

Is the clinical outcome after cartilage treatment affected by subchondral bone edema?

Giuseppe Filardo · Elizaveta Kon · Alessandro Di Martino ·
Francesco Perdisa · Maurizio Busacca · Francesco Tentoni ·
Federica Balboni · Maurilio Marcacci

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Abstract

Purpose Subchondral bone edema is a common finding after cartilage treatment, but its interpretation is still debated. The aim of this study is to analyse the presence of edema after matrix-assisted autologous chondrocyte transplantation (MACT) for knee cartilage lesions at different follow-up times and its correlation with the clinical outcome.

Methods Two hundred and forty-eight magnetic resonance imagings (MRIs) of patients treated with a hyaluronic acid-based MACT for lesions of the knee articular surface were considered. The MRIs belonged to 116 patients (mean age at surgery 28.6 ± 10.3 years, average

defect size 2.4 ± 1.0 cm²), 57 affected by degenerative cartilage lesions, 27 traumatic and 32 were osteochondritis dissecans (OCD). MRI follow-up was performed from 6 to 108 months after treatment. Other than its presence or absence, the subchondral bone edema was evaluated using a 3-level grading considering extension and hyperintensity, and with the WORMS score edema classification. The IKDC subjective score was collected at the time of every MRI.

Results An analysis of the entire MRI group showed that edema is not constantly present through the follow-up, but presents a particular and well-defined trend. Edema was present within the first 2 years and was then markedly reduced or disappeared at 2 and 3 years ($p = 0.044$). Afterwards the level of edema increased again ($p < 0.0005$) and remained steadily present at medium/long-term follow-up. Patellar lesions presented significantly lower edema ($p = 0.012$), whereas OCD lesions presented more edema at all follow-up ($p = 0.002$) and a different trend, with an increasing level of edema over time. No correlation was found between edema and clinical outcome.

Conclusions Edema after MACT is present during the first phases of cartilage maturation up to 2 years of follow-up, and then tends to disappear. However, after a few years, it tends to reappear. Less edema was found in the patella, whereas more edema was found in the OCD, where subchondral bone is primarily involved. Interestingly, the presence of edema was not correlated with a poorer clinical outcome. Whether this might be a prognostic factor at longer follow-up remains to be determined, but our results give some indication on what to expect on both MRI edema and clinical outcome after MACT.

Level of evidence Case series, Level IV.

G. Filardo · E. Kon (✉) · A. Di Martino · F. Perdisa ·
F. Tentoni · F. Balboni · M. Marcacci
Biomechanics Laboratory-II Clinic, Rizzoli Orthopaedic
Institute, Via Di Barbiano, 1/10, 40136 Bologna, Italy
e-mail: e.kon@biomec.ior.it

G. Filardo
e-mail: g.filardo@biomec.ior.it

A. Di Martino
e-mail: a.dimartino@biomec.ior.it

F. Perdisa
e-mail: francescoperdisa@gmail.com

F. Tentoni
e-mail: francesco.tentoni@gmail.com

F. Balboni
e-mail: balboni.federica@gmail.com

M. Marcacci
e-mail: m.marcacci@biomec.ior.it

M. Busacca
Radiology and Diagnostic Imaging Department,
Rizzoli Orthopaedic Institute, Bologna, Italy
e-mail: maurizio.busacca@ior.it

Keywords Subchondral bone edema · Cartilage lesion · Matrix-assisted autologous chondrocyte implantation · Knee

Introduction

Among the surgical approaches proposed over the years to treat chondral or osteochondral lesions, regenerative procedures have been developed with the aim of replacing the damaged chondral surface with a hyaline-like tissue [21]. Since being applied in humans in 1987, this cell-based approach has gained increasing acceptance, and recent studies highlight the long-term durable nature of this form of treatment, due to the production of hyaline-like cartilage that is mechanically and functionally stable and integrates into the adjacent articular surface [30, 37]. However, these good results had to be weighed against the number of problems observed with the standard autologous chondrocyte implantation (ACI) methods. To overcome them, so-called matrix-assisted autologous chondrocyte transplantation (MACT) techniques have been developed, which use a tissue-engineering approach to create cartilage-like tissue in a 3-dimensional culture system in an attempt to address all concerns related to the cell culture and the surgical technique [12, 7, 20]. After their introduction into the clinical practice more than one decade ago, several scaffolds have been developed and good clinical results have been reported at medium-term follow-up for different treatment indications [2, 8–11, 38].

