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SCIENTIFIC ARTICLE

Repair tissue quality after arthroscopic autologous collagen-induced chondrogenesis (ACIC) assessed via T2* mapping

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Abstract
Objective A novel single-stage approach using arthroscopic microdrilling and atelocollagen/fibrin-gel application is employed for cartilage repair of the knee. The purpose of our study was to investigate the morphological and biochemical MRI outcome after this technique.
Materials and methods A retrospective case series of ten patients (mean age 45 years) with symptomatic chondral defects in the knee who were treated arthroscopically with microdrilling and atelocollagen application was analyzed. All defects were ICRS grade III or IV and the sizes were 2–8 cm^2 intra-operatively. All patients underwent morphological MRI and T2-star mapping at 1.5 T at 1-year follow-up. The magnetic resonance observation of cartilage repair tissue (MOCART) score was assessed. T2* relaxation time values of repair tissue and a healthy native cartilage area was assessed by means of region of interest analysis on the T2* maps.
Results The mean MOCART score at 1-year follow-up was 71.7±21.0 ranging from 25 to 95. The mean T2* relaxation times were 30.6±11.3 ms and 28.8±6.8 ms for the repair tissue and surrounding native cartilage, respectively. The T2* ratio between the repair tissue and native cartilage was 105 %±30 %, indicating repair tissue properties similar to native cartilage.
Conclusions An arthroscopic single-stage procedure using microdrilling in combination with atelocollagen gel and fibrin-glue can provide satisfactory MRI results at 1-year follow-up, with good cartilage defect filling. The T2* values in the repair tissue achieved similar values compared to normal hyaline cartilage.

Keywords Cartilage repair · Autologous matrix-induced chondrogenesis (AMIC) · Autologous collagen-induced

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Introduction

Cartilage defects are common in young to middle-aged persons. Although considerable progress in cartilage repair techniques has been achieved within the past decades, it is still challenging [1].

The development of single-stage cartilage repair techniques aims to provide simple and effective treatment for articular cartilage defects [2]. In comparison to the two-stage autologous chondrocyte implantation (ACI), single-stage techniques do not use cultured cell implantation, but rely on cell recruitment from the bone marrow. These *marrow stimulation techniques* (MST) have undergone major development by the use of scaffolds and matrices [3].

Scaffolds were designed to provide an ideal environment for cartilage regeneration. They give mechanical stability and modulate the cell phenotype [4]. In single-stage scaffold-based MST, bone marrow derived mesenchymal stem cells are recruited and promote the formation of cartilaginous repair tissue. The repair tissue after microfracturing without the use of a scaffold consists mainly of fibrocartilage and is prone to early degeneration [4]. Therefore the use of scaffolds in combination with MST has been suggested to provide an environment for the formation of hyaline-like cartilage repair tissue [4, 5].

Cell-free collagen type I gel or matrix scaffolds in combination with marrow stimulation techniques have been used successfully for cartilage repair [3, 5–10]. A promising technique is the so-called autologous collagen-induced chondrogenesis (ACIC). It includes microdrilling and collagen type I gel application and can be performed arthroscopically [11].

With advancement in MRI technology quantification of the biochemistry of cartilage repair tissue in vivo has become possible [12–14]. T2* mapping is a fast quantitative MRI sequence that allows tissue characterization regarding collagen structure and water content [15–22]. It has been demonstrated that it can provide sufficient sensitivity to cartilage changes, even at 1.5 T [23–25].

Our hypotheses were that the ACIC technique will provide (1) good cartilage repair tissue growth and (2) provide similar biochemical properties of the repair tissue in comparison to the native cartilage.

