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ARTHROSCOPY AND SPORTS MEDICINE

# Presence of subchondral bone marrow edema at the time of treatment represents a negative prognostic factor for early outcome after autologous chondrocyte implantation

**Philipp Niemeyer · Gian Salzmann · Matthias Steinwachs · Norbert P. Südkamp · Hagen Schmal · Philipp Lenz · Wolfgang Köstler**

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**Abstract**

*Introduction* Since introduction of autologous chondrocyte implantation (ACI), various factors have been described that influence the clinical outcome. The present paper investigates the influence of bone marrow edema at time of treatment on clinical function before and in the early clinical course after ACI.

*Methods* 67 patients treated with ACI for cartilage defects of the knee joint were included. Presence of subchondral bone marrow edema was graded as absent (1), mild (2), moderate (3) or severe (4) using magnetic resonance (MR) imaging before surgery. All patients were assessed in terms of clinical function before surgery and 6 as well as 12 months after ACI using IKDC and Lysholm scores. Presence of subchondral edema was correlated with functional outcome.

*Results* In 18 patients edema on initial MRI was graded as "absent", while 17 patients had grade 2 edema, 19 patients had grade 3 edema and 13 patients had grade 4 edema. IKDC score increased significantly from 49.8 points (SD ± 14.9) to 72.3 points (SD ± 17.5) at 12 months ($p < 0.01$). At all time points investigated, patients of group "4" showed inferior results to all other groups ($p < 0.05$). In addition, in patients without any edema, better clinical function was detected compared to all other groups before surgery ($p < 0.05$) and compared to group 3 at 6 months following ACI ($p < 0.05$).

*Conclusions* Presence of severe subchondral bone marrow edema seems to correlate with knee function in patients with cartilage defects and may be a reliable prognostic factor for the early clinical course after ACI.

**Keywords** Subchondral edema · Autologous chondrocyte implantation · Cartilage repair · Cartilage defect · Cell transplantation · Knee joint

## Introduction

Autologous chondrocyte implantation (ACI) is a common and accepted surgical treatment for symptomatic full thickness cartilage defects of the knee [1, 2]. Since its introduction in 1994, different technical modifications have been developed, most of them intending to lead to easier surgical application or to a more reliable cell delivery and more homogenous cell distribution in the defect [3–8]. Defect location has been identified as an important prognostic factor, since obviously defects being located on the femoral condyles are associated with a better clinical outcome compared to patella defects [4, 9, 10]. In addition, there seems a tendency for improved outcome in younger patients with traumatic defects compared to older patients, comparable to alternative regeneration techniques [11, 12]. Furthermore, degeneration grade of the joint was identified as a further prognostic factor [13]. Except for these important observations, the identification of further prognostic factors that influence the patient's outcome following ACI are not available.

Since MRI plays an important role in the diagnosis of a cartilage defect and in the further clinical course following

P. Niemeyer (✉) · G. Salzmann · N. P. Südkamp · H. Schmal · P. Lenz · W. Köstler
Department of Orthopedic Surgery and Traumatology, Freiburg University Hospital, Hugstetter Str. 55, 79095 Freiburg, Germany
e-mail: philipp.niemeyer@uniklinik-freiburg.de

M. Steinwachs
Department of Cartilage Regeneration and Orthobiologics, Schulthess Clinic, Zurich, Switzerland

ACI, in the present study, subchondral edema as visualized on MRI was investigated concerning its relevance on function and pain of patients with cartilage defects, which were treated with ACI. To correlate the presence and extent of subchondral edema at the time of surgery and with the clinical course following ACI procedure was the purpose of the present study. This is not only interesting from the radiographic and surgical point of view, but also with regard to the fact that there is a general trend in cartilage repair to consider articular cartilage, subchondral bone plate and subchondral bone as an important functional unit.

## Materials and methods

Between October 2005 and October 2007 a total of 96 patients underwent ACI for isolated or multiple cartilage defects of the knee joint. All patients have been enrolled in the current study prospectively. For the current analysis, patients with more than one cartilage defect have been excluded ($n = 29$). Therefore, 67 patients were available for the current study. One patient was lost for follow-up (follow-up rate = 98.5%). Minimum follow-up in the present study was 12 months.

