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Clinical evaluation of T_2 values of patellar cartilage in patients with osteoarthritis

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Summary

Objective: The transverse relaxation time constant, T_2, of articular cartilage has been proposed as a biomarker for osteoarthritis (OA). Previous studies have not clearly defined the relationship between cartilage T_2 values and clinical methods of grading OA or known factors associated with OA. This study compared T_2 values of patellar cartilage grouped by radiographic stage of patello-femoral OA and by body mass index (BMI).

Methods: T_2 values of patellar cartilage were calculated for 113 subjects using images acquired on a 1.5 T clinical scanner. Radiographs of the patello-femoral joint were graded for OA grading using the Kellgren–Lawrence scale.

Results: No differences of T_2 values were found across the stages of OA ($P = 0.25$), but the factor of BMI did have a significant effect ($P < 0.0001$) on T_2 value.

Conclusions: The results indicate the T_2 values are not sensitive to changes in radiographic stages of OA. In addition, differences of T_2 values with BMI signify structural changes occurring within the patello-femoral joint and that BMI may be considered a factor for a potential increase of T_2 values. Future studies comparing different OA grading methods with T_2 mapping may highlight the sensitivity of T_2 mapping in a clinical setting.

Key words: Patella, Osteoarthritis, MRI, T_2, Radiography.

Introduction

Osteoarthritis (OA) is the leading cause of disability for adults in the United States[1] afflicting more than 21 million people[2]. OA can greatly impair an individual's activities of daily living by reducing diarthrodial joint mobility and function. Different options exist for treatment of OA, however, selection of the proper treatment relies on an accurate OA grading of the afflicted joint. Grading of OA is commonly performed using radiography. A radiographic OA grading protocol typically assigns one of several stages to a joint based on joint space width, continuity of bony contours, presence and size of osteophytes and overall joint appearance. Although OA grading and measurement of joint space width on a radiograph are often used to select the appropriate treatment for OA[3,4], radiographic staging of the joint has limitations. First, because a radiograph is a two dimensional projection of x-rays through a three dimensional body, it is difficult to determine the precise location of any specific regional pathology. In addition, the orientation of the patient relative to the x-ray source may produce inconsistent and non-repeatable radiographic images[5]. Second, radiographs only show structures which attenuate the original x-ray beam. Thus, while hard tissues (bones) are visible on the radiograph, soft tissues (cartilage, ligaments, and joint capsule) commonly affected by OA are not visible. An alternative imaging technique is magnetic resonance imaging (MRI). MRI provides a direct, repeatable, high tissue contrast, non-destructive and non-ionizing method of visualizing bodily structures *in vivo*[6,7]. MRI has been actively used as a tool in the investigation of OA. MRI may detect the compositional changes of articular cartilage in a joint afflicted with OA[8,9].

T_2-weighted images have been used to detect degenerated cartilage. T_2-weighted images have been shown to identify grades 3 and 4 chondromalacia to a high level of sensitivity (83%) and specificity (97%)[10]. The same study also found T_2-weighted images to underestimate the presence of surface fibrillation and surface defects. This underestimation of degeneration has been verified by other investigators[11,12]. Using T_2-weighted images alone is unlikely to show early degeneration of cartilage[13].

Recently, the transverse relaxation time constant, T_2, of articular cartilage has been proposed as a biomarker for OA[14,15] and may be more useful than traditional T_2-weighted images for clinical OA diagnosis. T_2 maps of cartilage have been successful in identifying localized degeneration of the tissue[16]. Previous investigators have shown T_2 values are dependent upon local water content, collagen fiber orientation and loss of type II collagen[17–22]. These variables are indicative of the presence of OA[23]. While these studies have provided important information about the physiological meaning of T_2 values, more work is needed to understand the clinical implications of T_2 values.

