

# Feasibility of arthroscopic 3-dimensional, purely autologous chondrocyte transplantation for chondral defects of the hip: a case series

S. Fickert · T. Schattenberg · M. Niks · C. Weiss · S. Thier

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## Abstract

**Introduction** The purpose of this retrospective study was to describe technical aspects of arthroscopic, purely autologous chondrocyte transplantation of the hip and to report short-term data of the postoperative outcome in a consecutive series of patients.

**Materials and methods** We retrospectively analyzed six patients with a full-thickness chondral defect of the hip joint. The defect was treated with an arthroscopically applicable 3-dimensional purely autologous chondrocyte transplant product (chondrosphere®; co.don® AG, Berlin, Germany) in a two-step surgical procedure. Patient-administered scores were assessed at baseline (day before transplantation) and at 6 weeks, 3, 6 and 12 months.

**Results** Six out of six initially included patients (five males, one female) with a median age of 32.5 years and an average defect size of 3.5 cm<sup>2</sup> were available for follow-up after a mean of 11.2 months. Five acetabular and one femoral defect were treated. An overall statistically significant improvement was observed for all assessment scores (NHS, mHHS and SF 36).

**Conclusion** In this study, we displayed the feasibility and technical aspects of arthroscopic matrix-associated, purely autologous chondrocyte transplantation as a treatment

option for full-thickness cartilage defects of the hip. The patient-administered assessment scores demonstrated an increase in activity level and quality of life after a 1-year follow-up.

**Level of evidence** Level IV, retrospective study.

**Keywords** Hip arthroscopy · Autologous chondrocyte transplantation · ACT · ACT3D · Cartilage defect

## Introduction

Over the past decade, there has been mounting evidence that Femoroacetabular impingement (FAI) may lead to the development of hip osteoarthritis [1, 4, 5, 26, 27, 30]. (FAI) is a pathomechanical hip process which leads to repetitive abutment between the femoral head–neck junction and the rim of the acetabulum, mainly anterolaterally [3–5, 9, 10, 12, 43]. This anatomic disorder may cause labral and chondral injury which leads to hip inflammation and pain [12–14, 26, 39, 46]. Particularly, CAM impingement is often associated with compression and shear forces upon cartilage leading to delamination even at early stages of the disease [1, 3, 5, 9, 26, 52].

Articular cartilage is a specialized structure with limited repair capacity. The appropriate therapy of articular cartilage lesions is important as retrospective study has revealed poorer outcomes in scenarios of significant cartilage damage [17, 25, 48–51]. Currently, there is no pharmacological agent that promotes the healing of articular cartilage lesions. Thus, physicians have attempted various surgical techniques such as marrow stimulation techniques, osteochondral transplantation and autologous chondrocyte transplantation (ACT) to restore articular surfaces [8, 35, 49]. These techniques are well established in the knee; however,

S. Fickert · T. Schattenberg · M. Niks · S. Thier (✉)  
Orthopaedic and Trauma Surgery Center, University Medical  
Centre Mannheim, University of Heidelberg, Theodor Kutzer  
Ufer 1–3, 68167 Mannheim, Germany  
e-mail: steffen.thier@umm.de

C. Weiss  
Medical Faculty Mannheim, Institute of Biostatistics,  
University Medical Centre Mannheim, University of Heidelberg,  
Mannheim, Germany

at the hip only a few case series have been reported [13, 25, 44, 48, 49, 51].

So far the microfracture procedure has been employed in hip arthroscopy for the treatment of full-thickness chondral defects [16, 17, 40, 44]. To date, there are few studies available on the results of this procedure while including only small numbers of patients [11, 13, 44, 48, 51].

One successful approach for cartilage defects of the knee is the autologous chondrocyte transplantation (ACT). This two-step procedure is regarded to achieve a high tissue quality in cartilage repair as the implantation of autologous cultured chondrocytes into chondral defects may replace damaged cartilage with hyaline or hyaline-like cartilage [6–8, 29, 31, 34, 36, 47].

