Normal T_2 Map Profile of the Entire Femoral Cartilage Using an Angle/Layer-Dependent Approach

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Purpose: To create standard T_2 map profiles from the entire femoral cartilage of healthy volunteers in order to assess regional variations using an angular and layer-dependent approach.
Materials and Methods: Twenty healthy knees were evaluated using 3T sagittal images of a T_2 mapping sequence. Manual segmentation of the entire femoral cartilage was performed slice-by-slice by two raters using MatLab. Inter- and intrarater reliabilities were calculated using intraclass correlation coefficient (ICC) and Bland–Altman analysis. T_2 values were analyzed with respect to specific locations (medial condyle, trochlea, and lateral condyle), angles to B_0, and layers of cartilage (whole, deep, and superficial).
Results: Inter- and intrarater reliability obtained from the entire femoral cartilage was excellent (ICC = 0.84, 0.86, respectively). The ICCs around the trochlea were lower than those of the medial and lateral condyle. Both the inter- and intrarater Bland–Altman plots indicated larger differences in pixel count are seen as the size of the angular segment becomes larger. T_2 values were significantly higher in the superficial layer compared to the deep layer at each femoral compartment ($P < 0.001$). A magic angle effect was clearly observed, especially within the whole and deep layer over the medial and lateral femoral condyles, except for the superficial layer at the medial condyle.
Conclusion: The normal T_2 map profiles of the entire femoral cartilage showed variations in ICCs by location and in T_2 values by angles and layers. These profiles can be useful for diagnosis of early cartilage degeneration in a specific angle and layer of each condyle and trochlea.

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Osteoarthritis (OA) is one of the most common chronic disorders worldwide, resulting in significant socioeconomic costs and morbidity.[1] A number of therapeutic modalities have been developed for regenerative treatment of OA, including chondroprotective and chondroregenerative drugs, osteochondral autografting, and autologous chondrocyte implantation.[2–4] In order to effectively utilize these procedures, it is important to detect early cartilage degeneration and understand its natural progression.

Magnetic resonance imaging (MRI) is an ideal modality to assess early cartilage degeneration because of its ability to noninvasively quantify structural and biochemical changes associated with the onset and progression of OA.[5–7] Novel MRI sequences for cartilage assessment, including T_2 mapping, T_1rho mapping, and delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), have been developed as cartilage degeneration biomarkers for the evaluation of OA.[8–15] T_1rho mapping and dGEMRIC have been shown to be able to detect cartilage proteoglycan content depletion, which represents one of the earliest changes in cartilage degeneration.[8,9] T_2 mapping is the most widely utilized technique for quantitative assessment of cartilage degeneration, and has been known to be sensitive to both the collagen matrix organization and water content of cartilage.[16–18] The

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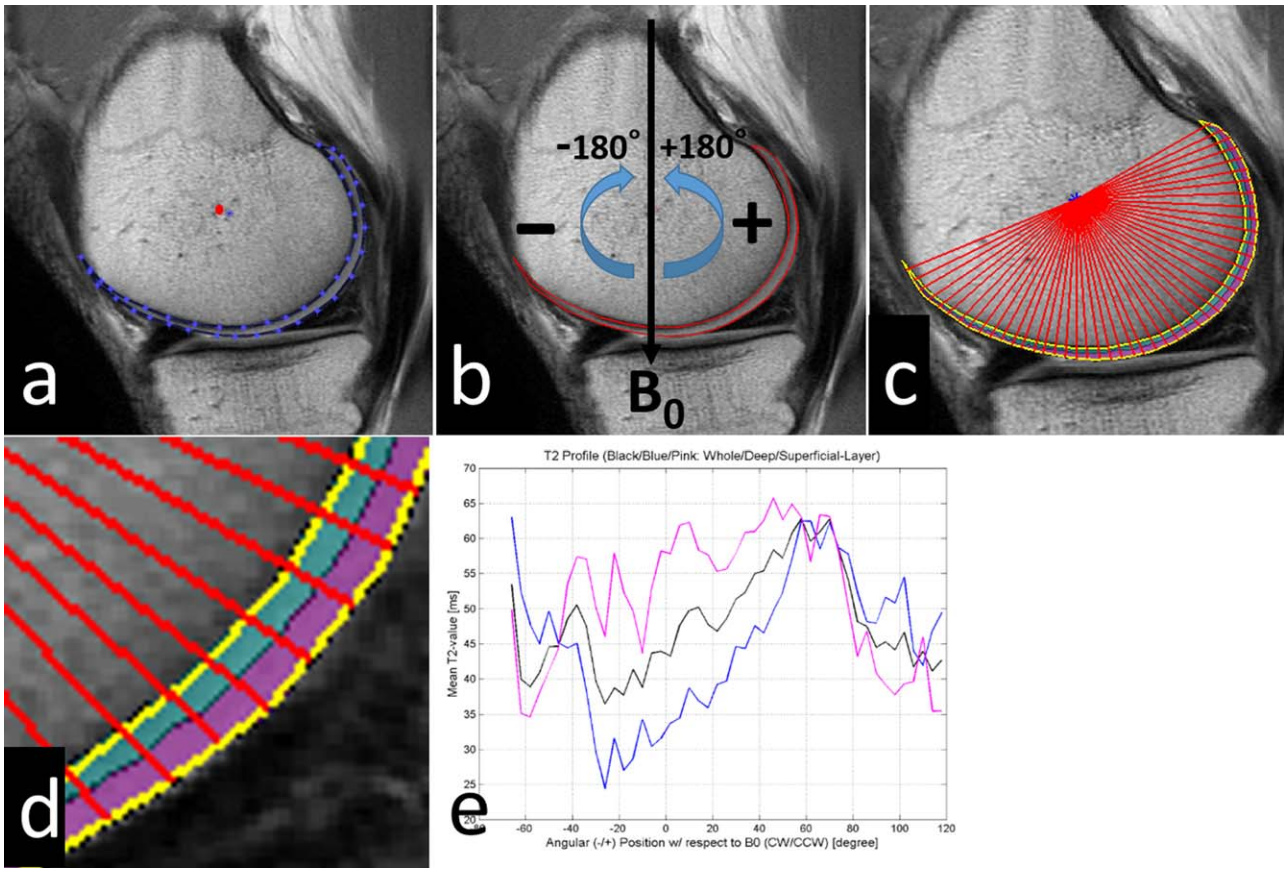