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Limited studies have been performed comparing *in vivo* cartilage T_2 values across various stages of OA. Mosher and colleagues have evaluated *in vivo* knee cartilage T_2 maps of asymptomatic subjects[24], of different age groups[16] and of different genders[15], however, subjects in these studies were asymptomatic for OA. Dunn and coworkers calculated T_2 values of femoral and tibial cartilage in 55 subjects with varying stages of knee OA[25]. Radiographs obtained for each subject were graded using the Kellgren and Lawrence (KL) scale and pain was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score. The study found regional T_2 values to increase as OA stage increased, with similar T_2 values for subjects with moderate and severe OA. The study had several limitations. First, T_2 values were calculated from sagittal images of the knee. This imaging plane allows for the magic angle effect of cartilage to artificially increase the calculated cartilage T_2 value due to curvature characteristics of the femoral cartilage relative to the main magnetic field[26]. Second, only two echo images were used to calculate T_2 values. Third, a limited cohort of subjects required the investigators to group subjects as "mild" OA (KL stages 1 and 2) or "severe" OA (KL stages 3 and 4). Clearly, data from additional echo times (TEs) would be beneficial for data accuracy. In addition, a large cohort of subjects would increase the statistical power of the study and would give a clear delineation of differences of T_2 values across clinical stages of OA. Finally, in a recent study, T_2 values of tibial, patellar and femoral cartilage at different stages of OA were evaluated *in vitro*[27]. A direct relation between the increase of T_2 values and the disruption of superficial collagen fibers was verified by histological examination. However, visual OA staging of the cartilage was performed using an unverified grading protocol.

Relating T_2 values of cartilage to a standard clinical OA staging method would be beneficial for determining the clinical applicability of T_2 mapping. In addition, statistically meaningful T_2 results require data acquisition from a large subject cohort. The purpose of this study was to use a large subject group to quantify differences of T_2 values of patellar cartilage across different stages of OA as defined by standard clinical radiological examination, using an MR dataset acquired using a clinically relevant multi-slice multi-echo fast spin echo (FSE) pulse sequence.

Methods

SUBJECTS

Following local institutional review board (IRB) approval with informed consent, 113 consecutive subjects (56.0 ± 11.0 y.o., range 33–82, 29M, 84F) were enrolled in the study. The consecutive subjects were recruited for an on-going study in our laboratory to evaluate the effects of exercise on OA. The inclusion criteria for subjects in the study were: 30 years of age or older, current symptoms of chronic stable (6-month) pain and/or stiffness in one or both knees during weight-bearing activities, the knee is a primary factor limiting physical or functional activity, radiographic signs of mild or moderate arthritis in any compartment of the knee and mild joint space narrowing ($\geq$2 mm remaining). The height (h (m)) and weight (w (kg)) of each subject were recorded to calculate body mass index (BMI) (31.8 ± 5.9 kg/m^2, range 20.1–52.9 kg/m^2).

DATA ACQUISITION

Standing lateral radiographs centered on the patella were obtained for each knee. Following the radiological exam, bilateral MR images of each subject's patellae were obtained. A series of axial T_2-weighted images were acquired across 10 slice locations spanning the length of the patella. All images were acquired using a 1.5 T GE Signa MR scanner with a dedicated transmit–receive knee coil. A multi-slice multi-echo FSE pulse sequence was used to acquire the images[28]. Nine echo images were acquired at each slice location, but only images from the last eight echoes were reconstructed for analysis. Data from the first echo image were discarded in calculating T_2 values to increase T_2 accuracy[28]. Imaging parameters for T_2 mapping were: Repetition time (TR) = 1000 ms, TE = 17–77 ms, slice thickness = 2 mm, slice spacing = 4 mm, in-plane resolution = 0.49 mm $\times$ 0.49 mm, Field of View (FOV) = 12 cm $\times$ 12 cm, acquisition matrix = 256 $\times$ 160 (zero filled to 256 $\times$ 256 for image reconstruction), and Band Width (BW) = 31.25 MHz. Radiographic and MR image acquisition were both performed either in the early morning or mid-afternoon. Data from 223 knees of the 226 knees (113 subjects) were analyzed; T_2-weighted image datasets from three patellae were of poor quality and were excluded from the study.

DATA ANALYSIS

Individuals were grouped based on their BMI (kg/m^2). The groups were defined as: Normal (BMI = 19–25), Overweight (BMI = 25–30), Obese (BMI = 30–40) and Morbidly Obese (BMI = 40+). Radiographs were graded for patellofemoral OA based on the KL scale[29] from 0 (no OA) to 4 (end-stage OA). This scale assigns a level of OA based on the evaluation of joint space width and the presence and size of osteophytes.

Custom written programs were used to calculate T_2 values from the MR images (MATLAB, Natick, MA)[30]. Patellar cartilage was manually segmented at each slice location by the same individual (MFK) for all subjects enrolled in the study. The cartilage was manually segmented using the first echo image (TE = 17 ms) to delineate the deep cartilage from the underlying subchondral bone and the last echo image (TE = 77 ms) to delineate the superficial cartilage from the surrounding joint space.

