In vivo evaluation of repair tissue quality after two cartilage repair techniques using sodium MR imaging at 7T: initial experience

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Purpose

Articular cartilage of adults show no or minimal potential for self-healing of chondral defects that exceed a critical size and often progress to osteoarthritis [1]. Therefore, various surgical procedures such as bone marrow stimulation (BMS) techniques including microfracture (MFX) and Pridie drilling or matrix-associated autologous chondrocyte transplantation (MACT) are available for the treatment of articular cartilage lesions in the knee joint. One of the objectives of these procedures is the formation of repaired tissue with sufficient glycosaminoglycan (GAG) content, that provide optimal biomechanical function of the repaired tissue [2]. Based on the fact that GAG molecules are counterbalanced by sodium ions, sodium imaging was successfully used for the evaluation of GAG content in cartilage of healthy humans [3] and recently for the first time in patients after MACT [4]. Therefore the aim of this study was to apply sodium imaging at 7T and compare sodium SNR, suggestive of GAG content, between the native cartilage and the repair tissue after BMS and MACT repair procedures.
Methods and Materials

Patients: In total 18 patients, 9 subjects (4 women, 5 men; range: 21.4-57.7 years) who underwent one of the BMS treatments (2 Pridie drilling, 7 MFX patients) and 9 MACT patients (3 women, 6 men; range: 24.6-56.0 years) were included in this study. For better comparability, each BMS patient was matched with one MACT patient according to age (BMS 36.7±10.7 years [mean±standard deviation]; MACT 36.9±10.0 years), postoperative interval (BMS 33.5±25.3 months; MACT 33.2±25.7 months) and similar defect location - medial femoral condyle (5 BMS; 5 MACT subjects), lateral femoral condyle (4 BMS; 2 MACT patients) or trochlea region (2 MACT subject). The mean defect size in MACT group was 509 mm² (range 339-724 mm²) and in BMS group was 249 mm² (range 153-369 mm²). All cartilage defects were caused by trauma or osteochondritis dissecans. Ethics approval was provided by local ethics commission and written consent was obtained from patients before measurements.

Image Acquisition: All measurements were performed on a 7T whole body system (Magnetom, Siemens Healthcare, Erlangen, Germany). For morphological evaluation of cartilage, proton-density weighted 2D-TSE sequence with fat suppression (Figs.1,2-Left) and T1-weighted 3D-GRE sequence were acquired using 28-channel knee array coil (Quality Electrodynamics LLC, Cleveland, OH). A 3D-GRE sequence optimized for sodium imaging in cartilage (Figs.1,2-Middle) (TR/TE: 10.0/3.77 ms; FOV: 199×199 mm²; 48 slices; 64×128 matrix size; resolution: 3.11×1.55×3.0 mm³; measurement time: 30:45 min.) was employed using a sodium-only circularly polarized knee coil (Stark Contrast, Erlangen, Germany). Proton imaging took about 13 minutes and sodium imaging less than 34 minutes.

Image Evaluation: All region-of-interest (ROI) evaluations were performed with the JiveX (VISUS Technology Transfer, Bochum, Germany) software. The mean sodium signal was measured from a region covering the whole cartilage repaired tissue and a neighbouring region of normal native cartilage, at least 8 mm distant from repaired tissue (Fig.1). All signal-to-noise (SNR) values were calculated as mean signal intensity in the ROI divided by standard deviation of ROI from signal-free area. Magnetic resonance observation of cartilage repair tissue (MOCART) scoring system with maximum achievable score of 100 points [5] was employed to evaluate morphologic condition of the repaired tissue.

Statistical Analysis: The analysis of covariance, t-test and Pearson correlation coefficient (R) was used for the statistical evaluations in SPSS software (SPSS Inc., Chicago, IL). A p-value of less than 0.05 was considered statistically significant.
Images for this section:

**Fig. 0:** Sagittal proton-density weighted two-dimensional turbo spin echo MR image with fat suppression (left), sagittal sodium three-dimensional gradient echo image (middle), and color-coded sagittal sodium three-dimensional gradient echo image (right) in 35-years-old woman obtained 50.6 months after MACT surgery. Cartilage repair tissue is situated between the two arrows. Red contours in the middle image represent the ROI analysis of repair tissue (left contour) and reference cartilage (right contour). Please mark that repair tissue voxels situated closest to the repair tissue - native cartilage interface are not included into the ROI evaluations.

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**Fig. 0:** Sagittal proton-density weighted two-dimensional turbo spin echo MR image with fat suppression (left), sagittal sodium three-dimensional gradient echo image (middle), and color-coded sagittal sodium three-dimensional gradient echo image (right) in 43-years-old woman obtained 42.0 months after MFX procedure. Cartilage repair tissue is situated between the two arrows. Magenta contours in the middle image represent the ROI analysis of repair tissue (right contour) and reference cartilage (left contour). Please mark that repair tissue voxels situated closest to the repair tissue - native cartilage interface are not included into the ROI evaluations.

