

Diagnostic and quantitative imaging of knee osteoarthritis

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Abbreviations and symbols

3D	Three-dimensional
B_0	Static magnetic field
B_1	RF magnetic field
B_{1SL}	Spin-lock RF magnetic field
BMI	Body mass index
CW	Continuous wave
DESS	Dual echo steady state
dGEMRIC	Delayed gadolinium enhanced magnetic resonance imaging contrast
ECM	Extracellular matrix
EQ-5D	Standardized measure of health outcome
FID	Free induction decay
FLASH	Fast low angle shot excitation
FLASHwe	Fast low angle shot excitation with water excitation
GAG	Glycosaminoglycan
$GdTPA^{2-}$	Gadopentetate dimeglumine
1H	Proton
h	Planck constant
\hbar	Reduced Planck constant
I	Nuclear spin angular quantum number
k	Boltzmann constant
KL	Kellgren-Lawrence
M_0	Net magnetization at equilibrium
MRI	Magnetic Resonance Imaging
m_s	Spin projection quantum number
M_{xy}	Magnetization in the xy plane
M_z	Magnetization in the z-axis
N_α	Population of the α state
N_β	Population of the β state
OA	Osteoarthritis
PG	Proteoglycan
PKR	Partial knee replacement
RF	Radio frequency
SL	Spin-lock
SPGR	Spoiled recalled gradient echo
T_1	Longitudinal relaxation time constant
T_{1p}	Longitudinal relaxation time constant in rotating frame
T_2	Transverse relaxation time constant
T_2'	Transverse relaxation due to magnetic field inhomogeneities
T_2^*	Total transverse relaxation rate
TE	Time-to-echo
TI	Inversion time
TKR	Total knee replacement
TKA	Total knee arthroplasty
TSL	Duration of spin-lock pulse
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
α state	Spin oriented parallel with respect to the external magnetic field
β state	Spin oriented antiparallel with respect to the external magnetic field
γ	Gyromagnetic ratio
θ	Tilt angle
μ	Magnetic moment
τ	Duration of the RF pulse
ω_0	Static magnetic field frequency
ΔE	Energy difference between β -state and α -state

1. Introduction to osteoarthritis

Rather than just a degenerative joint disease, osteoarthritis (OA) is an active process of cartilage destruction and regeneration [1, 2]. In a diseased joint the balance of these two processes is disturbed and cartilage degeneration has become the dominating process, which leads to the progression of the disease. OA is not solely a result of a dysfunction in cartilage, but a condition of the entire joint [3]. The most usual joints to bear OA are synovial joints, i.e. located in knees, ankles, hip, neck, and in the fingers. In this review, methods used in diagnosing and studying articular cartilage degeneration are presented and discussed.

It is estimated that just in the United States of America there are over 27 million adults suffering from OA [4]. In European population of individuals aged 40-75 years, the prevalence of symptomatic and radiological knee OA was 2.5 % for men and 6.6 % for women [5]. A study conducted in 1997 found that in a sample of 5 industrial countries (Australia, Canada, France, United Kingdom and United States) the cost of OA was from 1 % to 2.5 % of the gross domestic product respectively [6]. Individually OA decreases significantly the overall healthiness of the patient. Restrictions in movement reduce the amount of suitable activities and might even force a change in occupation. Added with the usual symptoms of pain and aching, a survey found that arthritis decreased quality of life measure, EQ-5D [7], even more than diseases such as breast cancer and anxiety disorder [8].

Better understanding of the pathophysiological factors causing OA is vital in developing methods for preventing, or at least slowing down, the process of cartilage degeneration.

2. Articular cartilage and the knee joint

Articular cartilage is a connective, load-bearing tissue in a knee joint, covering the articulating surfaces of femoral and tibial condyles and patella with a thickness usually varying between 1.5 to 4 millimeters [9]. Articular

cartilage prevents a direct contact between bony surfaces, thus enabling virtually frictionless articulation between them.

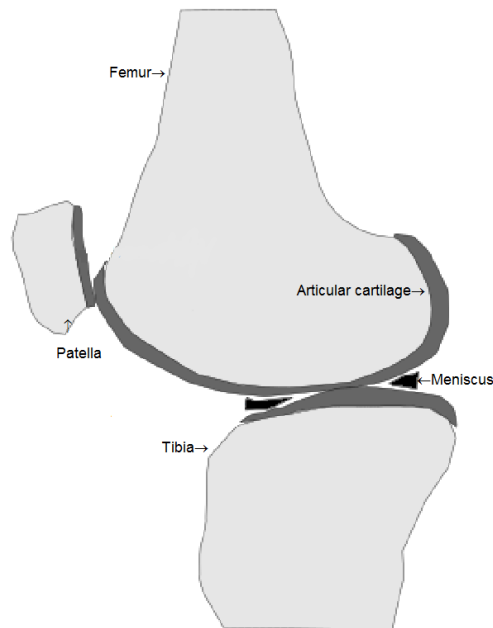


Figure 1. Simplified anatomy of the knee joint.

