Autologous chondrocyte implantation for traumatic full-thickness cartilage defects of the knee in 14 patients: 6-year functional outcomes

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KEYWORDS
Cell therapy;
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Summary

\textbf{Background:} Autologous chondrocyte implantation (ACI) was introduced in 1987 in Sweden by Brittberg and Peterson for the treatment of severe chondral defects of the knee. Here, our objective was to evaluate mid-term outcomes of ACI in young athletic patients with deep chondral defects of the knee after trauma.

\textbf{Hypothesis:} ACI is effective in filling full-thickness chondral defects of the knee.

\textbf{Patients and methods:} We prospectively monitored 14 patients, with International Cartilage Repair Society grade III or IV lesions, who underwent ACI between 2001 and 2006. Standard evaluation measurements were used. Mean age at surgery was 37.7 years (range, 30–45). A history of surgery on the same knee was noted in ten (67%) patients. The defect was on the medial femoral condyle in 11 patients, lateral femoral condyle in two patients, and both femoral condyles in one patient. Mean defect surface area after debridement was 2.1 cm\textsuperscript{2} (1–6.3).

\textbf{Results:} After a mean follow-up of six years, improvements were noted in 12 (86%) patients, with an International Knee Documentation Committee (IKDC) score increase from 40 (27.6–65.5) to 60.2 (35.6–89.6) (\(P=0.003\)) and a Brittberg-Peterson score decrease from 54.4 (11.8–98.2) to 32.9 (0–83.9) (\(P=0.02\)), between the preoperative assessment and last follow-up. The visual analogic scale pain score decreased from 66.3 (44–89) to 23.2 (0–77) (\(P=0.0006\)). In two (14%) patients, no improvements were detectable at last follow-up. The remaining 12 patients were satisfied and able to resume sporting activities, albeit at a less strenuous level. Two ACI-specific complications occurred, namely, periosteal hypertrophy treated with debridement in one patient and transplant delamination in another.

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Discussion: Our findings are consistent with previous reports but cover a longer follow-up period. Although the outcomes are promising, longer follow-ups are needed to confirm the long-term effectiveness of ACI.
Level of evidence: IV, prospective therapeutic study.
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Introduction

The treatment of deep chondral defects located in load-bearing areas and measuring more than 1 cm² (grades III and IV in the International Cartilage Repair Society [ICRS] classification) continues to generate considerable interest [1]. Grade III defects reach the subchondral bone, whereas grade IV lesions extend into the subchondral bone. In one study, patients younger than 40 years of age with grade IV lesions accounted for 5% of all arthroscopies [2]. Knee cartilage injuries are often due to acute traumatic injuries. Of patients with acute traumatic hemarthrosis of the knee, 5% to 10% have deep chondral defects [3].

Chondral defects can cause early osteoarthritis [4,5] because the hyaline joint cartilage has a limited intrinsic potential for repair. Chondrocytes are unable to migrate to the site of injury. Partial or superficial defects (as opposed to deep defects) can undergo spontaneous repair from the adjacent cells. The filling of deep defects, in contrast, requires cell migration over considerably greater distances. Techniques used to repair deep chondral defects have included microfracture [6] and mosaicplasty [7]. Microfracture techniques lead to the production of fibrocartilage, which has less mechanical strength compared to native cartilage. Mosaicplasty consists in transplanting hyaline cartilage plugs taken from non-load-bearing sites.

Autologous cartilage implantation (ACI) is an alternative to microfracture and mosaicplasty. ACI leads to the synthesis of hyaline cartilage containing type II collagen [8]. The first ACI procedure in a human patient was performed in Sweden in 1987 to treat a knee injury. The team led by Britberg and Peterson [9] published a study of ACI outcomes in 1994 [10]. They used autologous chondrocytes collected from the injured knee then subjected to cell engineering techniques designed to enhance their regenerative capabilities.

The objective of this prospective study was to evaluate the medium-term functional outcomes of ACI in 14 athletes with post-traumatic cartilage defects of the knee. Our hypothesis was that ACI might be effective in filling deep chondral defects at the knee.

Patients and methods

Patients

Between 2001 and 2006, we included 14 patients in a prospective single-centre study. Our institutional review board approved the research protocol (study #010028) and all patients gave their written informed consent prior to study inclusion.

Inclusion criteria were a visual analogic scale (VAS) pain score less than 40/100, age 18 to 50 years, grade III or IV chondral defect in a load-bearing area, defect size less or equal to 1 cm², and written informed consent. We excluded patients with greater than five of knee varum or valgum, knee laxity, and/or radiological evidence of knee osteoarthritis.

