An Investigation Into the Efficacy of MRI T2 in an OA Population

by

Nicole Dray

Submitted to the Department of Electrical Engineering and Computer Science

in Partial Fulfillment of the Requirements for the Degrees of

Bachelor of Science in Electrical Engineering and Computer Science

and Master of Engineering in Electrical Engineering and Computer Science

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ABSTRACT

Several *in vitro* studies have shown that T2 is sensitive to some of the pathologic changes that occur in osteoarthritis (OA) such as hydration and the subsequent changes in macromolecular concentration, macromolecular structure, and tissue architecture. In this *in vivo* analysis, several techniques such as mean T2 and new techniques such as threshold analysis were used to determine if they could differentiate level of OA based on radiographic metrics such as the Kellgren/Lawrence scale (K/L) and Joint Space Grade (JSG) and delayed gadolinium-enhanced MRI of cartilage (dGEMRIC). In general, mean T2 in various regions of interest, normalized T2 as a function of distance from the bone, z score, comparison with dGEMRIC index, and threshold analysis were unable to differentiate between the level of OA or accurately represent important features in the images. In these OA images, the main features that appeared with disease were T2 mottling and both low and high lesions. Because of these heterogeneities in T2, none of the techniques presented in this investigation lead to conclusive results, and further work needs to be done for T2 to be diagnostic in an OA population.

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Purpose

The purpose of this investigation is to determine if MRI T2 can be effectively used to evaluate patients with osteoarthritis (OA). T2 is an important technique because it is sensitive to several constituents of cartilage including hydration, collagen, and the glycosaminoglycan (GAG). In OA, changes in the cartilage occur that result in changes in structure and concentration of water, collagen, and GAG. Because T2 is sensitive to these changes, it could give insight into structure, function, and pathophysiology of cartilage in OA. However, few studies have investigated T2 *in vivo.* This study will investigate the efficacy of T2 as a metric for clinical OA evaluation.

Introduction

Cartilage Composition and Structure

Cartilage is an important component of joints, as it distributes mechanical load and acts as a smooth surface over which the other components of the joint can move during activity. The main components of cartilage are collagen, water, mobile ions, proteoglycans, and some cells [1]. Glycosaminoglycan (GAG), which is part of a proteoglycan, carries a negative charge *in vivo.* GAG molecules tend to repel each other and therefore give cartilage much of its compressive strength [2]. Collagen consists of fibers that link to give cartilage its tensile strength. Using scanning electron microscopy, collagen structure has been analyzed in healthy cartilage. At the radial zone, the cartilage is oriented roughly perpendicular to the bone. In the intermediate zone, the collagen fibers are oriented in a somewhat random manner, and in the superficial zone, the fibers are almost parallel to the articular surface [1].

Osteoarthritis (OA)

Osteoarthritis (OA) is a debilitating disease that affects millions of people in the United States. OA is characterized by changes in the cartilage and articular cartilage degeneration itself. In the early stages of OA, collagen damage occurs in the form of denaturation and loss of the collagen fibrils [3]. In addition to the collagen degradation that occurs in OA, GAG concentration decreases [4]. These changes the cartilage matrix result in tissue that has a higher water content in OA patients than in healthy patients [5]. Sadly, once the patient presents with symptoms of OA and is properly diagnosed using radiography, the disease has often progressed to a severe state where treatment is extremely limited and joint replacement eventually becomes necessary for continued function of the joint.

Imaging Early OA

Therefore techniques are actively being developed to detect OA in its early stages in order to understand more about the disease and possible treatment options. The current techniques used for evaluation include arthroscopic surgery, x-ray, and magnetic resonance imaging (MRI). Because of the invasive nature of surgery, researchers strive to establish non-invasive techniques. X-ray techniques, including CT, are non-invasive, but they cannot give much information about soft tissues, like cartilage. In addition, they present unwanted radiation exposure to the patient [6]. Therefore, we direct our focus to MRI techniques to learn about the properties of articular cartilage.

Grading OA

There are a few currently used techniques for grading OA using both radiography and MR. One of these schemes is the Kellgren/Lawrence scale, which uses radiography to detect the presence of osteophytes and joint space narrowing. The Kellgren/Lawrence (K/L) scale has five grades: 0, 1, 2, 3, and 4, where the higher the grade, the more severely diseased the joint is considered to be. In K/L 0, there are no osteophytes. If the presence of osteophytes is doubtful, then the joint is graded with K/L 1. In K/L 2, there are minimal osteophytes, and there may be some joint narrowing, cysts or sclerosis. A joint with K/L 3 is characterized as having moderate or definite osteophytes with joint space narrowing. A K/L 4 joint has large, definite osteophytes with severe joint space narrowing.

Another radiographic technique to grade the progression of OA is the Joint Space Grade (JSG). Joint Space Grade has four grades: 0, 1, 2, and 3. Similar to the case of the K/L, the higher number represents the more disease progression based on narrowing of the joint.

Several MR techniques have been validated in grading the progression of OA. MRI analysis of cartilage morphometry is a technique that accurately calculates cartilage volume and thickness. In this technique [7], high resolution MR images are obtained and used to calculate cartilage volume and thickness. Over time, this technique can be used to quantitatively monitor changes in cartilage that occur with increasing disease severity. While MRI analysis of cartilage morphometry gives insight into cartilage morphology, it

does not represent the underlying physiology. For that, other MR techniques such as sodium imaging, diffusion imaging, and diffusion tensor imaging have been developed to probe the different components of cartilage: proteoglycans, collagen, and water. Sodium MR imaging has been shown to be sensitive to proteoglycan depletion *in vivo* [8]. Diffusion weighted imaging [9] and diffusion tensor imaging [10] have been shown to be sensitive to collagen in cartilage.

A promising technique using MR to analyze cartilage physiology called dGEMRIC has been developed to visualize GAG concentration in joint cartilage. dGEMRIC (delayed gadolinium-enhanced MRI of cartilage) uses the negatively charged contrast agent Gd-$DTPA^{2-}$ as a measure of fixed charge density in the cartilage, which is caused by GAG concentration [11]. In this technique, the patient is administered the contrast agent and T1 weighted imaging is performed. The charge on the Gd-$DTPA^{2-}$ causes it to be excluded from areas with high GAG concentration (and hence a high area of negative charge). Therefore, on the dGEMRIC images, areas with high T1 are those with low GAG and vice versa. The GAG concentration can then be quantified using an equation that yields the approximate fixed charge density.

Background Information

MRI

When a patient is placed in the MRI scanner, he is subjected to an external magnetic field (B0). The protons in the body align themselves either parallel to the magnetic field or anti-parallel to it. These parallel and anti-parallel protons cancel each other's net magnetization. However, more protons will take the parallel orientation because it is the

lower energy state, and there will therefore be a net magnetization of the patient in the direction of B0. Protons precess (rotate) around the field lines of B0. This new magnetic field within the patient does not give us any information because magnetization longitudinal to B0 cannot be measured directly. In order to make appropriate measurements, the magnetization must be transversal to B0. Therefore, a radio frequency pulse is used to perturb the spins resulting in a decrease in the longitudinal magnetization and an increase in the transversal magnetization of the precessing protons. We can then measure the amount of time it takes for the longitudinal magnetization to return to its original value and for its transversal magnetization to do the same. Two very important parameters are gained from these measurements: T1 is the longitudinal relaxation time constant, and T2 is the transversal relaxation time constant. T1 and T2 are important because they are determined by interactions between water and the macromolecules that make up cartilage such as GAG and collagen. T2, in particular, is very sensitive to hydration. Because the water content tends to increase in diseased cartilage, T2 can be used to visualize abnormalities because the increased water mobility in the tissue will result in a longer T2 [12]. However, this sensitivity to hydration does have a few drawbacks. The fact that T2 is so sensitive to water means that it will be highly variable if the water content should change. This water content, in itself, is highly variable and will be noticeably different after periods of activity. In addition, because T2 is a measure of water's interaction with GAG and collagen (among other macromolecules,) T2 will also vary upon the GAG concentration, collagen concentration, and collagen structure. To further complicate T2, it has shown dependence on orientation. This dependence is called the "magic angle effect." When collagen fibers that make up the cartilage are

oriented 55° relative to B0, dipolar interactions between water molecules and the collagen fibers decrease. When this T2 relaxation mechanism decreases, it results in longer measured T2 values [13]. Therefore, in situations like a sagittal image of the knee, the cartilage around the femoral condyle has several different orientations relative to B0. Attention must be paid to those regions of interest (ROIs) where the cartilage may be oriented 55° relative to it to avoid complicating factors caused by the magic angle effect.

Previous Studies

Previous in vitro T2 studies

Prior *in vitro* studies on T2 have investigated its properties in healthy cartilage and have shown its dependency upon various factors. Histology is the gold standard method of analysis for cartilage quality. One study [14], examined cartilage using both T2 and histology, and they found a good correlation between the appearance of the T2 image and the histological and biochemical structure of the cartilage. With this knowledge that there is physical data that can be acquired from T2, other studies were performed that looked into other aspects of cartilage T2.

A well documented phenomenon of T2 in cartilage is its laminar appearance [14]. Lower T2s are usually seen in the area closest to the bone surface, and higher T2s are observed at the articular surface. It is hypothesized that the variation observed in T2 across the cartilage depth reflects the variation in collagen structure and orientation [1].

In addition to this dependence of T2 across cartilage depth, there is a dependence of T2 on its orientation in the scanner known as the magic angle effect. Ex vivo studies have

documented this angular dependence [15, 16]. At 55 degrees relative to the magnetic field, T2 is longer and the original difference between the T2 values across cartilage depth decreases, thus making the cartilage T2 appear more homogeneous.

One study [17] looked at T2 in healthy cartilage, GAG depleted cartilage, and cartilage with both GAG and collagen depleted. This study noted that T2 decreases as the concentration of GAG and collagen increase in the superficial cartilage, with collagen dominating this effect. Collagen is dominant because it is more abundant in tissue. No change was observed in the deep cartilage T2. T2 was also measured in suspensions with the same GAG and collagen concentrations as the cartilage. From this it was concluded that the matrix itself does not significantly alter T2, but changes in other factors like collagen concentration greatly alter T2.

With this established, other *in vitro* studies have looked at T2 in healthy and diseased groups. Data indicates that T2 values tend to increase with the progression of OA with T2 generally higher in moderate OA than very mild OA or normal [18, 19]. In one study, the spatial pattern on T2 demonstrated a mottled appearance when collagen disruption was present. T2 lesions were seen that did not correlate to GAG concentration or collagen orientation [17]. This shows that T2 is indeed sensitive to other factors that may include hydration or molecular-level variations.

Previous in vivo T2 studies

Many in vivo studies have supported the data obtained in vitro. The sensitivity of T2 to hydration was observed in a T2 study that examined the cartilage shortly after exercise

(when the cartilage was compressed and the water content low) and after recovery. This study showed that because T2 is sensitive to hydration *in vivo* that it can be used as an analytical tool [20].

The laminar appearance of T2 has been found *in vivo* as well by examining the "uncovered, weight-bearing cartilage" of the knee. In this region, the cartilage is oriented roughly parallel to B0 and therefore, magic angle effects were not a complicating factor. Using normalized distance from the bone to articular surface, it was found that he found that T2 increased toward the articular surface in normal, asymptomatic individuals [21].

The existence of the magic angle effect has also been shown *in vivo*, but one study indicates that the magic angle effect does not seem to be as strong in vivo as it was hypothesized from in vitro experiments [13]. Using the same method of normalized distance from the bone as previously described, the *in vivo* data showed much less sensitivity to the magic angle effect than prior *in vitro* studies. It is hypothesized that the difference between the posterior femoral cartilage and other compartments of the femoral condyle is based more on function than on orientation. The femoral posterior cartilage is oriented 55 degrees from the external magnetic field, however, it is also non-weight bearing cartilage, and as a result, it is less compressed and contains more water in the most superficial 20% of the cartilage thickness than in weight-bearing cartilage.

Other *in vivo* studies have examined T2 as it varies with age, gender, and disease. OA generally occurs in older individuals and is found more often in women [22]. One study

examined T2 maps using the normalized distance technique on young, asymptomatic men and women. It was determined that there is no difference in spatial dependency of T2 in men vs. women [23]. Therefore, gender is not a complicating factor in examining T2.

Mosher et al showed that age, is indeed a complicating factor in T2 because T2 tends to increase with age even if symptoms do not appear [24]. This study was conducted by taking T2 maps of the patellofemoral joints of 25 asymptomatic and 6 symptomatic volunteers. Line profiles were generated for T2 as it varies from the bone to the articular surface, and 95% prediction intervals were generated based on the data from the asymptomatic patients. The 95% prediction interval is defined to be the "the T2 range for a given normalized distance where there is a 95% probability that the next measured T2 will occur." The images for the symptomatic patients were visually inspected for focal lesions and normalized line profiles were made through those lesions. A minimum patellar cartilage thickness of 3mm was used. The 95% prediction interval was calculated from the age-matched asymptomatic group. Lesions were then categorized as abnormal if three adjacent T2 values on the interpolated T2 map were outside the 95% prediction interval for the asymptomatic patients of that age group. The symptomatic patients were then categorized into three pattern groups based on the T2 pattern observed. Five out of the six symptomatic volunteers had a statistically significant focal T2 increase, and these cases typically involved this increased T2 in the radial zone, which the authors could not detect in the asymptomatic cohorts.

Dunn et al [25] performed a study on 7 healthy patients, 20 with mild OA, and 28 with severe OA. The Kellgren/Lawrence grading system was used to assess the severity of OA. Healthy patients were those having K/L 0, patients with mild OA were those with a K/L of 1 or 2, and patients with severe OA were those having K/L 3 or 4. In this experiment, the knee cartilage was segmented into four compartments, which included the medial femoral, lateral femoral, medial tibial, and lateral tibial cartilage. The cartilage thickness ranged from 0.4 to 6.0 mm, which corresponds to 2-30 pixels. After the cartilage had been segmented, the images underwent statistical analysis to determine the variance of T2 between age groups and gender and adjusted for age only. T2 values greater than 200 msec were excluded, and the mean T2 was calculated for each group. The per-pixel and per-compartment z scores were calculated using the T2 mean and standard deviation for healthy patients according to the following equation:

$$\text{z score} = \frac{(\text{Voxel}_i - \text{Mean}_{\text{healthy}})}{\text{SD}_{\text{healthy}}}$$

The z score was found pixel-by-pixel and each OA patient's cartilage compartment was compared to the healthy patients. Z score maps were generated using a MATLAB program. It was determined that the average z score per compartment in each compartment except the lateral tibia was at least 2 ms greater in OA patients than in healthy patients. This paper makes some interesting suggestions. First, it states that changes in cartilage that lead to observed changes in T2 happen in early OA, and therefore we do not observe a difference in T2 between mild and severe OA. In addition, K/L may not be the best grading system because it is dependent upon the presence of osteophytes, which should not affect T2, and K/L is dependent upon changes in bulk

cartilage, which may only reflect progression of disease after it has surpassed the point of T2 sensitivity (ie. OA).

Shortcomings of Previously Used Analytical Schemes

Studies performed to date using T2 techniques do not adequately represent the data obtained from an OA patient population. The normalized distance technique has advantages because it acknowledges the inherent change of T2 over cartilage depth and attempts to account for it by normalizing distance from the bone. This scheme works very well for patients with full-thickness cartilage, but often in OA patients, there is very little cartilage thickness due to degradation. In more severe cases of osteoarthritis, the cartilage can be so thin that the clinical resolution used would not be fine enough to get the necessary number of data points across the depth. Figure 1 shows an example of an OA knee with cartilage of variable thickness. In this knee, the anterior and central femoral compartments show evidence of cartilage thinning, with extreme thinning in the central femoral condyle. Here, we cannot use normalized distance because the cartilage is so thin. We cannot accurately compare the thin osteoarthritic cartilage found in Figure 1 with that of a healthy patient because the composition of the osteoarthritic cartilage has not been quantified.

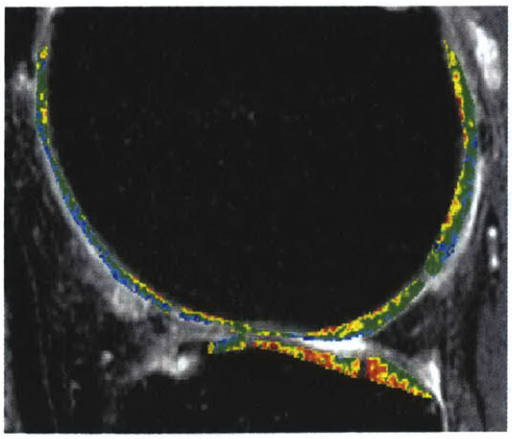


Figure 1: An example of an OA patient with cartilage of variable thickness. (DE269lat)

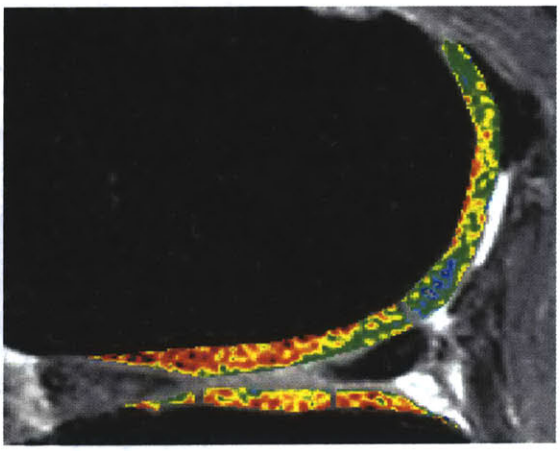


Figure 2: An OA patient with both high and low lesions in the lateral femoral condyle. (GM204 lat).

Another analysis scheme that would not meet the needs of our patient population is the z score technique used to analyze healthy and diseased cartilage. This occurs because averages are compared over such a large portion of cartilage, significant data can be lost. For example, if we analyze Figure 2, there is an area of low T2 (red) in the central and posterior tibial compartments. Looking in the more posterior end of the posterior tibial compartment, there is an area of high T2 (blue). If we were to use this technique on this section of cartilage, the low lesion would give a low z score, and the high lesion would give a high z score. However, the z scores would then be averaged over the entire compartment, and would likely cancel each other's effects. Therefore, this technique may give insufficient results in an OA population. Dunn et al. suggest that analyzing T2 in weight bearing regions designated by the margin of the meniscus may be helpful, but they did not do that in their experiment because some patients in their study had severe meniscal damage, and therefore they were unable to locate it on images.

Methods

Data Acquisition

For most of the techniques tested, data was obtained from the MAK study. The study, Mechanical Factors in Arthritis of the Knee (MAK), is a joint study of OA in the knee led by Dr. Leena Sharma at Northwestern University, and it tracks the progression of OA in patients previously documented with the disease. In addition to other tests, such as blood serum testing, mechanical and radiographic tests were performed to determine varus/valgus alignment, laxity, proprioception and strength, joint space narrowing, and K/L grade. dGEMRIC imaging was also performed on the patients to visualize GAG in the cartilage by administering a double dose of the contrast agent Gd-DTPA^{2-} based on the patient's weight and then taking T1 images. T2 images were also taken at this time at 1.5T after the Gd-DTPA^{2-} administration. T2 has previously been shown to not be affected by Gd-DTPA with clinical doses [26]. The MAK MRI data is from 28 patients total, yielding 56 lateral and medial images. However, in two of the patients, there was no cartilage in the medial compartment, thus limiting the study to 54 images, 28 lateral and 26 medial. The scanning of the patients was performed at several different times, and in the beginning of the study, T2 data was not obtained. When 7 of the first patients who had initially been scanned without T2 returned for follow up visits, T2 and dGEMRIC were taken, but the radiographic testing was not repeated. Therefore, when comparing the images to radiographic data such as K/L or JSG, these 7 patients are excluded yielding 40 lateral and medial images, 21 lateral and 19 medial. The images were taken at 1.5T with a TR/TE of 3500/19 and 65. The FOV was 14 cm, and the matrix was 256x256, yielding a resolution of 547 μm and a thickness of 3 mm. The

256x256 matrix in-plane matrix was zero-fill interpolated in k-space to a 512x512 matrix. Sagittal images were taken of the patellofemoral joint through both the lateral and medical condyles of the knee. These images were then transferred to the BIDMC for image analysis.

Preliminary Image Analysis

T1 and T2 maps of the tibiofemoral condyle after the administration of the gadolinium contrast agent (T1(Gd) and T2(Gd), respectively) were generated with a fit routine using Matlab (TheMathWorks, MA). For each patient, the three most central images of both the lateral and medial condyles were examined for the following qualities: the most easily identifiable cartilage, interesting lesions or abnormalities, and the best T2 fit and map. The best image was chosen and manually segmented into six smaller compartments using the anterior and posterior edges of the menisci. The femoral condyle was segmented into anterior, central, and posterior compartments, with the line between the central and anterior compartments originating at the anterior edge of the anterior meniscus, and similarly, the central and posterior compartments were separated with a line originating from the posterior edge of the posterior meniscus. The tibial condyle was segmented into anterior, central, and posterior compartments, with the line between the central and anterior compartments originating at the posterior edge of the anterior meniscus. A line originating at the anterior edge of the posterior meniscus separated the central and posterior compartments of the tibial condyle. The limits for the T2 map were set to be 10 ms to 80 ms because it was hypothesized that values outside this range could likely be due to partial voluming with bone or fluid.

For each compartment, the average T2, average dGEMRIC, standard deviation of T2, standard deviation of dGEMRIC, and percentage of pixels above or below a chosen threshold value were calculated. The central femoral compartment was the main compartment used in most of the analysis techniques because it is weight-bearing cartilage, and the potential complication of the magic angle effect could be avoided. Figure 3 shows an example of the segmented central femoral compartment.

