$T_{1\rho}$ relaxation in articular cartilage: a literature review

BSc thesis
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<tr>
<td>3D</td>
<td>Three-dimensional</td>
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<tr>
<td>ACL</td>
<td>Anterior cruciate ligament</td>
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<tr>
<td>$B_0$</td>
<td>Strength of external magnetic field</td>
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<td>$B_{SL}$</td>
<td>Strength of spin-lock magnetic field</td>
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<td>BMEL</td>
<td>Bone marrow edema-like lesion</td>
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<td>CT</td>
<td>Computed tomography</td>
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<td>ECM</td>
<td>Extracellular matrix</td>
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<td>$G_x$</td>
<td>Strength of gradient field in x-direction</td>
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<td>GAG</td>
<td>Glycosaminoglycan</td>
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<td>KL</td>
<td>Kellgren-Lawrence</td>
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<tr>
<td>$M_0$</td>
<td>Net magnetization</td>
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<tr>
<td>$M_{xy}$</td>
<td>Transverse component of net magnetization</td>
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<td>$M_z$</td>
<td>Longitudinal component of net magnetization</td>
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<td>MRI</td>
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<td>NMR</td>
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<td>OA</td>
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<td>PG</td>
<td>Proteoglycan</td>
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<tr>
<td>$R_{1\rho}$</td>
<td>Spin-lattice relaxation rate in the rotating frame ($=1/T_{1\rho}$)</td>
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<td>$R_2$</td>
<td>Spin-spin relaxation rate ($=1/T_2$)</td>
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<td>RF</td>
<td>Radio frequency</td>
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<tr>
<td>$T_1$</td>
<td>Spin-lattice relaxation</td>
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<td>$T_{1\rho}$</td>
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<td>$T_2$</td>
<td>Spin-spin relaxation</td>
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<tr>
<td>TE</td>
<td>Time to echo</td>
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<td>TR</td>
<td>Time to repetition</td>
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<td>TSL</td>
<td>Time of the spin-lock</td>
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<td>WOMAC</td>
<td>Western Ontario and McMaster Universities Osteoarthritis Index</td>
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<td>WORMS</td>
<td>Whole-Organ Magnetic Resonance Imaging Score</td>
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<td>Z-score</td>
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<td>$\gamma$</td>
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<td>$\omega_0$</td>
<td>Larmor frequency</td>
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<td>$\omega_{SL}$</td>
<td>Spin-lock frequency</td>
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1 Introduction

Osteoarthritis (OA) is a debilitating disease that affects the joints. The disease affects primarily old people, while obesity and knee injuries are also risk factors for the onset of knee OA. It is the most common joint disease in the world. The primary reason behind OA is still unknown. No cure for stopping progressing OA has been found at the moment and joint replacement is the only form of effective treatment for late stage OA. [1]

With the future development of biological drugs for OA, non-invasive techniques for confirming the validity and effect of treatment becomes more important. Several techniques have been used for diagnosing the biochemical and morphological changes related to early OA, including radiography, magnetic resonance imaging (MRI), computed tomography (CT), arthrography and ultrasound imaging. At the moment joint space narrowing confirmed by radiography imaging has been the only way of diagnosing OA. Arthrography is not the favoured method, since it is an invasive procedure which does not provide information on the content of the tissue itself. The biggest drawback of radiography and CT images is the lack of using the biochemical changes happening in cartilage as an additional way of diagnosis. MR imaging is a non-invasive method which provides good contrast between different types of tissue while also being sensitive to changes in tissue content itself. Conventional $T_1$, $T_2$, and proton density weighted imaging sequences have been found to be deficient in imaging early-stage molecular changes. $T_{1\rho}$ relaxation, or spin-lattice relaxation in a rotating frame, has been identified as a non-invasive marker of early-stage OA since $T_{1\rho}$ relaxation time has been found to potentially correlate with diminishing proteoglycan content in articular cartilage, which happens in early OA.

My BSc thesis is a literature review of articles about $T_{1\rho}$ relaxation in cartilage. A systematic search for English-language articles published between 1995 and 2017 was performed using Scopus, Web of Science, PubMed and Google Scholar using the search terms “MRI”, “T1rho”, “relaxation”, “dispersion”, “osteoarthritis”, “articular cartilage”, among others. I categorized the articles by the method of their study, such as in vivo and in vitro studies in different environments. The relevancy of the found articles was assessed based on their importance and impact and the most relevant publications were included in this review.

2 Theoretical background

2.1 Articular cartilage

Articular cartilage is the soft tissue found at the ends of bones in joints, which require a smooth and lubricated surface to help the normal motion of the joint. Articular cartilage also is required for absorbing shock and distributing load evenly in load-bearing joints. The structure of articular cartilage is different from most types of tissue, since it has
no blood vessels, lymphatics or nerves. It consists of a highly organized structure called a dense extracellular matrix (ECM). ECM is mainly composed of water (65-80 %), collagen (15-20 %) and proteoglycans (PG) (3-10 %). Collagen fibres in cartilage are divided depthwise into three layers which have the collagen fibres oriented differently in regards with each other. In the topmost, superficial layer, the fibres are densely packed and parallel to the cartilage surface, in the middle zone the fibres are orientated randomly and in the deepest zone, the radial zone near the bone surface the fibres are oriented perpendicular to the cartilage surface. Articular cartilage also has highly specialized cells called chondrocytes which are responsible for maintaining, repairing and remodelling the ECM constantly. The changes happening in articular cartilage in OA are shown in Figure 1. In early OA, the PG content starts to decrease. Collagen content does not decrease but the fibre size and arrangement is altered which causes the water content in the joint to start to increase. As the disease progresses, the changes in ECM cause the cartilage to lose its load-bearing capabilities and start to wear. [2, 3]

Figure 1: Articular cartilage and degeneration in osteoarthritis (OA). Changes at early OA include hydration, loss of proteoglycan (PG), thinning and loosening of collagen. Changes in late stages include further loss of collagen and PG, dehydration, extensive fibrillation and cartilage thinning, and eventually denudation of the subchondral bone. [4]

2.2 Magnetic resonance imaging

Magnetic resonance imaging, or MRI, does not use ionizing radiation for imaging, like eg. conventional X-ray imaging, nuclear medicine or CT do, but instead it utilizes nuclear magnetic resonance (NMR). NMR is based on the interactions between atomic nuclei and magnetic fields. The nuclei is made of protons and neutrons, which causes the nuclei to have a net positive charge. Nuclei with an odd number of protons have a magnetic moment or "spin" that can be considered analogous to the proton spinning around its own axis. In MRI, the atom used in imaging has to have a spin different from zero. Some
of these nuclei in tissue are sodium, phosphorus and hydrogen. The most commonly used atom in MRI is hydrogen which has a single proton. This is due to its abundance in the body which causes a stronger signal, compared to e.g. sodium. When atoms are placed in a strong external magnetic field \( B_0 \), the spins of the protons in the atoms line up either parallel or anti-parallel with the magnetic field. The net magnetization \( M_0 \) of the sample is still oriented parallel to the external magnetic field, because slightly more protons align parallel to the field than anti-parallel. This is explained quantum mechanically, since the anti-parallel state is the higher energy state and requires more energy. The nuclei have internal angular momentum, which causes them to rotate around the external field axis in a frequency specific to each nucleus. This angular frequency is called the Larmor frequency which can be calculated using the following equation:

\[
\omega_0 = \gamma B_0
\]

where \( \gamma \) is the gyromagnetic ratio of a nucleus (for hydrogen atoms \( \gamma = 2.67 \cdot 10^8 \text{ rad s}^{-1} \text{T}^{-1} \), usually presented as scalar frequency \( \gamma/2\pi = 42.58 \text{ MHz} \text{T}^{-1} \)) and \( B_0 \) is the strength of the external magnetic field. [5]