However, in the literature most of the studies are focused on the clinical outcome at different follow-up times, but the repaired tissue obtained is systematically evaluated only rarely [33, 34, 36].

For the time being, the preferred method for cartilage evaluation is magnetic resonance imaging (MRI), a non-invasive, multi-planar technique capable of producing high-resolution, high-contrast images in serial contiguous slices. MRI enables morphological assessment of the cartilage surface, as well as its internal structure, thickness, volume and the subchondral bone, and some studies have shown a good correlation with cartilage histology [27]. It is non-invasive and repeated scans can be carried out, thereby allowing longitudinal monitoring at different time points of the treated site. Furthermore, in contrast with the small biopsy specimens used for histology assessment, which are from a discrete location and can offer only limited information, MRI can provide information on the whole area. MRI is considered as the standard method for the evaluation of the morphologic status of cartilage defects, and it may also be useful for analyzing the maturation processes of the repair tissue in

the postoperative period and the results obtained with surgical techniques through specifically developed scores [1, 15, 23, 24, 32]. However, besides some sporadic studies, suggesting that MRI might predict the clinical outcome [19, 24, 25], a recent meta-analysis showed that for the majority of the parameters, limited or no correlation was found and only 28 % of the studies could show a correlation with a composite score [4]. Since the available scores were mainly designed for the evaluation of cartilage layer, other aspects influencing the clinical outcome might be underestimated or ignored.

Recently, there has been increasing interest and awareness, concerning the importance of the subchondral bone, which may be involved in the pathological process not only primary, such as in osteochondritis dissecans (OCD), osteonecrosis and trauma, but also secondary in degenerative cartilage lesions [26, 28]. Similarly, subchondral bone may play a key role also in the altered joint environment after surgical treatment for chondral lesions. The definition of the changes at the subchondral bone level is important to understand the maturation and evolution of the treated articular compartments, and this structure is becoming the focus both of imaging evaluation and of the development of procedures tailored to the entire osteochondral unit [3, 18, 27]. However, whereas the role of subchondral bone edema is well known and has been profusely studied with respect to OA development or osteonecrosis [3, 18, 26], most of the studies on cartilage treatment actually lack data on subchondral bone changes to document their extent, frequency, timing of presentation and correlation with other factors, to understand their significance and their possible influence on the outcome of cartilage surgery.

The main purpose of this study was therefore to document the presence of edema in the subchondral bone following surgical treatment for chondral and osteochondral knee lesions, focusing on the analysis of MRIs obtained from short to medium/long-term follow-up after MACT. The secondary aim was to determine factors that may influence the presence of subchondral bone edema over time and to understand how it may influence the clinical results, obtained after cartilage treatment.

Materials and methods

The bioengineered tissue Hyalograft C[®] (Fidia Advanced Biopolymers Laboratories, Padova, Italy), consisting of cultured autologous chondrocytes seeded on hyaluronan-based scaffold Hyaff 11[®], was implanted by an arthroscopic technique or a mini-arthrotomy approach, based on the lesion location and the surgeon's preference [20].