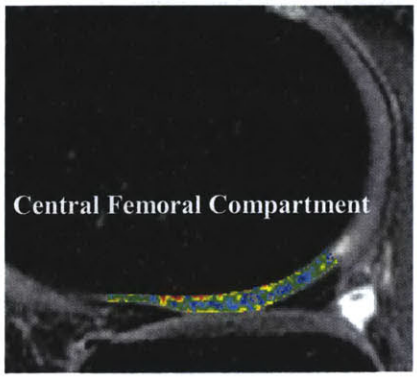


Figure 3: The highlighted compartment is the central femoral compartment as defined by the outer edges of the menisci. This was the primary region on analysis for this study.

Statistical analysis was performed using Microsoft Excel. To determine if a given dataset was significantly different, an F test was performed on two of the samples to determine if they had equal or unequal variance. If the P value produced by this test were less than 0.05, a t-test for unequal variances was performed on the two samples to give the reported two-tailed p value. If the F test P value were greater than 0.05, a t-test for equal variances was performed to give the reported two-tailed p value. Data was considered to be statistically significant if the two-tailed p value from the t-test was less than 0.05.

T2 Analysis Techniques I: Previously Used Techniques on MAK Dataset

Mean T2 of Lateral Femoral and Medial Femoral Compartments

Most of the previously listed techniques take an average of T2 over a given ROI and compare it to other samples. This technique was also used on this dataset using the previously mentioned method.

Results of Mean T2 of Lateral Femoral and Medial Femoral Compartments

Figure 4 shows a graph of the mean T2 for the lateral femoral compartment versus K/L, and figure 5 shows a graph of the mean T2 for the lateral femoral compartment vs. JSG. Figures 6 and 7 show the T2 average for the medial femoral compartment versus K/L and JSG, respectively. This experiment uses the same ROIs as defined by Dunn [25]. In figures 4-7, the diamonds represent each individual data point, while the bar represents the average for that K/L or JSG value.

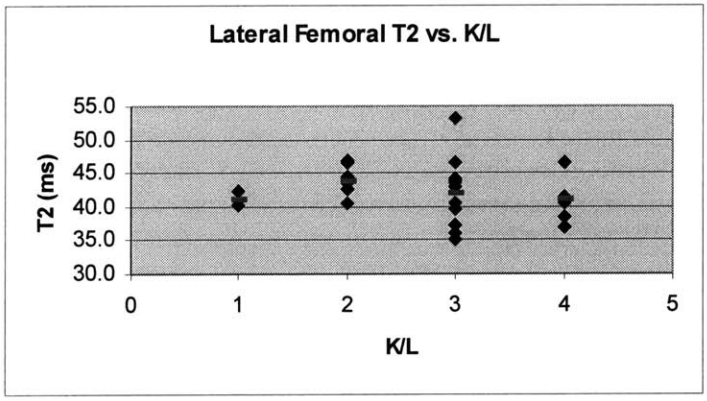


Figure 4: Average T2 for the lateral femoral compartment by K/L grade.

The following table shows the statistics performed on the lateral femoral T2 by K/L. Table 1 shows the results of this statistical study. Each lateral femoral T2 mean for each K/L grade was compared against the lateral femoral T2 mean for each other K/L grade. The column labeled n gives the number of lateral femoral samples with that K/L, and the mean column gives the mean lateral femoral T2 for that K/L grade. The last column,

gives the two-tailed p value for the comparison between the lateral femoral mean T2 of K/L A versus K/L B. From Table 1, it can be seen that mean lateral femoral T2 has a statistically significant increase of 3.0 ms from K/L 1 to K/L 2 and a statistically significant decrease in mean lateral femoral T2 of 3.7 ms from K/L 2 to K/L 3. No other statistically significant relationships were found between lateral femoral T2 by K/L grade.

K/L A	n A	Mean T2 A	K/L B	n B	Mean T2 B	p value
1	2	41.4	**2**	8	44.4	0.046
1	2	41.4	**3**	8	40.7	0.851
1	2	41.4	**4**	3	45.0	0.233
2	8	44.4	**3**	8	40.7	0.047
2	8	44.4	**4**	3	45.0	0.688
3	8	40.7	**4**	3	45.0	0.148

Table 1: This table shows the number, and mean for each K/L grade and the p value obtained when comparing the lateral femoral T2 means of K/L grade A to K/L grade B.

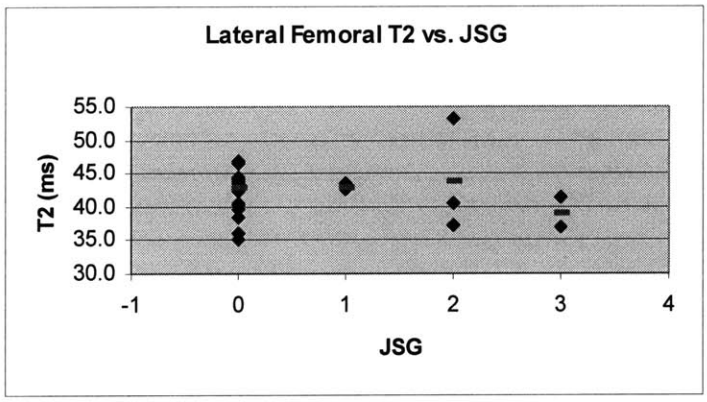


Figure 5: Average T2 for the lateral femoral compartment by JSG.

Table 2 shows the statistical analysis performed on the mean T2 of the lateral femoral compartment by joint space grade. In this analysis, there were no significantly different lateral femoral T2 means by JSG because no t-tests yielded a p value less than 0.05. In addition, comparisons to JSG 3 could not be made because there was only 1 lateral image with this joint space grade.

JSG A	n A	Mean T2 A	JSG B	n B	Mean T2 B	p value
0	16	43.4	**1**	2	43.1	0.903
0	16	43.4	**2**	2	38.9	0.109
0	16	43.4	**3**	1	41.1	N/A
1	2	43.1	**2**	2	38.9	0.146
1	2	43.1	**3**	1	41.4	N/A
2	2	38.9	**3**	1	41.4	N/A

Table 2: This table shows the number, and mean for each joint space grade and the p value obtained when comparing the lateral femoral T2 means of JSG A to JSG B.

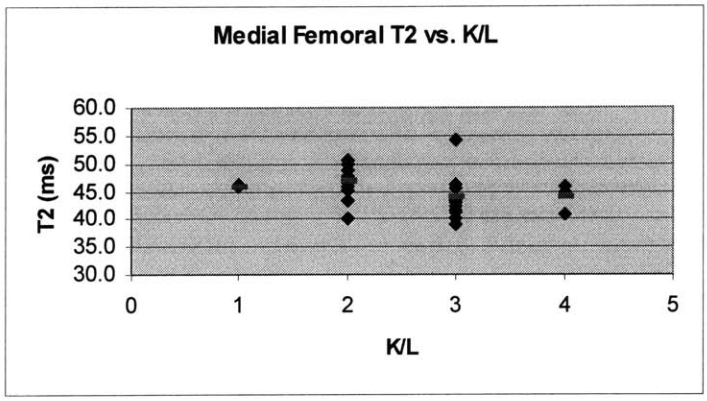


Figure 6: Average T2 for the medial femoral compartment by K/L grade.

Table 3 shows the results of the statistical analysis performed on the mean T2 of the medial femoral compartment by K/L grade. In this analysis, there were no significantly different medial femoral T2 means by K/L. In addition, no comparisons to K/L 4 could be made because there was only 1 medial image with K/L 4.

K/L A	n A	Mean T2 A	K/L B	n B	Mean T2 B	p value
1	2	46.1	**2**	8	46.3	0.915
1	2	46.1	**3**	8	43.2	0.161
1	2	46.1	**4**	1	46.0	N/A
2	8	46.3	**3**	8	43.2	0.057
2	8	46.3	**4**	1	46.0	N/A
3	8	43.2	**4**	1	46.0	N/A

Table 3: This table shows the number, and mean for each K/L grade and the p value obtained when comparing the medial femoral T2 means of K/L grade A to K/L grade B.

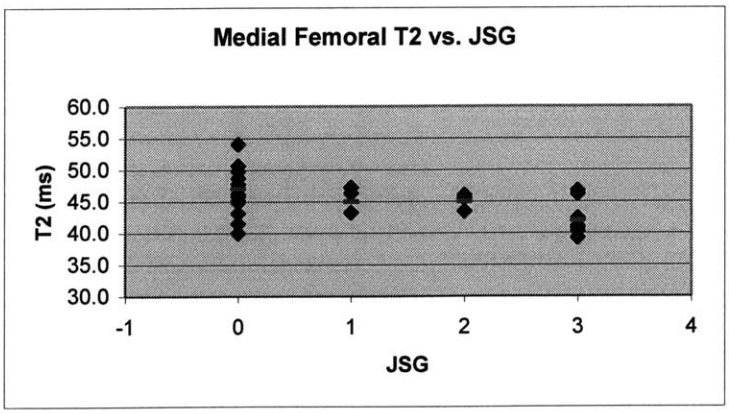


Figure 7: Average T2 for the medial femoral compartment by JSG.

Table 4 shows the results of the statistical analysis performed on the mean T2 of the medial femoral compartment by joint space grade. No significant differences were found between the mean medial femoral T2 by JSG.

JSG A	n A	Mean T2 A	JSG B	n B	Mean T2 B	p value
0	11	45.8	**1**	2	44.8	0.673
0	11	45.8	**2**	2	45.8	0.978
0	11	45.8	**3**	4	42.3	0.079
1	2	44.8	**2**	2	45.8	0.589
1	2	44.8	**3**	4	42.3	0.349
2	2	45.8	**3**	4	42.3	0.181

Table 4: This table shows the number, and mean for each joint space grade and the p value obtained when comparing the medial femoral T2 means of JSG A to JSG B.

To compare this dataset in the same way as Dunn [25], the K/L comparison was repeated in the mean lateral femoral T2. Dunn et al defined OA severity as mild (K/L 1 or 2) or severe (K/L 3 or 4). When the mean lateral femoral T2 values were pooled into mild OA and severe OA categories, the statistical analysis was repeated again to determine if there was a significant difference between the two. The p value between the mean lateral femoral T2 for mild OA and that for severe OA was 0.206, which is not statistically significant.

Discussion of Mean T2 of Lateral Femoral and Medial Femoral Compartments

The only t-tests that yielded statistically significant p values were the comparisons between the mean lateral femoral T2 of K/L 1 to that of K/L 2 and the comparison between the mean lateral femoral T2 of K/L 2 to that of K/L 3. The test between K/L 1 and K/L 2 showed an increase in T2 with disease, and the test between K/L 2 and K/L 3 showed a decrease with disease. However, when this data was pooled into mild OA and severe OA categories, the mean lateral femoral T2 was no longer significantly different. These results are consistent with Dunn's findings, which indicate that mean T2 does not differentiate between severities of OA. While the findings based on K/L grade alone may seem interesting, the number of samples is small (at most 8 for K/L 2 and 3) and the means are still too close to be clinically useful. For example, the image found in Figure 2 has a mean lateral femoral T2 of 35.1 ms, which puts it as the point with the lowest average T2 value for both its K/L (3) and JSG (0) values. In this case, the high lesion that we observe in the posterior femoral compartment cannot be detected because the large low lesion in the central femoral compartment has negated its appearance in the mean. There are other problems with this technique. A set of images may have the same average for a given compartment, but there are important features of the image, which cannot be detected using the average T2. Figures 8 and 9 show lateral images with T2 averages in the lateral femoral compartment that only differ by 1.1 ms (the actual averages are 40.3 and 41.4, respectively). From these images, it can be seen that the image in Figure 9 has a low lesion that is masked, whereas the image in Figure 8 shows the normal laminar T2 pattern.

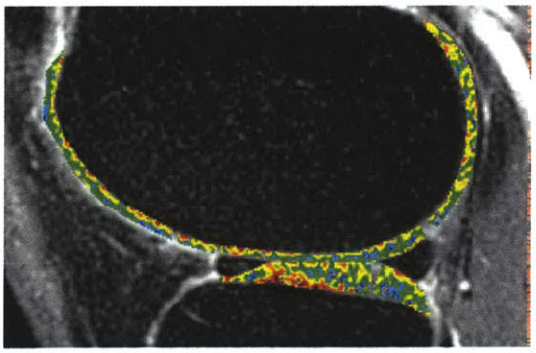


Figure 8: Lateral image with average femoral T2 40.3 ms. This image exhibits a normal, laminar pattern.

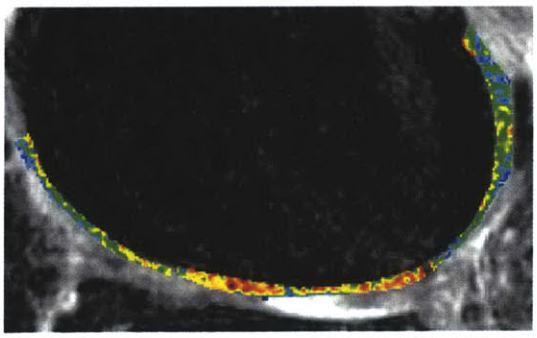


Figure 9: Lateral image with average femoral T2 of 41.4 ms. This image has a low lesion in the central femoral compartment.

Mean T2 of Central Femoral Compartment

As previously stated, the bulk of this research focused on the central femoral compartment because it is weight-bearing cartilage that is not as susceptible to magic angle effects. The mean T2 of this ROI was calculated using the previously mentioned method. In addition, the mean of the lateral and medial femoral condyles proved to be too large of an ROI over which to take the mean. Therefore, a smaller ROI was used to see if it would produce significant results.

Results of Mean T2 of Central Femoral Compartment

To determine if mean central femoral T2 could differentiate based on OA severity, the central femoral T2 means for all of the images with proper radiographic data were plotted against K/L and JSG. Figures 10 and 11 show central femoral T2 for the MAK patients as a function of K/L and JSG with the averages for each grade shown as a bar. As can be seen from these graphs, there was no clear separation based on these values alone.

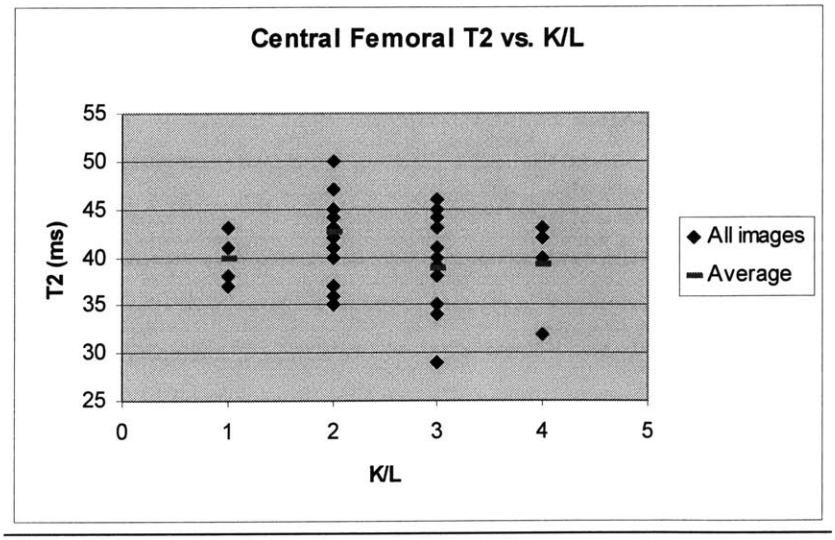


Figure 10: Central Femoral T2 vs. K/L for MAK images.

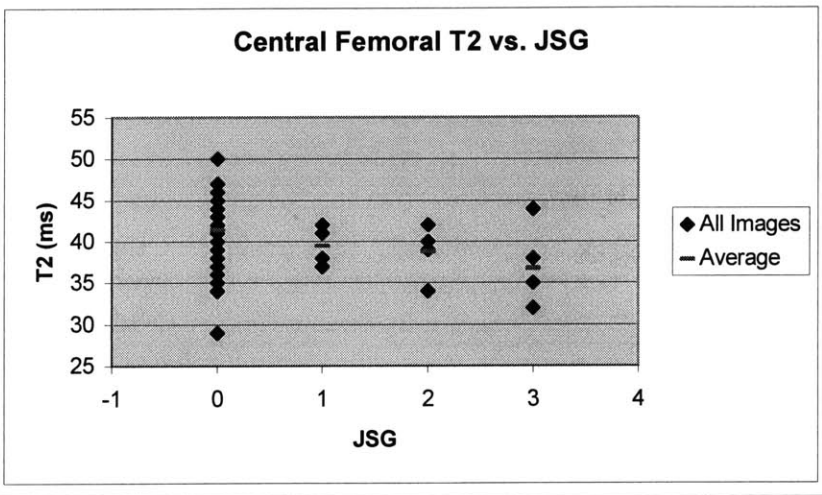


Figure 11: Central Femoral T2 vs. JSG for MAK images.

The following table summarizes the results using this technique. The first column gives the K/L or Joint Space Grade, the second column gives the number of images with that K/L or JSG, the third column gives the average central femoral T2 for all of the images with that grade, the fourth column gives the lowest T2 for that grade, and the last column gives the highest central femoral T2 value for that grade.

K/L	n	Average T2	Low T2	High T2
1	4	39.8	37	43
2	16	42.6	35	50
3	16	38.8	29	46
4	4	39.3	32	43

JSG	n	Average T2	Low T2	High T2
0	27	41.5	29	50
1	4	39.5	37	42
2	4	38.8	34	42
3	5	36.8	32	44

Table 5: Summary of central femoral T2 versus K/L and JSG.

One observation from these graphs is that the average T2 tends to decrease with disease. In order to determine if this decrease is statistically significant, F-tests were performed, followed by t-tests to determine if the resulting two-tailed p value was less than 0.05. Table 6 summarizes the statistical analysis results by K/L, and Table 7 summarizes the statistical analysis results by JSG.

K/L A	n A	Mean T2 A	K/L B	n B	Mean T2 B	p value
1	4	39.8	**2**	16	42.6	0.227
1	4	39.8	**3**	16	38.8	0.685
1	4	39.8	**4**	4	39.3	0.867
2	16	42.6	**3**	16	38.8	0.021
2	16	42.6	**4**	4	39.3	0.191
3	16	38.8	**4**	4	39.3	0.850

Table 6: This table shows the number, and mean for each K/L grade and the p value obtained when comparing the central femoral T2 means of K/L grade A to K/L grade B.

JSG A	n A	Mean T2 A	JSG B	n B	Mean T2 B	p value
0	27	41.5	**1**	4	39.5	0.414
0	27	41.5	**2**	4	38.8	0.270
0	27	41.5	**3**	5	36.8	0.041
1	4	39.5	**2**	4	38.8	0.730
1	4	39.5	**3**	5	36.8	0.322
2	4	38.8	**3**	5	36.8	0.501

Table 7: This table shows the number, and mean for each joint space grade and the p value obtained when comparing the central femoral T2 means of JSG A to JSG B.

From Table 6, the only statistically significant change in mean central femoral T2 with K/L grade was a decrease in mean T2 by approximately 3.8 ms from K/L 2 to K/L 3. Similarly, from Table 7 we see that there was a significant decrease by approximately 4.7 ms from JSG 0 to JSG 3. This was the only significant change in mean central femoral T2 by JSG.

To determine if there could be a relationship between change in T2 and OA severity based on whether the involved or uninvolved compartments were analyzed, the data was separated and then compared. Involved compartments were defined as having a JSG of 1 or greater, and uninvolved compartments were those with JSG 0. Figure 12 shows a scatter plot of the central femoral T2 means versus K/L with the blue diamonds representing the central femoral T2 means of uninvolved compartments and the pink bars representing the central femoral T2 means of involved compartments.

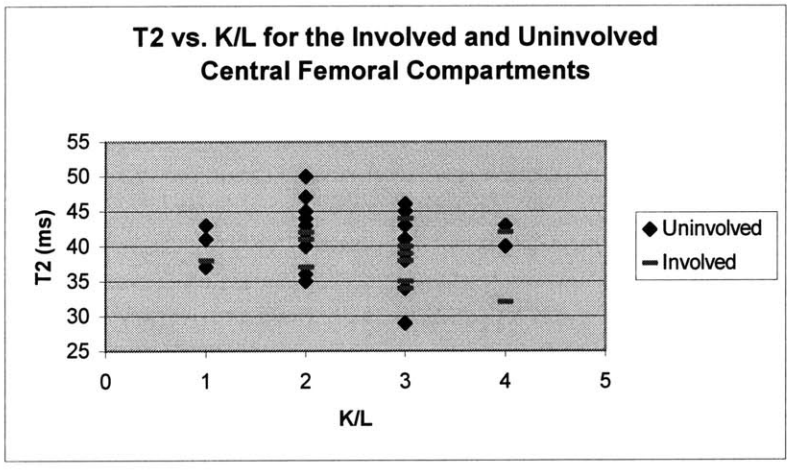


Figure 12: Central Femoral T2 means versus K/L for the uninvolved (diamond) and the involved (bar) compartments.

Initially, the uninvolved and involved compartments were analyzed separately by K/L grade to determine if there were any statistically significant mean central femoral T2

differences. In the uninvolved compartments, no significant relationships were found when the central femoral means were compared against each other K/L grade. Table 8 shows the results of the statistical analysis performed on the uninvolved compartments when comparing each K/L grade to the others. In this table, the K/L U columns represent the K/L grade for the uninvolved compartments.

K/L U A	n A	Mean T2 A	K/L U B	n B	Mean T2 B	p value
1	3	40.3	**2**	13	43.2	0.314
1	3	40.3	**3**	9	39.4	0.795
1	3	40.3	**4**	2	41.5	0.677
2	13	43.2	**3**	9	39.4	0.090
2	13	43.2	**4**	2	41.5	0.617
3	9	39.4	**4**	2	41.5	0.619

Table 8: This table shows the number, and mean for each K/L grade and the p value obtained when comparing the central femoral T2 means of K/L grade A to K/L grade B for the uninvolved compartments only.

