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Advances in Magnetic Resonance Imaging for the assessment of degenerative disc disease of the lumbar spine

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Abstract

The intervertebral disc is characterized by a tension-resisting annulus fibrosus, and a compression-resisting nucleus pulposus composed largely of proteoglycan. Both the annulus and the nucleus function in concert to provide the disc with mechanical stability. Early disc degeneration begins in the nucleus with proteoglycan depletion. Quantitative MRI techniques have been developed to non-invasively quantify the earliest degenerative changes that occur within the disc. Our ability to identify and quantify these early biochemical changes will provide a better understanding of the pathophysiology of disc degeneration and facilitate the study of interventions that aim to halt or reverse the degenerative process.

Keywords

quantitative MRI; intervertebral disc; annulus fibrosus; nucleus pulposus; proteoglycan; disc degeneration

INTRODUCTION

Degenerative disc disease (DDD) of the intervertebral disc (IVD) is the most common cause of back-related disability among North American adults [1]. This sometimes debilitating condition affects nearly 12 million people in the United States, and may generate direct and indirect costs exceeding 50 billion dollars annually in health-related expenditures. The radiographic evaluation of patients with DDD often begins with plain film radiography and a standard T1- and T2-weighted MRI to assess for structural changes within the nucleus and

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annulus indicative of disc degeneration including a loss of T2-weighted MRI signal, loss of disc height, disc bulge or herniation, posterior element arthrosis, stenosis, and potential vertebral body compromise. While standard MRI is able to detect these later stage developments, it is not able to provide a quantitative measure of the early changes that characterize early DDD. This limitation has led to the search for quantitative, non-invasive measures to evaluate the earliest changes involved in the initiation of the degenerative cascade. Such an imaging tool will be important for the evaluation of the patients with early DDD, and also in the assessment of disc regenerative or restorative technologies that aim to halt or reverse the degenerative process.

BACKGROUND

The IVD has 3 sub-structures: the annulus fibrosus (AF), which envelops the gel-like nucleus pulposus (NP), and the endplates. The proteoglycan (PG) rich NP is comprised of a network of randomly distributed collagen fibrils in a hydrated extra-fibrillar matrix. In contrast, the AF is highly organized. It has 15–40 lamellae (layers) enveloping the NP. In each lamella, collagen fibers are positioned at a 30° angle to the axial axis of the spine [2,3]. 70–80% of the NP and about 65% of the AF consist of water [4]. After water is removed, an IVD is composed of collagens (50–70%), proteoglycans (10–50%), and other non-collagenous proteins (up to 25%) [4,5]. Collagen in the AF gives the IVD its tensile strength. The glycosaminoglycan (GAG) branches of the PG are negatively charged, and they bind water. This water-binding property of GAG gives an IVD its hydrostatic pressure, which resists loading.

The initial stage of DDD is marked by PG degradation and subsequently a reduced capacity of the NP to bind water [6,7]. In later stages of the disease, morphological changes such as a loss of disc height, annular tears and rim lesions, and osteophyte formation materialize [8]. Previous studies have implicated DDD with low back pain [9–11]. During the initial PG degradation, the PGs of NP breakdown to clusters of short aggregated and non-aggregated molecules, the GAG content decreases, and the NP's capacity to bind water reduces [12,13]. The increased modulus and decreased hydrostatic pressure triggers the NP to undergo a phase change, from a fluid-like material to a more solid-like material [14–16]. Mechanical function of degenerated motion segments is compromised in all loading conditions [17,18]. The current standard surgical treatment for lower back pain with advanced IVD degeneration is lumbar spinal fusion. However, if DDD can be detected at an earlier stage, the condition may benefit from emerging alternative treatments (e.g., nucleus replacement, total disc arthroplasty, cell therapy, growth factor therapy) [19–21]. Evaluation of the viability of potential DDD therapies and longitudinal monitoring of DDD progression demands an objective and quantitative imaging strategy, one that is sensitive to the biochemical changes in the early stages of DDD. In this section, we will begin with a brief overview of conventional diagnostic quantitative MRI strategies (T_1 and T_2 relaxation mapping, dGEMRIC), followed by emerging novel quantitative MRI techniques (sodium, magic echo, and $T_{1\rho}$) that show promise as noninvasive, accurate diagnostic imaging tools for the quantitative assessment of early stage DDD.

