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### Permalink

<https://escholarship.org/uc/item/6wk0z7vz>

### Journal

The American Journal of Sports Medicine, 40(12)

### ISSN

0363-5465

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### Publication Date

2012-12-01

### DOI

10.1177/0363546512461594

Peer reviewed



Published in final edited form as:

*Am J Sports Med.* 2012 December ; 40(12): 2700–2708. doi:10.1177/0363546512461594.

## Do Cartilage Repair Procedures Prevent Degenerative Meniscus Changes? Longitudinal T<sub>1ρ</sub> and Morphological Evaluation at 3.0T

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### Abstract

**Background**—Cartilage repair (CR) procedures are widely accepted for treatment of isolated cartilage defects at the knee joint. However, it is not well known whether these procedures prevent degenerative joint disease.

**Hypothesis/Purpose**—CR procedures prevent accelerated qualitative and quantitative progression of meniscus degeneration in individuals with focal cartilage defects.

**Study Design**—Cohort Study; Level of evidence 2b

**Methods**—A total of 94 subjects were studied. CR procedures were performed on 34 patients (n=16 osteochondral transplantation, n=18 microfracture); 34 controls were matched. An additional 13 patients received CR and anterior cruciate ligament (ACL) reconstruction (CR&ACL) and 13 patients received only ACL reconstruction. 3.0T MRI with T<sub>1ρ</sub> mapping and sagittal fat-saturated intermediate-weighted fast spin echo (FSE) sequences was performed to analyze menisci quantitatively and qualitatively (Whole-Organ Magnetic Resonance Imaging Score, WOMBS). CR and CR&ACL patients were examined 4 months (n=34; n=13), 1 (n=21; n=8) and 2 (n=9; n=5) years post CR. Control subjects were scanned at baseline and after 1 and 2 years, ACL patients after 1 and 2 years.

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### CONFLICT OF INTEREST

No conflict of interest for any authors.

**Results**—At baseline, global meniscus  $T_{1\rho}$  values were higher in individuals with CR ( $14.2\pm 0.6$ ms;  $P=0.004$ ) and in individuals with CR&ACL ( $17.1\pm 0.9$ ms;  $P<0.001$ ) when compared to controls ( $12.8\pm 0.6$ ms). After two years, there was a statistical difference between  $T_{1\rho}$  at the overlying meniscus above cartilage defects ( $16.4\pm 1.0$ ms) and  $T_{1\rho}$  of the subgroup of control knees without cartilage defects ( $12.1\pm 0.8$ ms;  $P<0.001$ ) and a statistical trend to the CR group ( $13.3\pm 1.0$ ms;  $P=0.088$ ). At baseline, 35% of subjects with CR showed morphological meniscus tears at the overlying meniscus; 10% of CR subjects showed an increase of WORMS meniscus score within the first year, none progressed in the second year. Control subjects with (without) cartilage defects showed meniscus tears in 30% (5%) at baseline; 38% (19%) increased within the first, and 15% (10%) within the second year.

**Conclusions**—This study identified more severe meniscus degeneration after CR surgery compared to controls. However, progression of  $T_{1\rho}$  values was not observed from 1 to 2 years after surgery. These results suggest, that CR may prevent degenerative meniscus changes.

### Keywords

Cartilage repair; meniscus;  $T_{1\rho}$ ; WORMS; 3.0T MRI

## INTRODUCTION

Articular cartilage defects have limited potential to regenerate and are associated with an early onset of osteoarthritis (OA) 8. Over the past decade, cartilage repair (CR) has been increasingly used to treat focal cartilage defects of the knee 35. The most common technique is microfracture (Mfx), which is used for smaller lesions not affecting the subchondral bone. For larger regions, besides autologous chondrocyte implantation (ACI), osteochondral transplantation (OCT) is the procedure of choice 41.

Noninvasive magnetic resonance imaging (MRI) is the most important diagnostic tool for monitoring the post-operative course of these patients 43, 48. 1.5T MRI of the knee is the current standard in clinical practice 20, 29, but evidence suggests that 3.0T MRI may be more advantageous. 3.0T MRI yields a stronger magnetic field strength, allowing for thinner sections, higher plane spatial resolution, and increased signal-to-noise ratio. In addition, 3.0T MRI is more sensitive to diagnosing meniscus pathology, a known contributor to early onset of OA 1, 40. Quantitative  $T_{1\rho}$  relaxation time measurements reflect early degenerative changes in the biochemical composition of cartilage such as proteoglycan loss and increase in water content 1, 24, 25, 40. It has recently also been applied to quantitatively and noninvasively detect meniscus degeneration 5, 39. Although the exact factors that contribute to a higher meniscus  $T_{1\rho}$  in subjects with osteoarthritis and a lower meniscus  $T_{1\rho}$  in healthy subjects are not clear yet, one study found a positive correlation between cartilage degeneration and increased  $T_{1\rho}$  values in the meniscus 38.

Multiple studies have examined results after CR on a descriptive level. A challenge remains to demonstrate that CR can prevent joint degeneration, beyond others, by clinical validating imaging outcomes 48. Few studies have used 3.0T MRI for follow-up, but little is known about meniscus degeneration as an outcome parameter after CR. However, evaluation of the

impact of meniscus degeneration is crucial to ensure quality control and the development of future treatment guidelines in patients post CR.

While  $T_{1\rho}$  relaxation time measurements of cartilage repair tissue have been described previously<sup>14</sup>, the purpose of this study was to evaluate meniscus degeneration, as measured by morphological assessment and quantitative  $T_{1\rho}$  meniscus measurements, at multiple longitudinal time points in patients who received CR surgery compared to controls. We hypothesized that patients who underwent CR would have higher meniscus  $T_{1\rho}$  values, indicating more degenerative meniscus changes at baseline, but no further meniscus degeneration during follow-up.