In all patients, indication for ACI was done during a routine arthroscopy of the affected knee joint. Significant corresponding cartilage lesions, uncontained defects and defects of the subchondral bone plate exceeding a depth of 3–4 mm were considered as exclusion criteria for ACI. ACI was performed as a cell-seeded collagen matrix-supported transplantation (ACI-CS) [3] with exception of one case in which a matrix-associated ACI was performed. Significant corresponding cartilage lesions, uncontained defects and defects of the subchondral bone plate exceeding a depth of 3–4 mm were considered as exclusion criteria for ACI in our study. During arthroscopy, chondrocytes were harvested using a standardized cartilage biopsy tool (Storz, Tuttlingen, Germany) from the intercondylar notch. In all patients, ACI was performed using a mini-open surgical approach. Anteromedial mini-arthrotomy was performed for defects located on the medial femoral condyle, in the trochlea as well as on the patella. For defects at the lateral femoral condyle, an anterolateral approach to the knee joint was chosen. After debridement of the defect, between 1 and 2 million chondrocytes per cm² (CartiGro® Autologous Chondrocytes, Metreon Bioproducts GmbH, Freiburg, Germany) defect were applied to the rough side of the porcine type I/III collagen membrane (ChondroGide©, Geistlich; Wolhusen, Switzerland). After 5–10 min, when adherence of the chondrocytes on the membrane was achieved, the cell/matrix constructs were transferred to the defect. Fixation of the cell/matrix constructs was performed as described earlier. In short, 6.0 PDS sutures were used in order to achieve a solid fixation in the surrounding tissue. The average of sutures per defect was about 4–8. In addition, fibrin glue (TissueCol©, Baxter; Unterschleissheim, Germany) was used to seal the defect and for additional fixation.

Continuous passive motion (CPM) was recommended to all patients following ACT-CS from day 1 after surgery for 6 weeks postsurgery. Patients were instructed to use CPM devices for up to 4 h per day. Limited weight bearing was recommended for 6 weeks after ACT-CS. Later, weight bearing was increased to full weight bearing by week 9 postsurgery. Individual limits of flexion were given additionally depending on the exact defect location in order to avoid early exposure of the regenerative cartilage to axial compression and shear forces.

For clinical assessment before surgery and in further clinical course Lysholm [14], subjective IKDC-2000 [15] and Tegner scores [16] were used according to the general recommendations. Follow-up investigations were performed at 6 and 12 months following surgery.

### Preoperative MRI evaluation

In all cases, preoperative MRI evaluation of subchondral bone marrow edema included the following sequences: sagittal T1-weighted imaging, sagittal T1 GE fat-suppressed imaging and coronal T2 fat-suppressed imaging. Bone marrow edema was graded as absent (1), mild (2), moderate (3) or severe (4) as recommended and introduced by Henderson et al. [17]. In order to receive more reliable and reproducible group assignment, different grades of subchondral bone edemas were standardized as follows. A patient was assigned to group “4” (see Fig. 5) and considered as a severe bone marrow edema, if the depth of the edema exceeded the width of the cartilage defect in either sagittal or coronal MRI scans. Patients in which subchondral edema measured 50–100% of the diameter of the cartilage defect were assigned to group “3” (see Fig. 4), while those in which smaller edemas were noted were assigned to group “2”. The complete absence of subchondral edemas was mandatory for assigning a patient to group “1”.

### Statistical analysis

For statistical analysis, the software SPSS Version 17.0 was used. Significant differences in between different points in time of the present study as well as different cohorts of patients and grade of bone marrow edema were evaluated using a one-way ANOVA test for all parametric data such as IKDC score and Lysholm score including a post hoc Tukey-HSD analysis. $p < 0.05$ was considered statistically significant, $p < 0.01$ was considered strongly significant.

