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MUSCULOSKELETAL

Feasibility of in vivo diffusion tensor imaging of articular cartilage with coverage of all cartilage regions

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Abstract
Objectives To investigate the value of diffusion tensor imaging (DTI) of articular cartilage to differentiate healthy from osteoarthritis (OA) subjects in all cartilage regions.
Methods DTI was acquired sagittally at 7 T in ten healthy and five OA (Kellgren-Lawrence grade 2) subjects with a line scan diffusion tensor sequence (LSDTI). Three healthy volunteers and two OA subjects were examined twice to assess the test-retest reproducibility. Averaged mean diffusivity (MD) and fractional anisotropy (FA) were calculated in each cartilage region (femoral trochlea, lateral and medial femoral condyles, patella, and lateral and medial tibia).
Results The test-retest reproducibility was 2.9 % for MD and 5.6 % for FA. Averaged MD was significantly increased (+20 %, $p<0.05$) in the OA subjects in the lateral femoral condyle, lateral tibia and the femoral trochlea compartments. Averaged FA presented a trend of lower values in the OA subjects (-12 %), which was only significant for the lateral tibia.
Conclusions In vivo DTI of articular cartilage with coverage of all cartilage regions using an LSDTI sequence is feasible, shows excellent reproducibility for MD and FA, and holds potential for the diagnosis of OA.
Key points
- *DTI of articular cartilage is feasible at 7 T in all cartilage regions*
- *DTI of articular cartilage can potentially differentiate healthy and OA subjects*

Keywords Articular cartilage · Diffusion tensor imaging (DTI) · Osteoarthritis · Reproducibility · 7 T

Abbreviations

ANOVA	Analysis of variance
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
FT	Femoral trochlea
KL	Kellgren-Lawrence score
LFC	Lateral femoral condyle
LSDTI	Line scan diffusion tensor imaging pulse sequence
LT	Lateral tibia
MD	Mean diffusivity
MFC	Medial femoral condyle
MRI	Magnetic resonance imaging
MT	Medial tibia
OA	Osteoarthritis
P	Patella
PG	Proteoglycan
SNR	Signal-to-noise ratio
T1w GRE	T1-weighted gradient echo

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Introduction

Articular cartilage is involved early on in the pathological process of osteoarthritis (OA) and thus represents a key tissue for the early diagnosis of OA [1–4]. Magnetic resonance imaging (MRI) has demonstrated high potential to assess the biochemical composition of articular cartilage. Ideally, the assessment of the integrity of the cartilage matrix should provide information on both the proteoglycan (PG) content and the collagen architecture. Most MRI parameters for biochemical assessment of the articular cartilage focus on its PG content [5–8]. The T2 relaxation time [9] and magnetization transfer [10] are the biomarkers that are partially sensitive to collagen [11–13].

Recently, diffusion tensor imaging (DTI) has been introduced as a biomarker sensitive to PG content and collagen architecture [14]. In ex vivo experiments, DTI showed an accuracy of 95 % to detect early cartilage damage as seen in histology [15]. The first DTI clinical study including OA subjects with early signs of disease in the patellar cartilage demonstrated excellent accuracy (92 %) in differentiating healthy form OA subjects [16]. In this work we extend our previous study on the patellar cartilage to all cartilage regions using the same acquisition technique. Since the signal-to-noise ratio (SNR) performance of the coil decreases with the distance to the coil elements, the sensitivity of DTI to detect changes in OA needs to be assessed separately.

Our objectives were: (1) to establish the technical feasibility of in vivo DTI in all articular cartilage regions, and (2) to assess potential differences in DTI parameters across the cartilage regions in healthy and OA populations.

