Advanced Quantitative Imaging Techniques

Feliks Kogan, PhD
Department of Radiology - Stanford University
fkogan@stanford.edu

Background and Objectives

Osteoarthritis (OA) remains a leading cause of disability, affecting more than half the population by the age of 65. Despite its prevalence, pathogenesis in OA is still poorly understood. There is great need for imaging biomarkers of early changes in OA in order to better understand the disease process as well as to develop new therapies[1,2]. Cartilage is thought to play a major role in the progression of OA. Cartilage is made up of a low density of chondrocytes and an extracellular matrix composed of water, a network of collagen composed predominantly of type II collagen fibers, and the surrounding proteoglycan (PG) macromolecules[3,4]. In the earliest stages of OA, prior to gross cartilage loss, the biochemical composition of cartilage breaks down. The concentration of PGs decreases and the structure of the collagen matrix breaks down, leading to an influx of water into these areas. MRI is increasingly being used to study and evaluate early OA changes in cartilage structure and composition[5-8]. While conventional MRI provides sufficient contrast to visualize cartilage morphology, more advanced imaging strategies are necessary for understanding the underlying biochemical composition of cartilage that begins to breakdown in the earliest stages of OA.

The objective of this course is to introduce advanced quantitative imaging techniques for characterizing cartilage structure and composition. These include T_2 relaxation time mapping, $T_{1\rho}$ relaxation time mapping, sodium MRI, delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), diffusion-weighted imaging (DWI), and chemical exchange saturation transfer of glycosaminoglycans (gagCEST). The advantages and challenges of each technique will be discussed.

Methods

Spin-Spin (T2) Relaxation Time Mapping: T_2 relaxation time mapping provides an indirect assessment of collagen structure and orientation, as it relates to free water content[9,10]. When breakdown of the collagen matrix occurs, the extra space is filled with free, unbound water leading to a local elevation in T_2 relaxation times. Thus, T_2 relaxation times are widely used as quantitative measures in clinical OA research to track cartilage degradation as well as observe natural spatial variations in collagen structure between various layers of cartilage[11-13]. A drawback to T2 relaxation time mapping is that measured relaxation times are affected by the orientation of collagen fibrils with respect to the B_0 field, a phenomenon referred to as the magic angle effect[14]. Additionally, there is evidence to suggest that T_2 relaxation may also be dependent on factors other than collagen structure, such as GAG content[15].

***Spin-Lattice Relaxation in the Rotating Frame ($T_{1\rho}$) Relaxation Time Mapping*:** $T_{1\rho}$ relaxation time mapping is quantitative technique used to map glycosaminoglycan (GAG) content within cartilage[9,16]. GAGs are negatively charged side-chains that are attached to the protein core of proteoglycans. With this technique, the magnetization is flipped into the transverse plane and then a "locking" RF pulse is applied. Protons then relax in the presence of a B_1 field with the time constant $T_{1\rho}$, allowing assessment of very slow molecular motions.[17] In cartilage, water protons that are associated with large macromolecules such as GAGs dissipate energy faster than free water protons and as such, regions with more free water as a result of GAG depletion have longer $T_{1\rho}$ relaxation times[10,18]. The amplitude of the spin-lock pulse is often limited by SAR restrictions and $T_{1\rho}$ mapping techniques used on clinical systems may not adequately decouple the residual dipolar interactions from the collagen network. Thus, similarly to T2 mapping, $T_{1\rho}$ is not as specific to GAG content as some other MR methods. Finally, long scan times are often necessary to conform to SAR regulations due to large amounts of energy deposited[19].