Extracellular matrix (ECM) forms the articular cartilage tissue. The main components of the ECM are collagen, proteoglycans (PGs) and chondrocytes. The main component of cartilage, water, is bound to remain within ECM by aforementioned protein structures [10]. PGs contain negatively charged glycosaminoglycans (GAGs) [11], which makes PGs hydrophilic molecules. Due to the repulsion between negatively charged GAGs, PGs distribute within the ECM. During compression, PGs are pushed closer increasing the repulsion between molecules. This increasing repulsion increases the stiffness of cartilage, whereas the collagen fibrils and water are responsible for the dynamic properties [12]. The pressurization of the water and the frictional resistance to water flow in the ECM dissipates energy in cartilage, accounting partly for the ability of articular cartilage to withstand mechanical loads [10]. Compared to other joint tissues, such as bone, articular cartilage has a very limited regenerative capacity and after cartilage tissue is damaged, full recovery of cartilage structure and functional capacity is unlikely [13].

Articular cartilage is divided into superficial, transitional and deep zones according to the structure and orientation of collagen fibrils (Figure 2). The

mechanical and structural differences between the different zones results in a highly anisotropic articular cartilage tissue [14].

Accounting for only 5 % of the cartilage thickness, superficial zone is the thinnest zone of cartilage [15]. The orientation of collagen fibrils is parallel to the cartilage surface, resulting in a superior tensile strength over other zones of cartilage. Superficial zone is the main reason causing the ability of cartilage to withstand tensile forces during articulation [16]. Superficial zone has also the highest concentration of water and collagen but a lower PG content compared to other zones [15].

In the transitional zone, collagen fibrils are starting to change their orientation with respect to cartilage surface from the perpendicular orientation of the deep zone to the parallel orientation of the superficial zone. Transitional zone makes up 20 % of cartilage tissue and has a lower concentration of water and collagen than superficial zone, but a higher PG concentration [15].

Constituting 75 % of cartilage tissue, deep zone is the thickest layer of the ECM. Collagen fibrils are oriented perpendicular to the cartilage surface and water concentration is at its lowest concentrations in this zone [17]. As the deep zone has the highest PG concentration, it is the main provider of resistance against heavy loads and compressive forces [16].

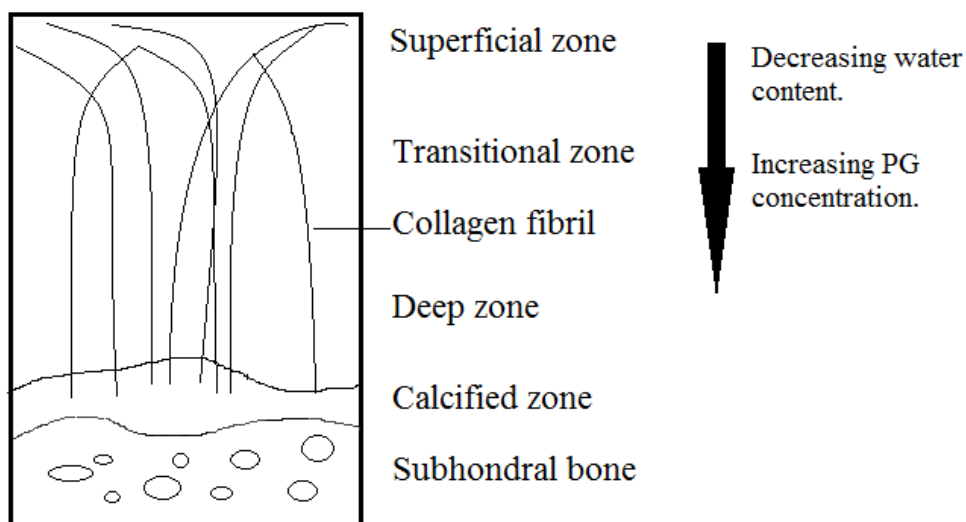


Figure 2. Different zones of articular cartilage

3. Risk factors for developing osteoarthritis

Certain risk factors increase the likelihood for developing OA. The significance of these factors is complex but some consensus of the main reasons exists. The main risk group for developing OA are postmenopausal females and the elderly. The prevalence of OA increases in the presence of risk factors such as systemic factors, joint trauma and continuous mechanical loading of the joint.