Materials and methods

Participants

MRI of the right knee was performed on ten healthy volunteers and on the symptomatic knees of five patients with tibiofemoral knee OA. Volunteer exclusion criteria were: any episode of continued knee pain in the past 3 years and any history of knee surgery or trauma. OA patients were selected from the NYU-HJD cohort followed by the division of Rheumatology [17, 18]. OA patients in the cohort had to fulfil the clinical criteria of the American College of Rheumatology for the diagnosis of knee OA. X-rays not older than 2 years (range, 8-19 months; average, 15.6±4.5 months) were available from each patient and used to assess the Kelgren-Lawrence (KL) grade. The study was approved by the Institutional Review Board and performed in compliance with HIPAA. All subjects provided written informed consent.

MRI protocol

MRI was performed on a 7-T whole-body MRI (Siemens Health Care, Erlangen, Germany) using a dedicated birdcage transmit, 28-channel receiver knee coil (QED, Cleveland, OH, USA).

MRI protocol included the LSDTI sequence and a T1-weighted gradient echo (T1w-GRE) sequence (Table 1). We acquired all diffusion-weighted images of each slice sequentially within less than 3.00 min before acquiring a second slice. With this acquisition strategy we prevented any image misalignment caused by motion during the total acquisition time (31 min) of the DTI measurements. All sequences were acquired in the sagittal plane perpendicular to the line tangent to the posterior aspects of the femoral condyles. The LSDTI images were acquired in exactly the same planes as the T1w-GRE images, so that for each low-resolution LSDTI image there was also a high-resolution GRE image.

Three healthy subjects and two OA subjects were examined two times with the knee repositioned to assess the reproducibility of the DTI parameters.

Image processing

From the LSDTI images the MD and FA were calculated using custom Matlab routines (Natick, MA, USA). The signal-to-noise ratio (SNR) was calculated by dividing the signal intensity by the standard deviation of noise, σ. Since images were sum-of-squares reconstructed, σ was calculated by fitting the background noise distribution to a non-central χ^2 distribution [19].

Table 1 Sequence parameters

	T_1-w GRE	LSDTI
TR (ms)	44	200
TE (ms)	6.12	42
Flip angle (°)	20	90/180
In-plane resolution (mm^2)	0.3×0.3	0.6×0.6
Slice thickness (mm)	1	3
Matrix size	512×437×104	256×128
iPat factor (GRAPPA)	3	–
Bandwidth (Hz/Pixel)	220	200
Number of slices	104	10
Acquisition time (min)	10.33	31.40
b values (s/mm^2)	–	1, 450
Diffusion time Δ (ms)	–	26
Diffusion gradient duration (ms)	–	18
Diffusion weightings	–	6
Diffusion encoding scheme	–	DSM6[a]
Dummy scans	–	3

[a] Downhill simplex method optimisation schema for six directions (Skare et al. [19])

Articular cartilage was segmented in the T1w-GRE images using in-house software PaCaSe [20]. Since T1w-GRE and LSDTI images had the exactly same image position, the segmentation performed in the T1w-GRE images were overlaid on the DTI parameter maps and rasterized to the resolution of the LSDTI images. Due to the better resolution and contrast of the T1w-GRE images, segmentation was more accurate (average precision in resegmentation=0.2 mm, data not shown) than in the LSDTI sequence (average precision= 0.5 mm, data not shown). Segmentation had to be corrected manually in two subjects on the posterior femoral condyles.

The segmented cartilage was automatically divided in two equal layers (deep and superficial, Fig. 1).The femoral cartilage was then subdivided in the trochlea and the lateral and medial condyles manually by identifying the maximum height of the intercondylar fossa. In total, we considered six cartilage regions for our analysis: femoral trochlea (FT), lateral femoral condyle (LFC), medial femoral condyle (MFC), medial tibia (MT), lateral tibia (LT) and the patella (P). Average and standard deviation of MD and FA were calculated for each cartilage region (global), as well as for each layer (deep and superficial).