## MATERIALS AND METHODS

### Subjects

A total of 94 subjects was analyzed in this study. A total of 34 subjects was treated with cartilage repair procedures (CR group) for isolated posttraumatic or degenerative full thickness cartilage defects at the knee (graded III and IV according to the International Cartilage Repair Society (ICRS) classification cite). A control cohort (n=34) was recruited, that was matched for Kellgren/Lawrence (KL) score<sup>18</sup> and gender (control group). Thirteen additional subjects received both cartilage repair as well as anterior cruciate ligament (ACL) reconstruction (CR&ACL group). A final additional 13 subjects received only ACL reconstruction (ACL group). The study was approved by the local Institutional Review Board and conducted in accordance with the Committee for Human Research at our institution. All subjects gave written informed consent prior to participation in the study. Data were prospective and nonrandomized.

### Surgery

The indication for CR surgery was made in consultation with the patient and confirmed during arthroscopy of the affected knee joint. Exclusion criteria for CR procedures were uncontained large defects of several joint regions, significant degenerative changes of the affected joint (KL >2), non-correctable ligamentous instability, varus or valgus malalignment of >5°, muscle loss, presence of inflammatory or metabolic disorders, obesity (Body mass index (BMI) >30 kg/m<sup>2</sup>) and age >55 years. Additional exclusion criteria for this study were MR contraindications and retropatellar CR. None of the patients received CR at two sites nor did any receive revision surgery during the observation period. The indication for ACL reconstruction was subacute, complete ACL rupture by clinically diagnosed anterior-posterior laxity (Lachman grades 2 to 3) with confirmation by MRI.

All procedures were performed by one surgeon. Mfx was used for a smaller lesions (<3cm<sup>2</sup>). For mostly larger defects, patients received OCT. The cartilage defect area was debrided until its edges were completely surrounded by healthy cartilage. Mfx surgery was performed during arthroscopy as described previously<sup>2,47</sup>. The cartilage defects treated by OCT (OATS, Arthrex, Naples, FL, USA) were assessed arthroscopically and subsequently treated by an arthrotomy of the knee<sup>2</sup>. Osteochondral grafts were harvested from the non-weight bearing non-articulating intercondylar notch region of the trochlea of the same knee during

surgery. A mean number of  $2.0 \pm 1.0$  transplanted cylinders was used. ACL reconstruction was performed with single bundle hamstring or patellar tendon graft <sup>22</sup>. During the postoperative period, weight bearing was limited to 15 kg for 6 weeks (3 weeks if only ACL reconstruction), and was gradually increased to reach full weight bearing after 8 – 12 weeks. Subjects underwent physiotherapy to strengthen the joint during follow-up.

## Imaging

Standard standing anteroposterior plain radiographs of the knee were obtained in all subjects at baseline. All subjects were scanned with a 3.0T General Electric (GE) Signa HDx MR scanner (General Electric Healthcare, Milwaukee, WI, USA) using an 8-channel phased array transmit/receive knee coil (Invivo, Orlando, FL, USA). For semi-quantitative Whole-Organ Magnetic Resonance Imaging Score (WORMS) assessment <sup>37</sup>, an intermediate-weighted (IW) fat-saturated FSE sequence (TR/TE = 4300/51 ms, FOV = 14 cm, matrix = 512 × 256, slice thickness = 2.5 mm, gap = 0.5 mm) was used. Sagittal 3D T<sub>1</sub>ρ sequences were used to quantify the meniscus relaxation time <sup>6,27,39</sup>. A spin-lock technique was followed by a SPGR acquisition using transient signals evolving towards steady state <sup>26</sup> with the following parameters: TR/TE = 9.3/3.7 ms, time of recovery = 1500 ms, FOV = 14 cm, matrix = 256 × 192, slice thickness = 3 mm, BW = 31.25 kHz, views per segment = 48, time of spin-lock (TSL) = 0/10/40 ms, frequency of spin-lock (FSL) = 500 Hz. Parallel imaging with array spatial sensitivity technique (ASSET) was performed with an acceleration factor of 2.

At the clinically important time points 4 months ( $4.0 \pm 1.1$  months; 34/34 CR subjects, n=16 OCT, n=18 Mfx; 13/13 CR&ACL subjects, n=2 OCT, n=11 Mfx) and 1 year after CR ( $11.8 \pm 2.8$  months; 21/34 CR subjects, n=10 OCT, n=11 Mfx; 8/13 CR&ACL subjects, n=2 OCT, n=6 Mfx), images were obtained. In 9/34 CR subjects (n=5 OCT, n=4 Mfx) and 5/13 CR&ACL subjects (n=2 OCT, n=3 Mfx) MR studies were obtained 2 years ( $24.6 \pm 1.2$  months) after surgery. Control subjects without ACL reconstruction (n=34) were scanned at baseline, and after 1 and 2 years. Patients with only ACL reconstruction (n=13) were scanned 1 and 2 years after surgery (see Appendix).

## Image analysis

Images were evaluated by two musculoskeletal radiologists separately (P.M.J., 4 years of experience; L.N., 6 years of experience); if scores were not identical consensus reading by both radiologists and another independent radiologist (T.M.L., 22 years of experience) was performed. Images were reviewed on picture archiving communication system (PACS) workstations (Agfa, Ridgefield Park, NJ). Regarding plain knee radiographs, subjects presenting with a KL score of more than 2 were excluded from CR surgery and from this study. A UCSF modified WORMS system was used to assess morphological abnormalities as presented in Table 1 <sup>38</sup>. The medial and lateral menisci were separated into the following compartments: anterior horn, meniscal body, and posterior horn. For prevalence analysis, “no meniscus defect”, “simple tear” and “complex tear” were differentiated. For progression analysis, any increase of entire meniscus WORMS score was considered as “progression”. Controls were divided into subjects with or without morphological cartilage defect. Bone marrow lesions (BMLs) of the compartment with cartilage repair were graded according to

the WORMS score and separated into BMLs  $\leq 2$ cm (WORMS score  $\leq 2$ ) and BMLs  $>2$ cm (WORMS score  $\geq 3$ ).