On average, the segmentation took approximately 45 min to 1 h for each individual (two patellae). T_2 values of patellar cartilage were calculated on a pixel-by-pixel basis by fitting the TE data and the corresponding signal intensity (SI) data to a mono-exponential equation:

$$SI(TE) = S_0 \cdot \exp(-TE/T_2)$$

Pixels with T_2 values greater than 200 ms were considered outliers and were excluded from the statistical analysis[25]. The percentage of pixels considered outliers for a joint was typically 1%. An average T_2 value generated from all analyzed pixels of each patella was used for the statistical analysis.

In addition, profiles of T_2 values through the depth of the tissue were calculated for the stages 0, 1, 2 and 3 of KL OA. Profile analysis of KL OA stage 4 patellae was not performed due to limited sample size. An automated program constructed nine equally spaced T_2 profiles, normal to the subchondral bone–cartilage interface. The program interpolated T_2 values at 20 points along each profile. The positions of the interpolated values along the profile were normalized by the length of the profile. Values at 0% depth represented values near the subchondral bone–cartilage interface and values at 100% depth represented values near the articular surface of the cartilage. The profile of

interpolated T_2 data was considered a valid representation of the T_2 data if the profile was longer than 2.34 mm (5 pixels) in length. The number of valid profiles included in generating the average profile was recorded. In addition, each profile was divided into three regions from the subchondral bone–cartilage interface to the articular surface for statistical analysis. The deep zone of cartilage was considered as 0%–30% of the profile, the middle zone of cartilage was considered as 30%–70% of the profile and the superficial zone of cartilage was considered as 70%–100% of the profile[31].

A two factor analysis of variance (ANOVA) was used to determine the effects of OA and BMI on patellar cartilage T_2 values. A second two factor ANOVA was performed to determine the effects of profile location (deep, middle, and superficial) and OA on cartilage T_2 values through the depth of the tissue. Significance for all statistical tests was taken at $P < 0.05$ with $\alpha = 0.05$. A Student–Neuman–Keuls (SNK) multiple comparison test was performed when statistical significance was achieved in the ANOVA tests (SAS Institute, Inc., Cary, NC).

The power of the study was calculated using a custom written MS Excel worksheet. For simplicity, the power analysis was based on a pairwise comparison of means using a paired *t* test using a type I error of 0.05 and a two sided test of hypothesis[32]. The harmonic mean and weighted standard deviation of the sample groups KL OA stage 0 and KL OA stage 3 were calculated[33] and used in the power analysis. We selected these groups for the power analysis based on their sample sizes to give the lower limit of power of the study. We selected these groups since only four patellae were graded KL OA stage 4 for patello-femoral OA. The sample size of our study enabled us to detect a 4 ms difference of T_2 values between the stages of KL OA with a power of 88%.

Results

The stage of OA did not have a significant effect on average T_2 value ($P = 0.25$), but the factor of BMI did have a significant effect ($P < 0.0001$). There was no significant interaction of these two factors, $P = 0.23$. A representative T_2 map of patellar cartilage of a subject at KL OA grade 1 is shown in Fig. 1. The T_2 values of patellar cartilage were approximately 65 ms for KL stages 0, 1, 2 and 3 with an increase to 73 ms for stage 4 KL OA (Fig. 2). Average calculated T_2 values of patellar cartilage across the KL stages of OA are shown in Table I. An additional one-way ANOVA was performed regrouping KL OA stages 1 and 2 together as "mild" OA subjects and KL OA stages 3 and 4 together as "severe" OA subjects. However, a difference of average T_2 value was not found with the new groupings ($P = 0.75$).

From the *post hoc* SNK test, Normal subjects had significantly lower T_2 values than other BMI groups (Fig. 3). Obese subjects had T_2 values similar to Overweight and Morbidly Obese subjects, but Morbidly Obese subjects had higher T_2 values than Overweight subjects. Average calculated T_2 values of patellar cartilage by BMI grouping are shown in Table II. A weak but significant correlation ($r = 0.30$, $P < 0.0001$) was found between average T_2 value and BMI (Fig. 4).