In order to receive a signal, the net magnetization must be tipped away from the external field. If a radio frequency (RF) pulse of the same frequency as the Larmor frequency is applied to the nuclei, the energy of the RF pulse tips the magnetization away from \( B_0 \). Usually magnetization is is easily described as vectors, with the external field \( B_0 \) being along the longitudinal \( z \)-axis, while the \( xy \)-plane is called a transverse plane. When the flip angle used is \( 90^\circ \), the magnetization is tipped to the transverse plane. The precession of the tipped net magnetization is shown in Figure 2. When the excitation pulse is turned off, the net magnetization returns back to the \( z \)-axis, to the direction of the external magnetic field \( B_0 \). This return process is called relaxation, in which a RF signal called the free induction decay (FID), is emitted by the protons, which is then received using a receiver coil. There are two different relaxation processes happening simultaneously; \( T_1 \), or spin-lattice relaxation and \( T_2 \), or spin-spin relaxation. \( T_1 \) relaxation describes the growth of the \( z \)-component \( M_z \) of the net magnetization \( M_0 \), while \( T_2 \) relaxation depicts the decay of the transverse component \( M_{xy} \) of the magnetization. \( T_2 \) relaxation is caused by protons interacting with each other in the transverse plane, which causes them to dephase one another. Both relaxation processes are measured using time constants \( T_1 \) and \( T_2 \), respectively. \( T_1 \) relaxation time constant is the time required for \( M_z \) to recover 63 % of the maximum value, while \( T_2 \) relaxation time constant is the time required for \( M_{xy} \) to decay to 37 % of the maximum. This is illustrated in Figure 3. The time constants are calculated using the following equations:

\[
T_1 : \ M_z = M_0 \left( 1 - \exp \left( -\frac{t}{T_1} \right) \right)
\]

\[
T_2 : \ M_{xy} = M_0 \left( \exp \left( -\frac{t}{T_2} \right) \right)
\]

where \( t \) is time and \( M_0 \) the strength of the original magnetization. [5, 6]
If there is only a single external field used for imaging, the protons throughout the sample have the same Larmor frequency. In order to spatially separate the signal received from different locations, additional gradient fields $G$ are applied. This causes the protons to rotate in a slightly different frequency or phase so they need a different excitation pulse compared to each other, and subsequently, they emit different RF signals from different locations. Three gradient fields are normally used for x-, y- and z-directions, respectively.

The gradient field in the x-direction $G_x$ increases the frequency longitudinally, so the protons in the sample are frequency encoded in the x-direction. In the y-direction however, the protons are usually phase encoded, so they rotate in different phases, which means the signal received in the y-direction is stronger or weaker, depending on the position and excitation pulse. The Larmor frequency in the presence of a gradient field for example in the x-direction is calculated with the following equation:

$$\omega_0 = \gamma \left( B_0 + x \cdot G_x \right) \quad (3)$$

where $x$ is the position and $G_x$ the strength of the gradient field. The signal emitted from the protons of the sample is then depending on the imaging sequence used either 2D- or 3D-Fourier transformed to produce an image. [5, 6]

The most commonly used imaging sequences, spin echo- and gradient echo sequences, in
MRI take advantage of a phenomenon called spin echo. $T_2$ relaxation actually consists of two simultaneous processes; $T_2$ and $T_2^*$, where $T_2$ relaxation is the dephasing of the spins caused by their interactions with one another, while $T_2^*$ relaxation is caused by field inhomogeneities of the external magnetic field. $T_2^*$ relaxation time is always smaller than $T_2$ time. The signal from $T_2$ decay is lost, but the $T_2^*$ relaxation in the transverse plane can be reversed using either another 180° RF pulse or turning the gradient fields on in an eligible sequence, which causes the dephasing to reverse and an “echo” signal to emerge. The time from the initial 90° excitation RF pulse to the echo is called the TE time (time to echo) which is used to measure $T_2$ times. TE time can be manipulated to provide different information from a sample (e.g., better contrast or suppression of signal from a specific tissue type), due to differing $T_2$ times in different tissue types. Another imaging parameter that can be altered to get different information from the sample is called the TR time (time to repetition), which is defined as the time between two excitation pulses. TR times are used to create better contrast between tissue types that have differing $T_1$ times, or to shorten the imaging time. [5, 6, 7]

### 2.3 $T_{1\rho}$ relaxation

$T_{1\rho}$ relaxation, or spin-lattice relaxation in the rotating frame, happens when a low power, low frequency pulse is applied to the magnetization after the initial excitation pulse. The magnetization will relax during the time of the spin-lock (TSL) in the rotating frame. The spin-lock pulse slows the magnetization process in the transverse plane by forcing the spins rotate in the pulse’s direction. This spin-lock field weakens the effects of for example, dipolar relaxation, chemical exchange and background gradients on the signal. The usual frequency of the spin-lock pulse ($\omega_{SL}$) is between $\gamma B_{SL} = 100$-few
thousand Hz. The vector diagram for $T_{1\rho}$ relaxation is illustrated in Figure 4. The initial short hard pulse is applied along the $x$-axis to rotate the longitudinal net magnetization $M_0$ into the transverse plane. Then a spin-lock pulse $B_{SL}$ along the $y$-axis with duration of TSL makes the magnetization rotate with a frequency of $\omega_{SL}$. The final short pulse rotates the magnetization back to the longitudinal direction. The amount of received signal in $T_{1\rho}$ imaging is often portrayed by the following, mono-exponential decay equation similar to the $T_2$ relaxation equation:

$$S \propto \exp\left(-\frac{T_{SL}}{T_{1\rho}}\right)$$

(4)

where $T_{1\rho}$ is the $T_{1\rho}$ relaxation time.

