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Clinical and radiographical ten years long-term outcome of microfracture vs. autologous chondrocyte implantation: a matched-pair analysis

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Abstract

Purpose To compare the clinical and radiographical long-term outcome of microfracture (MFX) and first-generation periosteum-covered autologous chondrocyte implantation (ACI-P).

Methods All subjects ($n = 86$) who had been treated with knee joint ACI-P or microfracture ($n = 76$) with a post-operative follow-up of at least ten years were selected. Clinical pre- and post-operative outcomes were analyzed by numeric analog scale (NAS) for pain, Lysholm, Tegner, IKDC, and KOOS score. Radiographical evaluation was visualized by magnetic resonance imaging (MRI). Assessment of the regenerate quality was performed by the magnetic resonance observation of cartilage repair tissue (MOCART) and modified knee osteoarthritis scoring system (mKOSS). Relaxation time (RT) of T2 maps enabled a microstructural cartilage analysis.

Results MFX and ACI of 44 patients (24 females, 20 males; mean age 38.9 ± 12.1 years) resulted in a good long-term outcome with low pain scores and significant improved clinical scores. The final Lysholm and functional NAS scores were significantly higher in the MFX group (Lysholm: MFX 82 ± 15 vs. ACI-P 71 ± 18 $p = 0.027$; NAS function: MFX 8.1 ± 3.5 vs. ACI-P 6.0 ± 2.5; $p = 0.003$). The MOCART score did not show any qualitative differences. KOSS analysis demonstrated that cartilage repair of small defects resulted in a significant better outcome. T2-relaxation times were without difference between groups at the region of the regenerate tissue.

Conclusion This study did not demonstrate coherent statistical differences between both cartilage repair procedures. MFX might be superior in the treatment of small cartilage defects.

Keywords Microfracture · Periosteum-covered autologous chondrocyte implantation · Knee osteoarthritis scoring system · Magnetic resonance observation of cartilage repair tissue

Introduction

Defects of articular cartilage have a high prevalence. In a retrospective study of 25,124 arthroscopies, 60% of the patients who suffered from knee pain had a chondral lesion [1]. Due to its limited capacity of self-repair, symptomatic cartilage lesions can extend and progress into degeneration of the whole joint [2]. Different regenerative treatments are available for symptomatic full thickness chondral defects. Among them, microfracture (MFX) and autologous chondrocyte implantation (ACI) are the most frequently used cartilage repair procedures [3]. It is a current debate, which cartilage repair technique is the most appropriate. Devitt et al. [4] reported in a meta-analysis of randomized controlled trials that clinical outcome of ACI was superior in large defects (> 4.5 cm^2). Smaller lesions did not show statistical differences at mid-term. However, they reported a significant higher failure rate in the MFX group at ten years. It is well-known that advanced cartilage repair procedures, such as ACI produce higher repair tissue (RT) quality compared with MFX [5]. However, the relationship between RT quality and clinical outcome remains unclear [6]. Quantitative magnetic

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resonance imaging (MRI) is a diagnostic tool to analyze RT after cartilage repair [7]. Cartilage T2-weighted mapping quantifies the cartilage ultrastructure [8]. A previous study of our group demonstrated a weak correlation of RT quantitative imaging, but a stronger correlation of qualitative imaging data and clinical outcome at ten years follow-up after ACI-P [9]. Aim of the study was to compare the ten years outcomes of ACI-P and MFX with quantitative and qualitative imaging of the RT correlating to clinical assessments.