From the statistical analysis of T_2 profiles, the stage of OA did not have a significant effect on T_2 value ($P = 0.084$), but the factor of zonal location did have a significant effect ($P < 0.0001$). There was no significant interaction of these two factors, $P = 0.98$. The *post hoc* SNK determined significant differences between the different zones of cartilage. The superficial zone had the highest T_2 values, 70.7 ± 19.7 ms, the middle zone had the lowest T_2 values, 65.9 ± 16.5 ms, and the deep zone had T_2 values higher than the middle zone, but lower than the superficial zone, 67.3 ± 18.3 ms. A plot of average T_2 profile through the depth of cartilage for each stage of KL OA is shown in Fig. 5.

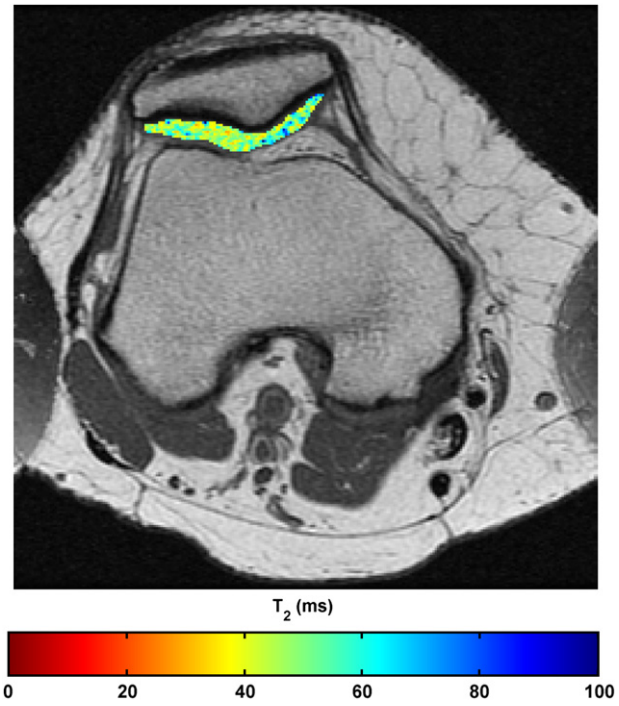

Fig. 1. A representative T_2 map of patellar cartilage superimposed on the first echo image for a subject graded as KL OA grade 1. Even graded radiographically as mild OA, elevated T_2 values are found near the subchondral bone–cartilage interface as well as near the articular surface on the medial aspect of the patella.

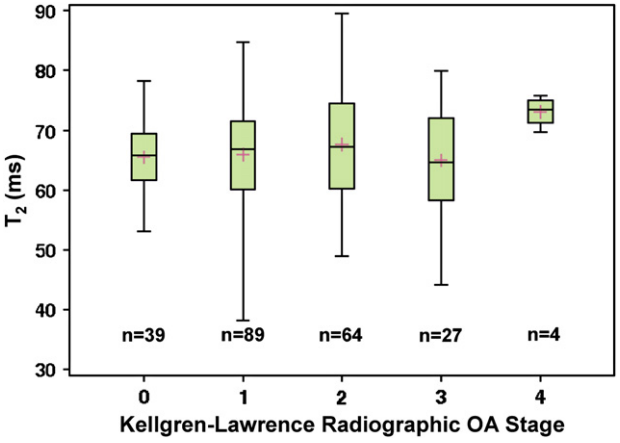

Fig. 2. Box-plot of T_2 values of patellar cartilage at each stage of KL radiographic OA grading. The box length represents the distance between the 25th and the 75th percentiles, the interior plus sign represents the mean, the interior horizontal line represents the median, and the vertical lines issuing from the box extend to the minimum and maximum T_2 values.

Table I
T_2 values of patellar cartilage at each stage of KL OA

KL OA stage	*n*	T_2 value (ms) (Ave. ± Std.Dev.)
0	39	65.5 ± 6.1
1	89	66.0 ± 9.4
2	64	67.7 ± 9.9
3	27	65.0 ± 8.7
4	4	73.1 ± 2.6

Table II
T_2 values of patellar cartilage by BMI

BMI description	BMI values (kg/m^2)	*n*	T_2 value (ms) (Ave. ± Std.Dev.)
Normal	19–25	24	59.8 ± 7.9
Overweight	25–30	64	64.9 ± 8.8
Obese	30–40	117	67.8 ± 8.2
Morbidly Obese	>40	18	71.5 ± 10.1

Discussion

In this study, T_2 values of patellar cartilage across the stages of OA as defined by radiological grading were examined. Understanding how calculated T_2 values relate to a standard clinical assessment of OA is important in determining the clinical applicability of this image analysis method. For clinical evaluation of T_2 mapping, it is important that the subjects included in the study accurately reflect the distribution of the disease in the general population.