Figure 4: Diagram of the magnetization evolution during a spin-lock experiment. A) The initial short hard pulse is applied along the $x$-axis to rotate the net magnetization $M_0$ into the transverse plane along with the $y$-axis $M_1$. B) A spin-lock pulse $B_{SL}$ along the $y$-axis with duration of TSL makes the magnetization rotate $\Theta^\prime$ with a frequency of $\omega_{SL}$. C) The final short pulse rotates the magnetization back to the longitudinal direction. [4]

The spin-lock frequency $\omega_{SL}$ is calculated the same way than the Larmor frequency, shown in Equation 1:

$$\omega_{SL} = \gamma B_{SL}$$

(5)

There are three types of $T_{1\rho}$ MR imaging; $T_{1\rho}$-weighted contrast imaging, mapping $T_{1\rho}$ values or measuring $T_{1\rho}$ dispersion. $T_{1\rho}$-weighted contrast imaging uses a spin-lock pulse, lets the $T_{1\rho}$ relaxation appropriately happen and then “stores” the $T_{1\rho}$ prepared magnetization along the longitudinal direction. $T_{1\rho}$ maps are created by maintaining the same spin-lock frequency in all measurements, while incrementing the spin-lock time and finally the $T_{1\rho}$ values are calculated for each voxel using Equation 4. $T_{1\rho}$ dispersion, on the other hand, is measured by keeping the spin-lock time constant and changing the spin-lock frequency. This provides macromolecular information (eg. proton exchange, composition of tissue and protein content) of the tissue and a representation of tissue at low frequencies. A few of the main mechanisms affecting $T_{1\rho}$ relaxation in cartilage are dipolar relaxation, quadrupolar relaxation and chemical exchange. The mechanisms’ importance is varying on the spin-lock frequency, but the dominant mechanism in different
frequency ranges is still unknown. Dipolar relaxation is mostly caused by the rotation of different molecules happening at different frequencies with each other, e.g. anisotropic water molecules in fibrous collagen network. Quadrupolar relaxation is caused by interactions between hydrogen molecules and other non-spherical molecules that have a spin over 1/2, such as 14-N. Chemical exchange is caused protons being exchanged in the tissue between different functional groups, such as bulk and hydration water and -NH and -OH-groups. [2, 4]

3 T₁ρ relaxation in articular cartilage: origin and association with biochemical composition and biomechanical properties

3.1 T₁ρ relaxation and dispersion in cartilage model systems and animal studies

Several studies have been conducted investigating T₁ρ relaxation and dispersion in various different types of environments, such as cartilage model systems and either native or enzymatically degraded animal cartilage samples, both in vivo or in vitro. Many different magnetic field strengths and spin-lock frequencies were used in these studies in the following section.

Duvvuri et al. studied the hypothesis of using T₁ρ imaging alone to be a reliable marker for PG loss. In vitro bovine articular cartilage enzymatically degraded using trypsin was used in the study and the relaxation times of the samples were first scanned with a 2 T scanner with a spin-lock frequency of \( \gamma B_{SL} = 500 \text{ Hz} \), after which the spatial distribution of the PG loss was confirmed on a 1.5 clinical system. They found that increase in T₁ρ values correlated with the loss of PG and that T₁ρ values could clearly demonstrate a minimum of 15 % depletion of PG. Duvvuri et al. concluded that serial T₁ρ measurements alone are enough to detect the longitudinal PG loss and the combination of T₁ρ imaging with other imaging methods, such as T₁ and T₂ imaging, only marginally improves the estimation of PG loss. [8]

Regatte et al. compared the behaviour of T₂ and T₁ρ relaxation times in PG-depleted cartilage. The study was conducted using a 4 T MR scanner and the spin-lock frequency used was 500 Hz. In vitro bovine articular cartilage that had its PG content enzymatically degraded with trypsin was used in this article for the measurements. Regatte et al. noticed that the relaxation rate \( R_{1ρ} (= 1/T_{1ρ}) \) correlates strongly and linearly with PG loss, while \( R_2 \) relaxation rate \( (= 1/T_2) \) correlated badly with it. This is illustrated in Figure 5. They also found the T₂ image taken before PG depletion to have 58 % poorer contrast and 43 % lower SNR to the equivalent T₁ρ image. While both T₁ρ and T₂ values were higher in PG-depleted cartilage, on average the T₁ρ values were found to be 60-80 % higher than T₂ values. [9]
Keenan et al. studied the correlation of $T_{1\rho}$ dispersion effects with cartilage initial elastic modulus and also with collagen and PG content in the cartilage. Cartilage modulus indicates cartilage deformation under mechanical stress and changes in it could be used to indicate cartilage health. The study used the $T_{1\rho}/T_2$ ratio for estimating $T_{1\rho}$ dispersion effects. A 3 T scanner with spin-lock frequencies of 500 and 1000 Hz was used for imaging in vitro human cadaver patellae. Keenan et al. found that $R_{1\rho}$ correlated with sulfated glycosaminoglycan (sGAG) content depending on spin-lock frequency. Also the initial elastic modulus increased when $T_{1\rho}/T_2$ ratio decreased, but, unexpectedly, $R_{1\rho}$ and $R_2$ values did not correlate with initial elastic modulus. This was speculated to be caused by ‘challenges of cadaveric cartilage’. This was identified by Keenan et al. as a possible limitation in the study, since the patellae used were obtained from cadavers and frozen up to nine months before the study. They speculated the freezing and subsequent thawing could affect the macromolecular structure of cartilage. The study also was limited to cartilage thicker than 1 millimetre with an intact surface, which only restricts the findings of this study to early OA cases. Keenan et al. concluded that the $T_{1\rho}/T_2$ ratio could be used to detect early changes in cartilage. [10]

Duvvuri et al. studied the effects of enzymatic degradation in articular cartilage using $T_{1\rho}$ as an indicator. The study used a 2 T scanner with the spin-lock frequency varying between 100-9000 Hz. Also images with a spin-lock frequency of 0 Hz were used as $T_2$ comparison images. The cartilage used in the study was in vitro bovine articular cartilage which was degraded enzymatically using trypsin (for PG degradation) and collagenase (for collagen degradation). This was done to simulate PG and collagen loss in the sample. The cartilage samples were imaged perpendicular to the external magnetic field. Duvvuri et al. found that the $T_{1\rho}$ value was higher in trypsin treated samples, which have the PG content degraded, compared to both collagen degraded and control samples, as illustrated in Figure 6. $T_{1\rho}$ values also increase when PG is degraded, which according to them suggests that $T_{1\rho}$ is selectively sensitive to PG con-
The $T_1$ images also had approximately 20% higher SNR compared to $T_2$ images. Duvvuri et al. also suggested that chemical exchange, in other words the exchange between free water molecules and the coupled water molecules in collagen, contributes to $T_1$ dispersion, while the coupling between NH and OH groups could also contribute. They found that $T_1$ images also show a zonal structure in the cartilage compared to $T_1$ images. Additionally, $T_1$ values in the centre of tissue were low and they grew when approaching the edge of the tissue, while $T_2$ values were uniform throughout the tissue. Duvvuri et al. suspected this happens because both PG and water content are higher in the center of the tissue while the edges of tissue contain more free water molecules. [11]

