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Cartilage repair surgery prevents progression of knee degeneration

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Abstract

Purpose To investigate, whether cartilage repair surgery for focal osteochondral defects at the knee results in less degenerative changes over 6 years in a MR imaging follow-up than morphologically initially identical defects in non-operated control subjects from the osteoarthritis initiative (OAI).

Methods A total of 32 individuals received baseline and follow-up MRI. In $n = 16$ patients with cartilage repair [osteochondral autograft transfer system (OATS), $n = 12$; spongiosa-augmented matrix-associated autologous chondrocyte implantation (MACI), $n = 4$] MRI was performed preoperatively and after 5.7 ± 2.3 year follow-up. Baseline MRIs of non-operated subjects from the OAI were screened for initially identical cartilage defects ($n = 16$). Morphological knee abnormalities were assessed using WORMS, AMADEUS and MOCART scores. A sagittal 2D MSME sequence was implemented for quantitative cartilage T2 relaxation time measurements in all (0, 2, 4, 6 and 8-years) follow-ups from the OAI and in the postoperative MRI protocol.

Results For both groups, focal osteochondral defects were located at the femoral condyle in 8/16 cases (5 medial, 3 lateral) and at the patella in 8/16 cases. At baseline, the mean cartilage defect size ± SD was 1.4 ± 1.3 cm^2 for the control group and 1.3 ± 1.2 cm^2 for the cartilage repair group (n.s.). WORMS scores were not significantly different between the cartilage repair group and the control group at baseline [mean difference ± SEM (95%CI); 0.5 ± 2.5 (− 4.7, 5.7), n.s.]. During identical follow-up times, the progression of total WORMS scores [19.9 ± 2.3 (15.0, 24.9), $P < 0.001$] and of cartilage defects scores in the affected ($P < 0.001$) and in the opposing ($P = 0.029$) compartment was significantly more severe in non-operated individuals ($P < 0.05$). In non-operated subjects, T2 values increased continuously from baseline to the 8-year follow-up ($P = 0.001$).

Conclusions Patients with cartilage repair showed less progression of degenerative MRI changes at 6-year follow-up than a control cohort from the OAI with initially identical osteochondral defects. Patients with focal cartilage defects may profit from cartilage repair surgery since it may prevent progression of early osteoarthritis at the knee joint.

Level of evidence Prognostic study, Level II.

Keywords Osteoarthritis · Cartilage · Knee · Cartilage repair · Osteochondral transplantation · MR imaging · Outcome

Introduction

Knee osteoarthritis (OA) is an increasingly prevalent musculoskeletal disorder [34]. OA is a major cause of disability and it is associated with rising rates of knee arthroplasties [22, 25]. (Osteo)chondral defects are a main risk factor for OA [7, 21, 29]. For focal full thickness cartilage defects at the knee, cartilage repair surgery represents an excellent therapeutic option, which aims to restore the cartilage tissue and function to prevent long-term OA. Different cartilage repair procedures include microfracture, autologous matrix-induced chondrogenesis (AMIC), matrix-associated autologous chondrocyte implantation (MACI) and osteochondral autograft transfer system (OATS) [31, 32, 38, 41, 46]. For osteochondral defects, either OATS or MACI combined with subchondral spongiosa transplantation for filling of the subchondral, bony defect (spongiosa-augmented MACI) may be applied [42, 44, 56]. Different studies confirm the improvement of clinical symptoms after cartilage repair [41]. Although randomized trials compared different cartilage repair techniques [5, 46, 49], there is no study, that includes subjects with and without treatment for identical

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osteochondral defects and that confirms that cartilage repair surgery indeed halts the progression to OA.

The osteoarthritis initiative (OAI) is a longitudinal, NIH initiated multi-center, prospective observational study of knee OA (https://oai.epi-ucsf.org/datarelease/StudyOverview.asp). The overall aim is to develop a public domain research resource to facilitate the scientific evaluation of biomarkers for OA as potential surrogate endpoints for disease onset and progression. Four clinical centers and a data coordinating center conduct the OAI, a public–private partnership, that bring together new resources and commitment to help find biochemical, genetic and imaging biomarkers for development and progression of OA. The OAI establishes and maintains a natural history database for OA that includes clinical evaluation data, radiological images, and a biospecimen repository from 4796 men and women [10].

Quantitative and qualitative magnetic resonance (MR) imaging is a well-established tool for non-invasive evaluation of articular cartilage and cartilage defects and for postoperative evaluation after cartilage repair [6, 31, 36, 45]. Cartilage T2 relaxation time measurements correlate with early cartilage matrix degeneration and predict the onset of early OA [29, 35]. In addition, efforts are being made to establish T2 relaxation time measurements for evaluation of cartilage repair tissue [2, 26, 28].

Since there is no study that compares the imaging outcome after cartilage repair surgery with conservative treatment for morphologically identical osteochondral defects, purpose of this longitudinal study was, to investigate, whether patients with cartilage repair at the knee present less progression of degenerative changes in a qualitative and quantitative mid-term MR follow-up than non-operated individuals from the OAI with initially identical osteochondral defects. The hypothesis was, that cartilage repair surgery prevents progression of early OA in patients with focal osteochondral defects at the knee. Consequently, patients with focal cartilage defects may profit from cartilage repair surgery in mid-term as compared to conventional therapy with respect to the development and progression of cartilage degeneration and early OA at the knee joint.

Materials and methods

A total of $N = 32$ individuals were included in this study (Fig. 1). A subset of 16/32 individuals were selected from the OAI database. Inclusion criteria for OAI subjects were available and complete MRI data of the right knee at the time points baseline, 2, 4, 6 and 8-year follow-up, age ≤ 55 years, body-mass-index (BMI) ≤ 30, Kellgren-Lawrence (KL) score < 2, no previous knee surgery and maximum compartment-specific cartilage Whole-Organ Magnetic Resonance Imaging score (WORMS) [8, 30] of ≥ 2 and ≤ 5. Subsequently, $n = 171$ subjects fulfilling these criteria were reviewed in consensus by a musculoskeletal Radiologist (PMJ; 9 years of experience) and a senior orthopedic surgeon (SB; 15 years of experience) to identify individuals with MR imaging criteria that were in line with an indication for cartilage repair surgery at the MFC, LFC or patella [31]. Thus isolated, focal, full-thickness cartilage defects [International Cartilage Repair Society (ICRS) score [50] of 3 or 4], contained by a solid and healthy appearing, surrounding hyaline cartilage were identified. MR images were excluded, if contraindications for cartilage repair surgery were present [41]. Twenty-five OAI patients fulfilled all inclusion and exclusion criteria and were defined suitable for cartilage repair.