A large cohort of subjects was used in the study, approximately 75% of which were female. Female gender is a significant risk factor for OA. A longitudinal study of knee OA showed that women have a 1.8 times greater risk of developing OA than men[34]. Arthritis is more prevalent among women than among men at all ages. These gender differences are most prominent when OA affects the knee (7.3% of women and 4.1% of men age 55–64 years, 18% of women and 8.3% of men age 65–74 years). For all grades of radiographic severity of OA, more women than men report knee pain. Among those over the age of 60, women are twice as likely to have symptomatic arthritis as men[35]. We believe the cohort of subjects used in this study is representative of the general population affected by OA. In addition, even though a majority of our subjects were female, inclusion of additional male subjects may not alter the findings of the study. Previous investigators found no difference in bulk T_2 values of patellar cartilage by gender[15]. The sample size of the current study results in a large power, 88% chance of detecting a difference of 4 ms, further emphasizing the lack of minimal differences of T_2 values by KL OA stage.

This study did not find a difference in T_2 values across OA stages. KL OA stage 4 subjects tended to have higher T_2 values than KL OA stages 1, 2 and 3, however, the limited sample size for this group ($n = 4$) prevents any definitive conclusions from being drawn. This finding is primarily due to two factors. First, the KL staging of a joint assigns an OA stage based on the overall radiographic appearance of a joint. A patello-femoral joint with joint space narrowing and the presence of osteophytes has cartilage which is already significantly deteriorated. Therefore, the KL staging will detect advanced stages of OA rather than the onset of the disease. If there is a rapid change of T_2 values during the onset of OA and not at later stages, then we would not expect to find differences of T_2 values using a KL protocol for staging OA. While several studies have evaluated T_2 values of cartilage after simulating the effects of OA by enzymatic degradation of collagen and proteoglycan content[36–38], no studies have evaluated the time course in change of T_2 values. Calculating T_2 values of cartilage using an animal model of OA [e.g. Ref 23] would be beneficial to determine the rate of changes of T_2 values and the clinical implications of this novel technique to assess OA.

Another factor which may have influenced our results was using an average T_2 value from each patella for statistical analysis. We often found focal increases of T_2 values on individual image slices during data processing. Statistical analysis using an average T_2 value of the patella would diminish the effect of focal increases of T_2 values on the total patellar T_2 value. Thus, while T_2 values have been shown to correlate very well with histological examination of degraded cartilage[39], the cartilage samples tend to be small enough to directly compare MR analytical output with histological staining methods. In evaluating T_2 values

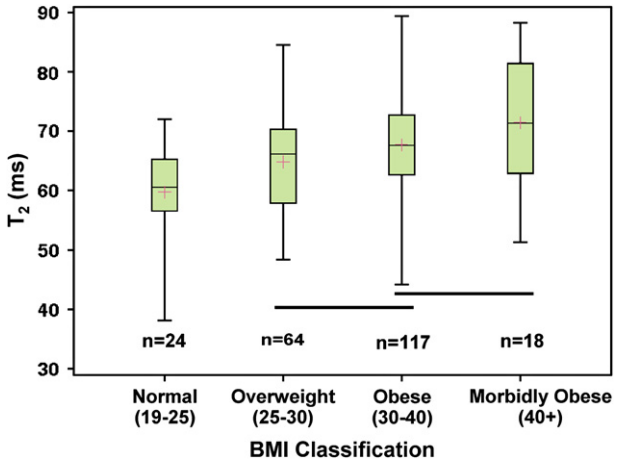

Fig. 3. Box-plot of T_2 values of patellar cartilage by BMI classification. Bars indicate similar groups. The box length represents the distance between the 25th and the 75th percentiles, the interior plus sign represents the mean, the interior horizontal line represents the median, and the vertical lines issuing from the box extend to the minimum and maximum T_2 values.