## Results

67 patients with a minimum follow-up of 12 months following ACI were evaluated in the current study. Mean age was 37.43 years (SD ± 8.82), mean defect size was 4.3 cm$^2$ (SD ± 1.6). All cartilage defects were graded stage 3 ($n = 25$) and stage 4 according to the ICRS classification. 31 defects were located on the medial (46.7%), 10 defects on the lateral femoral condyle (15.2%), 3 lesions were found in the trochlea groove (4.5%), while 22 patella defects were treated (33.3%). Among those patients without subchondral edema the distribution of the defect location included ten patients with defects of the medial femoral condyle (55.5%), three patients with defects located on the lateral femoral condyle (16.7%), while four patients had lesion of the patella (22.2%) and in one case a trochlea defect was treated (5.6%). The incidence of subchondral edema did not differ depending on defect location ($p = 0.862$) or size ($p = 0.677$). The presence and extent of subchondral bone marrow edema depending on the defect location is given in Fig. 1. No significant differences were found regarding the incidence of bone marrow edema with regard to defect location. According to the Henderson criteria, 18 patients were assigned to group "1" = no subchondral edema; 17 patients to group "2" = mild edema; 19 patients to group "3" = moderate edema and 13 patients to group "4" = severe edema.

Concerning the entire study group, a significant increase in knee function with regard to the Lysholm score and the IKDC score was found comparing preoperative data with 6 month as well as 12 month controls. Lysholm score increased from 60.3 points (SD ± 11.5) preoperative to 72.2 points (SD ± 15.5) at 6 months ($p < 0.01$) and to 77.9 (SD ± 17.7) at 12 months following ACI ($p < 0.01$). Analogous significances were found concerning the IKDC score which increased from 49.8 points (SD ± 14.9) to 65.5 points (SD ± 15.1) at 6 months ($p < 0.01$) and 72.3 points (SD ± 17.5) at 12 months ($p < 0.01$).

Clinical scores depending on the degree of subchondral edema is displayed in Fig. 2 (Lysholm score) and in Fig. 3 (IKDC score) including relevant significances between different groups. Concerning the influence of the presence of bone marrow edema in the initial MRI on preoperative knee function, a significant better function according to the IKDC score was found in patient without edema (grade 1) compared to those in which bone marrow edema was present [$p$ ($\text{IKDC}_{\text{grade 1 vs. grade 2}}$): 0.014; $p$ ($\text{IKDC}_{\text{grade 1 vs. grade 3}}$): 0.001; $p$ ($\text{IKDC}_{\text{grade 1 vs. grade 4}}$): 0.001]. In addition, patients with a large bone marrow edema were inferior to patients with mild or moderate edema [$p$ ($\text{IKDC}_{\text{grade 2 vs. grade 4}}$): 0.001; $p$ ($\text{IKDC}_{\text{grade 3 vs. grade 4}}$): 0.008]. No further statistically significant differences were found concerning preoperative knee function. With regard to the clinical results

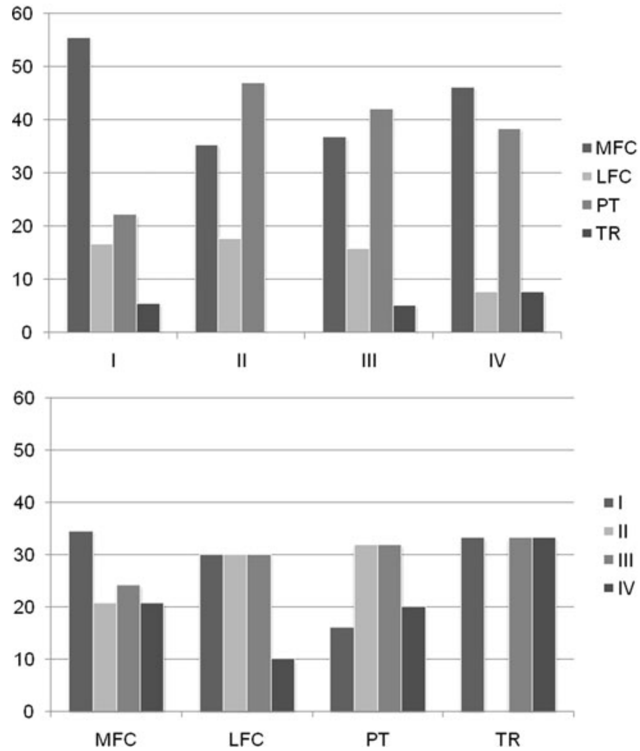


**Fig. 1** Incidence of subchondral edemas (percentages given on $y$-axis) depending on the grade of the edema (*upper image*) and defect localization (*lower image*): *MFC* medial femoral condyle, *LFC* lateral femoral condyle, *PT* patella, *TR* trochlea groove