Materials and methods

Patients

The study was performed in a retrospective design including ten symptomatic patients undergoing arthroscopic cartilage repair of the knee. Inclusion criteria for surgery were isolated symptomatic ICRS/Outerbridge grade III/IV cartilage lesions and defect sizes between 2 and 8 cm^2. Patients with osteoarthritis (Kellgren-Lawrence grade II or more), more than 5° of malalignment and age over 65 years were excluded from ACIC. The mean age of the patients was 45.1 years (SD 12.4; range, 26–63 years). The lesions were located on the patella in six, medial femoral condyle (MFC) in five, lateral femoral condyle (LFC) in one, and trochlea in two cases (four had two lesions). The mean defect size after debridement was 4.5 mm^2 (SD 2.1). Two patients presented with cartilage defects after previous knee trauma, eight patients had a gradual onset of pain and no known trauma within the last year before surgery. All patients in this cohort had intact ligaments.

Between April 2009 and June 2010, 17 patients underwent an ACIC procedure of the knee. Ten of these patients had MRI scans with T2* mapping at 1-year postoperatively and were included in the study. Only those patients received MRI scans, whose insurance covered the cost. All patients gave oral and written consent and the research was performed following the Declaration of Helsinki principles.

Surgical technique

Standard arthroscopic portals were used to evaluate the knee using normal saline under pressure (approximately systolic blood pressure). If a meniscal tear was present, a partial meniscectomy was performed at this stage (two patients). After defect assessment, the articular cartilage lesions were

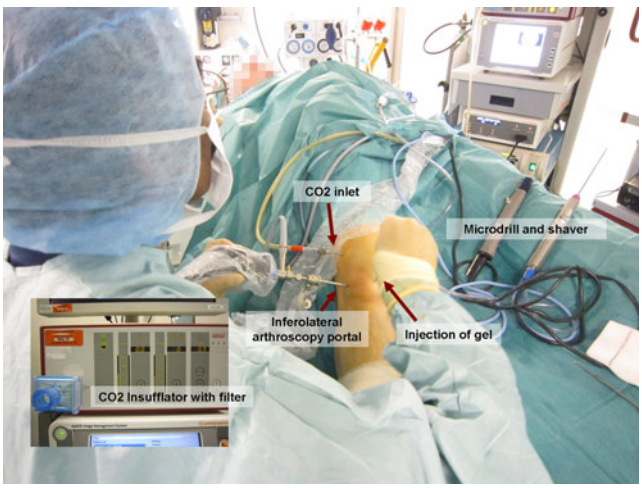

Fig. 1 Instrument setup during arthroscopic cartilage repair using the autologous collagen-induced chondrogenesis (ACIC) technique

Table 1 Magnetic resonance parameters

Sequence	PD FSE tra	T1 TIRM sag	T2 3D-DESS	T1 TIRM cor	T2 3D-True-FISP	T2* map tra	T2* map sag
Repetition time (ms)	3,300	4,000	19.28	4,000	11.23	613	613
Echo time (ms)	40	33	6.03	32	4.97	4.8; 13.0; 21.3; 29.6; 37.8; 44.6; 51.5	4.8; 13.0; 21.3; 29.6; 37.8; 44.6; 51.5
Field of view (mm)	160×160	160×160	160×160	160×160	150×150	160×160	160×160
Matrix	320×240	320×256	320×320×266	256×256	256×241×212	256×256	256×256
Voxel size (mm)	0.7×0.5×4.0	0.6×0.5×3.0	0.5×0.5×1.5	0.6×0.6×4.0	0.6×0.6×0.6	0.6×0.6×3.0	0.6×0.6×3.0
Slice thickness (mm)	4	3	1.5	4	0.60	3	3
Interslice gap (mm)	0.8	1.2	0.3	0.4	0.12	0.6	0.6
Number of slices	25	23	64	23	176	11	11
Echo trains/slice	51	31	–	26	–	–	–
Turbo factor	5	8	–	8	–	–	–
Bandwidth Hz/Px	203	195	145	195	190	260	260
Averages	1	2	1	2	1	2	2
Examination time (min)	2:53	4:14	5:27	3:34	5:40	02:38	02:53

Magnetic resonance parameters for morphologic imaging and T2 mapping sequences

PD FSE proton density weighted fast spin echo sequence, *T1 TIRM* T1 weighted turbo inversion recovery magnitude sequence, *T2 3D-DESS* T2-weighted three-dimensional double-echo steady-state sequence, *T2 True FISP* T2 weighted true fast imaging with steady-state precession sequence, *T2* mapping*: Gradient echo based T2-star mapping

carefully debrided down to the subchondral bone using curette and shaver. The aim was to establish a stable shoulder at the margin of the defect. Microdrilling was performed using the 45º-angled drill (PowerPick drill, Arthrex, UK). The drill holes were made at a 3-mm interval to a depth of 6 mm. The arthroscopy setup is shown in Fig. 1.