Methods

This study was approved by the local ethical committee (EK262-13). Clinical assessments were performed by an independent investigator and radiologic evaluation was realized by an independent blinded (to the clinical data) radiologist with specialty in MR-based knee joint cartilage evaluation. All patients who were treated by ACI-P ($n = 86$) between January 1997 and December 2001 or MFX ($n = 76$) between January 2001 and December 2006 were included. In the ACI-P group, 59 (69% follow-up rate) patients were available for clinical and radiographical evaluation. In the MFX group, 22 (29% follow-up) patients participated. Twenty-two matched pairs were selected with the main criteria defect localization (medial femoral condyle, lateral femoral condyle, trochlea, retro patella) and sex as well as additional criteria age and body mass index (BMI). Clinical knee joint examination was performed for all included patients, and the numeric analog scale (NAS) for pain (0 no pain, 10 strongest pain), functional numeric analog scale (0 immobility, 10 no restriction), the modified Lysholm score, Tegner activity scale, subjective International Knee Documentation Committee (IKDC) score and Knee injury and Osteoarthritis Outcome Score (KOOS) were used. MR examination was performed at the same time with a 1.5-T MRI scanner (Siemens Avanto; Siemens Medical Solutions, Erlangen, Germany) and an eight-channel knee coil. A standard knee protocol was used with the following sequences: fast spin-echo proton density weighted (repetition time [TR]/echo time [TE], 2810/31 ms) in coronal and sagittal planes; fast spin-echo proton density weighted with spectral fat saturation (TR/TE, 3370/36 ms) in transversal, coronal, and sagittal planes; and fast spin-echo T2-weighted with spectral fat saturation (TR/TE 5880/60 ms) in sagittal plane. The spatial resolution was 320 × 320 to 384 × 384 pixels in field of view (FOV) of 1002 mm. T2 maps were calculated from multi-echo spin-echo acquisition with the following protocol: TR 1500 ms, 10 TEs (9, 18, 27, 36, 45, 54, 63, 72, 81, 90 ms), FOV 16 cm, acquisition matrix 256 × 256 and frequency of 240 Hz/pixel. Calculation of the colored T2-weighted map was performed by a standard software (Siemens, syngo®). Evaluation of the resulting images was enabled by the radiologist specialized in knee joint cartilage and an orthopaedic surgeon. The following regions of interest (ROIs) were drawn manually from the subchondral bone to the chondral surface perpendicular to the magnetic field in femoral regions and parallel to the magnetic field retropatellar areas of a previously described protocol [10]: repair tissue, interface regions, adjacent, opposing, and reference cartilage from a non-weight bearing region tibial or femoral (Fig. 1). The modified Knee Osteoarthritis Scoring System (mKOSS) was applied for evaluation of degenerative changes. The previously described magnetic resonance observation of cartilage repair tissue (MOCART) score was used to assess RT quality [11].

Statistics

SPSS (v 19; IBM) was used for statistical analysis. Data were tested for normal distribution by the Kolmogorov-Smirnow test. *T* test was chosen in case of normal distribution; non-normally distributed data was analyzed by the Mann-Whitney or Wilcoxon signed-rank test. Correlation analysis was performed by the Spearman correlation coefficient (r). $P < 0.05$ was defined as statistically significant.

Results

Patient characteristics

A total of 44 patients were included in this study. Twenty-four females and 20 males with a mean age of 38.9 ± 12.1 at surgery and mean body mass index of 27.2 ± 6.1 participated. The mean number of cartilage defects was 1.36 ± 0.5. The mean defect size was 3.56 ± 2.3 cm^2 and significantly different between MFX and ACI (MFX 2.37 ± 1.6; ACI 4.74 ± 2.3; $p < 0.001$). Localization of the defect was in 12 matched pairs of the medial femur condyle, one at the lateral femur condyle, five retropatellar, and four at the trochlea. A total of 18 patients had a previous surgery at the same knee joint. At index surgery, 27 patients had a co-pathology, treated by concomitant surgery, and incidence was significantly different between MFX and ACI (MFX: 17 patients; ACI: 10 patients; $p = 0.03$). A subgroup analysis was performed to exclude the defect size as potential confounder of the clinical and radiographical results. All patients with a defect size above the median were included in the MFX group and vice versa in the ACI-P group. The median of this subgroup was 3.52 ± 1.57 cm^2 in MFX and 2.09 ± 1.04 cm^2 in ACI-P ($p = 0.378$). Further characteristics are displayed in Table 1.

