A Prospective Multicenter Study on the Outcome of Type I Collagen Hydrogel-Based Autologous Chondrocyte Implantation (CaReS) for the Repair of Articular Cartilage Defects in the Knee

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Investigation performed at the Department of Orthopaedic Surgery, University of Aachen, Aachen, Germany; and the Department of Orthopaedic Surgery, University of Würzburg, Würzburg, Germany

Background: The Cartilage Regeneration System (CaReS) is a novel matrix-associated autologous chondrocyte implantation (ACI) technique for the treatment of chondral and osteochondral lesions (Outerbridge grades III and IV). For this technology, no expansion of the chondrocytes in a monolayer culture is needed, and a homogeneous cell distribution within the gel is guaranteed.

Purpose: To report a prospective multicenter study of matrix-associated ACI of the knee using a new type I collagen hydrogel (CaReS).

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

Methods: From 2003 to 2008, 116 patients (49 women and 67 men; mean age, 32.5 ± 8.9 years) had CaReS implantation of the knee in 9 different centers. On the basis of the International Cartilage Repair Society (ICRS) Cartilage Injury Evaluation Package 2000, the International Knee Documentation Committee (IKDC) score, pain score (visual analog scale [VAS]), SF-36 score, overall treatment satisfaction and the IKDC functional status were evaluated. Patient follow-up was performed at 3, 6, and 12 months after surgery and annually thereafter. Mean follow-up was 30.2 ± 17.4 months (range, 12-60 months). There were 67 defects of the medial condyle, 14 of the lateral, 22 of the patella/trochlea, and 3 of the tibial plateau, and 10 patients had 2 lesions. The mean defect size was 5.4 ± 2.4 cm². Thirty percent of the defects were <4 cm² and 70% were >4 cm².

Results: The IKDC score improved significantly from 42.4 ± 13.8 preoperatively to 70.5 ± 18.7 (P < .001) at latest follow-up. Global pain level significantly decreased (P < .001) from 6.7 ± 2.2 preoperatively to 3.2 ± 3.1 at latest follow-up. There also was a significant increase of both components of the SF-36 score. The overall treatment satisfaction was judged as very good or good in 88% by the surgeon and 80% by the patient. The IKDC functional knee status was grade I in 23.4%, II in 56.3%, III in 17.2%, and IV in 3.1% of the patients.

Conclusion: Matrix-associated ACI employing the CaReS technology for the treatment of chondral or osteochondral defects of the knee is a safe and clinically effective treatment that yields significant functional improvement and improvement in pain level. However, further investigation is necessary to determine the long-term viability and clinical outcome of this procedure.

Keywords: CaReS; type I collagen hydrogel; matrix-associated ACI; chondral and osteochondral lesion of the knee; prospective study


with high patient numbers, larger defects, and longer procedure times when compared with debridement,\textsuperscript{19} mosaicplasty,\textsuperscript{7} or osteochondral cylinder transplantation.\textsuperscript{18} Despite higher initial medical costs, as compared with other procedures, ACI is economically feasible in the long run as validated by a number of cost-effectiveness analyses.\textsuperscript{21,25,41} In opposition to these encouraging results, ACI has several disadvantages that have to be addressed; the use of periosteum can result in transplant hypertrophy, calcification, and delamination.\textsuperscript{5,29,37,38,40} In the absence of an intact or complete surrounding cartilage rim, the periosteal flap can often only be fixed with difficulty or not at all, counteracting the development of sufficient neotissue at the defect site.\textsuperscript{2} Harvest of the periosteal flap requires either a larger arthrotomy or an additional incision, and this adds time to the preparation of the transplant and the overall surgery; any increase in the incision length can extend the interval of preparation of the transplant and the overall surgery; any process results in a homogeneous cell distribution and sufficient surrounding cartilage rim, the periosteal flap can often only be fixed with difficulty or not at all, counteracting the development of sufficient neotissue at the defect site.\textsuperscript{2} Harvest of the periosteal flap requires either a larger arthrotomy or an additional incision, and this adds time to the preparation of the transplant and the overall surgery; any increase in the incision length can extend the interval of postoperative pain caused by the larger surgical access and increase the risk of complications like arthrofibrosis.\textsuperscript{3,22}, and finally, poor quality chondrocytes or cutting of the periosteal flap can lead to qualitatively insufficient regeneration of the tissue or to complete transplant failure.\textsuperscript{8,9,28,39}