The same analysis was performed on the involved compartments only, and similar to the uninvolved compartments, no statistically significant relationships for mean central femoral T2 were found between K/L grades. Table 9 shows the results of this analysis, where the K/L I columns represent the K/L grade for the involved compartments. A p value could not be obtained for comparisons between K/L 1 because there was only one image for which the JSG was greater than zero and the K/L was equal to one.

K/L I A	n A	Mean T2 A	K/L I B	n B	Mean T2 B	p value
1	1	38.0	**2**	3	40.0	N/A
1	1	38.0	**3**	7	37.9	N/A
1	1	38.0	**4**	2	37.0	N/A
2	3	40.0	**3**	7	37.9	0.379
2	3	40.0	**4**	2	37.0	0.528
3	7	37.9	**4**	2	37.0	0.807

Table 9: This table shows the number, and mean for each K/L grade and the p value obtained when comparing the central femoral T2 means of K/L grade A to K/L grade B for the involved compartments only.

The final analysis that was performed on uninvolved and involved compartments was a comparison between the central femoral T2 means of each uninvolved compartment with a given K/L grade and the involved compartment of that K/L grade (ie. K/L 1 uninvolved was compared with K/L 1 involved.) Table 10 shows the results of this analysis, and as we see from the resulting p values, no statistically significant results were obtained. Therefore, mean central femoral T2 did not differentiate between involved and uninvolved compartments based on K/L.

K/L Uninvolved	n	Mean T2	K/L Involved	n	Mean T2	p value
1	3	40.3	**1**	1	38.0	N/A
2	13	43.2	**2**	3	40.0	0.258
3	9	39.4	**3**	7	37.9	0.511
4	2	41.5	**4**	2	37.0	0.480

Table 10: This table shows the number, and mean for each uninvolved K/L grade and each involved K/L grade. The p value shown was obtained when comparing the involved central femoral T2 means of each K/L to the uninvolved central femoral T means of the same K/L grade.

Discussion of Mean T2 of Central Femoral Compartment

In all of the analyses of mean central femoral T2, only two instances yielded significant results. These were a decrease in mean central femoral T2 by 3.8 ms from K/L 2 to K/L 3 and a decrease in mean central femoral T2 by 4.7 ms from JSG 0 to JSG 3. These small differences in mean central femoral T2 would likely not be useful when trying to devise a scheme to analyze clinical data. The fact remains that the numbers produced are too similar to adequately reflect the differences observed in the images. Even images that are very different in appearance and radiographic score can have similar central femoral T2 means.

The following images are examples of information loss that can occur even when a smaller ROI like the central femoral compartment is used to obtain a T2 mean. Figures 13 and 14 show two MAK images with average central femoral T2 values that differ by 1.1 ms (35.9 and 34.8 ms, respectively.) The central femoral compartments of these images are very different in appearance. Figure 14 exhibits the normal, laminar T2 pattern, while Figure 13 has low T2 mottling that extends outward toward the articular surface. However, because the T2 averages for the central femoral compartments are so close, it is unlikely that these numbers would reflect the differences that can be observed visually.

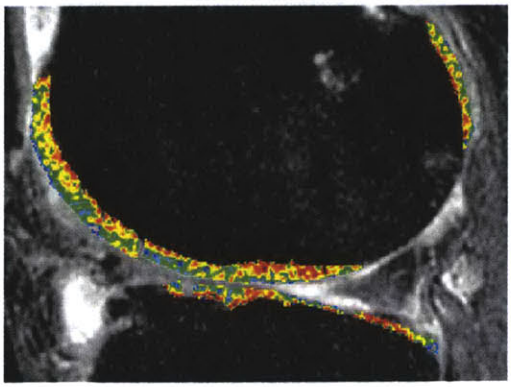


Figure 13: MAK image with average central femoral T2 35.9 ms. This image shows a low T2 area that is not limited to the radial zone. (PZ153 lat)

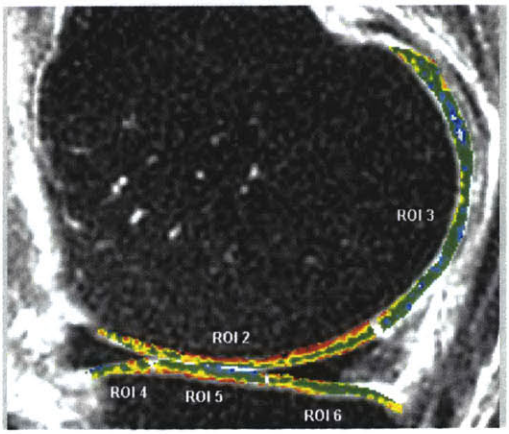


Figure 14: MAK image with average central femoral T2 34.8 ms. This image has a normal, laminar appearance. (RW290 med)

One trend that can be noted from these results is that mean central femoral T2 tends to decrease with increasing K/L. This is not in accordance with the results of previous studies, which have measured an increase in T2 with increased diseased state measured in K/L. In most of the more diseased knees, the T2 images showed low T2 lesions in the central femoral compartment or low T2 mottling, which decreased the average T2 for that compartment.

Mean T2 of Posterior Femoral Compartment

It was originally hypothesized that the observed decrease of mean central femoral T2 could be due to the ROI used because much of the literature reports an increase in T2 with disease. Therefore, the T2 averages for the posterior femoral compartment were calculated separately as a function of K/L and JSG according to the previously described protocol. The posterior femoral compartment was chosen because it is non-weight bearing and is oriented differently so it is therefore sensitive to different magic angle effects than the central femoral compartment.

Results of Mean T2 of Posterior Femoral Compartment

Figure 15 shows the mean posterior femoral T2 versus K/L, and Figure 16 shows the mean posterior femoral T2 versus JSG. In both of these plots, the blue diamonds represent the posterior femoral T2 mean for each image with corresponding radiographic data, and the pink bars represent the average for the posterior femoral means in that K/L or joint space grade.

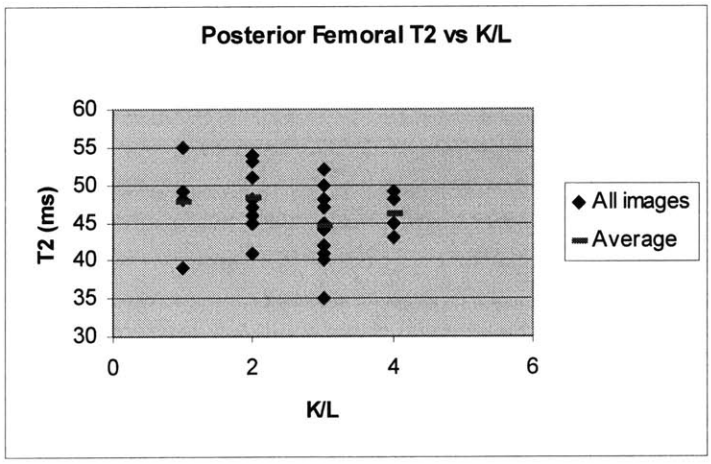


Figure 15: Posterior Femoral T2 vs. K/L for MAK images.

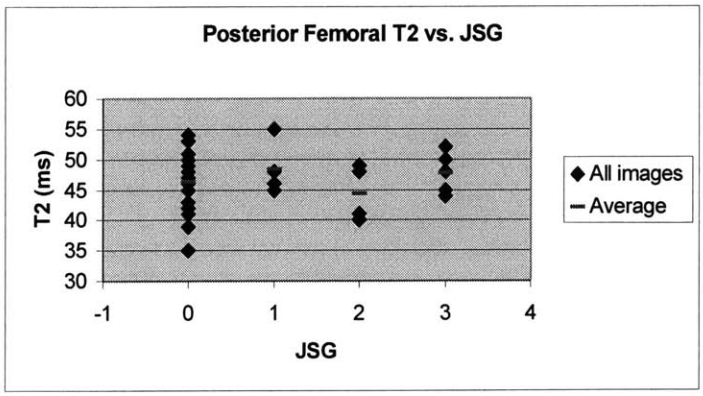


Figure 16: Posterior Femoral T2 vs. JSG for MAK images.

Table 11 summarizes the mean posterior femoral T2 as a function of K/L and JSG. The first column gives the K/L or joint space grade, the second gives the number of images with that grade, the third gives the average mean posterior femoral T2 for that grade, and the last two columns give the lowest mean posterior femoral T2 for that grade and the highest, respectively.

K/L	n	Average T2	Low T2	High T2
1	4	47.8	39	55
2	16	48.3	41	54
3	16	44.5	35	52
4	4	46.3	43	49

JSG	n	Average T2	Low T2	High T2
0	27	46.4	35	54
1	4	48.5	45	55
2	4	44.5	40	49
3	5	47.8	44	52

Table 11: Summary of posterior femoral T2 versus K/L and JSG.

From Figures 15 and 16 and Table 11, we see that there is no easily observable pattern for mean posterior femoral T2 as a function of K/L or JSG. In fact, the average values increase, decrease, and increase again with increasing K/L and JSG. To determine if any of these average T2 changes were statistically significant, a statistical analysis was

performed using the previously described protocol. The results of this statistical analysis as a function of K/L grade are shown in Table 12.

K/L A	n A	Mean T2 A	K/L B	n B	Mean T2 B	p value
1	4	47.8	**2**	16	48.3	0.826
1	4	47.8	**3**	16	44.5	0.270
1	4	47.8	**4**	4	46.3	0.690
2	16	48.3	**3**	16	44.5	0.020
2	16	48.3	**4**	4	46.3	0.345
3	16	44.5	**4**	4	46.3	0.490

Table 12: This table shows the number, and mean for each K/L grade and the p value obtained when comparing the posterior femoral T2 means of K/L grade A to K/L grade B.

From Table 12, there was only one K/L relationship that proved to be statistically significant, and this was a decrease in mean posterior femoral T2 by 3.8 ms from K/L 2 to K/L 3. Table 13 shows the results of the same statistical analysis performed as a function of JSG. In these tests on JSG, no significant correlations were found.

JSG A	n A	Mean T2 A	JSG B	n B	Mean T2 B	p value
0	27	46.4	**1**	4	48.5	0.422
0	27	46.4	**2**	4	44.5	0.475
0	27	46.4	**3**	5	47.8	0.541
1	4	48.5	**2**	4	44.5	0.263
1	4	48.5	**3**	5	47.8	0.796
2	4	44.5	**3**	5	47.8	0.254

Table 13: This table shows the number, and mean for each joint space grade and the p value obtained when comparing the posterior femoral T2 means of JSG A to JSG B.

To determine if there were a relationship between mean central femoral T2 and mean posterior femoral T2, the two were plotted against each other, and a regression line was drawn. Figure 17 shows this plot and regression, which shows a positive relationship between central femoral and posterior femoral T2. A regression analysis was performed on this data, and the p-value was 0.0620, which is not statistically significant.

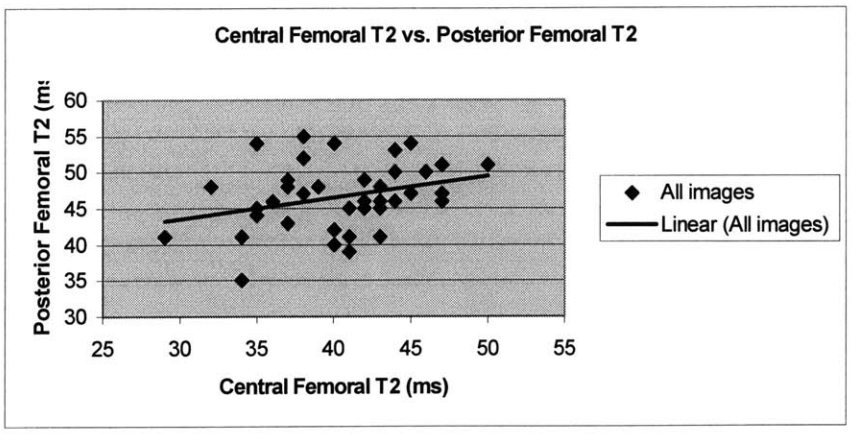


Figure 17: Mean central femoral T2 vs. mean posterior femoral T2 for all images.

The images were then separated by JSG into involved and uninvolved compartments and re-plotted in the same way. Figure 18 shows the mean central femoral T2 vs. posterior femoral T2 for the uninvolved compartments, and Figure 19 shows the mean central femoral T2 vs. posterior femoral T2 for the involved compartments.

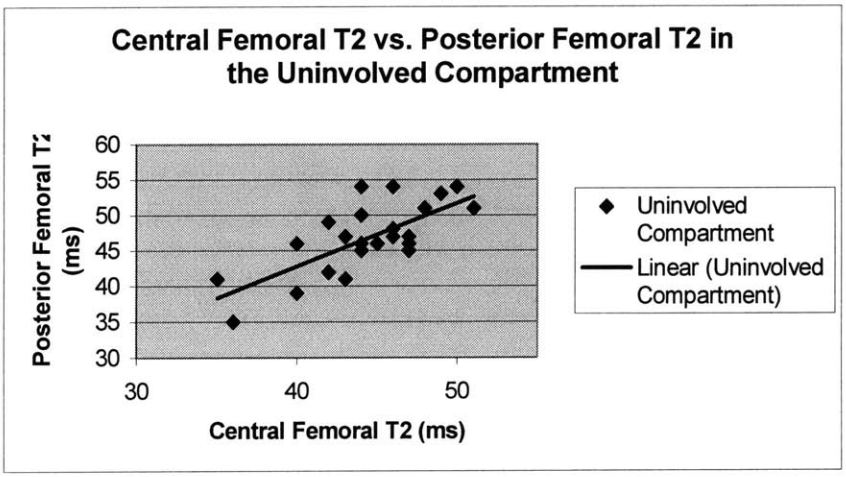


Figure 18: Mean central femoral T2 vs. mean posterior femoral T2 for the uninvolved compartment.

From this figure, it is clear that a strong positive correlation exists between the central femoral T2 and posterior femoral T2 in the uninvolved compartment. The regression analysis showed this high correlation, which had a p-value of 4.15×10^{-5}.

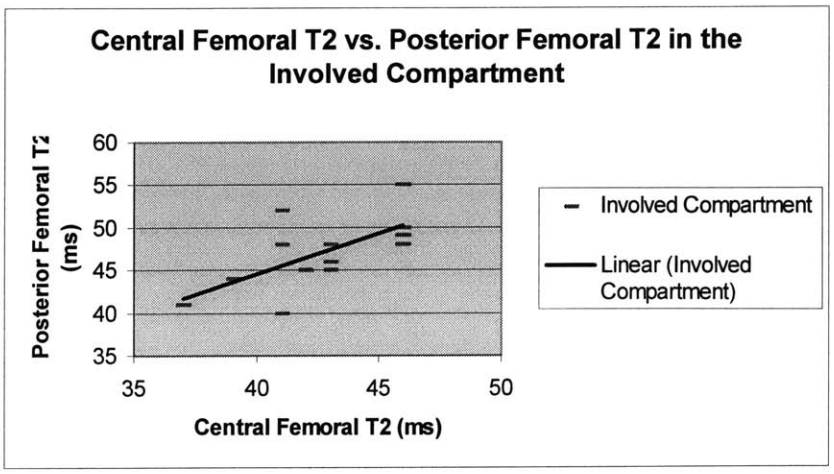


Figure 19: Mean Central Femoral T2 vs. Posterior Femoral T2 in the Involved Compartment

The involved compartments also show a strong positive correlation between central femoral T2 and posterior femoral T2. The regression analysis yielded a p-value of 0.015, which show this positive relationship is statistically significant.

Discussion of Mean T2 of Posterior Femoral Compartment

From the investigation on the posterior femoral compartment, we see that there is no observed relationship between mean posterior femoral T2 and increasing JSG. The only statistically significant change in posterior femoral T2 was a 3.8 ms decrease in posterior femoral T2 from K/L 2 to K/L 3. All other comparisons between K/L grades and between joint space grades showed no differentiation based on mean posterior femoral T2. When the central femoral and posterior femoral means of all of the images were compared, there was a positive relationship that was not statistically significant. However, when the involved and uninvolved compartments were separated, the positive relationship between central femoral T2 and posterior femoral T2 was highly correlated

and statistically significant. Therefore, the central femoral and posterior femoral means tend to track one another separately for the involved and uninvolved compartments.

The finding of decrease of mean T2 in the posterior femoral compartment supports the findings of a decrease in T2 with disease in the central femoral compartment. It is believed that this decrease has not been previously reported in *in vivo* studies. While some may argue that this trend could be due to the presence of Gd-DTPA2-, prior work has observed that Gd-DTPA2- does not have a large effect on T2 under clinical conditions. The main visible features of OA cartilage in this dataset were low lesions and T2 mottling, which has not been previously described in reports of T2 in OA *in vivo*. It has, however, been demonstrated in *in vitro* [13]. Menezes et al observed low lesions and T2 mottling, as well as high lesions. In the *in vitro* studies, low T2 was found to be associated with interventions that might impact the collagen matrix, and T2 mottling was found to be associated with disorganized collagen on light microscopy [13].

T2 as a Function of Normalized Distance From the Bone

An intensive study of T2 as a function of normalized distance from the bone was not performed on this dataset for many reasons. Mosher et al [24] used an automated subroutine to draw line profiles through each pixel from the bone to the articular surface. This drawing of line profiles was performed for every pixel in the given ROI. Mosher used patellar cartilage, which tends to be thicker than femoral cartilage, and therefore his resolution was accurate enough to give ten normalized data points on a segment of cartilage with least 3mm in thickness. An accurate representation of T2 as a function of

normalized distance from the bone for this dataset would require such a subroutine. This subroutine, however, was not generated because it was time prohibitive given the fact that the data had already been reported and the speculation that this method would not be useful in this dataset. In this OA population, the cartilage thickness was highly variable, and seldom was there an ROI that had cartilage with a thickness greater than 3mm. If this technique were to be used, we would need higher resolution scans in order to generate an accurate representation of T2 changing with cartilage depth. In Mosher's experiment on symptomatic patients, he drew line profiles directly through a suspected lesion and then compared that profile to a composite profile for normal patients to determine if it were outside the 95% prediction interval and hence, a legitimate lesion. There are several cases in this dataset where the line profile method would succeed in differentiating an abnormal ROI from a normal one, and most of these would be obvious using other methods as well. For example, the image in Figure 2 has a large low lesion in the central femoral compartment. If a line profile were to be drawn through this lesion, it would show an obviously different variation pattern than in a normal image such as the image shown in Figure 8. In the case of other MAK images that do not have gross lesions but may have some T2 mottling, such as Figure 1, the location for the line profile would have to be carefully determined, which introduces a qualitative component to the study of T2.

T2 Analysis Techniques II: New T2 Analysis Techniques on MAK Dataset

Qualitative Grading of T2 images: Pattern Analysis

Mosher's study on T2 in symptomatic volunteers demonstrated the need for some qualitative analysis on T2 images. When studying the mean T2 of a given ROI, one of

the major drawbacks of that technique is that information about the appearance of the image was lost in the averaging. An image that appeared normal could have a similar mean T2 to an image that was mottled or had visible lesions. Therefore, the images were qualitatively analyzed by pattern and then quantitatively analyzed by K/L, JSG, and dGEMRIC grade to determine if pattern could differentiate T2 based on the severity of OA.

The qualitative grading passed several iterations until the patterns could be grouped into categories that accurately represented what was observed in the image. Figure 20 shows examples of the four different pattern categories used to group the images.

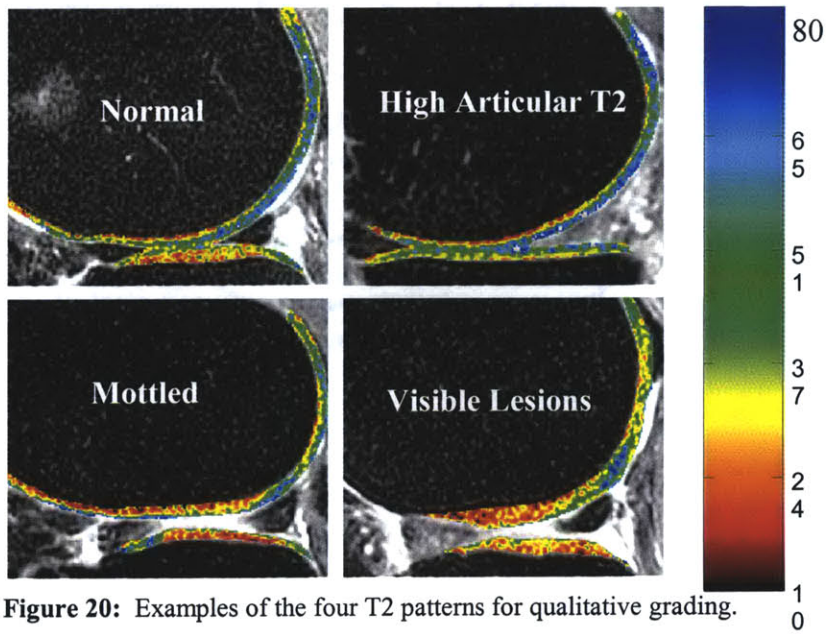


Figure 20: Examples of the four T2 patterns for qualitative grading.

The normal image has low T2 at the bone surface that increases outward toward the articular surface. This is the normal, laminar appearance that was previously described. Some of the image had high articular T2, which was described as a laminar pattern with articular T2 that was high (blue). These voxels may have T2 values that lie outside of the

80 ms cutoff, and as a result are dropped from the T2 map. The mottled images had low and high T2 portions of the ROI, but the low region extended outward toward the articular surface in some locations, and the normal/high region extended inward toward the bone in other locations. The final category had obvious high and low visible lesions. Each image was placed into one of these categories based on its appearance in the central femoral compartment only. After categorization, each category was analyzed using the quantitative grading schemes to determine if there was a clear separation of central femoral T2 based on pattern.

