QUANTITATIVE MAGNETIC RESONANCE IMAGING OF ARTICULAR CARTILAGE IN OSTEOARTHRITIS

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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_2 and $T_{1\rho}$) 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.

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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, $T_{1\rho}$ 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

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

Imaging Technique	Affected By:	<i>In Vitro</i> Studies:	<i>In Vivo</i> Studies:
Cartilage volume and thickness calculations	<ul style="list-style-type: none"> Hydration Loading 	<ul style="list-style-type: none"> Cohen <i>et al.</i> (Cohen <i>et al.</i>, 1999) Peterfy <i>et al.</i> (Peterfy <i>et al.</i>, 1994) Sittek <i>et al.</i> (Sittek <i>et al.</i>, 1996) 	<ul style="list-style-type: none"> Blumenkrantz <i>et al.</i> (Blumenkrantz <i>et al.</i>, 2004b) Cicuttini <i>et al.</i> (Cicuttini <i>et al.</i>, 2004a; Cicuttini <i>et al.</i>, 2004c; Cicuttini <i>et al.</i>, 2004d; Cicuttini <i>et al.</i>, 2004e) Eckstein <i>et al.</i> (Eckstein <i>et al.</i>, 2005; Eckstein <i>et al.</i>, 2006; Eckstein <i>et al.</i>, 2002a; Eckstein <i>et al.</i>, 2002b) Gandy <i>et al.</i> (Gandy <i>et al.</i>, 2002) Lindsey <i>et al.</i> (Lindsey <i>et al.</i>, 2004) Peterfy <i>et al.</i> (Peterfy <i>et al.</i>, 1994) Raynauld <i>et al.</i> (Raynauld <i>et al.</i>, 2003; Raynauld <i>et al.</i>, 2006; Raynauld <i>et al.</i>, 2004) Wluka <i>et al.</i> (Wluka <i>et al.</i>, 2002; Wluka <i>et al.</i>, 2004)
T ₂ mapping	<ul style="list-style-type: none"> Integrity of collagen network Hydration 	<ul style="list-style-type: none"> David-Vaudey <i>et al.</i> (David-Vaudey <i>et al.</i>, 2004) Goodwin <i>et al.</i> (Goodwin and Dunn, 1998; Goodwin <i>et al.</i>, 1998; Goodwin <i>et al.</i>, 2004) Lammentausta <i>et al.</i> (Lammentausta <i>et al.</i>, 2006) Menezes <i>et al.</i> (Menezes <i>et al.</i>, 2004) Watrin-Pinzano <i>et al.</i> (Watrin-Pinzano <i>et al.</i>, 2004a; Watrin-Pinzano <i>et al.</i>, 2004b; Watrin-Pinzano <i>et al.</i>, 2005) Xia <i>et al.</i> (Xia, 1998; Xia <i>et al.</i>, 1994) 	<ul style="list-style-type: none"> Dardzinski <i>et al.</i> (Dardzinski <i>et al.</i>, 2002; Dardzinski <i>et al.</i>, 1997) Dray <i>et al.</i> (Dray <i>et al.</i>, 2005) Dunn <i>et al.</i> (Dunn <i>et al.</i>, 2004) Mosher <i>et al.</i> (Mosher <i>et al.</i>, 2004; Mosher <i>et al.</i>, 2000; Mosher <i>et al.</i>, 2001; Mosher <i>et al.</i>, 2005) Smith <i>et al.</i> (Smith <i>et al.</i>, 2001)
T _{1ρ} mapping	<ul style="list-style-type: none"> Macromolecular concentration including GAG, collagen Hydration 	<ul style="list-style-type: none"> Akella <i>et al.</i> (Akella <i>et al.</i>, 2001) Duvvuri <i>et al.</i> (Duvvuri <i>et al.</i>, 1997) Menezes <i>et al.</i> (Menezes <i>et al.</i>, 2004) Mlynarik <i>et al.</i> (Mlynarik <i>et al.</i>, 2004; Mlynarik <i>et al.</i>, 1999) Regatte <i>et al.</i> (Regatte <i>et al.</i>, 2002) Wheaton <i>et al.</i> (Wheaton <i>et al.</i>, 2004; Wheaton <i>et al.</i>, 2005) 	<ul style="list-style-type: none"> Li <i>et al.</i> (Li <i>et al.</i>, 2007; Li <i>et al.</i>, 2005; Li <i>et al.</i>, 2006) Pakin <i>et al.</i> (Pakin <i>et al.</i>, 2006a; Pakin <i>et al.</i>, 2006b) Regatte <i>et al.</i> (Regatte <i>et al.</i>, 2003; Regatte <i>et al.</i>, 2006; Regatte <i>et al.</i>, 2004)
dGEMRIC	<ul style="list-style-type: none"> GAG concentration 	<ul style="list-style-type: none"> Bashir <i>et al.</i> (Bashir <i>et al.</i>, 1996b; Bashir <i>et al.</i>, 1999) Kurkijarvi <i>et al.</i> (Kurkijarvi <i>et al.</i>, 2004) Lammenstausta <i>et al.</i> (Lammenstausta <i>et al.</i>, 2006) Nieminen <i>et al.</i> (Nieminen <i>et al.</i>, 2004a; Nieminen <i>et al.</i>, 2004b) Nissi <i>et al.</i> (Nissi <i>et al.</i>, 2004) Samosky <i>et al.</i> (Samosky <i>et al.</i>, 2005) 	<ul style="list-style-type: none"> Burstein <i>et al.</i> (Burstein <i>et al.</i>, 2001) Cunningham <i>et al.</i> (Cunningham <i>et al.</i>, 2006) Gillis <i>et al.</i> (Gillis <i>et al.</i>, 2001) Kim <i>et al.</i> (Kim <i>et al.</i>, 2003) Kimelman <i>et al.</i> (Kimelman <i>et al.</i>, 2006) McKenzie <i>et al.</i> (McKenzie <i>et al.</i>, 2006) Roos <i>et al.</i> (Roos and Dahlberg, 2005) Tiderius <i>et al.</i> (Tiderius <i>et al.</i>, 2006) Williams <i>et al.</i> (Williams <i>et al.</i>, 2004; Williams <i>et al.</i>, 2005)