Clinical outcome

Subsequent surgeries were performed in 34% of all cases during the follow-up period. In the ACI group, 13 patients had undergone 23 surgical interventions. The most frequent post-

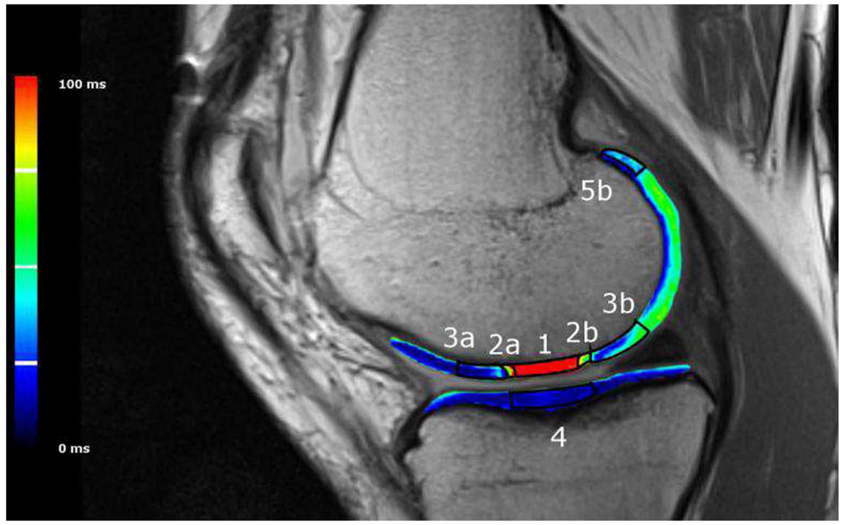

Fig. 1 Representative T1-weighted magnetic resonance (MR-) scan of the knee joint. Color coded T2-weighted maps evaluated the regions of interest (ROI; 1 = repair tissue, 2a = interface anterior, 2b = interface posterior, 3a = adjacent cartilage anterior, 3b = adjacent cartilage posterior, 4 = opposing cartilage, 5a/b = reference cartilage). Relaxation time is visualized in spectral colours (blue: 0 ms, red: 100 ms)

operative complication was transplant hypertrophy (8 patients). In contrast, only five re-operations were performed in two patients of the MFX group (ACI vs. MFX; $p < 0.001$). The results of all clinical tests are summarized in Table 2. At the time of ten years, post-operative follow-up patients reported in 41% that they were "very satisfied," 41% "satisfied," 16% "neutral," and 2% "unsatisfied" without difference between MFX and ACI ($p = 0.714$). Pain decreased in the NAS from 7.2 ± 2.3 pre-operatively to 2.4 ± 2.4 post-operatively ($p < 0.001$) without statistical difference between the treatments. In contrast, the functional rating scale was significantly different between MFX and ACI-P. The function increased from 3.6 ± 2.7 pre-operatively to 8.1 ± 3.5 post-operatively ($p < 0.001$) in the MFX group, whereas NAS function did not differ after ACI-P (pre-operatively: 6.1 ± 1.8; post-operatively: 6.0 ± 2.5; $p = 0.965$). However, post-operative differences were not significant after subgroup analysis with equal defect size ($p = 0.144$). Lysholm scores increased significantly from 43 ± 22 to 82 ± 15 ($p < 0.001$) in the MFX group and from 42 ± 25 to 71 ± 18 ($p < 0.001$) in the ACI-P group. The post-operative outcome was significantly higher after MFX ($p = 0.027$). Additionally, the subgroup analysis demonstrated the same result (MFX: 86 ± 10; ACI 68 ± 22; $p = 0.025$). Pre-operative Tegner activity score was significantly lower in the MFX group compared with ACI-P (MFX: 2.8 ± 2.3; ACI-P 5.0 ± 2.7; $p = 0.006$). Post-operatively, the activity score increased only in the MFX group, which resulted in a final equal level of both treatments (MFX: 4.6 ± 1.3; ACI-P 4.1 ± 1.5; $p <$ 0.001). The IKDC score was post-operatively not different between both treatment groups (MFX: 72 ± 20; ACI-P 65 ± 18; $p = 0.211$). Osteoarthritic changes were assessed by the KOOS, which did not show significant differences between the MFX and ACI-P groups. Interestingly, after subgroup analysis post-operative KOOS sports and quality of life scores were significantly higher after MFX (KOOS sports: MFX 75 ± 20; ACI-P 46 ± 35; $p = 0.028$; KOOS quality of life: MFX 66 ± 24; ACI-P 41 ± 30; $p = 0.046$).