3.1 Systemic factors

It is well known that the incidence rates of OA increase with age [18-20]. This statement is also valid for knee OA [20]. Age is considered to be most important single factor in the development of the joint disease [21]. A probable explanation for the importance of age is the possible reduction in regenerative capacity of cartilage tissue [22].

OA is more common among females than males and the likelihood of which is at a peak level near menopause [23]. High prevalence of postmenopausal females with OA can provoke a mindset that decrease in oestrogen-levels has some pathogenic effect. Further investigations, however, have not yet found enough consistency between oestrogen-levels and the development of OA [24, 25]. Nonetheless, some researchers still firmly believe oestrogen to be a relevant factor [26].

3.2 Mechanical loading of the joint

People with higher mechanical stress on their joints are more likely to suffer from knee cartilage degradation at some point of their lives. This increased stress is usually a result of obesity [27, 28], area of work, especially if it consists of frequent knee bending, [29] or a decrease in muscular strength. Weak quadriceps in particular have been linked with OA [30]. The connection between the disease and obesity is higher with females than males [28, 31, 32] and for women over 50 years, weight reduction can reduce the likelihood of knee OA by 25.1% to 48.3% [33].

3.3 Obesity – fat

Prevalence of obese people with knee OA might be easily dismissed with a statement that obesity increases mechanical stress on knee joint, thus resulting in knee cartilage degeneration. The idea that obesity has only a mechanical link with OA might, however, be an incorrect statement. Obesity has a significant association with the prevalence of OA of the hands [34]. This finding cannot be explained by a higher mechanical stress of the joint and according to some investigators this might indicate that body mass index (BMI) is not a risk factor, but obesity is [34]. This statement is somewhat contradictory as mechanical loading is known to be an important factor [27, 28]. Fat is, nevertheless, believed to have an impact on stem cells involved in tissue repair [35].

3.4 Other factors

The list of different risk factors linked with OA is vast. Some other known factors linked with OA are heredity, subchondral bone density and joint injury [21, 27]. As the regenerative capacity of cartilage tissue is very limited, a joint injury, particularly of the ankle or knee, even in youth sports, is likely to have a link with OA developed later in life [36].

4. Different stages and symptoms of osteoarthritis

The progression of OA is generally divided into three stages: early stage, intermediate stage and advanced OA. In the early stage of OA, the cartilage matrix is damaged. Earliest stage of OA is not generally visible in diagnostic images of the knee, but occurs at a molecular level in the cartilage matrix [37, 38]. At this stage the water content is increased and PG concentration in the cartilage surface decreases.

The damaged ECM initiates chondrocyte response which tries to stop the cartilage loss. During the chondrocyte response, degenerated areas are degraded enzymatically and new ECM macromolecules are synthesized to

counterbalance the degrading tissue. If the chondrocyte synthetic response declines over time, cartilage tissue is progressively lost [39, 40].

If chondrocyte response fails to stabilize the balance between cartilage degeneration and repair, progressive loss of cartilage leads to advanced stage of the disease. Common symptoms for a patient to seek professional care, e.g., pain and stiffness of the joint, indicate advanced stage of OA.

Symptoms of advanced OA are usually a result of cartilage thinning which might have resulted in areas of the joint where two bony surfaces are in direct contact [41]. As articular cartilage is an aneural tissue [42], joint pain does not, however, directly relate to cartilage loss. Other possible symptoms and signs are swelling of the joint, occasional locking or limitations in the movement of the joint [43]. As the ailment gets worse, restrictions of movement also tend to increase [29].

5. Diagnosis

OA can be diagnosed with several different methods. First step towards the diagnosis of OA is usually an appointment with a doctor. Patient can be forwarded to further examinations if verification for the diagnosis is needed. These studies are generally medical imaging procedures such as radiography or magnetic resonance imaging. Imaging is used if a more accurate illustration of the current state or progression of the disease is needed.

5.1 Physical examination

Physician studies the different symptoms and their magnitudes by hand. During physical examination, physician examines the joints for painful and swollen areas. Range of motion is also of special interest in knee OA. Physical examination is a cheap and a simple method for the diagnosis of OA.

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a standardized questionnaire, which was developed for assessing pain, physical function and stiffness in patients suffering from knee or hip OA [44]. WOMAC can also be used for assessing other arthritic

conditions such as lower back pain [45], rheumatoid arthritis [46] and juvenile rheumatoid arthritis [47], but should be utilized with caution as it has been found to have a low test-retest reliability [48].