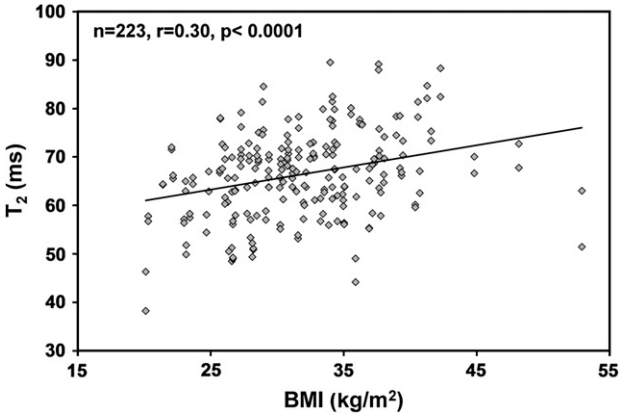

Fig. 4. Correlation of T_2 values with BMI. A weak but significant correlation was found between the two variables.

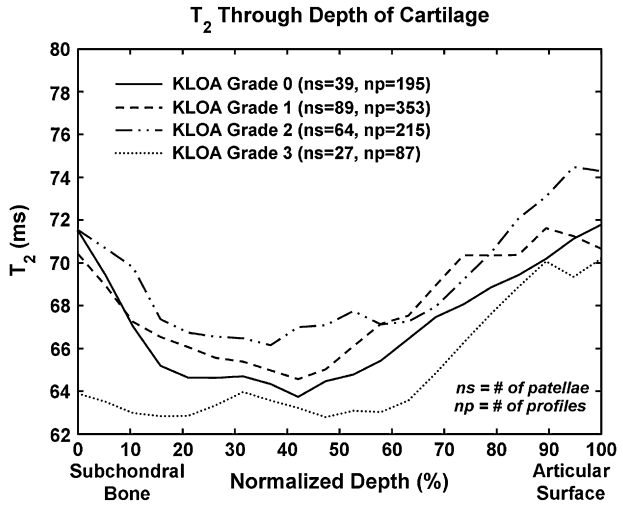

Fig. 5. Average profiles of T_2 values through depth of cartilage for each stage of KL radiographic OA grading. No differences of average T_2 profile were found among the stages of OA. T_2 values in regions through the depth of the tissue were significantly different from each other ($P < 0.0001$). The curves significantly reduced in T_2 value from the deep zone (0%−30% depth) to the middle zone (30%−70% depth) and significantly increased in value in the superficial zone (70%−100% depth). The number of patellae and number of valid profiles included in the analysis are displayed.

at the scale of the whole joint, enough of the entire articular surface may need to be fibrillated during OA to increase the average patellar T_2 value. In addition, the slice spacing used in the study (4 mm) did not cover the whole region of patellar cartilage. It is difficult to speculate the effect of including data from additional slices, however, we anticipate the trend found in the study would remain the same.

Average T_2 profiles through the depth of the tissue did not differ by OA stage, but regional differences were present. While the shape and magnitude of our profiles are similar to what have been previously reported[15,40], we did not detect differences of profiles by KL OA stage. This is likely due to the state of the disease which can be detected using a radiographic staging protocol, as described above. Differences among the profiles may be found if an alternative OA staging protocol is used which is sensitive to the time scale of changes of T_2 values.

The regional distribution of T_2 values using an FSE imaging sequence in this study is similar to what has been shown in previous studies using a standard single-echo spin echo (SE) imaging sequence[15,24]. The expected low T_2 values in the deep zone of cartilage[20] were not found. The elevated T_2 values from 0% to 20% depth of the tissue are likely due to the confounding factors of magnetization transfer, stimulated echoes and volume averaging near the cartilage−bone interface[28]. However, the rise in magnitude of T_2 values from 50% depth relates well to the transitional and superficial regions of the tissue[26].

Surprisingly, the profile analysis showed the average stage 3 KL OA T_2 profile is lower than the profiles of stages 0, 1 and 2. We attribute this finding primarily to two factors. First, stage 3 patellae had fewer profiles available for analysis. Only 87 profiles were considered valid for comparison to the other stages of OA. This represents a 55% reduction in number of profiles available when compared to the next larger group of profiles, OA stage 0. Second, the profile length threshold we applied may have unintentionally biased the results. For example, a subject may have had a knee graded as PF OA stage 3, however, the profiles within a region of high OA may have been excluded from the analysis since the minimum length of 2.34 mm (5 pixels) was not met. Additionally, the same patella may have had regions which had little to no OA present and had profiles which met the minimum profile length for inclusion in analysis. In this situation, the "better health" of the valid profiles from stage 3 OA subjects may have resulted in lower T_2 values. In contrast, while stages 0, 1 and 2 subjects had more profiles available for analysis, some profiles within these stages may have had elevated T_2 values but were included in the grouping since the minimum profile length was achieved. This would result in an overall elevation of the average T_2 profile for these stages as compared to stage 3. We subsequently reduced the threshold value to define a valid profile, however, the relationships among the T_2 profiles remained similar.

