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Assessing patterns of T2/T1rho change in grade 1 cartilage lesions of the distal femur using an angle/layer dependent approach

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Abstract

Purpose—To assess changes in the patterns of T2 and T1rho values with in grade 1 cartilage lesions of osteoarthritis (OA) patients compared to healthy controls.

Materials and Methods—Twenty healthy knees and 25 OA knees were examined on a 3T scanner. Areas of signal heterogeneity within the cartilage of the distal femur were identified using fat suppressed proton density-weighted imagines. T2 and T1rho values in each OA patient with grade 1 lesions were compared to average T2 and T1rho values of the corresponding areas in healthy subjects.

Results—A total of 28 areas including grade 1 lesion were identified. Compared to normal cartilage, the majority of grade 1 cartilage lesions demonstrated either no significant change or a statistically significant increase in both T2 values (18/28, 64%) and T1rho values (23/28, 82%). Compared to T2, T1rho demonstrated a greater proportion of statistically significantly higher values in OA patients than those from the normal controls. However, T2 and T1rho values in grade 1 lesions can be decreased, or demonstrate mixed patterns compared to those in healthy cartilage.

Conclusion—Our results suggest that early degenerative cartilage lesions can demonstrate various patterns of T2 and T1rho changes.

Keywords

T2 relaxation time; T1rho relaxation time; knee cartilage; osteoarthritis; Grade 1 lesion

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Introduction

Osteoarthritis (OA) is one of the most common disorders affecting society, causing tremendous socioeconomic cost and morbidity [1, 2]. It is important to detect early degenerative changes in cartilage and understand its natural progression in order to utilize new and advanced therapies [3–6]. Novel magnetic resonance imaging (MRI) sequences, such as T2 and T1rho mapping, delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), sodium MRI, and diffusion tensor imaging, have recently been developed as cartilage degeneration biomarkers, and enable us to evaluate collagen content and orientation, proteoglycan content, mobility of tissue water, and compressibility of regional cartilage [7–11]. T2 values of cartilage are known to be associated with the content, orientation, and anisotropy of collagen fibers [12]. T1rho values of cartilage have been reported to have a strong correlation with depletion of proteoglycan content, which is one of the earliest changes in cartilage degeneration [13]. Previous studies have demonstrated spatial variation in the T2 and T1rho values of healthy and damaged knee cartilage [14–19]. Recently, T2 and T1rho mapping profiles of the entire femoral cartilage in healthy patients have demonstrated regional variations of those values throughout the femoral condyles [20–22].

Many prior studies have found higher T2 and T1rho in OA patients compared to healthy controls, and have shown evidence that these higher T2 and T1rho are correlated with the severity of OA [14–18, 23–31]. However, in clinical practice, signal heterogeneity with areas of both high and low signal are often seen in regions of early cartilage degeneration. One of the most well-known grading systems of cartilage lesions using arthroscopy is Outerbridge's classification [32], which has been modified for use in MRI [7]. In this classification, grade 1 cartilage lesions (signal heterogeneity) also include areas of low cartilage signal intensity, therefore cartilage T2 and T1rho are expected to be decreased in these low signal areas. However, to our knowledge, there has been no study that has reported decreased T2 and T1rho in early OA cartilage or focused on T2 and T1rho changes in grade 1 cartilage lesions with signal heterogeneity. The purpose of this study was to assess patterns of T2 and T1rho changes of grade 1 lesions in OA patients compared to healthy controls, thereby elucidating the efficacy of T2 and T1rho measurements in detecting early cartilage degeneration.