5.2 Arthroscopy

Surgeon inserts an endoscope (arthroscope) through a small cut to the joint. This endoscope contains a small video camera, which provides a direct visualisation of the joint. Arthroscopy is the only method that can directly visualize the joint as it would appear for the naked eye. Arthroscopy can be used to examine the joint and treating it. Treatment can include trimming of cartilage or repair or surgical removal of meniscus (arthroscopic meniscectomy).

5.3 Imaging techniques

5.3.1 X-ray imaging of knee osteoarthritis

X-ray imaging is a fast and inexpensive procedure for the imaging of joints. In weight-bearing radiography, knees are imaged while the patient is standing. Weight-bearing radiography has been the standard examination routine since the importance of weight-bearing in exhibiting changes in the radiological features of OA was demonstrated [49].

In plain radiography cartilage is almost invisible – cartilage thinning is observed indirectly by studying joint space narrowing on weight-bearing radiographs. This is a major drawback as indirect analysis can lead to errors in evaluation of the joint space width [50]. Partly due to its low cost, prevalence of radiographic imaging devices and rapid imaging time, weight-bearing radiography continues to be a commonly used imaging method in the diagnosis of OA.

Presence of radiographic features indicates OA. Common radiographic features associated with OA are joint space narrowing, osteophytes, subchondral cysts, increased density of subchondral bone, subchondral cavities and bone malalignment [51].

Kellgren-Lawrence grading system (KL) is a semi-quantitative scoring system, that is used to classify the state of the disease based on the presence of radiographic markers [52]. Progression of the disease can be studied by following the appearance and prevalence of these markers. Different KL-scores correspond to particular stages of the disease.

Table 1. Kellgren-Lawrence grading system

Grade of the disease	Radiographic markers
0, Normal knee	No visible markers.
1, Doubtful OA	Possible joint space narrowing and osteophyte formation.
2, Minimal OA	Possible joint space narrowing and clear osteophytes.
3, Moderate OA	Joint space narrowing, multiple osteophytes and sclerosis. Bone deformations are also possible.
4, Definite OA	Large osteophytes, serious joint space narrowing, clear sclerosis and bone deformations.