trabecular bone loss on the opposite side of the knee joint (Blumenkrantz *et al.*, 2004b; Lindsey *et al.*, 2004). Cartilage degeneration is also associated with changes in subchondral bone architecture (Bobinac *et al.*, 2003), as well as changes in trabecular bone proximal to the joint line (Blumenkrantz *et al.*, 2004b). Other factors associated with cartilage loss include mensical damage and bone marrow oedema (Raynauld *et al.*, 2006; Torres *et al.*, 2006). 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

Figure 1: An example of femoral and tibial cartilage segmentation. This image was acquired at 1.5T with an in-plane resolution of $0.234 \times 0.234 \text{ mm}^2$ and a slice thickness of 2 mm.

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 T_2 -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 T_2 -weighted images and have been shown to correspond to arthroscopically demonstrable abnormalities (Broderick *et al.*, 1994; Peterfy, 2002).

Cartilage T_2 maps are created using the following process: Typically, T_2 -weighted multi-echo, spin echo images with varying echo times (TE) and identical repetition times (TR) are acquired. Second, T_2 maps are computed (Figure 3) assuming exponential signal decay. T_2 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 T_2 measurements. Cartilage T_2 is affected by hydration and the integrity of the collagen matrix; however, the relationship between T_2 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 T_2 (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 T_2 . These *in vitro* studies demonstrate that the biochemical changes associated with cartilage degeneration are related to elevated T_2 ; however, the effects of proteoglycan concentration on T_2 must be further evaluated.

Figure 2: An example of a femoral cartilage thickness map demonstrating the variation in cartilage thickness throughout the femur.

The relationship between T_2 relaxation time and the mechanical properties of cartilage is under investigation. A recent *in vitro* study by (Lammentausta *et al.*, 2006) has shown that T_2 relaxation time in human patellar cartilage is significantly correlated to Young's Modulus, suggesting that T_2 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 T_2 with respect to the main magnetic field (B_0) can provide specific information about the collagen ultra-structure (Xia, 1998). Goodwin *et al.* (Goodwin *et al.*, 1998) have described how T_2 will vary with depth from the articular surface due to collagen fibril orientation to B_0 . 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

Figure 3: An example of T_2 calculation using four T_2 -weighted images acquired with different echo-times (TE). The graph shows signal (S) as a function of time. T_2 is calculated for each pixel in an image using the above equation, and is defined as the time at which the signal decays to 37% of the maximum signal.

Figure 4: Representative Z-score maps of a control, a mild OA subject, and a severe OA subject. The maps show elevated regions of T_2 in OA subjects. The regional variations in femoral and tibial cartilage compared to control subjects is also evident. Adapted from Dunn *et al.* (2004).

shown that the “magic-angle effect” may not be the major determinant of T_2 heterogeneity in high-curvature articular cartilage (Mosher *et al.*, 2001).

In vivo MR imaging studies have demonstrated that cartilage T_2 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 T_2 values are associated with the severity of OA, and variations exist between tibial and femoral cartilage T_2 (Dunn *et al.*, 2004). Dunn *et al.* used Z-score maps to compare cartilage T_2 values of OA subjects to those in control subjects. Voxel based Z-scores were generated in each compartment of the articular cartilage for the T_2 images. A voxel in a Z-image was calculated by $(\text{Voxel} - \text{Mean}_{\text{normal,compartment}}) / \text{SD}_{\text{normal,compartment}}$, where Voxel is the T_2 in the voxel of interest, $\text{Mean}_{\text{normal,compartment}}$ is the mean T_2 for all voxels of the normal knees in that compartment, and the $\text{SD}_{\text{normal,compartment}}$ is the standard deviation of the same normal T_2 distribution. The Z-score maps normalize the T_2 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 T_2 values. Studies have evaluated the spatial distribution of cartilage T_2 : Dray *et al.* (2005) found no difference between mean T_2 values in OA cartilage; however, they showed visual differences in the spatial distribution of the T_2 values. These results demonstrate the necessity to characterize and quantify the spatial distribution of cartilage T_2 values. Recent studies have used texture analysis to quantify the differences in spatial distribution of T_2 values and reported that entropy of cartilage T_2 is significantly greater in osteoarthritic cartilage than in healthy cartilage (Blumenkrantz *et al.*, 2005). By non-invasively evaluating cartilage integrity, T_2 relaxation time may provide insight on the heterogeneity of cartilage degeneration in OA.

The relationship between T_2 and cartilage morphology has been evaluated cross-sectionally and longitudinally. Studies have shown an inverse relationship between

cartilage T_2 and cartilage thickness (Blumenkrantz *et al.*, 2004b; Dunn *et al.*, 2004). A recent study has shown that higher medial cartilage T_2 results in greater loss of medial cartilage volume at twelve months, demonstrating a relationship between cartilage T_2 and cartilage volume (Blumenkrantz *et al.*, 2004a). A longitudinal study showed significant ($p < 0.05$) increases in mean cartilage T_2 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).