The data of patients that received cartilage repair procedures at the knee at our institution were evaluated retrospectively. Inclusion criteria were available preoperative MR examinations, follow-up times of at least 2 years and preoperative cartilage defects that had an identical appearance on MR imaging as the identified defects from the 25 OAI subjects. Of $n = 31$ cartilage repair patients identified, $n = 16$ patients agreed to participate in this study. Exclusion criteria were pregnancy, claustrophobia, pace-maker, total knee arthroplasty and other MR contraindications. Finally, those $n = 16$ patients that had received cartilage repair surgery were matched regarding defect location and morphology to $n = 16$ non-operated OAI subjects; in total $N = 32$ individuals were finally included in this study.

Surgery

Of the $n = 16$ cartilage repair patients, 12/16 received OATS procedures and 4/16 received spongiosa-augmented MACI [39]. Indications for cartilage repair surgery were symptomatic chondral or osteochondral defects grade 3 or 4 according to the International Cartilage Repair Society (ICRS) classification [50] in patients ≤ 55 years old with a BMI ≤ 30 and a KL score < 2. Contraindications were advanced degenerative changes of the knee joint, opposing cartilage defects, overlying meniscus lesions, ligament ruptures or other severe other concomitant knee pathologies [41]. OATS transplantation was performed using an OATS system (OATS, Arthrex, Naples, FL, USA) [39]. For spongiosa-augmented MACI, during an initial arthroscopic surgery healthy articular cartilage was harvested [17]. Chondrocytes were isolated (Genzyme, Perth, Western Australia), cultured for 6–8 weeks and seeded onto a collagen membrane (ACI-Maix, Matricel GmbH, Herzogenrath, Germany). During a second surgery, spongiosa plugs were harvested from the distal femur or the iliac crest, implanted into the bony defect and covered by the MACI membrane. One patient had an additional high tibial osteotomy. Three patients had additional replacements of the medial patellofemoral ligament.

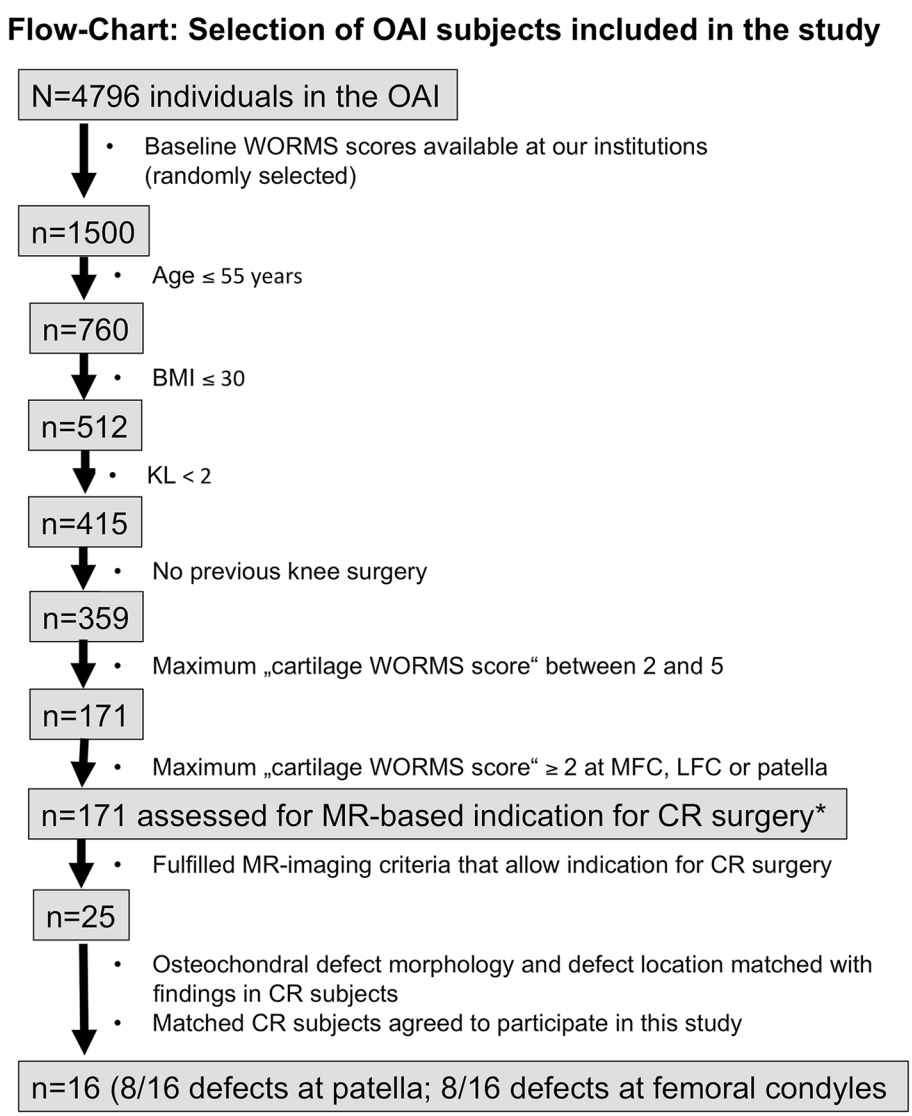

Fig. 1 Flow-chart of the selection of the subjects included in this study. Asterisk: MR-based indications for cartilage repair surgery were isolated, full thickness (osteo)chondral defects with contained borders, no opposing cartilage defect or overlying meniscus defect and no major degenerative changes of the knee joint. *OAI* osteoarthritis initiative, *MR* magnetic resonance, *WORMS* Whole-Organ-Magnetic-Resonance-Imaging-Scores, *BMI* body-mass-index, *KL* Kellgren–Lawrence score, *MFC* medial femoral condyle, *LFC* lateral femoral condyle, *CR* cartilage repair

MR imaging of OAI subjects

MR knee examinations of right knees of OAI subjects were obtained with four identical 3T MR scanners using identical standard knee coils (Siemens, Erlangen, Germany) at baseline, 2, 4, 6 and 8-year follow-ups. For morphological analysis pulse sequences were used as previously mentioned in detail [29, 48]. Quantitative T2 relaxation time maps were acquired using a sagittal 2D multislice multiecho (MSME) spin echo (SE) sequence [repetition time (TR) 2700 ms, 7 echo times (TEs) 10, 20, 30, 40, 50, 60, 70 ms, field of view (FOV) 12 cm, slice thickness 3 mm, in-plane spatial resolution $0.313 \times 0.446 mm^2$, bandwidth 250 Hz/pixel].

