patients in this study exhibited improvements over preoperative knee function at the most recent follow-up regardless of ACI location, concurrent MAT, or subsequent surgery.

Keywords: autologous chondrocyte implantation; pediatric; adolescent; chondral lesion

Articular cartilage lesions in pediatric and adolescent patients can result from acute chondral injury as a result of knee trauma or from osteochondritis dissecans (OCD) lesions.19-21,25 Chondral injuries are relatively common in pediatric and adolescent patients, but these lesions may be unrecognized or diagnosed in a delayed fashion.21 Patients with articular cartilage lesions often have symptoms that significantly impair their quality of life and ability to participate in athletic activities.10 If nonoperative treatment fails, surgical options include drilling or fixation (for OCD lesions), microfracture, autologous chondrocyte implantation (ACI), or osteochondral grafts.8,16 ACI has been established as a reliable option...
to relieve pain and improve functional outcomes in adult patients with symptomatic chondral lesions of the knee.\textsuperscript{3,4} It has been proposed that results of ACI may be superior in pediatric and adolescent patients compared with their adult counterparts.\textsuperscript{6,14} However, only a few studies to date report on the outcomes of ACI in pediatric and adolescent patients.\textsuperscript{14,17,19,20}

Although the early results of ACI in patients younger than 18 years demonstrated 88% to 96% good or excellent results,\textsuperscript{14,17,18,29} existing studies primarily reported either clinical outcomes or functional scores that have not been validated in the setting of cartilage repair.\textsuperscript{1,2,7,13,24} Most studies have not included general measures of health or measures of health-related quality of life. Use of validated outcomes and health-related quality of life scores is important to demonstrate whether surgical interventions are successful, and these outcomes are important to insurers and hospitals considering the economic aspects of various treatment options. In 2011, the International Cartilage Repair Society (ICRS) published recommendations for patient-moment options. In 2011, the International Cartilage Repair Society (ICRS) published recommendations for patient-reported outcomes to provide validated outcomes in patients with articular cartilage lesions undergoing cartilage repair procedures.\textsuperscript{24} It recommended use of the International Knee Documentation Committee (IKDC) subjective score and the Knee Injury and Osteoarthritis and Outcome Score (KOOS) as primary outcome scores and a general measure of health as an additional outcome to assess the overall benefit to the patient’s health from cartilage repair.\textsuperscript{1,24}

This study analyzed functional outcome scores validated for cartilage repair and health-related quality of life scores after ACI in adolescent patients. In subgroup analyses, we determined whether lesion location, concurrent meniscal allograft transplantation (MAT), and subsequent procedures after ACI would affect final outcome scores. Our hypothesis was that adolescent patients would experience improvements in both validated knee-specific functional scores and health-related quality of life scores after ACI.

METHODS

Patient Selection and Inclusion/Exclusion Criteria

After institutional review board approval was received for this study, all patients younger than 18 years who were clinically indicated for ACI between 1999 and 2011 with a minimum 2-year clinical follow-up were identified from a prospectively collected database. Inclusion criteria were age younger than 18 years at the time of ACI surgery and a minimum of 2 years of clinical follow-up. During the study period, 49 ACIs were performed in patients younger than 18 years, and 37 patients were available for a minimum 2-year clinical follow-up (75.5%). Informed consent to participate was provided from the legal guardians of all patients.

ACI was indicated for symptomatic grade 4 cartilage lesions of the femoral condyle, trochlea, or patella. Contraindications included subchondral bone loss (treated with osteochondral grafting instead), osteoarthritic changes, inflammatory arthritis, and patient inability to adhere to the postoperative rehabilitation program. Any malalignment or ligamentous insufficiency was addressed at the time of cartilage repair.