$T_{1\rho}$ mapping

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 ($T_{1\rho}$ -weighted imaging) (Akella *et al.*, 2001; Duvvuri *et al.*, 1997; Regatte *et al.*, 2003). A $T_{1\rho}$ sequence, consisting of a three-pulse cluster and gradient crushers, prepares the $T_{1\rho}$ -weighted magnetization. Briefly, first, a $\pi/2$ 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 $\pi/2$ 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. $T_{1\rho}$ can be calculated by fitting the signal (S) intensity obtained for different spin-locking times (TSL) using equation 1. Quantitative $T_{1\rho}$ imaging methods are well-suited for probing macromolecular slow motions at high static fields in cartilage.

$$S(\text{TSL}) \propto e^{(-\text{TSL}/T_{1\rho})} \quad (1)$$

In vitro studies have evaluated the relationship between $T_{1\rho}$ relaxation time and the biochemical composition of

Figure 5: Colour-coded $T_{1\rho}$ map overlays on SPGR images in the posterior femoral cartilage. (a) a healthy volunteer, male, 30; (b) a patient with early OA, female, 27. The $T_{1\rho}$ values were 40.05 ± 11.43 ms in the volunteer and 50.56 ± 19.26 ms in the patient, respectively.

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_2 and $T_{1\rho}$ in cartilage have been explored. Mlyranik *et al.* (1999) showed that the $T_{1\rho}$ relaxation times were slightly longer than the corresponding T_2 values, but both parameters showed almost identical spatial distributions. Menezes *et al.* (2004) have recently shown that $T_{1\rho}$ and T_2 changes in articular cartilage do not necessarily coincide, and might provide complimentary information. These investigators showed that $T_{1\rho}$ and T_2 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_2 (Regatte *et al.*, 2006), 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_2 and $T_{1\rho}$ values between OA patients and controls. A significant correlation was found between average $T_{1\rho}$ and

T_2 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_2 (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_2 was insignificant ($p = 0.202$) (Majumdar *et al.*, 2006), demonstrating that patients with similar average T_2 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_2 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 lack 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 values using a large region of interest (ROI)

Figure 6: $T_{1\rho}$ maps (first row) and T_2 maps (second row) for a healthy control (a), a patient with mild OA (b), and a patient with severe OA (c). a) Control: The average $T_{1\rho}$ value was 40.1 ± 11.4 ms and T_2 value was 33.3 ± 10.5 ms in cartilage. (b) A patient with early OA (male, 66). The average $T_{1\rho}$ value was 45.5 ± 14.5 ms and T_2 value was 35.0 ± 10.9 ms in cartilage. (c) A patient with advanced OA (male, 46). The average $T_{1\rho}$ value was 55.4 ± 26.0 ms and T_2 value was 43.8 ± 11.1 ms in cartilage. The maps illustrate the differences between $T_{1\rho}$ and T_2 (arrows) and demonstrate differences in cartilage heterogeneity between OA severity and between T_2 and $T_{1\rho}$ maps.

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-DTPA²⁻) signal intensity and T_1 relaxation time. When injected in subjects, intra-venous Gd-DTPA²⁻ 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-DTPA²⁻ 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 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).

Figure 7: An example of sagittal images of the knee (identical window and level) used to measure T_1 relaxation time and determine the distribution of Gd-DTPA^{2-} in cartilage. A fast gradient echo sequence is used with the following scanning parameters: $\text{TI}_1/\text{TI}_2/\text{TI}_3/\text{TI}_4/\text{TI}_5 = 130/200/400/800/2100$ ms, $\text{TR} = 6.2$ ms, resolution = $0.625 \times 0.625 \times 3$ mm³, FOV = 16 cm. The images reflect an uptake of Gd-DTPA^{2-} as demonstrated by the increasing image signal intensity, particularly in the cartilage.

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 T_2 quantification and Gd-DTPA^{2-} 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, T_2 mapping, $T_{1\rho}$ 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 $T_{1\rho}$, T_2 , 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

- Akella SV, Regatte RR, Gougoutas AJ, Borthakur A, Shapiro EM, Kneeland JB, Leigh JS, Reddy R (2001) Proteoglycan-induced changes in $T_1\rho$ -relaxation of articular cartilage at 4T. *Magn Reson Med* **46**: 419-423.
- Altman R, Fries J, Bloch D (1987) Radiographic assessment of progression in osteoarthritis. *Arthritis Rheum* **30**:11.
- Bashir A, Gray M, Burstein D (1996) Gd-DTPA^{2-} as a measure of cartilage degradation. *Mag Reson Med* **36**: 665-673.
- Bashir A, Gray ML, Hartke J, Burstein D (1999) Nondestructive imaging of human cartilage glycosaminoglycan concentration by MRI. *Magn Reson Med* **41**: 857-865.
- Blumenkrantz G, Dunn TC, C L, Ries MD, Link TM, S. SL, C. ND, Majumdar S (2004a) Cartilage T_2 as a marker of progression of osteoarthritis. *Proc Ann Meet Am Coll Rheumatol*, San Antonio, TX, abstr 234.
- Blumenkrantz G, Lindsey CT, Dunn TC, Jin H, Ries MD, Link TM, Steinbach LS, Majumdar S (2004b) A pilot, two-year longitudinal study of the interrelationship between trabecular bone and articular cartilage in the osteoarthritic knee. *Osteoarthritis Cartilage* **12**: 997-1005.

