Abstract

Magnetic resonance imaging of articular cartilage has recently been recognized as a tool for the characterization of cartilage morphology, biochemistry and function. In this paper advancements in cartilage imaging, computation of cartilage volume and thickness, and measurement of relaxation times ($T_1$ and $T_2$) are presented. In addition, the delayed uptake of Gadolinium DTPA as a marker of proteoglycan depletion is also reviewed. The cross-sectional and longitudinal studies using these imaging techniques show promise for cartilage assessment and for the study of osteoarthritis.

Key Words: magnetic resonance imaging, osteoarthritis, cartilage, collagen, proteoglycan.

Introduction

Osteoarthritis: Prevalence and Risk Factors

Osteoarthritis (OA) is a heterogeneous and multi-factorial disease characterized by the progressive loss of hyaline articular cartilage and the development of altered joint congruency, subchondral sclerosis, intraosseous cysts, and osteophytes. It affects approximately 14% of the adult population (Forman et al., 1983) and is the second most common cause of permanent disability among subjects over the age of fifty (Peyron, 1984). The initiation and pathogenesis of OA can be affected by many factors including altered mechanical loading and previous knee injury.

The relationships between knee OA and heavy mechanical work, obesity and malalignment are well established (Kohatsu and Schurman, 1990; Lindberg and Montgomery, 1987). Previous studies have demonstrated that weight gain increases the risk of OA (Manninen et al., 2004), while weight loss reduces the risk (Felson et al., 1992). Sharma et al. (2001a; 2001b) have shown that varus alignment at baseline is associated with a 4-fold increase in the odds for medial OA progression, while valgus alignment at baseline is associated with a 5-fold increase in the odds for lateral OA progression. Cicuttini et al. have shown that malalignment at baseline is associated with cartilage loss over two years (Cicuttini et al., 2004c).

Relative to other risk factors, post-traumatic OA (that follows injuries that deform the articular surface or alter joint geometry), tends to develop relatively soon after the index injury (e.g., two years (Wright, 1990)) because of the severity of this biomechanical input to the disease process. In a five-year follow-up of thirty-two patients who underwent surgery for anterior cruciate ligament (ACL) tear, 72% complained of knee pain, 66% had knee swelling, and 37% reported impaired activities of daily living (Feagin, 1979; Wright, 1990). Numerous articles have reported an increased incidence of knee OA following meniscal surgery (Daniel et al., 1994; Fairbank, 1984; Lynch et al., 1983). In a three to ten year (average 3.8) follow-up of 196 patients with meniscal tears associated with ACL injury, Lynch et al. (1983) observed radiographic changes consistent with degenerative joint disease (joint-space narrowing, osteophytes and articular surface flattening) in 88% of the 140 patients who underwent partial or complete meniscectomy. These studies suggest that traumatic injury and surgical intervention are risk factors for OA.
Natural History
The initial stages of OA include proteoglycan loss, increased water content, and disorganization of the collagen network. With further degeneration, cartilage tissue becomes ulcerated causing proteoglycans to diffuse into the synovial fluid, thus decreasing water content in cartilage. The intermediate stages of OA include cartilage thinning, fibrillation, and decreased proteoglycan and water content. In the late stages of OA, collagen, proteoglycan, and water content are further reduced, and the collagen network is severely disrupted (Dijkgraaf et al., 1995).

