AGE DEPENDENCY OF CARTILAGE MAGNETIC RESONANCE IMAGING T2 RELAXATION TIMES IN ASYMPTOMATIC FEMALES

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ABSTRACT

Objective: Because the MRI transverse relaxation time (T2) of cartilage is sensitive to organization of collagen fibers in cartilage, it may be a noninvasive image marker for senescent changes in cartilage collagen and early cartilage degeneration. The purpose of this study is to determine age dependent differences in cartilage T2 in healthy asymptomatic women.

Methods: Quantitative T2 maps of patellar cartilage from 30 asymptomatic female adults age 22 to 86 years were obtained using a 3.0 T MRI scanner. The study population was stratified by age into four cohorts: 18-30, 31-45, 46-65, and 66-86 years. Spatial differences in cartilage T2 were determined as a function of normalized distance from bone. Older groups were compared to the age 18 to 30 group to determine effect of age on cartilage T2. Regions were considered statistically different if mean T2 between groups differed with a p < .05.

Results: Mean cartilage T2 profiles are nearly identical for the two youngest populations. Compared to the age 18 to 30 year old group, T2 values were statistically significantly longer in the superficial 40% of cartilage for the age 46 to 65 cohort, and over the entire cartilage thickness for the age 66 to 86 year old group.

Conclusion: The location of T2 elevation for individuals over age 45 is consistent with the theory that senescent changes of cartilage collagen begin near the articular surface, and progress to deeper cartilage with advancing age.

Keywords: Cartilage, Osteoarthritis, Magnetic Resonance Imaging, MRI-T2, Aging, Gender

Running Title: Age Dependency of Cartilage T2
Age is a recognized risk factor in development of osteoarthritis (OA) (1). Epidemiology studies demonstrate a linear increase in OA in individuals under age 45, with an exponential increase in later ages (1). Understanding of both OA and basic connective tissue aging would benefit if specific parameters in cartilage could be identified that reflect senescent modification of tissue. Because magnetic resonance imaging (MRI) can directly visualize articular cartilage, it is likely to be a useful modality in the study of cartilage aging and OA. Current clinical MRI techniques demonstrate joint anatomy, and can be used to determine morphologic parameters such as cartilage volume, thickness, and presence of focal, superficial cartilage lesions (2). More recently techniques have been described for generating spatially localized quantitative maps of MRI relaxation times of cartilage (3). These MRI parametric mapping techniques have the potential to identify and localize specific biochemical, and structural changes within the extracellular cartilage matrix.

The transverse relation time (T2) is a measurable MRI time constant that is sensitive to the slow molecular motion of mobile protons. In articular cartilage the T2 relaxation time has a linear correlation with tissue water content (4), and is sensitive to loss of collagen content (5), and collagen fiber orientation (6) in the extra-cellular matrix. There is a strong inverse correlation between spatially localized cartilage T2 values and cartilage birefringence observed with polarized light microscopy (7-9). Regions with highly organized collagen fiber structure, such as the deep radial zone of cartilage, are characterized by short T2 values, while areas with more random arrangement of fiber orientation, and lower birefringence on polarized light microscopy have longer T2 values.
Factors that decrease collagen fiber anisotropy or increase mobility of cartilage water, reduce the relative contribution of this residual dipolar interaction, and elevate cartilage T2. The sensitivity of cartilage T2 values to structural modification of the collagen matrix makes it a potentially useful image marker for age related changes in cartilage and early OA.

A preliminary study by Mosher et al demonstrated an age dependent elevation in superficial cartilage T2 in asymptomatic male volunteers age 46 to 65 years compared to volunteers age 18 to 30 years (10). This study was limited to male volunteers, younger than age 65. It remains to be determined if a similar pattern of cartilage T2 elevation is present in asymptomatic females where changes in hormone levels may influence cartilage composition and structure. Additional studies are needed to determine if the observed elevation in superficial cartilage T2 persists or changes in older populations. The purpose of the study is thus twofold: first, to determine if an age dependent elevation in cartilage T2 occurs in asymptomatic women, and second, to determine spatial dependency of cartilage T2 in the elderly population age 66 and over.
PATIENTS AND METHODS