Operative technique

ACI was performed in two steps as recommended by Britberg and Peterson [9]. Arthroscopy was performed with a tourniquet. The defect was inspected and its size was determined with the help of a probe of known dimensions. Cartilage was collected from the upper part of the medial femoral condyle of the same knee for culturing prior to re-implantation. In the operating room, the cartilage samples were placed in a sterile container filled with 0.9% saline at room temperature. The samples were then taken to the cell culture laboratory.

At the laboratory, after enzymatic digestion of the extracellular matrix, the cells were grown to monolayers exhibiting dedifferentiation (phenotypic instability) with a fibroblast-like appearance and limited matrix production (collagens types I and III and non-cartilage proteoglycans) followed by re-differentiation. The mean number of harvested cells was 161,375 (32,000 to 375,000) and the mean weight of collected cartilage was 402.9 mg (240 to 780 mg).

Cell implantation was performed six weeks later. Prophylactic antibiotic therapy was given at the time of anesthesia induction. An arthrotomy incision was made, and the chondral lesion was debrided (Fig. 1). A periosteal flap taken from the superomedial part of the tibia was sutured, in its original orientation, to the surrounding rim of normal cartilage, using Vicryl 5/0 or 6/0 (Fig. 2). The cultured chondrocytes were injected under the flap (suspended in 0.5 mL [0.2 to 1 mL] in a syringe in a sterile package). The mean number of implanted chondrocytes was $13.3 \times 10^6$ ($0.2 \times 10^6$ to $27 \times 10^6$). Fibrin glue was used to seal the rim of the lesion. Mean operative time was 96 minutes (57–150 minutes).

Postoperative care was standardized. Continuous passive mobilization from 0 to 60 was started on day 3. Weight bearing was forbidden for six weeks. Resumption of sporting activities was allowed after six months.

All procedures were performed by the same senior surgeon (BM).

Evaluation

Patients were evaluated preoperatively then after three, six, nine, and 12 months; after 3.5 years; and at last
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follow-up. Three scores were determined at each evaluation. The VAS pain score could range from 0 (no pain) to 100 (worst pain imaginable). The subjective International Knee Documentation Committee (IKDC) scale has ten items and a maximal value of 100; scores of 90 to 100 indicate excellent outcomes, 80 to 89 good outcomes, 70 to 79 fair outcomes, and less than 70 poor outcomes. The Brittberg-Peterson score [11] is obtained using a 13-item questionnaire on daily activities and can range from 0 (no symptoms) to 130 (worst possible symptoms).

Statistical analyses were performed using JMP 7.0 software. The Wilcoxon signed-rank test was used to compare quantitative data. Values of $P$ smaller than 0.05 were considered significant.

Results

Mean follow-up was six years (3.3–7.8 years). Mean age at ACI was 37.7 years (30–45 years). The seven men and seven women participated actively in sporting activities; six were competitive athletes, six regular recreational athletes, and two occasional recreational athletes. Mean body mass index was 26 kg/m$^2$ (18.7–32.6 kg/m$^2$) (Table 1).

All the study patients had deep chondral defects (ICRS grade III in three patients and IV in 11 patients) caused by an injury sustained during sporting activities ($n=11$), motor vehicle accidents ($n=2$), or work ($n=1$). Ten patients had had 11 previous procedures on the same knee consisting in microfracture ($n=3$), Pridie procedure ($n=1$), meniscectomy ($n=2$), anterior cruciate ligament repair ($n=2$), and arthroscopic debridement ($n=3$).

Mean time from injury to ACI was 2.9 years (0.5–7 years). The defect was on the medial femoral condyle in 11 patients, the lateral femoral condyle in two patients, and both condyles in one patient. Mean defect size was 2.1 cm$^2$ (1–6.3 cm$^2$).

Complications

We recorded two early complications (hemarthrosis drained on day 8 and pulmonary embolism) and three late complications (periosteal hypertrophy managed with debridement, transplant delamination, and reflex sympathetic dystrophy syndrome). No infections occurred. At last follow-up, the patient with periosteal hypertrophy had a functional Brittberg-Peterson score of 52 and an IKDC score of 78. The patient with transplant delamination had a functional Brittberg-Peterson score of 84 and an IKDC score of 36.

Functional outcomes

The mean VAS pain score was 65.5/100 (44–80) preoperatively and 29/100 (0–66) after three months ($P=0.0006$) then remained stable over time (Fig. 3). A single patient had no improvement in pain intensity at last follow-up.