Materials and Methods

Study population

A total of 43 subjects were enrolled in this study, with a control of 20 healthy volunteers and 23 OA patients recruited during the time period of January 2013 to March 2014. Inclusion criteria of the control group consisted of healthy volunteers aged 18 to 40 without any prior history of knee symptoms or knee surgery. A total of twenty knees from 20 healthy volunteers (mean age 28.9 years, range 19–38 years; 13 men and 7 women) were evaluated [20, 21]. Inclusion criteria of the OA group consisted of patients aged 18 or greater, who had been clinically diagnosed with OA. A board certified orthopaedic surgeon (RS) recruited OA patients, including 18 early OA patients (20 knees) (Kellgren-Lawrence (KL) osteoarthritis score of 1 or 2; mean age 49.7 years, range 19–79 years; 5 men and 13 women) and 5 advanced OA patients who were scheduled for knee arthroplasty (5 knees)

(KL score of 3 or 4; mean age 70 years, range 62–90 years; 2 men and 3 women). Two early OA patients underwent bilateral knee MRIs. The study protocol was approved by the institutional review board, and all subjects gave written informed consent before any study-related procedures were done.

Imaging protocol

All MR studies were performed on a 3T scanner (Achieva, Philips Healthcare, Netherlands) with an 8-channel knee coil. Three sagittal images were acquired including fat suppressed (FS) proton density-weighted imaging (PDWI), T2 mapping, and T1rho mapping sequences with true sagittal angulation parallel to the magnetic static field (B_0). The acquisition parameters were as follows. FS PDWI: 2D turbo spin-echo; repetition time (TR)/echo time (TE)=4311/30 ms, number of excitation (NEX)=2, and total acquisition time=3 minutes 35 seconds. T2 mapping: 2D turbo spin-echo; TR/TE=2700/13, 26, 39, 52, 65, 78, 91 ms, NEX=1 and total acquisition time=13 minutes 26 seconds. T1rho: 3D FSPROSET (PRinciple Of Selective Excitation Technique); TR/TE=6.4/3.4 ms, flip angle=10°, echo train length (ETL)=64, NEX=1, spin-lock frequency=575 Hz, time of spin-lock (TSL), 20, 40, 60, and 80 ms, and acquisition time=4 minutes 9 seconds \times 4. All images were obtained with field of view (FOV)=140 \times 140 mm, slice thickness/gap=3/0 mm, image matrix =512 \times 512, number of slices=31 and effective in-plane spatial resolution=0.27 \times 0.27 mm.

Cartilage segmentation of the entire femoral condyle

Cartilage segmentation of the entire femoral condyle was performed in the same manner described in our previous studies using an in-house developed and implemented software in MatLab (MathWorks, Natick, MA) [20–22]. Manual cartilage extraction of OA patients was performed on each T2 and T1rho image (on a slice-by-slice basis) by YK, a board-certified orthopaedic surgeon, with 14 years of experience. Images with TE=26 in T2 and TSL=20 in T1rho were chosen for segmentation due to the higher signal-to-noise ratio compared to other images. T2 and T1rho angle/layer-dependent profiles were created by angular segmentations in steps of 4 -degrees over the length of the segmented cartilage (with the angle 0 defined along B_0), and by partitioning cartilage into deep (0–50%) and superficial (51–100%) layers. The segmentation and entire processing took about 30 to 40 minutes for each knee.

Normalization of slice number

After segmentation, it was necessary to normalize the entire femoral cartilage of all subjects due to variations in knee size among subjects. We first reformatted coronal sections from sagittal images of knee MRI data using the software Medical Image Processing, Analysis and Visualization (MIPAV, Center for Information Technology, National Institutes of Health, Bethesda, MD). We converted sagittal knee cartilage images into 23 normalized slices for each subject. We choose to use 23 normalized slices because the mean transverse diameter of the femoral cartilage of the 20 healthy volunteer knees was 68.9 mm.

T2 and T1rho values

We calculated the average T2 and T1rho values at each normalized slice in both the deep and superficial layers with 4-degree stepwise analysis. Mapping for both T2 and T1rho was carried out based on monoexponential fitting on a pixel-by-pixel basis. Subsequently, in each OA patient, we created an excel spreadsheet and 2D-profiles of T2 and T1rho values in each layer. Spreadsheets and profiles of average T2 and T1rho values from 20 healthy subjects created in our previous study were used as a control and standard of reference [20–22].