Current concepts of matrix-associated chondrocyte transplantation (MACT) employ purely autologous products such as the autologous 3-dimensional chondrocyte product co.don chondrosphere (co.don AG, Teltow, Germany). This technique offers several advantages regarding growth and phenotypic stability, while consisting of human autologous spheroids in 0.9 % NaCl suspension. The spheroids derive from human autologous chondrocytes, which can produce cartilage-specific matrix and are able to build a 3-dimensional structure under defined cell culture conditions [32, 33].

Since 2004, co.don chondrosphere has been used in clinical practice for the treatment of chondral defects in the knee up to 10 cm<sup>2</sup>, classified as International Cartilage Repair Society (ICRS) grade 3 or 4 [32]. To date, however, a systematic evaluation of the improvement in functionality, mental and physical health, quality of life, and tolerability in association with the cartilage repair after transplantation of chondrosphere has not yet been performed in the hip.

The hip joint displays an excellent example of a congruous and spheroidal joint. Consequently the improved coverage leads to restricted space in the hip joint, which limits the range of therapeutic options. Accordingly, the transfer of the purely arthroscopic MACT technique to the hip remains challenging.

The purpose of this study was describing technical aspect of the arthroscopic MACT of the hip joint. Additionally, we report short-term data on postoperative outcome of the first six patients by using established scoring systems (Modified-Harris-Hip-Score, Non-Arthritic-Hip-Score, SF 36).

## Hypothesis

The arthroscopic MACT for the treatment of chondral defects of the hip is a feasible procedure that results in improved postoperative outcome.

## Materials and methods

This retrospective investigator-initiated trial was conducted according to the principles of the Declaration of Helsinki (World Medical Association). Approval was obtained by the local independent ethics committee. Our institution is authorized for withdrawal of starting material for donation and procurement according to directive 2004/23/EC.

### Participants and trial conduct

In a retrospective case series, we report data on the first six patients with a focal cartilage defect of the hip treated by an arthroscopically conducted purely autologous chondrocyte transplantation. Male or female patients between 18 and 50 years of age with isolated cartilage defects of the hip joints according to ICRS grades 3 and 4 and intact subchondral bone lamella and surrounding cartilage were included. Patients with more than one defect, opposing defects or radiographic signs of osteoarthritis higher than grade I according to Kellgren and Lawrence were excluded. Furthermore, patients unable to follow a standardized rehabilitation protocol were excluded.

Preoperative diagnostics included clinical and functional examination, standardized anterior–posterior (pelvis centered) and cross-table (hip centered) radiographs as well as magnetic resonance arthrography of the hip (Siemens, 1.5 T) [18, 42].

Evidence of FAI was determined by the evaluation of the  $\alpha$ -angle, the offset-ratio and lateral center-edge angle [53].

For the detection of cartilage injury we used magnetic resonance arthrography [3]. Patients with signs of a chondral defect in the mr-arthrography were eligible for inclusion.

On the day before arthroscopy, inclusion and exclusion criteria were checked, and patients filled in the questionnaires to assess their current state of health, pain, and functionality. During arthroscopy, the cartilage defect was classified macroscopically according to the International Cartilage Repair Society score of the knee, and biopsies and blood samples were taken for the cultivation of the chondrocytes as described above. Only defects classified as grade IIIa–IV, according to ICRS, were included (Table 1). About 4–6 weeks after biopsy and cultivation, spheroids were then transplanted in a second surgical procedure. The chondral defects were treated using the co.don chondrosphere (co.don<sup>®</sup> AG, Berlin).

### Instruments for subjective assessments

The following subjective questionnaires were used to evaluate patient outcome on the day before index arthroscopy,

**Table 1** Assessment of patient specific intraarticular findings

Patient	Localization	Defect-size (cm <sup>2</sup> )	ICRS	Labral treatment	Cause of defect
1	Anteromed. acetabulum	3.75	3c	Reconstruction	CAM-FAI
2	Anterosup. femoral head	2	3c	No treatment	Traumatic cause
3	Anteromd.–anterolat. acetabulum	5	3c	Partial resection	CAM-FAI
4	Anteromd.–anterolat. acetabulum	6	3d	Partial resection	CAM-FAI
5	Anterolat. acetabulum	1.8	3d	Reconstruction	CAM-FAI
6	Anteromd.–anterolat. acetabulum	2.5	3a	Reconstruction	CAM-FAI

which was defined as baseline and at 6 weeks, 3, 6 and 12 months after ACT3D: (1) Short-Form Health Survey (SF-36) evaluating the general health with mental and physical components; (2) the modified Harris Hip Score (MHHS) assessing pain and functional parameters of daily living; and (3) the Non Arthritic Hip Score (NAHS) rating symptoms, sports activities and function [15, 45].