Results of Qualitative Grading of T2 images: Pattern Analysis

This pattern analysis was not pursued because it was very difficult to place each image in just one pattern category. For example, there were some images that had a normal appearance in some sections of the central femoral compartment, mottled appearance in another section of that compartment, and in some cases, the mottling was so severe that it could be considered as a large lesion. Figure 21 shows an example of such an image. In the anterior end of the central femoral compartment, we see a high T2 area that includes T2 points that are above the 80 ms cutoff and hence drop out of the T2(Gd) map. This high T2 region extends downward toward the bone and therefore could be considered mottling, but it could also be considered as a lesion. In the center of the central femoral compartment, there is a low T2 area that originates at the bone and extends outward to the articular surface. This area presents the same problem as the high T2 area. It could be considered as mottling, but it could be a low T2 lesion. Just to the posterior side of the low T2 region, there is a region that shows the normal, laminar pattern, and to the posterior end of the normal region, there is an area of very thin cartilage with high T2.

This image would be very difficult to place in one category, and hence the qualitative grading system was changed in favor of a normal/abnormal scheme rather than specific patterns.

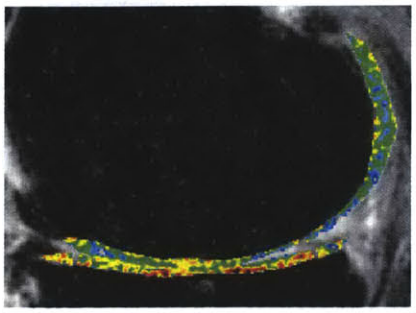


Figure 21: Example of an image that would be difficult to categorize using the four pattern system.

Qualitative Grading of T2 Images: Normal/Abnormal T2 Pattern

At this point in the experiment, a set of T2 images for 5 asymptomatic patients was obtained. These asymptomatic images were used as a baseline off of which the MAK images were recategorized. The central femoral compartment of each image was analyzed for abnormalities. A normal T2 pattern was defined as the typical laminar appearance with low T2 at the bone and higher T2 at the articular surface. In addition, images that did not have a laminar appearance but had a more solid appearance with some low T2 areas in the radial zone or small amounts of mottling were categorized as normal. Images with a large amount of mottling that extended through the entire cartilage thickness, or visible lesions were categorized as abnormal. As a result, most of the images that had been originally categorized as having high articular T2 were recategorized as normal because they were laminar in pattern. The assignment of normal or abnormal T2 pattern eliminated the problem posed by the image in Figure 21 because it would no longer need to be categorized with a specific pattern type. It could simply be

categorized as an abnormal image because most of the central femoral cartilage has an abnormal T2 appearance. Once the images were categorized as normal or abnormal, the central femoral T2 means were compared against K/L, JSG, and dGEMRIC index. In an effort to summarize the data, a "score" was given to each image for both T2 and dGEMRIC. A T2 score of 0 indicated a normal T2 pattern, while a T2 score of 1 indicated an abnormal T2 pattern. Similarly, a dGEMRIC score of 0 indicated a mean central femoral dGEMRIC index of greater than 400, while a dGEMRIC score of 1 indicated a mean central femoral dGEMRIC index of less than 400.

Results of Qualitative Grading of T2 Images: Normal/Abnormal T2 Pattern

After each image was classified as normal or abnormal T2 pattern, 26 out of the 54 images with matching T2 and dGEMRIC data were classified as normal T2 pattern, and 28 out of the 54 images were classified as having abnormal T2 pattern. Out of the 40 images with matching T2 and radiographic data, 19 were classified as having a normal T2 pattern, and 21 were classified as abnormal. The central femoral T2 means from the normal T2 pattern images were compared against those from the abnormal T2 pattern images. Table 14 shows the results of the statistical analysis performed on these two data subsets. The column labeled n gives the number of each T2 pattern type, the second column gives the average central femoral T2 of each T2 pattern type, and the last column gives the two-tailed p value obtained when the normal T2 pattern central femoral T2 values were compared against the abnormal T2 pattern central femoral T2 values.

	n	Average T2	two-tailed p
Normal T2 Pattern	26	42.9	0.0000896
Abnormal T2 Pattern	28	38.3	

Table 14: Summary of number, average T2, and p value obtained when comparing normal T2 pattern images to abnormal T2 pattern images.

Figure 22 shows the central femoral T2 for images with normal T2 pattern and those with abnormal T2 pattern as a function of K/L grade. There is no clear separation between normal and abnormal pattern based on K/L. Table 15 shows the number and mean T2 of each normal and abnormal K/L grade along with the p value obtained when the central femoral T2 values of each normal K/L grade was compared to those of the abnormal K/L grade. No statistically significant relationships were found when comparing a normal T2 pattern K/L grade to its abnormal counterpart.

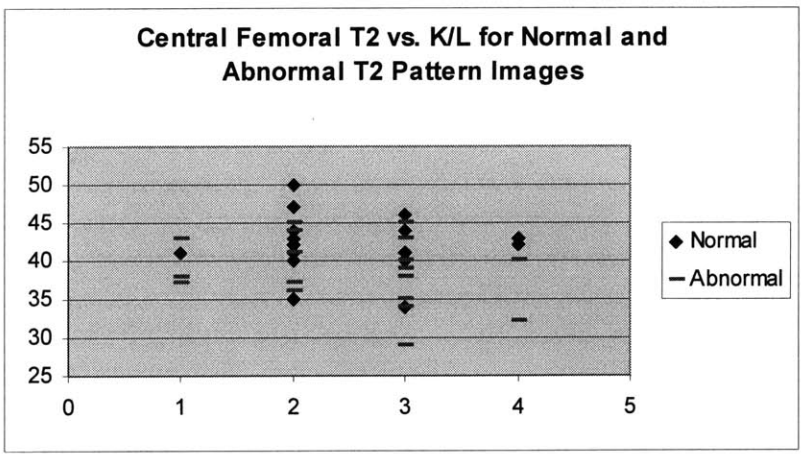


Figure 22: Central Femoral T2 vs. K/L separated by normal and abnormal T2 pattern.

K/L A	n A	Mean T2 A	K/L B	n B	Mean T2 B	p value
1 Normal	1	41.0	**1 Abnormal**	3	39.3	N/A
2 Normal	11	43.5	**2 Abnormal**	5	40.6	0.222
3 Normal	5	41.0	**3 Abnormal**	11	37.7	0.195
4 Normal	2	42.5	**4 Abnormal**	2	36.0	0.248

Table 15: This table shows the number, and mean for each normal and abnormal T2 pattern K/L grade and the p value obtained when comparing the central femoral T2 means of normal K/L grade A to abnormal K/L grade B.

Figure 23 shows the central femoral T2 values for normal and abnormal T2 pattern images as a function of JSG. Similar to K/L, there is no clear separation between normal and abnormal T2 pattern based on K/L. Table 16 is structured similarly to Table 15, and it compares each normal T2 pattern JSG with its abnormal T2 pattern counterpart. The only t-test that could be performed was on the normal set of JSG 0 and the abnormal set of JSG 0 because all other JSGs had an n of 1 for either normal or abnormal T2 pattern images. The relationship between normal pattern T2 images with JSG 0 and abnormal T2 pattern images was statistically significant, yielding a p value of 0.026.

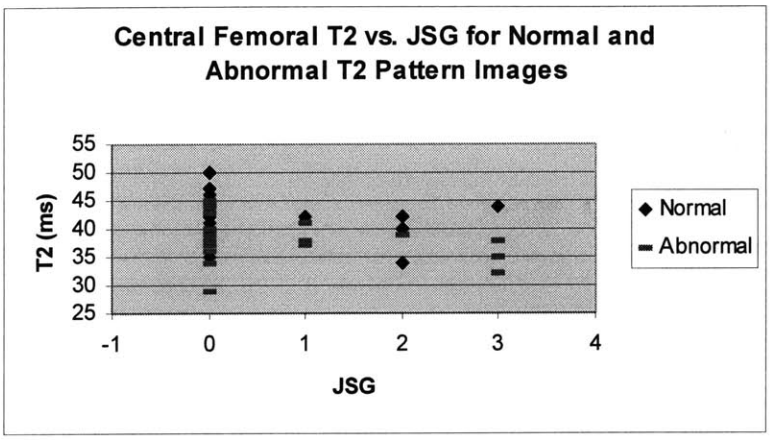


Figure 23: Central Femoral T2 vs. JSG separated by normal and abnormal T2 pattern.

K/L A	n A	Mean T2 A	K/L B	n B	Mean T2 B	p value
1 Normal	14	43.4	**1 Abnormal**	13	39.5	0.026
2 Normal	1	42.0	**2 Abnormal**	3	38.7	N/A
3 Normal	3	38.7	**3 Abnormal**	1	39.0	N/A
4 Normal	1	44.0	**4 Abnormal**	4	35.0	N/A

Table 16: This table shows the number, and mean for each normal and abnormal T2 pattern JSG and the p value obtained when comparing the central femoral T2 means of normal JSG A to abnormal JSG B.

Figure 24 shows the central femoral T2 vs. the central femoral dGEMRIC index separated by normal T2 pattern and abnormal T2 pattern. A t-test was performed to determine if there was a significant relationship between the central femoral dGEMRIC

of normal T2 pattern images and the central femoral dGEMRIC of abnormal T2 pattern images. The results of this statistical analysis are shown in Table 17. The relationship between dGEMRIC of normal pattern T2 and abnormal pattern T2 was not significant.

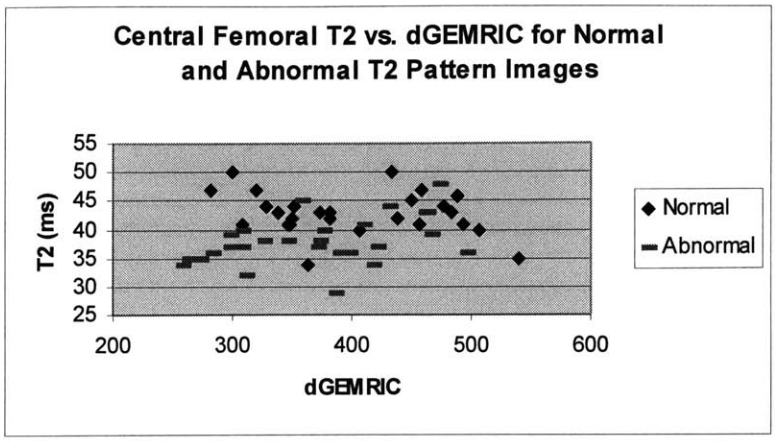


Figure 24: Central Femoral T2 vs. dGEMRIC index separated by normal and abnormal T2 pattern.

	n	Average dGEMRIC	two-tailed p
Normal T2 Pattern	26	400.2	0.113
Abnormal T2 Pattern	28	369.0	

Table 17: Summary of number, average dGEMRIC, and p value obtained when comparing the dGEMRIC index of normal T2 pattern images to abnormal T2 pattern images.

The images were then separated based on T2 and dGEMRIC scores. Figure 25 shows a bubble plot indicating the number of images that fell into each T2 and dGEMRIC score. This includes data from the 40 images that had matching T2, dGEMRIC, and radiographic data.

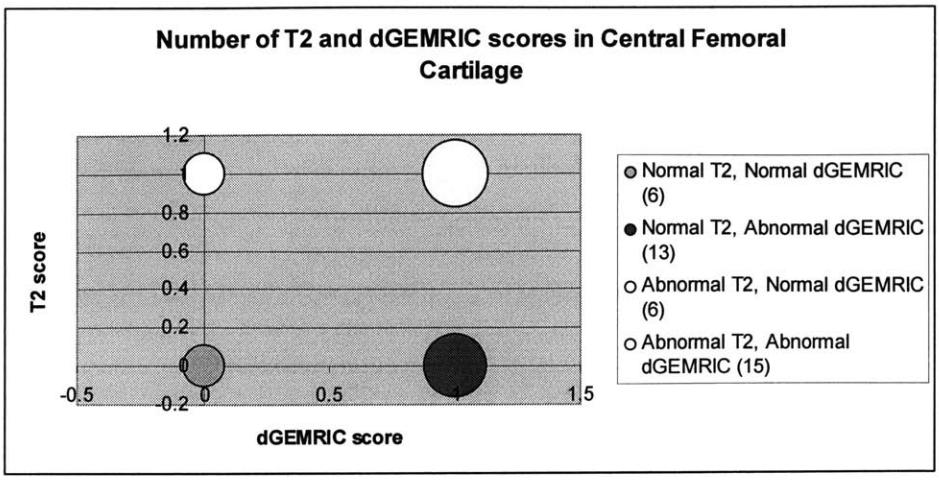


Figure 25: Number of each image that fell into each T2 and dGEMRIC score combination.

Figure 26 shows the average T2 for each T2 and dGEMRIC score combination. The highest average T2 was 43.0 ms for Normal T2/Abnormal dGEMRIC, and the lowest T2 average was 37.2 ms for the Abnormal T2/Abnormal dGEMRIC category. Statistical analysis was performed on the T2 values for each T2/dGEMRIC score set, and the results are shown in Table 18. Statistically significant relationships of T2 mean were found between normal T2/normal dGEMRIC and abnormal T2/abnormal dGEMRIC, normal T2/abnormal dGEMRIC and abnormal T2/abnormal dGEMRIC, and abnormal T2/normal dGEMRIC and abnormal T2/abnormal dGEMRIC.

T2 Score A	dG Score A	n A	Mean T2 A	T2 Score B	dG Score B	n B	Mean T2 B	p value
0	**0**	6	41.7	**0**	**1**	13	43.0	0.512
0	**0**	6	41.7	**1**	**0**	6	41.7	1.000
0	**0**	6	41.7	**1**	**1**	15	37.2	0.044
0	**1**	13	43.0	**1**	**0**	6	41.7	0.439
0	**1**	13	43.0	**1**	**1**	15	37.2	0.0085
1	**0**	6	41.7	**1**	**1**	15	37.2	0.024

Table 18: This table shows the number, and mean T2 for each T2 score/dGEMRIC score combination and the p value obtained when comparing the central femoral T2 means of T2 score/dGEMRIC score A to T2 score/dGEMRIC score B.

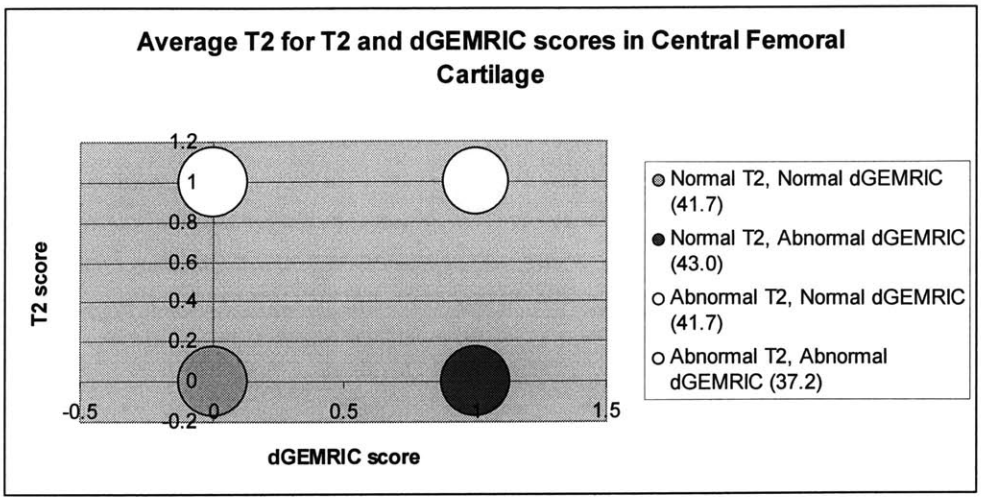


Figure 26: Average T2 value for each T2 and dGEMRIC score category.

Figure 27 shows the average K/L grade for each T2 and dGEMRIC score category. The lowest average K/L grade was 2.33 for normal T2/normal dGEMRIC, and the highest average K/L grade was 2.60 for the abnormal T2/abnormal dGEMRIC category. Statistical analysis was performed on all pairs of T2 and dGEMRIC score, and no significant relationships were found between K/L grade and T2/dGEMRIC score combination.

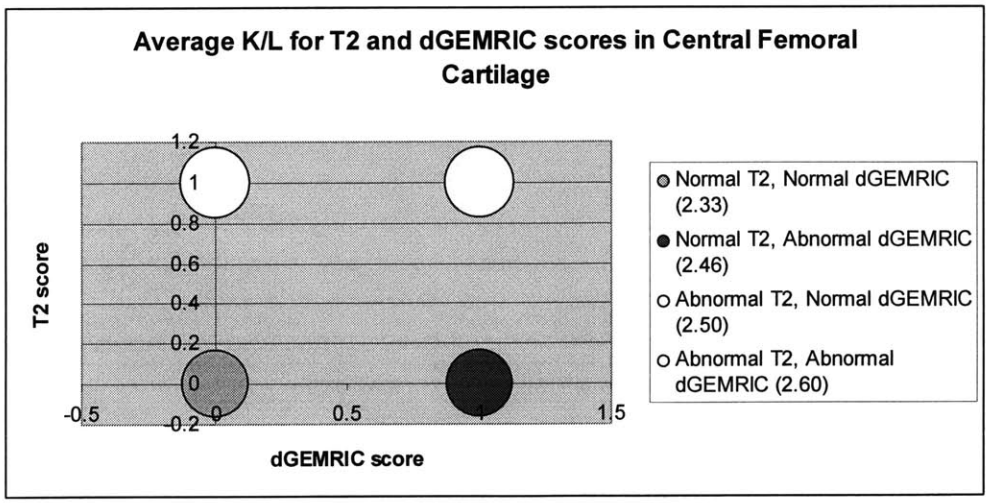


Figure 27: Average K/L grade for each T2 and dGEMRIC score category.

Figure 28 shows the average JSG for each T2 and dGEMRIC score category. The lowest average JSG grade was 0.33 for normal T2/normal dGEMRIC, and the highest average K/L grade was 0.93 for the abnormal T2/abnormal dGEMRIC category. Statistical analysis was performed on all pairs of T2 and dGEMRIC score, and no significant relationships were found between K/L JSG and T2/dGEMRIC score combination.

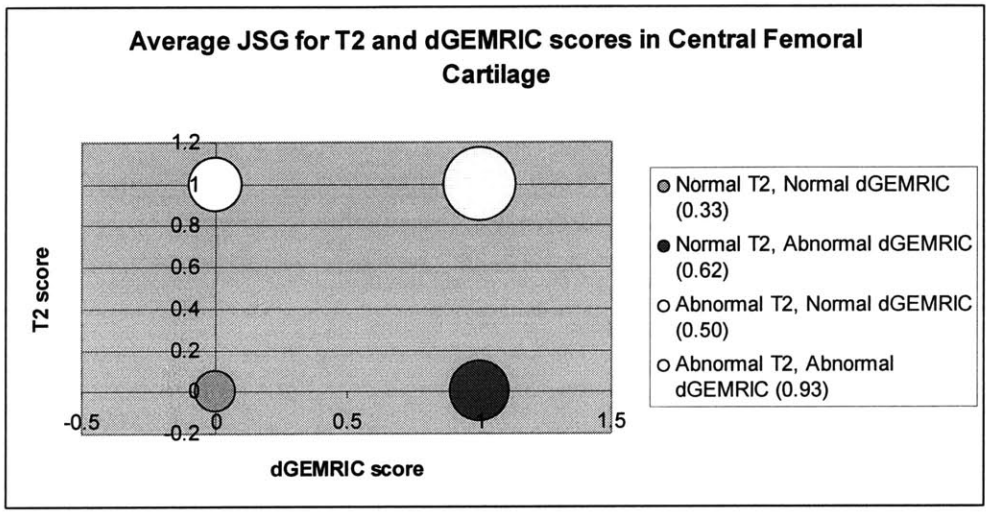


Figure 28: Average JSG for each T2 and dGEMRIC score category.

Discussion of Qualitative Grading of T2 Images: Normal/Abnormal T2 Pattern

From Figure 24, it appears that more abnormal T2 pattern images fall below T2 of 40 ms versus above 40 ms. This agrees with the findings that showed a statistically significant relationship between the central femoral T2 values of the abnormal T2 pattern images and normal T2 pattern images. The main finding from this T2 pattern investigation was the significant difference between T2 mean of the normal pattern images and T2 mean of the abnormal pattern images. This observation is likely due to the way that T2 images were categorized. Most of the images that were categorized as abnormal had low T2 mottling and low T2 lesions. Those that had intermediate T2 values with some low T2 at the bone surface and some high T2 areas between the bone surface and the articular

surface were classified as normal T2 pattern images. This classification parameter was used because several of the asymptomatic patients had similar patterns where there was a small amount of low T2 at the bone surface and intermediate T2 from the bone surface to the articular surface with some higher T2 regions. Figure 29 shows an example of a MAK image that was classified as normal T2 although it has high T2 areas that could be considered as high T2 mottling. Figure 30 shows an example of an asymptomatic patient with the same pattern features. If these had been classified as abnormal, the mean T2 for the abnormal T2 pattern images would likely increase, thus decreasing the difference between the T2 for normal pattern images and the T2 for abnormal pattern images.

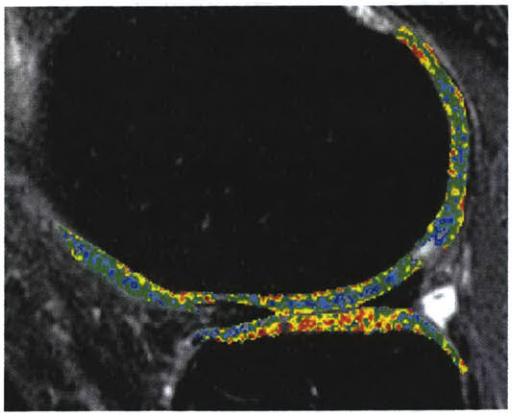


Figure 29: A MAK image that was categorized as normal.