With regard to these shortcomings, experimental and clinical research has been driven to the development of matrix-associated procedures of ACI, whereby biocompatible cell carriers are used as a vehicle for secure delivery of primary chondrocytes, without or after previous cell culture expansion, to the defect site.\textsuperscript{10,12,14} Today, clinical experience using collagen hydrogels or membranes, a copolymer of polyglycolic (PGA)/polylactic (PLA) acid (polyglyactin, vicryl) and polylactic-anone, and hyaluronic acid has been reported.\textsuperscript{32,16,22,30,39} The 3-dimensional hydrogel (Cartilage Regeneration System [CaReS], Arthro Kinetics, Krems, Austria) used in this study is based on collagen type I, which has been prepared from rat tail tendons. The embedding of autologous chondrocytes and cultivation process of the chondrocyte-laden hydrogel is performed subsequent to cell extraction from the original cartilage biopsy specimen under good manufacturing practice (GMP) conditions and requires no additional processing. By providing a 3-dimensional environment immediately after cell isolation and during further cultivation of the CaReS implant for 10 to 12 days in autologous serum, the risk of chondrocyte dedifferentiation, as seen in repeated monolayer expansion, is minimized. Furthermore, the manufacturing process results in a homogeneous cell distribution and sufficient mechanical stability of the implant for surgical handling. Additionally, CaReS implants can be manufactured custom made in height or size, as required by the operating surgeon, and therefore can provide an exact fit in the defect. This prospective study reports on the experience of surgeons in different centers using CaReS for the biological reconstruction of chondral and osteochondral defects of the knee joint. It follows the recommendations of the Tissue Regeneration and Tissue Substitute Task Force of the German Orthopaedic Society on autologous chondrocyte transplantation\textsuperscript{9} and provides clinical results for 116 patients up to 5 years after CaReS treatment.

**MATERIALS AND METHODS**

**Study Design and Outcome Measurements**

The study received institutional review board approval of the participating centers. From 2003 to 2008, we performed a prospective multicenter study to evaluate the therapeutic effect of the treatment with CaReS. Patients suffering from a chondral or osteochondral defect of the knee caused by trauma, degeneration, or osteochondritis dissecans (OCD) were included based on the criteria according to the treatment guidelines for ACI published by the International Cartilage Repair Society (ICRS) and the Joint Advisory Board of the German Societies for Traumatology and Orthopaedic Surgery.\textsuperscript{9,55} In accordance with these publications, inclusion criteria were isolated cartilage defects (ICRS grades III and IV) with regular adjacent cartilage, maximum ICRS grade II changes of the opposing cartilage surface (no kissing lesion), intact meniscal (maximum partial meniscectomy of 1/3), knee axis deviation of the lower extremity less than 5°, closed epiphysis (age, 16-50 years), and regular soft tissue balancing (joint stability, patella alignment). Ligament reconstruction, correction of axis deviation (if >5°), or patella maltracking was performed at the time of the implantation. Exclusion criteria were osteoarthritis or rheumatoid arthritis, metabolic arthropathy (gout, pseudogout), body mass index (BMI) >30, infectious diseases, drug abuse, pregnancy, borreliosis, and neurological or tumorous diseases.