MR imaging of cartilage repair subjects

Since cartilage repair subjects were included at a different institution, the acquired MR protocol was different from the OAI protocol. Clinical and quantitative MR imaging of both knees of cartilage repair subjects was performed after 2–10 year follow-up after unilateral cartilage repair surgery using a 3T MR scanner (Ingenia, Philips Healthcare, Best, The Netherlands) and a dedicated eight-channel knee coil (Medical Advances Milwaukee WI, USA). Both knees were examined to compare T2 values at the ipsilateral injured knee with the contralateral healthy knee. Further, bilateral imaging allowed intraindividual adjustment of T2 values, since no preoperative T2 relaxation time maps were available for this cohort. Morphological sequences of the contralateral knees were considered to exclude any major cartilage pathology or other joint pathology. The following sequences were acquired: (i) a coronal intermediate weighted (IMw) fat-saturated (fs) turbo spin echo (TSE) sequence [TR/TE 3363/44 ms, field of view (FOV) 14 cm, slice thickness 3 mm, spatial resolution $0.4 \times 0.4\ mm^2$, bandwidth 187 Hz/pixel], (ii) sagittal IMw fs TSE (TR/

TE 4202/44 ms, FOV 14 cm, slice thickness 3 mm, spatial resolution $0.4 \times 0.4 mm^2$, bandwidth 187 Hz/pixel), (iii) transverse IMw fs TSE (TR/TE 5455/40 ms, FOV 14 cm, slice thickness 3 mm, spatial resolution $0.3 \times 0.4\ mm^2$, bandwidth 201 Hz/pixel], (iv) sagittal T1w TSE (TR/TE 785/13 ms, FOV 14 cm, slice thickness 3 mm, spatial resolution $0.4 \times 0.4\ mm^2$, bandwidth 143 Hz/pixel). Quantitative T2 relaxation time maps were acquired using a sagittal MSME SE sequence (TR 2200 ms, 5 TEs plus one simulated echo 20, 30, 40, 50, 60 ms, FOV 14 cm, slice thickness 2.5 mm, spatial resolution $0.4 \times 0.4\ mm^2$, bandwidth 251 Hz/pixel). In addition, preoperative clinical MR images were available for all cartilage repair patients.

MR image analysis

Semi-quantitative morphological analyses

MR images were reviewed on picture archiving communication system (PACS) workstations (Easy Vision, Philips, Best, The Netherlands) and were evaluated by one radiologist (ASG, 5 years of experience). WORMS gradings were used to assess cartilage, meniscus, ligamentous and bone marrow abnormalities of the knee joint, as previously described [24, 27, 30, 47, 48, 54]. The baseline osteochondral defect was scored using the ICRS score [50] and the Area Measurement And DEpth and Underlying Structures (AMADEUS) score [31]. The postoperative cartilage repair area was additionally assessed using the Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) score [15]. For the AMADEUS score and for the MOCART score a score of 100/100 represented optimal findings.

T2 relaxation time measurements

T2 relaxation time maps were calculated pixel-wise from MSME spin-echo images using a monoexponential non-negative least squares fit analysis with a custom-built software (IDL, Creaso, Gilching, Germany) [11]. For quantitative analyses of OAI MSME SE T2 relaxation time maps, the first echo was excluded from the fitting process, to obtain more reliable values by eliminating the effects from stimulated echo signal on the calculated values [2, 37, 53]. Using the custom-built software, manual segmentation of artefact-free cartilage areas in 5 compartments [patella, medial femoral condyle (MFC), lateral femoral condyle (LFC), medial tibial plateau (MT) and lateral tibial plateau (LT)] was performed by placing regions-of-interest (ROIs) on every slice by one medical student (JZ), supervised by an experienced radiologist (ASG).

For quantitative analyses of MSME SE T2 relaxation time maps of cartilage repair patients, a first non-acquired echo was integrated in the MR sequence protocol to eliminate the effects from stimulated echo signal on the calculated values. Using OsiriX Lite v.7.0.2 (32 bit) segmentation was performed similarly in six compartments: patella, trochlea, MFC, LFC, MT, LT. In knees with cartilage repair, the region of the cartilage repair tissue was segmented separately. Besides compartment-specific values, global T2 values were calculated as mean values of all analyzed compartments. The affected compartment was defined as the compartment in which cartilage repair was performed; the opposing compartment was defined as the compartment articulating with the affected compartment. For subjects with cartilage repair, relative T2 values were calculated by dividing ipsilateral T2 values by contralateral T2 values ($T2_{relative} = T2_{ipsilateral}/T2_{contralateral}$).

Reproducibility of MR imaging measurements

Intra- and interreader agreement in our group was determined previously. The intrareader linear weighted Cohen's kappa values for WORMS scores ranged between 0.76 and 0.95 [30]. The interreader kappa values for WORMS scores ranged between 0.65 and 0.89 [30]. The intra- and interreader ICC for total AMADEUS scores was 0.97 and 0.96, respectively [31]. The intrareader root mean square error coefficient of variation (RMS CV; %) for cartilage T2 relaxation time measurements ranged between 1.7 and 2.6% [28]. The interreader RMS CV was 1.6% [30, 54]. Pilot studies for the OAI confirmed good to high rescan reproducibility of MR cartilage measures and cartilage T2 relaxation time measurements [18, 40]. For T2 values ICCs ranged from 0.61 to 0.98 and RMS CVs ranged from 4 to 14% [40].

IRB approval

The study was approved by the local Institutional Review Boards (Ethikkommission Technical University of Munich, Germany; 174/15). The OAI study protocol, amendments, and informed consent documentation including analysis plans were reviewed and approved by the local institutional review boards. Data used in the preparation of this manuscript were obtained from the OAI database, which is available for public access at http://www.oai.ucsf.edu/. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. All subjects gave written informed consent prior to participation in the study.