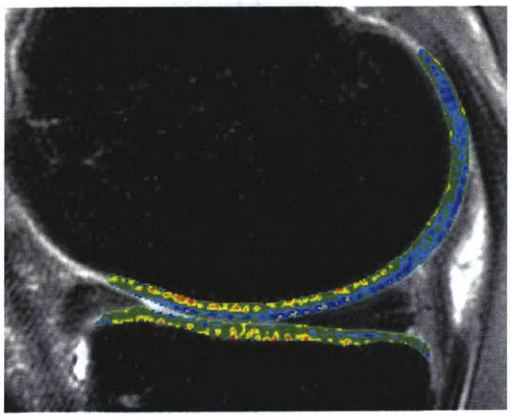


Figure 30: An example of an asymptomatic T2 pattern.

Figures 31-35 give examples of different T2/dGEMRIC score combinations. Figure 31 shows a patient with normal T2 pattern and normal dGEMRIC. Figure 32 shows a patient with normal T2 pattern and abnormal (low) dGEMRIC. Figure 33 shows an example of a patient with abnormal T2 pattern and normal dGEMRIC. Figures 34 and 35 both show patients with abnormal T2 pattern and abnormal dGEMRIC. From these

images, it can be observed that images with similar T2 patterns can have widely varying dGEMRIC values and vice versa.

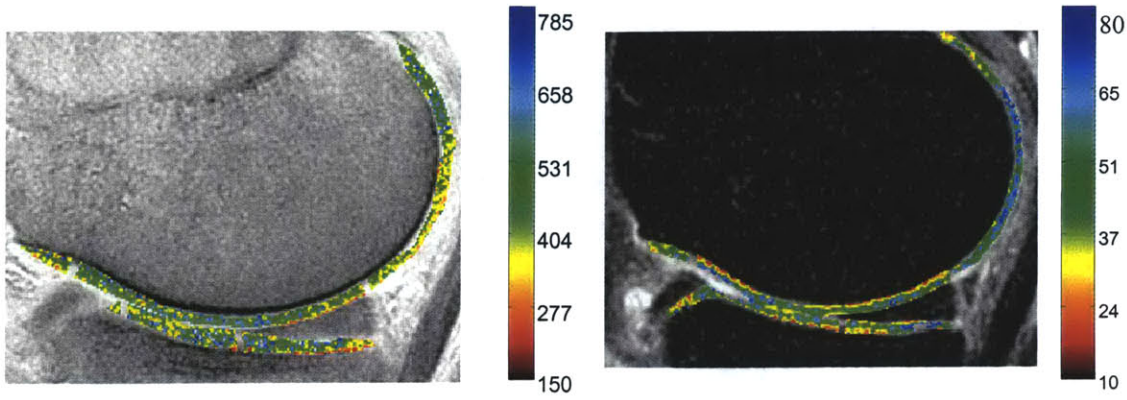


Figure 31: An example of a patient with normal dGEMRIC (left) and normal T2 pattern (right).

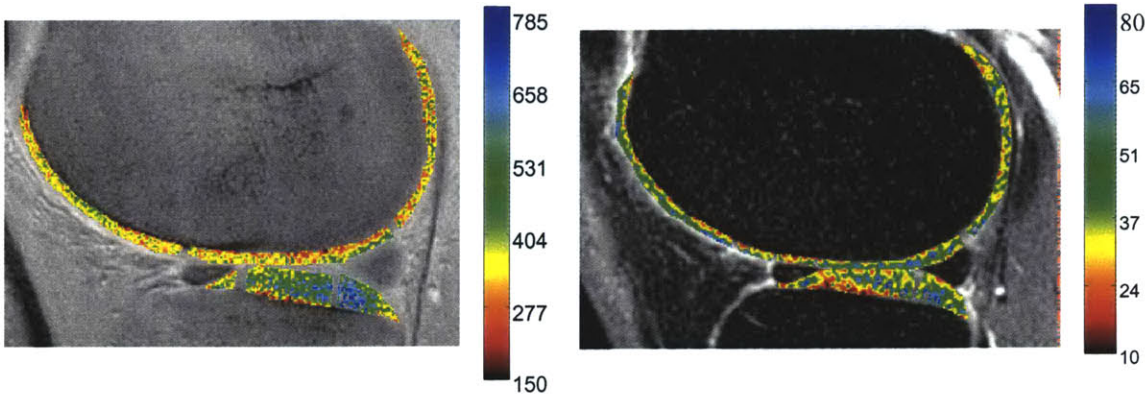


Figure 32: An example of a patient with abnormal dGEMRIC (left) and normal T2 pattern (right).

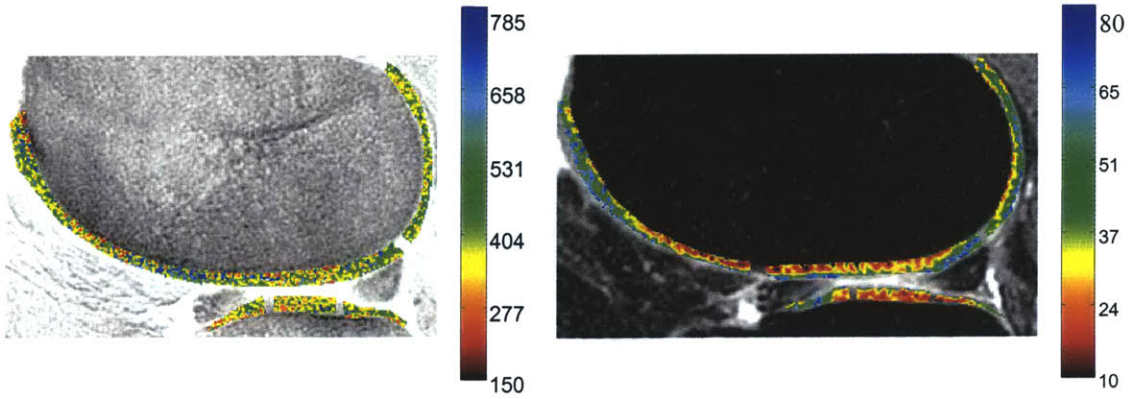


Figure 33: An example of a patient with normal dGEMRIC (left) and abnormal T2 pattern (right).

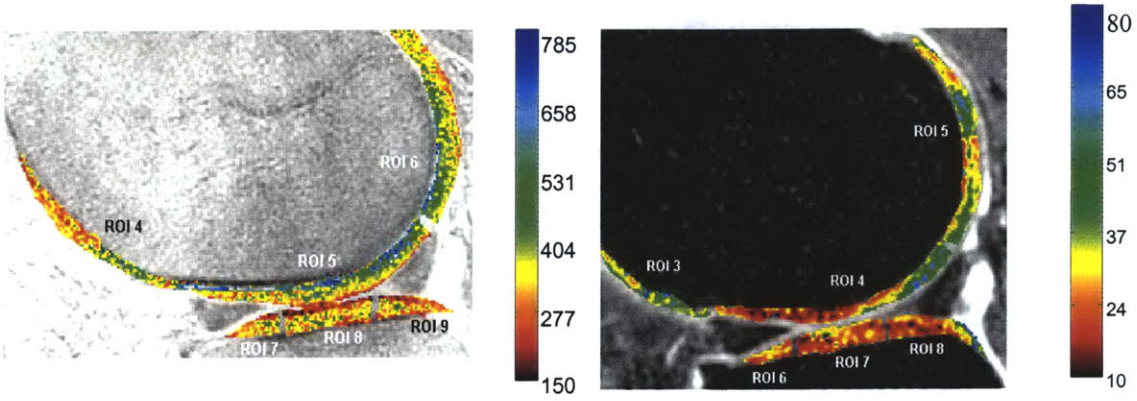


Figure 34: An example of a patient with abnormal dGEMRIC (left) and abnormal T2 pattern (right).

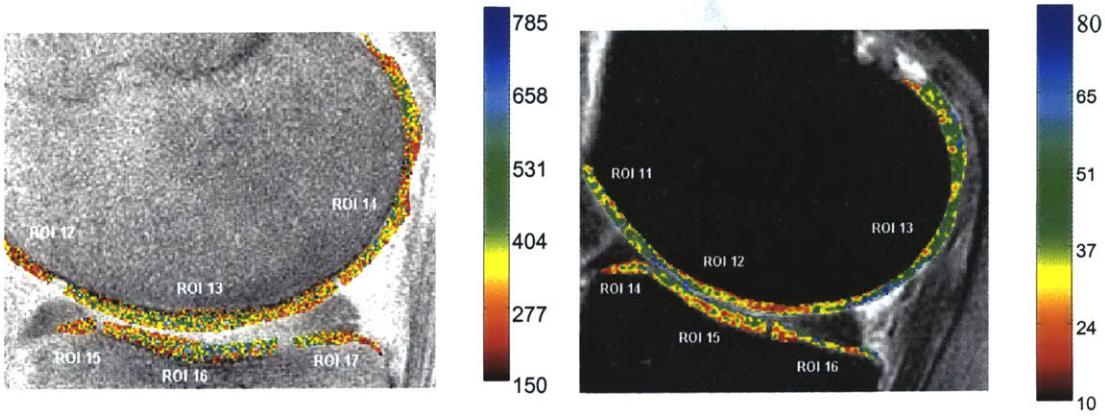


Figure 35: A less extreme example of a patient with abnormal dGEMRIC (left) and abnormal T2 pattern (right).

There were no statistically significant differences between K/L or JSG based on T2 and dGEMRIC score. T2 pattern could not differentiate between OA grades based on these radiographic metrics.

In addition to this technique, a more granular analysis was performed categorizing images as having one of three pattern categories: 1) normal T2 pattern, 2) mild T2 pattern abnormality, and 3) gross T2 pattern abnormality. This technique, however, was not pursued because it did not give results that clearly separated T2 pattern based on any of the radiographic measures.

There are several important conclusions to take away from this qualitative grading scheme despite the fact that it did not yield definite results differentiating T2 pattern based on OA grade. This technique shows the need for some qualitative grading as Mosher performed in his study on symptomatic patients. The appearance of T2 images is very important, and due to the heterogeneity of T2, purely quantitative measures often result in the loss of this crucial information. However, the main drawback of this technique is its qualitative nature, which introduces a subjective component to the data analysis. Therefore, an investigator must proceed with great caution before embarking on a T2 pattern analysis.

dGEMRIC vs. T2

T2 and dGEMRIC have already been studied together in the qualitative grading analysis, but a major component of this investigation involved comparing central femoral T2 and central femoral dGEMRIC in a more quantitative way. The images were segmented, and

the central femoral T2 and central femoral dGEMRIC were found according to the previously described method. The T2 and dGEMRIC values were then compared using statistical analysis to determine if there were any relationships between central femoral T2 and dGEMRIC index. Normal dGEMRIC values were those having a mean over the central femoral compartment that was greater than 400. Abnormal dGEMRIC values were defined as having a mean dGEMRIC index less than 400.

Results of dGEMRIC vs. T2

The central femoral T2 values of images with normal dGEMRIC were compared against those having abnormal dGEMRIC for the 54 images that had matching T2 and dGEMRIC information. First, an f-test was performed on the T2 values corresponding to normal dGEMRIC and the T2 values corresponding to abnormal dGEMRIC to determine if they had equal variances. Then a t-test was performed to determine if they were statistically significant. The results for this statistical analysis are shown in Table 19 where the first column gives the dGEMRIC category (normal vs. abnormal), the second column gives the number of images (out of 54) in each dGEMRIC category, the third column gives the average central femoral T2 values for each all of the images that fall into that dGEMRIC category, and the last column gives the two-tailed p value obtained from the t-test comparing the central femoral T2 values of the normal dGEMRIC images to the abnormal dGEMRIC images. As we see, the difference between the central femoral T2 values for normal versus abnormal dGEMRIC was not statistically significant according to our criteria.

	n	Average CF T2	two-tailed p
Normal dGEMRIC	21	41.9	0.089
Abnormal dGEMRIC	33	39.7	

Table 19: Summary of number, average central femoral T2, and p value obtained when comparing the central femoral T2 values of normal dGEMRIC images to abnormal dGEMRIC images.

Figure 36 shows a scatter plot of central femoral T2 versus central femoral dGEMRIC. This plot includes the 54 images that had matching T2 and dGEMRIC data. Regression analysis was performed to determine if there were a significant trend between T2 and dGEMRIC. For this analysis, the p value of the trendline was 0.179, and hence, not statistically significant. It is included in the figure although it is not significant.

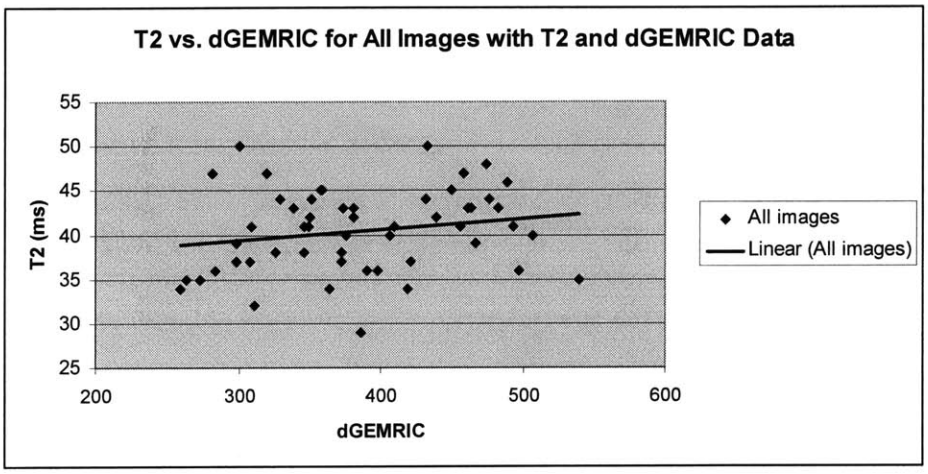


Figure 36: T2 vs. dGEMRIC data for all 54 images with matching T2 and dGEMRIC data.

In order to determine if there were a significant relationship between T2 and dGEMRIC based on whether the involved vs. uninvolved compartment were analyzed, the 40 images with matching T2, radiographic, and dGEMRIC data were examined. Similar to the previously described test, all 40 images were analyzed using regression analysis to determine if there were a statistically significant relationship between central femoral T2 and dGEMRIC. Figure 37 shows a scatter plot and trendline for T2 vs. dGEMRIC data for the image with matching T2, dGEMRIC, and radiographic data. The p value given by

the regression analysis was 0.497. Therefore, the trend shown in this figure is not significant.

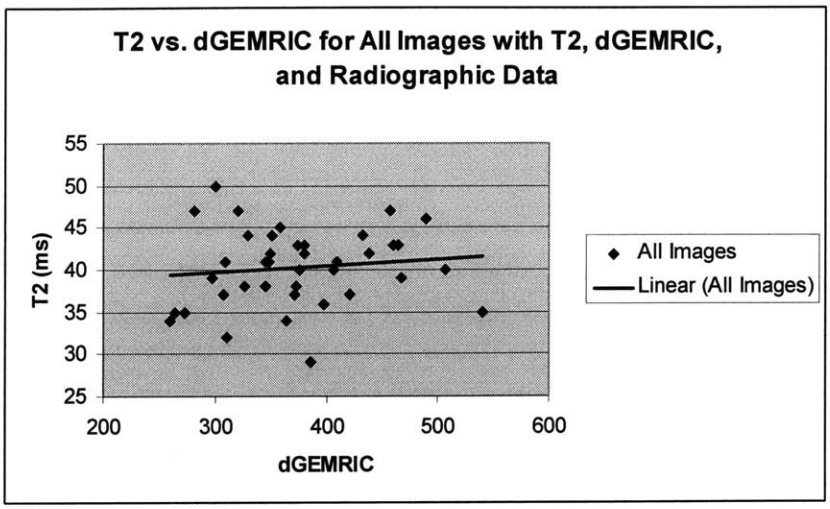


Figure 37: T2 vs. dGEMRIC data for all 40 images with matching T2, dGEMRIC, and radiographic data.

Because this data had matching radiographic data, it could be separated by involved and uninvolved compartments. Figure 38 shows a scatter plot of central femoral T2 vs. dGEMRIC data separated based on whether the compartment is uninvolved or involved. Trendlines are shown for both uninvolved and involved data. Table 20 gives a summary of the T2 and dGEMRIC data separated by uninvolved and involved compartments. The last column gives the p value obtained by regression analysis on the T2 and dGEMRIC data for each compartment type. As we see from the table, neither is statistically significant according to the aforementioned criteria for significance. However, the involved compartment has a relationship between T2 and dGEMRIC that is more highly correlated than the uninvolved compartment.

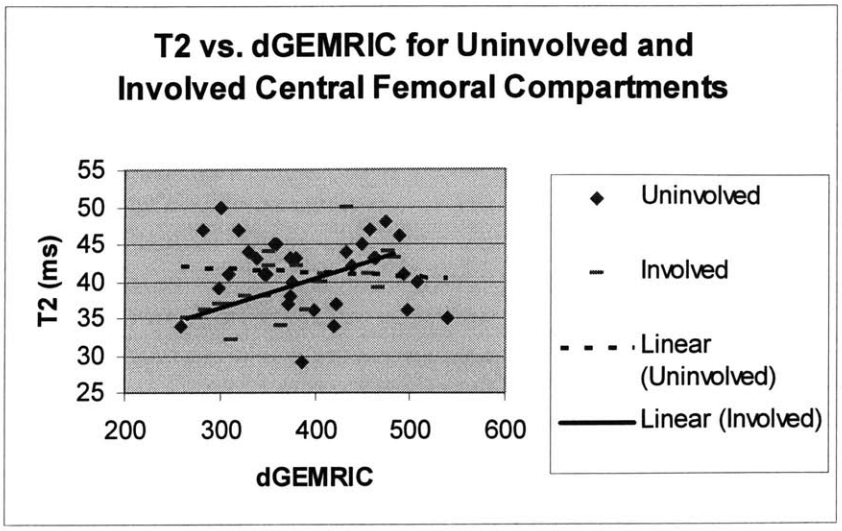


Figure 38: T2 vs. dGEMRIC data for uninvolved and involved compartments for images having matching T2, dGEMRIC, and radiographic data.

	n	Average CF T2	Average CF dGEMRIC	p value
Uninvolved Compartment	27	41.5	380	0.753
Involved Compartment	13	38.2	351	0.073

Table 20: Summary of number, average central femoral T2, average central femoral dGEMRIC, and p value obtained when comparing the T2 and dGEMRIC values of the uninvolved and involved compartments separately.

Discussion of dGEMRIC vs. T2

These studies on dGEMRIC and T2 show that T2 is not differentiated based on dGEMRIC grade. From this study we see that even for widely varying dGEMRIC grades (and therefore disease grades), T2 remains fairly insensitive. Figure 39 shows a dGEMRIC image (left) and a T2(Gd) map (right) for the same patient. In this case, the central femoral dGEMRIC index was low (~300) and the central femoral T2 mean was approximately 35 ms. Figure 40 shows a dGEMRIC image (left) and a T2(Gd) map (right) for a different patient. This patient has a high central femoral dGEMRIC index (~500), but the central femoral T2 mean is still approximately 35 ms. These two images show that T2 can be highly insensitive to large changes in dGEMRIC index, and therefore disease state.

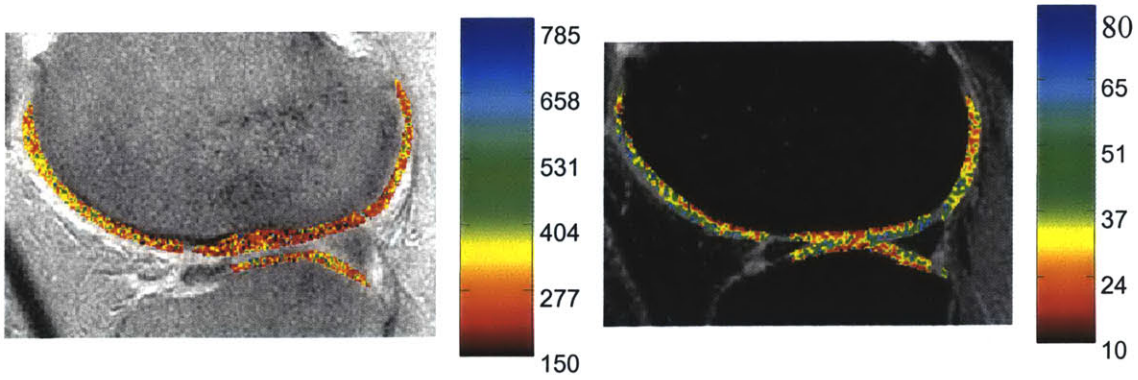


Figure 39: An example of a patient with low central femoral dGEMRIC (left) and central femoral T2 (right) of approximately 35 ms.

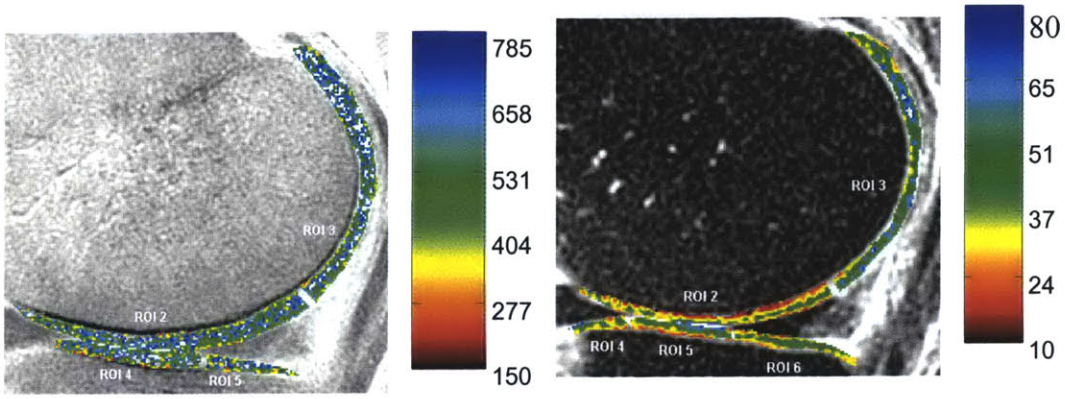


Figure 40: An example of a patient with high central femoral dGEMRIC (left) and central femoral T2 (right) of approximately 35 ms.