$T_{1\rho}$  sequences were transferred to a remote workstation (SPARC; Sun Microsystems, Mountain View, CA) and analyzed by using software developed at our institution with an interactive display language (IDL; Research Systems, Boulder, CO) environment. Segmentation of the anterior and posterior horn of the medial and lateral meniscus in every section was performed by one radiologist and supervised by a senior radiologist<sup>39</sup>. Sagittal imaging precluded the meniscus body segmentation.  $T_{1\rho}$  maps were reconstructed by fitting the  $T_{1\rho}$  images pixel by pixel using a Levenberg Marquardt mono-exponential fitting algorithm developed in-house<sup>53</sup>.

### Reproducibility measurements

Reproducibility was calculated in a randomly selected sample of 10 image data sets for each compartment. For WORMS measurements, each subregion of the images was graded twice by two radiologists on two separate occasions. Linear weighted Cohens Kappa's values were calculated. Inter-observer kappa was 0.89 for cartilage defects. Intra-observer kappa was 0.91 and 0.95. For bone marrow abnormalities, inter-observer kappa was 0.80, intra-observer kappa was 0.81 and 0.87. Inter-observer kappa was 0.80 for meniscus defects. Intra-observer kappa was 0.89 and 0.95. The mean coefficient of variation (CV, %), determined for  $T_{1\rho}$  measurements of the meniscus in our laboratory was 4.1%<sup>5,53</sup>.

### Statistical analysis

Mean  $T_{1\rho}$  values were calculated for both menisci and globally (mean of the value for medial and lateral meniscus) from the segmented regions of interest. Statistical processing was performed with JMP software Version 9 (SAS Institute, Cary, NC, USA). Statistics were obtained applying multivariate regression models, that adjusted in one model for KL score, gender and age, by adding these variables as covariates for each of the analyses. For  $T_{1\rho}$  values measurements, one-way analysis of variance (ANOVA) and two-way Students t-test were applied. For morphological analysis Mann-Whitney-U test was used. Results were considered as significantly different if  $P < 0.05$ . Mean values are presented  $\pm$  Standard Error of the Mean (SEM), if not stated otherwise.

## RESULTS

### Subject characteristics

Of a total of 94 subjects in this study, 34 subjects were treated with only CR (21 male, 13 female), 13 with CR and ACL reconstruction, and 13 only with ACL reconstruction, respectively. The CR and control group ( $n=34$ ) were gender and KL score matched (Table 2). Age was significantly different between the CR and control group ( $35 \pm 11$  (Standard deviation (SD)) years versus  $47 \pm 11$  (SD) years). CR was performed 20/34 times at the medial femoral condyle, 10/34 times at the lateral femoral condyle and 4/34 times at the trochlea (only Mfx). Screening controls for cartilage defects revealed that 13/34 control subjects presented cartilage defects (medial 7/34; lateral 6/34) at baseline.

### Baseline meniscus $T_{1\rho}$ analysis

At baseline, patients without surgery (control group) presented the lowest  $T_{1\rho}$  values (global  $T_{1\rho}$ :  $12.8 \pm 0.6$  ms; Table 3; Figure 1). Considering both menisci separately, the medial meniscus showed slightly higher values than the lateral meniscus in controls at baseline ( $13.1 \pm 0.6$  ms versus  $12.5 \pm 0.6$  ms,  $P=0.073$ ). The CR group showed significantly higher global  $T_{1\rho}$  value of  $14.2 \pm 0.5$  ms 4 months after surgery ( $P=0.004$  versus controls). The CR&ACL group showed the highest  $T_{1\rho}$  values 4 months after surgery ( $17.1 \pm 0.9$  ms;  $P<0.001$  versus controls).

Comparing  $T_{1\rho}$  values of the overlying meniscus above the cartilage repair regions with the overlying meniscus above untreated cartilage defect regions in the control subgroup with cartilage defects at baseline, no significant difference was detected at baseline ( $14.7 \pm 0.7$  ms versus  $14.8 \pm 0.9$  ms; Figure 2). However, differences with a statistical trend were found between the control subgroup with cartilage defects and the global meniscus  $T_{1\rho}$  of the control subgroup without cartilage defects ( $12.5 \pm 0.8$  ms;  $P=0.055$ ) and a significant difference was found between the CR group and the control subgroup without cartilage defects ( $P=0.001$ ). In contrast,  $T_{1\rho}$ , for each of the four separately segmented meniscus parts, the difference between the CR group and the control group was not significant at baseline, due to different CR locations.

### Meniscus $T_{1\rho}$ at follow-up

Global Meniscus  $T_{1\rho}$  in the CR group did not increase in the first ( $14.1 \pm 0.7$  ms) and second year ( $13.2 \pm 0.9$  ms) after surgery (Figure 1). Global  $T_{1\rho}$  values in the control group were stable during follow-up with  $13.0 \pm 0.6$  ms after 1 year and  $13.1 \pm 0.6$  ms after 2 years. The CR&ACL group did not show a further increase over time, but still showed a significant difference to the control group after 2 years ( $P=0.037$ ).

In the subgroup of controls without cartilage defects ( $n=21$ ), global  $T_{1\rho}$  values were stable over time and there was no significant difference to  $T_{1\rho}$  of the overlying meniscus above the cartilage repair region ( $n=9$ ) after two years ( $12.1 \pm 0.8$  ms versus  $13.3 \pm 1.0$  ms;  $P=0.112$ ; Figure 2). However, there was a statistical trend for a difference between  $T_{1\rho}$  of the overlying meniscus above the cartilage repair region and  $T_{1\rho}$  of the overlying meniscus above the untreated cartilage defect ( $16.4 \pm 1.0$  ms) after two years ( $P=0.088$ ) and a statistical difference between  $T_{1\rho}$  of the overlying meniscus above the untreated cartilage defect and global  $T_{1\rho}$  of the control subgroups without cartilage defects after two years ( $P<0.001$ ).

Absolute  $T_{1\rho}$  progression was also calculated between the different timepoints and showed the same trend, but no statistically significant difference ( $P>0.05$ ).