Statistical analysis

Statistical processing was performed with SPSS version 20.0 (SPSS Institute, Chicago, IL, USA) (FB, PMJ). Data was reported using means ± standard deviation (SD) and

two-sided *t* test. Paired *t* tests were applied for comparisons between the cartilage repair group and the control group. Independent *t* tests were applied for comparisons between different cartilage repair sites and different cartilage repair techniques, respectively. Mean differences between groups ± standard error of the mean (SEM) and 95% confidence intervals (95% CI, lower value, upper value) were determined. Pearson's correlations were calculated to assess correlations of the different parameters. All tests were performed based on a 0.05 level of significance.

Retrospective power analyses were performed to calculate the required sample size. For important comparisons with statistically significant differences between the two groups in this study, power analysis for comparison of matched pairs with continuous values (Student's sample *t* test) was performed using an alpha of 0.05, a power of 0.95 and a two-tailed test.

Results

Subjects

For individuals with cartilage repair ($n = 16$; male 12; female 4; 26 ± 8 years) the mean follow-up time was 5.7 ± 2.3 years. For individuals from the control subjects from the OAI ($n = 16$; male 6; female 10; 51 ± 3 years) follow-up times were 2, 4, 6 and 8 years. The matched follow-up time of the control cohort was 5.6 ± 1.4 years. One subject from the OAI had received total knee arthroplasty during follow-up.

Defect characteristics at baseline

Defect locations were identical for the cartilage repair group and for the OAI group (8/16 patella, 5/16 MFC, 3/16 LFC). At baseline, the mean cartilage defect size ± SD was 1.4 ± 1.3 cm^2 for the OAI group and 1.3 ± 1.2 cm^2 for the cartilage repair group (n.s.). For each group, $n = 4$ defects had a defect size of 2 cm^2 or larger. ICRS scores were 3.6 ± 0.5 and 3.8 ± 0.4 (n.s.). AMADEUS scores were 53.1 ± 17.3 and 48.1 ± 16.8 (n.s.).

WORMS scores

At baseline, total WORMS scores were not significantly different between the two groups (n.s.; Table 1). During identical follow-up times, the increase in total WORMS scores was significantly more severe in individuals that did not receive surgery ($P < 0.001$; Table 1). In the retrospective power analysis, the total sample size needed for comparisons of the progression of WORMS scores between the two groups was 8. Cartilage defects at the affected compartment ($P < 0.001$) and at the opposing compartment ($P = 0.029$) as well as BMEP at the affected compartment (< 0.001) and at the opposing compartment ($P = 0.041$) showed a more severe progression in the non-operated control cohort (Fig. 2). The increase of total WORMS scores was not significantly different between the two cartilage repair techniques or between the cartilage repair sites (n.s.).

Longitudinal WORMS in OAI subjects

During 8 years of follow-up, the progression of total WORMS scores was significant between all 2-year follow-up

Table 1 WORMS scores at baseline and follow-up

	OAI group (mean ± SD)	CR group (mean ± SD)	Difference ± SEM	Lower, upper 95% CI	*P* value
Baseline					
Total WORMS	18.3 ± 8.8	17.8 ± 5.9	0.5 ± 2.5	(− 4.7, 5.7)	n.s.
Cartilage: affected compartment	2.7 ± 1.6	3.0 ± 1.3	− 0.3 ± 0.4	(− 1.2, 0.5)	n.s.
Cartilage: opposing compartment	0.6 ± 1.5	1.1 ± 1.5	− 0.4 ± 0.4	(− 1.3, 0.4)	n.s.
BME: affected compartment	1.0 ± 1.2	1.8 ± 1.2	− 0.8 ± 0.4	(− 1.6, 0.1)	n.s.
BME: opposing compartment	0.3 ± 0.7	0.2 ± 0.4	0.1 ± 0.2	(− 0.4, 0.5)	n.s.
Progression					
Total WORMS	14.0 ± 7.8	− 5.9 ± 4.8	19.9 ± 2.3	(15.0, 24.9)	< 0.001
Cartilage: affected compartment	0.9 ± 1.1	− 2.3 ± 1.5	1.2 ± 0.5	(2.1, 4.3)	< 0.001
Cartilage: opposing compartment	0.3 ± 0.7	− 0.1 ± 0.3	0.4 ± 0.2	(0.0, 0.8)	0.029
BME: affected compartment	0.3 ± 0.8	− 0.2 ± 1.1	1.8 ± 0.3	(1.2, 2.6)	< 0.001
BME: opposing compartment	0.1 ± 0.3	− 0.1 ± 0.3	0.3 ± 0.1	(0.0, 0.5)	0.041

Mean ± standard deviation (SD), mean differences ± standard error of the mean (SEM), lower and upper 95% confidence intervals (CI) and *P* values are provided for comparisons of total WORMS scores as well as WORMS subscores for cartilage and bone marrow edema in the affected and in the opposing knee compartment found in the osteoarthritis initiative (OAI) group versus those found in the cartilage repair (CR) group