FIGURE 1: Articular segmentation with angle/layer dependent approach. (a) After manual cartilage extraction, the central point of the cartilage (red dot) was automatically approximated. (b) Static magnetic field (B_0) was defined as 0°, with negative/positive angles located anterior/posterior to the central point. (c) Radial lines from a central point divided cartilage into 4-degree segments. (d) Segmentation of cartilage into deep (0–50%) and superficial layers (51–100%) of relative thickness. (e) T_2 profiles were generated for whole thickness, deep, and superficial layers of cartilage.

damaged collagen-proteoglycan matrix and increased water content in degenerating cartilage has been reported to raise T_2 values,[12] which has been observed in patients with OA.[10] The cartilage T_2 value has been known to be dependent on location in the joint as well as layer (deep or superficial) of cartilage.[19,20] It is also known that the T_2 value of cartilage is influenced by its orientation relative to the static magnetic field (B_0) due to the magic angle effect.[21] Although many researchers have described T_2 mapping of the knee cartilage in healthy populations, there are variations in the T_2 values of healthy cartilage because of inconstant and varying definitions and limited number of subregions within the literature.[19,22–32] Several studies have described the 3D distribution of T_2 values in the entire femoral cartilage.[33,34] However, these studies did not consider the effect of cartilage angle and layer dependency on T_2 values.

The purpose of this study was to determine standard T_2 map profiles of the entire femoral cartilage of young healthy volunteers with an angle and layer-dependent approach. Further goals include establishing basic information regarding T_2 mapping of the femoral condylar cartilage in the diagnosis of early knee OA.

Materials and Methods

Study Population

Twenty healthy volunteers (13 male and 7 female) without any history of knee pain or prior knee surgery were enrolled between January 2013 and June 2013. The mean age was 28.9 years (range, 19–38 years) and the mean weight measured 73 kg (range, 50–100 kg). The study protocol was approved by the Institutional Review Board, and all volunteers gave written informed consent before any study-related procedures were done.

Image Acquisition

One knee from each volunteer was scanned for an equal number of left/right knees using a 3T MR scanner (Achieva, Philips Healthcare, Best, Netherlands) with an 8-channel receive-only knee coil. There were no restrictions for all the subjects to perform daily activity and walk to the MRI suite before imaging. The imaging protocol consisted of a 2D, true sagittal to B_0, turbo spin-echo T_2 mapping sequence with the following acquisition parameters: repetition time (TR) / echo time (TE), 2700/13 msec, 26, 39, 52, 65, 78, and 91 msec; bandwidth, 243 Hz/pixel; number of excitation, 1; field of view, 140 × 140 mm; slice thickness/gap, 3/0 mm; flip angle, 90°; image matrix, 512 × 512; number of slices, 31; effective inplane spatial resolution, 0.27 × 0.27 mm; acceleration

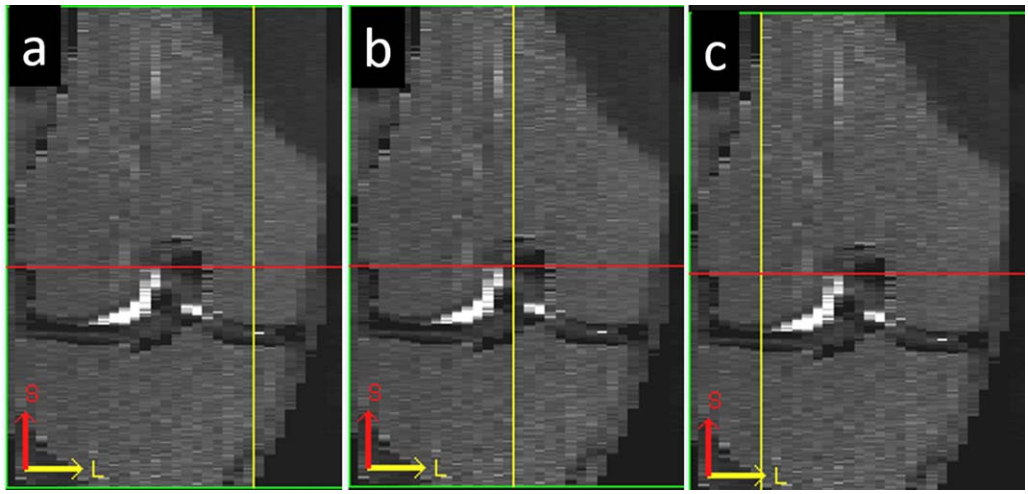

FIGURE 2: Definition of three anatomical landmarks using reconstructed coronal images in MIPAV: (a) medial condyle, (b) trochlea, and (c) lateral condyle.

factor, 2.2; and total acquisition time, 13 minutes 26 seconds. Parallel imaging was used on all imaging sequences utilizing sensitivity encoding (SENSE) for MRI. Routine knee sequences including fast spin echo 2D fat suppressed (FS) sagittal proton density-weighted images (PDWI), non-FS coronal PDWI, FS coronal PDWI, non-FS axial PDWI, and FS axial PDWI were also included in the protocol. This was done to confirm the normal appearance of each knee, as well as for use in future clinical applications.

