# DTI of articular cartilage can predict early cartilage damage as assessed by histopathology

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**Introduction:** Articular cartilage is early involved in the process of joint degradation in osteoarthritis (OA). Thus, the assessment of the integrity of the cartilage matrix plays a central role in the early diagnosis of OA. Recently, diffusion tensor imaging (DTI) of articular cartilage has been proposed as a biomarker for early degeneration of the cartilage matrix [1]. Several ex vivo experiments have demonstrated the relationship between the DTI parameters (mean diffusivity [ADC] and fractional anisotropy [FA]) with the constituents of the cartilage matrix [2-5]. However, the value of DTI for the early diagnosis of OA has not been assessed so far. The aim of this work was to investigate the value of DTI of articular cartilage as predictor for early cartilage damage as assessed by histopathology.

**Methods:** 41 cylindrical samples were drilled from 25 human patellae harvested within 24 hours after death (age (34±14) y). Samples were examined on a 17.6-T MRI scanner (Bruker Advance, Bruker Biospin GmbH, Rheinstetten, Germany) using a 5-mm birdcage coil. Samples underwent histology with safranin-O staining for histopathology assessment of OA with the OARSI score, which ranges from 0 (healthy) to 6 (cartilage erosion) [6]. The MRI protocol included a diffusion-weighted spin-echo sequence for DTI (TR/TE=938/15.0 ms, b-values 0, 550 s/mm², 6 directions, FOV=12.8×12.8 mm², slice thickness=800 µm, in plane resolution=50×100 µm², bandwidth=130.0 kHz, acquisition time=2:20 h, 10 averages). Cartilage was segmented and maps of ADC and FA were calculated. Average ADC and FA over the whole cross-sectional area of the cartilage ($ADC_{100\%}$, $FA_{100\%}$) and over the 50% superficial cartilage ($ADC_{50\%}$, $FA_{50\%}$) were calculated.

Table 1 MRI parameters and in OARSI scores [1]

| | OARSI 0 | OARSI 1 | OARSI 2 | OARSI 3–4 |
|---|---|---|---|---|
| Samples | 14 | 9 | 12 | 6 |
| **$ADC_{100\%}$**[†] | 1.05 (0.07) | 1.12 (0.09) | **1.17 (0.10)**[‡] | **1.23 (0.09)**[‡] |
| **$ADC_{50\%}$**[†] | 1.11 (0.06) | **1.18 (0.06)**[‡] | **1.22 (0.11)**[‡] | **1.39 (0.14)**[‡] |
| $FA_{100\%}$ | 0.25 (0.12) | 0.17 (0.05) | 0.16 (0.06) | 0.17 (0.04) |
| $FA_{50\%}$ | 0.10 (0.04) | 0.09 (0.03) | 0.08 (0.02) | 0.09 (0.04) |

[1]Mean (standard deviation); ADC ($\times 10^{-3}$ mm²/s)
[†]Significant trend;[‡]Significant difference to the OARSI=0 group

Samples were grouped according to their OARSI score to assess differences in MRI parameters according to the histopathology grade of OA. OA samples (OARSI≥1) were compared to the healthy samples (OARSI=0) for each MRI parameter (100% and 50%-average) using unpaired two-sided Wilcoxon test. The trend of ADC and FA (100% and 50%-average) with the OARSI score was assessed with the two-sided nonparametric Cuzick's test for trend. An overall P-value of 0.05 was chosen to indicate statistical significance.

The prognostic value of DTI parameters for OA was investigated with logistic regression. All samples were grouped in two groups, one with OARSI score 0 (healthy) and the other with OARSI score greater than zero (OA). A univariate logistic regression model was fitted to every MRI parameter (50% and 100%-average) and a bivariate model to all possible pair wise combination of MRI parameters. In each model the significance of the coefficients was tested with the Wald test and the goodness-of-fit with the $\chi^2$ test on the sum of squares of the deviance residuals. The diagnostic performance of each logistic regression model was evaluated with the receiver-operating characteristic (ROC)-curve analysis (sensitivity (Ss), specificity (Sp) and area under the curve (AUC)). The prediction error (i.e. the fraction of incorrectly classified samples) of a logistic model was assessed with 10-fold cross-validation. The data was split into 10 equally-sized groups. A model was fitted to 9/10 of the data and tested on the remainder 1/10. Process is repeated using each 1/10 group as test data.