#### Endpoints

Primary endpoint was the subjective improvement of symptoms and functionality displayed in the MHHS, NAHS and SF36 at 12 months after ACT3D compared to baseline (day before transplantation).

#### Operation technique and treatment with chondrosphere

Using the supine approach with ~10–15 mm joint distraction the defect area with localized cartilage defect was investigated utilizing two arthroscopic portals (anterolateral and anterior) and classified according to ICRS during index arthroscopy. The treatment of associated pathologies such as labral tears and CAM deformity was performed in the first operation.

After harvesting 200–300 mg of full-thickness cartilage from non-weight bearing areas of the hip (head-neck junction) during index arthroscopy, the specimens were sent together with 200 ml pre-operatively taken autologous patient serum in a special transport container. The culture process takes ~4–6 weeks. In vitro formation of 3-dimensional cartilage-like tissue was achieved without using any scaffolds [2, 33].

In a second arthroscopical procedure, the transplantation of the MACT product was conducted. The patient was placed in supine position and two arthroscopic portals (anterolateral and anterior) were established. Chondral defects were examined for any unstable cartilage flaps while debrading to produce a stable rim with good perpendicular margins. Calcified parts of the subchondral bone lamina were abraded.

For the transplantation constant fluid irrigation was stopped. To assure an ideal adhesion of the chondrospheres, the defect was kept as dry as possible. This was achieved by creating a third posterolateral portal to be used as drainage.

No suction was used on this portal to avoid the loss of any chondrospheres during implantation.

After complete preparation of the defect the transplant combined with an applicator system was taken out of the cooling reservoir. Either the anterior or anterolateral portal was used for transplantation, depending on which was more suitable. The adhesive properties of the chondrospheres facilitated a dropwise implantation in the defect without any further fixation. Subsequently, the chondral defect was carefully seeded with chondrospheres and enclosed medium through the deformable applicator. As the spheres were placed on the bottom of the defect they were immediately spread with a hook. The bonding of the transplant was obtained after 20 min. The bonding of the matrix is completed when its surface turns hydrophobic.

All patients reported to have rigidly followed the standardized postoperative rehabilitation protocol. Regular continuous passive motion (CPM) therapy was conducted for 6 weeks with a minimum usage of 6 h daily. The rehabilitation program included partial weight bearing for 6 weeks. Patients with labral repair were furthermore restricted to a flexion of maximum 60° over 6 weeks. Follow-up visits were performed at 6 weeks, 3, 6 and 12 months after chondrosphere. Besides functional scoring, data concerning pain medication, changes in concomitant medications, tolerability of the treatment and the occurrence of any adverse events (AEs) were gathered. Return to sports was administered 6 months after transplantation.

#### Statistics

Statistical calculations were performed using the SAS system, release 9.2 (SAS Institute Inc., Cary, NC, USA). Quantitative variables are given by mean value  $\pm$  standard deviation, categorical parameters by absolute and relative frequencies. A test result has been regarded as statistically significant for  $p < 0.05$ . Due to our small sample sizes test results with  $0.05 < p < 0.10$  are considered as slightly significant.

In order to evaluate changes over time, for each score system a repeated measures analysis has been performed. The SAS procedure PROC MIXED has been used as this procedure is very efficient in the case of missing values. In

the case of a significant test result, Dunnett test has been done to compare the score values at each evaluation point with the baseline value.

Pearson's or Spearman's correlation coefficient has been assessed, as appropriate, to test for association between score values and other quantitative parameters.