The second part of the procedure was performed under dry arthroscopic conditions using carbon dioxide (CO_2) insufflation. For patella and trochlea lesions, a patella clamp (AO or Lewin bone clamp) was applied to lift the patella and further open the joint.

For the injection procedure, two 1-ml syringes and a Y-shaped mixing catheter connected to a 20-gauge needle (inner diameter 0.9 mm, length 90 mm) were used. Into one syringe 1 ml of fibrinogen (Tisseel, Baxter, Thetford, UK) was filled, and the other syringe was filled with 0.9 ml of porcine atelocollagen (CartiFill, RMS Innovations U.K., Hertfordshire, UK) and 0.1 ml of thrombin (50 IU). The 20-gauge needle was inserted through one of the portals or an appropriate separate portal to access the lesion.

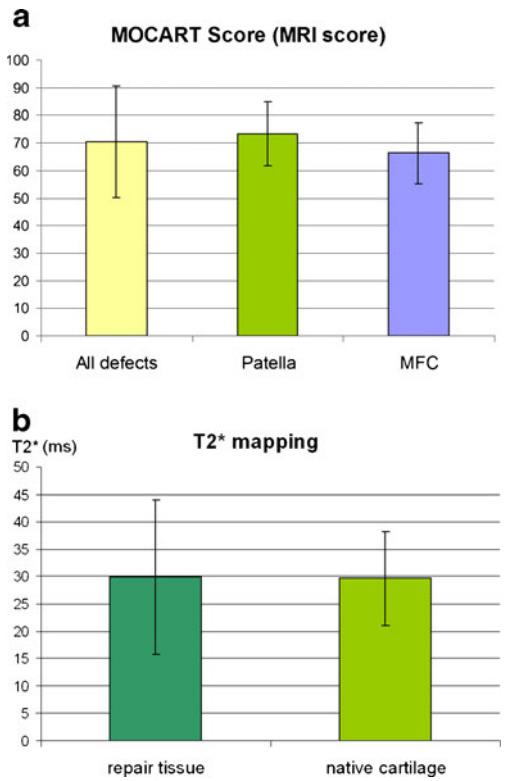

Fig. 2 **a** The average MR observation of cartilage repair tissue (MOCART) scores 1 year after autologous collagen-induced chondrogenesis (ACIC) are comparable to those obtained by other authors after similar cartilage repair techniques. The *bars* indicate mean values and the *whiskers* represent 95 % confidence intervals. **b** The mean T2* values of the repair tissue are similar in comparison to native cartilage. This might suggest similar biochemical composition in both types of tissue. The *bars* indicate mean values and the *whiskers* represent 95 % confidence intervals