Image Processing

CARTILAGE SEGMENTATION OF THE ENTIRE FEMORAL CONDYLE. Manual cartilage extraction of the entire femoral condyle was performed on each T_2 image by a board-certified orthopedic surgeon (R1) and a board-certified radiologist subspecialized in musculoskeletal radiology (R2) independently. For intrarater reliability analysis, R1 performed a second cartilage segmentation for each subject at least 3 months after the first segmentation. Segmentation was performed on images with a TE value of 26 msec. This value was chosen due to the superior contrast between synovial fluid and cartilage, superior contrast between cartilage and the subchondral bone plate, and due to the higher signal-to-noise ratio compared to images from other TE values. Once the cartilage was segmented by manually placing vertices along the boundary, their x and y coordinates were used in a circle-fitting algorithm by assuming a circular cartilage shape about an imaginary center position in the subchondral bone, whose coordinates were estimated in a least squares manner. We used the best fit center for each slice (Fig. 1a). Additional boundary vertices with finer spacing were then interpolated and used for computation of slope angles for the radial vectors from the center position to each boundary vertex. For each slope angle (in steps of 1-degree) the farthest (closest to the articular surface) and nearest (closest to the bone) boundary vertices were recorded while the radial points between the boundary vertices were approximated by a linear interpolation and recorded for subsequent angle/layer-based segmentation of cartilage. T_2 angle/layer-dependent profile was investigated in this study by angular segmentations in steps of 4-degrees over the length of the segmented cartilage (the angle 0 defined along B_0), and by partitioning cartilage into deep (0–50%) and superficial (51–100%) layers (Fig. 1b–e). All of the image processing described above was performed using an in-house developed and implemented software run in MatLab (MathWorks, Natick, MA).

Normalization of Slice Numbers

To define normalized slice numbers for each subject, 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), and defined the center of the medial femoral condyle (MC), lateral femoral condyle (LC), and femoral trochlea (T) in each subjects (Fig. 2). We converted a total of 31 slices into 23 normalized slices for each subject, based on three anatomical landmarks for every 3-mm slice thickness, (eg, MC+3, MC+6, T-3). Normalization was necessary due to variations in knee size among the subjects. We choose to use 23 normalized slices because the mean transverse diameter of the 20 knees was 68.9 mm. Figure 3 shows an overview of the image processing and normalization workflow.

T_2 values

Once the cartilage boundaries were transferred onto the corresponding T_2 maps, the segmented pixels with T_2 values between 1.0 and 100 msec were used for the subsequent analyses to exclude the influence of outliers such as synovial fluid and chemical shift artifact (>100 msec), and T_2 values due to poor fit (0 msec). We calculated the average T_2 values at each normalized slice with respect to each angle and layer. Then we created a 2D-surface map of each cartilage layer. We also made 3D-graphs using a custom MatLab program where T_2 profiles were shown as approximate curved surfaces. Additionally, we calculated the average T_2 values at representative angles including −90, −70, −54, −30, 0, +30,

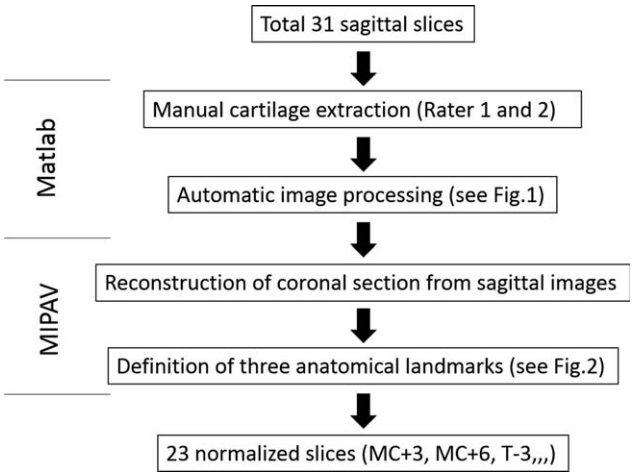

FIGURE 3: Flow diagram of image processing and normalization of slice numbers using MatLab and MIPAV.

+54, +70, and +90 degrees for comparison of T_2 values between magic angle and others.