MRI evaluation

MRI evaluation was performed for all 44 patients. All T2-measured regions of interest are summarized in Table 3. Reference cartilage T2-relaxation time was on average 43 ± 7 ms and significantly higher compared with all other ROIs ($p < 0.001$). The RT was on average 34 ± 10 ms and only different to the opposing cartilage ($p = 0.001$), but not to interface or adjacent regions. T2-relaxation time in reference cartilage of the MFX group was significantly higher compared with ACI-P (MFX: 46 ± 5 ms; ACI-P 39 ± 7 ms; $p = 0.001$). The subgroup analysis showed the same result. No other statistical differences could be detected in relaxation time analysis. Qualitative MR evaluation is displayed in Table 4. The mean mKOSS after MFX was significantly lower compared with ACI-P (MFX: 11.9 ± 2.9; ACI-P 15.4 ± 3.7; $p = 0.001$). Main differences were the development of osteophytes (MFX: 0.6 ± 0.7; ACI-P 1.4 ± 0.9; $p = 0.002$) and bone marrow oedema (MFX: 1.1 ± 1.1; ACI-P 2.1 ± 1.0; $p = 0.003$). In contrast, no statistical differences in mKOSS were detected after subgroup analysis, which suggests that defect size plays an important role in the development of osteoarthritis. The MOCART score resulted in a mean of 54.1 ± 12.8 in the MFX cohort and 49.8 ± 13.6 after ACI-P without statistical significance between both groups ($p = 0.284$). Among the subscales, integration and structure of the RT was superior in MFX compared with ACI-P (integration: MFX 11.1 ± 3.4; ACI-P 8.6 ± 4.7; $p = 0.049$; structure: MFX 2.1 ± 2.5; ACI-P 0.7 ± 1.8; $p = 0.044$). Pathologies of the subchondral bone were detected in all MRI sequences of the MFX group (MFX: 0 ± 0; ACI-P: 1.6 ± 2.4). In the whole study group, there was a significance in the correlation between qualitative,

Table 1 Characteristics of patients ($N = 44$)

	Total	MFX	ACI-P	p
Number of patients (n)	44	22	22	1.0
Male/female	24/20	12/10	12/10	1.0
Age, years	38.9 ± 12.1	40.5 ± 13.5	37.4 ± 10.6	0.408
Post-operative interval, years	10.4 ± 1.4	10.2 ± 1.7	10.6 ± 1.1	0.333
Body mass index, kg/m^2	27.2 ± 6.1	27.3 ± 5.6	27.1 ± 6.8	0.949
Affected knee, right/left	31/13	14/8	17/5	0.322
Defect size, cm^2	3.56 ± 2.3	2.37 ± 1.6	4.74 ± 2.3	< 0.001
Number of defects	1.36 ± 0.5	1.5 ± 0.6	1.23 ± 0.4	0.102
Defect location				
Medial femoral condyle	24	12	12	1.0
Lateral femoral condyle	2	1	1	1.0
Trochlea	8	4	4	1.0
Patella	10	5	5	1.0
Previous surgeries ($n = 18$ patients)				
Intra-articular loose-body	2	1	1	
Synovia- and plica- resection	3	3	0	
Meniscus	12	8	4	
Abrasion	4	2	2	
Cartilage repair	6	3	3	
Others	3	1	2	
Concomitant surgeries ($n = 27$ patients)				
Intra-articular loose-body	5	3	2	
Synovia- and plica- resection	13	13	0	
Meniscus	9	9	0	
Cartilage repair	6	0	6	
Others	4	1	3	
Post-operative surgeries ($n = 18$ patients)				
Intra-articular loose-body	3	0	3	
Synovia- and plica- resection	6	2	4	
Meniscus	4	1	3	
Abrasion	10	2	8	
Cartilage repair	1	0	1	
Others	4	0	4	