Imaging of Osteoarthritis of the Knee

Radiography
Primary evaluation of arthritis has relied primarily on plain radiography (Altman et al., 1987), which depicts only gross osseous changes that tend to occur late in the disease. Early changes in the cartilage and other articular tissues are not directly visible. Cartilage loss can only be indirectly inferred by the development of joint-space narrowing, which can be highly unreliable even with careful attention to proper technique (Rogers et al., 1990). False-positive rates as high as 20-40% have been reported for this parameter. In addition, plain radiographs are insensitive to focal cartilage loss, and widening of the joint space despite significant cartilage loss can occur in one compartment of the knee simply as a result of narrowing in the other compartment (Chan et al., 1990). Furthermore, meniscal position and degeneration affect joint-space narrowing (Hunter et al., 2006b), demonstrating that joint-space narrowing is unspecific to global cartilage loss and can implicate various morphologic changes in the joint. Radiographic changes reflect the pathologic changes in cartilage and bone, but they do not generally correlate with the severity of pathologic joint destruction. Since the pathologic/radiographic findings of disease do not always correlate with joint symptoms in cross-sectional studies, the pathologic aspect of the disease does not always correlate with the clinical prevalence or natural history of OA. Dougados et al. (1992) reported that although radiographic progression was rare by crude Kellgren and Lawrence (Kellgren and Lawrence, 1957) grading, some symptomatic improvement with current treatment was seen over one year of follow-up. Longer term studies have shown that radiographic progression occurs in up to two-thirds of the patients and that improvement is rare (Schouten et al., 1992; Spector et al., 1992). Radiographic progression was more prevalent in patients who had earlier evidence of structural changes, femoral or tibial sclerosis.

Magnetic Resonance Imaging of Knee OA
Magnetic resonance (MR) imaging is ideal for monitoring arthritis. MR offers multi-planar capabilities, high spatial resolution without ionizing radiation, and superior contrast between joint tissues; thus it has gained popularity as a modality for assessing OA. By combining this contrast with moderate in-plane resolution (469 microns x 938 microns) and relatively thin slices (1.5 mm) on a 1.5 T scanner, Recht, et al. (1993) showed 96% sensitivity and 95% specificity for detecting cartilage abnormalities visible in cadaveric knees following pathological section. Several studies have graded cartilage lesions in OA subjects and compared the severity of these lesions, with other findings such as meniscal defects, the presence of marrow lesions, and radiographic and clinical scores (Felson et al., 2001; Felson et al., 2003; Link et al., 2003).

Quantitative MR methods for measuring the relaxation properties in cartilage may aid in the diagnosis of early OA prior to irreversible morphologic changes. This article will review MR imaging quantification techniques for cartilage assessment and their applications to OA imaging. Cartilage volume and thickness measurements, $T_2$ mapping, $T_1$ mapping, and dGEMRIC imaging will be discussed. A summary with a limited list of references for the techniques reviewed is presented in Table 1. While MR derived measurements of water diffusion have also been studied in articular cartilage, given the limited scope of this review, these aspects will not be discussed in this paper.

Quantitative MR Imaging to Measure Knee Cartilage Thickness and Volume
High-resolution MR images have been used to quantify cartilage volume and thickness in OA. MR sequences that best delineate the cartilage from the surrounding tissues such as fat-suppressed spoiled gradient echo and fast double echo and steady state (DESS) with water-excitation, are used for segmentation. To date, a fully automated technique for cartilage segmentation has not been established due to the inherently low contrast between cartilage and surrounding tissues (Eckstein et al., 2006). The cartilage is segmented slice-by-slice using a semi-automatic technique such as region growing (Peterfy et al., 1994), edge detection (Kshirsagar et al., 1998), or shape modelling (Solloway et al., 1997). An example of segmentation is illustrated in Figure 1, in which the femoral and tibial knee cartilage is segmented. Cartilage volume is calculated by summing the pixels in the segmented regions, and cartilage thickness can be determined using methods such as the Euclidean Distance Transformation (Stammberger et al., 1999), or by calculating a vector perpendicular to the articular cartilage or bone surface (Cohen et al., 1999; Losch et al., 1997). Cartilage thickness maps, which illustrate the regional variations in cartilage thickness, are helpful for visualizing focal differences in cartilage thickness (Figure 2). The inter-and intra-observer reproducibility of these techniques ranges from approximately 1-9% and has been elegantly summarized by Eckstein et al. (2006).