according to IKDC score at 6 months following ACI, again patients with grade 4 bone marrow edema performed significantly worse compared to all other patients [$p$ ($\text{IKDC}_{\text{grade 1 vs. grade 4}}$): 0.001; $p$ ($\text{IKDC}_{\text{grade 2 vs. grade 4}}$): 0.002; $p$ ($\text{IKDC}_{\text{grade 3 vs. grade 4}}$): 0.017]. Patients without bone marrow edema performed better compared to those with moderate bone marrow edema [$p$ ($\text{IKDC}_{\text{grade 1 vs. grade 3}}$): 0.027]. At 12 months after ACI, only significances were found when comparing patients with grade 4 edema to those with any other type of edema [$p$ ($\text{IKDC}_{\text{grade 1 vs. grade 4}}$): 0.001; $p$ ($\text{IKDC}_{\text{grade 2 vs. grade 4}}$): 0.001; $p$ ($\text{IKDC}_{\text{grade 3 vs. grade 4}}$): 0.002]. No additional differences were found.

## Discussion

Autologous chondrocyte implantation (ACI) is a well-accepted surgical treatment for isolated cartilage defects of the knee joint. However, the success rate varies between 80 and 90% depending on the reference. Various factors that influence clinical outcome following ACI have been described and technique-associated complications have been analyzed.

Nevertheless, full thickness cartilage defects lead to an affection of the subchondral bone, which is generally not

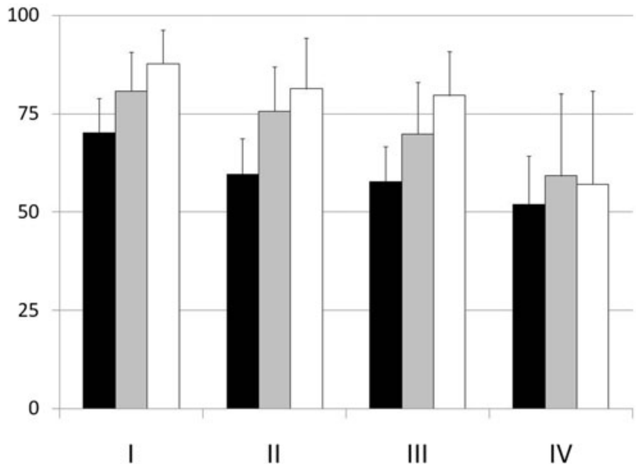


**Fig. 2** Lysholm score (*Y*-axis) before surgery (*black columns*), 6 months (*grey columns*) and 12 months (*white columns*) following ACI depending on the presence and extent of subchondral bone marrow edema. Significances are given in the "Results" section

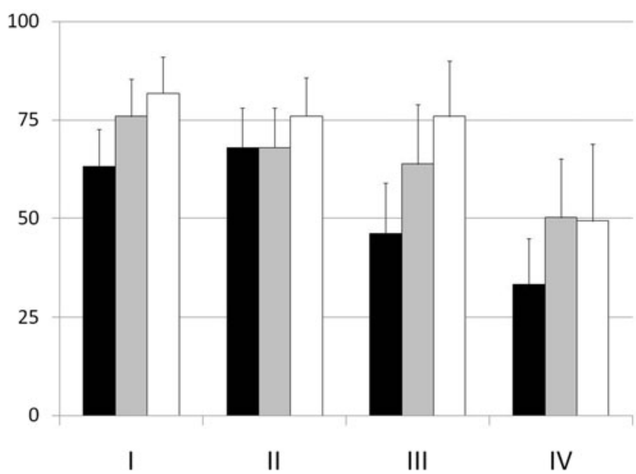


**Fig. 3** IKDC score (*Y*-axis) before surgery (*black columns*), 6 months (*grey columns*) and 12 months (*white columns*) following ACI depending on the presence and extent of subchondral bone marrow edema. Significances are given in the "Results" section