Evaluation of degenerative cartilage lesions

Areas of signal heterogeneity within the cartilage over the femoral condyles and trochlea in healthy subjects and OA patients were identified using FS PDWI based on the consensus of 2 investigators (YK, HY). After an interval of four weeks, they re-evaluated the images and finalized selection of the grade 1 lesions. Slice number and angle with respect to B0 were recorded, and corresponding T2 and T1rho relaxation times were extracted from calculated entire femoral condylar profiles. In addition to simple grade 1 lesions, areas containing a combination of grade 1 and grade 2 lesions (grade 2 defined as partial thickness defect \leq 50%) or a combination of grade 1 through grade 3 lesions (grade 3 defined as partial thickness defect $>$ 50%) were also included for evaluation, and designated as grade 1–2, and grade 1–3 lesions, respectively.

Statistical analysis

Differences in T2 and T1rho values between early/advanced degenerative change and normal cartilage were assessed using the unpaired *t*-test and Mann-Whitney test for normal and non-normal distributed data, respectively. Each effect size in these comparisons between early/advanced degenerative change and normal cartilage was calculated by one of the authors (TH). Statistical analyses were performed using R version 3.2.3 for MAC(R Development Core Team, Vienna, Austria). *P* values less than 0.05 were considered to be statistically significant.

Results

Identification of grade 1 cartilage degeneration

A total of 28 degenerative cartilage lesions which had a component of grade 1 (grade 1, grade 1–2, and grade 1–3) were identified in the OA group (Table 1). Twenty-two of the 28 lesions were identified in 13 patients from the early OA group, and the remaining 6 lesions were identified in 3 patients from the advanced OA group. In the volunteer group, there were two grade 1 lesions without a clear history of pain; one was within the trochlea (34-year-old male) and the other was within the medial femoral condyle (33-year-old female). The frequency of grade 1 lesions in the volunteer group was much less than that of the patient cohort.

Comparison of T2 and T1rho values

Cartilage with signal heterogeneity in the OA patients, including both the early and advanced OA patients, demonstrated higher median T1rho values compared to the matched

regions in normal controls in each deep and superficial layer, although without statistical significance. Additionally, higher median T2 values in the deep layer of cartilage and lower median T2 values in the superficial layer of cartilage were observed, but also without statistical significance (Figure 1a). When OA patients were divided into early OA and advanced OA subgroups, in the early OA subgroup, there was a tendency for higher cartilage T2 and T1rho values in the deep layer, and lower cartilage T2 and T1rho values in the superficial layer compared to healthy subjects (Figures 1b and 1c). In the advanced OA group, a tendency for higher T1rho values in the deep and superficial layers was more apparent. T1rho values in the deep layer of advanced OA patients were significantly higher than those of healthy controls ($p=0.031$). T1rho values in the superficial layer of advanced OA patients also tended to be higher compared with healthy controls, but without a statistically significant difference ($p=0.094$) (Figure 1c). T2 values in the advanced OA group showed a similar pattern to those of the early OA group (Figure 1b).

Patterns of T2 and T1rho values in deep and superficial layers

Table 1 shows conceivable patterns of change in the T2 and T1rho values between normal and OA subjects with respect to the deep and superficial layers of cartilage. In OA patients, lesions without a significant decrease in cartilage T2 or T1rho value (i.e. no significant change or significantly higher relaxation times compared to the control) in either the deep layer, superficial layer, or both layers, accounted for 64% (18/28 lesions) for T2 and 82% (23/28 lesions) for T1rho. The percentage of lesions with a higher relaxation time in both the superficial and deep layers compared to normal controls were 7% (2/28 lesions) for T2, and 54% (15/28 lesions) for T1rho (Table 1, Figure 2). On the other hand, 36% (10/28 lesions) for T2 and 18% (5/28 lesions) for T1rho showed statistically significantly lower relaxation times in at least one or both layers in OA patients compared to the normal control (Table 1, Figure 3).

Patterns of change in T1rho relaxation times did not always correspond to changes in T2. For example, Figure 4 shows that T2 values in OA patients demonstrate no significant change in the deep and superficial layers compared to the control, while T1rho values show a statistically significant increase in value in both the deep and superficial layers.