Longitudinal studies have been used to quantify cartilage changes in OA and have found a variety of results. Gandy et al. reported no changes in cartilage volume in OA subjects (Gandy et al., 2002), while other studies (Eckstein et al., 2006) have shown an approximate loss of 4-6% of cartilage annually. It is interesting to note a large standard deviation in percentage of cartilage loss, which is indicative of the heterogeneity of the disease.

MR imaging studies have evaluated the relationship between changes in cartilage and other knee joint tissues in OA. Lindsey et al. and Blumenkrantz et al. have found that cartilage loss on one side of the knee joint is related to...
A recent longitudinal study by Hunter et al. (2006a) has demonstrated that enlarging bone marrow lesions are associated with cartilage loss in OA. An inverse relationship between pain, as measured by the Western Ontario and McMaster Universities scoring system (WOMAC), and cartilage volume has been demonstrated (Cicuttini et al., 2002; Hunter et al., 2003; Lindsey et al., 2004; Wluka et al., 2004). Therefore, the measurement of cartilage volume using MR imaging provides longitudinal quantification of cartilage loss in OA and establishes links between cartilage loss and degenerative changes in other tissues of the knee joint.

### T₂ mapping

Quantitative T₂ relaxation time is a non-invasive marker of cartilage degeneration because it is sensitive to tissue hydration and biochemical composition. Immobilization of water protons in cartilage by the collagen-proteoglycan matrix promotes T₂ decay and renders the cartilage low in signal intensity on long-TE (T₂-weighted) images, while

---

**Table 1**: A summary (with a limited list of references) of the quantitative imaging techniques for cartilage evaluation.