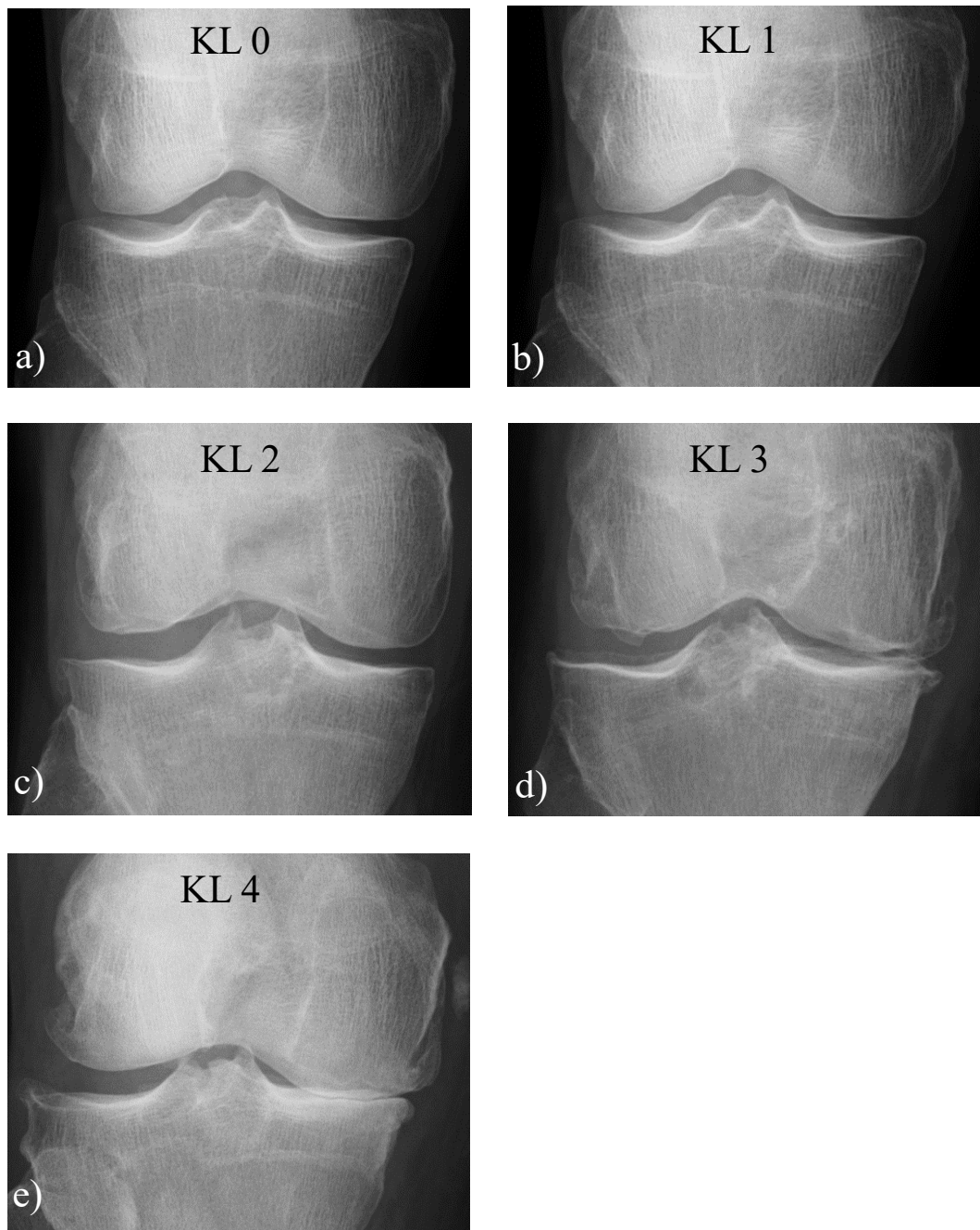


Figure 3. Different Kellgren-Lawrence grades in the knee. Classification is based on table 1: a) No radiographic markers; b) Possible joint space narrowing and possible osteophytes; c) Definite osteophytes and joint space narrowing; d) Definite joint space narrowing, osteophytes and possible bone deformations; e) Severe joint space narrowing, large osteophytes, bone deformations and severe sclerosis. (Source: Jukka Hirvasniemi, Novel x-ray-based methods for diagnostics of osteoarthritis, PhD. thesis, 2015, ACTA UNIVERSITATIS OULUENSIS).

5.3.2 Magnetic resonance imaging of knee osteoarthritis

Development of magnetic resonance imaging (MRI) has substantially increased our knowledge on articular cartilage and bone physiology [53]. An analysis of longitudinal studies of patients with knee OA concluded that using only radiography as a measure of OA misses lots of knees with cartilage loss, whereas cartilage loss was more frequently detected with MRI [54]. MRI distinguishes cartilage from the surrounding tissue [54] and articular cartilage can be analysed directly without any conversions from joint space narrowing to the actual thickness of cartilage. As MRI does not expose patients to ionizing radiation, it is a sensible choice for the study of OA. The main disadvantages of MRI are relatively long imaging times, the cost of imaging and the fact that MRI scanners are generally available only in central hospitals.

Although considered to be the best imaging technique for the study of OA [55], MRI does have its drawbacks. It is prone to imaging artifacts such as partial volume effects, aliasing and intensity inhomogeneities. The relatively small size of cartilage is also problematic as the limited resolution of this imaging technique can lead to major errors in the evaluation of cartilage morphology (thickness and volume) [53]. T_2 , transverse relaxation rate, of cartilage is both a blessing and a curse. The severity of OA is often indicated by an increase in T_2 values [56]. The small T_2 time of bone, on the other hand, is the reason for rapid signal decay, which complicates the imaging of the joint.

6. Treatment of osteoarthritis

Joint pain and stiffness relate to advanced stage of the disease. In the late stage of OA, patient might have severe cartilage loss and possibly severe restrictions in movement. If OA has progressed to a late stage and the patient experiences severe symptoms, only treatment method is surgical intervention. The aim of this surgery is to remove pain and improve mobility [41].

6.1 Joint replacement surgery (Replacement arthroplasty)

Joint replacement surgery is a common surgical intervention in the treatment of severe OA. In joint replacement surgery the arthritic parts of the joint are replaced by a prosthesis. Total knee replacement surgery (TKR), also known as total knee arthroplasty (TKA), and partial knee replacement surgery are common and widely endorsed procedures for patients with major symptoms such as severe pain or substantial moving disabilities [57]. In partial knee replacement surgery, the most affected part of the knee joint is replaced, whereas in TKR the entire joint is replaced.

Surgical interventions are known to be highly successful. Two separate studies found that for TKR the prevalence of satisfactory patients was 81 % and 88 % [58, 59]. Although the satisfaction rate is high, patients who are satisfied with the operation might still have occasional pain or restrictions of movement. Operations might improve the quality of life of a patient, but they do not cure the disease.