Statistical Analysis

Individual angular segments, each spanning 4° over the length of the segmented cartilage, were used as the basis for all comparative tests. The inter- and intrarater reliability of T_2 values were assessed using intraclass correlation coefficient (ICC) analysis. ICC results of 0.60–0.74 were considered "good" and ICC results higher than 0.74 as "excellent".[35] For the evaluation of the inter- and intrarater reliability of the segmented area (number of pixels), Bland–Altman analysis was performed using only the overlapping data from the common slice/angular-ranges resulting from each test.[36] Differences in cartilage T_2 values between the deep and superficial layer at the center of each femoral compartment were assessed using an unpaired *t*-test and Mann-Whitney test for normal and nonnormal distributed data, respectively. T_2 values between femoral compartments, and T_2 values at different angles were compared using a Kruskal-Wallis test and Steel-Dwass post-hoc test. Statistical analyses were performed using R v. 3.0.2 for Windows software (R Development Core Team, Vienna, Austria), except for the Bland–Altman analyses of segmented areas, which were calculated using MatLab. *P* values less than 0.05 were considered statistically significant.

Results

T_2 relaxation time mapping for the entire femoral cartilage was successfully performed in all 20 healthy knees. There was no cartilage defect, meniscal damage, or ligament injury found in this study.

Inter- and Intrarater Reliability

The ICCs in T_2 value for inter- and intrarater reliability are shown in Fig. 4. The inter- and intrarater ICCs of the entire femoral cartilage were either "good" or "excellent" for each layer (ICC = 0.62 to 0.94). The ICCs with respect to each normalized slice showed that the inter- and intrarater ICCs around the trochlea and both edges of the condyles were lower than those around the center of the medial and

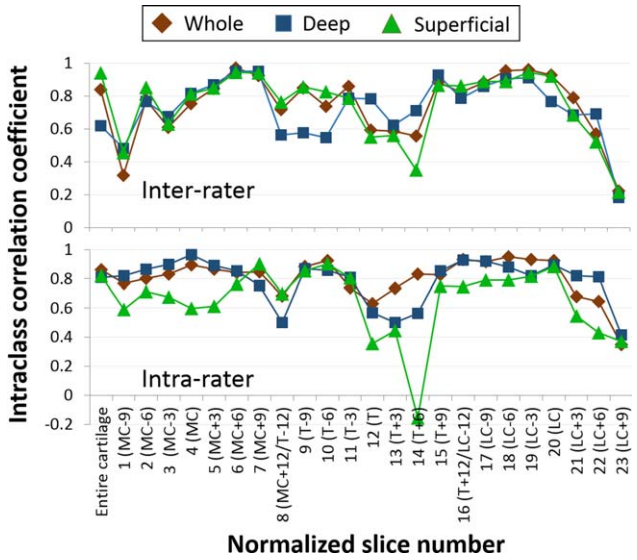

FIGURE 4: Inter- and intrarater reliability of T_2 values in each layer of the cartilage with respect to each normalized slice number. MC, medial condyle; T, trochlea; LC, lateral condyle. Phrases shown in parentheses indicate the center of femoral compartment ± distance (mm).

lateral condyle. The Bland–Altman analyses in segmented pixel number for inter- and intrarater reliability are shown in Fig. 5. The Bland–Altman plots showed that the size of angular segments from operator R1 was slightly larger on average than that of operator R2 (by 7 ± 13.3 (mean ± SD) pixels or 0.51 ± 0.97 mm^2 for the whole layer). The mean difference in size was slightly smaller from the repeated segmentations by operator R1 (by 5 ± 12.4 pixels or 0.36 ± 0.90 mm^2 for the whole layer). Both the inter- and intrarater Bland–Altman plots showed a statistically significant positive linear trend ($r = 0.15$ and 0.20, respectively) indicating larger differences in pixel count as the size of the angular segment became larger. Ninety-four percent of the interrater data points and 93% of the intrarater data points were within ±2 SD of their respective linear fitted curve on the Bland–Altman plots.

T_2 Values

T_2 values for the superficial and deep layers within the center of each of the three femoral compartments are shown in Table 1. The average T_2 value was significantly higher in the superficial layer than in the deep layer. The T_2 value at the trochlea was significantly higher than those in each layer at the medial ($P < 0.01$) and lateral condyle ($P < 0.05$) except the superficial layer at the lateral condyle. There was no significant difference in the T_2 value between the medial and lateral condyle in the whole and deep layer, but there was a significantly higher T_2 value within the superficial layer at the lateral condyle compared to at the medial condyle ($P < 0.01$). The 2D- and 3D-graphs showed inhomogeneous distribution of cartilage T_2 values, and demonstrated