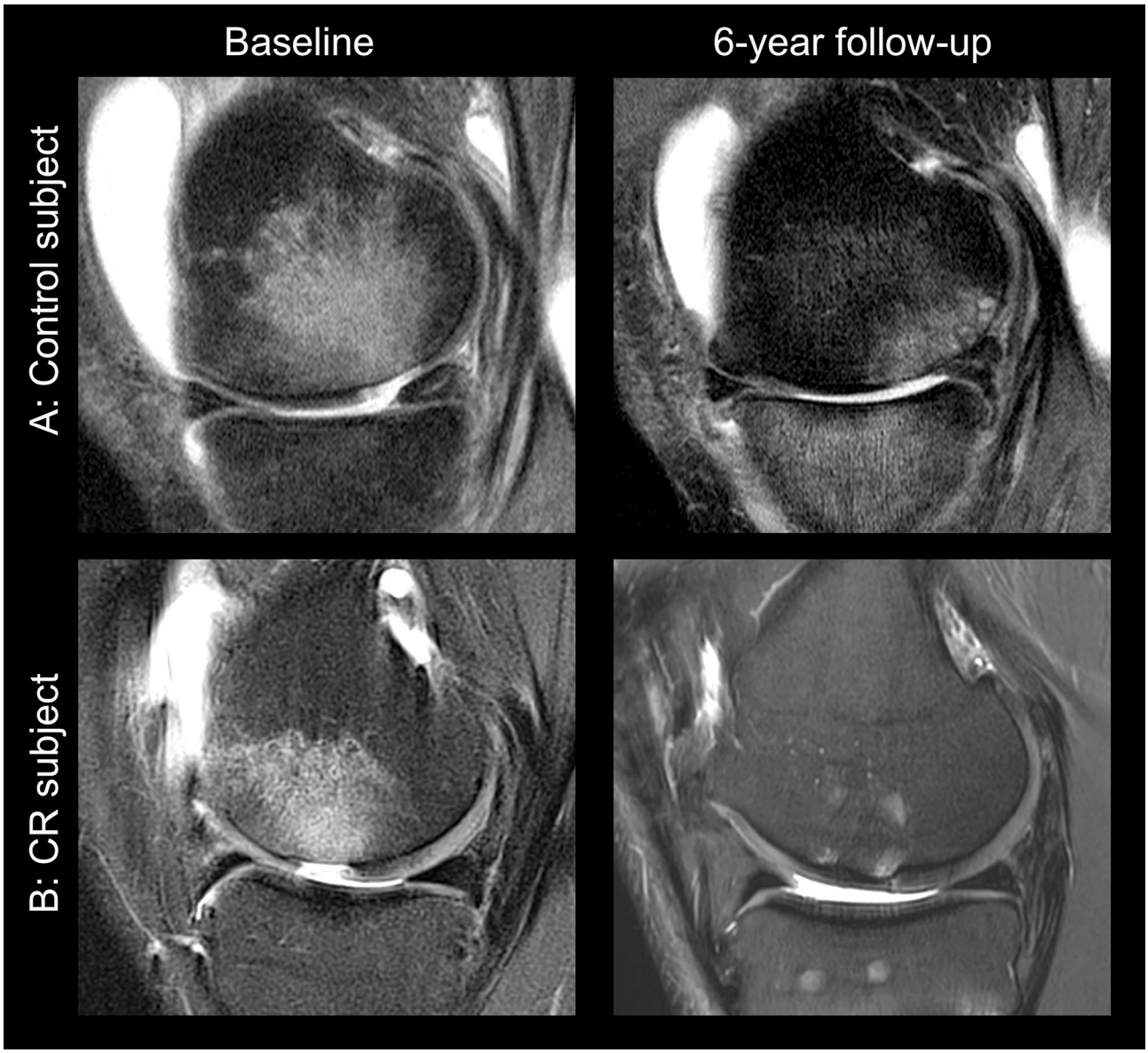

Fig. 2 Baseline versus 6-year follow-up MRI of a morphological osteochondral defect at the medial femoral condyle. **a** Individual from the osteoarthritis initiative group (control) who showed massive progression of the focal cartilage defect to osteoarthritis over time. **b** Individual who showed a good outcome with complete filling of the initial osteochondral defect after cartilage repair surgery (CR)

time points, respectively. The mean difference between the two time-points was most severe between the 2 and 4-year follow-up for total WORMS scores [3.6 ± 1.3 (0.9, 6.3), $P = 0.012$; Fig. 3] and for cartilage WORMS scores [3.8 ± 1.1 (1.5, 6.1); $P = 0.003$]. In the affected compartment, the increase in cartilage WORMS scores was most severe in the first 2 years of follow-up [0.5 ± 0.1 (0.1, 0.9); $P = 0.020$].

T2 relaxation times: cartilage repair group

In individuals who received cartilage repair procedures global T2 values showed no significant difference between ipsi- and contralateral knees (mean ± SD, 37.8±3.3 ms versus 38.3±3.5 ms; n.s.; Table 2). There was no significant difference for T2 values of the affected of the opposing compartment or of the cartilage repair compartment between the ipsilateral and the contralateral knee (n.s.; Fig. 4). Although not significant, $T2_{relative}$ for the affected compartment was lower in case of cartilage repair at the LFC (mean ± SD, 0.95±0.2 ms) than in case of cartilage repair at the patella (1.0±0.1 ms; n.s.) and at the MFC (1.03±0.1 ms; n.s.).