Volunteer Recruitment

Volunteers were recruited from the community using print advertisements and screened to exclude volunteers with a known contraindication for MRI. Inclusion criteria included healthy female adults greater than 18 years of age. Additional exclusion criteria were history of prior trauma, orthopedic surgery, chronic disease requiring medical treatment, and joint pain or stiffness. The study population of 30 asymptomatic female adults age 22 to 86 years was stratified by age into four cohorts: 18 to 30 years (n=8), 31 to 45 years (n=7), 46 to 65 years (n=8) and 66 to 86 years (n=7). After the nature of the procedure was explained, all participants provided informed consent to participate in the study, which was approved by the institutional review board. Additional demographic data collected at time of the MRI study included height, weight, and self-assessment of level of exercise. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters. All MRI studies were conducted in the morning to minimize the potential effect of diurnal variation on cartilage T2 measurements. Premenopausal female volunteers were studied between days 7 and 14 of their menstrual cycle.

MRI Data Acquisition

Subjects were randomized for study of either the right or left leg. To minimize variation in T2 due to magic angle effects, all subjects were imaged supine with the patellar articular surface oriented parallel with the direction of the applied magnetic field. The imaging location was centered over the mid pole of the patella as defined by a sagittal
scout image through the center of the patellofemoral joint. This targeted the analysis to
the thickest region of patellar cartilage, and further decreased magic angle effects by
excluding peripheral cartilage near the superior and inferior pole. Quantitative MRI T2
maps were acquired with a Bruker 3.0 T MR imaging-spectrometer (Medspec S300;
Bruker Instruments, Ettlingen, Germany) using a dedicated 24 cm gradient insert, and 15
cm linear Litz coil (Doty Scientific, Columbia, South Carolina, USA). A multi-slice
multi-spin echo sequence was used to obtain axial source images of the patellofemoral
joint from 5 sections with a TR/TE: 1500/8-88 ms, echo train length: 11, 3 mm section
thickness with a 1 mm intersection gap, 76 kHz receiver bandwidth, 256 x 256 image
matrix, and a 14 cm field of view. The resultant in-plane pixel resolution was 0.55 mm.
Total image acquisition time was 6.4 minutes.

**Data Analysis**

**Subjective T2 scoring**

Magnitude images and T2 maps were calculated from 10 spin-echo images by means of
linear least squares curve fitting, on a pixel-by-pixel basis with CCHIPS/IDL software
(Cincinnati Children’s Hospital Image Processing Software/ Interactive Data Language,
(RSI, Inc. Boulder, CO) (11). The first echo was excluded from the fit to reduce error
resulting from signal produced by stimulated echoes (12). Prior spectroscopic
measurements have demonstrated a mono-exponential T2 decay of normal cartilage (13).
Thus, fitting of the signal intensity (SI) for the $i^{th}$, $j^{th}$ pixel as a function of time, $t$, can be
expressed as follows:
\[ SI_{i,j}(t) = SI_{0_{i,j}} \cdot \exp(-t/T_{2_{i,j}}), \]

Where \( SI_{0_{i,j}} \) is the pixel intensity at \( t = 0 \) and \( T_{2_{i,j}} \) is the T2 time constant of pixel \( i,j \). A magnitude image is generated from the pixel \( SI_{0_{i,j}} \) data, and a T2 map is generated from the \( T_{2_{i,j}} \) data (14). Magnitude images were analyzed in gray scale, and quantitative T2 maps were analyzed as a color-coded image, using an ordinal rainbow color scale.

A musculoskeletal radiologist (TJM) with eight years of experience interpreting cartilage T2 maps subjectively evaluated color-coded T2 maps, and gray scale anatomic images from all five sections according to the following criteria:

- **Score 0:** Normal
- **Score 1:** Focally elevated cartilage T2
- **Score 2:** Full thickness elevated cartilage T2
- **Score 3:** Diffusely elevated cartilage T2
- **Score 4:** Full thickness cartilage defect

For each subject the highest score for the medial patellar facet, median patellar ridge, and lateral patellar facet was recorded, and used to calculate the severity and prevalence of subjective T2 abnormalities for each cohort. A Cochran-Mantel-Haenszel test for trend was used to test the hypothesis that higher T2 scores occur in older cohorts. For this analysis adjustment was made for the dependency of the three observations from each individual. To determine intra-observer variability of the subjective analysis, T2 scoring was repeated 23 weeks later, with the reviewer blinded to subject identity and prior T2 scores. Intra-observer agreement was determined using a weighted kappa analysis, where
Kw <0.20 was interpreted as poor agreement, < 0.40 fair, <0.60 moderate, <0.80 good, and 0.80 to 1.00 as very good agreement.