- Blumenkrantz G, Dunn TC, Carballido-Gamio J, Link TM, Majumdar S (2005) Spatial heterogeneity of cartilage T_2 in osteoarthritic patients. In OARSI. Boston, MA
- Bobinac D, Spanjol J, Zoricic S, Maric I (2003) Changes in articular cartilage and subchondral bone histomorphometry in osteoarthritic knee joints in humans. *Bone* **32**:284-290.
- Boesen M, Jensen KE, Qvistgaard E, Danneskiold-Samsøe B, Thomsen C, Ostergaard M, Bliddal H (2006) Delayed gadolinium-enhanced magnetic resonance imaging (dGEMRIC) of hip joint cartilage: better cartilage delineation after intra-articular than intravenous gadolinium injection. *Acta Radiol* **47**: 391-396.
- Borthakur A, Shapiro EM, Beers J, Kudchodkar S, Kneeland JB, Reddy R (2000) Sensitivity of MRI to proteoglycan depletion in cartilage: comparison of sodium and proton MRI. *Osteoarthritis Cartilage* **8**: 288-293.
- Broderick L, Turner D, Renfrew D, Schnitzer T, Huff J, Harris C (1994) Severity of articular cartilage abnormality in patients with osteoarthritis: evaluation with fast spin-echo MR vs arthroscopy. *AJR* **162**: 99-103.
- Burstein D, Velyvis J, Scott KT, Stock KW, Kim YJ, Jaramillo D, Boutin RD, Gray ML (2001) Protocol issues for delayed Gd(DTPA)(2-)-enhanced MRI (dGEMRIC) for clinical evaluation of articular cartilage. *Magn Reson Med* **45**: 36-41.
- Chan W, Stevens M, Lang P, Sack K, Majumdar S, Stoller D, Genant H (1990) Structural changes of osteoarthritis of the knee: radiography, CT, and MR imaging correlation. *Radiology* **177** (P): 183.
- Cicuttini F, Wluka A, Wang Y, Stuckey S (2002) The determinants of change in patella cartilage volume in osteoarthritic knees. *J Rheumatol* **29**: 2615-2619.
- Cicuttini F, Wluka A, Davis S, Strauss BJ, Yeung S, Ebeling PR (2004a) Association between knee cartilage volume and bone mineral density in older adults without osteoarthritis. *Rheumatology (Oxford)* **43**: 765-769.
- Cicuttini F, Wluka A, Hankin J, Wang Y (2004b) Longitudinal study of the relationship between knee angle and tibiofemoral cartilage volume in subjects with knee osteoarthritis. *Rheumatology (Oxford)* **43**: 321-324.
- Cicuttini F, Wluka A, Hankin J, Wang Y (2004c) Longitudinal study of the relationship between knee angle and tibiofemoral cartilage volume in subjects with knee osteoarthritis. *Rheumatology* **43**: 321-324.
- Cicuttini FM, Wluka AE, Hankin J, Stuckey S (2004d) Comparison of patella cartilage volume and radiography in the assessment of longitudinal joint change at the patellofemoral joint. *J Rheumatol* **31**: 1369-1372.
- Cicuttini FM, Wluka AE, Wang Y, Stuckey SL (2004e) Longitudinal study of changes in tibial and femoral cartilage in knee osteoarthritis. *Arthritis Rheum* **50**: 94-97.
- Cohen ZA, McCarthy DM, Kwak SD, Legrand P, Fogarasi F, Ciaccio EJ, Ateshian GA (1999) Knee cartilage topography, thickness, and contact areas from MRI: *in-vitro* calibration and *in-vivo* measurements. *Osteoarthritis Cartilage* **7**: 95-109.
- Cunningham T, Jessel R, Zurakowski D, Millis MB, Kim YJ (2006) Delayed gadolinium-enhanced magnetic resonance imaging of cartilage to predict early failure of Bernese periacetabular osteotomy for hip dysplasia. *J Bone Joint Surg Am* **88**: 1540-1548.
- Daniel D, Stone M, Dobson B, Fithian D, Rossman D, Kaufman K (1994) Fate of the ACL-injured patient: a prospective outcome study. *Am J Sports Med* **22**: 632-644.
- Dardzinski BJ, Laor T, Schmithorst VJ, Klosterman L, Graham TB (2002) Mapping T_2 relaxation time in the pediatric knee: feasibility with a clinical 1.5-T MR imaging system. *Radiology* **225**: 233-239.
- Dardzinski BJ, Mosher TJ, Li S, Van Slyke MA, Smith MB (1997) Spatial variation of T_2 in human articular cartilage. *Radiology* **205**: 546-550.
- David-Vaudey E, Ghosh S, Ries M, Majumdar S (2004) T_2 relaxation time measurements in osteoarthritis. *Magn Reson Imaging* **22**: 673-682.
- Dijkgraaf LC, de Bont LG, Boering G, Liem RS (1995) The structure, biochemistry, and metabolism of osteoarthritic cartilage: a review of the literature. *J Oral Maxillofac Surg* **53**: 1182-1192.
- Ding C, Cicuttini F, Scott F, Cooley H, Jones G (2005) Knee structural alteration and BMI: a cross-sectional study. *Obes Res* **13**: 350-361.
- Dougados M, Gueguen A, Nguyen M, Thiesse A, Listrat V, Jacob L, Nakache JP,
- Gabriel KR, Lequesne M, Amor B (1992) Longitudinal radiologic evaluation of osteoarthritis of the knee. *J Rheumatology* **19**: 378-383.
- Dray N, Williams A, Prasad PV, Sharma L, Burstein D (2005) T_2 in an OA population: Metrics for reporting data? Proc Ann Meeting Int Soc Magn Resonance Med (ISMRM) Miami, FL, abstr 1995.
- Dunn TC, Lu Y, Jin H, Ries MD, Majumdar S (2004) T_2 Relaxation time of cartilage at MR iMaging: comparison with severity of knee osteoarthritis. *Radiology* **232**: 592-598.
- Duvvuri U, Reddy R, Patel SD, Kaufman JH, Kneeland JB, Leigh JS (1997) T1rho-relaxation in articular cartilage: effects of enzymatic degradation. *Magn Reson Med* **38**: 863-867.
- Eckstein F, Muller S, Faber SC, Englmeier KH, Reiser M, Putz R (2002a) Side differences of knee joint cartilage volume, thickness, and surface area, and correlation with lower limb dominance – an MRI-based study. *Osteoarthritis Cartilage* **10**: 914-921.
- Eckstein F, Heudorfer L, Faber SC, Burgkart R, Englmeier KH, Reiser M (2002b) Long-term and resegmentation precision of quantitative cartilage MR imaging (qMRI). *Osteoarthritis Cartilage* **10**: 922-928.
- Eckstein F, Charles HC, Buck RJ, Kraus VB, Remmers AE, Hudelmaier M, Wirth W, Evelhoch JL (2005) Accuracy and precision of quantitative assessment of cartilage morphology by magnetic resonance imaging at 3.0T. *Arthritis Rheum* **52**: 3132-3136.
- Eckstein F, Cicuttini F, Raynauld JP, Waterton JC, Peterfy C (2006) Magnetic resonance imaging (MRI) of articular cartilage in knee osteoarthritis (OA): morphological assessment. *Osteoarthritis Cartilage* **14** Suppl A: A46-75.
- Fairbank T (1984) Knee joint changes after meniscectomy. *Bone Joint Surg* **30**: 664-670.