**Fig. 4** Coronal T2-weighted MRI of a patient with a full thickness cartilage defect of the lateral femoral condyle with a grade 3 subchondral edema. Depth of the subchondral edema is slightly smaller compared to the coronal diameter of the cartilage defect but above 50%

included in the treatment itself; unless there is a significant osseous defect as in patients with osteochondritis dissecans (OD). The current paper focuses on the relevance and the influence of subchondral bone marrow edema at the time of surgery on function of the affected knee joint before and after ACI, because subchondral edema is a pathology of increasing interest not only in patients with cartilage defects and osteoarthritis, but also in further systemic or local diseases [18].

Traumatic bone marrow edema has been described by Mink and Deutsch in 1989 in patients with anterior cruciate ligament tears [19]. In the meantime, several publications have described a significant relationship between subchondral edema and overlying articular cartilage [20]. In an experimental animal model, traumatic subchondral edema was associated with a loss of the zonal organization of articular cartilage [20] and therefore seems directly to affect the joint surface. Furthermore, recent studies have demonstrated the importance of subchondral nutrition of the native cartilage [21] and regenerative cartilage in autologous transplants [22]. In addition, several clinical studies have shown that subchondral lesions might heal into subchondral sclerosis, which might be of different biomechanical stiffness compared to original native subchondral bone, which could lead to an increase of shear forces affecting the overlaying cartilage [23–25]. These findings clarify the important association between changes in the subchondral bone and the cartilage and the necessity to understand this as a functional unit. The importance of subchondral bone is also represented by the fact, that in most scoring systems established to objectively follow patients after cartilage repair procedures, the presence and size of subchondral edema has been included as a relevant parameter [26, 27].

Concerning the overall incidence of subchondral edema, in 73% of our patients the presence of subchondral edema was detected by MRI at the time of surgery. This observation goes along with other studies that describe an incidence in full thickness cartilage defects between 55 and 83% [28, 29]. The incidence of bone marrow edema in the current study could not be correlated with defect size or location. This observation needs to be considered against the background that only full thickness defects were

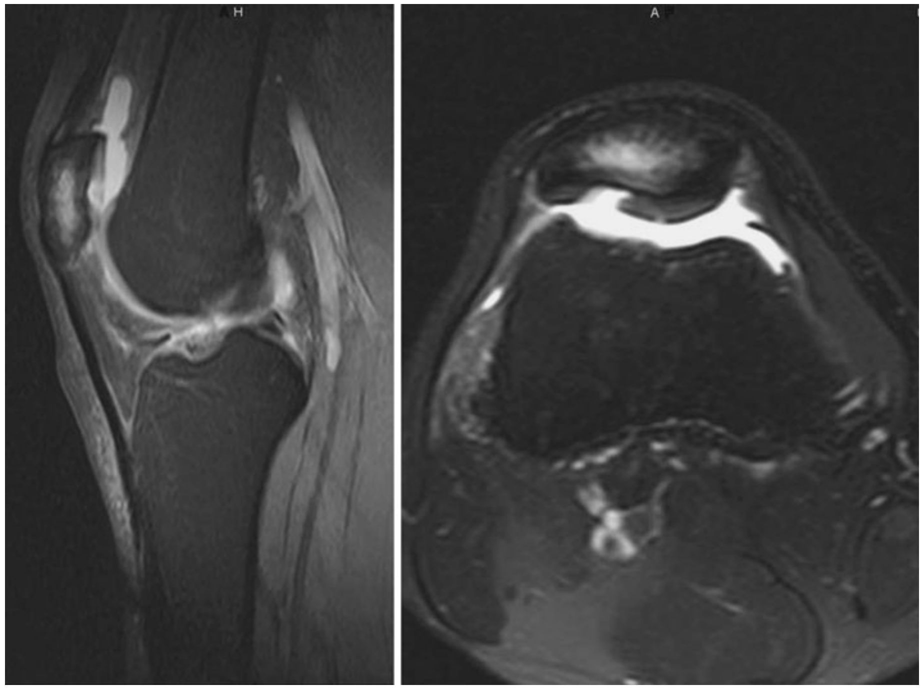


**Fig. 5** Grade 4 subchondral bone marrow edema in a patient with isolated and circumscribed full thickness cartilage defect of the lateral facet of the patella. Depth of the edema significantly exceeds the width of the cartilage defect