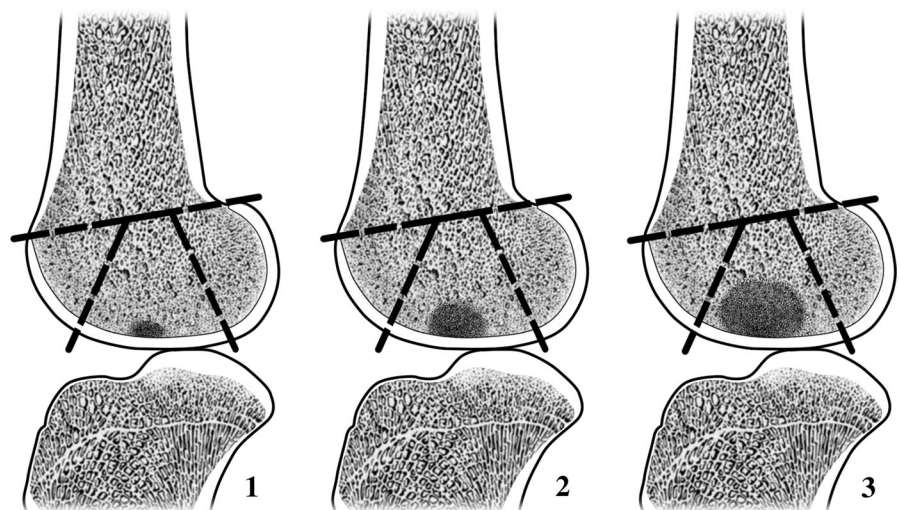
Experienced knee surgeons selected patients according to defined criteria: traumatic, degenerative focal grade III-IV chondral knee defects or osteochondritis dissecans (ICRS evaluation package) [17] involving femoral condyles, patella or trochlea, complaining of clinical symptoms (pain, swelling, locking and giving way). Exclusion criteria were BMI higher than 30, untreated tibio-femoral or patello-femoral misalignment or knee instability, diffused arthritis or bipolar (“kissing”) lesions, and those with infective, tumor pathology or other general medical conditions (diabetes, rheumatoid arthritis, etc.). All patients were prospectively followed yearly, and their clinical outcome was evaluated with the IKDC subjective score [17]. The operation was considered to have failed whether the patient needed a re-operation because of symptoms related to the primary defect. Although this study focused on the clinical outcome and imaging evaluation was not performed systematically, postoperative MRIs of most patients were collected. Therefore, MRIs were evaluated at different follow-ups retrospectively for a descriptive analysis of the edema level and its correlation with the prospectively evaluated clinical outcome.

Two hundred and forty-eight MRIs in T2-weighted FAT SAT and PD weighted FAT SAT sequences were considered and evaluated in consensus by an MRI experienced radiologist and an orthopedic surgeon. The MRIs belonged to 116 patients with mean age at surgery of 28.6 ± 10.3 years and mean BMI of 24. Sixty-one patients (52.6 %) had undergone previous knee surgery. These operations included 18 anterior cruciate ligament reconstructions (ACL), 20 meniscectomies and 1 meniscal suture, 3 lateral releases, 1 tibial fracture synthesis, 1 patellar plastic, 1 patellar tendon suture, 1 hardware removal and 18 cartilage

procedures: 5 shavings, 4 debridements, 3 microfractures, 3 loose body removals, 1 autologous osteochondral transplantation and 2 mosaicplasties. In 55 patients (47.4 %), combined procedures were performed: 9 meniscectomies and 4 collagen meniscal implants, 23 ACL repair and 2 PLC reconstructions, 8 osteotomies and 2 lateral releases. The evaluated MRIs belonged to 57 knees affected by degenerative cartilage lesions, 32 traumatic lesions and 27 OCDs. Thirty-three MRIs documented results of knees with multiple lesions. The site of the defects was the medial femoral condyle (MFC) in 60 cases, lateral femoral condyle (LFC) in 30 cases, trochlea in 10 cases, whereas in 16 MRIs the patella was involved. The average size of the defects was $2.4 \pm 1.0 \text{ cm}^2$. MRI follow-up was performed from 6 to 108 months after treatment, and MRIs were divided according to the postoperative period they were performed in: before 12 months of follow-up (16 MRIs), from 12 to 23 months (46 MRIs), from 24 to 35 months (22 MRIs), from 36 to 47 months (27 MRIs), from 48 to 59 months (39 MRIs), from 60 to 71 months (42 MRIs) and at follow-ups longer than 72 months (56 MRIs). Other than its presence or absence (yes or no), the subchondral bone edema was evaluated using a 3-level grading considering extension and hyperintensity (0: no edema; 1: small edema or slightly hyperintense; 2: large edema or highly hyperintense), and the WORMS score classification of the subarticular marrow abnormalities [29]: altered signal intensity in the epiphyseal marrow was graded from 0 to 3 on the extent of regional involvement (0 = none; 1 = <25 % of the region; 2 = 25–50 % of the region; 3 = >50 % of the region) (Fig. 1).