## Results

### Baseline characteristics

A total of six patients (five men, one woman) aged between 25 and 45 years were included in this investigation for the treatment with ACT3D. All patients completed follow-up examinations. The average time of follow-up was 11.2 months. According to ICRS classification all patients were diagnosed with a full-thickness chondral defect of the hip IIIa–IIIc. Three defects were located on the anterolateral–anteromedial acetabulum, one on the anterolateral acetabulum, one on the anteromedial acetabulum and one on the anterosuperior femoral head. The average defect size was 3.5 cm<sup>2</sup>. All acetabular defects were caused by CAM-impingement. The femoral lesion was of traumatic cause. None of the chondral lesions were associated with a concomitant defect. Duration of symptoms (pain, impairment in general health, and daily life functions) varied between 5 and 17 months. None of the patients had undergone surgical treatment of the affected hip before.

During index arthroscopy, five patients received additional treatment in the affected hip: offset reconstruction was performed in five patients, three received additional labral repair and two partial resection of the labrum. The operation time for the ACT3D was 107 min on average (Min/Max, 81–139 min). The demographic data and baseline characteristics of the study population are illustrated in Table 2.

### Radiographic assessment

One patient showed radiographic evidence of a mild hip dysplasia. One patient showed radiographic evidence of osteoarthritis grade I according to Kellgren and Lawrence. Five of six patients showed a reduced head–neck offset (range 1–6 mm) and an increased  $\alpha$ -angle (range 64°–76°).

### Functional outcome evaluation

Clinical efficacy of ACT3D was evaluated in terms of functional, symptomatic testing according to several well-established clinical outcome scores [Non-Arthritic-Hip Score (NAHS), Modified-Harris-Hip Score (MHHS) and short-form health survey (SF-36 Score)]. Compared to baseline, all three rating scales displayed significant improvement

**Table 2** Demographic data and baseline characteristics of study population

Demographics	Cases
Age in years	33 (Range 25–45)
Body mass index (kg/m <sup>2</sup> )	26 (Range 20–31)
Gender (male/female)	5/1
Locality of defect	
Anterolateral–anteromedial	3
Anterolateral	1
Anteromedial	1
Femoral head	1
Number of defects	
1	6/6
Defect size	
<2 cm <sup>2</sup>	1
2.0–6.0 cm <sup>2</sup>	5
>6 cm <sup>2</sup>	0
Labral tear	5/6
Repair	3
Partial resection	2
Total number of patients	6

12 months after chondrosphere, as illustrated in detail for each score in the following.

### Non-arthritic-hip score (NAHS)

Patients who underwent chondrosphere of the hip showed an overall improvement according to the Non-Arthritic-Hip score when comparing to baseline [median score at baseline: 67.5 % (SD 22.2); 12 months after chondrosphere: 95.6 % (SD 4.4)]. 6 weeks after surgery no improvement was monitored. 3 months after surgery improved scoring results were noted. At 12 months after chondrosphere significant improvement has been noticed ( $p = 0.02$ ).

### Modified-harris-hip score (mHHS)

12 months after chondrosphere patients improved significant in the Modified-Harris-Hip Score compared to baseline [ $p = 0.04$ ; median score at baseline: 74.5 points (SD 17.2); 12 months after chondrosphere: 98.0 points (SD 2.8)]. 3 months after surgery improved scoring results were monitored.

### SF-36 physical and mental score

Patients who underwent chondrosphere of the hip showed an overall improvement according to SF-36 physical subscores, when comparing to baseline data before chondrosphere [median baseline: 47.8 points

(SD 21.4); 12 months: 93.4 points (SD 2.7),  $p < 0.01$ ]. The SF-36 mental subscores did not show significant improvement comparing to baseline data. [Median baseline: 57.4 points (SD 27.8); 12 months: 90.1 points (SD 6.5),  $p = 0.09$ ].

### Subgroup analyses

Two variables were categorized (size of defect and labral treatment) and analyzed in regard to their potential influence on the outcome following chondrosphere of the hip.

### Defect size

Considering functional outcome, evaluation of defect size did not prove to be of significant influence on functional outcome in the NAHS ( $p = 0.3$ ) or the physical subscore of the SF36 ( $p = 0.8$ ). In contrast, the defect size displayed a significant influence in the mHHS ( $p = 0.03$ ).

### Treatment of labral pathology

Results of functional outcome assessment were evaluated with respect to the treatment of labral tears (refixation vs. resection). Considering functional outcome evaluation, neither repair nor partial resection did prove to be of significant influence for functional outcome (NAHS  $p = 0.7$ , mHHS  $p = 0.3$ , physical subscore SF36  $p = 0.9$ ).