- Feagin J (1979) The syndrome of the torn anterior cruciate ligament. *Orthop Clin North Am* **10**: 81-90.
- Felson DT, Chaisson CE, Hill CL, Totterman SM, Gale ME, Skinner KM, Kazis L, Gale DR (2001) The association of bone marrow lesions with pain in knee osteoarthritis. *Ann Intern Med* **134**: 541-549.
- Felson DT, McLaughlin S, Goggins J, LaValley MP, Gale ME, Totterman S, Li W, Hill C, Gale D (2003) Bone marrow edema and its relation to progression of knee osteoarthritis. *Ann Intern Med* **139**: 330-336.
- Felson DT, Zhang Y, Anthony JM, Naimark A, Anderson JJ (1992) Weight loss reduces the risk for symptomatic knee osteoarthritis in women. The Framingham study. *Ann Intern Med* **116**: 535-539.
- Forman M, Malamet R, Kaplan D (1983) A survey of osteoarthritis of the knee in the elderly. *J Rheumatol* **10**: 282-287.
- Gandy SJ, Dieppe PA, Keen MC, Maciewicz RA, Watt I, Waterton JC (2002) No loss of cartilage volume over three years in patients with knee osteoarthritis as assessed by magnetic resonance imaging. *Osteoarthritis Cartilage* **10**: 929-937.
- Gillis A, Bashir A, McKeon B, Scheller A, Gray ML, Burstein D (2001) Magnetic resonance imaging of relative glycosaminoglycan distribution in patients with autologous chondrocyte transplants. *Invest Radiol* **36**: 743-748.
- Goodwin DW, Dunn JF (1998) High-resolution magnetic resonance imaging of articular cartilage: correlation with histology and pathology. *Top Magn Reson Imaging* **9**: 337-347.
- Goodwin DW, Wadghiri YZ, Dunn JF (1998) Micro-imaging of articular cartilage: T_2 , proton density, and the magic angle effect. *Acad Radiol* **5**: 790-798.
- Goodwin DW, Wadghiri YZ, Zhu H, Vinton CJ, Smith ED, Dunn JF (2004) Macroscopic structure of articular cartilage of the tibial plateau: influence of a characteristic matrix architecture on MRI appearance. *AJR Am J Roentgenol* **182**: 311-318.
- Hunter DJ, March L, Sambrook PN (2003) The association of cartilage volume with knee pain. *Osteoarthritis Cartilage* **11**: 725-729.
- Hunter DJ, Zhang Y, Niu J, Goggins J, Amin S, LaValley MP, Guermazi A, Genant H, Gale D, Felson DT (2006a) Increase in bone marrow lesions associated with cartilage loss: a longitudinal magnetic resonance imaging study of knee osteoarthritis. *Arthritis Rheum* **54**: 1529-1535.
- Hunter DJ, Zhang Y, X. T, M L, Niu J, Amin S, Guermazi A, Genant H, Gale D, Felson DT (2006b) Change in Joint Space Width: Hyaline Articular Cartilage Loss or Alteration in Meniscus. *Arthritis Rheum* **54**: 2488-2495.
- Kellgren J, Lawrence J (1957) Radiologic assessment of osteoarthritis. *Ann Rheum Dis* **16**: 494-502.
- Kim YJ, Jaramillo D, Millis MB, Gray ML, Burstein D (2003) Assessment of early osteoarthritis in hip dysplasia with delayed gadolinium-enhanced magnetic resonance imaging of cartilage. *J Bone Joint Surg Am* **85-A**: 1987-1992.
- Kimelman T, Vu A, Storey P, McKenzie C, Burstein D, Prasad P (2006) Three-dimensional T_1 mapping for dGEMRIC at 3.0 T using the Look Locker method. *Invest Radiol* **41**: 198-203.
- Kohatsu N, Schurman D (1990) Risk factors for the development of osteoarthritis of the knee. *Clin Orthop* **261**: 242-246.
- Konig H, Sauter R, Delmling M, Vogt M (1987) Cartilage disorders: a comparison of spin-echo, CHES, and FLASH sequence MR images. *Radiology* **164**: 753-758.
- Kshirsagar AA, Watson PJ, Tyler JA, Hall LD (1998) Measurement of localized cartilage volume and thickness of human knee joints by computer analysis of three-dimensional magnetic resonance images. *Invest Radiol* **33**: 89-299.
- Kurkijarvi JE, Nissi MJ, Kiviranta I, Jurvelin JS, Nieminen MT (2004) Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) and T_2 characteristics of human knee articular cartilage: topographical variation and relationships to mechanical properties. *Magn Reson Med* **52**: 41-46.
- Lammentausta E, Kiviranta P, Nissi MJ, Laasanen MS, Kiviranta I, Nieminen MT, Jurvelin JS (2006) T_2 relaxation time and delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) of human patellar cartilage at 1.5 T and 9.4 T: Relationships with tissue mechanical properties. *J Orthop Res* **24**: 366-374.
- Lehner K, Rechl H, Gmeinwieser J, Heuck A, Lukas H, Kohl H (1989) Structure, function, degeneration of bovine hyaline cartilage: assessment with MR imaging *in vitro*. *Radiology* **170**: 495-499.
- Li X, Han ET, Crane JC, Link TM, Ma B, Blumenkrantz G, Keshari K, Newitt DC, Majumdar S (2005a) Development of *in vivo* multi-slice spiral T_1 mapping in cartilage at 3T and its application to osteoarthritis. *Proc Ann Meeting Int Soc Magn Resonance Med (ISMRM)* Miami, FL, abstr 479
- Li X, Han ET, Ma CB, Link TM, Newitt DC, Majumdar S (2005b) *In vivo* 3T spiral imaging based multi-slice T_1 mapping of knee cartilage in osteoarthritis. *Mag Res Med* **54**: 29-96.
- Li X, Lozano J, Ma CB, Bauer JS, Link TM, Majumdar S (2006) Quantitative assessment of bone marrow edema and the overlying cartilage in OA and ACL injuries using MR imaging and spectroscopic imaging at 3T. *Proc Ann Meeting Int Soc Magn Resonance Med (ISMRM)*, Seattle, WA, abstr 60.
- Lindberg H, Montgomery F (1987) Heavy labour and the occurrence of gonarthrosis. *Clin Orthop* **214**: 235-236.
- Lindsey CT, Narasimhan A, Adolfo JM, Jin H, Steinbach LS, Link T, Ries M, Majumdar S (2004) Magnetic resonance evaluation of the interrelationship between articular cartilage and trabecular bone of the osteoarthritic knee. *Osteoarthritis Cartilage* **12**: 86-96.
- Link TM, Steinbach LS, Ghosh S, Ries M, Lu Y, Lane N, Majumdar S (2003) Osteoarthritis: MR imaging findings in different stages of disease and correlation with clinical findings. *Radiology* **226**: 373-381.
- Losch A, Eckstein F, Haubner M, Englmeier KH (1997) A non-invasive technique for 3-dimensional assessment of articular cartilage thickness based on MRI. Part 1:

Development of a computational method. *Magn Reson Imaging* **15**: 795-804.

Lynch M, Henning C, Glick K (1983) Knee joint surface changes: long-term follow-up meniscus tear treatment in stable anterior cruciate ligament reconstructions. *Clin Orthop Rel Res* **172**: 148-153.

Manninen P, Riihimäki H, Heliovaara M, Suomalainen O (2004) Weight changes and the risk of knee osteoarthritis requiring arthroplasty. *Ann Rheum Dis* **63**: 1434-1437.

Majumdar S, Li X, Blumenkrantz G, Saldanha K, Ma CB, Kim H, Lozano J, Link T. (2006) MR imaging and early cartilage degeneration and strategies for monitoring regeneration. *J Musculoskelet Neuronal Interact* **6**: 382-384.

McKenzie CA, Williams A, Prasad PV, Burstein D (2006) Three-dimensional delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) at 1.5T and 3.0T. *J Magn Reson Imaging* **24**: 928-933.

Menezes NM, Gray ML, Hartke JR, Burstein D (2004) T₂ and T1rho MRI in articular cartilage systems. *Magn Reson Med* **51**: 503-509.

Mlynarik V, Szomolanyi P, Toffanin R, Vittur F, Trattnig S (2004) Transverse relaxation mechanisms in articular cartilage. *J Magn Reson* **169**: 300-307.

Mlynarik V, Trattnig S, Huber M, Zembsch A, Imhof H (1999) The role of relaxation times in monitoring proteoglycan depletion in articular cartilage. *J Magn Reson Imaging* **10**: 497-502.

Mosher TJ, Dardzinski BJ, Smith MB (2000) Human articular cartilage: influence of aging and early symptomatic degeneration on the spatial variation of T₂ – preliminary findings at 3 T. *Radiology* **214**: 259-266.

Mosher TJ, Smith H, Dardzinski BJ, Schmithorst VJ, Smith MB (2001) MR imaging and T₂ mapping of femoral cartilage: *in vivo* determination of the magic angle effect. *AJR Am J Roentgenol* **177**: 665-669.

Mosher TJ, Collins CM, Smith HE, Moser LE, Sivarajah RT, Dardzinski BJ, Smith MB (2004) Effect of gender on *in vivo* cartilage magnetic resonance imaging T₂ mapping. *J Magn Reson Imaging* **19**: 323-328.