Clinical experimentation on hyaluronan-based MACT was approved by the Hospital Ethics Committee and Internal Review Board of (Prot. 0039633) and informed

Fig. 1 WORMS subarticular marrow abnormality score: a score from 0 to 3 (0 = none; 1 = <25 % of the region; 2 = 25–50 % of the region; 3 = >50 % of the region) is assigned to the subchondral bone according to the degree of alteration in the specific anatomic region



consent was obtained from all patients. This technique has been used in our Institute (Rizzoli Orthopaedic Institute, Bologna, Italy) since 2000.

Statistical analysis

All continuous data were expressed in terms of the mean and the standard deviation of the mean. Median and 25th and 75th percentiles were used for ordinal scores. Categorical variables are expressed as frequency and percentages. The Kolmogorov–Smirnov test was performed to test normality of continuous variables. The repeated measures general linear model (GLM) with the Sidak test for multiple comparisons was performed to assess differences at different follow-up times. The repeated measures GLM was also used as a multivariate analysis to assess the influence of potential predicting factors on the follow-up evolution. The ANOVA test was performed to assess the differences between groups of continuous, normally distributed and homoscedastic data, the Mann–Whitney test was used otherwise. The ANOVA test followed by the Scheffè post hoc pairwise comparison was used also to assess the differences between groups of continuous, normally distributed and homoscedastic data, the Kruskal–Wallis test followed by the Mann–Whitney test with the Bonferroni correction for multiple comparison was used otherwise. The Spearman rank correlation was used to assess correlation between rank and continuous data; the Kendall tau correlation was used for ordinal data. The Fisher Chi square test was performed to investigate the relationships between dichotomous variables. Pearson's Chi square test evaluated by Exact Methods for small samples was performed to investigate the relationships between grouping variables.

For all tests, $p < 0.05$ was considered significant.

All statistical analysis was performed using SPSSv.19.0 (IBM Corp., Armonk, NY, USA).

Results

The evaluation throughout the different time periods showed that edema was not constantly present at the different follow-ups, but presented a particular and well-defined trend ($p = 0.001$): edema was present in the first period up to 2 years (49.2 % of MRIs showed signs of edema), it was markedly reduced or disappeared at 2 and 3 years (29.8 % of MRIs), and then it increased again (60.4 % of MRIs presented edema at medium/long-term follow-up). The analysis performed with the WORMS edema classification and the 3-level classification confirmed the same trend (Table 1, Fig. 2). The presence of edema was significantly lower in patellar lesions: 25.8 % versus

Table 1 Subchondral bone edema changes after MACT scored over time with 3-level grading (a) and WORMS score (b), respectively

	<24 months	24–41 months	>42 months
a			
Absent	50 %	70.2 %	40.3 %
Small/slightly hyperintense	25.8 %	14.9 %	33.8 %
Large/highly hyperintense	24.2 %	14.9 %	24.2 %
25° p, median, 75°p	1, 1.5, 2	1, 1, 2 $p = 0.011$	1, 2, 3 $p = 0.003$
b			
Absent	48.4 %	70.2 %	39.6 %
<25 %	17.7 %	12.8 %	21.6 %
25–50 %	22.6 %	14.9 %	16.5 %
>50 %	11.3 %	2.1 %	22.3 %
25°p, median, 75°p	0, 1, 2	0, 0, 1 $p = 0.044$	0, 1, 2 $p < 0.0005$

55.6 % ($p = 0.002$), as confirmed both by the 3-level classification: 25th percentile 1 versus 1, median 1 versus 2 and 75th percentile 2 versus 3 ($p = 0.003$), and by the WORMS edema classification: 25th percentile 0 versus 0, median 0 versus 1 and 75th percentile 1 versus 2, respectively ($p = 0.012$). Also, when comparing the edema associated to lesions of different femoral areas, its presence was not uniformly distributed: the central part of the condyle showed the highest presence of edema, whereas less edema was observed at the trochlea level ($p < 0.0005$ for all three evaluations used to document edema in this study).