The mean preoperative subjective IKDC score (Fig. 4) was 41 (28–65.5). At last follow-up, the IKDC score indicated an excellent outcome in three patients, a good outcome in five patients, and a fair outcome in six patients. The IKDC score improvement was statistically significant ($P=0.003$).

The mean Brittberg-Peterson score was 54 (11.8–98.2) preoperatively, 20 (1.8–47.5) after one year and 30 (0–84) at last follow-up (Fig. 5) ($P=0.02$). This score failed to improve in two patients (from 45 to 58 in one patient and from 58 to 84 in the other).

![Figure 1](image1.png) Cartilage defect after debridement.

![Figure 2](image2.png) Repair using autologous chondrocyte implantation under a periosteal flap.

![Figure 3](image3.png) Mean visual analogic scale pain scores over time.
Table 1  Study population.

<table>
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<th>Patients</th>
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Figure 4  Subjective International Knee Documentation Committee (IKDC) score.

Figure 5  Brittfberg-Peterson score.

At last follow-up, 12 (86%) patients were improved. The three evaluation scores showed similar time patterns, with significant improvements as early as six months after ACI.

Discussion

Our prospective study was designed to determine whether ACI in athletes with post-traumatic knee cartilage defects produced functional improvements similar to those reported in the literature [11]. Strong points of our study include the six-year follow-up and prospective design. The limitations are the small sample size and absence of a control group.

Our results are consistent with those reported previously but were obtained after a longer follow-up. In previous studies, 10% to 30% of patients were unsatisfied with the results [12,13] (Table 2).

One year after ACI, 86% of patients [14,15] had improvements in their functional scores, which were sustained after three years (84% in the prospective study by Micheli et al. [13]). In a retrospective study, the rate of good results after five years was 89% (84% in our study). The Brittfberg-Peterson score deteriorated after five years, as reported previously after mosaicplasty [19].

Krishnan et al. [20] have indicated that criteria associated with better ACI outcomes consist of young age, a time since injury shorter than two years, a single defect, location of the defect on the trochlea or lateral condyle, and less than two previous procedures on the same knee. In our study, the patients with defects less than 1 cm² in size had previously undergone other cartilage repair procedures that had decreased the size of the defect but failed to achieve complete filling. Given the persistent symptoms in these patients, we performed ACI. In our study, risk factors were the mean age older than 30 years, the 2.6-year time from injury to ACI, the small proportion of lateral condyle lesions (3/14 patients), and the large number of previous procedures on the same knee (10/14 patients).

ACI failure occurs chiefly within the first two years. Failure rates of 5% to 16% have been reported [21,22]. A crucial step is a careful preoperative evaluation of risk factors for failure [23] such as marked knee varum or valgum, meniscal lesions, and knee laxity, which were exclusion criteria in our study. Strict compliance with the postoperative rehabilitation program is necessary to prevent failure [24].

Transplant hypertrophy is the most common ACI-specific complication and becomes apparent three to seven months after the procedure. Niemeyer et al. [25] identified four major specific complications: transplant hypertrophy, disturbed fusion of the regenerated cartilage with the surrounding cartilage, insufficient amount of regenerated cartilage, and delamination. Non-specific complications...
Table 2  Literature review.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Number of patients</th>
<th>Study design</th>
<th>Defect size (cm²)</th>
<th>Follow-up (years)</th>
<th>Proportion improved (%)</th>
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<td>4.7</td>
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<td>Prospective</td>
<td>5.33</td>
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<td>89</td>
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<td>58</td>
<td>Prospective</td>
<td>5.7</td>
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<td>14</td>
<td>Prospective</td>
<td>2</td>
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</table>

reported after ACI consist of motion range limitation, chondromalacia, synovitis, infection, and deep vein thrombosis. Mishaps in the chondrocyte culturing process were identified for 5% of 304 cultures performed in 1996 [26] and consisted of contamination, cell death, culture failure, and identification errors.

The optimal size of the cell inoculum remains debated. Cell numbers ranging from 2.6 to 30 million per milliliter have been used. With autologous cells, the number of available cells is limited by the amount of cartilage that can be collected.

Coverage of the chondrocytes with a periosteal flap is the first-generation method used for ACI. Problems with this method include cell leakage due to incomplete sealing, incomplete integration of the flap into the surrounding cartilage and flap hypertrophy [13,27], and uneven chondrocyte distribution throughout the defect. These problems can be avoided by using a collagen or matrix membrane [8,28,29].