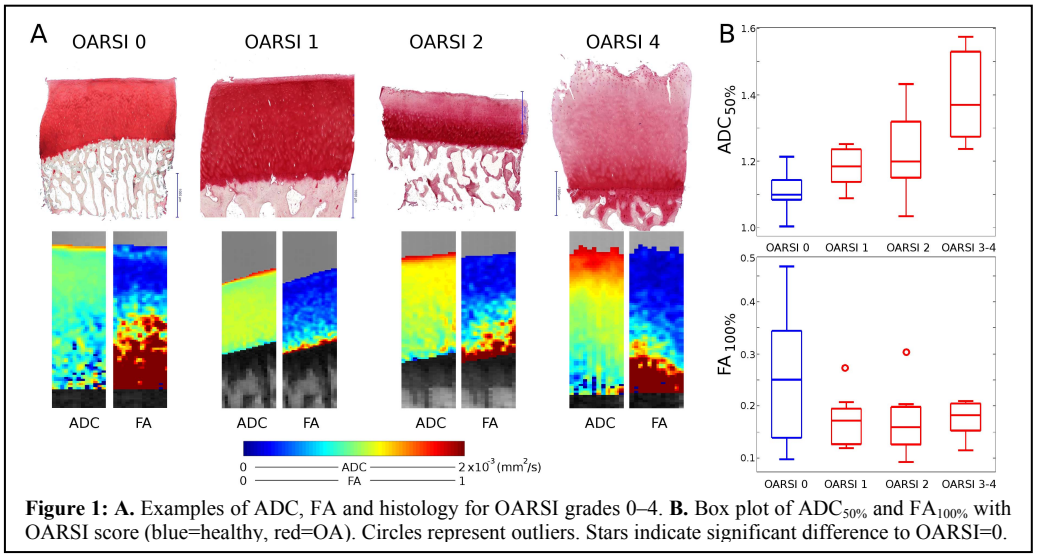


**Figure 1: A.** Examples of ADC, FA and histology for OARSI grades 0–4. **B.** Box plot of $ADC_{50\%}$ and $FA_{100\%}$ with OARSI score (blue=healthy, red=OA). Circles represent outliers. Stars indicate significant difference to OARSI=0.

**Results**: Examples of the maps for histology grades 1–4 are shown in Fig. 1A. Mean MRI parameters in each OARSI group are summarized in Table 1. The ADC 100% and 50%-average showed a significant trend of increased values with the OARSI score. The ADC 50% was significantly higher even for OARSI 1, which is the first histopathology evidence of cartilage degeneration (Fig. 1B). Univariate logistic regression analysis demonstrated that $ADC_{100\%}$, $FA_{100\%}$ and $ADC_{50\%}$ were significant ($P<0.05$) predictors for OA ($ADC_{100\%}$: $\beta_0$= 12.6, $\beta_1$= -1.3, odds-ratio (OR, 95% confidence interval)=0.26 [0.09–0.74]; FA100%: $\beta_0$= -2.9, $\beta_1$= 1.12, OR=3.1 [1.2–7.7]; $ADC_{50\%}$: $\beta_0$= 21.3, $\beta_1$= -1.89, OR=0.15 [0.04–0.50]). All univariate models provided a significant fit to the data ($\chi^2$ test, $P<0.05$). $ADC_{50\%}$ and $ADC_{100\%}$ had the highest diagnostic performance for early degenerative changes ($ADC_{100\%}$: Sp=72.7%, Ss=83.3%, AUC=80.3; $ADC_{50\%}$: Sp=72.7%, Ss=83.3%, AUC=84.3). Models based on $ADC_{50\%}$ and $ADC_{100\%}$ had a prediction error of 24%. Bivariate logistic regression models improved the classification performance. $ADC_{50\%}$–$FA_{100\%}$ led to the best bivariate model ($\beta_0$=18.5 ($P<0.05$), $\beta_1$= -1.8 ($P<0.05$), $\beta_2$= 0.83 ($P>0.05$), OR(ADC)=0.17 [0.04–0.68], OR(FA)=2.3 [0.8–6.5]), with a very good classification performance (Sp=77.8%, Ss=92.9%, AUC=88.6) and a prediction error of 22%. The $ADC_{50\%}$–$FA_{100\%}$ logistic regression model correctly classified 93% (13/14) of OARSI 0 samples, 66% (6/9) of OARSI 1 samples, 75% (9/12) of OARSI 2 samples and 100% of OARSI 3–4 samples.

**Conclusions:** DTI parameters are sensitive to the earliest histopathology changes in cartilage during OA. A logistic regression model based on DTI parameters is able to correctly classify more than 3 of 4 (78%) samples as healthy or OA in a collective of low OARSI score (predominantly 1 and 2).

**References:** [1] Filidoro L et al. Magn Reson Med 2005;53:993; [2] Meder et al. Osteoarthritis Cartilage 2006;14:875; [3] de Visser et al. Osteoarthritis Cartilage 2008;16:689; [4] Deng X et al. Magn Reson Imaging 2007;25:168; [5] Raya et al. Invest Radiol 2011;18:330; [6] Pritzker et al. Osteoarthritis Cartilage 2006;14:13.