Data acquisition was performed using the ICRS Cartilage Injury Evaluation Package 2000 based on standardized case report forms as part of the ICRS Cartilage Repair Evaluation Package and included patient demographics, surgical history of the involved knee, lesion type and origin, size and location of the defects, relevant surgical aspects as well as patient subjective evaluations, and surgeon's clinical examination.\textsuperscript{34} On this basis, the International Knee Documentation Committee (IKDC) score, pain (visual analog scale [VAS]), SF-36 score, overall treatment satisfaction, and the IKDC functional status were evaluated. Patient follow-up was performed at 5, 6, 12, 24, 36, 48, and 60 months with a follow-up of 80.2 ± 17.4 months. The minimal follow-up period was 12 months, and the maximum was 60 months.
Figure 1. CaReS treatment of a chondral defect of the medial condyle in a 35-year-old man. (A) Chondral defect of 3 x 2.5 cm in diameter. (B) Stamping out of the defect using a specially designed sharp metal punch. (C) Defect after debridement with intact subchondral plate. (D) Implant after modeling before wound closure.

Patients were asked to answer questionnaires based on the following scoring systems: ICRS knee functional status based on a 4-level scale; IKDC subjective knee evaluation form (knee symptoms, function, and activity level = IKDC score); and IKDC current health assessment form, which consists of a descriptive questionnaire concerning 5 dimensions, including mobility, self-care, usual activities, pain or discomfort, and anxiety or depression (related to the SF-36 Health Survey = SF-36 score). The SF-36 survey includes a Physical Component Summary (PCS) and a Mental Component Summary (MCS) on a scale from 0 (bad condition) to 100 (optimal condition). For the determination of IKDC score and the SF-36 score, individual scores were added together and transformed onto a scale from 0 to 100. Also, for the assessment of pain, question number 3 from the subjective knee evaluation form (If you have pain, how severe is it?), which is ranged on a scale from 0 to 10 (0 = no pain, 10 = worst pain imaginable), was analyzed. Additionally, the degree of the overall treatment satisfaction, judged by the patient as well as the surgeon, was rated on a 5-point scale (very good to very bad) at every follow-up time point.

Radiological images (anteroposterior, lateral, Merchant view, and full-leg weight-bearing standing radiograph) as well as magnetic resonance imaging (MRI) were taken before surgery and at the follow-up periods. Because of varying cartilage MRI sequences used by the different study centers, a systemic evaluation has not been performed.

Surgical Technique and Implant Preparation

An initial arthroscopic procedure of the knee was performed to determine the location and size of the defect, as well as the consistency and firmness of the adjacent articular cartilage and the integrity of the menisci and ligaments. A cartilage biopsy specimen was taken from a nonweightbearing area using a special instrument (cartilage biopsy tool, Arthro Kinetics). The specimen was immediately placed in buffered, serum-free medium. About 120 to 140 mL of whole blood was taken from the patient for the cultivation of the implant under GMP conditions. In this process, chondrocytes were isolated from the cartilage biopsy specimen by collagenase digestion, the released cells were centrifuged, and the obtained cell number and viability were assessed. Chondrocytes were suspended in a double-buffered HEPES solution and gently mixed with type I collagen (6 mg/mL) from rat tails in equal parts to obtain a final concentration of 3 mg type I collagen/mL. The collagen-chondrocyte mixture was allowed to polymerize at 37°C in a humidified atmosphere. Each implant was fabricated with a diameter of 34 mm and 2 times the height (6-8 mm) of the articular cartilage at the defect site. The chondrocyte-seeded implants were cultured in autologous serum for a period of 10 to 13 days (37°C, 5% CO2) and then shipped to the study center within 24 hours. Before shipment, quality control of each implant had to meet defined requirements, such as cell viability higher than 80% and expression of type II collagen as determined by real-time quantitative polymerase chain reaction (rt-PCR).