<table>
<thead>
<tr>
<th>Imaging Technique</th>
<th>Affected By:</th>
<th>In Vitro Studies:</th>
<th>In Vivo Studies:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cartilage volume and thickness calculations</td>
<td>• Hydration</td>
<td>• Cohen et al. (Cohen et al., 1999)</td>
<td>• Blumenkrantz et al. (Blumenkrantz et al., 2004b)</td>
</tr>
<tr>
<td></td>
<td>• Loading</td>
<td>• Peterfy et al. (Peterfy et al., 1994)</td>
<td>• Cicuttini et al. (Cicuttini et al., 2004a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Sittek et al. (Sittek et al., 1996)</td>
<td>• Cicuttini et al., 2004d; Cicuttini et al., 2004e)</td>
</tr>
<tr>
<td></td>
<td>• T₁ mapping</td>
<td>• David-Vaudey et al. (David-Vaudey et al., 2004)</td>
<td>• Eckstein et al. (Eckstein et al., 2005)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Goodwin et al. (Goodwin and Dunn, 1998; Goodwin et al., 1998; Goodwin et al., 2004)</td>
<td>• Eckstein et al., 2006; Eckstein et al., 2002a; Eckstein et al., 2002b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lammentausta et al. (Lammentausta et al., 2006)</td>
<td>• Gandy et al. (Gandy et al., 2002)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Menezes et al. (Menezes et al., 2004)</td>
<td>• Lindsey et al. (Lindsey et al., 2004)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Warin-Pinzano et al. (Warin-Pinzano et al., 2004a; Warin-Pinzano et al., 2004b; Warin-Pinzano et al., 2005)</td>
<td>• Peterfy et al. (Peterfy et al., 1994)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Xia et al. (Xia, 1998; Xia et al., 1994)</td>
<td>• Raynauld et al. (Raynauld et al., 2003; Raynauld et al., 2006; Raynauld et al., 2004)</td>
</tr>
<tr>
<td></td>
<td>• T₂ mapping</td>
<td>• Li et al. (Li et al., 2006)</td>
<td>• Wluka et al. (Wluka et al., 2002; Wluka et al., 2004)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pakin et al. (Pakin et al., 2006a; Pakin et al., 2006b)</td>
<td>• Smith et al. (Smith et al., 2001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Regatte et al. (Regatte et al., 2002; Regatte et al., 2006; Regatte et al., 2004)</td>
<td>• Li et al. (Li et al., 2007; Li et al., 2005; Li et al., 2006)</td>
</tr>
<tr>
<td>Macromolecular concentration including GAG, collagen</td>
<td>• Hydration</td>
<td>• Akella et al. (Akella et al., 2001)</td>
<td>• Pakin et al. (Pakin et al., 2006a; Pakin et al., 2006b)</td>
</tr>
<tr>
<td></td>
<td>• Duvvuri et al. (Duvvuri et al., 1997)</td>
<td>• Mlynarik et al. (Mlynarik et al., 2004; Mlynarik et al., 1999)</td>
<td>• Regatte et al. (Regatte et al., 2003; Regatte et al., 2006; Regatte et al., 2004)</td>
</tr>
<tr>
<td></td>
<td>• Menezes et al. (Menezes et al., 2004)</td>
<td>• Wheaton et al. (Wheaton et al., 2004; Wheaton et al., 2005)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mlynarik et al. (Mlynarik et al., 1997)</td>
<td>• Wheaton et al. (Wheaton et al., 2004; Wheaton et al., 2005)</td>
<td></td>
</tr>
<tr>
<td>dGEMRIC</td>
<td>• GAG concentration</td>
<td>• Bashir et al. (Bashir et al., 1996b; Bashir et al., 1999)</td>
<td>• Burstein et al. (Burstein et al., 2001)</td>
</tr>
<tr>
<td></td>
<td>• Kurkijarvi et al. (Kurkijarvi et al., 2004)</td>
<td>• Lammentausta et al. (Lammentausta et al., 2006)</td>
<td>• Cunningham et al. (Cunningham et al., 2006)</td>
</tr>
<tr>
<td></td>
<td>• Nieminen et al. (Nieminen et al., 2004a; Nieminen et al., 2004b)</td>
<td>• Nieminen et al. (Nieminen et al., 2004a; Nieminen et al., 2004b)</td>
<td>• Gillis et al. (Gillis et al., 2001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Nissi et al. (Nissi et al., 2004)</td>
<td>• Kim et al. (Kim et al., 2003)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Samosky et al. (Samosky et al., 2005)</td>
<td>• Kimelman et al. (Kimelman et al., 2006)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• McKenzie et al. (McKenzie et al., 2006)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Roos et al. (Roos and Dahlberg, 2005)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Tiderius et al. (Tiderius et al., 2006)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Williams et al. (Williams et al., 2004; Williams et al., 2005)</td>
</tr>
</tbody>
</table>

---

The measurement of cartilage volume using MR imaging provides longitudinal quantification of cartilage loss in OA and establishes links between cartilage loss and degenerative changes in other tissues of the knee joint. This information can be used to monitor disease progression and assess the efficacy of therapeutic interventions.
mobile water protons in synovial fluid retain their high signal. Loss of collagen and proteoglycan in degenerating cartilage increases the mobility of water, thus increasing its signal intensity on T₂-weighted images (Konig et al., 1987). Signal intensity is further augmented in degenerative disease by the elevation of cartilage water content (i.e., proton density) that accompanies matrix loss (Lehner et al., 1989). Consistent with this, foci of high signal intensity are often seen within the cartilage of osteoarthritic knees with OA on T₂-weighted images and have been shown to correspond to arthroscopically demonstrable abnormalities (Broderick et al., 1994; Peterfy, 2002).

Cartilage T₂ maps are created using the following process: Typically, T₂-weighted multi-echo, spin echo images with varying echo times (TE) and identical repetition times (TR) are acquired. Second, T₂ maps are computed (Figure 3) assuming exponential signal decay. T₂ is defined as the time at which the signal decays to 37% of the maximum signal.