The relationship of decreasing T2 with increasing disease (decreasing dGEMRIC) was observed, but it is not statistically significant according to the outlined criteria. However, it agrees with the previously observed decrease in T2 with increasing disease (decreasing dGEMRIC). The lack of correlation between T2 and dGEMRIC in the uninvolved compartment argues against Gd-DTPA2- exerting a dominating effect on T2.

T2 Threshold Analysis

Another method that was used to analyze T2 data in this OA population was threshold analysis. In this technique, the central femoral compartment of each image with matching T2, dGEMRIC, and radiographic data was analyzed. The percentage of pixels

in the central femoral compartment with T2 values above and below certain thresholds was obtained using a MATLAB subroutine. Out of the 40 total images with matching T2, dGEMRIC, and radiographic data, five images were excluded due to errors in calculating the percentages with the MATLAB subroutine. Therefore, 35 images were analyzed. Out of these 35 images, 18 were lateral images, 17 were medial images, but they were analyzed together. As previously stated, pixels with T2 values below 10 ms and above 80 ms were excluded. The threshold values used were percentage of pixels less than 20, 30, and 50 ms and greater than 60 and 70 ms. Because of the exclusion of pixels outside the 10-80 ms range, the pixels with T2 values less than 20 ms actually represents the percentage of pixels between 10 and 20 ms. Similarly, pixels reported as having T2 greater than 70 ms are actually pixels with T2 between 70 and 80 ms. The percentage values for each threshold were compared against K/L and JSG to determine if this representation of T2 data could differentiate images based on disease grade.

Results of T2 Threshold Analysis

To begin analyzing this data, the percentage values for each threshold were plotted by K/L grade to determine if there were any clear separation of T2 percentages by disease grade. Figure 41 shows the percentage of central femoral pixels with T2 values less than 20 ms sorted by K/L. As we can see, there is no clear separation based on percentage less than 20 ms. Statistical analysis was performed looking for statistically significant relationships between the percentage of pixels with T2 values less than 20 ms of each K/L grade to each other K/L grade. No significant relationships were found. Because the n is small for K/L 1 and K/L 4, the images were grouped into low K/L (K/L grades 1 and 2) and high K/L (K/L grades 3 and 4) categories. These groups were then compared for

statistical significance using an f test for variance followed by a t test for significance. Table 21 shows the results of this statistical analysis on low K/L and high K/L. The first column gives the K/L group, the second gives the number of images in each group, the third gives the average percentage of pixels with T2 values less than 20 ms, and the last column gives the two-tailed p value obtained from the t test comparing the percentages for each group. In this case, the relationship between the percentage of pixels with T2 less than 20 ms was not significant based on high or low K/L.

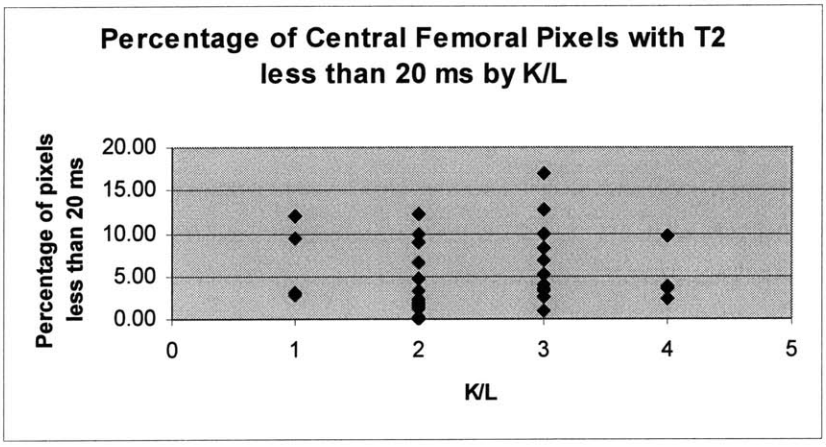


Figure 41: Percentage of central femoral pixels with T2 less than 20 ms sorted by K/L grade.

	n	Average Percent <20 ms	p value
K/L 1 and 2	20	4.31	0.194
K/L 3 and 4	15	6.21	

Table 21: Statistical analysis of percent pixels less than 20 ms by low K/L (1 & 2) and high K/L (3&4).

Figure 42 shows the percentage of central femoral pixels with T2 values less than 30 ms by K/L grade. In this plot, there is no clear separation, but there is a trend toward higher percentages (ie. more pixels with lower T2) between K/L 2 and K/L 3. This trend is verified by statistical analysis. Table 22 shows the results of the statistical analysis on low K/L and high K/L with respect to percentage of pixels less than 30 ms. In this case,

the data was statistically significant, with a p value of 0.00521. The percentage of pixels less than 30 ms did differentiate T2 based on disease grade by 11.8 percentage points.

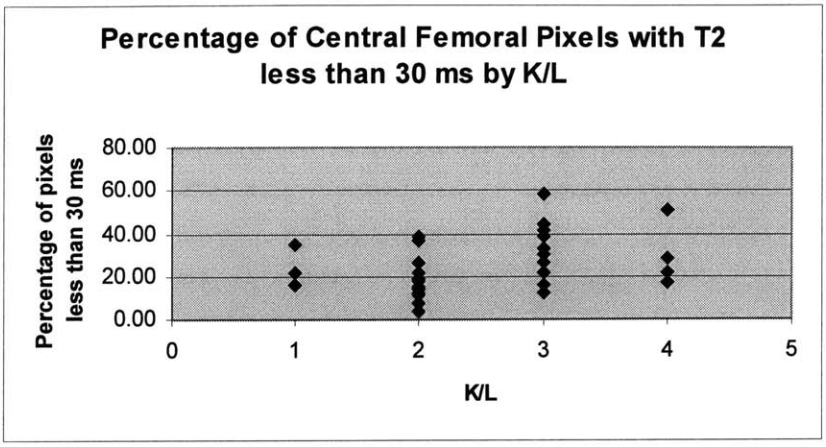


Figure 42: Percentage of central femoral pixels with T2 less than 30 ms sorted by K/L grade.

	n	Average Percent <30 ms	p value
K/L 1 and 2	20	19.6	0.00521
K/L 3 and 4	15	31.4	

Table 22: Statistical analysis of percent pixels less than 30 ms by low K/L (1 & 2) and high K/L (3&4).

Figure 43 shows the percentage of central femoral pixels with T2 values less than 50 ms by K/L grade. Similar to the plot of percentages less than 30 ms, there is no clear separation, but there is a trend toward higher percentages between K/L 2 and K/L 3. This trend is verified by statistical analysis. Table 23 shows the results of the statistical analysis on low K/L and high K/L with respect to percentage of pixels less than 50 ms. The increase in percentage of T2 less than 50 ms was significant, with a p value of 0.00360. The percentage of pixels less than 50 ms did differentiate T2 based on disease grade by 11.1 percentage points.

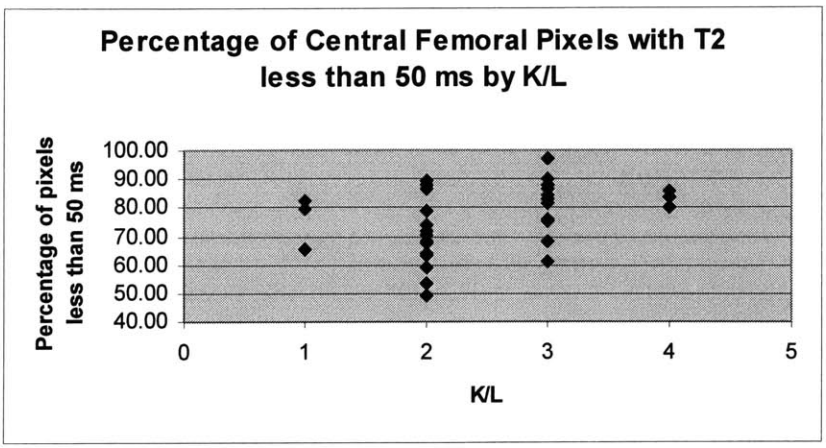


Figure 43: Percentage of central femoral pixels with T2 less than 50 ms sorted by K/L grade.

	n	Average Percent <50 ms	p value
K/L 1 and 2	20	70.7	0.00360
K/L 3 and 4	15	81.8	

Table 23: Statistical analysis of percent pixels less than 50 ms by low K/L (1 & 2) and high K/L (3&4).

Figure 44 shows the percentage of central femoral pixels with T2 values greater than 60 ms by K/L grade. A trend is more difficult to determine visually, but as table 24 shows, there is a statistically significant relationship between percentage of pixels above 60 ms for low K/L grades and high K/L grades. The p value was 0.0357, and represented a difference of 4.6 percentage points. Similar to the other findings, fewer high T2 pixels were found in the more diseased cases.

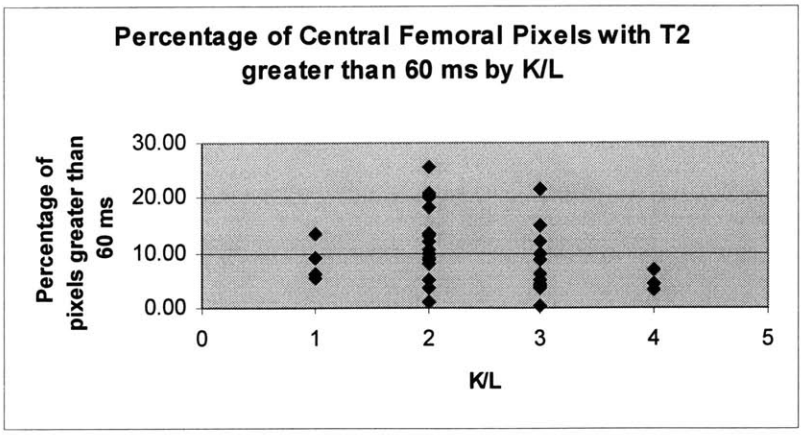


Figure 44: Percentage of central femoral pixels with T2 greater than 60 ms sorted by K/L grade.

	n	Average Percent >60 ms	p value
K/L 1 and 2	20	11.8	0.0357
K/L 3 and 4	15	7.2	

Table 24: Statistical analysis of percent pixels greater than 60 ms by low K/L (1 & 2) and high K/L (3&4).

Figure 45 shows the percentage of central femoral pixels with T2 values greater than 70 ms by K/L grade. There was no clear observable trend, and as table 25 shows, there was no significant relationship between high and low K/L grades.

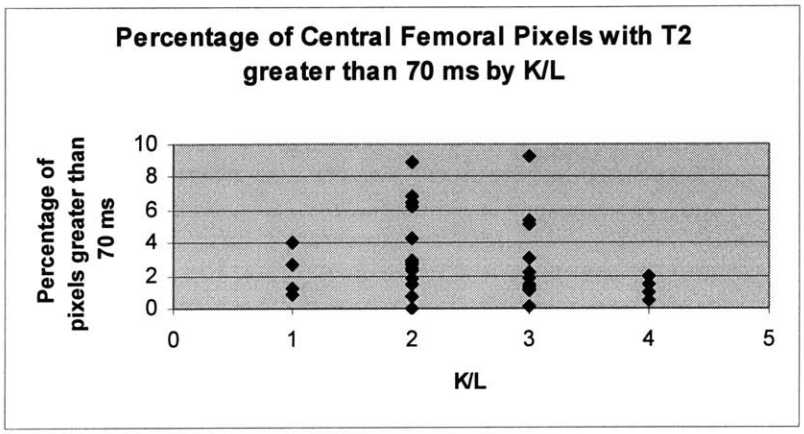


Figure 45: Percentage of central femoral pixels with T2 greater than 70 ms sorted by K/L grade.

	n	Average Percent >70 ms	p value
K/L 1 and 2	20	3.4	0.284
K/L 3 and 4	15	2.5	

Table 25: Statistical analysis of percent pixels greater than 70 ms by low K/L (1 & 2) and high K/L (3&4).

The threshold analysis was then performed using joint space grade as a radiographic metric for comparison. Statistical analysis was performed between uninvolved and involved compartments. Figure 46 shows the percentage of pixels with T2 values less than 20 ms by JSG. Table 26 shows the results of the statistical analysis on the percentage of pixels with T2 less than 20 ms for the uninvolved and involved compartments. There was no statistically significant relationship.

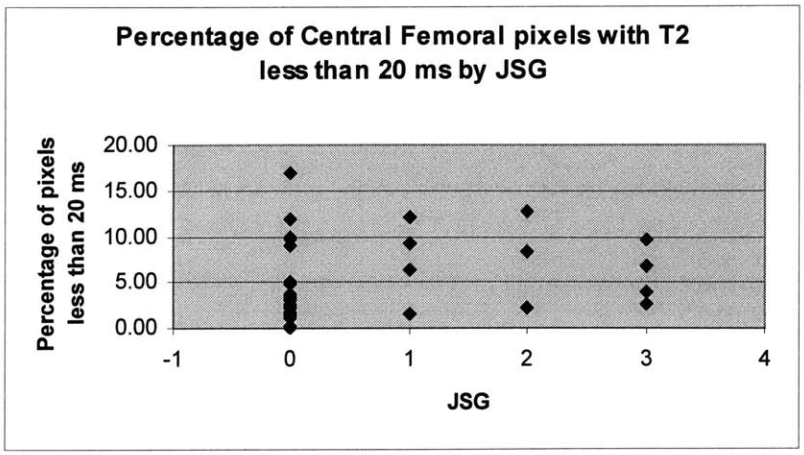


Figure 46: Percentage of central femoral pixels with T2 less than 20 ms sorted by JSG.

	n	Average Percent <20 ms	p value
Uninvolved	24	4.3	0.0908
Involved	11	6.9	

Table 26: Statistical analysis of percent pixels less than 20 ms by uninvolved and involved compartments.

Figure 47 shows the percentage of central femoral pixels with T2 values less than 30 ms by JSG. Table 27 shows the statistical analysis performed on the uninvolved and involved compartments using this 30 ms threshold. There was a statistically significant increase in percentage (by 9.4 percentage points) from the uninvolved to the involved compartments. This again, shows that a higher percentage of low T2 pixels were found in the more diseased cases.

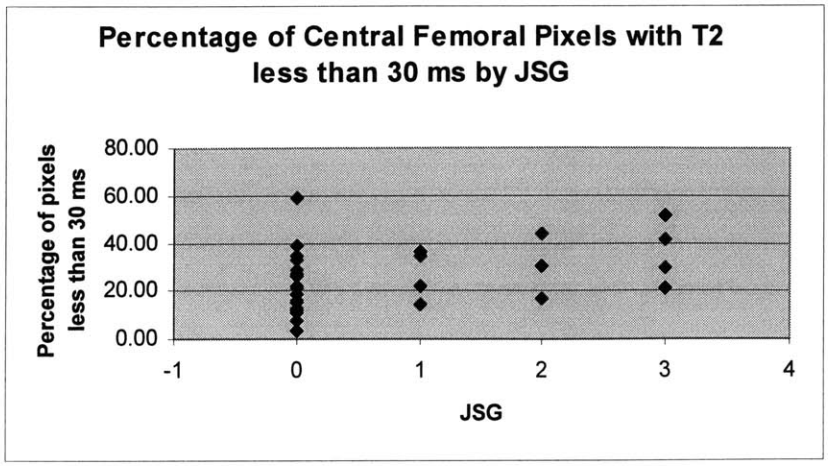


Figure 47: Percentage of central femoral pixels with T2 less than 30 ms sorted by JSG.

	n	Average Percent <30 ms	p value
Uninvolved	24	21.7	0.0425
Involved	11	31.1	

Table 27: Statistical analysis of percent pixels less than 30 ms by uninvolved and involved compartments.

Figure 48 shows the percentage of central femoral pixels with T2 values less than 50 ms by JSG. Table 28 shows the statistical analysis performed on the uninvolved and involved compartments. For the 50 ms threshold, there was no significant relationship between the uninvolved and involved compartments.

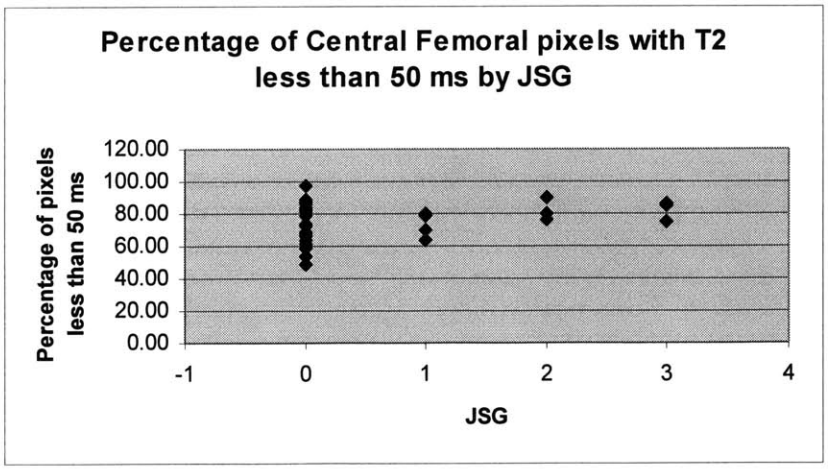


Figure 48: Percentage of central femoral pixels with T2 less than 50 ms sorted by JSG.

	n	Average Percent <50 ms	p value
Uninvolved	24	73.7	0.205
Involved	11	79.2	

Table 28: Statistical analysis of percent pixels less than 50 ms by uninvolved and involved compartments.

The percentage of central femoral pixels with T2 greater than 60 ms is shown by JSG in figure 49. Table 29 shows the statistical analysis performed on the uninvolved and involved compartments. For the 60 ms threshold, there was no statistically significant relationship between the uninvolved and involved compartments.

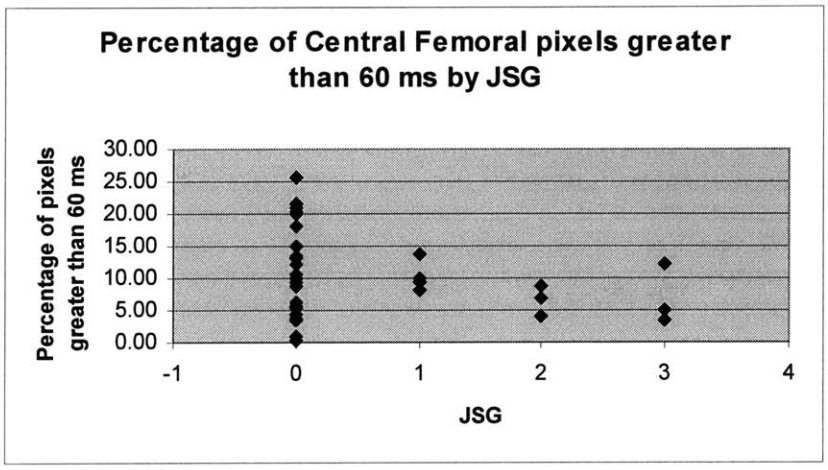


Figure 49: Percentage of central femoral pixels with T2 greater than 60 ms sorted by JSG.

	n	Average Percent >60 ms	p value
Uninvolved	24	10.8	0.0933
Involved	11	7.7	

Table 29: Statistical analysis of percent pixels greater than 60 ms by uninvolved and involved compartments.

Figure 50 shows the percentage of central femoral pixels with T2 values greater than 70 ms by JSG. Table 30 shows the statistical analysis performed on the uninvolved and involved compartments. For the 70 ms threshold, there was no significant relationship between the uninvolved and involved compartments.

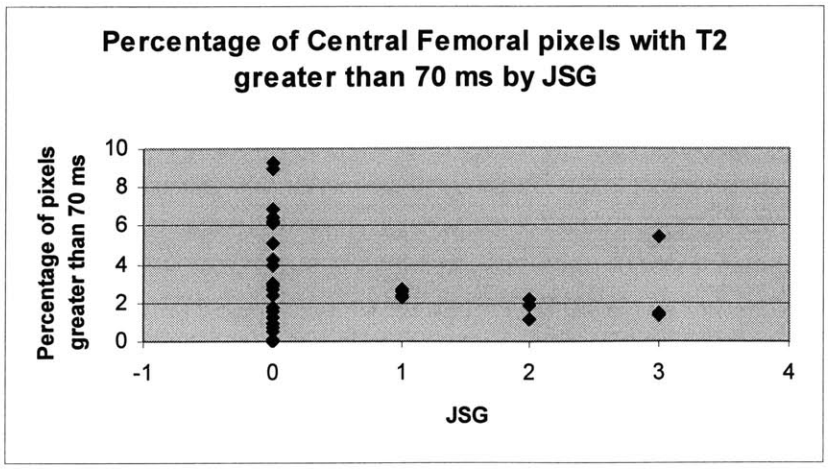


Figure 50: Percentage of central femoral pixels with T2 greater than 70 ms sorted by JSG.

	n	Average Percent >70 ms	p value
Uninvolved	24	3.4	0.135
Involved	11	2.3	

Table 30: Statistical analysis of percent pixels greater than 70 ms by uninvolved and involved compartments.

Discussion of T2 Threshold Analysis

The results of analysis using this technique are consistent with results of other techniques for this dataset in that we see lower T2 (more low T2 pixels) with disease progression. This technique gave statistically significant results when comparing low K/L to high K/L for threshold values of 30, 50, and 60 ms, and it gave statistically significant results when comparing involved and uninvolved compartments when using 30 ms as a threshold. Although some very low p values were obtained for this technique, the problem still remains that the numbers do not necessarily reflect what we see in the image. Figure 51 shows two images, A and B. Image A has a normal, laminar T2 pattern, and image B has a large amount of low T2 mottling. Table 31 shows a summary of their visual appearance, mean central femoral T2, and percentages below and above the threshold values tested.