The calculated T_2 values of this study are within the range of T_2 values reported in the literature[14], however, our T_2 values of patellar cartilage tended to be slightly higher than the previous reports of patellar T_2 values[15,18,27,41]. We attribute this finding to the image acquisition process. All images were acquired using a multislice multi-echo FSE pulse sequence. This pulse sequence has been demonstrated to result in increased calculated T_2 values relative to images acquired with a SE sequence[28]. The increase of T_2 values due to pulse sequence has been confirmed on our scanning equipment using a T_2 phantom. T_2 values calculated from images of an FSE sequence were approximately 5% higher than T_2 values calculated from images of an SE sequence. This error is similar in magnitude to what has been previously reported[28]. If the calculation of T_2 values using an FSE pulse sequence is able to display additional information about the articular cartilage in a minimal amount of time, then this study will further emphasize the usefulness of T_2 mapping in a standard clinical scanner.

We do not believe that T_1 saturation would have a significant effect on the calculation of our T_2 values. The TR value for this study (1000 ms) is slightly less than the TR of 1500 ms used by other investigators performing *in vivo* analysis using 1.5 T clinical scanners. We agree it would be beneficial to have an increased TR value to minimize T_1 contribution to the contrast in the images. Assuming T_1 of cartilage to be 600 ms, a TR of 1000 ms only decreases the available signal at the initial 90 degree slice-selective pulse by approximately 10% when compared to a TR of 1500 ms. Although 10% less signal is available for generating the T_2-weighted images, the value of T_2 is independent of the magnitude of the signal available at each TE. The time constant T_2 signifies approximately 37% of the original signal will be available for measurement at $TE = T_2$. Subsequent scanning of a T_2 phantom showed no effect in calculated T_2 values as TR was increased from 1000 ms to 1500 ms.

A shorter TR was used in this study to limit the amount of time a subject was in the scanner. All subjects were scanned during normal clinic hours in our hospital. If the calculation of T_2 values using an FSE pulse sequence is able to display additional information about the articular cartilage in a minimal amount of time, then this study will further emphasize the usefulness of T_2 mapping in a standard clinical scanner.

Furthermore, the TE times chosen for this study are comparable to the TE values used by previous investigators to evaluate T_2 values of cartilage [e.g., Refs. [16−18]]. As

mentioned above, we believe our elevated T_2 values are due to the known effect of stimulated echoes from a multi-echo sequence with slice-selective pulses.

A limitation of the study was manually segmenting cartilage for T_2 analysis. Axial Spoiled Gradient Recalled (SPGR) images were not available for delineation of the patellar cartilage. Limited time was available on the MR scanner since all scanning was performed during normal operating hours of the clinic. We did not want to lengthen the amount of time the subjects spent in the scanner. The present protocol required each participant to be in the scanner for 1 h for acquisition of the T_2 weighted series. The T_2 weighted image scanning series was appended to the scanning protocol for the previously stated on-going study to evaluate the effects of exercise on OA. We have subsequently evaluated the intra-examiner and inter-examiner repeatability of T_2 values based on our manual segmentation method. We found excellent intra-examiner and inter-examiner repeatability with differences <1.5 ms and <1 ms, respectively.

Finally, an interesting finding of our study is the weak but significant positive correlation of T_2 with BMI. This indicates that BMI may be considered a factor for a potential increase of T_2 values. The direct relation of T_2 values with BMI indicates significant structural changes of cartilage are occurring within the patella. Previous investigators have studied the gait characteristics of subjects with knee patello-femoral OA and a high BMI and found individuals with high BMI values made functional changes during their gait cycle to compensate for the symptoms of OA[42]. The results of this present study indicate that individuals with high BMI also have structural changes occurring at the joint as indicated by the increased T_2 values.

T_2 mapping of patellar cartilage may provide a non-invasive method for accurate staging of OA within the knee. Additional studies evaluating different methods of T_2 mapping may highlight the benefits and sensitivity of T_2 mapping in a clinical setting.

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