Mosher TJ, Smith HE, Collins C, Liu Y, Hancy J, Dardzinski BJ, Smith MB (2005) Change in knee cartilage T₂ at MR imaging after running: a feasibility study. *Radiology* **234**: 245-249.

Nieminen MT, Menezes NM, Williams A, Burstein D (2004a) T₂ of articular cartilage in the presence of Gd-DTPA2. *Magn Reson Med* **51**: 1147-1152.

Nieminen MT, Toyras J, Laasanen MS, Silvennoinen J, Helminen HJ, Jurvelin JS (2004b) Prediction of biomechanical properties of articular cartilage with quantitative magnetic resonance imaging. *J Biomech* **37**: 321-328.

Nissi MJ, Toyras J, Laasanen MS, Rieppo J, Saarakkala S, Lappalainen R, Jurvelin JS, Nieminen MT (2004) Proteoglycan and collagen sensitive MRI evaluation of normal and degenerated articular cartilage. *J Orthop Res* **22**: 557-564.

Peterfy CG (2002) Imaging of the disease process. *Curr Opin Rheumatol* **14**: 590-596.

Peterfy CG, van Dijke CF, Janzen DL, Gluer CC, Namba R, Majumdar S, Lang P, Genant HK (1994)

Quantification of articular cartilage in the knee with pulsed saturation transfer subtraction and fat-suppressed MR imaging: optimization and validation. *Radiology* **192**: 485-491.

Peyron JG (1984) The epidemiology of osteoarthritis. In Moskowitz R, ed. *Osteoarthritis Diagnosis and Management*. W. B. Saunders, Philadelphia, pp. 9-27.

Raynauld JP, Kauffmann C, Beaudoin G, Berthiaume MJ, de Guise JA, Bloch DA, Camacho F, Godbout B, Altman RD, Hochberg M, Meyer JM, Cline G, Pelletier JP, Martel-Pelletier J (2003) Reliability of a quantification imaging system using magnetic resonance images to measure cartilage thickness and volume in human normal and osteoarthritic knees. *Osteoarthritis Cartilage* **11**: 351-360.

Raynauld JP, Martel-Pelletier J, Berthiaume MJ, Labonte F, Beaudoin G, de Guise JA, Bloch DA, Choquette D, Haraoui B, Altman RD, Hochberg MC, Meyer JM, Cline GA, Pelletier JP (2004) Quantitative magnetic resonance imaging evaluation of knee osteoarthritis progression over two years and correlation with clinical symptoms and radiologic changes. *Arthritis Rheum* **50**: 476-487.

Raynauld JP, Martel-Pelletier J, Berthiaume MJ, Beaudoin G, Choquette D, Haraoui B, Tannenbaum H, Meyer JM, Beary JF, Cline GA, Pelletier JP (2006) Long term evaluation of disease progression through the quantitative magnetic resonance imaging of symptomatic knee osteoarthritis patients: correlation with clinical symptoms and radiographic changes. *Arthritis Res Ther* **8**: R21.

Recht M, Kramer J, Marcelis S, Pathria M, Trudell D, Haghighi P, Battens D, Resnick D (1993) Abnormalities of articular cartilage in the knee: analysis of available MR techniques. *Radiology* **187**: 473-478.

Regatte RR, Akella SV, Borthakur A, Kneeland JB, Reddy R (2002) Proteoglycan depletion-induced changes in transverse relaxation maps of cartilage: comparison of T₂ and T_{1rho}. *Acad Radiol* **9**: 1388-1394.

Regatte RR, Akella SV, Borthakur A, Kneeland JB, Reddy R (2003) *In vivo* proton MR three-dimensional T1rho mapping of human articular cartilage: initial experience. *Radiology* **229**: 269-274.

Regatte RR, Akella SV, Wheaton AJ, Lech G, Borthakur A, Kneeland JB, Reddy R (2004) 3D-T1rho-relaxation mapping of articular cartilage: *in vivo* assessment of early degenerative changes in symptomatic osteoarthritic subjects. *Acad Radiol* **11**: 741-749.

Regatte RR, Akella SV, Lonner JH, Kneeland JB, Reddy R (2006) T1rho relaxation mapping in human osteoarthritis (OA) cartilage: comparison of T1rho with T₂. *J Magn Reson Imaging* **23**: 547-553.

Rogers J, Watt, Dieppe P (1990) A comparison of the visual and radiographic detection of bony changes at the knee joint. *BMJ* **300**: 367-368.

Roos EM, Dahlberg L (2005) Positive effects of moderate exercise on glycosaminoglycan content in knee cartilage: a four-month, randomized, controlled trial in patients at risk of osteoarthritis. *Arthritis Rheum* **52**: 3507-3514.

Samosky JT, Burstein D, Eric Grimson W, Howe R, Martin S, Gray ML (2005) Spatially-localized correlation

of dGEMRIC-measured GAG distribution and mechanical stiffness in the human tibial plateau. *J Orthop Res* **23**: 93-101.

Schouten J, van den Ouweland F, Valkenberg H (1992) A 12 year follow up of osteoarthritis of the knee in the general population on prognostic factors of cartilage loss in osteoarthritis of the knee. *Ann Rheum Dis* **51**: 932-937.

Sharma L (2001a) Local factors in osteoarthritis. *Curr Opin Rheumatol* **13**: 441-446.

Sharma L, Song J, Felson DT, Cahue S, Shamiyeh E, Dunlop DD (2001b) The role of knee alignment in disease progression and functional decline in knee osteoarthritis. *Jama* **286**: 188-195.