Figure 6: The $T_1$ dispersion plots for normal, PG-degraded and collagen-degraded samples. All samples show significant dispersion, but the $T_1$ value of the PG degraded sample is significantly higher at any spin-lock frequency. [11]

In a follow-up study Duvvuri et al. investigated the effect of proton exchange to water $T_1$ dispersion in different biological environments. The measurements were made using model systems; peptide solutions with both N-14 and N-15 were used to simulate the protein in cartilage and chondroitin sulfate (CS) type C solutions simulated PG in cartilage. Also, the dispersion was measured using *in vitro* bovine articular cartilage that had its PG content enzymatically degraded using trypsin. A 2 T scanner was used in the study, while the spin-lock frequency was varied between 100 and 2000 Hz. Duvvuri et al. found that $T_1$ relaxation rate $R_1$ in water increased with peptide and CS concentration in the model systems. Decreased concentrations of peptide and CS indicate a loss of PG in cartilage, so they suggested $T_1$ to be sensitive to cartilage PG content. In bovine articular cartilage the $R_1$ dispersion profile in different spin-lock frequencies followed a bi-Lorentzian function. This is shown in Figure 7. Duvvuri et al. proposed that due to the dispersion profile being bi-Lorentzian, there are at least two dispersion processes in water between 100-6000 Hz. The longitudinal relaxation rate was
found to be low in both NH and OH groups, so quadrupolar relaxation was found to be an unsubstantial relaxation method in both model solutions at low frequencies. Low frequency $T_{1\rho}$ correlation rate increased as the PG content decreased while higher frequency correlation rates were unaffected. Duvvuri et al. concluded that this was likely due to proton exchange of NH and OH groups with water being the dominant dispersion mechanism in low frequencies, while in the higher frequencies dispersion could be dominated by exchange of entire water molecules between free and bound states. [12]

Figure 7: Dependence of water $R_{1\rho}$ relaxation and dispersion in articular cartilage on PG loss is shown as a bi-Lorentzian function. [12]

Regatte et al. also studied the possibility of measuring GAG content in cartilage using $T_{1\rho}$ imaging. The research was conducted using chondroitin sulfate (CS) phantoms that were spectroscopied using a 2 T spectrometer and spin-lock frequencies of $\gamma B_{SL} = 250$ and 750 Hz, and enzymatically degraded in vitro bovine articular cartilage that had its GAG content depleted using trypsin. The bovine samples were then imaged with a 4 T medical scanner with spin-lock frequencies of $\gamma B_{SL} = 100$ and 750 Hz. Regatte et al. discovered that $T_{1\rho}$ values in CS phantoms decreased as GAG content increased. The GAG data obtained from the phantoms had an “excellent agreement” with the GAG data measured from the imaging experiments. Also the imaging sequences used in the study were well below the SAR limits for human studies in all spin-lock frequencies under 750 Hz. [13]
Akella et al. explored the possible connection between PG content loss and $T_{1\rho}$ relaxation times. In the study they used *in vitro* bovine articular cartilage samples that had their PG content enzymatically degraded using trypsin. The external magnetic field used was 4 T and the spin-lock frequencies ranged between $\gamma B_{SL} = 0$–1500 Hz. Akella et al. found that $T_{1\rho}$ values were greater in PG-depleted cartilage compared to normal tissue at all spin-lock frequencies. Additionally, $T_{1\rho}$ values correlated strongly with PG content and nearly a linear correlation was found, as illustrated in Figure 8. Akella et al. also measured the SAR levels of the experiment at $\gamma B_{SL} = 750$ Hz and they were “well under” requirements for human levels. [14]

![Figure 8: PG-induced variation on cartilage $T_{1\rho}$ times. Each data point is an average of data obtained from five specimens. The error bars indicate standard error of mean in the $T_{1\rho}$ and PG measurements. The solid line indicates the linear fit to the experimental data. A strong correlation ($R^2 = 0.987$ and slope = 1.08) between change in PG and $T_{1\rho}$ times is obvious. One can see that with an over 50 % PG depletion, $T_{1\rho}$ increased from 110 to $~170$ ms. [14]](image)

In another study of theirs, Akella et al. researched the possibility of eliminating the laminar appearance in $T_{1\rho}$ images. The laminar appearance in $T_2$ images is caused by residual dipolar interaction, which happens due to the different collagen fiber orienta-
$T_2$-weighted images suffer from variation between signals received from different parts of collagen, which results in the appearance of laminae in images. The effect is minimized when the target is oriented in the “magic angle” ($\approx 55.4^\circ$) relative to the external magnetic field. Akella et al. used a 1.5 T clinical scanner to scan in vivo human patellae and a 4.7 T small-bore MRI scanner for in vitro bovine cartilage plugs. The spin-lock frequencies used varied between $\gamma B_{SL} = 250$-4000 Hz. The samples were orientated both parallel and at the magic angle to the external magnetic field. Akella et al. found that as the spin-lock frequency grows, less laminae appear in the image at both imaging angles used in the study, which suggests that $T_{1\rho}$ imaging doesn’t require the sample to be at a specific angle, so all angles are fine for imaging. They also found that when the spin-lock frequency is under 500 Hz, most of the laminar appearance is reduced significantly so the residual dipolar coupling constant must be also under 500 Hz. $T_{1\rho}$ images with $\gamma B_{SL} = 500$ Hz have superior signal even at the magic angle compared to $T_2$ images. $T_{1\rho}$ values increase at both angles as a function of $\gamma B_{SL}$ until 2000 Hz. The in vivo images showed that the $T_{1\rho}$ image at $\gamma B_{SL} = 500$ Hz has no laminae compared to the $T_2$ image. Akella et al. concluded that if the spin-lock frequency is higher than the residual dipolar interaction, the effect it causes is eliminated from MR images. [15]

Wheaton et al. investigated the correlation between $T_{1\rho}$ values and the fixed charge density (FCD) in tissue, since it had been previously found using sodium MRI, that FCD and PG content in tissue were directly correlated. They first imaged a controlled model of in vitro bovine articular cartilage, which had been enzymatically degraded of its PG content using trypsin. Also, a physiological model of in vitro human articular cartilage obtained from knee replacements were imaged. The equipment used in the study was a 4 T clinical MR scanner, with the spin-lock frequency being $\gamma B_{SL} = 500$ Hz. The spatial maps of $T_{1\rho}$ values and FCD were taken using sodium MRI. Wheaton et al. confirmed that FCD content decreased when trypsin concentration increased or in other words when PG content decreased. Also, $T_{1\rho}$ values increased while PG content lowered. The rate of $T_{1\rho}$ values $R_{1\rho}$ correlated with FCD content in both the control model and the physiological model. Wheaton et al. then concluded that changes in $T_{1\rho}$ values is caused mainly by PG loss, rather than collagen loss. [16]