Other than defect location, also etiology influenced the presence of edema: OCD lesions had more edema at all follow-ups ($p = 0.002$) and also a different trend ($p = 0.038$), with an increasing level of edema over time. In particular, Fig. 3 shows a generally higher level of edema, a longer time required to observe the postoperative phase of edema decrease, and afterwards a trend of edema that worsened with higher values at medium/long-term follow-up with respect to lesions limited to the cartilage layer, as confirmed both by the 3-level analysis of edema extent and hyperintensity ($p = 0.004$) and by the WORMS edema classification ($p = 0.005$) (Fig. 3).

Further analysis was performed to determine the parameters that influenced the presence of edema: age, sex, BMI, lesion size, previous and combined surgery did not influence the edema level in this survey. However, when considering compartments with both cartilage lesion and partial meniscectomy (pooling together cases with previous or combined meniscectomy with respect to the cartilage implant), edema was found more frequently ($p = 0.01$), and both the WORMS and the 3-level classifications

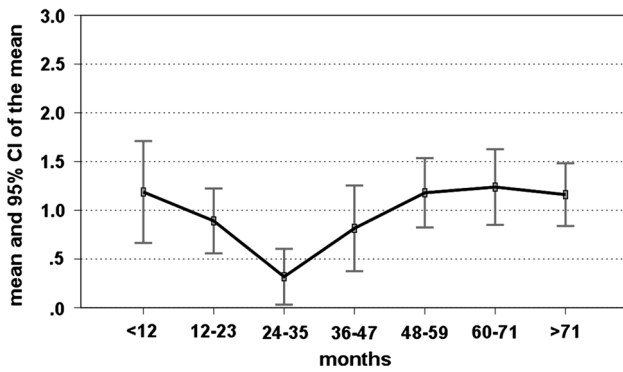


Fig. 2 Edema was commonly present before 24 months of follow-up, then its presence diminished at 2 and 3 years, and afterwards the level of edema increased again and remained steadily present at medium/long-term follow-up

confirmed the higher presence of edema in these more compromised joint compartments ($p = 0.04$ and $p = 0.006$, respectively).

No correlation was found between edema and clinical outcome at all follow-up times. A further subanalysis of patients' subgroups showed that MRIs with large or hyperintense edema were correlated with lower IKDC subjective scores in the group of patients affected by multiple lesions ($p = 0.009$; $\eta^2 = 0.272$).

Discussion

The most important finding of the present study was that edema was not constantly present throughout the postoperative period, but presented a particular and well-defined trend after MACT.

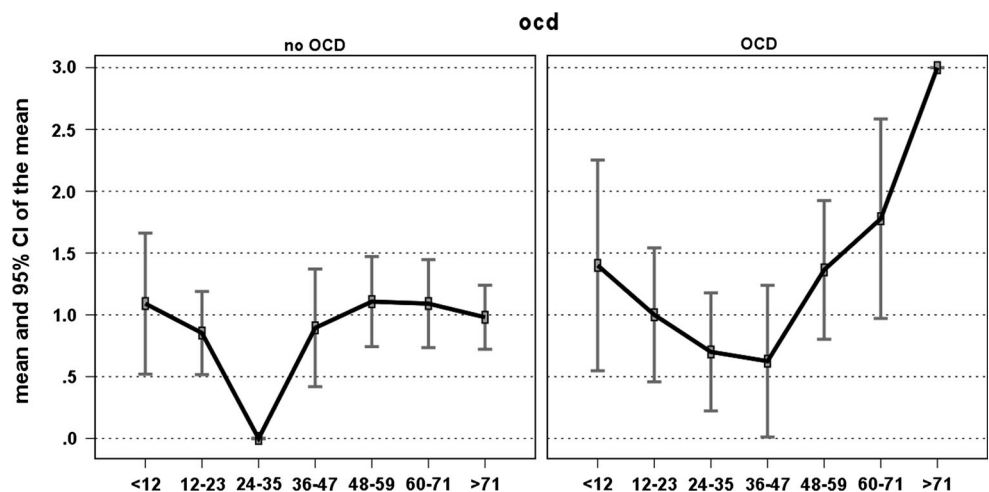
Up to now, most attention has been placed on the chondral layer, whereas subchondral bone changes after cartilage regenerative procedures have been considered