The surgical procedure was performed following intravenous antibiotics and exsanguination of the lower extremity using a tourniquet. Depending on the location of the defect, a medial or lateral parapatellar arthroscopy was used to access the defect site. Chondral defects (Figure 1A) were debrided down to the subchondral bone, and the edges of the defect were trimmed using a sharp metal punch (Figure 1B). The CaReS implants were prepared using a metal punch 1 mm wider than the corresponding...
TABLE 1

Patient Description and Baseline Characteristics

<table>
<thead>
<tr>
<th>Number or Mean (Standard Deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Men, n</td>
</tr>
<tr>
<td>Women, n</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
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<tr>
<td>Overall pain level preoperatively</td>
</tr>
<tr>
<td>No. of lesions treated, n</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>%</td>
</tr>
<tr>
<td>8.6</td>
</tr>
<tr>
<td>Genesis of defect(s), n</td>
</tr>
<tr>
<td>Trauma/regeneration</td>
</tr>
<tr>
<td>Osteochondritis dissecans</td>
</tr>
<tr>
<td>Size of cartilage lesion treated, cm²</td>
</tr>
<tr>
<td>No. of lesions ≤4 cm²</td>
</tr>
<tr>
<td>No. of lesions &gt;4 cm²</td>
</tr>
<tr>
<td>Location of cartilage lesion, n</td>
</tr>
<tr>
<td>Femoral condyle, medial</td>
</tr>
<tr>
<td>Femoral condyle, lateral</td>
</tr>
<tr>
<td>Patella/trochlea</td>
</tr>
<tr>
<td>Tibial plateau</td>
</tr>
<tr>
<td>Multiple lesions</td>
</tr>
<tr>
<td>%</td>
</tr>
<tr>
<td>12.1</td>
</tr>
<tr>
<td>19.1</td>
</tr>
<tr>
<td>2.6</td>
</tr>
<tr>
<td>8.6</td>
</tr>
</tbody>
</table>

punch utilized for trimming the cartilage defect. The base of the cartilage defect was coated with fibrin glue (Tissucol, Baxter, Vienna, Austria) before the implant was transferred into the defect using a specific metal spatula. Because of the hydrogel's ability to release more than 50% of its water content, the CaReS implant was fabricated twice the height of the defect and could easily be adapted to the individual shape of the cartilage defect (Figure 1, C and D). The modeling was done with the blunt end of a forceps. In cases of osteochondral lesions, the subchondral bone was augmented with autologous cancellous bone harvested from the tibial head or the iliac crest. Alternatively, autologous bone cylinders from the iliac crest were used to reconstruct the subchondral plate.

Rehabilitation Program

For isolated femoral and tibial defects, the knee joint was immobilized for 48 hours in a brace locked at 10° of flexion after surgery. Knee flexion was limited to 30° during the first 3 weeks and to 60° for another 3 weeks, with partial weight-bearing for 12 weeks (15 kg for 6 weeks and 30 kg for the following 6 weeks). When a reconstruction of the subchondral bone was performed, nonweightbearing was encouraged for at least 6 weeks. We also recommended assisted physical therapy and bicycle training after 6 weeks, and training for enhanced muscle formation was started after 12 weeks. For lesions involving the patella or trochlea groove, the knee joint was immobilized in 30° of flexion for 48 hours after surgery. The range of motion was limited from 30° to 90° of flexion for 3 weeks. No active extension against resistance was allowed for 12 weeks, whereas patients were allowed full weightbearing 48 hours after surgery. In all cases, continuous passive motion (CPM) was recommended for 6 weeks. Physical activity, such as noncontact sports activity, swimming, and biking, was allowed after 6 months. More competitive activity loads, such as soccer or track and field athletics, were allowed 12 months after surgery.

Statistical Analysis

Statistical analysis was performed using the SPSS software package for Windows version 16.0 (SPSS Inc, an IBM Company, Chicago, Illinois). P values ≤.05 were considered statistically significant. The Kolmogorov-Smirnov test was used to test variables for normal distribution. According to the type of distribution, parametric or nonparametric tests were used. Changes of the IKDC were analyzed using the t test for paired samples. For the comparison of subgroups (diagnosis, size, and location) concerning the IKDC scores and pain levels, analysis of variance followed by post hoc analysis using the Bonferroni test was performed. The nonparametric Wilcoxon test was applied to evaluate differences within the IKDC current health assessment form.