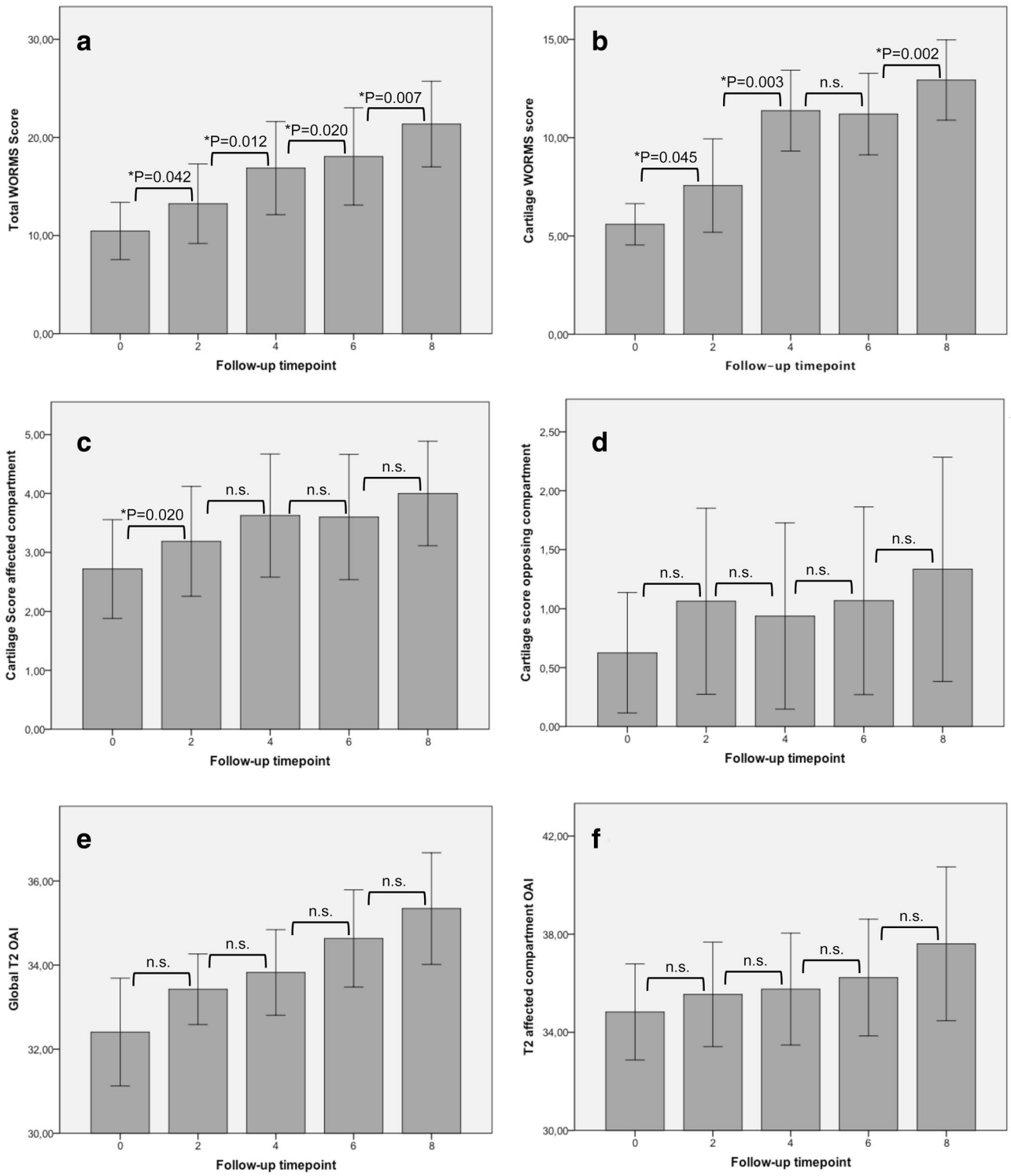

Fig. 3 Longitudinal evaluation of the OAI cohort. Mean ± standard deviations are presented for total WORMS scores (**a**), cartilage WORMS scores (**b**), cartilage scores in the affected (**c**) and in the opposing (**d**) compartment as well as global T2 relaxation time values (**e**) and T2 relaxation time values in the affected compartment (**f**) at the time-points baseline (0), 2, 4, 6 and 8-year follow-up for the OAI. Asterisks indicate statistically significant differences ($P < 0.05$). Error-bars: 95% confidence interval

Table 2 Cartilage T2 times in the ipsilateral versus contralateral knee of individuals with cartilage repair

T2 values	Ipsilateral (ms)	Contralateral (ms)	Difference ± SEM	Lower, upper 95% CI	*P* value
Global	37.8 ± 3.3	38.3 ± 3.5	− 0.4 ± 0.7	(− 1.8, 1.0)	n.s.
Cartilage repair tissue	43.3 ± 7.4	40.5 ± 5.0	2.8 ± 1.8	(− 1.1, 6.7)	n.s.
Affected compartment	39.4 ± 3.9	39.9 ± 4.7	− 0.5 ± 1.2	(− 3.1, 2.2)	n.s.
Opposing compartment	35.2 ± 5.0	34.3 ± 4.5	0.9 ± 1.1	(− 1.4, 3.3)	n.s.
Patella	37.4 ± 2.8	38.0 ± 3.6	− 0.6 ± 0.5	(− 1.7, 0.5)	n.s.
Trochlea	37.8 ± 3.7	37.2 ± 3.8	0.7 ± 1.0	(− 1.4, 2.9)	n.s.
MFC	41.1 ± 4.0	40.7 ± 4.6	0.5 ± 0.9	(− 1.4, 2.3)	n.s.
LFC	42.2 ± 5.2	44.3 ± 5.0	− 3.1 ± 1.6	(− 6.4, 0.2)	n.s.
MT	33.1 ± 5.5	33.6 ± 6.8	− 0.4 ± 1.2	(− 3.0, 2.1)	n.s.
LT	31.6 ± 4.6	35.6 ± 5.5	− 4.1 ± 0.9	(− 6.0, − 2.1)	< 0.001

MFC medial femoral condyle, *LFC* lateral femoral condyle, *MT* medial tibia plateau, *LT* lateral tibia plateau, *SEM* standard error of the mean, *CI* confidence interval

T2 relaxation times: OAI group

In the OAI group, T2 values increased from 32.9 ± 2.5 ms at baseline to 35.3 ± 2.1 ms at 8-year follow-up ($P = 0.001$; Figs. 3, 5). Based on these results, in the retrospective power analysis, the total sample size needed for comparisons of T2 values at baseline and at follow-up for the control cohort from the OAI was 15. The difference in global T2 values between baseline and 2-year follow-up [mean difference 0.9 ± 1.8 ms (− 0.1, 1.9); $P = 0.066$], represented the highest increase between two time points.

AMADEUS, ICRS and MOCART scores

The total AMADEUS score showed no significant correlation with MOCART scores or with an increase in WORMS scores in either group (n.s.). However, the cartilage defect size at baseline was significantly associated with an increase in total cartilage WORMS in the control group ($R = 0.56$; $P = 0.035$), but not in the cartilage repair group ($R = -0.08$; n.s.). Presence of a bony defect as well as ICRS scores correlated significantly with $T2_{relative}$ in the opposing compartment in the cartilage repair group ($R = 0.59$, $P = 0.017$ and $R = 0.51$, $P = 0.042$, respectively). Moreover, the AMADEUS score correlated significantly with $T2_{relative}$ of the cartilage repair region ($R = 0.54$, $P = 0.030$). For the cartilage repair group, the mean post-operative MOCART score was 77.5 ± 18.9. A decrease in WORMS BMEP scores over time was associated with better defect filling ($R = -0.55$, $P = 0.029$).

Discussion

The most important finding of the present study was, that during identical MR follow-up times, the progression of whole knee joint degeneration and of cartilage defects in the affected and in the opposing knee compartment was significantly less severe in individuals with cartilage repair surgery than in non-operated individuals. In non-operated individuals, cartilage T2 values increased continuously from baseline to the 8-year follow-up, indicating progressive cartilage matrix degeneration. The cartilage defect size at baseline was significantly associated with an increase in total cartilage WORMS in the control group, but not in the cartilage repair group. In the cartilage repair group, presence of a bony defect as well as higher ICRS scores were associated with higher cartilage $T2_{relative}$ values in the opposing compartment, suggesting more severe cartilage matrix degeneration in case of bony involvement. Further, a decrease of BMEP over time was associated with better defect filling after cartilage repair surgery, suggesting better cartilage repair tissue in cases where the subchondral bone recovers.