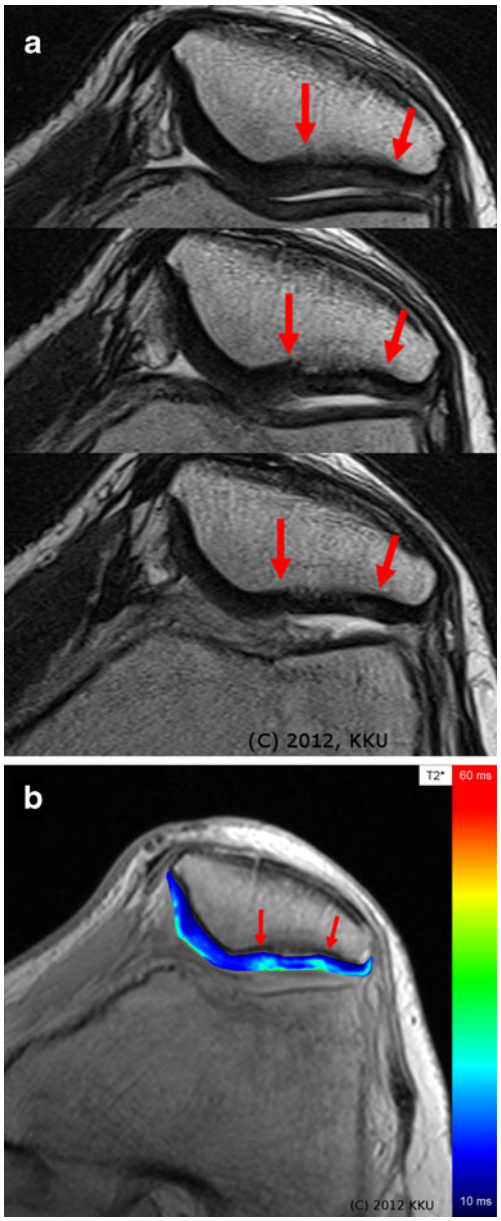

Fig. 3 Morphological (**a**) and biochemical (**b**) results 1 year after ACIC of the lateral patella facet in a 40-year-old male. The morphological appearance on PD FSE shows a good outcome with complete defect fill. Quantitative (biochemical) imaging in this subject shows slightly elevated T2* values in the integration zone (tidemark native cartilage/repair tissue). Clinically, the patient does well

Under arthroscopic vision, the gel was applied into the defect. The carbon dioxide pressure and the adhesiveness of the gel allowed attachment even against gravity especially to patella defects. The gel usually hardens within 5 min. The gel could then be shaped in situ once hardened using a McDonalds dissector.

Once this was established, the carbon dioxide was switched off and the knee was insufflated with normal saline under pressure. The stability of the graft was further ascertained by moving the knee through the full range of motion several times

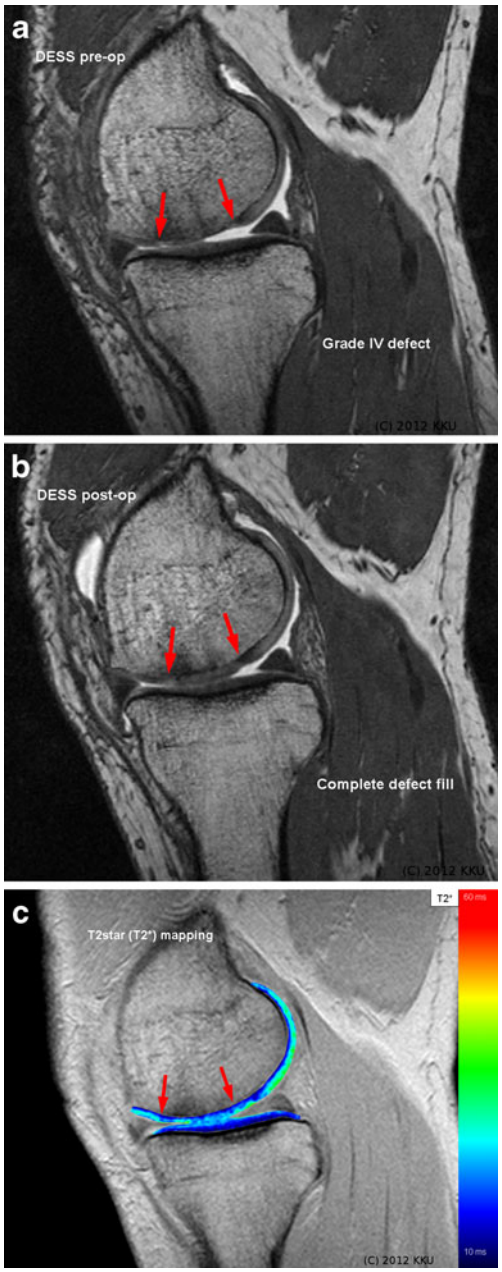

Fig. 4 Example case of a 51-year-old male patient (no. 2 in Table 1) undergoing autologous collagen-induced chondrogenesis (ACIC). The 3D DESS MRI shows the preoperative ICRS grade IV defect on the medial femoral condyle (**a**), which is completely filled with repair tissue 12 months after the arthroscopic ACIC procedure (**b**). **c** On the T2* map, one can observe similar T2* values in the cartilage repair tissue (34± 6 ms) in comparison to the surrounding weight-bearing native cartilage (36±6 ms)