Outcome Assessment

Patient demographic data were collected, including age, sex, body mass index, site of chondral lesion, size of chondral lesion, prior knee surgeries, and concomitant knee injuries and procedures performed. A standard clinical examination was performed and functional outcome scores were collected preoperatively and postoperatively at final follow-up. The functional outcome scores utilized were the KOOS, the IKDC subjective form, and Short Form—12 (SF-12). Primary outcome scores were the IKDC subjective score and the Knee Injury and Osteoarthritis Outcome Score—Quality of Life (KOS-QOL) subscore. Secondary outcomes were the SF-12 and other KOOS subscores. Subsequent knee surgeries after the index ACI were also recorded.

Surgical Technique

ACI and postoperative rehabilitation was performed similarly to previous publications.\textsuperscript{15,22} Diagnostic arthroscopy was performed, and 100 to 200 mg of articular cartilage was harvested from the intercondylar notch. Cartilage processing was performed by Genzyme, resulting in isolation and expansion of chondrocytes. At the second surgery for implantation, the cartilage lesion was identified and was carefully debrided with curettes to create vertical walls and remove the calcified cartilage. The lesion size was measured. A periosteal patch was harvested from the anteromedial tibia to match the lesion size, or a synthetic type I/III collagen membrane (off-label usage) was sized to the defect. The periosteal patch or type I/III membrane was sutured to the walls of the lesion using interrupted 6-0 Vicryl (Ethicon) and sealed with fibrin glue (Baxter) in a watertight fashion. Chondrocytes were then injected beneath the patch.

Postoperative Rehabilitation

Patients wore a hinged knee brace locked in full extension, weightbearing as tolerated for 6 weeks for isolated treatment of patellofemoral lesions and nonweightbearing for...
condylar lesions or patellofemoral lesions performed with a concomitant tibial tubercle osteotomy. Knee range of motion began with continuous passive motion on postoperative day 1 for 6 to 8 hours per day; patients began at 0° to 30° and progressed with flexion of 5° per day. Flexion to 90° was obtained by 4 to 6 weeks. Gentle isometric strengthening began at 2 to 4 weeks. Active range of motion progressing to full range of motion and full weight-bearing occurred at 7 to 12 weeks. At 12 to 16 weeks after surgery, functional activities progressed. Return to running and high-impact activities was permitted at 12 to 16 months depending on symptom reduction.

Statistical Analysis

Descriptive statistics were calculated to summarize patient demographic variables, with means and standard deviation for continuous variables and frequencies with percentages for categorical variables. For the primary analysis, data for continuous variables and frequencies with percentages were used for between-group comparisons. One-way analysis of variance, Fisher exact tests, and unpaired Student t tests were used as appropriate to compare the groups.

For the first subgroup analysis, 3 patient groups were retrospectively defined: (1) patellofemoral ACI with or without a concurrent realignment procedure (PF-ACI group), (2) femoral condyle ACI alone (condyle-ACI group), and (3) femoral condyle ACI with concurrent MAT (MAT-ACI group). Preoperative and final follow-up scores within each group were compared with paired t tests. Functional score improvements from preoperative to final follow-up were used for between-group comparisons. One-way analysis of variance, Fisher exact tests, and unpaired Student t tests were used as appropriate to compare the groups.

For the second subgroup analysis, 2 groups were defined based on whether patients had subsequent surgery after ACI or not. Unpaired Student t tests were used as appropriate to compare the groups.

A significance level of \( P < .05 \) was used in all cases. JMP Pro 12 software (SAS Institute Inc) was used for statistical analysis.

RESULTS

Patient Demographics and Chondral Lesion Characteristics

A total of 37 patients were analyzed, with a mean age of 16.7 ± 1.5 years (range, 13-18 years) at the time of ACI and mean follow-up of 4.6 ± 2.4 years (minimum, 2 years; range, 2.0-10.6 years). Table 1 summarizes chondral lesion characteristics, concomitant procedures, and patient demographics. There were 15 male patients (40.5%). Concomitant procedures were performed in 22 of 37 patients (59.5%). Open physes were present on preoperative knee radiographs from 6 of 37 patients (16.2%). Lesion size averaged 2.2 cm². All patients underwent prior knee surgery, with an average of 2.1 ± 0.9 prior procedures (range, 1-3) (Table 2). The time from ACI biopsy to implantation was 0.8 ± 0.7 years. A periosteal patch was used in 25 of 37 patients (67.6%), and collagen membrane was used in the remaining 12 patients (32.4%).