Wheaton et al. also explored the possibility of measuring changes in PG content using $T_{1\rho}$-weighted imaging. The spin-lock frequency was $\gamma B_{SL} = 500$ Hz, while a 4 T scanner was used for the measurements. The study used pig articular cartilage, which first was imaged in vivo after it had its PG content degraded using IL-1β injections to the joint, after which the pigs were killed and ex vivo images were taken of the cartilage. The effects of the injections were afterwards confirmed by histological analysis. Wheaton et al. found that $T_{1\rho}$ values were significantly elevated in PG degraded samples compared to controls. Also, $R_{1\rho}$ values were found to be linearly correlated and statistically significantly correlated with FCD content, as found in their previous study. Wheaton et al. found two main limitations in the study: $T_{1\rho}$-weighted images were limited to single slice imaging only and the in vivo $T_{1\rho}$ images had a poor resolution compared to the
In vitro images, so no correlation was attempted between $T_{1\rho}$ values, FCD content and histological data. [17]

In another study of theirs, Wheaton et al. studied the possibility of using $T_{1\rho}$ as a marker to assess the different biomechanical and biochemical properties of cartilage. In vitro bovine cartilage explants, that had their PG content degraded with IL-1β, were used in the study. The explants were divided into four groups based on IL-1β treatment time. A 4.7 T research scanner was used to scan the samples, with the spin-lock frequency being $\gamma B_{SL} = 500$ Hz. Wheaton et al. found that changes in biomechanical content (such as the uniaxial aggregate compressive modulus and hydraulic permeability) increased $T_{1\rho}$ relaxation times. Also, PG loss was followed by only a small change in collagen content. Additionally, $T_{1\rho}$ times increased steadily with treatment time in cross-sectional profiles. They found mid-zone $T_{1\rho}$ values increasing in a "statistically important" manner, while the PG content change was also strongly correlated with $T_{1\rho}$ value changes. Likewise, Wheaton et al. found $R_{1\rho}$ values to strongly correlate with both biochemical and biomechanical characteristics of cartilage, which implicated the potential of using $T_{1\rho}$ imaging as an assessment tool for changes in cartilage. [18]

### 3.2 In vitro studies of $T_{1\rho}$ relaxation in human articular cartilage

Human articular cartilage in vitro was used for $T_{1\rho}$ relaxation studies in the following section, in order to simulate a more relevant environment for cartilage degradation in human patients happening during OA.

In their study Kester et al. wanted to investigate whether OA cartilage was missing PG or collagen compared to healthy knees. They had a group of five in vitro knee cartilage samples obtained from knee replacement surgeries compared with a control group of 20 healthy subjects. The system used in the study was a 3 T MR imaging device while the spin-lock frequency used was $\gamma B_{SL} = 575$ Hz. Kester et al. noticed that no difference in cartilage thickness was found between patients and controls but both $T_{1\rho}$ and $T_{2}$ values were either significantly higher or higher in OA patients, depending on the portion of the knee. The study had several limitations according to Kester et al.; the OA group had a small sample size of 5 subjects, age difference between the two groups was significant (mean age of 28.9 years in the control group v. 70 years in the OA group), which could possibly explain the differences in $T_{1\rho}$ and $T_{2}$ values in itself (this is discussed more in Section 4.2 and shown in Figure 11 of this thesis.). The lack of long-term follow ups due to the OA patients having their knee replaced was also identified as a limitation. Kester et al. concluded that $T_{1\rho}$ and $T_{2}$ could be used in detecting early OA, as cartilage in early OA could have no changes in thickness but elevations in $T_{1\rho}$ and $T_{2}$ values. [19]

In their study, Mlynárík et al. investigated the link between diminishing PG content and $T_{1\rho}$ relaxation times along with comparing $T_{1}$, $T_{1\rho}$ and $T_{2}$ as markers for PG depletion in cartilage. For this, they used in vitro human articular cartilage from patients undergoing total knee or hip replacements. Prior to surgery, the patients received a dou-
ble dose of Gd-PDPA to use as an additional contrast agent. A 3 T scanner with the spin-lock frequency being 2500 Hz was used in this study. Mlynárik et al. found that on average $T_{1\rho}$ values were compared to $T_2$ values. $T_{1\rho}$ images also had less susceptibility artefacts on the tissue-air surface but, which results to $T_{1\rho}$ relaxation times being higher on the cartilage surface than $T_2$ values. On the other hand, $T_{1\rho}$ values did not increase in the deepest parts of cartilage and $T_2$ maps had subtle intensity variations that were not visible in on the $T_{1\rho}$ map. Mlynárik et al. found that $T_{1\rho}$ and $T_2$ relaxation maps were spatially almost identical, in contrast to a previous study by Duvvuri et al. [11]. It was found that the Gd-PDPA did not have significant effects on $T_2$ values while $T_{1\rho}$ values did decrease in regions with lesions due to the contrast agent. The exact reason of contrast agents affecting relaxation times is still unknown. Regardless of this, Mlynárik et al. concluded that $T_1$ imaging in the presence of Gd-PDPA could be the most potential tool in detecting the loss of PG content, while $T_{1\rho}$ imaging did not offer substantial improvement from $T_2$ imaging since they suspect both techniques are more reliant on changes in water content. [20]

Mlynárik et al. also studied $T_{1\rho}$ relaxation and dispersion in cartilage in another study. The measurements aimed to see the relaxation rates $R_{1\rho}$ and $R_2$ in various external magnetic fields and spin-lock frequencies. The study used *in vitro* human articular cartilage obtained from knee and hip replacement surgeries, which were then imaged in both 2.95 and 7.05 T with spin-lock frequency ranging between $\gamma B_{SL} = 0-2500$ Hz. A technical restriction with the 7.05 T scanner limited the used spin-lock frequency to $\gamma B_{SL} = 1000$ Hz. The samples were aligned at 0°, at the “magic angle” at approximately 55° and at 90° relative to the external field. Mlynárik et al. found that $T_{1\rho}$ and $T_2$ values are dependant on the static magnetic field. They found that $R_{1\rho}$ values did not depend on the orientation of the sample in the transitional zone, unlike $R_2$ values. Mlynárik et al. propose that the lack of $R_{1\rho}$ dispersion in the transitional zone dependless of the spin-lock frequency used means the dominant contribution of chemical exchange, meaning interactions between NH and OH groups in cartilage and water, is highly improbable. They suggest that dipolar interaction is the dominant relaxation method at small magnetic fields under 3 T due to “slow anisotropic motion of water molecules in the collagen matrix”, while chemical exchange is the dominant method in magnetic fields over 3 T. This is in contrast with the study conducted by Duvvuri et al. [12], which suggests chemical exchange to be the dominant mechanism at low magnetic fields. [21]