Figure 5 demonstrates a mixture of statistically significantly higher and lower relaxation times of cartilage within a region containing a grade 1 lesion, depicted in a detailed view with 4-degree segments. In some OA patients, these dynamic distributions of both increased and decreased relaxation times in the same region resulted in average T2 and T1rho values which were not found to have a significant difference from the control.

There were 9 lesions with grade 1 cartilage degeneration which included the magic angle ($\pm 54^\circ$). In the region about the magic angle ($\pm 50-58^\circ$), there was a trend of lower T2 and T1rho values in both the deep and superficial layers in OA patients compared to the normal control, but without a statistically significant difference (Figure 6).

Discussion

Many studies have reported that higher cartilage T2 and T1rho values are seen in OA patients [14–18, 23–31]. In addition, they concluded that T1rho measurements were superior to T2 values in differentiating OA patients from healthy subjects. In this study, compared to normal cartilage, the majority of grade 1 cartilage lesions demonstrated either no significant change or a statistically significant increase in both T2 values (18/28, 64%) and T1rho values (23/28, 82%). Our data also suggests that T1rho values are more sensitive than T2 values for detecting the previously reported pattern of higher relaxation times in early cartilage degeneration lesions compared to normal controls in both the deep and superficial layers, because significantly elevated values in OA patients compared to healthy controls were more frequently identified with T1rho than T2.

On the other hand, there were a fair number of lesions which demonstrated significantly lower T2 and T1rho values within either the deep, or more frequently the superficial layer, or both layers, in OA patients compared to the normal controls. Additionally, occasionally a non-synchronized pattern of changes in T2 and T1rho values was observed (e.g., no significant difference in T2 values, but a significantly higher T1rho value) within the same lesion. These findings are likely compatible with the clinical observation of grade 1 cartilage lesions demonstrating signal heterogeneity on MRI, where not only high signal intensity areas are seen, but are actually intermixed with low signal areas [7]. The underlying etiology for these areas of decreased T2 or T1rho values is not well understood. However, compositional changes in the extracellular matrix, such as with breakdown of collagen and a decrease in proteoglycan and water content may result in lower signal intensities in grade 1 lesions [33]. Since lower T2 values are more frequently seen than lower T1rho values in grade 1 lesions, collagen may play an important role in this phenomenon. Further histological and biochemical studies of grade 1 lesions with signal heterogeneity are needed in order to elucidate the underlying pathophysiology.

The reasons for not finding a significant difference in T2 or T1rho values of grade 1 lesions compared with healthy cartilage are two fold. First, when both increased and decreased T2 or T1rho values coexist within the same lesion, they may counteract each other and result in average values which do not reach statistical significance. In fact, those grade 1 lesions showed higher standard deviations than the matched region in normal controls (data not shown). The application of texture mapping analysis within the areas of interest may be helpful in order to gain a more detailed assessment of variance within each segment in the future. Second, T2 and T1rho mapping may not be sensitive enough to detect very early cartilage degeneration in some cases due to very subtle signal changes. However, the number of lesions without a significant change in T1rho values in the deep and superficial layers was only one third of that with T2; this finding also suggests that T1rho is more sensitive than T2 for detecting early cartilage degeneration.

In this study, we created a 2D profile of T2 and T1rho values over the entire femoral cartilage of both the deep and superficial layers in each OA patient in order to compare these values with normal control maps which we had previously created from healthy volunteers [20–22]. There are regional variations in T2 and T1rho values even in healthy subjects [16, 20–22],

and degeneration can occur anywhere in the articular cartilage. Therefore, T2 and T1rho maps of the entire femoral cartilage of both normal control and OA patients are necessary to accurately identify regions of abnormal cartilage T2 and T1rho values in OA patients. The relative increase or decrease in T2 and T1rho values of grade 1 lesions in OA patients is dependent on the location within the knee because of normal regional variations in T2 and T1rho values. Two examples of the location-dependence for T2 and T1rho include the region about the magic angle and the region of the distal trochlea.