6.2 Treatment methods for early stage osteoarthritis

Treatment methods for early stages of OA, such as weight reduction and increasing joint-friendly exercise that build up muscle strength but do not stress the joint (such as swimming), are far more cost-effective treatment methods compared to surgical intervention. The goal of these methods is mainly to treat the symptoms and slow down the progression of the disease. Exercise is considered to be one of the most important treatment methods in knee OA [60, 61].

Treatment methods for early OA usually decelerate the progression of the disease, but are not helpful for a late stage OA, which underlines the importance of early diagnosis and the development of new treatment methods for the early stage OA. Unfortunately the problem of reliably identifying the earliest stage of OA remains unresolved.

7. Magnetic resonance imaging

7.1 Introduction to nuclear magnetic resonance

Magnetic resonance imaging (MRI) is based on the interaction between a nuclear spin and an external magnetic field. The quantized value of the nuclear spin angular momentum quantum number (\mathbf{I}) describes the characteristics of a nucleus in an external field: a spin with a spin quantum number \mathbf{I} has $2\mathbf{I}+1$ possible energy states, where \mathbf{I} is the magnitude of \mathbf{I} . The nuclei interact with the external field by moving from one energy state to another. Spins with zero spin quantum number have only one possible energy state in an external field, and thus they do not interact with the external field. As the interaction occurs only when $\mathbf{I} \neq 0$, MRI can only be used to study nuclei with nonzero spins – nuclei with uneven proton number or uneven nucleon number.

A particle with $\mathbf{I} = \frac{1}{2}$, e.g., ^1H , in a magnetic field B_0 , can only have two possible energy states, spin oriented parallel to the field (α state) or spin oriented anti-parallel to the field (β state). In an external magnetic field (\mathbf{B}_0) oriented parallel to z-axis, $\mathbf{I} = \frac{1}{2}$ -particle can have only discrete energies

$$E = -\boldsymbol{\mu} \cdot \mathbf{B}_0 = \mu_z B_0 = -\gamma m_s \hbar B_0 \quad (1)$$

where $\boldsymbol{\mu}$ is the magnetic moment, γ is the gyromagnetic ratio, m_s is the spin projection quantum number, $\hbar = \frac{h}{2\pi}$, where h is the Planck constant. Now $m_s = \frac{1}{2}$ is for the α -state and $m_s = -\frac{1}{2}$ for the β -state.

In a sample with no external magnetic field, spins are randomly oriented as there is no energy difference between the two states. The random orientations of spins cause the net magnetization of the sample to be zero. In an external field, however, according to equation (1), spins oriented parallel to the field have lower total energy than spins oriented anti-parallel to the field. The α -state is thus, according to Boltzmann distribution, the more probable energy state and therefore a small population difference emerges. The ratio of spins at different states is given by the Boltzmann distribution

$$\frac{N_\alpha}{N_\beta} = e^{-\frac{E_\alpha - E_\beta}{kT}} = e^{\frac{\Delta E}{kT}} = e^{\frac{\hbar\gamma B_0}{kT}} \quad (2)$$

where N_α and N_β are the number of spins in states α and β respectively, k is the Boltzmann constant, ΔE is the energy difference between states and T is the absolute temperature. As the α -state is more probable, a small magnetization (\mathbf{M}_0) parallel to the external field arises as a net sum of the magnetizations of individual spins.

A classical picture of a nucleus in an external magnetic field is a magnetic moment slightly tilted away from the z -axis. The magnetization vector is rotating about the direction of the magnetic field with angular frequency

$$\omega_0 = \gamma B_0 \quad (3)$$

where ω_0 (rad/s) is defined as the Larmor frequency of the nucleus. In the case of proton ($I = 1/2$) the rate of Larmor precession is proportional to the energy difference of the two states

$$\omega_0 = \frac{\Delta E}{\hbar} \quad (4)$$

The magnetization (\mathbf{M}_0) arising from a sample can be manipulated with radiofrequency (RF) energy. RF energy is an additional magnetic field (\mathbf{B}_1), generated by the RF coil, oscillating at or near the Larmor frequency. The additional B_1 -field applied at the Larmor frequency in the xy -plane for a time τ rotates magnetization (\mathbf{M}_0) through an angle θ

$$\theta = -\gamma B_1 \tau \quad (5)$$

By manipulating the strength of the B_1 field or the duration of the RF pulse (τ), any given tilt angle (θ) can be achieved.

Signal in MRI experiments is the electromagnetic force induced into RF coil by the oscillating magnetization, specifically it is proportional to the xy -projection of the magnetization.