### Comparison of Mfx and OCT in the CR group

Subjects with Mfx ( $n=18$ ) showed higher  $T_{1\rho}$  at the overlying meniscus than OCT subjects ( $n=16$ ; Figure 3).  $T_{1\rho}$  decreased at the 1 and 2 year time-point in subjects with Mfx. In subjects with OCT  $T_{1\rho}$  only decreased in the second year of follow-up. However, these results did not show any significant difference.

### Correlation of bone marrow lesions with meniscus T<sub>1ρ</sub>

At baseline, CR subjects with BMLs  $\leq 2$  cm (correlating with a WOMBS score  $\leq 2$ ) showed slightly higher T<sub>1ρ</sub> values at the overlying meniscus ( $15.5 \pm 1.3$  ms; 14/34) than CR subjects with BMLs  $>2$ cm ( $14.1 \pm 1.0$  ms; 20/34;  $P=0.088$ ). However, after two years BMLs  $\leq 2$  cm ( $n=4$ ) were associated with lower meniscus T<sub>1ρ</sub> values than BMLs  $>2$ cm ( $n=5$ ;  $12.1 \pm 1.8$  ms versus  $14.5 \pm 2.1$  ms;  $P=0.095$ ). Presence of large BMLs 1 year after CR was not significantly associated with meniscus T<sub>1ρ</sub> after 2 years ( $P=0.203$ ).

### ACL reconstruction

Individuals with only ACL reconstruction (ACL group,  $n=13$ ) had a global meniscus T<sub>1ρ</sub> value of  $14.3 \pm 0.8$  ms 1 year after surgery ( $P=0.031$  versus control group). The medial meniscus showed lower T<sub>1ρ</sub> values than the lateral meniscus ( $13.8 \pm 0.8$  ms versus  $14.6 \pm 0.8$  ms,  $P=0.204$ ). In individuals with only ACL reconstruction, the medial and lateral meniscus both showed higher T<sub>1ρ</sub> values at the 2 year follow-up time-point compared to the 1 year time-point (medial:  $15.7 \pm 1.0$  ms;  $P=0.027$ ; lateral:  $15.7 \pm 0.9$ ;  $P>0.05$ ). The absolute difference of the T<sub>1ρ</sub> values between the two time-points was higher in the medial meniscus. At the 2 year time-point, global meniscus T<sub>1ρ</sub> in the ACL group ( $n=13$ ) was significantly higher than in the CR group ( $n=34$ ;  $P=0.009$ ).

### Morphological meniscus lesions at baseline

At baseline 15 % (5/34) and 20 % (7/34) of the CR group presented with simple and complex morphological meniscus tears, respectively, at the overlying meniscus (Figure 4 and Table 4). The control subgroup without cartilage defects (21/34) showed significantly less meniscus tears (0 % (0/21) simple tears; 5 % (1/21) complex tears;  $P=0.001$ ). The control subgroup with untreated cartilage defects (13/34; 15 % (2/13) simple tears; 15 % (2/13) complex tears) showed no significant difference of meniscus tears to the CR group ( $P=0.838$ ), but significantly more meniscus tears than the control subgroup without cartilage defects ( $P=0.006$ ). The CR&ACL group showed more meniscus tears than all other groups (medial meniscus 92 % (12/13); lateral meniscus 69 % (9/13)). Subjects in the ACL group (only ACL reconstruction) had medial meniscus tears in 35 % (5/13) and lateral meniscus tears in 31 % (4/13) at 1 year after surgery.

### Progression of morphological meniscus lesions

Any increase in the entire WOMBS score was considered as progression of morphological meniscus lesions (Table 5). During follow-up, 10 % of the CR group (2/10) showed an increase at the overlying meniscus in the first postoperative year; none progressed in the second postoperative year (0/9). Within the subgroup of control subjects without cartilage defects 19 % (4/21) increased in the first, 10 % (2/21) in the second year. Within the subgroup with untreated cartilage defects 38 % (5/13) increased in the first, 15 % (2/13) in the second year. The differences between the groups were however not significant ( $P>0.05$ ). In the CR&ACL group, 14 % and 29 % of subjects showed an increase at the medial and lateral meniscus, respectively, within the first postoperative year. Within the second year, 20 % showed an increase at the medial and also 20 % at the lateral meniscus. An increase of



morphological meniscus lesions was found in 19 % of subjects with ACL surgery between the first and second postoperative year.

## DISCUSSION

This longitudinal study analyzed meniscus degeneration as an outcome parameter after cartilage reconstruction procedures. Noninvasive MRI is used for monitoring the post-operative course of these patients to ensure quality control and development of future treatment guidelines. In this study, evaluation of the menisci was performed semi-quantitatively by morphological analysis (WORMS) and quantitatively by meniscus  $T_{1\rho}$  relaxation time measurements at several time-points during a two-year 3.0T MRI follow-up. Four months after surgery, patients with CR and ACL reconstruction had a significantly higher meniscus  $T_{1\rho}$  than controls, while  $T_{1\rho}$  was the highest in subjects who received both surgeries. During follow-up, individuals with only ACL reconstruction and controls with cartilage defects showed a further increase in  $T_{1\rho}$  values, while  $T_{1\rho}$  values in CR subjects did not (Figure 5). Being aware of the methodological limitations, these findings suggest that individuals with CR surgery may benefit from this procedure as it appears to prevent meniscus degeneration and potentially early onset of OA.