RESULTS

Patient Data and Baseline Characteristics

Between 2003 and 2008, a total of 194 patients were included in the study. Forty-four of those had to be excluded because they did not meet the inclusion criteria. Twelve patients were lost during the follow-up. Twenty-two patients had only a follow-up of 6 months. We report on 116 patients who received CaReS treatment in 9 different study centers with a continuous follow-up between 12 and 60 months after surgery. The mean follow-up was 50.2 ± 17.7 months, with 38.6% of the patients completing the 12-month follow-up, 12.1% with 24 months, 17.2% with 36 months, 19% with 48 months, and 12.1% with 60 months (Table 1). Only 18.1% of the patients had no previous surgery of the index knee, while 81.9% of the patients had already undergone a surgical procedure. Of these, 66.9% received previous cartilage surgery, and 25% received surgery without cartilage repair. Concurrent procedures during CaReS implantation were performed in 25% of the patients (Appendix 1, available in the online version of this article at http://ajs.sagepub.com/supplemental/).

IKDC Score

The overall IKDC score in the 116 patients significantly improved from 42.2 ± 13.8 preoperatively to 70.5 ± 18.7 (P < .001) at a mean follow-up of 30.2 months (Figure 2). At different time points, the IKDC score increased statistically significantly from 42.2 ± 13.8 preoperatively to 47.3 ± 16.2 at 3 months, to 59.3 ± 18.0 at 6 months, and to 68.7 ± 17.5 at 12 months. Follow-up examinations at 24 (70.4 ± 19.2), 36 (70.7 ± 15.1), and 48 (68.8 ± 18.3) months after surgery showed a plateau phase with no further significant changes. After 60 months, a significant improvement of the IKDC score (73.2 ± 15.8) compared
Adverse Events

A total of 27 adverse events or complications in 22 patients were reported. Five patients developed joint effusion during the first 3 months after implantation that required joint aspiration. In 3 cases, a cartilage biopsy had to be repeated because of failed quality control of the implant in terms of cell number or cell viability. Revision arthroscopy of the index knee because of pain or restricted movement was carried out in 8 patients. In 2 cases, implant hypertrophy was identified. One implant was destroyed 7 days after implantation by a loose body overlooked during biopsy harvest; 1 graft failed, and the patient received a marrow-stimulating cartilage procedure at a hospital not participating in the study. One patient had capsule adhesions, 2 patients showed a synovitis of the upper recessus, and in 1 case, a cyclops lesion after concurrent anterior cruciate ligament reconstruction was seen in addition to cartilage hypertrophy at the site of biopsy harvest. Postoperative hypesthesia of the infrapatellar nerve was reported once with remission after 12 months. One patient developed a neuma of the infrapatellar nerve after revision arthroscopy that was excised in an open procedure (Appendix 2, available online).

DISCUSSION

Obvious intrinsic disadvantages of first-generation ACI, including monolayer expansion of chondrocytes and use of a periosteal flap, have driven considerable research efforts to the development of matrix-associated techniques, which guarantee safe delivery of cells to the defect without the necessity of a periosteal flap. Our report includes data from 116 patients treated in 9 centers using CaReS, a type I collagen hydrogel–associated ACI technique for the treatment of isolated knee cartilage defects, including a 1- to 5-year follow-up period (mean, 30.2 months).