T_1 AND T_2 RELAXATION MAPPING

In MRI, variable parameters such as repetition time (TR), echo time (TE), and spin-lock time (TSL) can be varied to achieve T_1 , T_2 , and $T_{1\rho}$ weighting effects of the images. Different tissues such as the AF and NP have unique T_1 , T_2 , and $T_{1\rho}$ relaxation time constants. These relaxation time constants determine the exponential decay curve for the MR signal (Equation 1). If a series of images are collected with varying TR, TE, or TSL values, one can apply an exponential fit on a pixel-to-pixel basis across all images (Figure 1), and determine the corresponding T_1 , T_2 , or $T_{1\rho}$ relaxation time constants. This process is called relaxation time mapping, and it yields a map of relaxation time constants, which are related to the biochemical

environment of water in the tissue. Hence, MRI relaxation time mapping is a noninvasive method to probe the tissue characteristics and quality. Earlier work by Chatani et al. has shown that AP and NP have different T_1 and T_2 relaxation time constants [22]. A study by Chiu et al. revealed that T_2 relaxation time constant has an inverse relationship with Thompson grade [23].

$$\begin{aligned} T_1 - \text{weighted} : S &= S_o \left(1 - e^{-TR/T_1} \right) \\ T_2 - \text{weighted} : S &= S_o e^{-TE/T_2} \\ T_{1\rho} - \text{weighted} : S &= S_o e^{-TSL/T_{1\rho}} \end{aligned} \quad \text{Equation 1}$$

DELAYED GADOLINIUM-ENHANCED MAGNETIC RESONANCE IMAGING CONTRAST

The IVD is an avascular structure. Nutrients such as oxygen and glucose are delivered to IVD via diffusion. Previous study by Antoniou et al. has established a direct correlation between diffusion rate and glycoaminoglycan content in the NP [24]. In recent study by Niinimäki et al., delayed gadolinium(Gd)-enhanced magnetic resonance imaging contrast (dGEMRIC) has been applied to study the diffusion characteristic of the IVD *in vivo* [25]. Gd is a T_1 shortening agent. Its presence in tissue speeds up tissue T_1 relaxation process. In a T_1 -weighted image, tissue experiencing Gd uptake would show up brighter. In the study by Niinimäki et al., a T_1 map was collected before and after intravenous injection of 0.2 mM/kg Gd-based contrast agent. The percentage decrease in T_1 after Gd injection correlates with grading of disc degeneration [25]. However, recent research has linked the usage of Gd-based MR contrast agent with a rare but severe medical condition known as nephrogenic systemic fibrosis (NSF) [26]. In response, the FDA announced a recommendation to limit Gd-based contrast agents unless it is deemed absolutely necessary.

SODIUM MRI

A novel method for MRI of IVD is Sodium MRI. Although conventional MRI relies on imaging proton nuclei in water, MRI can also be performed on more physiologically relevant nuclei such as sodium (^{23}Na) and Phosphorus (^{31}P) among others. Sodium MRI is a highly accurate and specific technique for assessing various pathologies, and it has been applied to *in vivo* applications to image heart infarction, brain, and spine [27–29]. Sodium MRI has been validated as a tool for quantitative measurement of the proteoglycan content via a measurement of tissue fixed charge density (FCD) which correlates to the amount of proteoglycan present [30,31]. In sodium MRI, the FCD is directly calculated from $[\text{Na}]$ measurements in a method developed by Lesperance *et al.* [32]. We recently demonstrated the feasibility of performing sodium MRI on *ex vivo* IVD specimens for the first time (Figure 2). In this image, a single high cervical IVD segment was imaged with a home-built MRI coil on a 3 Tesla Siemens Trio MRI scanner. A tube containing 300mM sodium concentration of saline was placed to the left of the disc to serve as a signal reference for quantifying the absolute concentration of sodium in the disc. Note the low signal from the vertebral bones due to the lower concentration of sodium (~50mM) of blood. It may soon be possible to determine IVD tissue quality (via a measurement of proteoglycan content) non-destructively and non-invasively on any clinical MRI scanner.

The sodium MRI signal is significantly lower than that of conventional proton MRI. One of the major factors contributing to the decreased signal is the lower natural abundance of ^{23}Na compared to proton. In the human body, typical proton concentration is around 110 M while

typical sodium concentration in healthy IVD is only around 300 mM. In order to compensate for the loss of measurable signal, sodium MRI typically employs fast MRI pulse sequences with a lot of signal averaging and hence long MRI scan times. However, recent advances in the gradient technology may enable one to achieve ultra-short TE (<200 μ s) that can significantly improve resolution and SNR. Radiofrequency coil technology (multiple channel capability) and parallel imaging approaches and tuned pre-amplifiers would further contribute to high SNR. These advances may potentially make the clinical sodium MRI feasible at 3T scanners. Further, the recent proliferation of 7T whole-body MRI scanners in clinical research centers could have a significant impact on sodium MRI and its potential for clinical use.

MAGIC ECHO MRI

One novel MRI pulse sequence that may be used to study biochemical changes in the intervertebral disc during degenerative disc disease is the “magic-echo” pulse sequence currently under development in our lab. This relaxation mapping technique uses a series of RF pulses to generate a ‘magic echo’ [33] as shown in Figure 3. While the spin echo relaxation time T₂ is insensitive to the loss of magnetization because of magnetic field inhomogeneities (T₂* effects), the magic echo relaxation time T_{2ME} is insensitive to the loss of transverse magnetization because of the static and magnetic dipole-dipole interaction between ¹H nuclei on water molecules.