Apart from autologous chondrocyte implantation<sup>16,34</sup>, Mfx and OCT are two alternatively applied CR procedures<sup>2,41</sup>. However, the outcome after these procedures with respect to prevention of further degenerative changes and early onset of OA of the knee is unclear. Most studies have evaluated clinical outcomes, and few have considered utilizing MRI as follow-up<sup>4,48,50</sup>. However, meniscus evaluation remains an important parameter with respect to evaluation of progression of early and advanced OA<sup>45</sup>. In fact, previous studies have used meniscus evaluation to assess the risk of OA as an outcome after surgery, particularly ACL reconstruction<sup>19,51</sup>. By evaluating the menisci, we confirmed previously reported findings that there exists an increased presence of more simple and complex meniscus defects in individuals with ACL and CR surgery<sup>10,30</sup>. Cartilage defects usually coincide with degeneration of the overlying meniscus as confirmed in our study<sup>45</sup>; individuals with cartilage defects or individuals after repair of cartilage defects presented more meniscus lesions. Additionally, in our study we detected higher meniscus  $T_{1\rho}$  values in individuals with CR, ACL reconstruction and untreated cartilage defects. Meniscus degeneration can be quantified and continuously monitored by  $T_{1\rho}$  mapping.  $T_{1\rho}$  has recently been used for non-invasive biochemical analysis of not only cartilage, but also for detection and monitoring of meniscus degeneration<sup>9,39</sup>.  $T_{1\rho}$  measurements of cartilage repair areas have been performed and results have been reported previously<sup>14</sup>. Studies have shown that cartilage degeneration correlates with meniscus degeneration<sup>53</sup>. Even though  $T_2$  relaxation time remains the more widely used technique in biochemically assessing cartilage integrity, studies have shown that  $T_{1\rho}$  relaxation time better correlates with cartilage pathology<sup>36,42</sup>. For meniscus evaluation both  $T_2$  and  $T_{1\rho}$  measurements appear to be useful<sup>53</sup>. Rauscher et al found that high meniscus  $T_{1\rho}$  values were associated with osteoarthritic knees<sup>39</sup>. In our current study, we found that subjects who underwent CR procedures showed no further increase of  $T_{1\rho}$  values in the meniscus over time. Consequently, if meniscus  $T_{1\rho}$  correlates with cartilage degeneration, it suggests that CR

surgery may halt the progression of intrameniscal degeneration and further joint degeneration.

Follow-up time-points at 4 months, 1 year and 2 years post CR surgery were chosen due to their clinical relevance. Most failures occur during the early post-operative period<sup>31,49</sup>. The healing process, involving cell proliferation, matrix production and matrix remodeling is especially crucial within the first post-operative year<sup>17</sup>. This outcome is also reflected by meniscus  $T_{1\rho}$  values: These show a particular improvement not within the first, but within the second year. On the contrary, clinically, many patients only report a benefit of the intervention for two years<sup>32,44</sup>. Although OCT is a more invasive, open procedure including arthrotomy of the knee joint, clinically, a better outcome up to 3 years after surgery was reported for OCT compared to Mfx<sup>12</sup>. Interestingly, for OCT, we found a slight decrease of  $T_{1\rho}$  values already within the first year of follow-up, while Mfx only lead to a decrease of  $T_{1\rho}$  values within the second year of follow-up. This finding is concordant with clinical findings<sup>23</sup>. MRI has been found to correlate with clinical outcome after Mfx<sup>32</sup>.

Although there is no definite correlation between CR histology and clinical outcome, there is evidence that in patients with good histological results, there is less therapy failure<sup>21</sup>. In case of OCT, preexisting cartilage is transplanted. This technique showed an improvement in MR findings between 4 months and 1 year postoperatively<sup>28</sup>. However, some histological changes to fibrous cartilage and modification of the repair area have been observed. In the case of CR procedures, which involve bone marrow stimulation, meniscus status improved over time. This is consistent with the literature, since a technique of bone marrow stimulation has been described, which allows a better healing of meniscus after meniscus repair<sup>11</sup>.

BMLs did not correlate with meniscus  $T_{1\rho}$  4 months or 1 year after surgery. However persisting huge BMLs 2 years after surgery showed a trend for a statistical correlation with a higher meniscus  $T_{1\rho}$ . This supports the presumption, that a persisting BMLs is associated with outcome after CR<sup>52</sup>. However, BMLs after 1 year did not predict 2 year meniscus  $T_{1\rho}$ .

Meniscus integrity is crucial for proper knee joint functioning and shock-absorption. An influence of meniscus lesions on further OA progression has been observed<sup>33</sup>. Meniscus defects and OA have also been associated with higher and less homogenous cartilage  $T_2$  relaxation time values<sup>15</sup>. Our study showed that patients with CR demonstrated improved meniscus  $T_{1\rho}$  values over time, which suggests that CR plays a role in halting OA progression as a postoperative outcome. In this context, particularly the findings regarding control individuals with and without morphological cartilage defects seem important. Individuals with untreated morphological cartilage defects had higher  $T_{1\rho}$  values at follow-up time points than at baseline, while controls without defects and CR subjects did not.

Meniscus  $T_{1\rho}$  in subjects with only ACL reconstruction (ACL group) increased over time. It is known, that although reconstructed, kinematics may not be completely restored. Anterior-posterior tibial translation is usually well restored, while rotational stability was observed to be still pathological after ACL reconstruction<sup>13,46</sup>. Therefore ACL reconstructed subjects still suffer from increased degeneration of the knee as detected by  $T_{1\rho}$  in our study. In the

ACL group, 1 year after surgery in particular the lateral meniscus showed higher  $T_{1\rho}$  values, which is consistent with previous T 53  $1\rho$  findings, as well as clinical MR findings that result from the kissing bone bruise. However, during the second year post ACL reconstruction,  $T_{1\rho}$  showed a larger increase at the medial meniscus than at the lateral meniscus, indicating a faster degeneration of the medial meniscus after ACL reconstruction, probably due to rotational instability<sup>3</sup>. In control patients, the medial meniscus showed slightly higher  $T_{1\rho}$  values and more morphological meniscus lesions, which is consistent with prior studies<sup>45</sup>. We found that patients with combined ACL and CR procedures showed the highest  $T_{1\rho}$  values, with slightly lower values at follow-up. This supports previously reported findings of reasonable outcomes for combined surgery<sup>7</sup>.