In vitro imaging studies have evaluated the relationship between biochemistry of cartilage and T₂ measurements. Cartilage T₂ is affected by hydration and the integrity of the collagen matrix; however, the relationship between T₂ and proteoglycan content remains controversial in literature. Proteoglycan loss in rat patellar cartilage induced by hyaluronidase degradation (which does not alter the collagen network) was associated with significantly increased global T₂ (Watrin-Pinzano et al., 2005). However, other studies (Borthakur et al., 2000; Mlynarik et al., 1999; Toffanin et al., 2001) found that the depletion of proteoglycan had minimal effects on T₂. These in vitro studies demonstrate that the biochemical changes associated with cartilage degeneration are related to elevated T₂; however, the effects of proteoglycan concentration on T₂ must be further evaluated.

The relationship between T₂ relaxation time and the mechanical properties of cartilage is under investigation. A recent in vitro study by (Lammentausta et al., 2006) has shown that T₂ relaxation time in human patellar cartilage is significantly correlated to Young’s Modulus, suggesting that T₂ quantification may predict the mechanical properties of cartilage.

The signal intensity of cartilage in an MR image is dependent on its orientation to the main magnetic field. An in vitro study using high-field (8.6T) microscopic MRI (mMRI) has suggested that the angular dependency of T₂ with respect to the main magnetic field (B₀) can provide specific information about the collagen ultra-structure (Xia, 1998). Goodwin et al. (Goodwin et al., 1998) have described how T₂ will vary with depth from the articular surface due to collagen fibril orientation to B₀. Imaging of the femoral condyles can be challenging due to the bulk curvature of the cartilage altering the depth-dependent fibril orientation. However, a comprehensive in vivo study has
shown that the “magic-angle effect” may not be the major determinant of T2 heterogeneity in high-curvature articular cartilage (Mosher et al., 2001).

In vivo MR imaging studies have demonstrated that cartilage T2 values are related to age, and vary from the subchondral bone to the cartilage surface (Dardzinski et al., 2002; Mosher et al., 2000). Dunn et al. have shown that the cartilage T2 values are associated with the severity of OA, and variations exist between tibial and femoral cartilage T2 (Dunn et al., 2004). Dunn et al. used Z-score maps to compare cartilage T2 values of OA subjects to those in control subjects. Voxel based Z-scores were generated in each compartment of the articular cartilage for the T2 images. A voxel in a Z–image was calculated by (VoxelI - Mean normal,compartment)/SD normal,compartment, where VoxelI is the T2 in the voxel of interest, Mean normal,compartment is the mean T2 for all voxels of the normal knees in that compartment, and the SD normal,compartment is the standard deviation of the same normal T2 distribution. The Z-score maps normalize the T2 results for each subject to the mean value of the control subjects. Figure 4 illustrates Z-score maps of a control, a mild OA subject, and a severe OA subject, respectively. These maps demonstrate the heterogeneity of cartilage T2 values. Studies have evaluated the spatial distribution of cartilage T2: Dray et al. (2005) found no difference between mean T2 values in OA cartilage; however, they showed visual differences in the spatial distribution of the T2 values. These results demonstrate the necessity to characterize and quantify the spatial distribution of cartilage T2 values. Recent studies have used texture analysis to quantify the differences in spatial distribution of T2 values and reported that entropy of cartilage T2 is significantly greater in osteoarthritic cartilage than in healthy cartilage (Blumenkrantz et al., 2005). By non-invasively evaluating cartilage integrity, T2 relaxation time may provide insight on the heterogeneity of cartilage degeneration in OA.

The relationship between T1ρ and cartilage morphology has been evaluated cross-sectionally and longitudinally. Studies have shown an inverse relationship between cartilage T2 and cartilage thickness (Blumenkrantz et al., 2004b; Dunn et al., 2004). A recent study has shown that higher medial cartilage T2 results in greater loss of medial cartilage volume at twelve months, demonstrating a relationship between cartilage T2 and cartilage volume (Blumenkrantz et al., 2004a). A longitudinal study showed significant (p < 0.05) increases in mean cartilage T2 between baseline and 12-months in the medial and lateral femur and the medial tibia for both mild and severe OA groups (Blumenkrantz et al., 2004b).