Statistical analysis

Test-retest reproducibility was calculated as root mean square average of the intra-individual coefficients of variation across the five subjects for each cartilage region globally and in both layers. For comparison between two groups, we used *t*-test after confirmation of the normal distribution of the data with the non-parametric Kolmogorov-Smirnov test. A paired *t*-test was used to test for differences between the deep and superficial layers. An unpaired *t*-test was used for comparison of healthy and OA subjects. Comparisons of more than two groups (e.g. differences across cartilage regions) were performed with the one-way analysis of variance (ANOVA) test with Bonferroni correction. An overall p value of 0.05 was chosen to indicate significant differences.

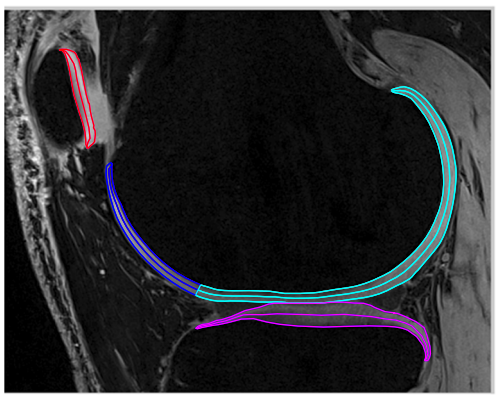

Fig. 1 Example of cartilage segmentation in the T_1w-GRE sequence of the healthy subject shown in Fig. 2. Colours indicate different cartilage regions: patellar (*red*), tibial (*magenta*), femoral condyle (*cyan*) and trochlear cartilage (*blue*). Each segmented cartilage is subdivided into two layers: the deep layer (close to the bone) and the superficial layer

Results

Participants

Healthy volunteers included three women and seven men with a mean age of 30.6±4.2 years. Five OA patients were included (mean age, 66.3±9.1 years, Fig. 2). All patients had KL 2.

DTI of healthy volunteers

DTI parameters in the healthy population are summarized in Figs. 3 and 4. Cartilage subdivision in layers was performed on all subjects. The average number of voxels per layer ranged from 313 for the deep layer of the MT to 890 for the deep layer of the FT (the smallest layer over all subjects included 116 voxels). Average MD over all regions in the deep layer, $(0.74\pm0.20)\times10^{-3}$ mm^2/s, was significantly lower than in the superficial layer, $(1.18\pm0.08)\times10^{-3}$ mm^2/s. FA was significantly higher in the deep layer (0.27±0.02) than in the superficial layer (0.24±0.02) in all cartilage regions.

There were no significant differences in MD or FA in global and superficial layers across the cartilage regions. However, significantly higher MD and lower FA values were found in the deep layer of femoral regions (FT, LFC, and MFC) compared with the tibia (LT and MT) and patella.

Test-retest reproducibility of MRI parameters

Test-retest reproducibility errors for MD and FA are summarised in Table 2. Average global test retest reproducibility over all cartilage regions was better for MD (2.9± 0.6 %) than for FA (5.6±1.8 %). Test-retest reproducibility was worse in the deep layer (MD, 6.0±2.9 %; FA, 7.4±2.8 %) than in the superficial layer (MD, 2.6±0.4 %; FA, 4.1± 1.3 %).

Signal-to-noise ratio

We observed significant differences in SNR among the cartilage regions (femur, patella and tibia), both globally and by layers (Table 3). The SNR of the superficial layer was always significantly higher than SNR of the deep layer. The patellar SNR was significantly higher than in the femur and the tibia. Diffusion-weighted images presented SNR values larger than 10 in all cartilage regions (range, 10.2-43). There were no significant differences in SNR between healthy and OA subjects.