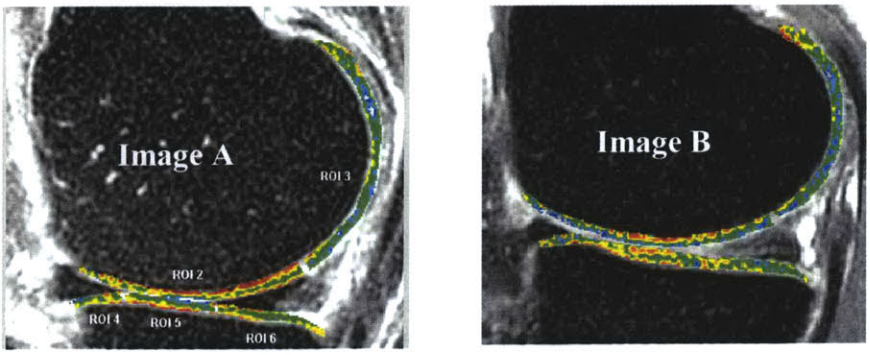


Figure 51: Image A (left) and image B (right) have different T2 appearances, but these differences are not represented in the threshold analysis.

ID	Visual Appearance	Mean T2	%<20	%<30	%<50	%>60	%>70
Image A	Normal pattern	40	3.2	18.3	63.7	12.3	2.4
Image B	Low T2 mottling	43	3.1	21.6	65.7	13.5	4.0

Table 31: Results of threshold analysis on Image A and Image B.

From Table 31, it can be observed that although these images have different appearances in the central femoral compartment, their numbers are very similar. Therefore, this technique still has drawbacks in that it does not accurately represent what can be observed from the images.

Two-Layer T2 Threshold Analysis

Because the T2 values in cartilage of the knee tend to increase with distance from the bone, the central femoral cartilage was segmented into two "layers" based on distance from the bone. The layer closest to the bone was designated as the radial layer and the layer farthest from the bone was designated as the articular layer. These were segmented manually using visual inspection to divide the cartilage into two layers of equal thickness based on cartilage thickness at each point across the central femoral compartment. The T2 threshold analysis was then performed in the same way described in the previous

section on T2 threshold analysis. The same 35 images were used because they had matching T2, dGEMRIC, and radiographic data. The percentage of pixels in the central femoral compartment with T2 values above and below the previously used threshold values were obtained using the MATLAB subroutine. As previously stated, pixels with T2 values below 10 ms and above 80 ms were excluded. Because of the exclusion of pixels outside the 10-80 ms range, the pixels with T2 values less than 20 ms actually represents the percentage of pixels between 10 and 20 ms. Similarly, pixels reported as having T2 greater than 70 ms are actually pixels with T2 between 70 and 80 ms. The percentage values for each threshold in the radial and articular layers were compared against K/L and JSG to determine if this representation of T2 data could differentiate images based on disease grade.

Results of Two-Layer T2 Threshold Analysis

As a preliminary analysis, the central femoral T2 means were plotted for the radial and articular layers by K/L grade. Figure 52 shows the T2 mean for the radial and articular layers of the 35 images in this dataset. A statistical analysis was performed on these mean T2 values by performing an f test for variance followed by a t test for significance. In this case, the data was groups into two K/L categories; low K/L included K/L grades 1 and 2, and high K/L included K/L grades 3 and 4. Table 32 shows the results of this statistical analysis on low K/L and high K/L for the radial and articular layers. The first column gives the designated layer (radial or articular) along with the K/L group being analyzed, the second gives the number of images in each group, the third gives the mean T2 in each layer of each K/L group, and the last column gives the two-tailed p value obtained from the t test comparing the means for the high and low K/L groups by layer.

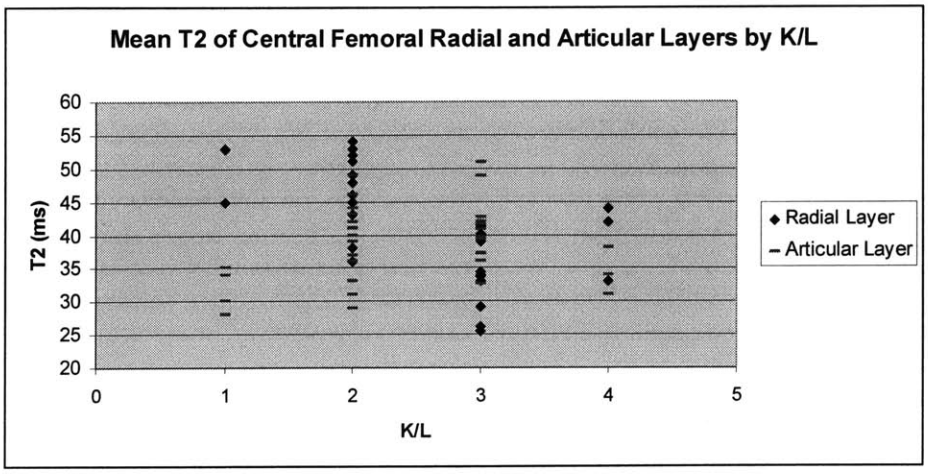


Figure 52: Mean T2 of central femoral radial and articular layers sorted by K/L.

	n	Central Femoral T2 mean	p value
Radial: Low K/L	20	47.3	4.82e-7
Radial: High K/L	15	35.9	
Articular: Low K/L	20	37.6	0.462
Articular: High K/L	15	39.0	

Table 32: Statistical analysis of mean T2 in the radial and articular layers by low and high K/L.

From this table, we see that the mean central femoral T2 in the radial layer is significantly different based on low versus high K/L. This, however, is not the case for the articular layer. There is no statistically significant relationship between the mean T2 based on disease grade using K/L as a metric. In the radial zone, we once again observe that in this dataset, the average T2 tends to decrease with disease.

Figure 53 shows a plot of the percentage of central femoral pixels in the radial and articular layers that have T2 values less than 20 ms sorted by K/L. Table 33 shows a summary of the statistical analysis performed on this data. It is similar in structure to Table 32, and it shows the two-tailed p value obtained when comparing the percentage of pixels below the threshold value for low K/L to those of high K/L. According to the

aforementioned criteria for statistical significance in this study, percentage less than 20 ms did differentiate between OA grade by K/L in the radial layer but not in the articular layer. In the radial layer, there were more low T2 pixels (higher percentage) in the more diseased cases (higher K/L) than in the low disease case.

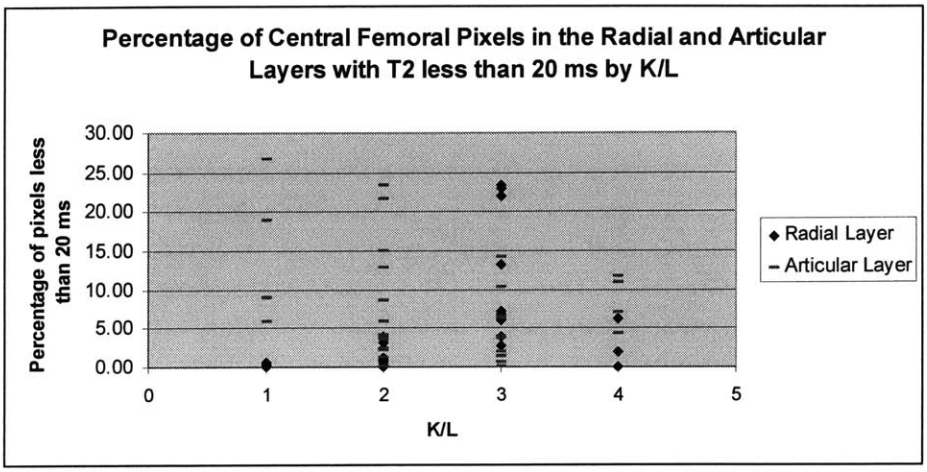


Figure 53: Percentage of pixels in the radial and articular layers less than 20 ms sorted by K/L.

	n	Average percent < 20 ms	p value
Radial: Low K/L	20	0.7	0.00199
Radial: High K/L	15	8.6	
Articular: Low K/L	20	8.6	0.175
Articular: High K/L	15	5.5	

Table 33: Statistical analysis of percent T2 less than 20 ms in the radial and articular layers by low and high K/L.

A plot of the percentage of central femoral pixels in the radial and articular layers with T2 values less than 30 ms by K/L is shown in Figure 54. Table 34 shows the results of statistical analysis on the 30 ms threshold data using low K/L and high K/L as a metric for severity of OA. Similar to the previous results for the two layer analysis, the radial layer was significantly different based on K/L with more low T2 pixels in the more diseased patients, whereas the articular layer was not.

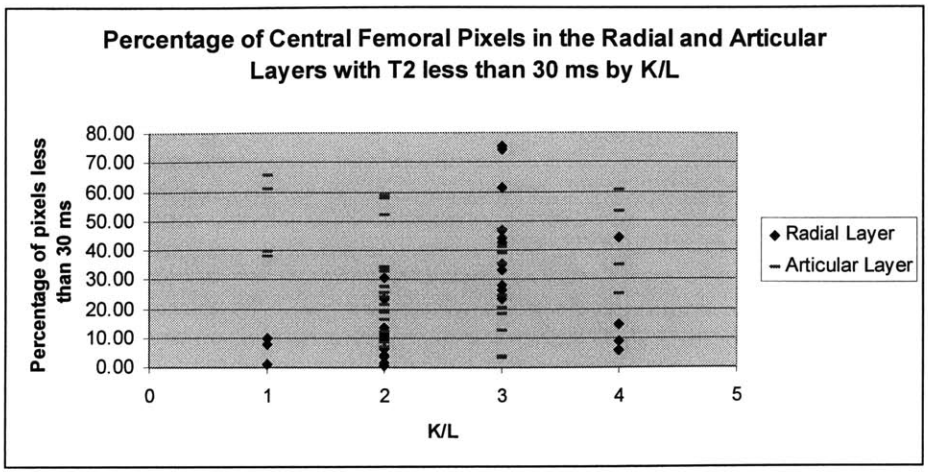


Figure 54: Percentage of pixels in the radial and articular layers less than 30 ms sorted by K/L.

	n	Average percent < 30 ms	p value
Radial: Low K/L	20	8.4	9.54e-5
Radial: High K/L	15	37.6	
Articular: Low K/L	20	37.7	0.601
Articular: High K/L	15	24.2	

Table 34: Statistical analysis of percent T2 less than 30 ms in the radial and articular layers by low and high K/L.

Figure 55 shows the percentage of the central femoral pixels in the radial and articular layers with T2 values less than 50 ms by K/L. As with the other threshold plots, there is no clear visual separation of percentages based on K/L grade. We do however, observe that there is a highly significant difference between the percent of pixels with T2 less than 50 in the radial zone based on low vs. high K/L. The results for the statistical analysis are shown in Table 35. However, there is no statistically significant relationship in the articular layer.

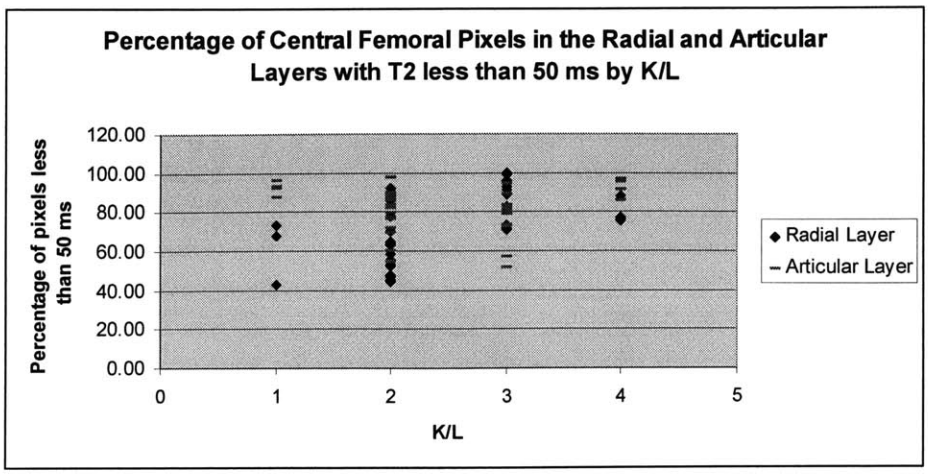


Figure 55: Percentage of pixels in the radial and articular layers less than 50 ms sorted by K/L.

	n	Average percent < 50 ms	p value
Radial: Low K/L	20	60.9	3.64e-6
Radial: High K/L	15	84.9	
Articular: Low K/L	20	81.1	0.944
Articular: High K/L	15	80.8	

Table 35: Statistical analysis of percent T2 less than 50 ms in the radial and articular layers by low and high K/L.

Figure 56 shows the percentage of central femoral pixels in the radial and articular layers with T2 values greater than 60 ms by K/L, and Table 36 shows a summary of the results of the statistical analysis for this data. As can be observed from the table, there was a highly significant difference between the percentage greater than 60 ms in the radial layer based on K/L, but there was no significant relationship in the articular layer. In this analysis of the radial layer, there were fewer high T2 pixels in the more diseased cases that had K/L of 3 or 4.

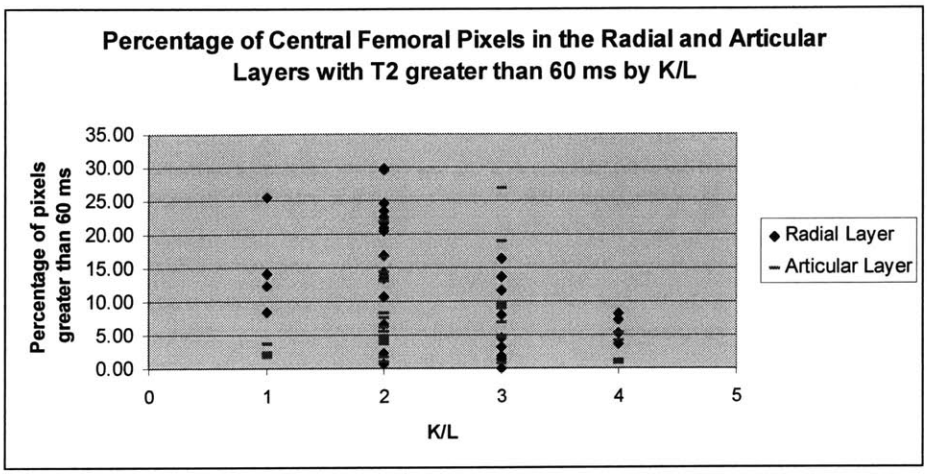


Figure 56: Percentage of pixels in the radial and articular layers greater than 60 ms sorted by K/L.

	n	Average percent >60 ms	p value
Radial: Low K/L	20	16.6	3.93e-5
Radial: High K/L	15	5.8	
Articular: Low K/L	20	7.1	0.553
Articular: High K/L	15	8.4	

Table 36: Statistical analysis of percent T2 greater than 60 ms in the radial and articular layers by low and high K/L.

Figure 57 shows the percentage of central femoral pixels in the radial and articular layers with T2 values greater than 70 ms sorted by K/L grade. Table 37 shows a summary of the statistical analysis performed on this data. Using the 70 ms threshold, there was a statistically significant difference between the average percentage with low K/L in the radial layer when compared to those with high K/L in the radial layer. There was no significant correlation observed in the articular layer.

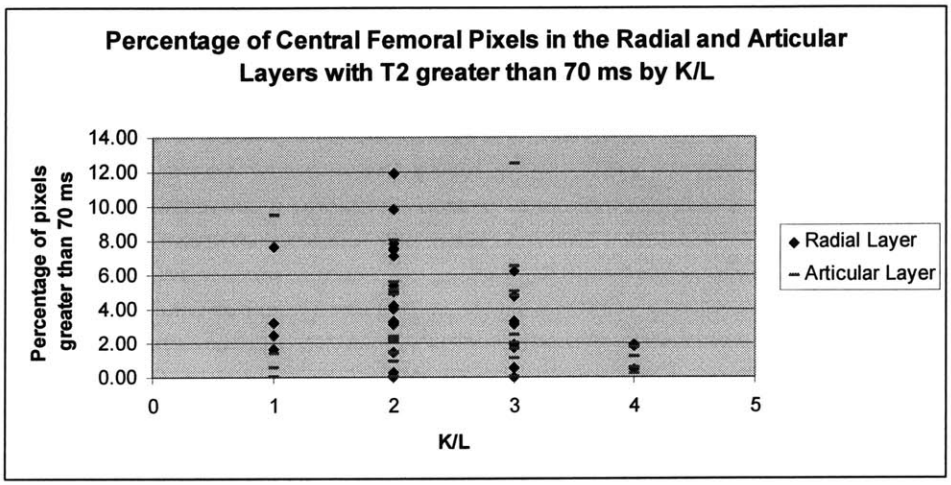


Figure 57: Percentage of pixels in the radial and articular layers greater than 70 ms sorted by K/L.

	n	Average percent >70 ms	p value
Radial: Low K/L	20	4.8	0.00202
Radial: High K/L	15	2.0	
Articular: Low K/L	20	2.5	0.703
Articular: High K/L	15	2.9	

Table 37: Statistical analysis of percent T2 greater than 70 ms in the radial and articular layers by low and high K/L.

A similar analysis was performed on the threshold data using joint space grade as a metric for OA severity. For statistical analyses, the uninvolved compartments were compared against the involved compartments in both the radial and articular layers. Figure 58 shows a plot of the mean T2 for the central femoral radial and articular layers sorted by JSG, and Table 38 shows the results of the statistical analysis on this data. In this case, mean T2 did not differentiate between uninvolved and involved compartments in neither the radial nor the articular layer as evidenced by the two-tailed p values being larger than 0.05.

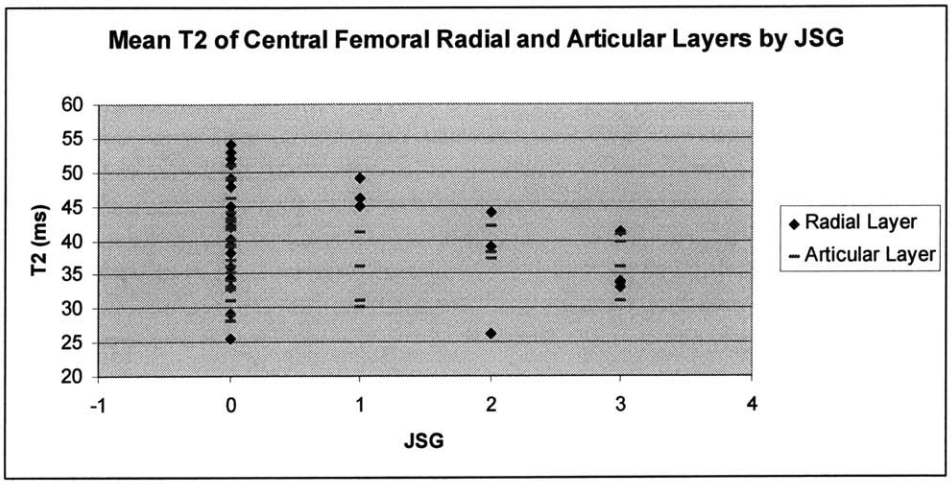


Figure 58: Mean T2 of central femoral radial and articular layers sorted by JSG.

	n	Central Femoral T2 mean	p value
Radial: Uninvolved	24	43.6	0.173
Radial: Involved	11	39.7	
Articular: Uninvolved	24	38.9	0.280
Articular: Involved	11	36.6	

Table 38: Statistical analysis of mean T2 in the radial and articular layers by uninvolved and involved compartments.

Figure 59 shows the percentage of the pixels in the central femoral radial and articular layers with T2 values less than 20 ms by JSG. Table 39 shows the results of the statistical analysis performed on this data, and similar to the mean, there was no significant difference observed based on whether the compartment was involved or uninvolved for both the radial and articular layers.

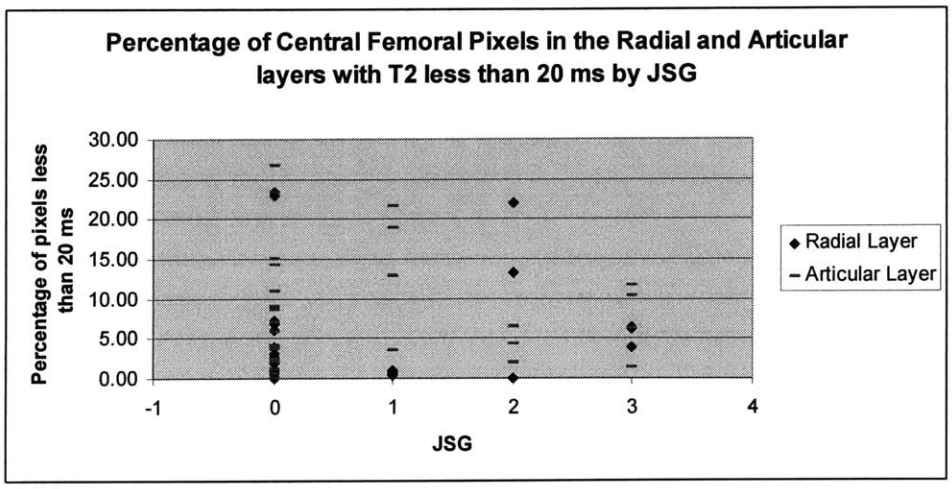


Figure 59: Percentage of pixels in the radial and articular layers less than 20 ms sorted by JSG.

	n	Average percent <20 ms	p value
Radial: Uninvolved	20	3.4	0.390
Radial: Involved	15	5.5	
Articular: Uninvolved	20	6.4	0.319
Articular: Involved	15	9.0	

Table 39: Statistical analysis of percent T2 less than 20 ms in the radial and articular layers by uninvolved and involved compartments.