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Results

The mean sodium SNR values in the patients after BMS techniques were 20.6±4.8 in native cartilage and 12.0±2.5 in repaired tissue. The patients after MACT procedure revealed the mean sodium SNR of 21.8±3.0 in native cartilage and 17.0±3.2 in repaired tissue (Fig.1). Sodium SNR was significantly lower in BMS (p<0.001) and MACT (p=0.002) repair tissue than in reference cartilage. These differences were influenced by surgery type (p=0.027), but not by age (p=0.075) and follow-up interval (p=0.154). Although there was no significant difference in the sodium SNR of native cartilage between patients after MACT and BMS treatment (p=0.528), significantly higher sodium SNR was observed in repaired tissue after MACT in comparison to BMS techniques (p=0.002) using independent sample t-test (Fig.1).

The mean MOCART scores were 75.0±16.6 points in BMS and 73.9±16.7 points in MACT patients. An independent samples t-test didn’t show significant difference in the morphology of repaired tissue after MACT and BMS treatment (p=0.889). No linear association between MOCART score and sodium SNR from repaired tissue was observed (R=0.111; p=0.662; R²=0.01). There was no correlation between patient's age and sodium SNR from reference cartilage (R=-0.329; p=0.182; R²=0.11) (Fig.2). Although no linear association between postoperative follow-up interval and sodium SNR in BMS repair tissue was found (R=-0.037; p=0.924; R²<0.01), moderate negative correlation was achieved between follow-up interval and sodium SNR in MACT repair tissue (R=-0.549; p=0.126; R²=0.30).
Fig. 0: Graph of mean sodium SNR values from reference cartilage (middle) and from repair tissue produced by BMS (left) and MACT (right) techniques. Note significant decrease in mean sodium SNR of repair tissue after BMS as well as after MACT in comparison to corresponding values from reference cartilage. Although there was no significant difference in the sodium SNR of reference cartilage between patients after MACT and BMS treatment (p=0.528), significantly higher sodium SNR was observed in repair tissue after MACT procedure in comparison to BMS techniques. Error bars stand for standard deviations, * represent the significant difference with p=0.002, and ** are assigned to p.
Fig. 0: As plot demonstrates, no linear correlation between patient’s age and sodium SNR from reference cartilage was observed ($R=-0.329; p=0.182; R^2=0.11$). Line on plot represent linear regression of data points obtained from patients after BMS (blue dots) and MACT (red dots) procedures.

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Conclusion

MACT, as a representative of cell-based cartilage repair techniques, relies on three-dimensional biodegradable scaffolds that should produce hyaline-like repair tissue [6]. On the other hand, BMS techniques fill the defect mostly with fibrocartilaginous repair tissue, which lacks the structural, biomechanical and biochemical properties of native hyaline cartilage [7]. Native cartilage is characterized by the GAG content that comprises 3% to 10% of extracellular matrix and provides cartilage with functional and structural properties for optimal joint function [2]. Under ideal conditions, repair tissue produced by the techniques for treatment of chondral defects should, over time, develop and maintain GAG content similar to hyaline cartilage. Despite the mentioned advantages of MACT, its role as an alternative to BMS techniques is not yet thoroughly defined. Therefore the ability to track changes in native cartilage and repair tissue noninvasively is critical for understanding of the impact of therapeutic procedures.

Using sodium MR imaging at 7T in patients after different cartilage repair surgeries, we found significantly lower sodium SNR in repair tissue after BMS and MACT treatment in comparison to corresponding reference native cartilage. Moreover, MACT repair tissue demonstrated significantly higher sodium SNR when compared to repair tissue after BMS. Our recent study demonstrated a strong correlation of sodium imaging with dGEMRIC and suggested sodium imaging to be indicative of GAG content in native cartilage as well as in repair tissue [4]. With the assumption that fibrocartilage demonstrates lower GAG content in comparison to native hyaline cartilage [8], the results of our study correspond well with histological studies which reported fibrocartilage after MFX [9] and hyaline-like repair tissue after MACT [10]. In accordance with Tins et al. [11], no relationship between morphological MOCART score and biochemical sodium imaging was observed. No correlation between native cartilage and patient age may suggest that there is no GAG depletion in the healthy cartilage caused by the age. However, this statement must be validated in the larger cohort of healthy volunteers.

A limitation of our preliminary study is the lack of direct histologic evaluation of GAG content in repair tissue due to national ethical guidelines. For further limitations we can account different follow-up intervals and the low number of patients in the compared groups.

Our results indicate that sodium MR imaging is able to distinguish not only between native hyaline cartilage and repair tissue, but also between different quality of repair tissue after MACT and BMS techniques. Furthermore, our results suggest that the MACT treatment provides higher GAG content and therefore repair tissue of higher quality in comparison to the BMS techniques. Based on our preliminary findings, a study including more patients, longer longitudinal follow-up, and direct histologic evaluation of repair tissue would be beneficial and could evaluate the possible use of sodium MR imaging to predict an efficacy of repair procedure.
References


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