Functional outcome was evaluated using both the ICRS 4-level scale for categorizing functional status and the IKDC subjective knee assessment questionnaire. At mean follow-up time, a significant improvement (P < .017) in IKDC score (70.5 ± 13.8) was observed, with 80% of the patients evaluating their postoperative condition as either very good or good and with significantly reduced pain levels at latest follow-up (6.7 ± 2.2 vs 3.2 ± 3.1; P < .001). In particular, our data clearly outline the benefit of CaReS in the treatment of patients with OCD who experienced a significantly higher increase in IKDC score and a significantly more pronounced reduction in pain as compared with patients with traumatic/degenerative genesis of the defect (Table 3). One can speculate that because of the opening of bone marrow spaces and blood vessels during debridement of the subchondral bone in OCD defects, chondroprogenitor cells gain access to the defect site and migrate into the

Pain

The pain level decreased significantly from a preoperative value of 6.7 to 3.2 at the mean follow-up (P < .001) (Table 3). For all groups (diagnosis, defect size, location, and number), a significant decrease in the pain level was found from preoperative to the mean follow-up. Comparing the subgroups, only in the diagnosis group (OCD vs trauma/degenerative) was a significant difference detected (P = .017) (Table 3).

IKDC Current Health Assessment Form (SF-36 Score)

The PCS and the MCS both increased significantly from preoperatively to the mean follow-up (Figure 3).

Overall Satisfaction

At the mean follow-up, surgeons rated 61% of the outcomes as very good, 27% as good, 9% as moderate, 1% as bad, and 2% as very bad. From the patients' point of view, 44% of the procedures were rated as very good, 36% as good, 13% as moderate, 6% as bad, and 2% as very bad (Figure 4).

IKDC Functional Knee Status

Preoperatively, 2.8% of the patients rated their knee function as unlimited (status I), 10.1% had major limitations (status II), 46.8% had major limitations (status III), and 40.4% had maximum limitation (status IV). At the mean follow-up, the actual status shifted to the following: I, 23.4%; II, 56.3%; III, 17.2%; and IV, 8.1%, respectively.
TABLE 2
International Knee Documentation Committee (IKDC) Score at Mean Follow-up Related to the Subgroups Concerning Diagnosis, Area, Location, and Type of Cartilage Defect

<table>
<thead>
<tr>
<th>IKDC Score (Standard Deviation)</th>
<th>n</th>
<th>Preoperative</th>
<th>Mean Follow-up, 30.2 mo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteochondritis dissecans</td>
<td>32</td>
<td>43.8 (14.0)</td>
<td>80.0 (1.9)</td>
<td>.005</td>
</tr>
<tr>
<td>Trauma/degenerative</td>
<td>84</td>
<td>41.8 (13.7)</td>
<td>66.9 (18.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Area</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4 cm²</td>
<td>35</td>
<td>40.0 (14.5)</td>
<td>66.2 (20.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>&gt;4 cm²</td>
<td>81</td>
<td>43.4 (13.4)</td>
<td>72.4 (17.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Location</td>
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<td></td>
</tr>
<tr>
<td>Medial femoral condyle</td>
<td>67</td>
<td>46.1 (14.1)</td>
<td>74.0 (18.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lateral femoral condyle</td>
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<td>41.3 (10.2)</td>
<td>78.3 (18.8)</td>
<td>&lt;.001</td>
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<tr>
<td>Patella/trochlea</td>
<td>22</td>
<td>36.5 (14.3)</td>
<td>60.6 (20.4)</td>
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<td>Number</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single lesion</td>
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<td>43.2 (13.9)</td>
<td>71.1 (18.8)</td>
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<tr>
<td>Multiple lesions</td>
<td>10</td>
<td>34.0 (9.7)</td>
<td>64.9 (17.9)</td>
<td>&lt;.001</td>
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TABLE 3
Changes in Pain Levels at Different Time Points and Related to the Subgroups Concerning Diagnosis, Area, Location, and Type of Cartilage Defect