First, T2 and T1rho values in OA patients in the region of the magic angle demonstrate a distinct pattern. In healthy volunteers, the T2 values are elevated in the region around the magic angle, especially in the deep layer [20]. In the present study, the median values of T2 and T1rho within grade 1 lesions in OA patients which included the magic angle actually tended to show lower values in both the deep and superficial layers compared to those of the controls. The second example involves the most distal trochlea, where, in healthy volunteers, T2 and T1rho are decreased, especially in the deep layer [20, 21], where FS PDWI normally demonstrates low signal intensity[34]. Therefore, increased T2 and T1rho values around the most distal trochlea should be considered abnormal. These examples highlight the fact that in order to accurately detect early cartilage degeneration using T2 and T1rho values, it is necessary to compare values between potential lesions and the expected values of normal cartilage in that specific region.

This study had several limitations. First, the study sample of healthy volunteers was small. In the future, larger samples of healthy volunteers from a wider age distribution will be needed in order to improve the accuracy of the data. Second, acquisition time was long. Faster acquisition times will be needed in order to incorporate T2 and T1rho mapping into clinical protocols. Third, manual segmentation of the entire femoral cartilage performed in this study was time-consuming. Automated or semi-automated segmentation will be essential for shorter post-processing times. Fourth, there may be variance in normalizing the entire femoral cartilage because of differences in the size of femoral cartilage among subjects. Larger samples will be needed to reduce this variance for future studies. Finally, we did not assess histological and biochemical changes within the lesions, which would be the next area of study.

In conclusion, we assessed T2 and T1rho values of the entire femoral cartilage of early and advanced OA patients utilizing an angle and layer dependent approach. Significantly elevated values in OA patients compared to healthy controls were more frequently identified with T1rho than T2, suggesting T1rho is more sensitive than T2 for early cartilage degeneration. T2 and T1rho values with signal heterogeneity can also be either lower, a mixture of higher and lower within the same lesion, or demonstrate no significant change. These findings emphasize that various patterns of T2 and T1rho change can be seen in grade 1 cartilage lesions.

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Highlights

- T1rho is more sensitive than T2 for early cartilage degeneration.
- T2 and T1rho values in grade 1 lesions can be decreased, or demonstrate mixed patterns compared to those in healthy cartilage.
- Early degenerative cartilage lesions can demonstrate various patterns of T2 and T1rho changes.

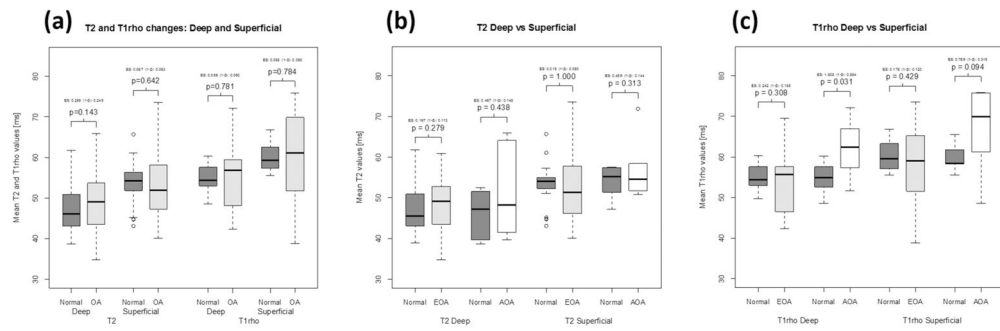


Figure 1. Comparison of T2 and T1rho values between degenerative lesions within (a) all OA patients and (b,c) early and advanced OA patients with corresponding areas in the normal control.