In cartilage, the proteoglycan (PG) is largely responsible for the high elasticity and resilience of tissue. PG consists of a central protein core to which a large number of negatively charged glycosaminoglycan (GAG) side chains are covalently attached. The PG content of cartilage can be probed using spin lattice relaxation in the rotating frame (T1ρ-weighted imaging) (Akella et al., 2001; Duvvuri et al., 1997; Regatte et al., 2003). A T1ρ sequence, consisting of a three-pulse cluster and gradient crushers, prepares the T1ρ-weighted magnetization. Briefly, first, a π/2 pulse applied along the x-axis flips the longitudinal magnetization into the transverse plane along the y-axis. Then, a long, low power pulse is applied along the y-axis to spin-lock the magnetization. The second π/2 pulse flips this spin-locked magnetization back to the z-axis. Residual transverse magnetization is then dephased by a crusher gradient. Magnetization stored along the z-axis is then read out by a fast spin echo (FSE) sequence or a gradient echo sequence. T1ρ can be calculated by fitting the signal (S) intensity obtained for different spin-locking times (TSL) using equation 1. Quantitative T1ρ imaging methods are well-suited for probing macromolecular slow motions at high static fields in cartilage.

\[ S(TSL) \propto e^{(-TSL/T_{1\rho})} \] (1)

In vitro studies have evaluated the relationship between T1ρ relaxation time and the biochemical composition of cartilage.
cartilage. Akella et al. have demonstrated that over 50% depletion of PG from bovine articular cartilage resulted in average $T_1^\rho$ increases from 110–170 ms (Akella et al., 2001). Regression analysis of the data showed a strong correlation ($R^2$=0.987) between changes in PG and $T_1^\rho$. Similar to $T_2$, in vitro studies have demonstrated regional variations of cartilage $T_1^\rho$. $T_1^\rho$ values were highest at the superficial zone, decreased gradually in the middle zone, and increased in the region near the subchondral bone (Akella et al., 2001). Wheaton et al. found correlations between $T_1^\rho$, relaxation time, proteoglycan, and mechanical properties of bovine cartilage explants including aggregate modulus and hydraulic permeability (Wheaton et al., 2005).

In vivo studies show increased cartilage $T_1^\rho$ values in OA subjects compared to controls (Li et al., 2005a; Regatte et al., 2004), which reflects the potential for $T_1^\rho$ imaging for non-invasive evaluation of diseased cartilage. Studies have used $T_1^\rho$ imaging to evaluate cartilage overlying bone marrow oedema (BME) caused by trauma. Average $T_1^\rho$ values in cartilage overlying BME were significantly higher than those in surrounding cartilage (51.8 ± 10.8 ms vs. 43.0 ± 8.3 ms, $p = 0.032$), demonstrating that macromolecular changes in cartilage may be related to BME (Majumdar et al., 2006).

The differences between $T_1$ and $T_1^\rho$ in cartilage have been explored. Myryanik et al. (1999) showed that the $T_1^\rho$ relaxation times were slightly longer than the corresponding $T_1$ values, but both parameters showed almost identical spatial distributions. Menezes et al. (2004) have recently shown that $T_1^\rho$ and $T_1$ changes in articular cartilage do not necessarily coincide, and might provide complimentary information. These investigators showed that $T_1^\rho$ and $T_1$ reflect changes that may be associated with proteoglycan, collagen content and hydration, and the true mechanism of $T_1^\rho$ may arise from a weighted-average of multiple biochemical changes occurring in cartilage in OA. Using this premise, it is possible that $T_1^\rho$ may have a dependence on the angular orientation of the collagen fibres.