only as a secondary aspect and documented in a few studies. Takahashi et al. [34] showed that subchondral bone edema can be present even before treatment but can even be caused by the treatment itself. Forty-one patients treated with ACI for femoral condyle lesions and evaluated both pre- and postoperatively showed that at 1 year 47 % of the implants presented edema beneath the grafts, 27 % of which appeared as a consequence of treatment, even if they were not able to correlate these findings with the clinical outcome, as confirmed also by Tins et al. [35] in a similar group of patients. Henderson et al. [16] evaluated 81 lesions at 1 year of follow-up at both tibio-femoral and patello-femoral levels, treated with ACI, and found the presence of edema in more than half of the MRIs. Dholander et al. [5] analyzed the preliminary results of a new scaffold-based chondrocyte allogenic implantation technique for cartilage repair of chondral and osteochondral knee lesions, and the analysis of the 1-year postoperative MRIs in 12 patients showed a 41.7 % presence of edema.

The documented presence of edema in the short-term postoperative phase can be interpreted as a normal evolution of the repair process, reflecting the effect of abnormal or excessive mechanical forces on the immature implant and therefore also at the subchondral bone level. Some studies support this hypothesis, showing that the maturation of the graft is accompanied by a reduction or resolution of the edema signal.

Trattnig et al. [36] treated 23 patients affected by knee cartilage lesions with a hyaluronic acid-based MACT: the imaging evaluation showed that the subchondral bone edema-like signal present at the beginning of the postoperative phase persisted at two years only in 13 % of the patients. Ventura et al. [38] used a collagen-based MACT for the treatment of knee surface lesions: the evaluation of 17 patients who presented both 2 and 5 years imaging MRIs showed a reduction of bone marrow edema with a

Fig. 3 Etiology influenced the presence of edema: OCD lesions had more edema at all follow-ups with an increasing level of edema over time. In particular, this figure shows a generally higher level of edema, a longer time required to observe the postoperative phase of edema decrease, and afterwards a trend of edema that worsened with higher values at medium/long-term follow-up with respect to lesions limited to the cartilage layer



12 % presence at the mid-term follow-up. Marlovits et al. [22] treated 24 lesions in 21 patients affected by knee lesions of the articular surface with a collagen MACT and followed 19 of them prospectively with both clinical and imaging evaluation for up to 5 years of follow-up. MRI analysis showed that subchondral bone edema had a peak at 3 months postoperatively, when it was detected in 71 % of cases. Afterwards, the prevalence of edema-like signal gradually declined reaching 47.4 % rate at 5 years.

These findings showed, however, that if on one hand, the initial edema may be due to the maturation processes and decreases over time, on the other hand, some subchondral bone changes may persist in a high percentage of patients. Also, other authors reported a persistent edema-like signal. Henderson et al. [15] reported that after ACI treatment for knee lesions, the percentage of edema-like signal at 2 years was stable with respect to the 1-year evaluation, with a prevalence of 50 %. Whereas the short-term persistence of edema-like signal might be attributed to graft immaturity and inability to cushion the underlining bone, this hypothesis of an initial maturation phase cannot explain the findings of other authors at longer follow-up, when the implants are no longer supposed to be immature. Kon et al. [19] evaluated 40 chondral lesions of the femoral condyles or trochlea treated with hyaluronic acid-based MACT. At 5–7 years of follow-up, the prevalence of MRIs presenting subchondral bone edema was 50 %. Ebert et al. [6] confirmed the persistence of altered signal at 5 years in 28 % of the 46 grafts treated with collagen-based MACT. Moreover, some patients were shown to present subchondral bone changes at mid-term follow-up more frequently: at 6 years, Filardo et al. recorded a prevalence of 65 % of altered bone signal in 26 knees treated with hyaluronic acid-based MACT for degenerative lesions [11]. Finally, Vasiliadis et al. [37] also documented the persistence of subchondral bone changes at the long-term evaluation at 13 years in 36 knees treated with ACI: 59 % showed edema-like signal.