There are several limitations of this present study. First, not all patients came back for 1 and 2 year follow-up. The low follow-up was due to a young patient clientele with high mobility, who are leaving the area and are not able to present for follow-up visits, as well as limited scan times at our institution and missing out or not reaching the right follow-up time-point. Second, age has been significantly different between both groups; since it is known as one of the most important risk factors for OA, results were adjusted for this parameter. Third, hamstring and patellar tendon grafts (bone-tendon-bone, BTB) were not differentiated, since the focus of this study was on CR and the number of subjects in each group would have been too small for further analysis. In the ACL group 9 Pat received BTB grafts and 4 patients hamstring grafts; in the CR&ACL group 4 patients received BTB grafts and 9 patients hamstring grafts. It may be interesting to evaluate the influence of different techniques in future studies. Fourth, results were not adjusted for lower limb alignment, which could potentially also slightly influence the results. However, subjects with an axis deviation  $>5^\circ$  were excluded. Last, only one clinical sequence was used, due to scan-time limitations.

In conclusion, in this study we used 3.0T MRI meniscus  $T_{1\rho}$  relaxation time measurements along with morphological meniscus assessment in a cross-sectional and two-year longitudinal analysis of individuals who underwent cartilage resurfacing procedures and compared the findings to normal controls. Meniscus  $T_{1\rho}$  values were higher in individuals with CR or cartilage defects at baseline compared to individuals without defects. While  $T_{1\rho}$  did not increase at the follow-up time-points in CR patients, increasing  $T_{1\rho}$  values were detected in patients with untreated cartilage defects or ACL reconstruction. Morphological meniscus defects showed a lower progression during the second year of follow-up after CR, compared to controls. These results suggest, that individuals with focal cartilage defects may benefit from cartilage repair procedures with regard to prevention of further meniscus matrix degeneration and consequently prevention of early OA at the knee.

## Acknowledgments

This research was supported by the National Institutes of Health grant R01 AR46905, K25 AR053633, P50 AR060752 and UO1 AR059507 and the OAI (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262).

## Appendix

N numbers of subjects included in this study. Four different groups were analyzed. The cartilage repair group (CR) as well as the group that had CR and reconstruction of the anterior cruciate ligament (CR&ACL) contained a subgroup that received osteochondral transplantation (OCT) and a subgroup that received microfracture (Mfx). The control group was subdivided into a subgroup with untreated morphological cartilage defects and a subgroup without cartilage defects. The group with only reconstruction of the anterior cruciate ligament (ACL) had no subgroups. Evaluated time-points were (1) baseline (controls) or 0.3 years post surgery (CR, CR&ACL group), respectively, (2) 1 year follow-up and (3) 2 year follow-up.

Group	Subgroup	N (baseline/ 0.3 years)	n (1 year)	n (2 year)
CR	All CR subjects	34	21	9
	Subgroup OCT	16	10	5
	Subgroup Mfx	18	11	4
Controls	All control subjects	34	34	34
	With cartilage defects	13	13	13
	Without cartilage defects	21	21	21
CR&ACL	All CR&ACL subjects	13	8	5
	CR&ACL subgroup OCT	2	2	2
	CR&ACL subgroup Mfx	11	6	3
ACL	All ACL subjects	0	13	13

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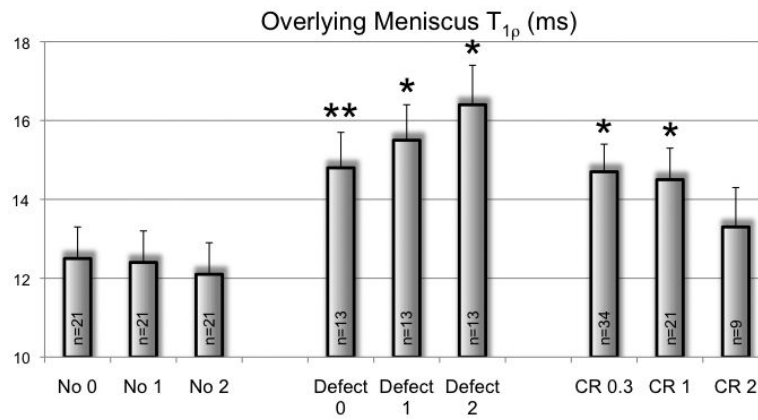
**What is known about the subject**

Although cartilage repair procedures are widely applied for localized cartilage defects, and multiple studies have examined results on a descriptive level, a challenge remains to demonstrate that CR can prevent joint degeneration, by clinical validating imaging outcomes. Noninvasive MRI is the most important diagnostic tool for monitoring the post-operative course of these patients. Since few studies have used MRI for follow-up, little is known about meniscus degeneration as an outcome parameter after CR. However, evaluation of the impact of meniscus degeneration is crucial to ensure quality control and the development of future treatment guidelines in patients post CR.

**What this study adds to existing knowledge**

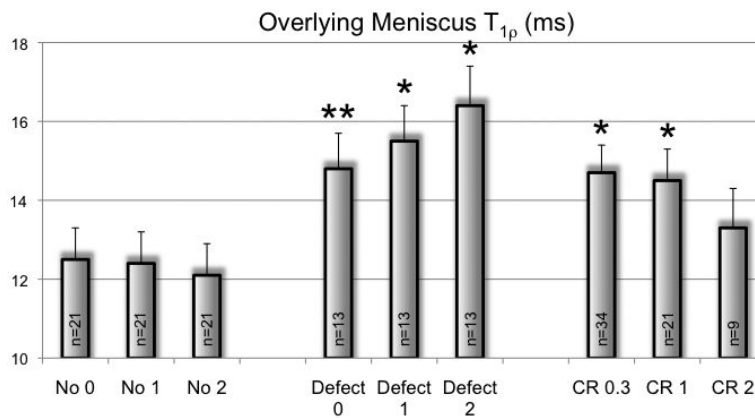
The longitudinal study represents a qualitative (WORMS) and quantitative ( $T_{1\rho}$ ) 3.0T MRI meniscus analysis of 94 individuals of whom 34 underwent cartilage repair procedures for isolated cartilage defects of the knee, 34 were Kellgren-Lawrence score and gender matched controls. Additionally, 13 subjects with ACL reconstruction and 13 subjects with both, ACL reconstruction and cartilage repair surgery were analyzed. We were able to identify higher meniscus  $T_{1\rho}$  values and more severe morphological meniscus lesions at four months after CR surgery compared to controls. However, in CR patients progression of  $T_{1\rho}$  values was not observed from 1 to 2 years after surgery, while in control subjects with cartilage defects  $T_{1\rho}$  values increased significantly. These results suggest, that individuals with focal cartilage defects may benefit from cartilage repair procedures with regard to prevention of further meniscus matrix degeneration and consequently prevention of early OA at the knee.