Clinical Outcomes

There were significant improvements from preoperative to final follow-up for knee-specific and health-related quality of life scores for the adolescent patients undergoing ACI (Table 3). For the primary outcome scores, the IKDC subjective score improved from 34.9 preoperatively to 64.9 postoperatively (mean improvement, 29.7 points [95% CI, 20.7 to 38.7 points]; \( P < .001 \)) and KOOS-QOL subscores
improved from 24.3 to 55.3 (mean improvement, 31.0 points [95% CI, 21.3 to 40.7 points]; P < .001). For secondary outcomes, all other KOOS subscales and the SF-12 physical component showed significant improvements (P < .008 in all cases), whereas the SF-12 mental component showing no improvement (P = .464) (Table 3). There were no differences in outcome scores between periosteal and collagen membrane ACI groups (P = .230 in all cases).

Fourteen of the 37 patients (37.8%) underwent subsequent surgery after ACI by the time of final follow-up. There were 24 procedures performed in these 14 patients, with some patients having more than 1 surgery (most commonly, debridement [54%], meniscectomy [11%], microfracture [9%], and loose body removal [9%]) (Table 4). The majority of surgeries were related to the prior ACI, including debridement or conversion to an osteochondral allograft (14 of 24; 58.3%). There was no difference in reoperation rate between periosteal and collagen membrane ACI groups (P = .721).

Subgroup Analysis by Lesion Location and Concurrent MAT

Eleven patients underwent ACI of the medial or lateral femoral condyle without MAT (condyle-ACI group), 14 underwent patellofemoral ACI (PF-ACI group), and 12 underwent ACI of the medial or lateral condyle with concurrent MAT (MAT-ACI group). There were no significant between-cohort differences in patient demographics, lesion size, or prior procedures (P > .05). Lesion location and concurrent procedures differed among groups (as expected based on the definition of the retrospective cohorts), and the majority of patients in the PF-ACI group underwent concomitant realignment (i.e., tibial tubercle osteotomy) procedures (P < .001). Of the 14 patients in the PF-ACI group, 9 underwent concurrent tibial tubercle osteotomy (TTO) with anteromedialization, 2 underwent medial patellofemoral ligament reconstruction, and 2 of the TTO patients also underwent lateral release.

### Table 3

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean Preoperative Score</th>
<th>Mean Final Follow-up Score</th>
<th>Mean Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IKDC subjective score</td>
<td>34.9</td>
<td>64.6</td>
<td>29.7 (20.7 to 38.7)</td>
<td>&lt;.001</td>
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<tr>
<td>KOOS-QOL subscore</td>
<td>24.3</td>
<td>55.3</td>
<td>31.0 (21.3 to 40.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF-12 score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical</td>
<td>36.6</td>
<td>42.9</td>
<td>6.3 (1.9 to 10.7)</td>
<td>.008</td>
</tr>
<tr>
<td>Mental</td>
<td>52.9</td>
<td>55.7</td>
<td>2.7 (–4.9 to 10.4)</td>
<td>.464</td>
</tr>
<tr>
<td>KOOS subscore</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>62.0</td>
<td>78.2</td>
<td>16.2 (6.5 to 25.9)</td>
<td>.002</td>
</tr>
<tr>
<td>Symptoms</td>
<td>57.0</td>
<td>73.6</td>
<td>16.6 (7.2 to 25.9)</td>
<td>.001</td>
</tr>
<tr>
<td>ADL</td>
<td>74.4</td>
<td>87.9</td>
<td>13.4 (5.5 to 20.9)</td>
<td>.001</td>
</tr>
<tr>
<td>Sports and recreation</td>
<td>27.0</td>
<td>61.0</td>
<td>34.0 (25.4 to 42.6)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

**ADL,** activities of daily living; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; KOOS-QOL, Knee Injury and Osteoarthritis Outcome Score–Quality of Life subscore; SF-12, Short Form–12.