followed by visual inspection. The skin was closed either by sutures or steri-strips. The theatre setup is shown in Fig. 1.

Rehabilitation

The patients underwent a standardized rehabilitation protocol. Patients were advised to partially bear weight on crutches for

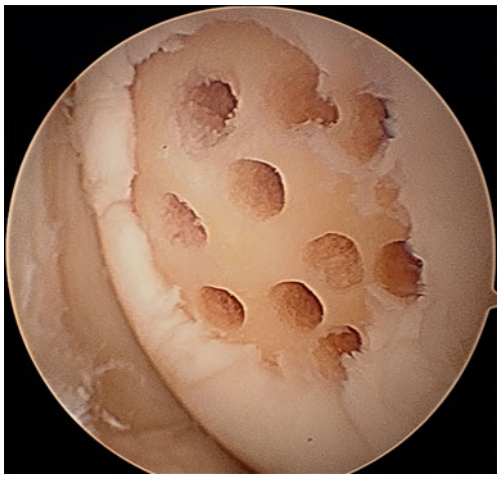

Fig. 5 Intraoperative image of drill holes on a medial femoral condyle (patient no. 3 in Table 1)

6 weeks after surgery. Gradually increased loads were applied during the first 6 weeks. Flexion was restricted only in patients with patellofemoral defects. In these patients, flexion to 30º was allowed within the first 2 weeks, and could be gradually increased to 90º at 6 weeks after surgery. After that, the full range of motion could be approached.

Magnetic resonance imaging

Every patient was examined on a 1.5-T MR unit (Avanto, Siemens Healthcare Inc, Erlangen, Germany) using a dedicated eight-channel knee coil. A specific cartilage MRI protocol including fast spin echo (FSE) and double echo steady-state (DESS) sequences was applied at 1-year follow-up. The complete MRI protocol with all imaging parameters can be seen in Table 1.

T2-star (T2*) mapping was performed in the same MR session as the morphological imaging, approximately 15 min after the patient entered the magnet room. The following parameters were used for T2* mapping: repetition time 613 ms, seven echo times from 4.8 to 51.5 ms and a voxel size of 0.6×0.6×3 mm. The acquisition time was 2:38 min for

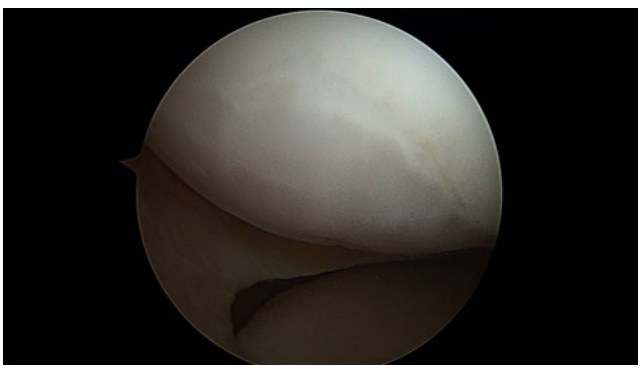

Fig. 6 Second-look arthroscopy after ACIC of the medial femoral condyle 1 year post-operatively (patient no. 10 in Table 1)