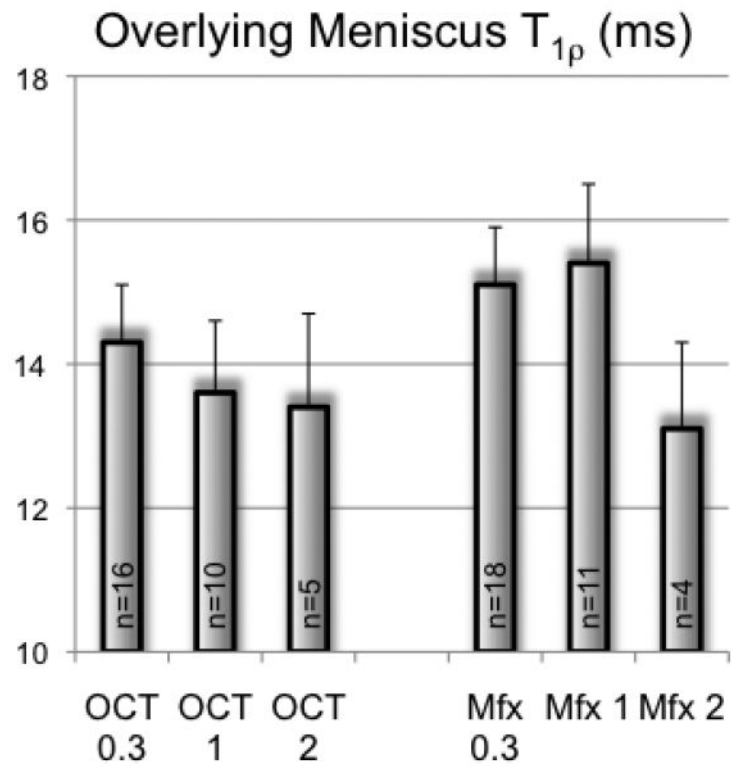
**Figure 1.**

Global meniscus  $T_{1\rho}$  values 0.3, 1 and 2 years after cartilage repair (CR) compared to subjects 0.3, 1 and 2 years after combined CR and anterior cruciate ligament reconstruction (CR&ACL) and to controls at baseline and after 1 and 2 years. \* $P < 0.05$ , compared to the control group at the according timepoint.



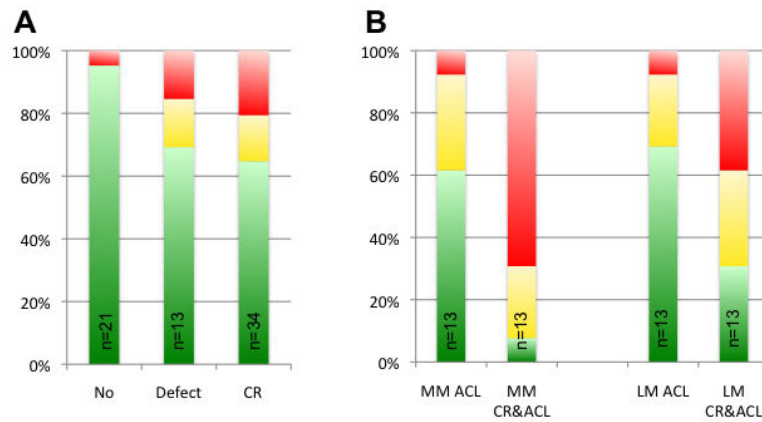
**Figure 2.**

Global meniscus  $T_{1\rho}$  values of the control subgroup without cartilage defect at baseline and after 1 and 2 years, compared to meniscus  $T_{1\rho}$  at the overlying meniscus above the cartilage defect in the control subgroup with cartilage defect (Defect) and compared to meniscus  $T_{1\rho}$  at the overlying meniscus above the cartilage repair region in the cartilage repair group (CR) 0.3, 1 and 2 years after surgery. \* $P < 0.05$ , compared to the control subgroup without cartilage defect (No) at the according timepoint. \*\*= $0.055$ .

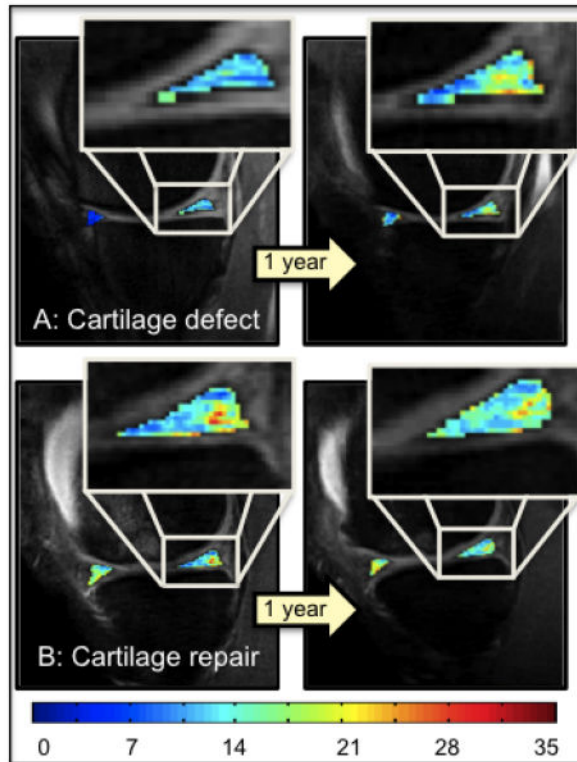


**Figure 3.**

T<sub>1ρ</sub> values of the overlying meniscus above the repair region in subjects with osteochondral transplantation (OCT) and subjects with microfracture procedure (Mfx) 0.3, 1 and 2 years after surgery. Differences between the groups were not significant (P>0.05).