Sitttek H, Eckstein F, Gavazzeni A, Milz S, Kiefer B, Schulte E, Reiser M (1996) Assessment of normal patellar cartilage volume and thickness using MRI: an analysis of currently available pulse sequences. *Skeletal Radiol* **25**: 55-62.

Smith HE, Mosher TJ, Dardzinski BJ, Collins BG, Collins CM, Yang QX, Schmithorst VJ, Smith MB (2001) Spatial variation in cartilage T₂ of the knee. *J Magn Reson Imaging* **14**: 50-55.

Solloway S, Hutchinson CE, Waterton JC, Taylor CJ (1997) The use of active shape models for making thickness measurements of articular cartilage from MR images. *Magn Reson Med* **37**: 943-952.

Spector TD, Dacre JE, Harris PA, Huskisson EC (1992) Radiological progression of osteoarthritis: an 11 year follow up study of the knee. *Ann of Rheum Dis* **51**: 1107-1110.

Stammberger T, Eckstein F, Englmeier KH, Reiser M (1999) Determination of 3D cartilage thickness data from MR imaging: computational method and reproducibility in the living. *Magn Reson Med* **41**: 529-536.

Tiderius CJ, Olsson LE, Leander P, Ekberg O, Dahlberg L (2003) Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) in early knee osteoarthritis. *Magn Reson Med* **49**: 488-492.

Tiderius CJ, Tjornstrand J, Akeson P, Sodersten K, Dahlberg L, Leander P (2004) Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC): intra- and interobserver variability in standardized drawing of regions of interest. *Acta Radiol* **45**: 628-634.

Tiderius C, Hori M, Williams A, Sharma L, Prasad PV, Finnell M, McKenzie C, Burstein D (2006) dGEMRIC as a function of BMI. *Osteoarthritis Cartilage* **14**: 1091-1097.

Toffanin R, Mlynarik V, Russo S, Szomolanyi P, Piras A, Vittur F (2001) Proteoglycan depletion and magnetic resonance parameters of articular cartilage. *Arch Biochem Biophys* **390**: 235-242.

Torres L, Dunlop DD, Peterfy C, Guermazi A, Prasad P, Hayes KW, Song J, Cahue S, Chang A, Marshall M, Sharma L (2006) The relationship between specific tissue

lesions and pain severity in persons with knee osteoarthritis. *Osteoarthritis Cartilage* **14**: 1033-1040.

Watrinn-Pinzano A, Ruaud JP, Cheli Y, Gonord P, Grossin L, Bettembourg-Brault I, Gillet P, Payan E, Guillot G, Netter P, Loeuille D (2004a) Evaluation of cartilage repair tissue after biomaterial implantation in rat patella by using T₂ mapping. *Magma* **17**: 219-228.

Watrinn-Pinzano A, Ruaud JP, Cheli Y, Gonord P, Grossin L, Gillet P, Blum A, Payan E, Olivier P, Guillot G, Netter P, Loeuille D (2004b) T₂ mapping: an efficient MR quantitative technique to evaluate spontaneous cartilage repair in rat patella. *Osteoarthritis Cartilage* **12**: 191-200.

Watrinn-Pinzano A, Ruaud JP, Olivier P, Grossin L, Gonord P, Blum A, Netter P, Guillot G, Gillet P, Loeuille D (2005) Effect of proteoglycan depletion on T₂ mapping in rat patellar cartilage. *Radiology* **234**: 162-170.

Wheaton AJ, Casey FL, Gougoutas AJ, Dodge GR, Borthakur A, Lonner JH, Schumacher HR, Reddy R (2004) Correlation of T1rho with fixed charge density in cartilage. *J Magn Reson Imaging* **20**: 519-525.

Wheaton AJ, Dodge GR, Elliott DM, Nicoll SB, Reddy R (2005) Quantification of cartilage biomechanical and biochemical properties *via* T1rho magnetic resonance imaging. *Magn Reson Med* **54**: 1087-1093.

Williams A, Gillis A, McKenzie C, Po B, Sharma L, Micheli L, McKeon B, Burstein D (2004) Glycosaminoglycan distribution in cartilage as determined by delayed gadolinium-enhanced MRI of cartilage (dGEMRIC): potential clinical applications. *AJR Am J Roentgenol* **182**: 167-172.

Williams A, Sharma L, McKenzie CA, Prasad PV, Burstein D (2005) Delayed gadolinium-enhanced magnetic resonance imaging of cartilage in knee osteoarthritis: findings at different radiographic stages of disease and relationship to malalignment. *Arthritis Rheum* **52**: 3528-3535.

Wluka AE, Stuckey S, Snaddon J, Cicuttini FM (2002) The determinants of change in tibial cartilage volume in osteoarthritic knees. *Arthritis Rheum* **46**: 2065-2072.

Wluka AE, Wolfe R, Stuckey S, Cicuttini FM (2004) How does tibial cartilage volume relate to symptoms in subjects with knee osteoarthritis? *Ann Rheum Dis* **63**: 264-268.

Wright V (1990) Post-traumatic osteoarthritis - A medicolegal minefield. *Br J Rheum* **29**: 474-478.

Xia Y (1998) Relaxation anisotropy in cartilage by NMR microscopy (muMRI) at 14-microm resolution. *Magn Reson Med* **39**: 941-949.

Xia Y, Farquhar T, Burton-Wurster N, Ray E, Jelinski LW (1994) Diffusion and relaxation mapping of cartilage-bone plugs and excised disks using microscopic magnetic resonance imaging. *Magn Reson Med* **31**: 273-282.