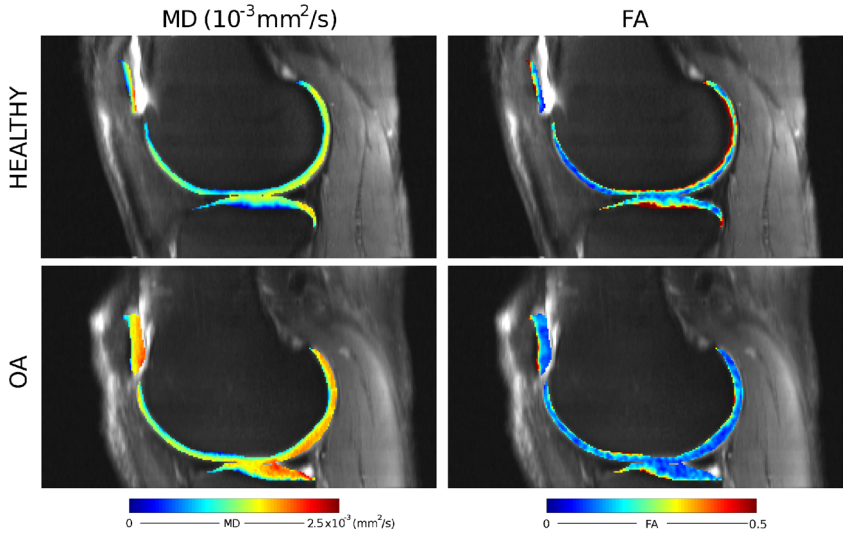

Fig. 2 Example of the MD and FA maps acquired on a healthy volunteer and an OA subject. The background image is the SNR map of the LSDTI image without diffusion weighting. MD showed higher values in the posterior condyle and in the posterior areas of the tibial cartilage compared with the healthy volunteer. The OA subject also presented lower FA in these areas

OA subjects

The global MD and FA averaged over all OA subjects were $(1.26\pm0.22)\times10^{-3}$ mm^2/s and 0.24±0.04. As in the healthy population, MRI parameters in OA subjects were significantly different between superficial and deep layers. We found no significant differences in either MD or FA across all cartilage regions in global and superficial layers. There were, however, significant differences in the deep layer (Figs. 3 and 4).

The average relative difference in MD over all cartilage regions in OA subjects compared with the healthy subjects was 20±19 % (Fig. 3). Differences were significant for the LT