**Figure 4.** Prevalence of morphological meniscus lesions. Green color indicates no meniscus lesion, yellow simple and red complex meniscus lesions. A: Lesions at the overlying meniscus above cartilage repair regions in the cartilage repair group (CR) and above cartilage defects in the control subgroup with cartilage defect (Defect) were compared to the control subgroup without cartilage defect (No). B: Lesions at the medial (MM) and lateral meniscus (LM) in the group with reconstruction of the anterior cruciate ligament (ACL; 1 year after surgery) and the group with combined CR and ACL surgery (CR&ACL), respectively.



**Figure 5.**

$T_{1\rho}$  color maps of the anterior and posterior horn of the medial meniscus of 1 year and 2 year follow-up time-points, overlaid with the first-echo images. Superior: Control subject with cartilage defect at the medial femoral condyle, who did not receive a cartilage repair (CR) procedure. Inferior: CR subject with osteochondral transplantation at the medial femoral condyle. Blue color indicates low, red color high meniscus  $T_{1\rho}$  values. Subjects with untreated cartilage lesion showed a higher increase in  $T_{1\rho}$  values over time compared to the subject with CR.

**Table 1**

Morphological meniscus (A) and cartilage (B) grading based on WORMS scoring with its according definitions.

<b>A: MENISCUS</b>	
<b>WORMS Grade of Meniscus parts Individually assessed for anterior horn, posterior horn, body of each meniscus</b>	<b>Definition</b>
0	normal meniscus
1	intra-substance abnormalities
2	non-displaced meniscus tear
3	displaced or complex tear
4	complete meniscus destruction/ maceration
<b>WORMS entire Meniscus grade Assessed for medial and lateral meniscus separatly</b>	<b>Grade of Meniscus parts</b>
0	Grade 0 in all meniscus parts
1	No grade > 1 in any part
2	Grade 2 in 1 part
3	Grade 2 in >1 part
4	Grade 3 in 1 or more parts
5	Grade 4 in 1 part
6	Grade 4 in >1 part
<b>Prevalence analysis</b>	<b>Definition</b>
No meniscus tear	entire meniscus grade <2 (no tear)
Simple meniscus tear	Entire meniscus grade =2 (non-displaced tear)
Complex meniscus tear	Entire meniscus grade >2 (complex tear)
<b>Progression analysis</b>	<b>Definition</b>
No progression	No increase of the entire meniscus grade over time
Progression	Increase of the entire meniscus grade over time
<b>B: CARTILAGE</b>	
<b>WORMS cartilage score</b>	<b>Definition</b>
0	No cartilage abnormality
1	Intrasubstance cartilage abnormalities
>1	Morphological cartilae lesion with volume loss
<b>Group</b>	<b>Definition</b>
No cartilage defect	WORMS 0 or 1
Cartilage defect	WORMS >1

**Table 2**

Epidemiological data of the analyzed groups. SD = Standard deviation; KL = Kellgren / Lawrence; ACL = Anterior cruciate ligament; CR = Cartilage Repair.

Parameter	Overall	Controls	CR	ACL	ACL&CR
N (total Number of patients)	94	34	34	13	13
Gender (male : female)	53 : 41	19 : 15	21 : 13	6 : 7	7 : 6
Age $\pm$ SD (years)	40 $\pm$ 12	47 $\pm$ 11	35 $\pm$ 11	37 $\pm$ 9	32 $\pm$ 11
Side (right : left)	56 : 38	20 : 14	20 : 14	5 : 8	11 : 2
KL score (0:1:2)	29 : 52 : 13	11 : 18 : 5	9 : 22 : 3	4 : 8 : 1	5 : 4 : 4

**Table 3**

Global meniscus  $T_{1\rho}$  relaxation time values  $\pm$  SEM (ms) after cartilage repair (CR), anterior cruciate ligament reconstruction and CR (CR&ACL) versus control without surgery (P overall (ANOVA),  $P=0.002$ ).

Surgery	n	Global $T_{1\rho}$	P (versus „No surgery“)
No surgery	34	12.8 $\pm$ 0.6	
CR	34	14.2 $\pm$ 0.5	0.004*
CR&ACL	13	17.1 $\pm$ 0.9	<0.001*



**Table 4**

Incidence of morphological meniscus defects in different groups. In the cartilage repair (CR) group, the overlying meniscus above the cartilage repair region was analyzed. In the control subcohort with cartilage defect, the overlying meniscus above the defect was analyzed. In the control subcohort without cartilage defect, the meniscus with the higher WORMS score was considered.

<b>Group</b>	<b>n</b>	<b>No defect</b>	<b>Simple tear</b>	<b>Complex tear</b>
Cartilage Repair	34	65 %	15 %	20 %
No surgery (all controls)	34	85 %	6 %	9 %
Control subgroup with cartilage defects	13/34	70 %	15 %	15 %
Control subgroup without cartilage defect	21/34	95 %	0 %	5 %

**Table 5**

Morphological meniscus changes measured by WORMS scoring between two time-points (in years). Percentage of subjects, which show an increase in the entire meniscus grading for the overlying meniscus above the cartilage repair region or the cartilage defect region, respectively. In controls without cartilage defect any increase of either meniscus was considered as progression.

<b>Group; time span (years)</b>	<b>N</b>	<b>Progression</b>
<b>CR; 0-1</b>	21	10 %
<b>CR; 1-2</b>	9	0 %
<b>Control; 0-1</b>	34	26 %
<b>Control; 1-2</b>	34	12 %
<b>Control subgroup with defect; 0-1</b>	13	38 %
<b>Control subgroup with defect; 1-2</b>	13	19 %
<b>Control subgroup without defect; 0-1</b>	21	15 %
<b>Control subgroup without defect; 1-2</b>	21	10 %