Figure 60 shows the percentage of central femoral pixels in the radial and articular layers with T2 less than 30 ms sorted by JSG, and Table 40 shows the statistical analysis on this data. Similar to the 20 ms threshold, no significant difference was found based on JSG in the radial and articular layers.

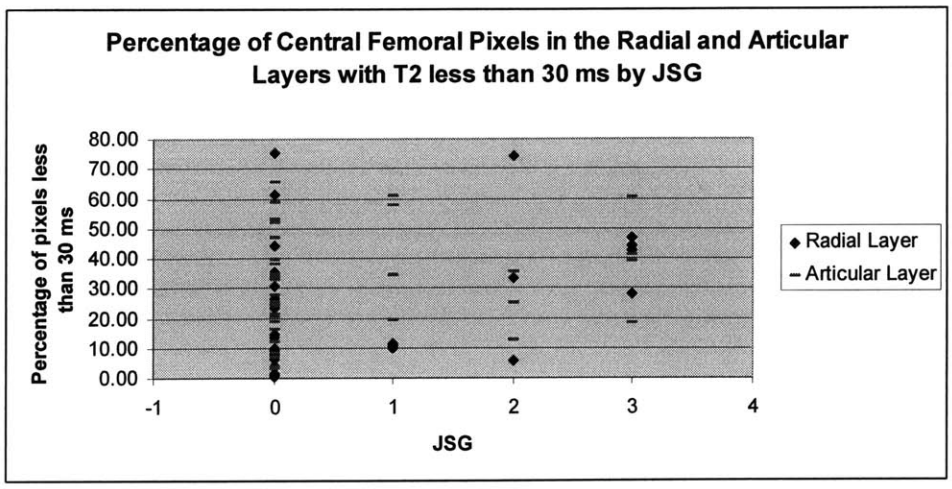


Figure 60: Percentage of pixels in the radial and articular layers less than 30 ms sorted by JSG.

	n	Average percent <30 ms	p value
Radial: Uninvolved	20	17.2	0.127
Radial: Involved	15	28.9	
Articular: Uninvolved	20	28.8	0.220
Articular: Involved	15	36.7	

Table 40: Statistical analysis of percent T2 less than 30 ms in the radial and articular layers by uninvolved and involved compartments.

The 50 ms threshold was also analyzed, and the data is shown as a function of JSG in Figure 61. Table 41 shows the statistical analysis on the data with the 50 ms threshold. While no differences were statistically significant, there was a higher percentage of pixels with T2 less than 50 ms in the articular layer of the involved compartment when compared to the articular layer of the uninvolved compartment, implying that with disease progression, there were more low T2 pixels in the articular layer. Again, while this is interesting to observe, it is not significant.

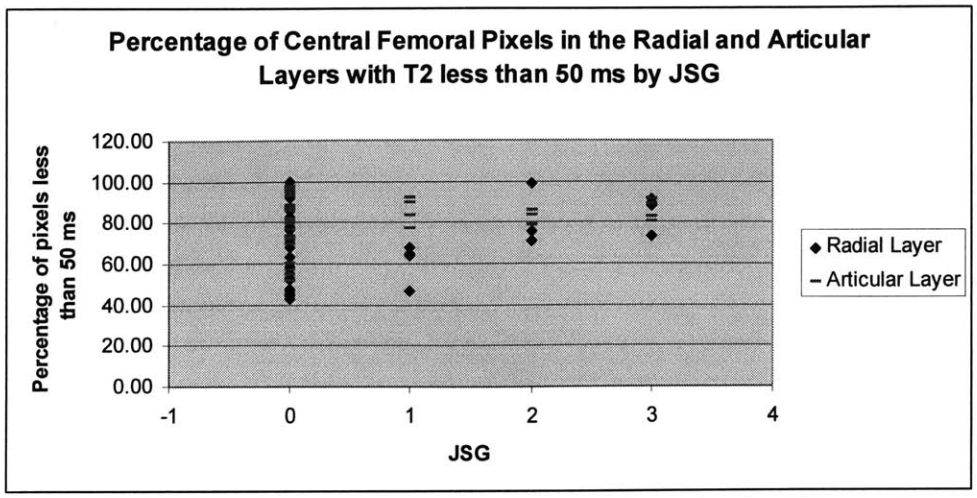


Figure 61: Percentage of pixels in the radial and articular layers less than 50 ms sorted by JSG.

	n	Average percent <50 ms	p value
Radial: Uninvolved	20	69.3	0.359
Radial: Involved	15	75.2	
Articular: Uninvolved	20	79.2	0.0941
Articular: Involved	15	84.8	

Table 41: Statistical analysis of percent T2 less than 50 ms in the radial and articular layers by uninvolved and involved compartments.

Figure 62 shows the percentage of central femoral pixels in the radial and articular layers with T2 greater than 60 ms sorted by JSG. From this plot, there is no visually observable difference between percentage above this threshold based on involved versus uninvolved compartments in either the radial or articular layers. This is verified in Table 42, which shows the results of the statistical analysis performed on the 60 ms threshold data. No statistically significant findings were observed.

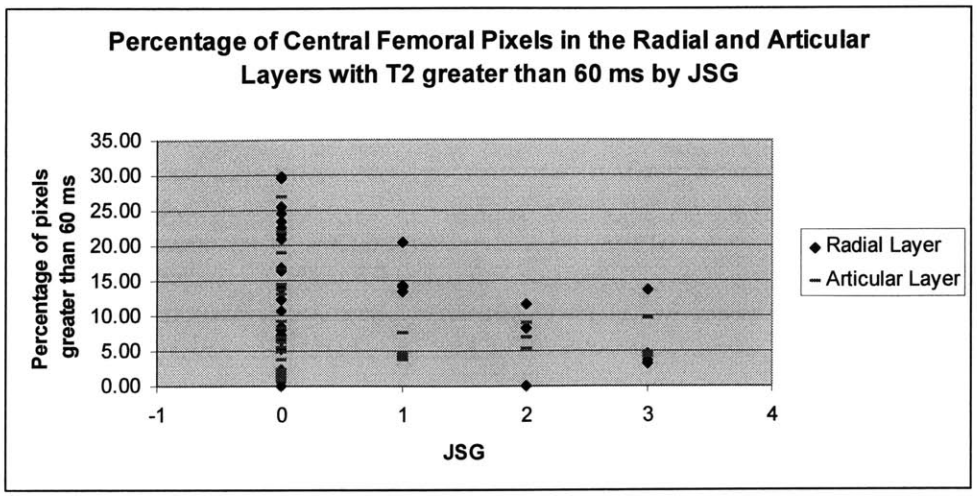


Figure 62: Percentage of pixels in the radial and articular layers greater than 60 ms sorted by JSG.

	n	Average percent >60 ms	p value
Radial: Uninvolved	20	13.0	0.319
Radial: Involved	15	9.7	
Articular: Uninvolved	20	8.5	0.117
Articular: Involved	15	5.8	

Table 42: Statistical analysis of percent T2 greater than 60 ms in the radial and articular layers by uninvolved and involved compartments.

Figure 63 shows a plot of the percentage of central femoral pixels in the radial and articular layers with T2 greater than 70 ms sorted by JSG. Table 43 shows a summary of the statistical analysis performed on data using this threshold. As with all of the other data using JSG as a metric for OA severity in the two layer threshold analysis, there were no statistically significant findings in either layer.

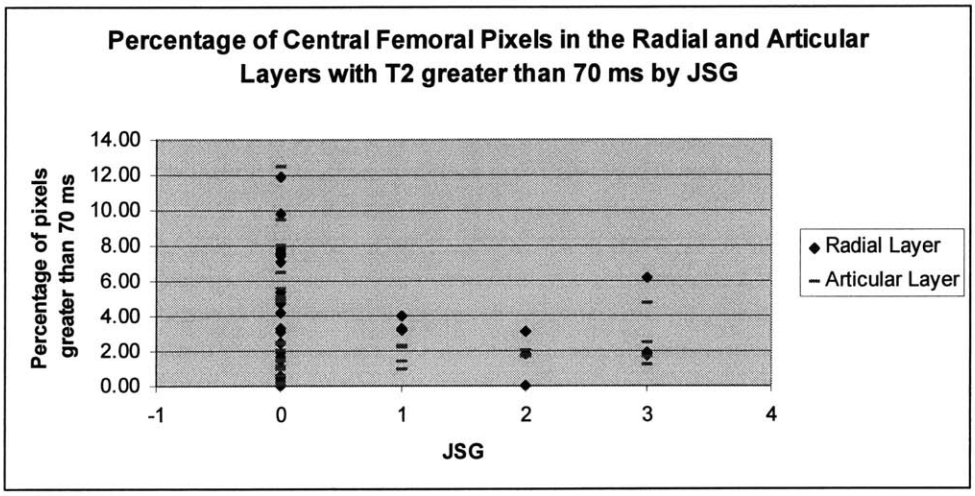


Figure 63: Percentage of pixels in the radial and articular layers greater than 70 ms sorted by JSG.

	n	Average percent >70 ms	p value
Radial: Uninvolved	20	4.0	0.154
Radial: Involved	15	2.7	
Articular: Uninvolved	20	3.0	0.208
Articular: Involved	15	2.0	

Table 43: Statistical analysis of percent T2 greater than 70 ms in the radial and articular layers by uninvolved and involved compartments.

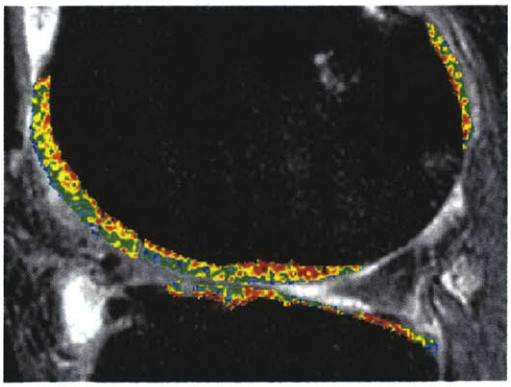
Discussion of Two-Layer T2 Threshold Analysis

In this two-layer analysis of percent of pixels above or below a threshold value in the radial or articular layer, the percentage was able to differentiate mild OA from severe OA based on K/L in the radial layer only. There were no statistically significant findings in the articular layer based on K/L, and there were no statistically significant finding using the two layer analysis based on JSG.

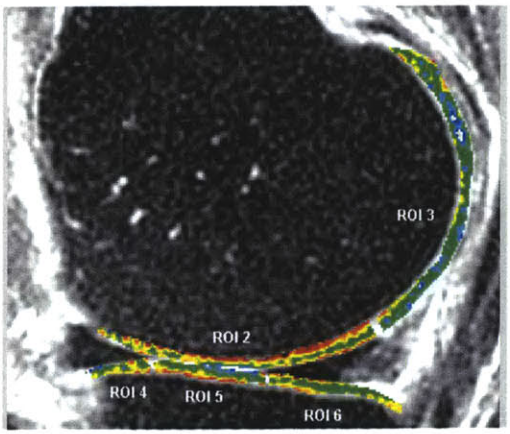
In some cases, this difference between percentage of pixels below or above a threshold value in the radial layer based on low K/L and high K/L was highly significant ($p<0.00001$). These cases used mean T2 in the radial layer, percent pixels below 30 ms in the radial layer, percent pixels below 50 ms in the radial layer, and percent pixels

above 60 ms in the radial layer. The other two thresholds tested had p values of approximately 0.002, which is also very significant according to the criterion for significance outlined in this experiment. The issue remains as to whether this is a good technique for quantitatively representing what we see in the images. Several comparisons were made between images with different T2 appearances to determine if the numbers represented what we see.

Figure 64 shows two images from the MAK study with different T2 appearances in the central femoral compartment. The image on the left belongs to MAK PZ153 lateral, and it has a large area of low T2 mottling. The image on the right belongs to MAK RW290 medial, and it has the normal, laminar T2 appearance that has been documented with T2 increasing with distance from the bone. Table 44 summarizes the mean T2 and the percent of pixels above and below the tested threshold values for the radial and articular layers. The numbers in red indicate the difference between percent for that mean or threshold value when compared to the other image.



MAK PZ153 Lateral



MAK RW290 Medial

Figure 64: Two images from the MAK dataset. MAK PZ153 has low T2 mottling/lesion, while MAK RW290 Medial has a normal, laminar appearance.

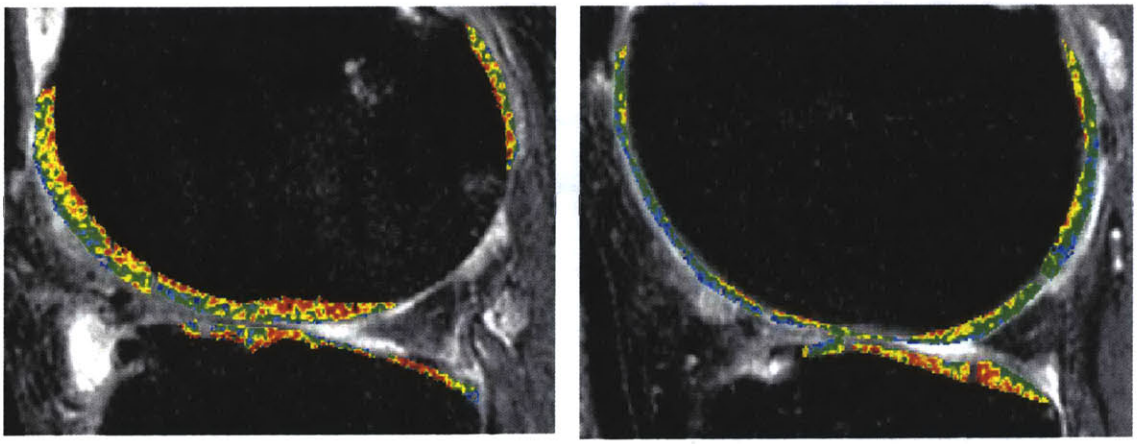
ID	Visual Inspection	Mean T2	%<20	%<30	%<50	%>60	%>70
PZ153 lateral	**Articular**						
	Low areas w/some high spots	44	1.06	12.5	72.25	9.75	2.97
	Radial						
	Low areas/ lesions	34	10.47	43.48	86.17	3.16	1.58
RW290 medial	**Articular**						
	Laminar normal high T2	45 (+1)	0 (-1.06)	1.53 **(-10.79)**	77.68 **(+5.43)**	10.70 (+0.95)	3.06 (+0.09)
	Radial						
	Laminar normal low T2	29 (-5)	23.35 **(+12.88)**	58.52 **(+15.04)**	97.53 **(+11.36)**	0.82 (-2.34)	0.00 (-1.58)

Table 44: Summary of threshold analysis on MAK PZ153 Lateral and MAK RW290 Medial.

These two images are very different in appearance, and the numbers reflect some of these differences. The means T2s are very similar in the articular layers, but RW290 has 5 ms lower average T2 in the radial layer, which reflects the more laminar appearance of this image. The bold numbers are the changes in percentage that were greater than 5%. In the articular layer, the PZ153 was expected to have larger percentages of low T2 because the mottling/low lesion extends outward into the articular layer. The articular layer of RW290 have mostly average T2 (~50 ms) with a very small amount of low T2 at the most outer edge. This is reflected in the numbers, but it is slightly surprising that the percentage for pixels less than 50 in the articular layer of RW290 is higher than that for PZ153. In this case, 50 ms maybe be too high a value to use as a cutoff. In the radial layer, from looking at the images, one would hypothesize that RW290 would have a greater percentage of low T2 because there are very few normal areas, most of the radial

layer is low (red.) PZ153 has some normal and even a few high spots in the radial layer due to the mottling and therefore, one would expect it to have a lower percentage of low T2. This is absolutely reflected in the numbers because all low categories (%<20, %<30, %<50) for RW290 medial have higher percentages than PZ153 lateral. For these two images, this technique is able to differentiate some of the important features of the images.

Another comparison between images was compared using MAK PZ153 Lateral, which as previously stated has a large low T2 area in the central femoral compartment and MAK DE269 Lateral, which has a fairly normal laminar T2 appearance. The figures are shown in Figure 65. Table 45 gives a summary of the threshold data on these two images.



MAK PZ153 Lateral **MAK DE269 Lateral**

Figure 65: MAK PZ153 Lateral (left) has a large T2 area in the central femoral compartment. MAK DE269 Lateral has a normal, laminar appearance.

ID	Visual Inspection	Mean T2	%<20	%<30	%<50	%>60	%>70
PZ153 lateral	**Articular**						
	Low areas w/some high spots	44	1.06	12.5	72.25	9.75	2.97
	Radial						
	Low areas/ lesions	34	10.47	43.48	86.17	3.16	1.58
DE269 lateral	**Articular**						
	Normal w/some low spots	44 (0)	0.00 (-1.06)	8.64 (-3.86)	76.97 (+4.72)	7.29 (-2.46)	1.92 (-1.05)
	Radial						
	Mild mottling	31 (-3)	10.96 (+0.49)	52.79 **(+9.31)**	95.22 **(+9.05)**	0.60 (-2.56)	0.20 (-1.38)

Table 45: Summary of threshold analysis on MAK PZ153 Lateral and DE269 Lateral.

Given the large difference in appearance observed in these images, these numbers are fairly close compared to the other comparison. The higher percentage of low T2 values in the radial layer of DE269 probably occurs because the there are some moderate areas of T2 in this image. Another surprising element of the numbers is that there are very few low T2 pixels in the articular layer of DE269, and there are many in the articular layer of PZ153 because the low T2 mottling/lesion extends beyond 50% of the cartilage thickness. It would be expected that the percentage of low T2 pixels in the articular layer of PZ153 would be much higher than the percentage of low T2 pixels in the articular layer of DE269. However, this is not the case, and in these images, the numbers do not reflect the differences between the images.

This two layer threshold technique gives the best numerical results to fit the data that can be seen in the images. One explanation for these highly correlated findings is that the

cartilage tends to be thin (or non-existent) in knees with high K/L when compared to images with low K/L. In this dataset, about half of the high K/L images had portions of the central femoral condyle that were completely denuded or had extremely thin cartilage. This technique divided the existing cartilage into two segments with equal thickness. In some cases where the cartilage was extremely thin, the radial layer had a thickness of only one or two pixels from the bone. In all of the images, regardless of cartilage thickness, we almost always see low T2 at the bone surface. This means that in the radial layer of a knee with thin or partially denuded cartilage, two phenomena will occur: 1) because we almost always observe low T2 at the bone surface, many of the total pixels in the ROI will have low T2 and 2) the number of total pixels will be small relative to a knee with thicker cartilage. Both of these factors combine to give a high percentage of low T2 pixels in the radial layer of the given image. Therefore, it may be possible that this technique tracks an artifactual byproduct of OA rather than physiological disease progression. However, this technique presents some interesting ideas for future work such as using absolute distance from the bone rather than relative distance as used in this technique and the normalized distance technique.

Conclusions

Several studies have shown that T2 is sensitive to some of the pathologic changes that occur in OA such as hydration and the subsequent changes in macromolecular concentration, macromolecular structure, and tissue architecture. In this *in vivo* analysis, several metrics for analyzing T2 data in an OA population were used on the MAK dataset. The previously proposed metrics for studying T2 *in vivo* in OA, such as mean

over an ROI and normalized distance from the bone, have not yielded differences large enough to be useful for clinical data analysis. In this dataset, these proposed techniques were used to determine if they could differentiate level of OA based on radiographic metrics such as K/L and JSG and dGEMRIC. While a few statistically significant correlations were found, in general, neither the mean femoral T2, the central femoral T2, nor the posterior femoral T2 were able to differentiate between the level of OA. In cases where there was a significant relationship between mean T2 and OA severity, the T2 was found to decrease with disease, which has not been previously reported *in vivo*. This observation is likely not due to the presence of Gd-DTPA^{2-}, as it has been shown not to have a dominating effect on T2 at clinical dosage and field strength [26]. In the MAK images, the main features that appeared with disease were T2 mottling and both low and high lesions. Menezes et al. [17] found low T2 to be associated with interventions that impact the collagen matrix. In the same study, T2 mottling was associated with disorganized collagen, which was verified using light microscopy.

T2 line profiles were not used in this dataset because cartilage thickness was highly irregular and in many cases, too thin to get accurate measurements.

Methods that have not been previously proposed in the literature were also used on this dataset. One such method was comparison with dGEMRIC index. There was no change in T2 with changing dGEMRIC in the uninvolved compartments, and in the involved compartments, there was a trend for decreasing T2 with decreasing dGEMRIC (increased disease) but this not statistically significant. The fact that T2 was not correlated with

dGEMRIC in the uninvolved compartment supports the findings that Gd-$DTPA^{2-}$ does not produce a dominating effect on T2.

Threshold analysis also produced statistically significant results, but again, it did not adequately represent the important features such as T2 mottling and lesions in images. When the radial and articular layers were analyzed separately using the threshold analysis, highly significant differences were noted in the radial layer of low K/L images when compared to high K/L images. While theses numbers are highly significant, it is questionable whether they are tracking disease progression or an inherent attribute of thinning cartilage, which can occur with disease.

While several studies have shown that T2 is sensitive to various changes that occur in OA, the inherent heterogeneities in T2 and the variable cartilage thickness make it difficult to use as a diagnostic tool in an OA population. As observed in this study, even with widely varying radiographic and dGEMRIC grades, the T2 mean in different ROIs only differs by a few milliseconds. Therefore, the standard metrics of mean T2, normalized T2, and z scores are difficult to apply. The insensitivity of mean T2 (and subsequent techniques relying on the mean over a ROI) may be due to the averaging of high and low T2 values that can accompany disease progression. The insensitivity could also be due to (or due in addition to averaging) cartilage degeneration mechanisms that can lead to simultaneously increasing and decreasing T2. For example, in the case of increased hydration and increased number of water interaction sites, these effects may compete to give a T2 value that would not be significantly different from that observed in healthy cartilage. Because of these heterogeneities, none of the techniques presented in

this investigation lead to conclusive results, and further work needs to be done for T2 to be diagnostic in an OA population.

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