Table 2 Patient characteristics and T2* evaluation results at 1-year follow-up

Pat. no.	Gender	Age (years)	Location 1	Location 2	Defect-size 1	Defect-size 2	T2* RT (ms)	T2* NC (ms)
1	f	44.6	Pat	MFC	2.0	2.3	50	28
2	m	50.9	Pat	MFC	2.3	7.5	30	30
3	f	58.4	MFC		5.3		27	36
4	m	26.5	LFC	Pat	3.2	3.2	14	18
5	f	63.9	MFC	Pat	7.8	2.3	29	39
6	m	40.7	Pat		3.2		14	19
7	m	30.3	Troch		4.4		46	38
8	f	57.6	Pat		6.8		25	27
9	m	38.1	Troch		4.0		42	38
10	m	39.8	MFC		2.0		30	23

Single case table of patient characteristics and T2* evaluation results. T2* sequences were only evaluated for defects in location 1 as described above
Pat. no. patient number, *RT* repair tissue, *NC* native cartilage, *Pat* Patella, *MFC* medial femoral condyle, *LFC* lateral femoral condyle, *Troch* Trochlea, *m* male, *f* female. Patient no. 2 is presented in Fig. 4, patient no. 3 is shown in Fig. 5, and patient no. 10 is shown in Fig. 6

the transversal slices and 2:53 min for the sagittal slices. Due to the clinical setup of the imaging center and scan time limitations, in case of multiple lesions only one defect was selected by the radiographers for T2* mapping. This selection was done randomly. The detailed MRI parameters can be found in Table 1.

Magnetic resonance imaging evaluation

All MRI evaluations were performed by a senior musculoskeletal radiologist (PB) with 15 years of experience in knee MRI and 5 years of experience in quantitative region of interest (ROI) evaluation. In general, axial slices were evaluated for patella locations and sagittal slices were used for the assessment of the femoral condyles and the trochlea.

For the structured morphological assessment the *MR observation of cartilage repair tissue* (MOCART) score was used for postoperative MR examinations [26]. A MOCART score of 0 represents the worst possible result and 100 the best possible MRI outcome.

In the T2* maps, the lesion was identified using the corresponding morphological images. One ROI each for the repair tissue and the adjacent native cartilage was manually drawn on a single slice through the center of each lesion. Care was taken to avoid partial volume effects with the joint fluid and the subchondral bone plate during the ROI evaluation. A T2* ratio was calculated as described by Domayer et al. [14]: T2* ratio=T2* repair tissue/T2* native cartilage×100.

No obvious imaging artefacts were visible on the morphological or quantitative MRI affecting our evaluation. The mean standard deviation of individual ROI measurements was 24.8±8.0 % of the measured T2 value for the repair tissue (range, 10.0 to 33.3 %) and 22.0±6.1 % (range, 9.7 to 28.2 %) what indicates a low noise level and good T2* map quality at the selected resolution of 0.6×0.6×3.0 mm.

Statistics

Descriptive statistics are given as mean±standard deviation (SD). A paired two-tailed *t* test was performed to compare the T2* values between the repair tissue and the native cartilage. In two out of ten patients, two areas of cartilage repair were included. Due to the low number of multiple datasets (patients with two lesions), this could not be addressed with statistical modeling. An alpha level of 0.05 was considered statistically significant.

Results

The postoperative MRI showed good repair tissue regeneration in most cases. The mean MOCART score at 1-year follow-up was 71.7±21.0 ranging from 25 to 95. The MOCART score for patella lesions was similar to lesions on the femoral condyles: 73.3±11.7 and 68.1±25.5, respectively (Fig. 2a).

The quantitative MRI evaluation shows mean T2* relaxation times of 30.6±11.3 milliseconds (ms) and 28.8±6.8 ms for the repair tissue and surrounding native cartilage, respectively (Fig. 2b). The T2* ratio between the repair tissue and native cartilage was 105 %±30 % indicating repair tissue properties similar to native cartilage. Figures 3 and 4 show examples of MRI outcomes, Table 2 shows single patient values (Figs. 5 and 6).

Discussion

The surgical regeneration of hyaline-like cartilage is still challenging. The ACIC method represents a novel single-stage cartilage repair technique that can be performed

arthroscopically. The first clinical results are promising [11]. However long-term outcomes are believed to depend on the biochemical repair tissue properties. The development of quantitative MRI techniques allows repair tissue characterization in vivo [12–14].