$T_1^\rho$ has a larger dynamic range than $T_1$ (Regatte et al., 2004), indicating that it may be more sensitive to degenerative changes occurring in cartilage OA. A recent study by Majumdar et al. investigated the differences in $T_1$ and $T_1^\rho$ values between OA patients and controls. A significant correlation was found between average $T_1^\rho$ and $T_1$ values within the cartilage, with a correlation coefficient $R^2=0.69$ and $p=0.017$. The average $T_1^\rho$ in OA patients (52.28 ms) was 19.1% greater than that of controls (43.90 ms) (Figure 5). The average $T_1$ (38.31 ms) in OA patients was only 9.6% greater than that of controls (34.94 ms). OA patients had a significantly ($p = 0.003$) increased cartilage $T_1^\rho$ compared to controls, while the increase in $T_1$ was insignificant ($p = 0.202$) (Majumdar et al., 2006), demonstrating that patients with similar average $T_1$ may have different $T_1^\rho$ or vice versa. These studies suggest that average $T_1^\rho$ may be used to distinguish OA cartilage from healthy cartilage, while $T_1$ may not be able to. Figure 6 shows $T_1^\rho$ and $T_2$ maps from a control subject, a subject with mild OA, and a subject with severe OA. The differences between the $T_1^\rho$ and $T_2$ maps are evident.

dGEMRIC Imaging

The change in GAG concentration evident in early OA is associated with a change in tissue fixed charge density (FCD). This change in FCD (arising due to the loss of proteoglycans), can be detected by differences in the uptake of a charged contrast agent such as Gd-DTPA$^2$- (Bashir et al., 1996). Delayed contrast-enhanced MRI of cartilage (dGEMRIC) can be used to study cartilage GAG content and distribution in the knee (Burstein et al., 2001; McKenzie et al., 2006; Roos and Dahlberg, 2005; Tiderius et al., 2006; Tiderius et al., 2003; Williams et al., 2005) and the hip (Boesen et al., 2006; Cunningham et al., 2006). In dGEMRIC imaging, negatively-charged, intra-venous Gd-DTPA$^2$- is absorbed in articular cartilage. The negatively charged GAG in articular cartilage repels the negatively charged contrast agent. In diseased cartilage, the contrast agent is easily absorbed due to the abundance of GAG. However, in healthy cartilage, the contrast agent is less likely to be absorbed due to the abundance of GAG. The distribution of Gd-DTPA$^2$- is calculated based on the $T_1$ relaxation time of the tissue.

In the dGEMRIC imaging protocol as suggested by Burstein et al., the contrast agent is injected intra-venously, the subject exercises for approximately 10 minutes, and imaging is performed after about 2-3 hours for the knee and 30-90 minutes for the hip (Burstein et al., 2001). The reproducibility of this technique is 10-15% for images taken two weeks to two months apart (Burstein et al., 2001). The inter-observer variability (6 investigators) for calculating $T_1^\rho$ values using a large region of interest (ROI)
in both the lateral and medial femoral weight-bearing cartilage was 1.3%-2.3%. The intra-observer reproducibility for \( T_1 \) measurements was 2.6% for the lateral femoral cartilage and 1.5% for the medial femoral cartilage (Tiderius et al., 2004). The low inter- and intra-observer variability for the dGEMRIC technique demonstrates the potential in vivo role of contrast-enhanced MR imaging in quantifying articular cartilage changes in OA.

Bashir et al. found that regions of cartilage degeneration (from trypsin or interleukin) showed histological differences, as well as differences in the post-contrast (Gd-DTPA\(^2\)) signal intensity and \( T_1 \) relaxation time. When injected in subjects, intra-venous Gd-DTPA\(^2\) is absorbed in articular cartilage two to eight hours post-injection, and this uptake is manifested as a signal intensity and \( T_1 \) change (Bashir et al., 1996).