Magic echo imaging has previously been used to acquire images of samples with short T₂ relaxation times. The groups of Kimmich, et al. and Briguet, et al. have shown signal enhancement in plastic plugs [34,35] and bovine Achilles tendon [33], respectively, using magic echo imaging. This technique is poised to become a useful probe of the intervertebral disc. In a magic echo relaxation map, the voxel intensity is proportional to the relaxation time rather than the signal. Magic echo relaxation maps provide spatial information about the magic echo relaxation time T_{2ME} throughout the tissue. By incrementing TE, the magic echo signal decays approximately like a single exponential function (Equation 2).

$$S(TE) = S_0 e^{-TE/T_{2ME}} \quad \text{Equation 2}$$

Preliminary studies were performed on 4 cadaveric spines and imaged using both standard spin echo and magic echo pulse sequences. Proton density, T₂ and T_{2ME} relaxation maps are shown from a representative spine from a 42 year old human male in Figure 4. The proton density weighted (TE/TR = 15/3000 ms) magic echo image is shown on the left and serves as reference for T₂ (middle) and magic echo T_{2ME} (right) relaxation maps. The discs shown are L4/L5 through T12/L1. T₂ and magic echo T_{2ME} maps were obtained using five identical echo times (15, 30, 45, 60 and 75 ms) as measured from the center of the slice selective sinc pulse to the echo time.

Observed T_{2ME} times in the IVD are significantly increased [(T_{2ME} – T₂) / T₂ ~ 35%] over spin echo T₂ relaxation times. Furthermore, Figure 5 shows Δ T_{2ME}s between the nucleus pulposus and adjacent endplate for two separate L4/L5 discs of 92.0 $\pm$ 7.8 ms and 93.7 $\pm$ 1.0 ms compared to Δ T₂s of 65.2 $\pm$ 5.3 ms and 71.5 $\pm$ 0.9 ms, respectively. The signal enhancement was also observed in two additional cadaveric spines. In addition, T_{2ME} maps reveal disc features not observed in T₂ maps. One example is the Δ T_{2ME} = 59.3 $\pm$ 2.5 ms difference between the hypo-intense region of the nucleus pulposus and the surrounding healthy nucleus observed in rostral portion of the L4/L5 disc (Figure 5 A & B). This difference may reveal biochemical differences not observable using standard spin echo imaging. Generally, the magic echo sequence provides greater dynamic range to T₂ mapping studies and may eliminate artifacts from dipolar orientation effects or, conversely, to modulate these orientation effects.

T_{1ρ} MRI

There has been considerable amount of work on biological tissues using T_{1ρ} MR spectroscopy and imaging dealing with tumors, muscle, myocardium, blood flow and cartilage [36–46]. In T_{1ρ} MRI, a long-duration, low-power radiofrequency (RF) pulse cluster referred to as “spin-lock” (SL) pulse cluster is applied to the magnetization in the transverse plane (Figure 6). The first RF pulse tips the longitudinal magnetization into the transverse plane. Next, a two phase-alternating spin-lock pulses are applied along the same direction as the transverse magnetization. During this time, the magnetization is said to be “spin-locked” and undergoes relaxation in the presence of a B₁ field of the spin-lock pulses in the rotating frame, a process similar to T₁ relaxation in the presence of main magnetic field, B₀. The phase-alternating spin-lock pulses are meant to refocus the effect of inhomogeneous RF fields [40]. The spin-locked magnetization will relax with a time constant T_{1ρ}, the spin-lattice relaxation in the rotating frame, during the spin-locking duration. The spin-lock field reduces the effect of dipolar relaxation and background gradients on the signal. Consequently, T_{1ρ} is always greater than T₂. In a typical T_{1ρ} mapping experiment, the duration of the SL pulse is incremented in tens of milliseconds while the amplitude of SL pulse ($\gamma B_1 \sim 500\text{Hz}$) is fixed.