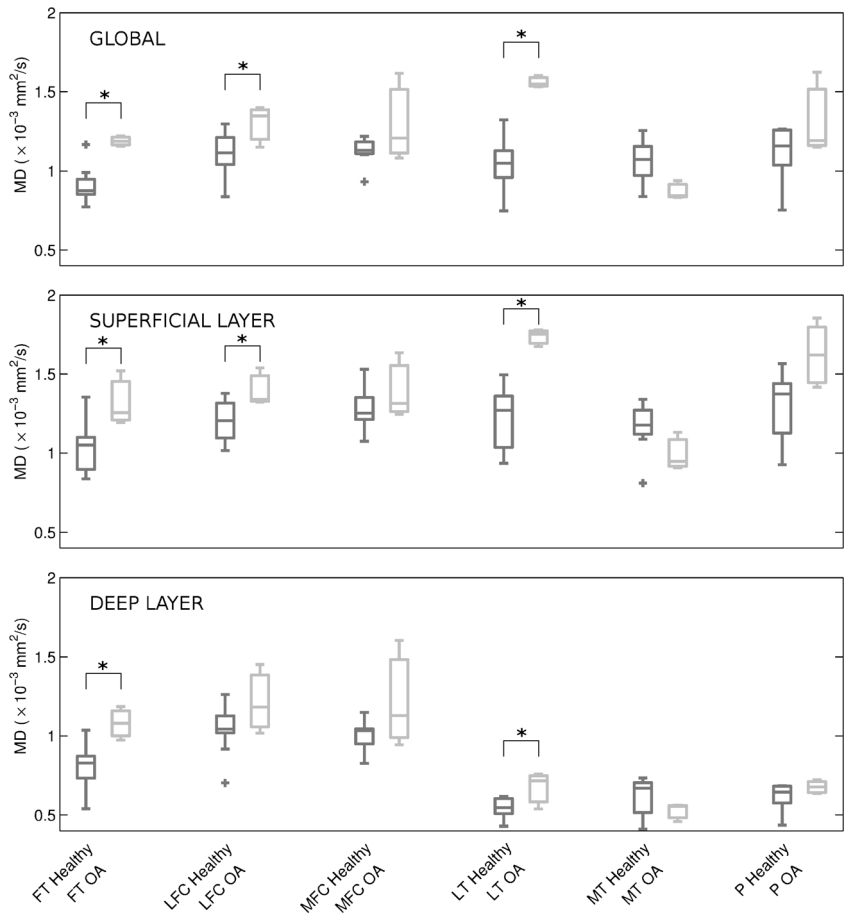

Fig. 3 *From top to bottom*, box plot diagrams of MD averaged over the full thickness of cartilage (global), and the superficial and deep cartilage layers. *Boxes* represent the interquartile range (i.e. the range from the 25th to the 75th percentile) with the *horizontal line* indicating the median. *Whiskers* include the full range of values. *Crosses* indicate extreme outliers (i.e. measurements which are more than three times the interquartile interval away from either edge of the box). *Dark grey* represents the values of the healthy population and *light grey* the values in the OA population. Significant ($p<0.05$) differences are indicated by an *asterisk*