Besides the persistence over time of altered signal at the subchondral bone level, an increase in edema-like signal has been also documented in a small case series: Genovese et al. [13] treated 15 chondral lesions in 13 patients with MACT and showed an increased presence of edema at 30 and 60 months (20 and 47 %, respectively) moreover, they observed that all patients with bone marrow edema at 30 months maintained it over time, thus suggesting that once edema is present at medium-term it does not later disappear, whereas other patients developed an altered signal later.

The studies available report some interesting findings on subchondral bone edema, but they mainly evaluate a small number of cases evaluated at specific follow-ups, thus making it difficult to understand the evolution of this aspect

over time and even more challenging to make hypotheses on the significance of the edema-like signal in the MRIs after a cartilage regenerative treatment.

This study evaluates a high number of MRIs collected in a large cohort of patients treated by the same surgical team with the same surgical technique, and shows the presence of subchondral bone changes from 6 to 108 months. The results show that an edema-like signal is not constantly found throughout the postoperative period, with respect to the smaller series previously reported in the literature on limited follow-up intervals, and we observed that it presents a specific trend: edema was present in the first postoperative phase, was markedly reduced or disappeared at 2 and 3 years, and then increased again and remained steadily present at medium/long-term follow-up. A reduction of edema in the initial phase supports the hypothesis of a maturation phase. In fact, bone marrow edema pattern on MRI does not necessarily imply an increase in marrow water content, but rather that regional water has been made more mobile, which is probably reflective of the remodeling process after graft placement [14]. Once the graft is mature, the MRI signal reduces accordingly. However, it is likely that the hyaline-like cartilage documented for MACT procedures [37] cannot sufficiently protect the subchondral bone from mechanical forces, which over time result in an abnormal bone stimulation that causes edema formation. The presence of more edema at the central condyle level with respect to the trochlea and the patella confirms the importance of the applied load. Similarly, joint compartments with meniscus damage, and therefore abnormal mechanical stresses, presented significantly more edema.

A peculiar pattern has been documented for OCD, which presented more edema at all follow-ups and a different trend, with an increasing level of edema over time. This might be explained by the bone implant, required to restore the articular level before MACT, which is probably not an optimal solution in terms of osteochondral regeneration.

Nonetheless, no correlation was found between edema and clinical outcome, regardless of lesion location or etiology. The heterogeneous patient population, the lack of test–retest reliability evaluation and the retrospective design of this study (with only part of the treated patients performing the MRI evaluations, probably representing a subgroup of patients not perfectly representing the general population) are important limitations and may explain this lack of correlation, which was found only in the most compromised cases of patients affected by multiple lesions. On the other hand, it is also possible that the high MRI sensitivity might allow early changes to be detected, which might represent a tissue reaction that is abnormal but not severe enough to affect the clinical outcome at medium-term follow-up. Moreover, since not all these MRIs were

performed with all specific cartilage sequences required by MOCART score [24], we could not correlate the cartilage analysis to our findings, which anyway still gave interesting cues on the role and evolution of subchondral bone edema.

The interpretation of an edema-like signal in MRIs after MACT still remains to be clarified by prospective studies with multiple consecutive evaluations to understand its evolution and significance over time. Moreover, specific scores focusing on this aspect are required to better describe and analyze presence and changes of edema. Development in MRI research with new available techniques, such as ultra-short TE imaging, is likely going to offer soon instruments to examine more in depth this important aspect [31]. A better understanding of this abnormal signal might help on one hand to study and compare cartilage treatments and on the other to manage properly patients undergoing MACT or other cartilage procedures. In this light, despite its limitations this study on a high number of MRIs contributes to both aspects, suggesting that the cartilage regeneration obtained with this procedure is not optimal, thus affecting the subchondral bone over time, but also that the observed alterations do not significantly affect the clinical outcome up to a mid-term follow-up.

Conclusion

Edema after MACT is present during the first phases of cartilage maturation for up to 2 years of follow-up, then tends to disappear. However, after a few years, an increasing level occurs again underneath the hyaline-like tissue formed. Less edema was found in the patella, whereas a higher and increasing edema was found in the OCD, where subchondral bone is primarily involved. Interestingly, the presence of edema was not correlated with a lower clinical outcome. Whether this represents a prognostic factor at longer follow-up remains to be determined.

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