**Bulk Cartilage T2**

For quantitative analysis, regions of interest (ROIs) were generated by segmentation of patellar cartilage from all five sections using an interactive subroutine in the CCHIPS/IDL software. There were two full thickness cartilage defects observed in the age 46 to 65 cohort, and three in the 66 to 86 year old cohort. These regions were excluded from quantitative analysis. For each subject the T2 value for pixels located within the cartilage ROIs from each of the five sections was averaged to determine the bulk cartilage T2 value. Preliminary analysis of the association of bulk cartilage T2 as a function of age indicated a difference in slope for individuals younger than, and older than 45 years of age. This was further evaluated by fitting the data for the two groups to a single change-point linear regression model.

**Cartilage Thickness and T2 Profiles**

For each ROI determined from the five MRI sections, the software automatically generated multiple perpendicular tangents to the cartilage/bone interface, terminating at the articular surface. On average 174 tangents were generated for each subject (range 62 to 236 tangents). Cartilage thickness was estimated by calculating the average length in mm and standard deviation of the computer generated tangents. Correlation of cartilage thickness with age was analyzed using a Pearson’s correlation coefficient. A two-tailed p-value less than 0.05 was interpreted as statistically significant.
Spatial variation in cartilage T2 was evaluated by generating T2 profiles for each cohort where T2 is determined as a function of normalized distance from bone. In the first step of this analysis the T2 of each pixel in the cartilage ROIs was evaluated as a function of distance from bone using the computer generated tangents described for analysis of cartilage thickness. On average 683 pixels were evaluated for each subject (range 260 to 944 pixels). Second, to allow comparison between individuals with different cartilage thickness, distance was normalized for cartilage thickness such that cartilage at the subchondral surface has a normalized distance of 0.0, and cartilage at the articular surface has a normalized distance of 1.0. Third, for each subject, pixels were clustered into 20 equal segments based on normalized distance from bone, and a mean T2 value was calculated for each segment. Fourth, to determine the mean T2 profile for each cohort, mean segmental T2 values for each subject in the group were pooled and the mean T2 ± standard deviation was calculated for each segment for the cohort. Finally, to determine effect of age on cartilage T2 as a function of distance from bone, older groups were compared to the age 18 to 30 group using an unpaired two-tailed t-test for each segment. The p-value for each segment was then interpolated to generate a profile of p-value as a function of normalized distance from bone. Segments of normalized T2 profiles were considered statistically different if the mean T2 differed with a p < 0.05.
RESULTS

Patient Demographics

Demographic information on the study population is summarized in Table 1. All subjects had a BMI < 30. Nine subjects had a BMI > 25. These included two subjects in the 18 to 30 year old group, 1 subject in the 31 to 45 year old group, 5 subjects in the 46 to 65 year old group, and 1 in the oldest group. None of the participants participated in a regular exercise program, or organized sports activity.

Subjective T2 scoring

Representative cartilage T2 maps from each of the four cohorts are presented in Figure 1. Spatial variation in cartilage T2 was observed in the color-coded T2 maps with shorter T2 values (light blue: T2 = 20 ms to 30 ms) in the deeper layers of cartilage near bone, and longer T2 values (red: T2 = 60 ms to 70 ms) near the articular surface. As shown in these representative T2 maps, longer T2 values and greater variability in cartilage T2 were observed in older individuals.

Results of subjective cartilage T2 scoring from the initial interpretation session are presented in Table 2. Focal cartilage T2 abnormalities were observed with greater severity and prevalence in the oldest population, however this was not statistically significant (p value = 0.11). In the youngest age group subjective T2 abnormalities were identified in 8% of sites and consisted of focal elevation in T2 confined to the superficial cartilage of the lateral facet (score 1). Focal T2 abnormalities were observed in 24% of the 31 to 45 year old cohort, and 21% and 48% of the 46 to 65 and 66 to 85 year old
cohorts respectively. In both the 46 to 65 and 66 to 85 year old cohort, full thickness cartilage defects (score 4) were identified despite the lack of clinical symptoms. No full thickness defects were identified in the two youngest cohorts. There was good intra-observer agreement between the two interpretation sessions with a weighted kappa statistic of 0.77.