Values are expressed as n or mean ± standard deviation

quantitative radiologic, and functional assessments: the NAS for function and the MOCART score ($r_s = 0.337$, $p = 0.026$) and KOSS ($r_s = 0.376$, $p = 0.014$). Furthermore, T2-relaxation time significantly correlated with NAS for function ($r_s = 0.319$; $p = 0.035$) and the Lysholm Score ($r_s = 0.316$; $p = 0.037$). Quantitative and qualitative radiologic evaluation correlated between MOCART subscore for RT integration and T2-relaxation time ($r_s = 0.307$, $p = 0.043$). The mKoss subscale osteophytes correlated as well with the T2-relaxation time ($r_S = -0.518$, $p < 0.001$) of the RT. In the MFX group, subgroups of the MOCART and KOSS significantly correlated with the T2-relaxation time of the RT. The ACI-P did not show any significant correlation.

Discussion

This study reported the 10 years long-term outcome comparison between MFX and ACI in a matched-pair analysis. Major findings of this study were good clinical and radiographical outcomes without general statistical differences between MFX and ACI-P. The clinical improvement was mirrored in the high patient satisfaction of 82%. This study demonstrated that MFX resulted in a significant higher Lysholm score and NAS for function when comparing to ACI-P. It is important to consider the mean defect size of the different treatments in our study (MFX 2.4 ± 1.6 cm^2; ACI-P 4.7 ± 2.3 cm^2; $p < 0.001$). ACI is indicated in large chondral defects (> 3cm^2), whereas

Table 2 Clinical scores of patients ($N = 44$)

	MFX	ACI-P	*p*
Patient satisfaction			
Very satisfied	9	9	
Satisfied	10	8	
Neutral	3	4	
Not satisfied	0	1	
NAS pain			
Pre-op	7.1 ± 2.7	7.3 ± 2.3	0.795
Post-op	2.1 ± 2.0	2.7 ± 2.6	0.434
NAS function			
Pre-op	3.6 ± 2.7	6.1 ± 1.8	0.012
Post-op	8.1 ± 3.5	6.0 ± 2.5	0.003
Lysholm			
Pre-op	43 ± 22	42 ± 25	0.869
Post-op	82 ± 15	71 ± 18	0.027
Tegner			
Pre-op	2.8 ± 2.3	5.0 ± 2.7	0.006
P	4.6 ± 1.3	4.1 ± 1.5	0.210
IKDC	72 ± 20	65 ± 18	0.211
KOOS symptoms	79 ± 18	75 ± 18	0.503
KOOS pain	80 ± 21	80 ± 20	0.985
KOOS activity of daily living	87 ± 17	85 ± 17	0.711
KOOS sports	74 ± 26	57 ± 32	0.059
KOOS quality of life	64 ± 26	49 ± 26	0.078