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Preoperative</th>
<th>3 mo</th>
<th>6 mo</th>
<th>12 mo</th>
<th>24 mo</th>
<th>36 mo</th>
<th>48 mo</th>
<th>60 mo</th>
<th>Mean Follow-up</th>
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<tr>
<td>Pain Level</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Mean</td>
<td>6.7</td>
<td>4.1</td>
<td>3.7</td>
<td>3.1</td>
<td>3.1</td>
<td>3.0</td>
<td>3.3</td>
<td>2.2</td>
<td>3.2</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>2.2</td>
<td>2.7</td>
<td>2.7</td>
<td>2.8</td>
<td>2.8</td>
<td>2.4</td>
<td>3.1</td>
<td>2.8</td>
<td>3.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean Pain Level (Standard Deviation)</th>
<th>n</th>
<th>Preoperative</th>
<th>Mean Follow-up, 30.2 mo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteochondritis dissecans</td>
<td>32</td>
<td>6.5 (2.2)</td>
<td>1.8 (2.1)</td>
<td>.017</td>
</tr>
<tr>
<td>Trauma/degenerative</td>
<td>84</td>
<td>6.7 (2.3)</td>
<td>2.3 (2.2)</td>
<td>&lt;.001</td>
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<tr>
<td>Defect size</td>
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<td></td>
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<tr>
<td>&lt;4 cm²</td>
<td>35</td>
<td>6.7 (2.0)</td>
<td>2.6 (3.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>&gt;4 cm²</td>
<td>81</td>
<td>6.6 (2.4)</td>
<td>2.0 (3.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Location</td>
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<tr>
<td>Medial femoral condyle</td>
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<td>6.4 (2.2)</td>
<td>3.0 (3.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lateral femoral condyle</td>
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<td>6.9 (1.7)</td>
<td>3.2 (2.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Patella/trochlea</td>
<td>22</td>
<td>6.7 (2.5)</td>
<td>3.8 (3.7)</td>
<td>.003</td>
</tr>
<tr>
<td>Number</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single lesion</td>
<td>106</td>
<td>6.5 (2.2)</td>
<td>3.2 (3.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Multiple lesions</td>
<td>10</td>
<td>8.2 (1.9)</td>
<td>3.2 (2.6)</td>
<td>.005</td>
</tr>
</tbody>
</table>

*Significant decrease in pain level between preoperative and mean follow-up points (30.2 months), P < .001.

hydrogel and therefore contribute in cartilage-specific extracellular matrix production, resulting in better cartilage regeneration. From the surgeon's perspective, in 88% of the treated patients, CaReS led to very good or good postoperative condition at latest follow-up. Processing of the implants was easy, and no major problems were reported; it has been shown that the incision length and the surgical times are low and postoperative transplantation–specific complications, like those seen with conventional ACI, are absent. Our multicentric study design is more robust than a monocentric design, given the fact that patients were treated in 9 different centers and obtained good clinical outcomes.

Nevertheless, some restrictions in the interpretation of our results have to be taken into account. This study is

References 1, 2, 4, 5, 25, 26, 31, 32, 36, 37.
As a retrospective cohort study, inclusion criteria were represented by consecutive series of patients with a hyaluronan-based scaffold (Hyalograft C, Fidia, Italy) laden with culture-expanded autologous chondrocytes, whereas no exclusion criteria were applied. Marzacci et al\textsuperscript{22} determined the symptomatic and functional 2- to 5-year outcomes from implantation in 192 consecutive patients based on the ICRS evaluation package. Over 90% of the documented patients improved according to the subjective score, mean IKDC score significantly improved at a follow-up of 17.2 months (72.2 ± 20.2) and 40.3 months (78.1 ± 22.0) after surgery in a comparable manner to the data presented within our investigation, and a limited complication rate was recorded in this study. The overall complication rate in conventional ACI procedure, such as graft hypertrophy, delamination, and graft failure, has been reported in between 20% to 30% of the surgeries.\textsuperscript{23} In contrast to other studies, we did not find worse results in patients pretreated by marrow stimulation techniques.\textsuperscript{27} In our investigation, 8 patients (6.9%) had to undergo revision arthroscopy because of pain or restricted movement, whereas in 2 (1.8%) patients, graft hypertrophy was evident, and graft failure was seen in 2 patients, in one case because of an oversewn loose bone in the knee joint. Still, for a direct comparison of different cartilage regeneration techniques, further investigations on larger patient cohorts over a longer follow-up period are necessary based on randomized and prospective study designs, in particular comparing conventional, cell quality-optimized,\textsuperscript{27} and matrix-associated ACI technology.