There are several studies that compare the clinical and imaging outcome of different cartilage repair techniques [4, 9, 14, 16, 23]. However, comparisons of non-operated individuals with focal cartilage defects that fulfill criteria for a justified indication of cartilage repair surgery is difficult, since denying indicated surgery is unethical [3]. In this study, in the control cohort the highest increase of cartilage defect scores in the affected knee compartment and of global T2 values was found within the first 2 years of follow-up. It was followed by the most severe progression of total WORMS scores between the follow-up years 2 and 4, indicating progressive degeneration from focal to global [13]. Other studies also reported a significant loss in total cartilage volume in the affected joint within 2 years of follow-up [7]. These findings underline, that cartilage defects should be treated in early disease course [55].

If the subchondral bone is involved, for cartilage repair either OATS or spongiosa-augmented MACI needs to be performed to restore not only the cartilage but also the subchondral bone [42, 44, 49, 56]. Particularly, in

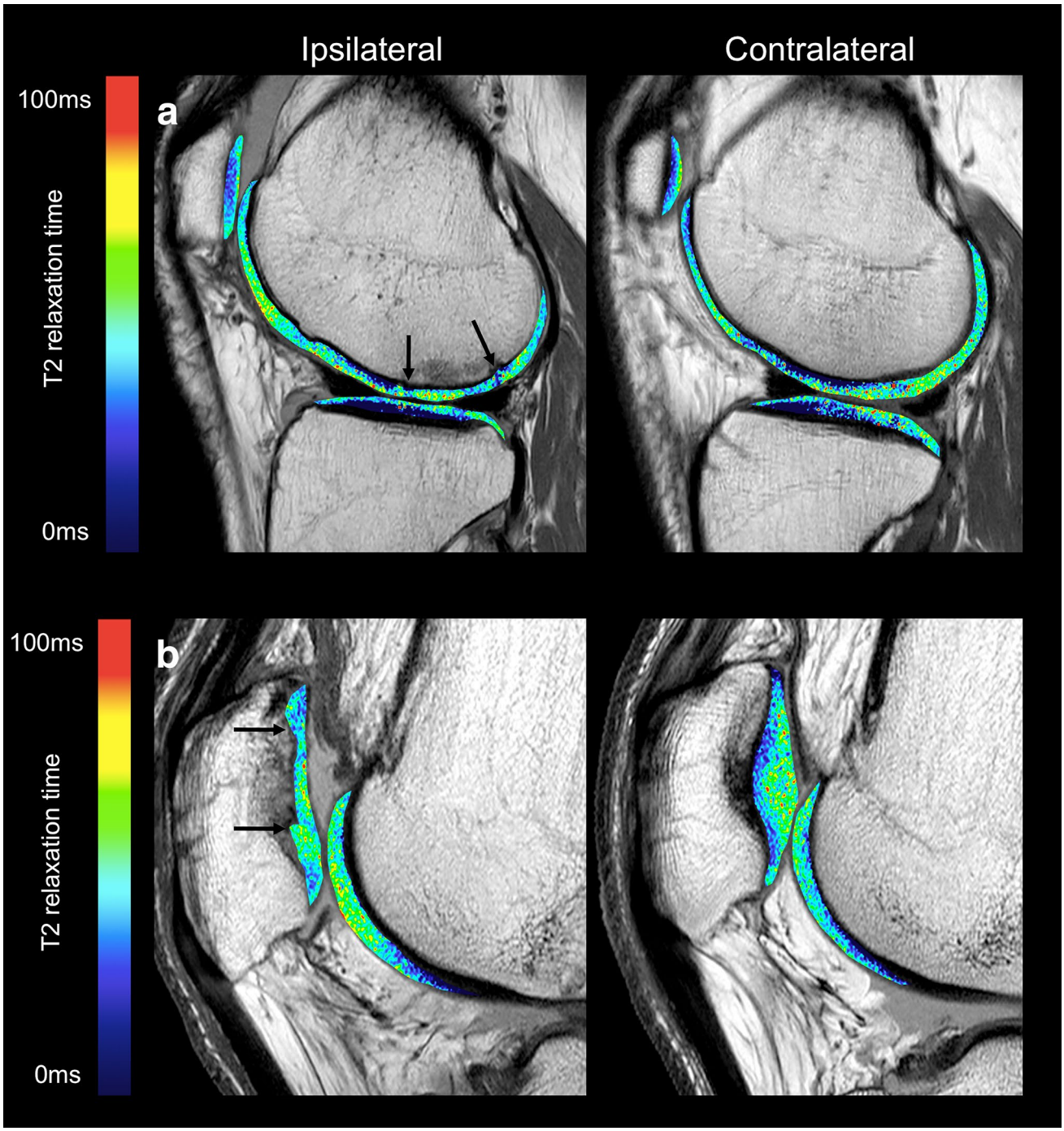

Fig. 4 Cartilage T2 relaxation time maps overlaying the first echo of the T2-weighted multi-slice-multi-echo spin-echo sequences from the ipsilateral and the contralateral knee of two patients who received osteochondral repair. **a** Patient with osteochondral repair at the lateral femoral condyle. **b** Patient with osteochondral repair at the patella. Arrows mark the borders of the osteochondral repair tissue. Blue colour represents low T2-values, indicating intact cartilage matrix tissue. Red colour represents high T2-values, indicating degenerated cartilage matrix tissue. Overall, T2-values were similar between ipsilateral and contralateral knees. T2 values at the lateral tibial plateau were lower at ipsilateral than at contralateral knees. In case of cartilage repair at the patella, the opposing trochlear compartment showed non-significantly higher T2-values than the contralateral knee

young patients, these techniques are preferred due to their superior outcome. This explains the frequency of these techniques in our young cohort with rather small defects. Subjects included in this study had rather small defects. Subjects from the OAI with large defects already showed local contraindications for cartilage repair, such