Values are expressed as n or mean ± standard deviation

Table 4 Qualitative MR evaluation MOCART score and KOSS

	MFX	ACI-P	*p*
MOCART score			
Overall	54.1 ± 12.8	49.8 ± 13.6	0.284
Subscale			
Defect filling	13.2 ± 4.0	13.9 ± 4.1	0.575
Integration	11.1 ± 3.4	8.6 ± 4.7	0.049
Surface	7.7 ± 2.5	7.7 ± 3.0	1.0
Structure	2.1 ± 2.5	0.7 ± 1.8	0.044
Signal Intensity	13.0 ± 7.7	10.0 ± 4.4	0.126
Subchondral lamina	2.1 ± 2.5	2.4 ± 2.6	0.767
Subchondral bone	0 ± 0	1.6 ± 2.4	0.005
Adhesions	2.5 ± 2.6	3.0 ± 2.5	0.556
Effusions	2.5 ± 2.6	2.1 ± 2.5	0.556
KOSS			
Overall	11.9 ± 2.9	15.4 ± 3.7	0.001
Subscale			
Cartilage defect	5.3 ± 0.9	5.7 ± 1.2	0.169
Osteophytes	0.6 ± 0.7	1.4 ± 0.9	0.002
Subchondral cysts	0.6 ± 1.0	0.9 ± 1.3	0.433
Subchondral bone marrow edema	1.1 ± 1.1	2.1 ± 1.0	0.003
Meniscus	2.7 ± 2.4	3.3 ± 1.7	0.388
Effusions	1.4 ± 0.9	1.8 ± 0.7	0.096
Baker cysts	0.1 ± 0.3	0.1 ± 0.3	1.0

Values are expressed as mean ± standard deviation

MFX is performed in small lesions ($< 3\text{cm}^2$) [12]. Nevertheless, it was demonstrated that clinical outcome after cartilage repair was better in small defects [13, 14]. Interestingly, in our study the Lysholm score of the MFX group was even significantly higher in the subgroup analysis, which compared results of both treatments with equal defect size (MFX 3.52 ± 1.6 cm^2; ACI-P 2.96 ± 1.0 cm^2; $p = 0.332$). It can be suggested that MFX is superior to ACI-P in small defects even after ten years follow-up. It could also be related to the fact that ACI-P is by definition the first-generation ACI requiring the use of a periosteum cover, which is nowadays not standard of care anymore. Younger studies comparing MFX with ACI often report a superior outcome for ACI, yet not at long-term observation. For direct comparison between clinical long-term outcomes of ACI and MFX, only one randomized controlled study from Knutsen et al. [15] in a 15 years follow-up of 80 patients is available. They reported no significant differences in all clinical scores (International Cartilage Repair Society [ICRS], Lysholm, Short Form-36 (SF-36), and Tegner forms). Intriguingly, treatment failure rate of both ACI and MFX was high (30–40%) without statistical difference. Repair tissue quality plays an important role in the durability of the transplant and the associated integrity of the whole joint. DiBartola et al. [16] found in a meta-analysis of cartilage regeneration in the knee joint, a significant correlation between histological outcome and cartilage repair technique. The quality of repair tissue was superior in ACI compared with MFX. Furthermore, Riboh et al. [5] demonstrated in a network meta-analysis that higher quality of repair tissue might reduce the re-operation rate in the long-term.

Table 3 T2-weighted relaxation times of cartilage in [ms] ($N = 44$)

Region of Interest (ROI)	MFX	ACI-P	*p*
Reference cartilage	46 ± 5	39 ± 7	0.001
Repair tissue (RT)	34 ± 8	33 ± 12	0.665
Interface	36 ± 11	31 ± 9	0.078
Anterior	34 ± 10	29 ± 11	0.083
Posterior	38 ± 13	33 ± 11	0.154
Adjacent	33 ± 7	32 ± 9	0.766
Anterior	30 ± 8	29 ± 11	0.844
Posterior	36 ± 11	35 ± 11	0.872
Opposing	27 ± 9	25 ± 9	0.391