**Bulk Cartilage T2**

As shown in Figure 2, there was little age dependency of bulk cartilage T2 for subjects younger than 45 years of age; however, there was an age dependent elevation and greater variability in T2 for subjects older than 45 years. Fitting the data for the two groups to a single change-point linear regression model indicated a significant slope (p<0.05) after 45 and a non-significant slope (p>0.05) for younger subjects.

**Cartilage Thickness**

As observed in Figure 3, there was wide variation in cartilage thicknesses for younger individuals, with the largest range observed in subjects age 18 to 30. There was a statistically significant inverse correlation of cartilage thickness with age (r= -0.51, two-tailed p-value = 0.006).

**Spatial Variation in Cartilage T2**

All patients demonstrated similar spatial dependency of cartilage T2 as a function of normalized distance from bone. Focally high T2 values were observed near the bone cartilage interface, decreasing in the deep 20% to 30% of cartilage, and then increasing.
monotonically toward the articular surface. Figure 4A demonstrates the mean cartilage T2 for each age group as a function of normalized distance from bone. Mean T2 profiles were nearly identical for the two youngest populations. For the 18 to 30 year old cohort mean cartilage T2 increased from a minimum of 43.2 ms ± 2.0 ms at a normalized distance of 0.15 to 63.2 ms ± 2.4 ms at the articular surface. Longer T2 values were observed primarily in superficial cartilage of the 46 to 65 year cohort where T2 ranged from a minimum of 47.0 ms ± 6.0 ms at a normalized distance of 0.20 to 76.0 ± 10.9 ms at the articular surface. Cartilage T2 was more diffusely elevated in the oldest population where the minimum T2 was 53.7 ms ± 10.8 ms at a normalized distance of 0.30 increasing to 79.5 ms ± 7.5 ms at the articular surface. As demonstrated in Figure 4B there was no statistically significant difference in mean T2 profiles between the two youngest populations. Cartilage T2 for the age 46 to 65 cohort was statistically significantly longer in the superficial 40% of cartilage compared to the age 18 to 30 group. The mean T2 profile for the age 66 and older group was significantly longer over the entire normalized distance.
DISCUSSION

These studies reveal age dependent differences in both morphology and T2 relaxation times of patellar cartilage in asymptomatic women. Although MRI parameters for T2 mapping are not optimized for high resolution to measure cartilage thickness, there was a statistically significant trend toward patellar thinning with increasing age. Similarly there was a trend for greater severity and prevalence of focal patellar T2 lesions in older populations. For individuals older than 45 years there was a positive correlation of cartilage T2 and age. Interestingly the location of elevated cartilage T2 differs with age, being limited to superficial cartilage in the 46 to 65 year old cohort, but involving the entire cartilage thickness in the oldest subjects.

Prior autopsy studies have demonstrated an age dependent decrease in patellar cartilage thickness with age (15). Despite the unique ability of MRI to image articular cartilage, there have been few studies evaluating age dependent differences in appearance of cartilage of asymptomatic individuals. These have primarily been limited to morphometric measures of cartilage such as volume, or mean thickness (16, 17). An early MRI study by Karoven demonstrated age dependent thinning of cartilage in the weight bearing portion of the femur, but not in the patella (18). Similar findings by Dalla Palma found an inverse correlation with cartilage thickness and age, which was strongest in the medial femoral condyle of male subjects (19). More recently Huldemaier et al demonstrated thinning of femoral cartilage of both sexes in the elderly compared to young subjects (20). A significant reduction in patellar cartilage was observed in elderly women, but not in elderly men. Results of our study demonstrate a trend toward
decreasing cartilage thickness with age. Despite using lower spatial resolution, and
different acquisition techniques, our values for mean cartilage thickness agree well with
measurements of 2.49 mm and 2.19 mm reported by Huldelmaier et al for comparable
young and elderly subjects respectively. In our study mean patellar thickness for the 18
to 30 year old cohort was 2.6 mm, and for the elderly cohort of comparable age (46 to 65
years) thickness averaged 2.0 mm. In addition to decreasing cartilage thickness with age,
we observed an increase in severity and prevalence of focal chondral lesions in
individuals over age 65 years, suggesting the presence of preclinical cartilage damage in
this population.