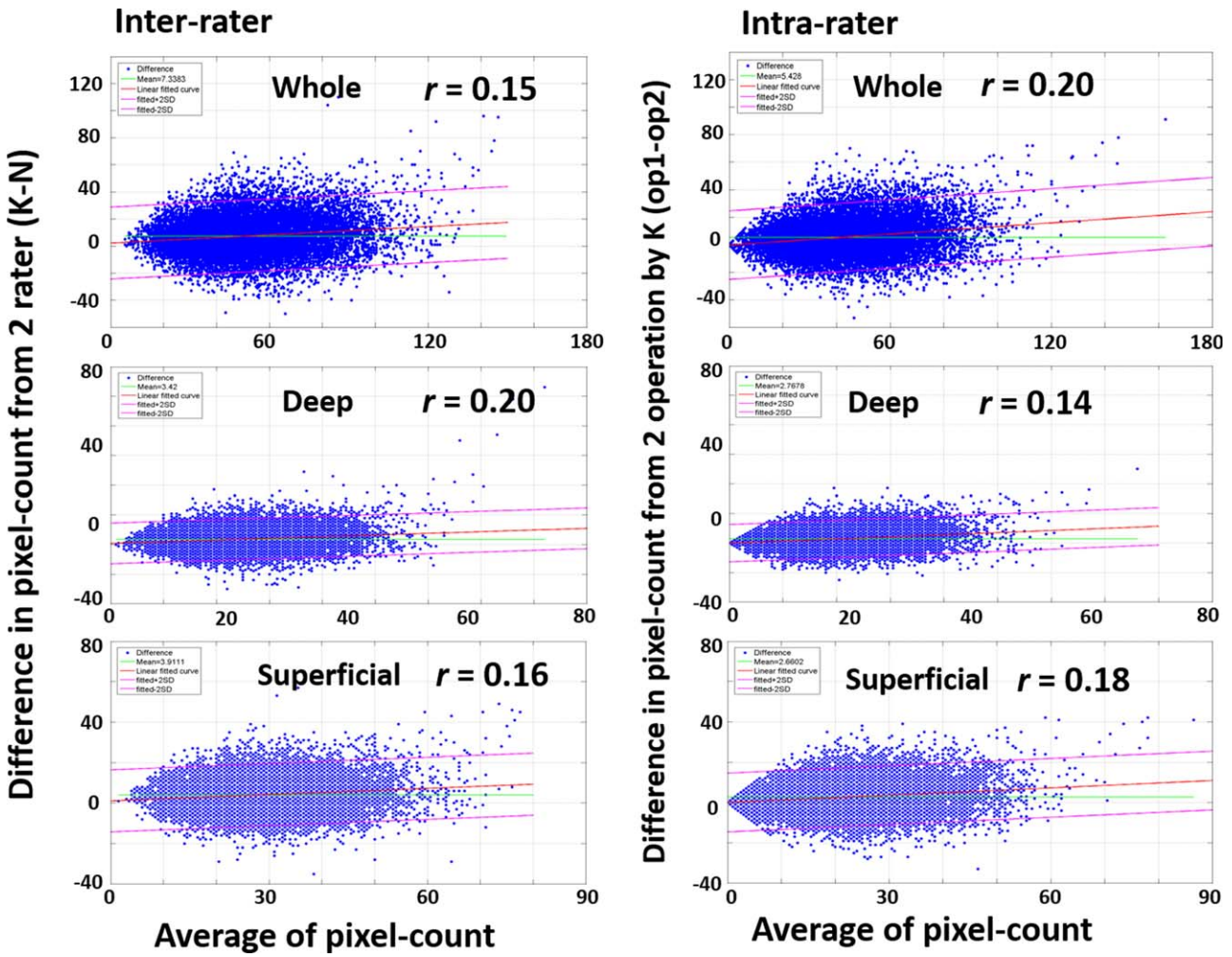

FIGURE 5: Bland–Altman plots of inter- and intrarater agreements in segmented pixel number with respect to each layer of femoral cartilage. The green line, red line, and pink line indicate mean difference, linear fitted curve, and fitted ±2 SD, respectively.

magic angle effect clearly in each layer, especially within the deep layer of the medial and lateral condyle (Figs. 6a–c, 7a–c). Scatterplots of T_2 values between magic angle and other representative angles demonstrate definite magic angle effect in each layer, especially within the whole and deep layer at ±54° over the medial and lateral femoral condyle,

TABLE 1. T_2 Values in Each Layer at the Center of Each Femoral Compartment

	Layer	Average	Median	SD	95% CI	Range	Deep vs. superficial
Medial condyle	Whole	49.8	47.9	6.0	48.2–51.4	43.0–67.2	
	Deep	48.0	46.0	8.1	45.8–50.2	38.8–74.0	$P < 0.01$
	Superficial	51.8	52.2	6.3	50.1–53.5	42.0–65.5	
Trochlea	Whole	50.8	49.7	2.4	49.4–51.0	44.9–55.1	
	Deep	47.9	47.4	3.9	46.6–49.2	41.0–55.7	$P < 0.01$
	Superficial	53.4	52.3	2.6	51.4–53.2	45.1–65.5	
Lateral condyle	Whole	49.0	49.2	4.4	47.8–50.2	40.8–57.4	
	Deep	44.5	44.3	4.2	43.3–45.5	37.7–52.4	$P < 0.01$
	Superficial	53.5	54.0	6.0	52.0–55.1	39.5–65.7	

SD, standard deviation; CI, confidential interval.