T2 and T2* mapping have the advantage of tissue characterization without the use of contrast agents. Furthermore, it is easy to implement into clinical routine and in particular T2* mapping offers fast examination times (approximately 3 min) with sufficient spatial resolution [19, 22]. It could also be demonstrated that T2 and T2* mapping deliver comparable results for cartilage mapping in the knee joint [18].

T2* relaxation time values are indicative for the water content, collagen content, and collagen fiber organization. Welsch et al. observed lower repair tissue T2 relaxation time values after microfracture in comparison to native cartilage [12]. Mamisch et al. demonstrated the same for T2* mapping [18]. These low T2* values in the repair tissue after microfracturing (MFX) can be interpreted as fibrous repair tissue, with relatively higher collagen type I content and lower water content.

The development of matrix-supported marrow stimulation techniques like autologous matrix-induced chondrogenesis (AMIC) and autologous collagen-induced chondrogenesis (ACIC) aims at regenerating hyaline-like repair tissue [5]. In our study, the T2* relaxation times of the repair tissue had similar values compared to the native cartilage. This might indicate a similar tissue structure as the surrounding hyaline cartilage with respect to collagen fiber content and water content. Unfortunately T2* mapping has only a low sensitivity for the proteoglycan (glycosaminoglycan) content, thus dGEMRIC scans (delayed gadolinium-enhanced MRI of cartilage) would be helpful to confirm the hyaline-like nature of the ACIC repair tissue in a future study.

The morphological scoring using the MOCART score demonstrates good cartilage repair tissue growth. The 1-year MOCART scores with a mean of 72 points are comparable to those after other techniques [6, 27, 28]. It is of note that cartilage lesions on the patella demonstrated similar morphological outcome in comparison to condylar lesions. This is interesting, since it is known that patellofemoral cartilage repair is challenging [1, 9, 29].

However, our sub-sample size was too small to draw definite conclusions.

Limitations of this investigation are the retrospective design of the study and the low number of patients. However, this was the maximum number of eligible patients. Furthermore, the defects were located in different compartments of the knee, which could have an effect on the outcome of the repair tissue. However, since our T2* evaluation was based on the comparison to adjacent native cartilage, the effect of the defect location on the absolute T2* star values are not crucial. There was only one reader for the MRI evaluation in our study. However, previous studies have already demonstrated a good intraobserver reproducibility of 0.86 and interobserver reproducibility 0.83 (intraclass correlation coefficient, ICC) for T2* mapping at 1.5 T [30]. Also the MOCART score is known for good to excellent interobserver agreement of ICC above 0.8 [31].

We are aware, that a 3.0-T scanner would deliver higher-resolution T2* maps than a 1.5-T scanner. However, 1.5-T systems are widely used in clinical practice. Our study demonstrates the feasibility of T2* mapping in a clinical setting with a short additional acquisition time of 2:38 min. We believe that our T2* mapping sequence delivered good image quality with a voxel size of 0.6×0.6×3.0 mm. However, due to the imaging resolution at 1.5 T, we did not perform a separate evaluation of deep and superficial regions of cartilage, as would be possible at 3.0 T [18]. We did only evaluate a single central slice through the repair tissue. We believe this is the safest way to avoid a bias by partial volume effects in the border areas of the repair tissue.

Further limitations of this study are in the nature of the T2* relaxation time itself. T2* is affected by the water content and collagen structure simultaneously. Thus, it is sometimes hard to distinguish mixed effects of both water content and collagen structure. Also metal particle related susceptibility artefacts may affect the T2* values in patients after marrow stimulation techniques, however, no such artefacts were visible on the morphological or quantitative MRI.

In conclusion, our study shows that arthroscopic autologous collagen-induced chondrogenesis (ACIC) is able to regenerate repair tissue with similar quantitative MRI properties as native hyaline cartilage. This might suggest the formation of hyaline-like repair tissue after ACIC.

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Conflict of interest None of the authors has a conflict of interest to declare.

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