Menezes et al. researched the $T_2$ and $T_{1\rho}$ values in multiple molecular environments in order to find primary reason for the values increasing. They used molecular suspensions of cartilage macromolecules (collagen and GAG), samples of *in vitro* young bovine articular cartilage, six samples ($N = 6$) were left untreated as controls, and others ($N = 6$) which were enzymatically degraded using trypsin (for reducing GAG content) or using IL-1β (for simulating complex degradation, $N = 3$). Also the study had *in vitro* human articular cartilage obtained from OA patients’ knee replacement surgeries ($N = 3$), from which GAG-depleted, normal and complex degradation areas were identified with a polarized light microscope. Menezes et al. noticed the small sample size for
human tissue as a limitation of the study. The measurements were conducted using a 8.45 T system and a spin-lock frequency of $\gamma B_{SL} = 100$ Hz. Menezes et al. discovered that both $T_1$ and $T_2$ values were elevated in trypsinized (GAG-depleted) bovine tissue compared to native bovine (collagen and GAG intact) tissue. IL-1β treatment on the samples was found to have no effect on $T_1$ relaxation times, while $T_2$ values were lowered. $T_1$ values also did not track GAG content in human cartilage samples, as the values of both $T_1$ and $T_2$ were not substantially different in human complex degradation areas compared to GAG-depleted or normal samples. This in turn could, according to Menezes et al., indicate that differences from the mean values in $T_1$ and $T_2$ cannot be accounted by concentration differences or molecule matrix orientations alone, but instead molecular-level differences, such as collagen or GAG molecule interactions with water or other molecules, play an important role. [22]

Regatte et al. investigated the differences between $T_1$ and $T_2$ relaxation times in OA cartilage. The study used a 4 T scanner with a spin-lock frequency of $\gamma B_{SL} = 500$ Hz. In vitro human articular cartilage ($N = 8$) was obtained from OA patients that underwent total knee replacements and divided into three groups based on OA severity; mild OA, moderate OA and severe OA. Regatte et al. found that both $T_1$ and $T_2$ values were capable of quantifying changes in early OA, but $T_1$ values in moderate OA samples were elevated more clearly compared to $T_2$ values. Also, $T_2$ values were not elevated in advanced OA samples, while $T_1$ values increased heavily from early OA cartilage. This is clearly shown in Figure 9. The level of degeneration noticed by $T_1$ and $T_2$ was confirmed by histological analysis. Limitations of the study was its limited sample size and the lack of isolation of collagen’s and PG’s effect on $T_1$ times. However, they suspected the contribution of collagen to relaxation times to be small and hypothesized the rise in values to be caused primarily due to PG loss. Regatte et al. concluded $T_1$ values to be a more sensitive marker in predicting and tracking OA status and detecting early cartilage degeneration compared to $T_2$ values. [23]

Taylor et al. conducted a comparison study between different MRI techniques in GAG content quantification. The study compared $T_1$, $T_2$ and $T_{1p}$ imaging in in vitro human cartilage samples (obtained from both cadavers and knee replacements) with and without administration of a gadolinium-based contrast agent. The study used a 3 T imaging system and a spin-lock frequency of $\gamma B_{SL} = 500$ Hz. Taylor et al. found that precontrast $T_{1p}$ values correlated well with precontrast $T_1$ values, but no correlation was found between other pre- or postcontrast MRI measures. Also postcontrast $T_1$ values did not correlate with $T_{1p}$ values which Taylor et al. found interesting, since both techniques have been found to be sensitive to PG loss. Taylor et al. also hypothesized that changes in precontrast $T_{1p}$ are somewhat related to other changes in the ECM rather than PG loss, because only a small portion of the ECM — about 4-6 % — is PG. However in early OA, PG is lost preferentially throughout the ECM, which could suggest $T_{1p}$ to be specific to their loss at the onset of the disease. Taylor et al. also found $T_{1p}$ values to have a higher dynamic range than $T_2$ values, which indicates $T_{1p}$ to have a more accurate ability to separate diseased tissue from healthy one. [24]
4 **In vivo** studies of $T_{1\rho}$ relaxation in human articular cartilage

Since $T_{1\rho}$-weighted imaging had been found to be a potential tool in detecting changes in cartilage samples of both animal and human *in vitro*, several studies have been conducted in *in vivo* human patients. Also studies comparing OA patients in several phases of the illness with healthy individuals have been conducted in recent times.

The most commonly used modern MRI scanners in medical imaging today have a static field of 3 Tesla, so most of the studies in the following chapters were conducted with a 3 T MR imaging system and using a spin-lock frequency $\gamma B_{SL} = 500$ Hz. If other values are not explicitly mentioned in this chapter, values listed here were used in the study.
4.1 Cartilage $T_{1\rho}$ relaxation in human knees

In their article Duvvuri et al. described their first experience of *in vivo* human knee $T_{1\rho}$ imaging and evaluated the possibility of $T_{1\rho}$ weighted fast spin-echo imaging in humans. They used a 1.5 T MR imaging system with spin-lock frequencies ranging between 0 and 375 Hz, with 0 Hz images used as $T_2$ weighted comparison images. The study used *in vivo* human patellar cartilage, with five healthy human volunteers and one volunteer with knee pain as subjects. Duvvuri et al. found that the $T_{1\rho}$ values were “uniformly higher” than $T_2$ values. The signal-to-noise ratio (SNR) of the $T_{1\rho}$ images was 20% larger compared to $T_2$ images. Also when compared to $T_2$ images, a potential cartilage lesion in the knee was seen more clearly in $T_{1\rho}$ images, with the difference in contrast being 25% better in $T_{1\rho}$ images. Duvvuri et al. then concluded that $T_{1\rho}$ “might be useful for the diagnosis of articular cartilage disease.” [25]

In their study Borthakur et al. investigated the dispersion of $T_{1\rho}$ in the human brain. They compared $T_{1\rho}$ and $T_2$ weighted images of *in vivo* healthy human brains (N = 5). SAR limits of the experiment were validated with agarose phantoms. The scanner was a 1.5 T MR imaging system, while the spin-lock frequencies varied between $\gamma B_{SL} = 62$-500 Hz. Borthakur et al. found that $T_{1\rho}$ images seemed sharper compared to $T_2$ images and the contrast was especially improved in regions between surrounding cerebrospinal fluid. They also noticed $T_{1\rho}$ values were also dependant on the spin-lock frequency used. Finally, they found the $T_{1\rho}$ values to be higher than $T_2$ values in all measured tissue types. A limitation identified by Borthakur et al. was the $T_{1\rho}$ imaging sequence being limited to single slice acquisition, due to the spin-lock pulse not being slice selective. [26]

A limitation found in their previous study [26], Borthakur et al. studied the possibility of taking three-dimensional $T_{1\rho}$ weighted images. The interest was to design and implement a 3D $T_{1\rho}$ sequence, that would be safe to use in humans eg, not exceeding SAR limits. The test used *in vitro* bovine patellae as test subjects and finally after safe SAR limits and temperature rise in tissue were calculated, a volunteer *in vivo* human patella as control. They used a 1.5 T MR scanner, the used spin-lock frequencies were 400 Hz in human imaging and 500 Hz in *in vitro* imaging and the flip angle used in the sequence was 35°. Borthakur et al. found that the three-dimensional sequences produced similar $T_{1\rho}$ values than regular two-dimensional sequences. The spin-lock frequencies and flip angle used did not result in any significant temperature change in the tissue, therefore Borthakur et al. concluded that the sequence is safe for use in imaging humans *in vivo*. [27]