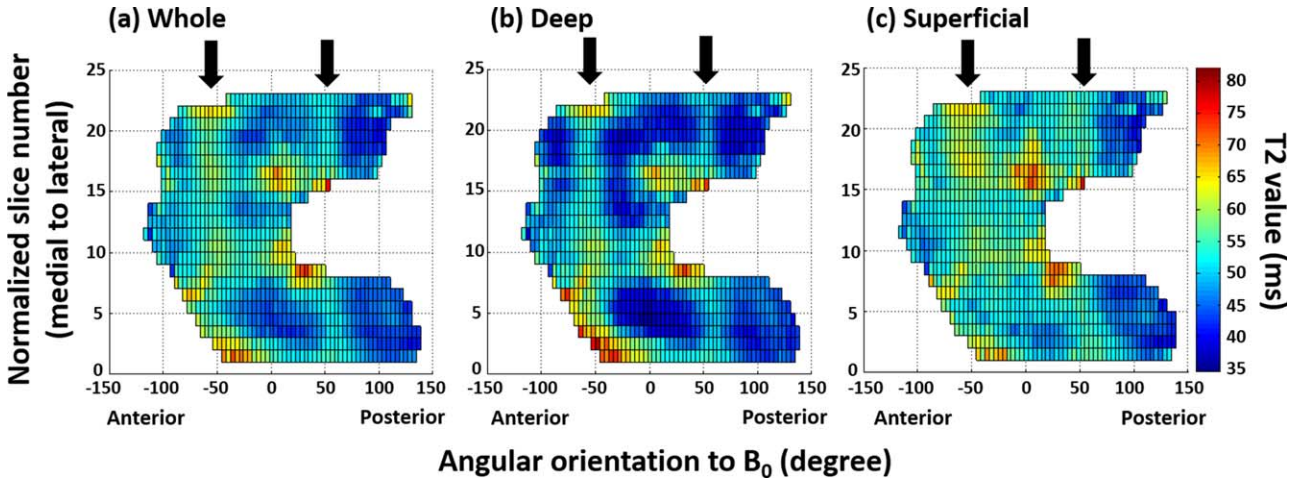

FIGURE 6: 2D surface maps displaying the T_2 profile of: (a) the whole layer, (b) the deep layer, and (c) the superficial layer of the entire femoral cartilage. Arrows indicate ±54.7° (the magic angle).

except for the superficial layer at the medial condyle (Fig. 8a–f).

Discussion

T_2 Mapping Analysis of the Entire Femoral Cartilage

Most of the previous studies performed cartilage T_2 mapping of the knee joint in the sagittal or coronal plane within a limited area of cartilage subregions.[19,22–32] Surowiec et al [32] reported significant differences in mean T_2 values between 21 subregions in healthy volunteers (range: 41.7–54.2 msec), suggesting that there is a normal variation of T_2 values within the knee. T_2 values of the three anatomical landmarks in our study were similar to those of previous studies (range: 44.3–52.3 msec).[27,32] Shiomi et al [34] reported the 3D distribution of T_2 values of the entire femoral cartilage in healthy volunteer knees, in which cartilage T_2 values for the internal half of the weight-bearing zone covered by meniscus were significantly higher than those in all other zones within both the medial and lateral condyles. However, there has been no previous study that evaluated the cartilage T_2 value of the entire femoral condyle with both angular orientation and cartilage layer taken into account. In the present study, we successfully evaluated the entire femoral cartilage T_2 profile of healthy volunteer knees. Excellent inter- and intrarater reliability in various locations from the medial to lateral condyle proved our angle and layer-dependent approach for the entire femoral condyle is a useful method for cartilage T_2 mapping analysis. However, differences in reliability within specific locations suggest limitation or difficulty in our approach for specific areas such as the trochlea and far medial or lateral condyle. These findings may be due to the poor contrast between cartilage and surrounding tissue, partial volume effect, or chemical shift artifact.[37]

T_2 Value and Cartilage Layer

The mean T_2 values of the superficial layer in our study were higher than those of the deep layer within each compartment, as reported in the previous study.[22] The superficial layer in our approach contained the histological transitional layer. This layer is characterized by a more random orientation of the collagen fibers and increased water content compared with those in the deep layer,[37] leading to a higher T_2 value. The magic angle effect was more apparent in the deep layer compared to the superficial layer within both the medial and lateral condyles, which was the opposite outcome of previous studies.[22,28] Mosher et al [22]

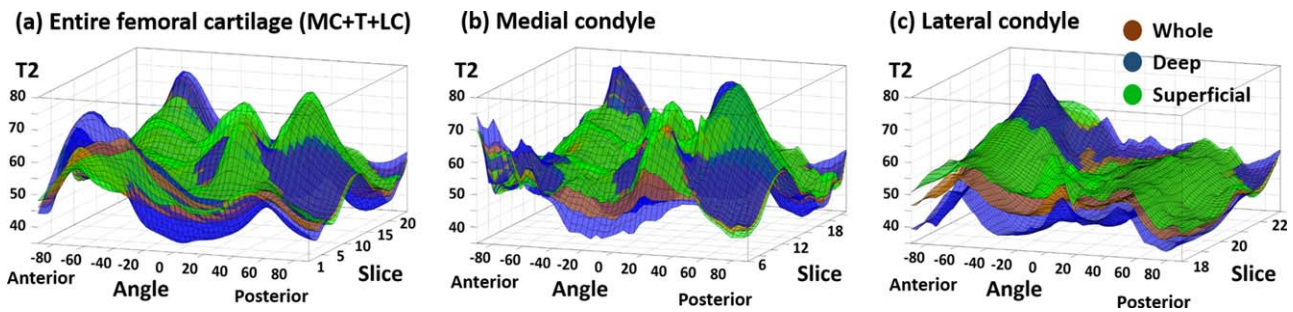

FIGURE 7: 3D graph of the T_2 profiles of: (a) the entire femoral cartilage, (b) cross-section at the center of the medial condyle, and (c) the lateral condyle. MC, medial condyle; T, trochlea; LC, lateral condyle.