T_{1ρ}-weighted MRI can generate tissue contrast based on variations in protein content. Previous studies have shown that T_{1ρ} MRI can map the distribution of PG in cartilage [47,48]. An in vivo feasibility study by Auerbach et al reported a significant correlation between T_{1ρ} and degenerative disc grade in asymptomatic 40–60 year old subjects [49]. A previous study in cadaveric lumbar spines from our laboratory demonstrated a significant linear correlation between T_{1ρ} and proteoglycan within the nucleus and degenerative grade, as assessed using the Pfirrmann classification [50]. In another study investigating the relationship between T_{1ρ} and IVD degeneration, nine human cadaver spine specimens (mean age: 45 years, range: 22–66 years) were scanned on a Siemens Sonata 1.5 T clinical MR scanner with the vendor-supplied 8-channel spine array coil. For each specimen, five T_{1ρ}-weighted images (TSL=15,30,45,60,75ms) were obtained using a spin-lock prepared spin-echo pulse sequence. Afterwards, a region of interest was selected in the L2/L3 IVD NP by a single observer. The mean T_{1ρ} value for each IVD NP's mean T_{1ρ} and standard deviation were obtained using ImageJ software. In Figure 7, the decrease in T_{1ρ} of the NP as a result of aging can be clearly seen from the overlaid T_{1ρ} maps as well as the T_{1ρ} vs. age plot (unpublished data). Recently, it was demonstrated that the T_{1ρ} relaxation time constant correlates strongly with PG changes in bovine cartilage whereas the correlation between T₂ relaxation time constant and PG change is less strong [51]. It has also been shown that in bovine as well as in *ex vivo* human cartilage, the T_{1ρ} relaxation time is significantly higher (~50%) than T₂. This increase in relaxation time value is reflected in the improved SNR in T_{1ρ} maps. Another advantage of T_{1ρ} imaging is that it provides a unique contrast between cartilage, fluid and other structures in the joint. The above advantages of T_{1ρ} imaging potentially lead to the detection of early degenerative changes with high accuracy and precision.

Ongoing research by our group has focused on the development of a pulse sequence capable of acquiring 3D T_{1ρ} maps of human spine IVDs within a clinically acceptable time frame (<30 min). This new MR pulse sequence (SLIPS) appends the T_{1ρ} magnetization preparation pulse (Figure 6) to a fast 3D acquisition scheme based on a balanced steady-state free precession technique. Previous often relied on 2D T_{1ρ}-prepped pulse sequences. The 2D images are not useful for assessing disc volume information. In addition, in longitudinal studies that measure disc height repeatedly, one cannot obtain the exact slice in subsequent scans. SLIPS address both problems by acquiring a 3D image that completely covers the IVD (Figure 8). 3D T_{1ρ} map can be calculated using a series of 5 3D images with TSL values ranging from 1 to 60 ms. Each IVD can then be segmented from the 3D T_{1ρ} map, and their volumes are subsequently calculated.

CONCLUSION

In conclusion, quantitative MRI has the potential to identify and quantify the early biochemical disc changes that characterize early DDD. Standard T1 and T2 relaxation mapping are capable of detecting biochemical changes in the NP but have limitations, including increased scan time, limited dynamic range, and a lack of consistency between in vivo and in vitro values. Recent advancements in MRI, such as sodium MRI, magic echo, and T₁ ρ MRI, have been shown to be even more sensitive to PG degradation in the NP. As these quantitative MRI methods are still in the research phase, their efficacy still needs to be more fully evaluated in a clinical setting. However, preliminary clinical data on sodium, magic echo, and T₁ ρ MRI have demonstrated great potential to become noninvasive quantitative diagnostic tools for early DDD.

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Figure 1. The pixel-to-pixel mapping process for T_2 . The pixel intensities of the same pixel from all four images are fitted onto an exponential curve.

Figure 2.
A sodium MR image of cadaver cervical IVD with a 300mM sodium phantom.

Figure 3.
The magic echo pulse sequence

Figure 4. Cadaveric lower lumbar spine T2 and magic echo relaxation maps from a 42 year old human male.

Figure 5.

L4/L5 IVD ex vivo disc from a 42 y/o male (A) including labeled averaged disc profile (B) across the zone of hypointensity. (C) A similar T2 relaxation profile obtained from the L4/L5 disc of a 29 y/o male. The upper T2 profile (pink curve) is a magic echo profile, while the lower T2 profile (purple) is spin echo profile.

Figure 6.
 $T_{1\rho}$ preparation pulse cluster.

Figure 7.

Image on the left shows a color $T_{1\rho}$ map overlaid on a T1-weighted image (grayscale) of the lumbar region from a 22 year-old and a 59 year-old human cadaver spine. The graph on the right plots average $T_{1\rho}$ value of the NP region for each L2/L3 IVD against its specimen's age. The standard deviation of all $T_{1\rho}$ values within each NP region was graphed as the error bar. A linear fit of the data points yielded a correlation coefficient of 0.82, which suggests a strong relationship between $T_{1\rho}$ of NP and the specimen's age.

Figure 8.

Consecutive 2D images of the human spine in vivo from a 3D SLIPS dataset. The subject was a 22 year-old male volunteer with no prior history of back injury or DDD. A total of five datasets were collected, with TSL values ranging between 1 to 60 ms. (Data shown has TSL=10ms.) The total scanning time was less than 10 minutes. The right side of this figure s include a $T_{1\rho}$ map of the 7th image slice in the original 3D dataset.