Results of this study indicate that compared to young asymptomatic volunteers, there is
elevation of patellar cartilage T2 values of asymptomatic females age 46 and older. The
age dependent elevation of cartilage T2 does not occur uniformly. For individuals age 46
to 65 longer T2 values are observed in the superficial 40% of cartilage. Despite
differences in methodology, these findings are nearly identical to previous published
results in asymptomatic male subjects in which the T2 values of the superficial 36% of
cartilage in the age 46 to 65 year old cohort was elevated compared to young subjects
(10). The prior study in asymptomatic males did not evaluate individuals over age 65.
Results of this study indicate after age 65 there is further elevation in cartilage T2 that
extends to deeper layers of articular cartilage, suggesting a progressive senescent change
in cartilage that begins at the articular surface.
Prior biochemical studies indicate aging is associated with structural and compositional changes in articular cartilage. With increasing age there is a decrease in total water content, and increase in concentration of proteoglycan (21, 22). Because cartilage T2 increases with water content (4), a senescent decrease in water content would not produce the observed increase in cartilage T2 in older subjects. Likewise several studies have shown that cartilage T2 is insensitive to changes in proteoglycan concentration (13, 23, 24), and it is therefore unlikely that change in proteoglycan content, or composition would account for the observed differences in cartilage T2. Of note, a recent study by Mosher et al in nanomelic chicken cartilage has shown that while the absence of aggrecan from the extra cellular matrix does not significantly change the bulk T2 value of cartilage, it does lead to a broader distribution of T2 values (13). It is possible that senescent loss of proteoglycans contributes to the greater variability in cartilage T2 we observe in subjects older than 45 years of age.

There is strong evidence to indicate elevation in cartilage T2 is secondary to structural changes in the type II collagen matrix. With restricted water mobility, anisotropy of the collagen matrix provides an efficient mechanism for T2 relaxation, resulting in relatively short T2 times (25). Because of residual dipole interactions between collagen fibrils and cartilage water, cartilage T2 is very dependent on orientation of the collagen fiber matrix relative to the applied magnetic field (6, 9, 26, 27). Water located in highly anisotropic environments can be selectively detected using double quantum filtered spectroscopic imaging (28). In cartilage strong quadrapolar splitting resulting from this interaction is observed in the deep radial zone, with a smaller degree of splitting at the articular surface.
Several studies have demonstrated a strong inverse correlation of cartilage T2 with collagen fiber anisotropy identified with polarized light microscopy. Nieminen and coworkers demonstrated an inverse correlation between T2 and cartilage zones demonstrating optical birefringence (8). Xia et al have also established a strong inverse correlation between polarized light microscopy and spatially resolved cartilage T2 microscopy (6, 7, 29), and have shown that both techniques demonstrate similar changes during skeletal maturation (30). Grunder et al has shown that the regional T2 response of cartilage to compressive loading is strongly correlated with regional changes in collagen fiber orientation observed with polarized light microscopy (31). The strong dependency of cartilage T2 on the highly ordered structure of the collagen matrix makes cartilage T2 mapping a sensitive, non-invasive technique to study structural changes in the collagen matrix, providing information analogous to that provided with polarized light microscopy.