3D dGEMRIC sequences have been implemented at 1.5 T and 3 T for use in clinical studies (McKenzie et al., 2006). Figure 7 illustrates sagittal images of the knee (identical window and level) that can be used to measure \( T_1 \) relaxation time and determine the distribution of Gd-DTPA\(^2\) in cartilage. The sensitivity of dGEMRIC is affected by various factors: For example, the amount of contrast agent absorbed in cartilage is dependent on the dose. A study by Burstein et al. showed that \( T_1 \) in patellar cartilage was 636 ± 70 ms after 1 dose and was 506 ± 38 ms after a double-dose. Their study reported that that a greater dose provides increased sensitivity (Burstein et al., 2001). Body mass index (BMI) also affects contrast concentration and must be carefully considered when designing cross-sectional studies (Tiderius et al., 2006).

dGEMRIC has been used to evaluate knee cartilage in OA patients (Williams et al., 2005). In OA, the dGEMRIC index is associated with joint space width, Kellgren Lawrence (KL) grading scale and malalignment. Varus malalignment is associated with a lower dGEMRIC index on the medial side, while the opposite trend is evident in valgus malalignment (Williams et al., 2005). Knee cartilage in a given KL score has a wide-range of dGEMRIC values, demonstrating that dGEMRIC may provide additional information to the radiographic classification of OA (Williams et al., 2005). Correlations between dGEMRIC index and pain, as measured by WOMAC, are evident in patients with hip dysplasia (Kim et al., 2003). dGEMRIC studies have evaluated potential therapies in OA, demonstrated that moderate exercise can improve knee cartilage GAG (estimated by \( T_1 \) in the presence of Gd-DTPA) in patients with high risk of OA (Roos and Dahlberg, 2005). Gillis et al. reported that dGEMRIC can be used to monitor GAG content in autologous chondrocyte transplantation (Gillis et al., 2001).
Studies have demonstrated a relationship between dGEMRIC and mechanical properties of cartilage (Lammentausta et al., 2006; Nissi et al., 2004). Kurkijarvi et al. found that dGEMRIC is correlated with compressive stiffness in non-arthritic human knee cartilage specimens (Kurkijarvi et al., 2004). In another study, tibial plateaus from patients undergoing total knee arthroplasty were indented to determine the relationship between compressive stiffness and GAG content. The strength of the correlation between GAG and local stiffness was dependent on the depth of the region in which the average GAG content was calculated. The highest correlations were found when GAG content was averaged in a region similar in depth to the indentation (Samosky et al., 2005), reflecting the heterogeneity of GAG distribution in cartilage. A study by Nieminen et al. indicated that the combination of T1ρ quantification and Gd-DTPA2- enhanced imaging best characterized the mechanical properties of cartilage (Nieminen et al., 2004b). These results suggest that the combination of quantitative MR imaging techniques may predict the mechanical properties of cartilage.

dGEMRIC is valuable in assessing early OA as it provides specific information on the distribution and content of GAG in cartilage. When implementing dGEMRIC, factors such as the concentration of contrast agent and the delay-time for imaging post-injection must be carefully considered. Research studies on contrast-enhanced MRI establish the utility for using dGEMRIC to evaluate diseased cartilage and warrant further studies to investigate the therapeutic efficacy of treatments for OA.

Summary and Conclusion

Quantitative MR imaging of cartilage volume and thickness, T2 mapping, T1ρ mapping and dGEMRIC have been used to study OA non-invasively. One of the fundamental goals of MR imaging in OA is to diagnose OA at an early stage, such that treatment may be implemented before irreversible morphologic degeneration occurs. Since T1ρ, T2, and dGEMRIC techniques are sensitive to different aspects of cartilage degeneration, future research on the combination of these techniques may be useful in the characterization of early OA. Quantitative MR imaging appears promising and may potentially provide information beyond morphological changes in articular cartilage, with regards to early cartilage degeneration and biochemistry. Relationships between MR parameters and biochemistry, loading, gene and protein expression, disease progression and pain are clearly warranted.

References


Blumenkrantz G, Dunn TC, Carballido-Gamio J, Link TM, Majumdar S (2005) Spatial heterogeneity of cartilage T\textsubscript{2} in osteoarthritic patients. In OARSI. Boston, MA


Dugoud M, Gueguen A, Nguyen M, Thiesse A, Listrat V, Jacob L, Nakache JP.