7.2 Relaxation mechanisms

After radiofrequency irradiation has disturbed magnetization from its equilibrium state (M_0), spins start reorienting back to the most energy-efficient state – parallel to the external magnetic field. The rate of this relaxation process is dependent on the molecular surroundings of the spin. Different tissues have different molecular surroundings, which causes the

relaxation process to be tissue dependent. Tissue-specific relaxation rates creates tissue contrast in magnetic resonance images.

Relaxation process can be modelled mathematically with Bloch equations [62]

$$\frac{dM_{xy}(t)}{dt} = -\frac{M_{xy}(t)}{T_2} \quad (6 a)$$

$$\frac{dM_z(t)}{dt} = \frac{M_0 - M_z(t)}{T_1} \quad (6 b)$$

where M_{xy} is the magnetization in transverse plane, M_z is the longitudinal magnetization and M_0 is the equilibrium magnetization (assumed to be initially parallel to z-axis). Transverse relaxation constant (T_2) is the rate how fast transverse magnetization disappears. Longitudinal relaxation constant (T_1) characterizes the rate of recovery of longitudinal magnetization.

7.2.1 Longitudinal relaxation (T_1 relaxation)

Spins are in thermal contact with the surrounding molecules. This thermal contact allows the exchange of energy between a spin and the molecular motion, i.e., the lattice [63]. The net magnetic field experienced by a spin is highly localized as it is dependent on the motion of the molecular surroundings of the spin and the motion and the magnetic moment of the spin itself, thus resulting in a tissue specific longitudinal relaxation rates.

Also known as spin-lattice relaxation, longitudinal relaxation characterizes the recovery of longitudinal magnetization after RF pulse is turned off. Radiofrequency radiation perturbs the spin populations of a sample. RF pulse oscillating at Larmor frequency can either excite nuclei to a higher state or stimulate an emission of energy resulting in a lower energy state. After the RF pulse is turned off, the excited spins exchange energy with the lattice until thermal equilibrium is reached, thus re-establishing the equilibrium magnetization \mathbf{M}_0 . The rate of the recovery of longitudinal magnetization is characterized by time constant T_1 .

Inversion recovery is an experiment which can be used to study the T_1 relaxation rates of tissues. Inversion recovery consists of π pulse and signal

acquisition at inversion times (TI). As the π pulse rotates the magnetization towards the $-z$ -direction, equation (6b) can be solved with the initial condition $M_z(0) = M_0$. The recovery of longitudinal magnetization can thus be modelled in the following way

$$M_z(t) = M_0 \left(1 - 2 \times e^{-\frac{t}{T_1}} \right) \quad (7)$$

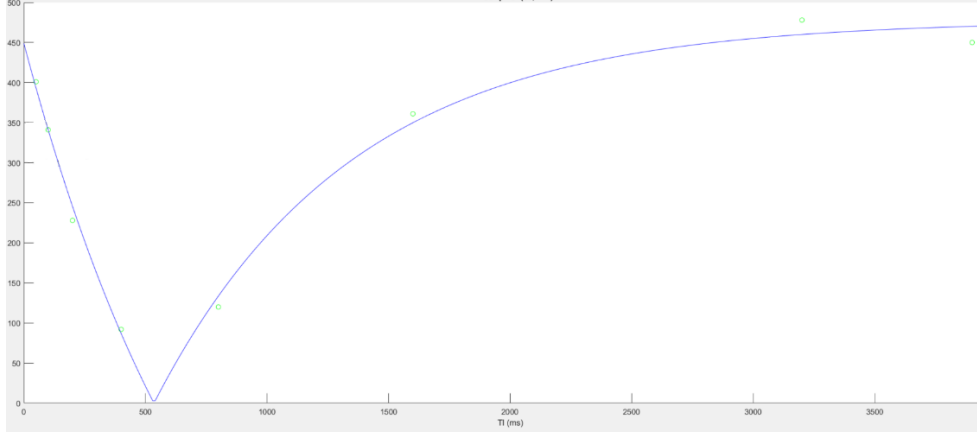


Figure 4. Recovery of longitudinal relaxation during inversion recovery experiment in a certain pixel of an image. Green markers are the signal acquired at certain time points. The curve represents the development of the magnitude of longitudinal magnetization. The recovery curve is found by fitting equation (7) to the data.