CONCLUSION

This prospective multicenter investigation reports on promising midterm clinical outcomes following CaReS treatment of cartilage lesions of the knee joint up to 5 years. Presented data reveal similar, in parts favorable, subjective outcome performance in comparison with those obtained by conventional ACI.

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Five-Year Outcome of Characterized Chondrocyte Implantation Versus Microfracture for Symptomatic Cartilage Defects of the Knee

Early Treatment Matters

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Background: Characterized chondrocyte implantation (CCI) results in significantly better early structural tissue regeneration than microfracture (MF), and CCI has a midterm clinical benefit over microfracture.

Purpose: This study was undertaken to evaluate the 5-year clinical outcome of CCI in a randomized comparison with MF for the treatment of symptomatic cartilage defects of the femoral condyles of the knee.

Study Design: Randomized controlled trial; Level of evidence, 1.

Methods: Participants aged 18 to 50 years with a symptomatic isolated International Cartilage Repair Society (ICRS) grade III or IV cartilage lesion of the femoral condyles between 1 and 5 cm² were randomized to either CCI or MF. Clinical outcomes were measured up to 60 months after surgery using the Knee Injury and Osteoarthritis Outcome Score (KOOS). The main outcome parameter was change from baseline in overall KOOS (oKOOS). Adverse events were monitored.

Results: Fifty-one participants were treated with CCI and 61 with MF. On average, clinical benefit was maintained through the 60-month follow-up period. The average change from baseline in oKOOS was not different between both groups (least squares [LS] mean ± standard error [SE] 18.84 ± 3.58 for CCI vs 13.21 ± 5.63 for MF; P = .116). Treatment failures were comparable (n = 7 in CCI vs n = 10 in MF), although MF failures tended to occur earlier. Subgroup analysis revealed that CCI resulted in better outcome in participants with time since symptom onset of less than 3 years, which was statistically significant and clinically relevant (change in oKOOS <3 years mean ± SE 25.96 ± 3.45 for CCI vs 15.28 ± 3.17 for MF; P = .026 vs oKOOS >3 years mean ± SE 13.09 ± 4.78 for CCI vs 17.02 ± 4.50 for MF, P = .554). Other subgroup analyses such as age (cutoff 35 years) did not show a difference. Female patients showed more failures irrespective of treatment.

Conclusion: At 5 years after treatment, clinical outcomes for CCI and MF were comparable. In the early treatment group, CCI obtained statistically significant and clinically relevant better results than MF. Delayed treatment resulted in less predictable outcomes for CCI. These results provide strong evidence that time since onset of symptoms is an essential variable that should be taken into account in future treatment algorithms for cartilage repair of the knee.

Keywords: autologous chondrocyte implantation; chondrocyte; chondral; regenerative medicine; Knee Injury and Osteoarthritis Outcome Score (KOOS); microfracture; cartilage repair; randomized controlled trial; long term

Articular cartilage lesions of the knee are known for their limited potential to heal spontaneously. Persistent defects in the condyle or patella will frequently become symptomatic and many progress toward secondary osteoarthritis (OA), affecting daily living and quality of life.8-19 The understanding of the relationship of structural changes in an affected joint and the subsequent development of OA could lead to new treatment strategies to prevent and treat this debilitating condition.16 Treatment modalities of joint surface lesions aim to restore pain-free joint function by promoting the formation of repair tissue that has the structure and durability of natural hyaline-like articular cartilage.14,20,42 Interventions intended to reestablish the cartilage surface by tissue repair include marrow stimulation techniques such as microfracture (MF),52 mosaicplasty,28 or regenerative approaches such as autologous chondrocyte implantation (ACI),7 and other variations on