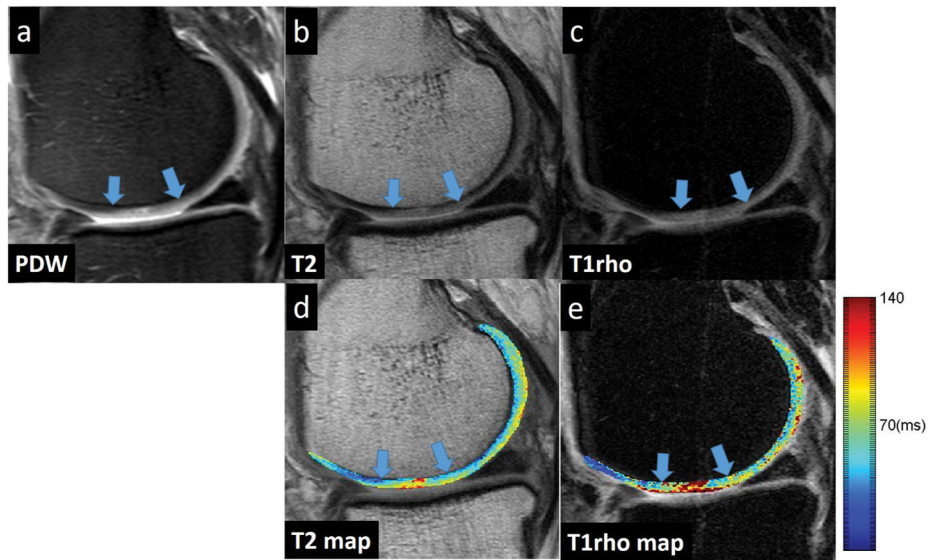


Figure 2.

A representative lesion in an OA patient where both T2 and T1rho values were significantly higher than those in the normal control within both the deep and superficial layers. Cartilage signal heterogeneity is observed over the central portion of the medial femoral condyle in the (a) routine FS PDWI, (b) T2 mapping image, and (c) T1rho mapping image. (d) T2 color map and (e) T1rho color map demonstrate increases in values in this area. The relaxation times within the area between the arrows was analyzed and statistically compared between this case and controls.

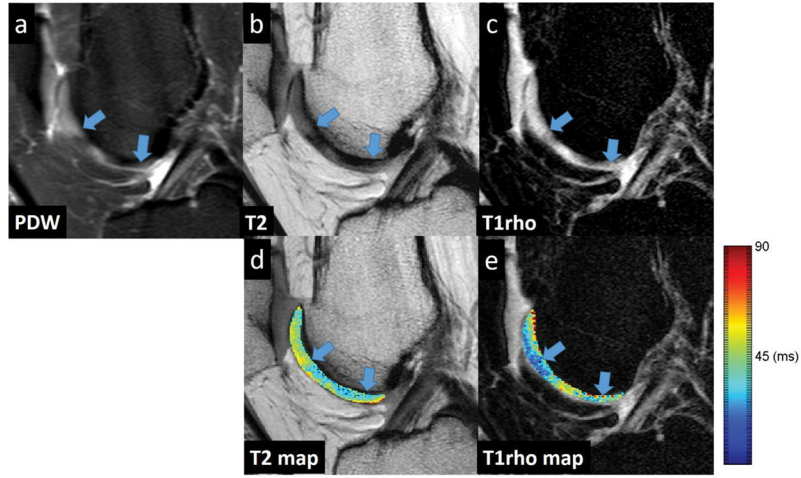


Figure 3. A representative lesion where both T2 and T1rho values in OA patients were significantly lower than in normal controls within both the deep and superficial layers. Cartilage signal heterogeneity is observed over the trochlea in the (a) routine FSPDWI, (b) T2 mapping image, and (c) T1rho mapping image. (d) T2 color map and (e) T1rho color map demonstrate a mix of increased and decreased in values in this area. Low signal in the most distal trochlea is normally seen, while low signal in the mid trochlea is abnormal. The relaxation times within the area between the arrows was analyzed and statistically compared between this case and controls.

