Microfracture Versus Autologous Chondrocyte Implantation for Articular Cartilage Lesions in the Knee

A Systematic Review of 5-Year Outcomes

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Background: Microfracture (MFx) and autologous chondrocyte implantation (ACI) are 2 surgical treatment options used to treat articular cartilage injuries of the knee joint.

Purpose: To compare the midterm to long-term clinical outcomes of MFx versus ACI for focal chondral defects of the knee.

Study Design: Systematic review.

Methods: A systematic review was performed by searching PubMed, the Cochrane Library, and Embase to locate studies (level of evidence I-III) comparing the minimum average 5-year clinical outcomes of patients undergoing MFx versus ACI. Search terms used were “knee,” “microfracture,” “autologous chondrocyte implantation,” and “autologous chondrocyte transplantation.” Patients were evaluated based on treatment failure rates, magnetic resonance imaging, and patient-reported outcome scores (Lysholm, Knee Injury and Osteoarthritis Outcome Score [KOOS], and Tegner scores).

Results: Five studies (3 level I evidence, 2 level II evidence) were identified that met the inclusion criteria, including a total of 210 patients (211 lesions) undergoing MFx and 189 patients (189 lesions) undergoing ACI. The average follow-up among all studies was 7.0 years. Four studies utilized first-generation, periosteum-based ACI (P-ACI), and 1 study utilized third-generation, matrix-associated ACI (M-ACI). Treatment failure occurred in 18.5% of patients undergoing ACI and 17.1% of patients undergoing MFx ($P = .70$). Lysholm and KOOS scores were found to improve for both groups across studies, without a significant difference in improvement between the groups. The only significant difference in patient-reported outcome scores was found in the 1 study using M-ACI in which Tegner scores improved to a significantly greater extent in the ACI group compared with the MFx group ($P = .003$).

Conclusion: Patients undergoing MFx or first/third-generation ACI for articular cartilage lesions in the knee can be expected to experience improvement in clinical outcomes at midterm to long-term follow-up without any significant difference between the groups.

Keywords: articular cartilage; autologous chondrocyte implantation; microfracture; focal chondral defects

After an injury, articular cartilage has limited to no ability to spontaneously repair largely because of its avascular status. When left untreated, full-thickness chondral defects can lead to degenerative joint symptoms such as pain, swelling, and joint dysfunction. Focal chondral defects (FCDs) that result in pain often necessitate surgical intervention, with a recent Norwegian study citing a national incidence of knee cartilage surgery of 56 per 100,000 person-years. Surgical treatment options include microfracture (MFx), osteochondral autograft/allo graft transplantation, and autologous chondrocyte implantation (ACI). MFx is often considered a first-line treatment option, given the ease and low cost of the procedure as well as the good short-term outcomes demonstrated with this procedure. However, recent evidence has
suggested that the outcomes of MFx of the knee may worsen after 5 years postoperatively, particularly for larger lesions.9,11,24,27 For this reason, it has recently been proposed that ACI be used more frequently as a first-line rather than salvage procedure for FCDs in the knee.12,13,16,26

METHODS

A systematic review of multiple databases was performed. Two independent reviewers searched PubMed, Embase, and the Cochrane Library up to November 8, 2016. The following search phrase was used: “knee AND microfracture AND (“autologous chondrocyte implantation” OR “autologous chondrocyte transplantation”).” A total of 350 studies were reviewed by title and/or abstract to determine study relevance based on inclusion/exclusion criteria. Inclusion criteria included studies that compared the clinical outcomes of ACI and MFx procedures (level of evidence I-III) at an average follow-up of at least 5 years. Studies were excluded if the average follow-up was less than 5 years, if they were nonclinical or noncomparative studies, or if they were studies unrelated to the knee. Five studies met inclusion and exclusion criteria (Figure 1).

Surgical Technique

Autologous Chondrocyte Implantation. Four of the 5 studies12,13,16,26 used first-generation, periosteum-based ACI (P-ACI). This is a 2-procedure process in which the first procedure involves knee arthroscopic surgery with collection of a cartilage biopsy specimen. The location of the biopsy sample was described in only 1 study16 in which the biopsy specimen was taken from the margin of the trochlea. After the culture of autogenous chondrocytes, the second stage of the procedure involves knee arthrotomy for implantation of the expanded chondrocytes. This involves removal of a flap of periosteum from the patient’s tibia and using it to cover the newly implanted chondrocytes. One study14 used third-generation, matrix-associated ACI (M-ACI). This procedure is similar, although rather than using a periosteal patch, chondrocytes were seeded on a hyaluronic acid–based scaffold (Hyaff 11) to obtain the bioengineered tissue Hyalograph C (Fidia Advanced Biopolymers). This graft was positioned within the defect location, where it remained tightly adhered without necessitating fibrin glue or sutures to fix the implant.

Microfracture. One study16 performed MFx with tapered awls with conical drill holes 0.5 to 1 mm in diameter, 4 mm deep, and approximately 3 to 4 mm apart. Holes were made in the lesion starting from the periphery to the lesion’s center. The other 4 studies did not detail their MFx technique.