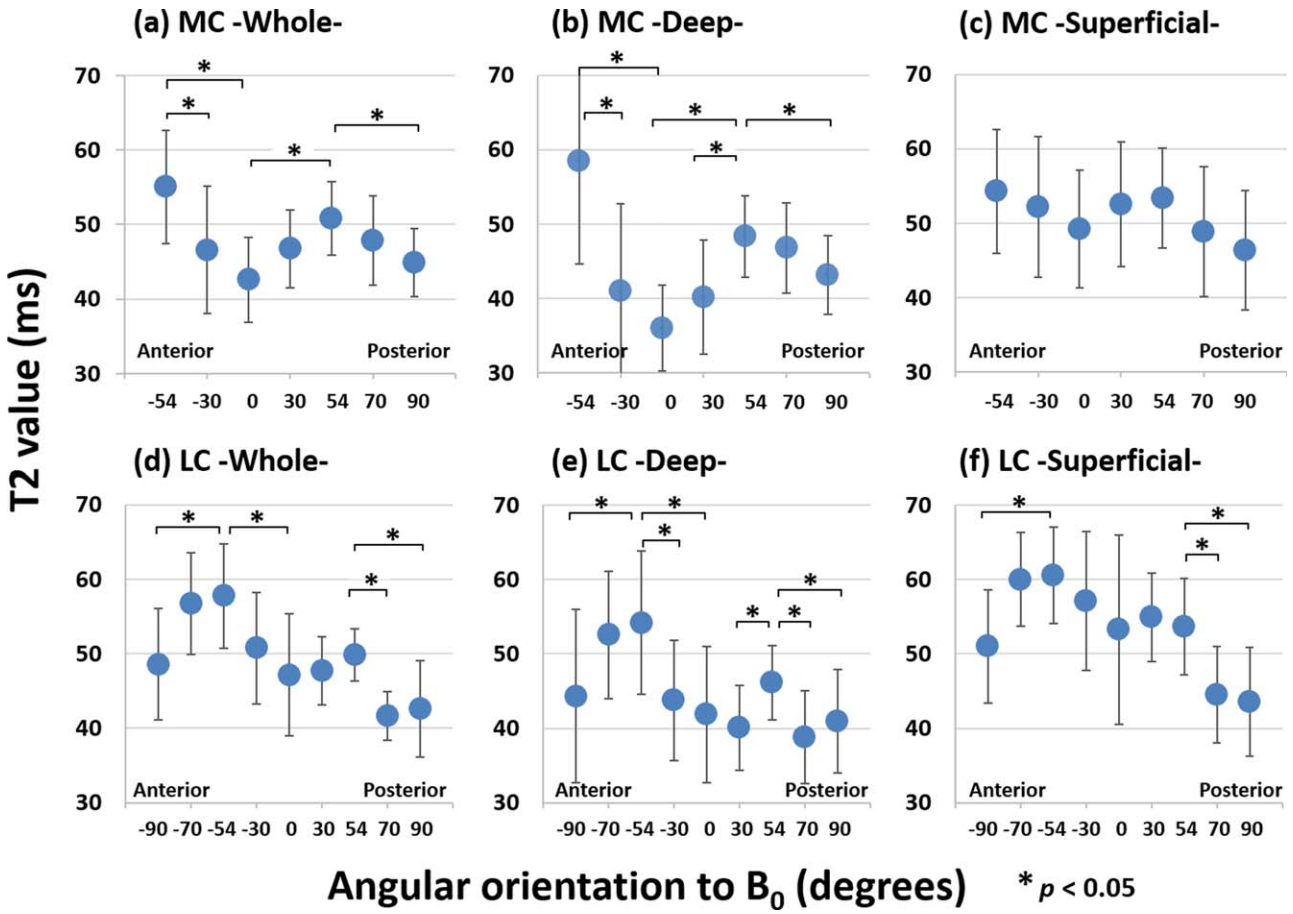

FIGURE 8: Comparison of T_2 values between magic angle and other representative angles with respect to each layer. MC medial condyle, T trochlea, LC lateral condyle.

reported that the difference in cartilage T_2 values between magic angle and B_0 in healthy volunteers was greater in the superficial layer, yet smaller than those reported in the previous ex vivo studies, and concluded that regional differences in the degree of cartilage compression in weight bearing are primarily responsible for the regional differences in the cartilage T_2 value. However, their results may be limited, as they evaluated only a single sagittal slice of the lateral condyle. Our results were consistent with the histological fact that collagen fibers are perpendicular to subchondral bone in the deep layer, and are more susceptible to the magic angle effect, while the superficial layer has structural anisotropy of collagen fibers from the transitional zone to the superficial zone, and receives less effect of anisotropic orientation.[37]

T_2 Values and Femoral Compartment

The T_2 profile was clearly different between the medial and lateral condyles in this study. The medial condyle has a circular shape in the sagittal plane, and is more likely to exhibit the magic angle effect at +54° with smooth sinusoid curve. On the other hand, the lateral condyle has an oval or box-like shape, and showed a sharp and narrow peak at +54° in the deep layer in our image-processing manner using circle-fitting algorithm. T_2 values at the trochlea were higher than those of the medial and lateral condyle, as previously reported.[32] The higher T_2 value at the lateral condyle than the medial condyle in the superficial layer may be explained by the basis that the medial condyle has a wider weight-bearing area than the lateral condyle,[34] and that weight-bearing areas have lower T_2 values than nonweight bearing areas.[38] Manual cartilage extraction was problematic at some locations. In particular, the worst inter- and intrarater ICCs were seen around the trochlea (Fig. 9a), where the cartilage–bone interface and cartilage surface were difficult to determine due to partial volume effect in T_2 sagittal image.[37]