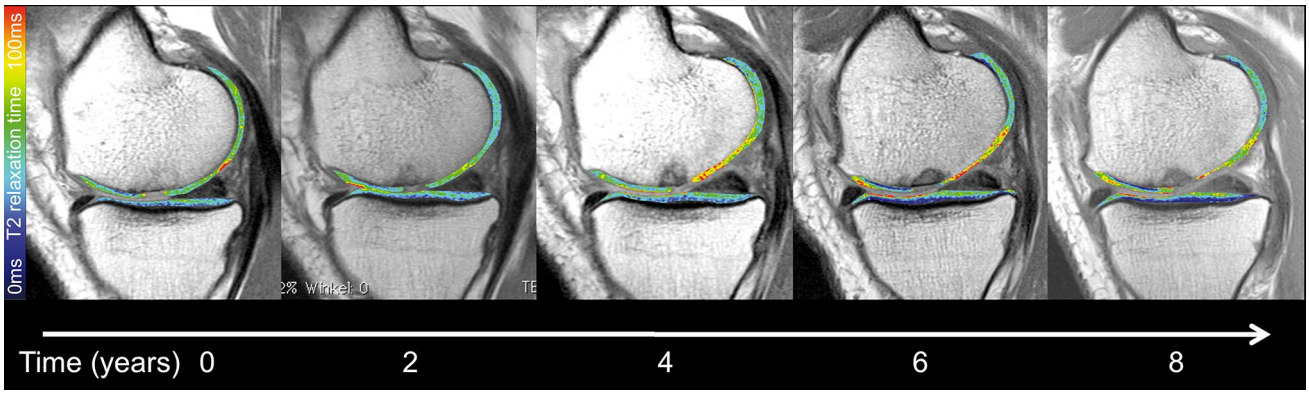

Fig. 5 Cartilage T2 relaxation time maps overlaying the first echo of the T2-weighted multi-slice-multi-echo spin-echo sequences from a non-operated individual from the OAI at baseline (0) and 2, 4, 6 and 8-year follow-up. Blue colour represents low T2-values, indicating intact cartilage matrix tissue. Red colour represents high T2-values, indicating degenerated cartilage matrix tissue. A continuous increase of T2-values and a progressive cartilage loss may be depicted in the affected compartment (medial femoral condyle) with the focal full thickness cartilage defect

as uncontained boarders of the defect, opposing cartilage defects, relevant meniscus tears or advanced OA. Consequently, there were no control subjects with large, contained cartilage defects that did not show contraindications for cartilage repair. Therefore, those cartilage repair patients with larger defects could not be considered and need further investigation in future studies.

Quantitative cartilage T2 relaxation times correlate with cartilage matrix degeneration, primarily with collagen disruption and increasing water contents [2, 29, 35]. Diverging results have been reported for the quantitative MR imaging evaluation of cartilage repair tissue, most likely due to the diverging underlying histology [26]. Although measuring about 3 ms, the difference between T2 values of the cartilage repair tissue and T2 values of the corresponding contralateral compartment was not significant in our study, most likely due to a high standard deviation. With OATS, hyaline cartilage is transplanted. However, the transplanted cartilage undergoes histological changes during follow-up and generally shows higher T2 values as compared to native cartilage [26, 52]. With MACI hyaline-like cartilage is developed, which may incorporate high T2 values due to hyaline components, but also low T2 values due to fibrous components [38, 52]. In contrast to findings 10 years after Mega-OATS procedures [28], in case of osteochondral transplantation with spongiosa-augmented MACI or OATS, ipsilateral T2 values were not elevated as compared to T2 values at the contralateral knee. Therefore, the outcome may be superior to the outcome after Mega-OATS. However, it has to be realized that Mega-OATS represents a salvage procedure for very large defects [1, 28]. $T2_{relative}$ in the opposing compartment was the highest in case of cartilage repair at the patella, confirming previously reported findings of a possibly inferior outcome after retropatellar MACI [20, 43].

The initial cartilage defect size correlated with an increase in total cartilage WORMS in the OAI group, but not in the cartilage repair group. This confirms, that with cartilage repair surgery good results may also be achieved in case of initially large cartilage defects [51]. ICRS scores and preoperative presence of bone defects correlated with $T2_{relative}$ of the opposing compartment, suggesting more severe cartilage matrix degeneration in case of bony involvement. Previously, it has been reported, that total MOCART scores do mostly not correlate with other imaging findings or T2 values [12, 26]. This is confirmed by our results, with the exception that a decrease in BME resulted in a better filling of the defect. This underlines the assumption of a synergetic effect of healing of the subchondral bone and the overlying cartilage repair tissue [19].

Some limitations have to be considered. Due to different MR scanners and protocols, T2 values between the two groups were not comparable. Second, no preoperative T2 mapping for the cartilage repair group was available. Third, although clinical parameters and imaging parameters that are important for the indication of cartilage repair surgery were considered in the patient selection process, parameters such as BMI, activity level, leg alignment, knee stability and concomitant surgery may have influenced the results. The conclusions may only be drawn for patients with OATS or spongiosa-augmented MACI with the respective defect size and location that was assessed in the present study. Further, although even asymptomatic cartilage defects progress, there is a general consensus that only clinically symptomatic defects justify an indication for cartilage repair surgery. It needs to be investigated in future studies, whether patients with cartilage repair surgery also perform better clinically in a mid-term follow-up than initially identical non-operated individuals [33]. Lastly, the OAI includes subjects ≥ 45 years

old. Consequently, the age difference between the groups was the most relevant limitation in this present study, which needs to be investigated further in future studies.

Conclusion

In summary, this is the first longitudinal quantitative and qualitative 3T MR imaging study with MR-based matching of subjects with and without cartilage repair surgery and with initially identical osteochondral defects at the knee. In conclusion, these favorable findings give rise for optimism regarding the efficacy of osteochondral transplantation with respect to prevention of further progression of degenerative changes at the knee joint. Clinically, patients with focal cartilage defects may profit from cartilage repair surgery since it may prevent the progression of early osteoarthritis, and therefore, prevent associated pain and disability of the knee joint.

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Compliance with ethical standards

Conflict of interest No conflict of interest for any of the authors.

Ethical approval The study was approved by the local Institutional Review Boards (Ethikkommission Technical University of Munich). The OAI study protocol, amendments, and informed consent documentation including analysis plans were reviewed and approved by the local institutional review boards. Data used in the preparation of this manuscript were obtained from the OAI database, which is available for public access at http://www.oai.ucsf.edu/. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

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