As has been demonstrated in prior in vivo cartilage T2 maps, we observe high T2 values near the bone cartilage interface (11). This zone is more difficult to interpret due to confounding artifact from volume averaging and chemical shift artifact. A similar zone of high T2 has been observed in several microimaging studies (8, 31-33). In a study comparing MRI microscopy T2 maps with polarized light microscopy, Nieminen et al demonstrated this zone corresponds to a region of cartilage with high chondrocyte density (8). It is possible that higher water content in the territorial matrix surrounding the chondrocyte results in relatively higher T2 values in this location.
Given the known dependency of cartilage T2 on anisotropy of the collagen matrix it is interesting to compare the similarity in location of T2 elevation with finding reported in prior animal and human histology studies. Several animal studies demonstrate loss of collagen fiber anisotropy of superficial cartilage in the earliest phase of cartilage damage, preceding gross fibrillation (34-36). Disorganization of the collagen matrix is observed early in canine femoral condylar cartilage following anterior cruciate ligament transaction (34). Using a canine valgus osteotomy model of slowly progressive OA, Panula and coworkers observed loss of superficial optical birefringence 7 months postoperatively, which occurred well before macroscopic changes of OA. Degeneration of superficial cartilage collagen is augmented with exercise. Long distance running leads to loss of superficial collagen fiber orientation in a dog model (35), and older guinea pigs (36). In a study evaluating collagen fibril structure in normal aging in humans, Hwang et al identified focal superficial fraying in the outer fibers of superficial cartilage in all individuals over 60 years of age (37). More recently immunohistologic studies demonstrate in both aging, and OA, early damage to type II collagen in the superficial and upper mid-zone, extending to the lower mid and deep zones of cartilage with increasing degeneration (38). These sites of collagen cleavage are correlated with sites of matrix metalloproteinase activity (39). Common to all of these studies is the observation that loss of collagen fiber anisotropy and early fiber degeneration begins near the articular surface. Results of this human in vivo study in which elevated T2 of superficial cartilage is observed in the 46 to 65 year old cohort, with full thickness elevation in T2 for individuals over age 65 is consistent with results of prior histology studies. The ability to monitor these changes noninvasively over time provides methodology to
identify important cofactors that may influence collagen denaturation. It is feasible to use these techniques with current clinical MRI scanners. Cartilage T2 mapping techniques such as those described in this study have been employed on 1.5T clinical scanners using standard clinical hardware, and relatively minor software modifications (40). Because of the high sensitivity to structural changes in type II collagen, cartilage T2 mapping may be a particularly useful technique in evaluating efficacy of therapy targeted toward inhibition of collagen breakdown such as matrix metalloproteinase inhibitors.

Results of this study cannot differentiate early degenerative changes of OA from normal cartilage aging. In fact the trend toward thinner cartilage, and greater prevalence of focal cartilage T2 lesions in the older populations suggests these individuals may have had gross preclinical cartilage damage. Because these studies were obtained in normal healthy volunteers it is not possible to directly correlate elevation in T2 with histological measures of cartilage collagen degradation. In future studies it would be useful to compare MRI T2 mapping results with immunohistology (39, 41), and biochemical serum markers (42) of type II collagen degradation and cleavage.

In conclusion, results of this study confirm preliminary findings of Mosher et al that after age 45 there is elevation in superficial patellar cartilage T2 (10). We have found in individuals over age 65 this elevation involves deeper layers of cartilage. Given the dependency of cartilage T2 on anisotropy of the type II collagen matrix, these findings suggest senescent changes of cartilage collagen begin near the articular surface, and progress to deeper cartilage with advancing age.
ACKNOWLEDGMENTS

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REFERENCES


TABLE 1: Demographic summary of study population (mean ± standard deviation)

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<th>46 to 65</th>
<th>66 to 86</th>
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TABLE 2: Subjective scoring of cartilage T2 maps

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<tr>
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FIGURE LEGENDS

FIGURE 1: Representative quantitative patellar cartilage T2 maps for the four cohorts. All groups demonstrated a similar spatial variation in cartilage T2 with longer values, shown in red and yellow, occurring near the articular surface. The T2 map of the 79 year old subject demonstrates relatively thin cartilage, with elevated T2 compared to T2 maps obtained from younger subjects.

FIGURE 2: Bulk cartilage T2 value as a function of age for subjects younger (●), and older (○) than 45 years of age. Fitting the data for the two groups to a single change-point linear regression model indicates a significant slope (p<0.05) after 45 and a non-significant slope (p>0.05) for younger subjects.

FIGURE 3: Cartilage thickness as a function of age. There is an inverse correlation of patellar cartilage thickness with age (r= -.51, 2-tailed p-value = 0.006).

FIGURE 4: Comparison of cartilage T2 profiles: (A) Mean cartilage T2 as a function of normalized distance from bone. All populations demonstrate spatial variation in cartilage T2 with longer values near the articular surface. Cartilage T2 profiles are similar for the two youngest cohorts. For the population age 46 to 65 years longer T2 values are present, particularly in superficial cartilage. In the oldest group longer T2 values are observed throughout the entire cartilage thickness. (B) p-values for t-test comparison of the older populations with age 18 to 30 year old group is presented as a function of normalized distance from bone. Horizontal line denotes the p=.05 value. There is no statistically significant difference in T2 between the two youngest groups. The T2 is
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