T_2 Values and Angular Orientation

Most previous studies analyzed cartilage T_2 values in comparison between subregions [25,32] or between weight-bearing and nonweight-bearing regions.[22,34] In this study, we analyzed the entire femoral cartilage in detail within steps of 4-degree. Angular orientation was seen to have a substantial effect on the T_2 values within both condyles. Although the circular shape of the medial condyle in the sagittal plane was suitable for evaluating the magic angle effect using our image-processing method, bimodal peaks of T_2 value at

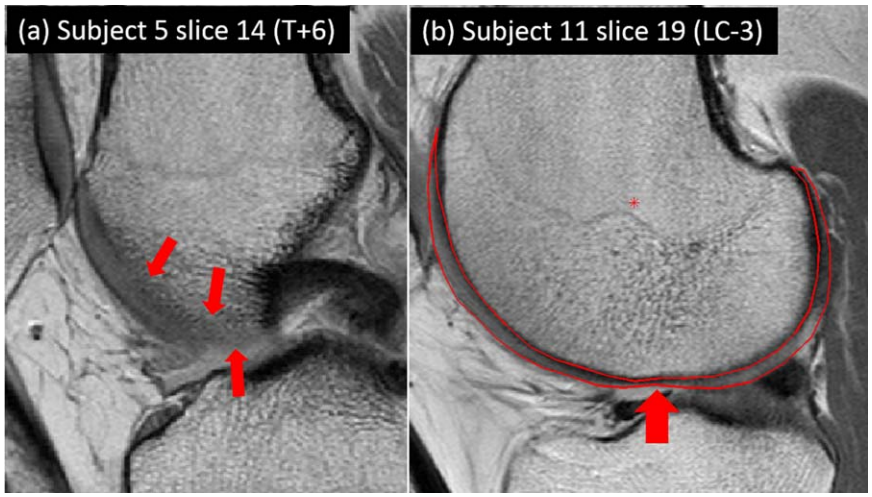

FIGURE 9: T_2 mapping images where manual cartilage extraction was difficult: (a) a transitional location between trochlea and lateral condyle with the worst inter- and intrarater reliability, and (b) lateral condyle with the lateral femoral notch. T, trochlea; LC, lateral condyle. Phrases shown in parentheses indicate the center of femoral compartment ± distance (mm).

±54° were clearly observed over the entire medial and lateral condyle. However, there were no significant differences between the magic angle and other angles within the superficial layer of the medial condyle. This might be due to underestimation of the differences due to a small number of study subjects. Another potential reason could be that the structural anisotropy of the collagen fibers within the superficial layer decreased the magic angle effect.[37] A large variation of the T_2 value at 0° in the superficial layer over the lateral condyle was probably due to a smoothly contoured thinning of the cartilage, the so-called "lateral femoral notch",[38] where it is easy to overestimate the cartilage thickness during manual extraction (Fig. 9b).

Cartilage T_2 values from this study demonstrated considerable variation with respect to each angular orientation and layer. These factors will have an impact during evaluation of subtle abnormalities of the femoral cartilage. The normal T_2 profile of the entire femoral cartilage shown in this study can be a helpful benchmark in the diagnosis of early cartilage degeneration.

Limitations

Our study has several limitations. First, acquisition time was long. Acquisition times would need to be short in order to include T_2 mapping sequences in clinical protocols. Shorter repetition time, shorter echo time, smaller matrix size, and limited slice number would contribute to a faster acquisition time,[30,31] although these settings could make image quality poor. Second, postprocessing, including manual segmentation of cartilage and normalization of slice number, was time-consuming. Automated or semiautomated segmentation and 2D/3D graph creation will likely become essential for shortening postprocessing time for future clinical applications. Third, the sample size of this study was small. We may need more samples to apply healthy T_2 mapping profile for a clinical atlas. We could have doubled the sample size by scanning both knees in each volunteer. Fourth, chemical shift artifact from a 3T magnet and the relatively narrow band width in this study might make discrimination between cartilage and subchondral bone difficult in some areas. Fifth, partial volume effect was inevitable with the 2D sequence in this study, and most prominent in the transitional area between the condyle and the trochlea, where the contour of the cartilage changes significantly.[37] Sixth, we did not assess other cartilage MRI techniques in this study such as dGEMRIC, which is known to be reliable for evaluating glycosaminoglycan content,[15,40] and T_1rho, which is reported to be a more sensitive indicator of early cartilage degeneration than T_2 mapping.[41] The next step of our study will be an assessment of the femoral cartilage in early OA patients using T_2 and T_1rho techniques. Seventh, the intrarater reliability was not assessed in both raters. In this study, we referred to previous studies regarding cartilage segmentation of the knee, in which the intrarater reliability test was performed in a single rater.[34,42] Finally, we included only young healthy volunteers in this study. A large cohort of patients with early cartilage degeneration would need to be studied in order to prove our angle and layer-dependent approach is clinically useful in the future.

In conclusion, this study demonstrated the standard T_2 map profile from the entire femoral cartilage of normal volunteers with an angle/layer-dependent approach. The inter- and intrarater reliability in T_2 value and segmented pixel number was overall high with various agreements dependent on location. Variations in T_2 value by angular orientation and cartilage layer was demonstrated throughout the femoral condyles. Our results can be useful for the diagnosis of early cartilage degeneration in a specific angle and layer of each condyle and trochlea by establishing a baseline normal T_2 mapping profile.

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