RESULTS

Of the 5 included studies, all had an average follow-up time of at least 5 years, with an overall average follow-up duration of 7.0 years (Table 1). Two of these studies12,13 included the same cohort of patients at 5 and 14.5 years postoperatively.

A total of 399 patients were included in this systematic review, including 189 lesions treated with ACI and 211 lesions treated with MFx (Table 2). In 1 study,16 a patient with 2 chondral lesions was treated with MFx. All
remaining patients in all studies had 1 lesion treated. Overall, no difference was found in lesion locations between the groups ($P = .78$). Only 1 study$^{14}$ specified that all lesions were found on the weightbearing surface of the medial or lateral femoral condyle or trochlea.

Overall, 17.8% of patients experienced treatment failure, including 18.5% in the ACI group and 17.1% in the MFx group ($P = .70$) (Table 3). No significant difference was found in treatment failure rates between the groups within any particular study. In the 1 study utilizing third-generation ACI,$^{14}$ 0 of 40 lesions treated with ACI experienced failure, and 1 of 40 lesions treated with MFx experienced failure ($P = .31$).

One study$^{12}$ found that, at 5-year follow-up, while both groups reported decreased pain scores using the visual analog scale (VAS) and increased Lysholm scores, neither group improved to a significantly greater extent (VAS: $P = .23$; Lysholm: $P = .28$). At 14.5-year follow-up, Knutsen et al$^{13}$ found that these trends continued in patients who did not experience treatment failure; VAS scores continued to decline from the 5-year to 14.5-year follow-up, while Lysholm scores continued to increase, although no significant difference in the extent of improvement was found between the groups (VAS: $P = .07$; Lysholm: $P = .27$). Likewise, Lim et al$^{16}$ found improvement in Lysholm scores in both groups at a similar rate from preoperatively to the 5-year follow-up ($P = .48$). Vanlauwe et al$^{26}$ used the overall KOOS and found that both treatment groups experienced improvements in scores from preoperatively to the 5-year follow-up. However, neither group improved at a significantly different rate than the other ($P = .12$). Only 1 study,$^{14}$ the only study included in this review that utilized M-ACI, found a statistically significant difference in score improvement between the 2 groups. In this study, Kon et al$^{14}$ found that Tegner scores improved for both groups from preoperatively to the 5-year follow-up, although significantly better improvement was observed in the ACI group compared with the MFx group ($P = .003$). Only 1 study$^{16}$ assessed postoperative MRI. One-year postoperative MRI showed Outerbridge grade 1 or 2 in 80% of knees treated with MFx and 81% of knees treated with ACI ($P = .69$).

**DISCUSSION**

Articular cartilage changes in the knee joint are a common occurrence.$^6$ When symptomatic, FCDs often necessitate surgical treatment. MFx is often considered the first-line surgical treatment option for FCDs,$^1,16,19,29$ with ACI often reserved as a salvage procedure.$^2,3,8,20$

Oussedik et al$^{22}$ recently performed a systematic review comparing the clinical outcomes of MFx versus ACI for articular cartilage lesions in the knee joint. However, this review included studies with all follow-up times (as short as 6 weeks) and noncomparative (level IV evidence) studies. Recent evidence has suggested that the outcomes of MFx of the knee may worsen after 5 years postoperatively, particularly for larger lesions.$^9,11,24,27$ Therefore, the authors of the current systematic review hypothesized that patients undergoing ACI would have significantly better outcomes than patients undergoing MFx at a minimum average follow-up of 5 years.

The results of this systematic review suggest that, at an average follow-up of at least 5 years (overall average, 7.0 years), no significant difference exists consistently in clinical outcomes (treatment failure rates, patient-reported

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**TABLE 1**

<table>
<thead>
<tr>
<th>Study</th>
<th>Level of Evidence</th>
<th>No. of Lesions</th>
<th>Average Patient Age, y</th>
<th>Follow-up, Minimum/Average, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knutsen et al$^{12}$ (2007)</td>
<td>I</td>
<td>80</td>
<td>NR</td>
<td>5/5</td>
</tr>
<tr>
<td>Knutsen et al$^{13}$ (2016)</td>
<td>I</td>
<td>80</td>
<td>NR</td>
<td>14/14.5</td>
</tr>
<tr>
<td>Kon et al$^{14}$ (2009)</td>
<td>II</td>
<td>80</td>
<td>34.8</td>
<td>5/5</td>
</tr>
<tr>
<td>Lim et al$^{16}$ (2012)</td>
<td>II</td>
<td>48</td>
<td>33.5</td>
<td>3/5.7</td>
</tr>
<tr>
<td>Vanlauwe et al$^{26}$ (2011)</td>
<td>I</td>
<td>112</td>
<td>33.8</td>
<td>5/5</td>
</tr>
</tbody>
</table>

$^a$NR, not reported.