Autologous chondrocyte implantation (ACI) vs. microfracture

Knutsen et al. [21,30] compared ACI with microfracture in 80 patients managed at four centers in Norway. The defect was trauma-related in 65% of cases, mean symptom duration was three years, and 94% of patients had had previous surgical procedures on the same knee. After two years, similar improvements were seen in the Lysholm score and pain score in the two groups. The pain score was improved in 78% of the ACI patients and 75% of the microfracture patients. The two-year failure rate was 5% with ACI and 2.5% with microfracture. Periosteal hypertrophy was the main reason for re-operation. Macroscopic arthroscopy findings after two years were not different in the two groups. Examination of 67 biopsies showed no between-group differences in terms of proportions of hyaline cartilage and of fibrocartilage filling the defects. The authors concluded that short-term outcomes were comparable with the two treatments. It is worth noting that partial weight-bearing was allowed in both groups, which may have contributed to induce periosteal flap lesions. The periosteal flap is particularly fragile after ACI.

Kon et al. [31] compared second-generation ACI (with a hyaluronan scaffold, Hyalograft C) and microfracture in 80 patients with a mean age of 29.8 years (40 patients in each group) in a non-randomised five-year study. Each procedure was performed in two different centres. Mean defect size was 2.4 cm² and over 50% of the defects were trauma-related. Subjective IKDC score improvements occurred in both groups: the score increased from 40 to 80 after ACI and from 40 to 70 after microfracture. Return to sports was similar in the two groups after two years but deteriorated subsequently in the microfracture group. The authors concluded that second-generation ACI was superior over microfracture.

Autologous chondrocyte implantation (ACI) vs. mosaicplasty

Two trials compared ACI with mosaicplasty, with conflicting results. Horas et al. [32] compared ACI and autologous osteochondral plug transplantation in 40 patients with single femoral condyle defects. In this single-centre, randomised, two-year trial, the Meyers and Tegner scores were similar in the two groups. The Lysholm score improvement occurred at a significantly slower pace in the ACI group. After two years, two ACI patients and three mosaicplasty patients were unconvinced that the procedure had been beneficial. Partial failure was diagnosed in one ACI patient, who underwent re-operation. No failures were reported in the mosaicplasty group. The biopsies showed that ACI produced chiefly fibrocartilage, with foci of hyaline-like cartilage near the subchondral bone. In the mosaicplasty group, the histological findings indicated good integration of the implants into the surrounding cartilage. Limitations of this study are the small sizes of both groups, short follow-up, and absence of a control group.

Bentley et al. [14] compared ACI and mosaicplasty in a randomised trial in 100 patients (mean age, 31 years), with post-traumatic cartilage defects. The modified Cincinnati score and objective clinical evaluation indicated good and excellent results in 88% of patients with ACI and 69% with mosaicplasty. Excellent or good repair as assessed by arthroscopy after one year was noted in 82% of patients after ACI and 34% after mosaicplasty. This is the only prospective randomised trial comparing ACI with mosaicplasty. The anatomic results as assessed arthroscopically were poorer after mosaicplasty, with 66% of unchanged or worsened defects according to ICRS criteria compared to only 18% after ACI. Biopsies were taken during the one-year arthroscopic evaluation in the ACI group only. They showed hyaline cartilage in seven of 19 patients, a mixture of hyaline cartilage and fibrocartilage in seven other patients, and only fibrocartilage in five patients. A periosteal flap was used early in
the study and a porcine collagen membrane later on. After one year, no difference related to this change in technique was noted. No complications directly related to either treatment method were recorded. The authors concluded that the one-year clinical outcomes were good with both methods and that the arthroscopy data indicated better repair in the ACI group.

The results of the two trials comparing ACI and mosaicplasty are divergent. Bentley et al. [14] concluded that the mosaicplasty outcomes were similar after one year but that the arthroscopy findings were more favorable after ACI. Horas et al. [32] reported a faster pace of clinical improvement over the first two years after mosaicplasty, with arthroscopy findings indicating that the regenerative cartilage was similar to the surrounding cartilage, whereas fibrocartilage predominated after ACI. Several differences in the surgical techniques are worth noting. The size of the mosaicplasty plugs was 10 or 16 mm in the study by Horas et al. compared to only 4.5 mm in the study by Bentley et al. Bentley et al. allowed immediate full weight-bearing. They recently reported better ten-year outcomes after ACI compared to mosaicplasty [15].

Conclusion

Our findings are encouraging, although the scores started to improve one year after the procedure then remained stable until last follow-up.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