***Sodium (^{23}Na) MRI*:** Rather than the conventional ^{1}H proton MRI, Sodium MR imaging captures signal from ^{23}Na ions. Positively charged sodium ions exist in association with the negatively charged GAG side-chains. This makes sodium MRI an excellent measure of GAG concentration[20,21]. Despite its specificity to GAG, sodium imaging has many challenges that have limited its clinical application[22]. Sodium ions have a different resonance frequency than protons and thus special MR hardware is needed to detect their signal. Additionally, the concentration of ^{23}Na ions in cartilage is significantly lower than that of ^{1}H protons, making SNR a concern. Long scan times, lower spatial resolutions or ultra-high fields are often necessary to obtain sufficient SNR. This also makes sodium imaging susceptible to motion and partial voluming, which leads to artificially decreased measurements of GAG concentration.

Delayed Gadolinium-Enhanced MRI of Cartilage (dGEMRIC): dGEMRIC provides an assessment of GAG concentration through the use of the intravenous contrast agent Gd(DTPA)$^{2-}$. The premise behind dGEMRIC imaging is that the negatively charged contrast agent Gd(DTPA)$^{2-}$ will distribute in cartilage in inverse relation to the negatively charged GAG concentration[23,24]. Following injection of the contrast agent and delay time to allow for diffusion into the tissue, T_1 mapping is performed. The paramagnetic properties of Gd(DTPA)$^{2-}$ cause nearby protons to relax more quickly, resulting in shorter T_1 relaxation times[23,25,26]. Thus, lower T_1 correlates to decreased GAG content. In addition to its dependence on GAG distribution, recent evidence also suggests that the diffusion of Gd(DTPA)$^{2-}$ into the cartilage may also be dependent on collagen content and diffusion direction[27]. Other drawbacks to this method include the invasive aspect of using a contrast agent as well as the added time necessary to allow for diffusion into the joint. Lastly, the use of gadolinium contrast agent poses health risks particularly for individuals with renal impairment[28].

Diffusion Weighted Imaging (DWI): Diffusion is the primary transport mechanism for nutrients into cartilage and is affected by the structure and composition of the collagen matrix[29]. In MRI, any random motion of water in the presence of a gradient that occurs after RF excitation causes a loss of signal when the gradient is refocused[30,31]. This is described by the apparent diffusion coefficient (ADC), which is measured by applying diffusion-sensitizing gradients (a pair of identical gradients on either side of a refocusing pulse) that break down phase coherence amongst mobile protons, reducing the MR signal from regions with mobile water. Higher ADC values indicate more translational movement of protons. Thus in cartilage, when the matrix breaks down, there is increased movement of water and elevated ADC, believed to be indicative of early cartilage degeneration[32,33]. Applications of DWI imaging in cartilage research are limited. The primary challenge of measuring diffusion in cartilage in vivo is the low SNR that results from the relatively long echo times in DWI sequences relative to the T_2 relaxation time of cartilage.

***GAG Chemical Exchange Saturation Transfer (gagCEST)*:** Chemical exchange saturation transfer (CEST) is a new MR contrast enhancement technique that enables the indirect detection of molecules with exchangeable protons. CEST makes MRI sensitive to the concentrations of endogenous metabolites and their environments[34]. GAGs in cartilage exhibit a concentration-dependent CEST effect between their hydroxyl (-OH) protons and bulk water protons. Thus, this technique allows for imaging of GAG distribution with high spatial resolution[35]. The high specificity to GAG without the need for special hardware or intravenous contrast makes gagCEST a promising method for studying cartilage matrix composition[36]. However, the exchange rate and proximity of resonance frequencies between GAG hydroxyl protons and bulk water protons make efficient and specific saturation of GAG hydroxyl protons challenging at 3T[37]. In addition, precise B_0 field maps and advanced post-processing tools are also required to correct for field inhomogeneities in order to obtain accurate quantitative results.

Conclusions

Advanced quantitative MRI is becoming increasingly important in studies of cartilage degeneration and in testing new therapies for prevention or delaying the progression of OA. While each technique provides has its own strengths and advantages, each also has several drawbacks that need to be overcome. Ongoing research shows promise in boosting the strength of these imaging techniques to be more sensitive to arthritic changes and to be used in larger-scale research studies.

References

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