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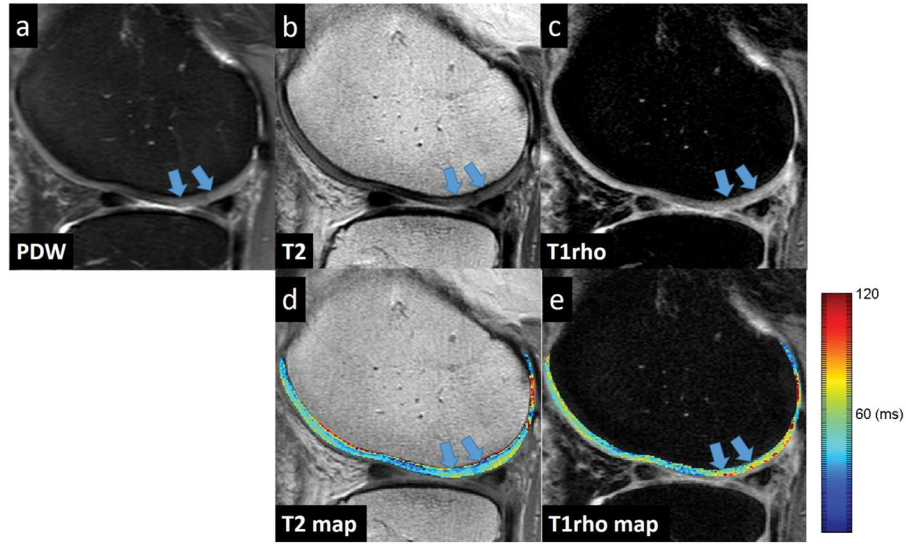


Figure 4. A representative lesion where T2 and T1rho value show a non-synchronized pattern. There was no significant difference in T2 values between this lesion and the normal control cartilage, whereas a significantly higher T1rho value was seen in the OA patient within both the deep and superficial layers. Subtle cartilage signal heterogeneity is observed over the posterior portion of the lateral femoral condyle in the (a) routine FS PDWI, (b) T2mapping image, and (c) T1rho mapping image. (d) T2 color map demonstrates no significant change compared the surrounding cartilage, while (e) T1rho color map demonstrates subtle increase in values in this area. The relaxation times within the area between the arrows was analyzed and statistically compared between this case and controls.

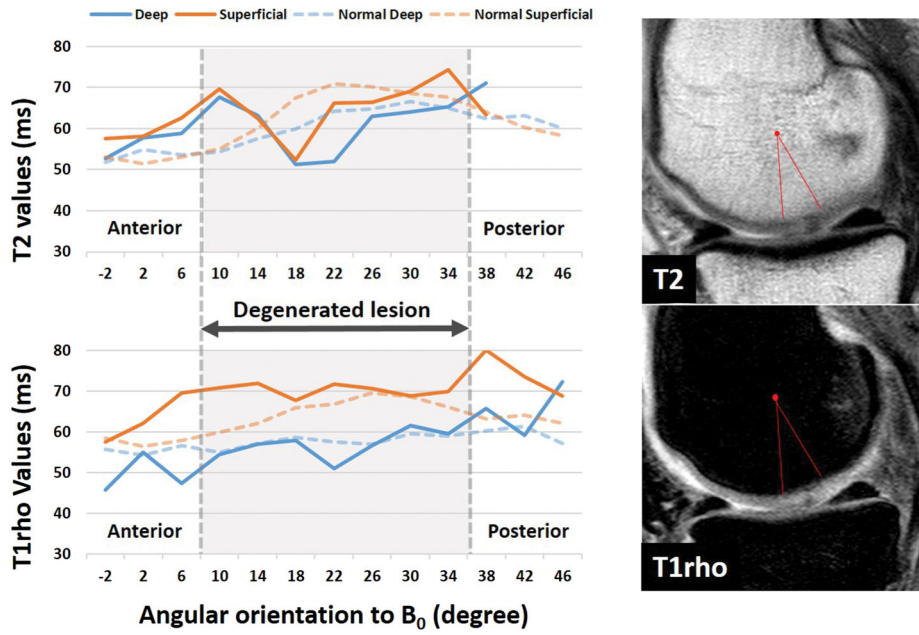


Figure 5. A representative lesion (shaded zone in left graph and area between red lines in right images) where on T2, a mixture of both higher and lower T2 values results in no significant difference on average between the OA patient and the normal control. In distinction, T1rho values in this patient were significantly lower than the normal control in the deep layer, and significantly higher than the control in the superficial layer within the same area.