included in the current study. Therefore, it seems comprehensible that other authors who included partial thickness defects in their studies describe an influence of defect grade concerning the incidence of associated subchondral edema [29]. Interestingly, the incidence of subchondral edemas in cartilage defects located on the medial femoral condyle was lower, while in patella defects the vast majority of defects included subchondral edemas in different characteristics. We found no reliable literature concerning the issue of the presence of subchondral edemas depending on the defect location to compare our results.

In our study, a significant correlation between the incidence and size of subchondral edema in patients with cartilage defects of the knee joint and defect-associated pain and knee function was found. Patients with no subchondral edema showed higher clinical scores on the Lysholm scale and according to the IKDC score compared to patients with subchondral edema independent of the degree and size of the edema. Within the patients with subchondral edema a correlation between size of the edema and knee function could not be detected. This observation was independent of the therapy applied, since preoperative MRI findings were correlated with preoperative clinical data. This observation seems feasible since no nociceptors are expressed within the cartilage, but in the underlying subchondral bone [30] and has been found in analogous matter for patients suffering from osteoarthritis of the knee [31]. Interestingly, an analogous relation between bone marrow edema and pain is also described for patients with transient osteoporosis of the hip joint [32]. In these patients, the presence and size of subchondral edema could be clearly associated with symptoms; also in patients with chronic back pain the contribution of subchondral signal abnormalities is considered to contribute to low back symptoms [33].

In addition to the differences observed prior to surgical treatment, we were able to identify the presence of subchondral edema at the time of ACI a negative prognosis factor for the early clinical outcome following ACI, until 12 months after surgery. To clarify, the subchondral edema at time of surgery independently from a further increase or decrease in 6 and 12 months postoperative controls. Interestingly, while significant differences between those patients without subchondral edema and all other patients were observed preoperatively, only a significant difference between patients without and those with large edema was found in the further clinical course following ACI with regard to the Lysholm score. A analogous trend was observed concerning the evaluation of knee function according to the IKDC score, nevertheless, using this score additional differences between patients graded “1” (no edema) and “3” (moderate edema) were found in supplement to the significance between group “1” and group “4” (severe edema). The trend that significant differences between different types and grades of subchondral edema get lost over time could be interpreted as an advice, those patients with subchondral edema might only be characterized by a prolonged clinical course following surgery and might end up in similar clinical results. A possible explanation for our observation that large bone marrow edema are correlated with inferior early clinical outcome following ACI could be that microcracks and neovascularization of the subchondral bone could lead to an abnormal remodeling of the overlying cartilage [34]. Studies with a longer clinical follow-up will help to clarify this.

Although we are aware of the preliminary character of the data and data concerning the influence of subchondral edema on final clinical outcome have to be evaluated before definite conclusions can be drawn, consequences for the treatment of patients with cartilage defects that go along with extensive subchondral edema have to be discussed. Since patients who underwent ACI for cartilage defects have to wait for several weeks before surgery can be performed while chondrocytes are expanded in vitro, there is possible time to address subchondral edema separately before ACI is performed. Several studies have demonstrated a positive influence of diverse medications including prostacyclin analogue drugs [35] and antiresorptive drugs such as bisphosphonates [36]. In addition, even surgical approaches such as retrograde drilling [37] in order to address subchondral edema before ACI is performed are considerable, since arthroscopy of the affected knee joint has to be performed for cell harvesting anyhow. To address long-term outcome of patients depending on the subchondral edema in order to evaluate if the phenomenon observed in this study is only temporary or permanent will also be a part of the following studies as the evaluation of possible treatment options. In addition, studies will be necessary in order to evaluate the influence of the presence, increase or decrease of subchondral edema in the clinical course following ACI which would also be of great interest.

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