**TABLE 2**

<table>
<thead>
<tr>
<th>Study</th>
<th>Lesion Size, Average (Range), cm$^2$</th>
<th>ACI Lesion Location, n</th>
<th>MFx Lesion Location, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knutsen et al$^{12}$ (2007)</td>
<td>4.9 (NR)</td>
<td>MFC: 34; LFC: 6</td>
<td>MFC: 36; LFC: 4</td>
</tr>
<tr>
<td>Knutsen et al$^{13}$ (2016)</td>
<td>4.9 (NR)</td>
<td>MFC: 34; LFC: 6</td>
<td>MFC: 36; LFC: 4</td>
</tr>
<tr>
<td>Kon et al$^{14}$ (2009)</td>
<td>2.4 (1-5)</td>
<td>MFC: 26; LFC: 12; T: 2</td>
<td>MFC: 28; LFC: 10; T: 2</td>
</tr>
<tr>
<td>Lim et al$^{16}$ (2012)</td>
<td>2.7 (NR)</td>
<td>MFC: 13; LFC: 5</td>
<td>MFC: 23; LFC: 7</td>
</tr>
<tr>
<td>Vanlauwe et al$^{26}$ (2011)</td>
<td>2.6 (1-5)</td>
<td>FC: 51</td>
<td>FC: 61</td>
</tr>
<tr>
<td>Total</td>
<td>3.5</td>
<td>MFC: 107; LFC: 29; FC: 51; T: 2</td>
<td>MFC: 123; LFC: 25; FC: 61; T: 2</td>
</tr>
</tbody>
</table>

$^a$ACI, autologous chondrocyte implantation; FC, unspecified femoral condyle; LFC, lateral femoral condyle; MFC, medial femoral condyle; MFx, microfracture; NR, not reported; T, trochlea.
outcome scores, or MRI) between patients undergoing MFx or ACI for knee articular cartilage lesions. Of all the clinical outcomes assessed in this systematic review, only one resulted in a significant difference between the groups in which Kon et al.14 found a significantly greater improvement in the Tegner score in patients treated with ACI.

One reason for the unanticipated results of this systematic review is that 4 of the 5 studies included used first-generation ACI (P-ACI). Superior results have been demonstrated with second-generation ACI (C-ACI, using a collagen scaffold cover) compared with first-generation ACI10,21 although little data exist comparing P-ACI versus M-ACI. One study by Zeifang et al.30 at short-term follow-up (up to 24 months), found no difference between M-ACI and P-ACI with respect to the International Knee Documentation Committee score, Tegner score, or Short-Form 36 score, although significantly higher Lysholm scores were found in the P-ACI group at latest follow-up. Despite the results of Zeifang et al’s30 study, it is interesting that the best results of ACI in the present systematic review were found with the 1 study utilizing M-ACI,14 and this may be related to the longer follow-up of this study (5 years) compared with that of Zeifang et al.20 (24 months). Currently, several clinical trials are underway in the United States investigating the outcomes of third-generation techniques, and longer term studies are necessary to compare the efficacy of M-ACI versus P-ACI, C-ACI, and MFx.

Previous studies have demonstrated better knee function scores for MFx in lesions <4 cm², with an even smaller threshold (<2 cm²) in the demanding athletic population. 19 In the studies included in this systematic review, 2 studies12,13 treated patients with an average lesion size of 4.9 cm². Lesions as large as these are likely not ideal candidates for MFx. However, the authors of these studies found that, at a minimum 14-year follow-up, patients who underwent ACI had a nonsignificantly greater failure rate compared with those who underwent MFx (42.5% vs 32.5%, respectively; \( P = .36 \)).

The strengths of this study include a comprehensive systematic review of high-quality (level I-III evidence) studies by 2 independent reviewers. In addition, this is the first systematic review to specifically compare the midterm to long-term outcomes of MFx versus ACI for FCDs in the knee joint. The limitations of this study should also be noted. In particular, only 5 studies were included in this systematic review. Treatment failure was not defined equally in all studies, and a variety of patient-reported outcome scores were used without much consistency between the studies. In addition, different generations of ACI (first and third generation) were included and grouped together into the ACI group to create a sample size large enough for clinical outcome comparisons. Only 1 of these studies14 used third-generation ACI (M-ACI), which is more commonly used now rather than the first-generation technique. Furthermore, only 1 study16 described the MFx technique used, and only 1 study14 specified that all lesions were on the weightbearing surface of the femoral condyles or trochlea. Two studies12,13 did not report the age of the included patients. Finally, some studies did not provide precise values for various patient-reported outcomes, thereby prohibiting the authors from performing a meta-analysis or calculating weighted averages for these scores.

### CONCLUSION

On the basis of the findings of this systematic review, patients undergoing MFx or first/third-generation ACI for articular cartilage lesions in the knee can be expected to experience improvement in clinical outcomes at midterm to long-term follow-up without any significant difference between the groups. Further studies must compare longer term follow-up of patients undergoing MFx or third-generation ACI for knee articular cartilage lesions of appropriate size for MFx treatment (<2-4 cm²).

### REFERENCES