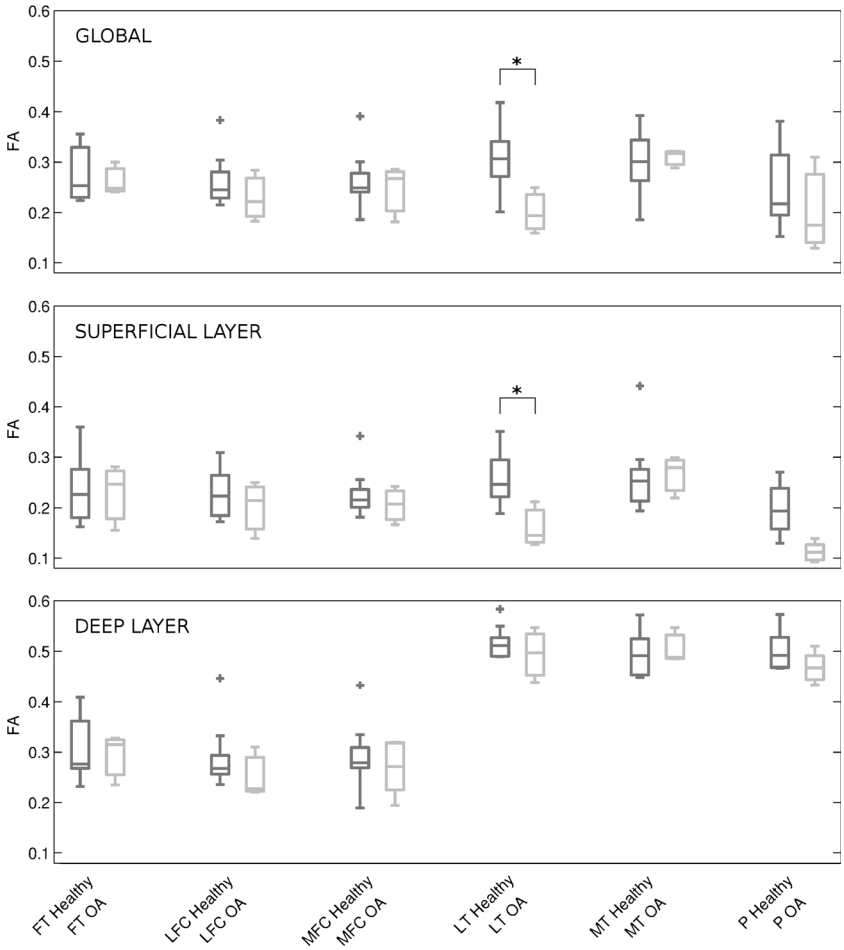

Fig. 4 *From top to bottom*, box plot diagrams of FA averaged over the full thickness cartilage (global), and the superficial and deep cartilage layers. *Boxes* represent the interquartile range (i.e. the range from the 25th to the 75th percentile) with the *horizontal line* indicating the median. *Whiskers* include the full range of values. *Crosses* indicate extreme outliers (i.e. measurements which are more than three times the interquartile interval away from either edge of the box). *Dark grey* represents the values of the healthy population and *light grey* the values in the OA population. Significant ($p<0.05$) differences are indicated by an *asterisk*

(+50 %), LFC (+31 %) and FT (+31 %), and non-significant in the MFC (+15 %), the MT (-17 %) and the P (+19 %). A layer-by-layer analysis showed a higher increase of MD in the superficial layer (+20±18 %) compared with the deep layer (+14±16 %).

Global FA showed lower values in OA subjects than in healthy volunteers in almost all cartilage regions (-5 %, FT; -13 %, LFC; -7 %, MFC; -35 %, LT; +3 %, MT; -17 %, P, mean -12 %), which was significant only for the LT (Fig. 4). Differences in FA between the healthy and OA populations were higher in the superficial layer (-19±12 %) than in the deep layer (-5±8 %). All OA subjects showed abnormal diffusion properties in at least one cartilage region, which indicates the potential of MD to discriminate between healthy volunteers and OA subjects.

Table 2 MD and FA test-retest reproducibility (in %)

Cartilage region	Layer	MD	FA
Femur	Global	2.21 (0.04)	4.31 (0.07)
	Deep	4.23 (0.15)	6.22 (0.12)
	Superficial	2.80 (0.03)	2.79 (0.03)
Tibia	Global	3.05 (0.04)	4.87 (0.04)
	Deep	9.41 (0.66)	5.37 (0.04)
	Superficial	2.1 (0.05)	5.34 (0.03)
Patella	Global	3.39 (0.11)	7.82 (1.50)
	Deep	4.40 (0.04)	10.66 (1.01)
	Superficial	2.79 (0.06)	4.12 (0.10)

Values represent the root mean square and standard deviation *in parentheses* of the coefficient of variation (in %)

Discussion

DTI of articular cartilage has been recently proposed as a biomarker with potential for the early diagnosis of OA. The ability of DTI to differentiate changes in PG and collagen has been demonstrated in several ex vivo experiments using enzymatic depletion of PG on cartilage samples [21–24]. There are only a few studies that have reported diffusion of articular cartilage in vivo, and most of them did not perform a full DTI measurement. All these studies measured D or MD values between 1.00 to 1.60 mm^2/s on knee articular cartilage of asymptomatic volunteers [25–27]. Azuma et al. [28] measured full DTI on the femoral trochlea of five healthy volunteers.

Table 3 SNR in all cartilage regions

Cartilage region	Layer	b=1 s/mm^2		b=450 s/mm^2	
		Mean	Range	Mean	Range
Femur	Global	30.3 (7.0)	23.1–50.5	17.9 (4.7)	13.3–32.8
	Deep	27.6 (6.8)	21.1–46.8	17.0 (4.6)	12.8–31.6
	Superficial	33.7 (7.4)	25.6–55.3	19.0 (4.8)	14.0–34.4
Tibia	Global	21.7 (4.0)	15.2–28.8	12.6 (1.3)	10.4–15.8
	Deep	18.9 (4.6)	14.4–29.4	11.8 (1.4)	10.9–15.9
	Superficial	23.6 (4.8)	14.0–32.1	13.3 (1.4)	10.2–15.8
Patella	Global	39.4 (12.8)	21.4–62.7	21.8 (6.3)	12.2–34.5
	Deep	31.7 (13.0)	14.4–29.4	19.7 (6.1)	10.8–29.2
	Superficial	46.6 (17.5)	14.0–32.1	24.6 (8.3)	10.8–43.0

Values represent the mean and standard deviation. SNR at b=450 s/mm^2 is the average over the six diffusion-weighted images

They measured MD values of 1.5 mm^2/s in the deep cartilage layer and 1.7 mm^2/s in the superficial layer. In the same study, Azuma et al. reported FA of 0.2 in the superficial layer and 0.3 in the deep layer.