### Table 4

Subsequent Procedures Performed After Autologous Chondrocyte Implantation in Adolescent Patients

<table>
<thead>
<tr>
<th>Procedure</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Debridement</td>
<td>19 (54.3)</td>
</tr>
<tr>
<td>Meniscectomy</td>
<td>4 (11.4)</td>
</tr>
<tr>
<td>Microfracture</td>
<td>3 (8.6)</td>
</tr>
<tr>
<td>Loose body removal</td>
<td>3 (8.6)</td>
</tr>
<tr>
<td>Meniscal repair</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Lateral release</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Medial patellofemoral ligament reconstruction</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Osteochondral allograft</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Revision autologous chondrocyte implantation</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Total procedures</td>
<td>35 (100.0)</td>
</tr>
<tr>
<td>Distinct surgeries</td>
<td>24</td>
</tr>
</tbody>
</table>

All 3 groups demonstrated significant improvements in IKDC subjective scores and KOOS-QOL subscores from preoperative to final follow-up (P < .022 in all cases) (Table 5). There were no differences in the amount of primary outcome score improvement between groups (P = .670 for IKDC subjective scores, P = .446 for KOOS-QOL subscores). The rate of subsequent surgery was 54.5% (6 of 11) in the condyle-ACI group, 25.0% (3 of 12) in the MAT-ACI group, and 35.7% (5 of 14) in the PF-ACI group (P = .361).

Subgroup Analysis by Subsequent Surgery

Comparisons of the 14 patients who underwent subsequent surgery after ACI to the 23 who did not show any differences in patient demographics, lesion location, or concurrent surgeries. Patients who did and did not go on to have subsequent surgery both revealed significant improvements in their primary outcome scores from preoperative to final follow-up (P < .017 for IKDC subjective scores and KOOS-QOL subscores in all cases) (Table 6). There was no difference in improvement in primary outcome scores for the
groups who did and did not undergo subsequent surgery ($P = .399$ for IKDC subjective scores; $P = .219$ for KOOS-QOL subscores).

### DISCUSSION

We found that ACI was an effective treatment for adolescent patients with symptomatic, large chondral lesions, resulting in significant improvements in knee-specific functional outcome scores and health-related quality of life scores regardless of ACI location, concurrent MAT, and subsequent surgery.

There are several small series reporting outcomes of ACI in pediatric and adolescent patients, which have shown high rates of good and excellent results. Mithöfer et al\(^{18}\) reported the initial series of ACI in 20 patients with a mean age of 15.9 years (range, 12-18 years), with 96% good or excellent outcomes and increases in outcome scores at approximately 4 years of follow-up, including a Lysholm score increase from 64 to 87. In their series, 20% of patients went on to further surgery, and only 60% of pediatric patients undergoing ACI returned to their previous level of sports participation. Micheli et al\(^{17}\) reported a registry-based multicenter study of 37 patients with a mean age of 16 years (range, 11-17 years) who underwent ACI, showing 88% favorable outcome at a minimum 2-year follow-up and significant improvement in modified Cincinnati Knee Rating System scores. The reoperation rate was 19%. They also reported that patients with follow-up longer than 4 years had improved results compared with those with only 2- to 4-year follow-up. Teo et al\(^{29}\) reviewed ACI in patients younger than 21 years with patellar OCD, showing improved outcome scores at 2-year follow-up with IKDC scores improving from 45 to 75 and Lysholm scores improving from 50 to 70. Macmull et al\(^{14}\) reported a series of 31 patients with a mean age of 16.3 years (range, 14-18 years) and a mean follow-up of 66.3 months, showing 84% good or excellent results and an improved visual analog scale pain score, Bentley Functional Rating Score, and modified Cincinnati Rating...
have suggested that MAT may be chondroprotective,11,12 the primary strength of our results is that they corroborate prior reports that ACI in the adolescent setting results in robust clinical improvements, while using high-level outcome metrics that provide sound evidence for the clinical utility of ACI in adolescents, and they offer justification for use and reimbursement of this technique in this age group. The minimal clinically important difference (MCID) for the IKDC subjective score is 16.7 points for articular cartilage defects; although the MCID for the KOOS-QOL subscore has not been established for articular cartilage defects, it is 8 to 10 points for osteoarthritis and anterior cruciate ligament tears.5,25,28 Our patients experienced average improvements of 29.7 for IKDC subjective scores and 31.0 for KOOS-QOL subscores, indicating that the improvements after ACI in adolescent patients were both statistically significant and clinically meaningful.