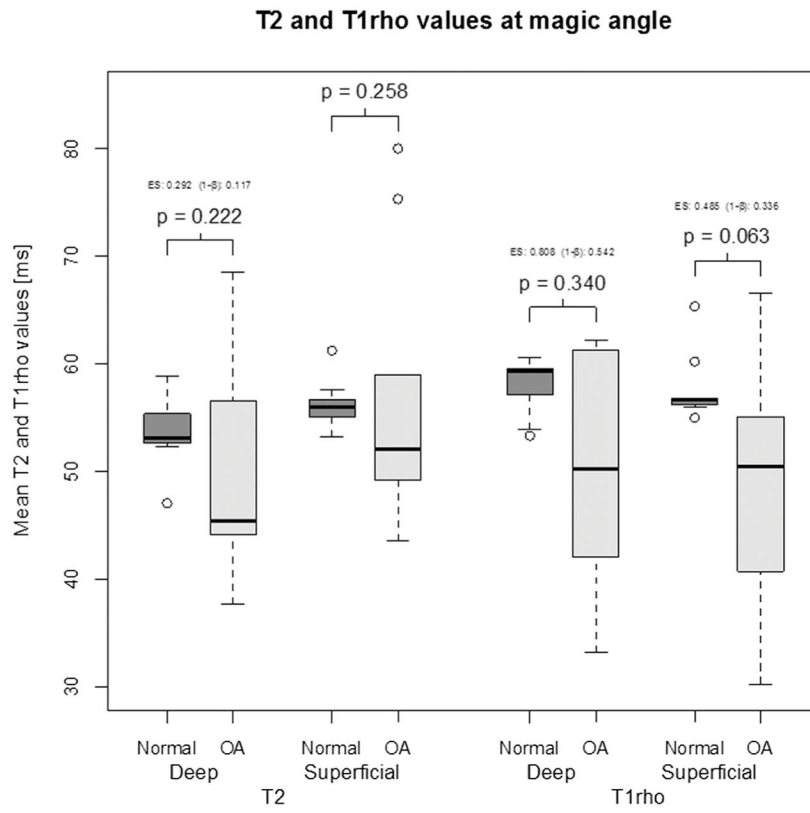


Figure 6. Comparison of T2 and T1rho value between normal and degenerative cartilage within the vicinity of the magic angle ($\pm 50\sim 58^\circ$).

Table 1

Patterns of T2 and T1rho differences between normal and OA subjects

	Cartilage layer		T2				T1rho			
	Deep	Superficial	Total	Grade 1	Grade 1-2	Grade 1-3	Total	Grade 1	Grade 1-2	Grade 1-3
Lesion without ↓	↑	↑	N=28	N=15	N=7	N=6	N=28	N=15	N=7	N=6
	→		2	1	1	-	15	7	5	3
	↑	→	5	3	-	2	1	1	-	-
	↑	→	2	2	-	-	4	3	-	1
	→	→	9	5	2	2	3	2	-	1
Total			18	11	3	4	23	13	5	5
Lesion with ↓	↓	↓	4	2	1	1	2	1	1	-
	↑	↓	1	-	1	-	1	-	-	1
	↓	↑	-	-	-	-	1	1	-	-
	→	↓	2	-	2	-	1	-	-	-
	↓	→	3	2	-	1	0	-	1	-
Total			10	4	4	2	5	2	2	1

Each of the 4 degree segments in OA patients was matched to the corresponding segment in normal controls and the matched locations were compared.

↑ indicates that relaxation times in OA subjects were statistically significantly higher than in normal controls.

↓ indicates that relaxation times in OA subjects were statistically significantly lower than in normal controls.

→ indicates there was no statistically significant difference in relaxation times between OA subjects and normal controls.

“Lesion without ↓” includes either no statistically significant change or a statistically significant increase in relaxation times.

“Lesion with ↓” includes statistically significant decrease in relaxation times in either deep or superficial layer.