### Complications

Two patients reported an adverse event within the first 2 weeks after arthroscopy. One patient complained a temporary hypoesthesia in both forefeet immediately after index arthroscopy. The symptoms were completely recurrent without any specific treatment by the time the patient was discharged from the hospital. Another patient complained pain at the scrotum with a localized redness for the initial 24 h after index arthroscopy. No postoperative infection was monitored.

## Discussion

The present study reports technical aspects of arthroscopic autologous chondrocyte transplantation in the hip joint and short-term results of the first six patients with respect to mental and physical health, pain and functionality in patients with isolated cartilage defects in the hip.

To date, little is known about the appropriate treatment of full-thickness cartilage lesions in the hip. Bone marrow stimulating techniques, commonly used in knee surgery, are described for the treatment of full-thickness cartilage

lesions in the hip [11, 13, 44, 48, 51]. The microfracture procedure was used first in arthroscopic approaches and described by several authors listed below (Table 3). These studies are case series without control groups and rather small patient numbers classified as EBM level IV. However, all authors could monitor a significant improvement in the functional outcome evaluation at follow-up ranging from 1, 6 to 10 years. The appropriate patient selection seems to be important to achieve good postoperative results [11–13, 28, 48, 50]. At 10-year follow-up 14 conversions to THA were reported by Byrd et al. [13]. As commonly known, osteoarthritis has to be seen as a contraindication for the microfracture procedure of chondral defects of the hip joint [11–13, 50].

Recently, a further treatment option was reported using fibrin adhesive for arthroscopic repair of acetabular chondral delamination [49]. 43 patients were treated with this technique. There was a significant improvement in the mHHS at a mean of 28 months (16–42 months) after surgery. Three patients had early (within 12 months of the index procedure) revision arthroscopy for iliopsoas pathology. The author concluded this technique to be a useful option in the treatment of early cartilage damage [49]. A limitation of this technique is the judgment of refixed cartilage quality. Long-term results are needed to confirm the effectiveness of this technique.

Brittberg et al. [8] initially introduced autologous chondrocyte transplantation for the treatment of full-thickness chondral defects in the knee in 1994. Over the past decades the initial concept has been further developed and became one of the best-evaluated treatments in orthopedic surgery with good long-term results and predominantly hyaline like repair cartilage [6–8, 29, 31, 34, 36, 47].

Due to the restricted joint space the arthroscopic application of the ACT at the hip remains difficult from the technical point of view, as many transplants need further fixation by suture or adhesives.

In this context Fontana et al. [25] reported their 5-year follow-up results of 15 Patients on the treatment of chondral defects of the hip with ACT in comparison to simple debridement. Although they also used a two-step procedure, they did not use a MACT transplant as their polymer-based scaffold was seeded after cultivation of the chondrocytes. The average defect size of 2.6 cm<sup>2</sup> was smaller than ours. Similar to our study they monitored a significant improvement in the patients treated with ACT in all outcome parameter. From the technical point of view the preparation of their scaffold may be more difficult. Before transplantation the defect size had to be assumed and the scaffold membrane had to be cut to exact fit. Then it had to be rolled to pass along the cannula. During implantation no further fixation of the scaffold has been used, as Fontana assumes the pressure of the femoral head against the acetabulum



**Table 3** Review of cartilage defects treated by microfracture of the hip

References	n	Size of defect (min/max)	Follow-up	Results	Side pathology	EBM
Byrd and Jones [11]	21	12.2 mm <sup>2</sup> (6/17.5 mm <sup>2</sup> )	32.6 months	mHHS 23.9 points improvement	17 Labral pathology 3 Accompanying lesions femoral head 3 Deg. rupturs lig. teres3 deg. rupturs lig. teres	IV
Philippon [44]	9	162 mm <sup>2</sup> (40/240 mm <sup>2</sup> )	1.61 years	91 % Defect filling 1/9 THA after 3 years 1/9 Femoral resurfacing at second-look	6/9 FAI 3/9 Adhesive capsulitis 1/9 Myositis ossificans 1/9 Femoral defect	IV
Singh [48]	6/27	Lesions up to 3 cm <sup>2</sup>	22 months	mHHS 10 points improvement NAHS 23 points improvement	9/27 Labral pathology 2/27 Loose bodies 22/27 Cam impingement 4/27 Pincer impingement	IV
Byrd and Jones [13]	27/52	Size not mentioned 1 Grade II, 14 Grade III, and 12 Grade IV lesions (Outerbridge)	10 years	mHHS 19 points improvement (mHHS 38 points improvement after exclusion of 14 arthritic patients) 14 Conversions to THA	30/52 Labral disorders 27/52 Chondral damage 14/52 Arthritic disorder 10/52 Dysplasia 9/52 Synovitis 7/52 Loose bodies 4/52 Avascular necrosis	IV