Despite these clinical results, we found a higher rate of subsequent procedures compared with prior reports, with 37.8% of our patients undergoing further surgery by the final follow-up. The differences could relate to differing indications for ACI between studies or differences in complexity of concomitant injuries in our series, given the much higher rate of concomitant MAT compared with the prior literature. This is likely related to the tertiary referral practice of the senior surgeon that includes patients meeting indications for MAT.

In subgroup analysis, we found that the IKDC and KOOS-QOL were significantly improved regardless of lesion location and concurrent MAT. In addition, patients who went on to subsequent surgery after ACI also had significant improvements in final follow-up scores. Reports of combined ACI and MAT in adult patients also demonstrate improved function but carry a relatively high rate of reoperation.8,27 There are mixed results on whether combined ACI and MAT is similar to or inferior to either procedure in isolation.4,27 Before our study, there were no reports of combined ACI and MAT in the adolescent population. Our findings for combined ACI and MAT in adolescent patients are in agreement with a study by Rue et al27 in adult patients, suggesting that results are comparable with either procedure in isolation. Theoretically, the simultaneous MAT in a patient with meniscal deficiency could protect the con- dylar ACI as the cartilage matures after surgery. Biomechanical data on contact mechanics and animal models have suggested that MAT may be chondroprotective,11,12 but clinical studies have not demonstrated a chondroprotective effect of MAT in patients.26

This study has several limitations. Our series has a small number of patients because ACI is not commonly performed in adolescents, which limits power especially for the subgroup analyses. Post hoc power analyses revealed power of 0.3 or lower to detect differences in reoperation rate and the primary outcome scores (IKDC subjective and KOOS-QOL) between the subgroups analyzed. Although the difference in mean IKDC subjective scores (between 56.1 for those with subsequent procedures and 71.6 for those without) was not statistically significant given the numbers of available patients, it is potentially clinically important. The patients are heterogeneous on multiple factors, including lesion location, prior procedures, patient demographics, and concurrent procedures. This makes drawing detailed conclusions about all factors involved in ACI outcomes difficult. We have summarized these factors as well as performed subgroup analyses to partly account for the heterogeneity. Direct comparison of outcomes to the previous literature of adolescent ACI is not possible because of differing outcome scores. In addition, the majority of patients in our study required concomitant procedures that may confound interpretation of the isolated outcome of the ACI portion of the procedure. Previous reports of ACI in pediatric and adolescent patients also have confounding concomitant procedures,14,17,18,29 although the types of concomitant procedures differed from previous reports with a higher rate of MAT in our series. We attempted to account for this by performing a subgroup analysis showing no difference in the primary outcome scores regardless of concurrent MAT. Our cohort consisted of a mixture of the peristeal patch and collagen membrane ACI techniques, which could contribute to a lack of internal validity. However, we found no difference in outcome scores and reoperation rates between the 2 groups. There is potential for limitation of the external validity of our results, since our procedures were performed at a tertiary referral center with a senior author specializing in complex cartilage restoration cases.

CONCLUSION

ACI is an effective treatment for adolescent patients with symptomatic, large chondral lesions, resulting in significant improvements in knee-specific functional outcome scores and health-related quality of life scores. Although patients must be cautioned on the relatively high reoperation rate (37.8%) and limitations in knee function even after ACI, all patients exhibited improvements over preoperative knee function at the most recent follow-up regardless of ACI location, concurrent MAT, or subsequent surgery.

REFERENCES


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