Osaki et al. investigated the change in cartilage after an anterior cruciate ligament (ACL) injury using $T_{1\rho}$ relaxation times as a marker. There were 63 patients divided into either a control group of healthy patients with no previous knee injuries or one of three groups of ACL injury patients who had not had regenerative surgery. The division to groups was based on the time after the injury; a group of “acute” patients with under 12 weeks after injury, a group of “chronic” patients with over 12 weeks but under two years...
from injury and another group of “long-term chronic” patients with two to five years after the injury. Osaki et al. found that the $T_{1\rho}$ values in the medial femoral condyle, which is the weight-bearing part in the knee, were significantly elevated in the “long-term chronic” group compared to the control group. Also elevated $T_{1\rho}$ values were found in patients in both “chronic” groups with medial meniscus injuries compared to the control group, while no significant difference was found between the same groups with no injuries, suggesting that $T_{1\rho}$ is capable of sensing early degeneration in cartilage. The study was problematic in several ways; Osaki et al. could not conclude that the cartilage degeneration was caused by the time after injury. They also couldn’t conclude the effect of meniscal injuries on cartilage damage in the “chronic” groups. Furthermore, the sample size of the “long-term chronic” group was small ($N = 7$) because ACL injuries left untreated for extended periods of time are rare. Osaki et al. also suggested that rather than using a separate control group, a better comparison could have been done using the other, healthy knee of the same subjects. [28]

4.2 Cartilage $T_{1\rho}$ relaxation in osteoarthritic patients

One common factor with studies mentioned in this chapter that must be taken into consideration, is that OA usually is found in older people, and Li et al. found [29] that $T_{1\rho}$ values also grow with age regardless of patient health, as is shown in Figure 10, so the age difference between healthy control subjects and test subject groups should be taken into consideration when interpreting $T_{1\rho}$ values in in vivo OA patient studies.

![Figure 10: Distribution of $T_{1\rho}$ values vs age in healthy volunteers [29].](image)
Li et al. also noticed that $T_1$ and $T_2$ values grow significantly when comparing OA patients to healthy controls. They also noticed that there was a larger range and effect size in $T_1$ values compared to $T_2$ values, which could indicate, according to Li et al., that $T_1$ is a more sensitive method of detecting cartilage degeneration. [29]

In their study Schooler et al. investigated the long-term relationship between $T_1$ values and patients with cartilage lesions in the medial compartment of the knee. The study had healthy subjects as a control group compared to OA patients with lesions in the medial cartilage. Both groups were imaged annually for three years. Schooler et al. found that the global $T_1$ values of the lesion group was higher at years 1 and 2, but not at the baseline or year 3. The global mean longitudinal $T_1$ values also “approached a significant difference” between the two groups. The lesion group’s $T_1$ mean values increased yearly until dropping off between years 2 and 3, while the control group had its $T_1$ values lowering consistently each year. One of the limitations of the study was the limited sample size in the later time points, due to subject attrition, among others. Another limitation was also the specific focus on medial knee cartilage lesions, which means according to Schooler et al, that the findings of the study cannot be applied to the whole knee. [30]

Bone marrow edema-like lesions (BMEL) are lesions present in the knee after traumatic injuries, such as ACL tears, or after the onset of OA. In their study, Li et al. studied the correlation between occurrences of BMEL and elevated $T_1$ and $T_2$ relaxation times. Li et al. used two subject groups; a control group of 8 healthy subjects without BMEL and 30 subjects with BMEL present in the knee, either through ACL injury or OA. A limitation of the study, however, was the age difference between the two groups, the control group being younger. Also only one image was taken per BMEL, due to long acquisition time. They compared weight-bearing portions of the cartilage with non-weight-bearing portions and found that the $T_1$ values of non-weight-bearing portions were significantly higher compared to the weight-bearing portions in the control group. Also, the mean $T_1$ Z-scores (standard scores) in BMEL-overlying cartilage were significantly higher than in surrounding tissue in ACL tear patients, but the same correlation wasn’t found in OA patients. Because water volume correlated with the elevation of BMEL volume, and also water content in BMELs was found to be higher than in the surrounding tissue only in ACL patients, Li et al. suggested that $T_1$ imaging was capable of identifying BMEL-induced regions in the knee. [31]

In addition to Li et al., Bolbos et al. studied the link between BMEL and elevated $T_1$ values. The study was done using in vivo human anterior cartilage with a control group of 15 healthy subjects compared with a patient group of 16 subjects with ACL tears with BMEL present. Bolbos et al. found, similarly to Li et al. [31], that $T_1$ values were significantly higher in non-weight-bearing parts compared to weight-bearing parts in control patients, while no significant difference was found between the two groups. At the lateral tibia, $T_1$ values grew significantly in BMEL-overlying cartilage compared to surrounding cartilage, consistent with Li et al. findings in their study. However, Bolbos et al. considered the lack of performing an arthroscopy for obtaining direct correlation with
BMEL and $T_{1\rho}$ to be a limitation in the study. Finally, they concluded that $T_{1\rho}$ could be able to identify BMEL-induced regions in cartilage. [32]

Li et al. also investigated the relationship between spatial correlation and distribution of $T_{1\rho}$ and $T_2$ times in another study. It compared a group of 10 healthy control patients with another group of 10 OA patients. The knees were imaged in both parallel and perpendicular orientations of the scanner. Li et al. found that the average Z-score for both $T_{1\rho}$ and $T_2$ values were elevated in the OA patient group compared to the control group. Li et al. proposed in the study that in early stages of OA, $T_{1\rho}$ values were more sensitive to PG loss while $T_2$ values were sensitive to loss of collagen content in the cartilage. The study suggested that in the late stage of cartilage degeneration $T_{1\rho}$ and $T_2$ values can be linked together. Li et al. found that while both $T_{1\rho}$ and $T_2$ relaxation times increase from bone/cartilage surface to cartilage surface, $T_{1\rho}$ values had a better dynamic range and a larger difference between the two subject groups. The study found that $T_{1\rho}$ values were higher in the central parts of tissue unlike $T_2$ values. The limitations in the study mostly were related to the imaging sequence used, for example, the usage of spiral acquisition in imaging which only allowed imaging in the axial direction, the limited image resolution restricted the analysis to the patellar cartilage and the 3D images that were used, were interpolated from 2D images which may cause artefacts. In their study, Li et al. proposed that patellar cartilage degeneration started from the central part of the tissue, and that $T_{1\rho}$ was a more sensitive marker compared to $T_2$ to early changes in cartilage related to OA. [33]