and the sharp margins of the chondral lesion after debridement contribute to the stability of the transplant.

Cartilage defects of the femoral head could not be addressed due to rigid scaffold properties [25]. In contrast, the spheroids employed in this study provided adhesion and integration to the native cartilage tissue and the subchondral bone plate without any additional materials required for fixation. This seems to be a major advantage of this technique especially in the hip. As these spheroids are purely autologous, the risk of rejections, incompatibilities or viral contaminations is minimized. Furthermore, they contain chondrocytes in an advanced differentiation state, producing cartilage-specific matrix before being transplanted [33]. It has been proposed that this treatment may accelerate the process of defect filling and consequently the improvement in functioning in daily life and sports activities.

CAM-Impingement is known to cause large defects of the acetabular cartilage and is commonly seen in young patients [38]. The most frequent localization of chondral defects in CAM-impingement is the anterior aspect of the acetabulum [3, 4, 39]. This patient subset is suitable for the arthroscopic treatment with ACT. All our patients presented cartilage defects in the anterior compartment of the hip as they are easily accessible for ACT. Defects of the femoral head can also be addressed by this procedure due to the adhesive properties of the spheroids. Cartilage defects in the posterior compartment of the hip, however, remain challenging.

Evidence is accumulating that a repair of a torn labrum should be performed rather than a partial excision [19–24, 37]. Based on these studies, the preservation of the labrum seems to be important for functionality of the hip joint and protection of the cartilage surfaces. In this study we were able to repair three of five coexisting labral defects as two patients presented a fibrous repair tissue which could not be repaired.

Inconsistent with the studies discussed above the different treatment options for labral pathology (resection vs. refixation) did not have significant influence in the postoperative outcome in this study. This demonstrates that the appropriate treatment of coexisting chondral defects may have a high influence on the overall outcome and postoperative activity level as previously described by several authors [9, 13, 20, 41, 49, 51].

To date, there is no consensus statement on the influence of defect size on postoperative outcome after hip arthroscopy. One study has been published reporting about correlation between defect size and postoperative outcome. Singh et al. [48] concluded that larger defect size may have an inferior postoperative outcome. Most studies did not correlate defect size with postoperative outcome [11, 13, 44, 51]. In our study, defect size did not prove to have a major influence on overall postoperative outcome.

Overall, the final scores after treatment with chondrospheres revealed statistically significant increased levels of activity and quality of life after 12 months' follow-up. This indicates that in terms of pain relief and improvement of hip function the chondrosphere seems to be an effective treatment method for full-thickness cartilage defects of the hip. Consistent with this hypothesis, one patient enrolled in this study showed radiographic signs of osteoarthritis before surgery. He showed the lowest improvement rate in the NAHS at 6 months compared to baseline and a decrease in the mHHS at 6 months compared to baseline.

### Limitations

Due to the small number of patients, the lack of a control group and the assessment of 12 months, this study shows several limitations. No second-look arthroscopies with chondral biopsies for histomorphological assessment or MRI-scans have been performed to improve the value of the presented data. Further limitations are a selection bias during patient inclusion as we only had FAI patients. The missing control group does not allow any conclusions. It is important to mention the different treatment options in regard to coexisting labral pathology.

### Conclusion

In this study, we displayed the feasibility and technical aspects of arthroscopic matrix-associated, purely autologous chondrocyte transplantation as a treatment option for full-thickness cartilage defects of the hip. The patient-administered assessment scores demonstrated an increase in activity level and quality of life after a 1-year follow-up.

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**Conflict of interest** None.

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