Values are expressed as mean ± standard deviation

T2 mapping is a well-established method for quantitative evaluation of the cartilage ultrastructure and an excellent tool for initial diagnostic of chondral lesions and follow-up evaluation after cartilage repair [9, 17]. Advantages of this technique are a high sensitivity in detecting cartilage pathologies without the need of contrast agent, which is necessary in the delayed gadolinium enhanced MRI of cartilage (dGERMRIC) technique [8, 18]. The T2-relaxation time is depending on the composition of articular cartilage, especially water and collagen [19]. Elevated T2 relaxation times are caused by degenerative changes, whereas lower relaxation times are an indicator for fibrocartilage [20]. Jungmann et al. [19] reported in a review article that T2-relaxation times after cartilage repair of both MFX and ACI were elevated the first years after surgery and subsequently decreased under the level of reference cartilage. Especially, repair tissue after MFX has been reported to develop a lower quality repair tissue similar to fibrocartilage [21]. In contrast, advanced cartilage repair techniques, such as osteochondral allograft transplantation (OAT) or ACI produced a hyaline like tissue [16]. However, in this study, T2-relaxation time of the regenerate (RT) was lower than reference cartilage and without significant differences between both surgical procedures. It suggests that neither MFX nor ACI are capable of producing a durable hyaline repair tissue after ten years follow-up. Histologic analysis of the repair tissue at long-term could sufficiently prove these findings. This study also analyzed the correlation between clinical scores and T2-weighted relaxation time of the repair tissue. There were significant correlations between some clinical scores (Lysholm score and NAS for function) and overall repair tissue T2-relaxation times. Regardless, analysis of the single treatment procedures did not result in significant correlations. Currently, evidence cannot suggest a correlation between the T2-weighted relaxation times and clinical outcomes [22]. Different scores have been introduced for qualitative assessment of the knee joint after cartilage repair. Among them, the MOCART score evaluates the quality of the regenerate, the filling of the defect, the integration, and structure of the surrounding cartilage [23]. At ten years follow-up, this study did not show any significant differences between MFX and ACI-P in the MOCART score. Previous studies reported similar levels in both cartilage repair techniques [9, 24]. In detail, the different cartilage repair procedures resulted in significantly different specific MOCART subscores. Integration to the surrounding tissue and structure of the adjacent cartilage were superior in the MFX group, whereas integrity of the subchondral bone was significantly higher in the ACI-P group. As previously reported by Salzmann et al. [9], for long-term outcome after ACI-P, there was no correlation between the MOCART score and clinical assessments in the different treatment groups. This study demonstrated a significant correlation between repair tissue integration and T2-relaxation time for the whole study group and the MFX cohort. Furthermore, there was a significant correlation between regenerate integration and clinical assessments (NRS for function, Tegner activity scale, and IKDC). These results highlight the importance of an effective integration for a successful long-term outcome of cartilage repair. To our best knowledge, there are no comparable long-term studies focusing on RT integration available. The ultimate aim of cartilage repair is to prevent or at least alter the development of osteoarthritic changes [25]. However, Knutsen et al. [15] reported in a randomized controlled trial that both MFX and ACI were not sufficient to prevent the progress of osteoarthritis at 15 years follow-up. They observed that about 50% of all patients had radiographical signs for early osteoarthritis (Kellgren Lawrence score ≥ 2) without significant differences between both cartilage repair methods. This study evaluated osteoarthritic changes by assessment of MRI sequences with the mKOSS. Interestingly, the MFX cohort had significant lower mKOSS score than the ACI-P group. However, this effect was neutralized in subgroup analysis with equal defect sizes. It could be demonstrated that defect size was significantly correlated with the mKOSS outcome ($r_s = 0.429$; $p = 0.004$). Reasonably, large defects have a higher risk to develop osteoarthritis even after cartilage repair [12]. A significant correlation between mKOSS and MOCART score demonstrated that repair tissue morphology and osteoarthritic changes are interconnected. Current research suggests that a disturbed joint homeostasis after cartilage injury can affect cartilage regeneration and finally result in early degeneration [26].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by the local ethical committee (EK262-13).

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