Stahl et al. studied the relations between $T_{1\rho}$ and $T_2$ values and knee abnormalities in early OA patients. They used a control group of 20 healthy patients and a group of 17 patients with mild OA, rated 1-2 in the Kellgren-Lawrence (KL) scale. The control group was divided into two groups (“sedentary” and “active”) by their activity. Stahl et al. found that $T_{1\rho}$ and $T_2$ relaxation times were significantly higher in the OA patient group, compared to controls. They also found that $T_{1\rho}$ values positively correlated with age between all subjects. Stahl et al. found that $T_{1\rho}$ values were significantly higher in patients with cartilage lesions compared to patients without them, while $T_2$ values were not statistically different, suggesting that $T_{1\rho}$ is more sensitive to cartilage degeneration to $T_2$ as a marker. Also, the average $T_{1\rho}$ values were higher in subjects with lesions in the “active” group compared to the “sedentary” group, while $T_{1\rho}$ values were lower in subjects without lesions in the “active” group compared to “sedentary” subjects. According to Stahl et al. this could indicate that higher $T_{1\rho}$ values are associated with the risk of developing lesions, and furthermore, the possibility of $T_{1\rho}$ assessing the quality of cartilage and the risk of getting OA. The limitations of this study included the significant age difference of the control and OA group and the division of subjects into groups based only on the subjective information on activeness provided by the study participants. [34]

In their study Zarins et al. assessed cartilage and meniscus degradation using $T_{1\rho}$ and $T_2$ measurements. The study compared a group of 19 healthy controls with 44 OA patients. OA severity was graded using the KL scale, while the clinical symptoms of OA
patients were assessed using the Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores. Zarins et al. found that the severity of meniscus degradation was directly related to the magnitude of $T_{1\rho}$ and $T_2$ values. Also, both $T_{1\rho}$ and $T_2$ imaging were able to differentiate different meniscal tear grades in the posterior horn of the medial meniscus, where tears most commonly are found. In articular cartilage however, $T_{1\rho}$ relaxation times correlated positively with the WOMAC scores, suggesting that $T_{1\rho}$ values are a better indication of cartilage degeneration than $T_2$ according to Zarins et al. [35]

Li et al. investigated the possibility of creating a spiral imaging sequence for in vivo human imaging. Spiral imaging can shorten echo time in imaging, while possibly reducing artefacts produced by flow and motion. Li et al. first measured the $T_{1\rho}$ values of the sequence on agar gel phantoms with differing concentrations, after which they imaged in vivo human patellae. The human subjects were divided into a control group of 10 healthy volunteers and 9 OA patients. The spin-lock frequencies used varied between 300 Hz and 700 Hz. Li et al. found that the difference between controls and OA patients in average $T_{1\rho}$ relaxation time was significant, while no significant difference for average $T_2$ time between the two groups was found, as seen in Figure 11. The figure also shows that patients with similar $T_{1\rho}$ values could have different $T_2$ values, possibly indicating that information from $T_{1\rho}$ and $T_2$ imaging could complement one another in diagnosing cartilage abnormalities. A significant difference in the average $T_{1\rho}$ values between groups was also found in all regions of cartilage, which suggests $T_{1\rho}$ quantification could be a better potential marker for detecting cartilage degeneration according to Li et al. A major limitation that was identified in the spiral imaging sequence was its current restriction to imaging only in the axial orientation, because the sequence doesn’t support the use of an anti-aliasing filter required for imaging in sagittal or coronal planes. [36]

Nishioka et al. conducted a study to research the connection between $T_{1\rho}$ and $T_2$ values and patellar cartilage degeneration. As a further improvement on other studies of the same subject, according to Nishioka et al. this was the first study to select the OA patients ($N = 78$) selected for the study to be of the same age group with an average age of 68.6 years. The spin-lock frequency used was $\gamma B_{SL} = 440$ Hz. The patients were divided into four groups, one “normal” group and three OA groups based on the severity of cartilage degeneration on the WORMS (whole-organ magnetic resonance imaging score) scale. Nishioka et al. found that the mean $T_{1\rho}$ and $T_2$ values in all OA groups were significantly higher compared to the “normal” group. $T_{1\rho}$ values had significant differences between different OA groups and there was a strong positive correlation between $T_{1\rho}$ values and OA progression. Similarly, $T_2$ values also had significant differences between different OA groups and there was a positive correlation between $T_2$ values and OA progression. However, no significant difference between “normal” cartilage and mild OA was found in $T_2$ values. The limitations Nishioka et al. identified in this study included the small cohort size and the usage of patellar cartilage. Because patellar cartilage is different biochemically to femoral cartilage, further investigation is required to see if the results from this study could be applied to the femoro-tibial joint. As a conclusion
Figure 11: Correlation between $T_{1\rho}$ and $T_2$ in 12 subjects. Although the correlation is significant, there is a non-point-to-point relationship, that is, patients with similar $T_2$ values may show different $T_{1\rho}$ values, as shown in the vertical dashed box, or vice versa, as shown in the horizontal dashed box. The dashed line shows a clear cut difference of the average $T_{1\rho}$ between healthy controls and OA patients, while there is a significant overlap of average $T_2$ values. Significant difference was found in average $T_{1\rho}$ values but not in $T_2$ values between healthy controls and patients. [36]

Nishioka et al. considered $T_{1\rho}$ values to be more sensitive to cartilage degeneration than $T_2$ values. While both $T_{1\rho}$ and $T_2$ values could be used to evaluate the degree of cartilage degeneration in patients in a similar age group, according to them, the effects of aging to said values cannot be ruled out. [37]

5 Summary

$T_{1\rho}$ relaxation time has been shown to be a potential indicator for detecting early OA, since some studies investigated here have found PG content loss in cartilage to correlate with increasing $T_{1\rho}$ relaxation times and the relaxation rate $R_{1\rho}$ is found to correlate with GAG content due to chemical exchange having the greatest contribution. On the other hand, some studies found no correlation with $T_{1\rho}$ relaxation times and PG content. $T_{1\rho}$ values have also been found to correlate with the severity of OA in patients. Compared to the nearest equivalent of $T_{1\rho}$ imaging that is in use today — $T_2$-weighted imaging — $T_{1\rho}$ imaging is found to be more sensitive to changes happening in cartilage in OA, while also having better signal and less artifacts in the images. $T_{1\rho}$ imaging sequences also have been found to be safe for in vivo imaging. Some challenges still remain regarding $T_{1\rho}$ relaxation, as the leading cause of $T_{1\rho}$ relaxation in different frequency
ranges is still unclear. It has been suggested that chemical exchange is the leading mechanism for $T_{1\rho}$ relaxation only at high spin-lock frequencies ($> 2$ kHz) or high static magnetic fields ($> 3$ T), therefore $T_{1\rho}$ relaxation cannot be used as a PG-specific MRI technique in clinical imaging. Also, the effect of age on $T_{1\rho}$ values has to be studied further, since growth in $T_{1\rho}$ values could not be accounted solely to OA. Only one study comparing in vivo OA patients to healthy controls didn’t have significant age differences between the two groups and while results have been promising, more research is needed. As a conclusion, $T_{1\rho}$ imaging looks to be a potentially valuable method in detecting OA related changes in cartilage in the future.
References