Two studies using in vivo DWI or DTI of the articular cartilage have demonstrated potential for the diagnosis of early changes in the articular cartilage after knee injury or in OA [16, 29]. Xu et al. [29] showed increased diffusivity in all cartilage regions ($1.76–1.88\times10^{-3}$ mm^2/s) in 32 patients after knee injury compared with a cohort of 30 healthy subjects ($1.43–1.45\times10^{-3}$ mm^2/s in all cartilage plates).

More recently, our group demonstrated the potential of DTI for the diagnosis of OA in the patellar cartilage [16]. In our previous study on the patellar cartilage, DTI demonstrated an accuracy of 92 % in differentiating ten OA subjects with early signs of cartilage damage from 16 healthy controls. In the present study we extend previous results from the patellar cartilage to all cartilage regions. We used the same protocol as we did for the patellar cartilage, but for the slice thickness that we increased from 2 to 3 mm to compensate the SNR decay towards the centre of the coil.

Key in the first clinical study with OA patients was the LSDTI sequence used. LSDTI sequence has an intrinsic low SNR performance, which can be compensated by the use of high fields and dedicated coils. In our measurements, SNR was greater than 10 in all cartilage regions and layers in the diffusion-weighted images, which is required to avoid bias caused by low SNR in the estimation of the diffusion parameters [30]. Since the SNR in the deep layers was higher than 10 in all cartilage regions, it is unlikely that the differences between the cartilage regions are a consequence of the differences in SNR. In our measurements we found that the differences between the deep and superficial layers of the tibia and the patellar cartilages in MD were much higher compared with published data in the literature [14, 16, 22]. These larger differences could be partially a consequence of partial volume effects. In this work we used a 3-mm slice thickness, which would have larger partial volume in the slice direction. Also, due to the excitation profile of the LSDTI sequence, partial volume effects are more prone in the phase-encoding direction (head to foot) and therefore especially evident in the tibial cartilage. Segmentation was performed in the GRE with 1-mm slice thickness, which can also contribute to partial volume effects in areas like the patellar cartilage that have a high curvature in the slice direction (medial to lateral).

The average change in OA subjects in MD and FA was in the same range as previously reported in OA subjects in the patellar cartilage (MD increase, +20 to +30 %; FA decrease, -25 to -13 %) [16] and in patients with knee injury (increase in MD, +20 to +30 %) [29].

An increase in MD with little or no change can be interpreted as indicative of a change in chemical composition (mostly PG) but no change in collagen structure. Our results are compatible with the accepted view that degradation of PG, which can be detected by an increase in MD, precedes the disruption of the collagen network, which would lead to a decrease in FA. Thus, a method like DTI that can assess both PG and collagen has potential to improve the diagnosis and staging of the earlier phases of OA and help to understand the natural history of the disease in vivo.

Our study has some limitations. The OA population only included five subjects, which limits the statistical power of the study. However, even with this small number of subjects we were able to identify significant differences in DTI parameters between healthy and OA subjects. All OA subjects coincidentally had KL 2, so that we were testing DTI in a population with already well-established OA and the potential of DTI for earlier phases of disease still needs to be investigated.

In conclusion, in vivo DTI of articular cartilage with coverage of all cartilage regions using a LSDTI sequence is feasible, shows excellent reproducibility for MD and FA, and holds potential for the diagnosis of OA.

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Some study subjects or cohorts have been previously reported in the ISMRM conference 2012.

Methodology: prospective, case-control study, performed at one institution

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