7.2.2 Transverse relaxation (T_2 relaxation)

A spin interacts with other spins within its molecular surroundings. During this interaction, spins exchange energy. A change in energy of a nucleus corresponds to a change of phase. Transverse relaxation is also known as spin-spin relaxation as it arises from the gradual dephasing of magnetic moments of individual spins in the transverse plane [64, 65]. T_2 characterizes the rate of transverse relaxation.

Inhomogeneities in the external magnetic field result in a location-dependent external magnetic field. According to equation (3), a slightly alternating magnetic field results in a range of different Larmor frequencies, which also causes loss of phase coherence resulting in the dephasing of transverse magnetization. This generally time independent relaxation rate is

referred as T_2' . By taking into account both the dephasing caused by spin-spin interactions, T_2 , and the effect of field inhomogeneities, T_2' , one ends up with the total transverse relaxation rate T_2^* defined as

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \frac{1}{T_2'} \quad (8)$$

The dephasing due to the time independent field inhomogeneities, T_2' , can be reversed with the aid of echoes. An echo is a time point where signal peaks due to the refocusing of the dephasing caused by field inhomogeneities. Echo can be achieved with spin echo experiment pulse or with the use of gradients (gradient echo). In spin echo, π -pulse acts as a refocusing pulse. By working out equation (6a), the functional form of the measured magnetization in spin echo experiment can be solved to be

$$M_{xy}(t) = M_0 e^{-TE/T_2} \quad (9)$$

The relaxation rate in the equation (9) does not take the effects of field inhomogeneities into account because signal is acquired at echoes (TE).

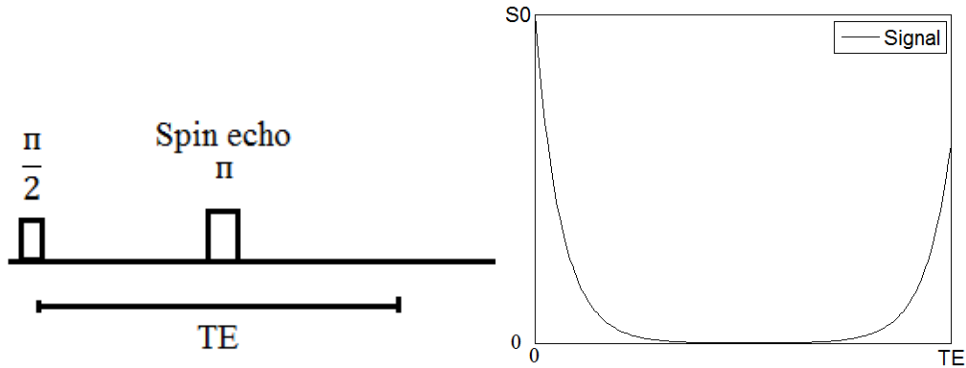


Figure 5. Spin echo experiment. Signal peaks at the echo (TE) due to the refocusing effect of π -pulse. Note that the signal at the echo is smaller in amplitude than at the beginning of the experiment. This is because spin echo does not refocus the effect of T_2 relaxation as it is result of local, time-dependent field variations.

7.2.3 Longitudinal relaxation in the rotating frame ($T_{1\rho}$ relaxation)

Spin locking is a process, in which individual spins are locked to the xy plane with the aid of additional magnetic field \mathbf{B}_{sl} . The net magnetization is tilted by an angle that is dependent on the spin-lock pulse. The additional magnetic field can be a composite of pulses or a continuous wave (CW) irradiation. After the spins have been locked, they precess around the generated spin lock field. The spins start relaxing similarly as in the case of longitudinal relaxation, but the relaxation takes place in the rotating frame. Rotating frame relaxation enables the study of relaxation at low magnetic fields [66] and it is characterized by the longitudinal relaxation constant in the rotating frame, $T_{1\rho}$. Relaxation process in the rotating frame can be modelled as follows

$$M(t) = M_0 e^{-\frac{TSL}{T_{1\rho}}} \quad (10)$$

where TSL is the duration of the spin lock field.

8. Quantitative magnetic resonance imaging

8.1 Quantitative morphological assessment

Morphological imaging is currently the standard clinical routine in the diagnosis of OA. The study of cartilage morphology includes evaluation of cartilage thickness and volume. MR sequences that have been used in the study of cartilage morphology are generally 3D protocols, as they depict cartilage as a 3D object.

Usual 3D protocols for the morphological imaging of cartilage are spoiled gradient recalled echo (SPGR) and fast low angle shot excitation (FLASH) [53, 67]. These protocols are usually performed with water-excitation (FLASHwe) or with fat-suppression, as they result in a better dynamic range between cartilage and surrounding tissues [53]. MRI has been proven to provide accurate results on cartilage morphology [67].

Dual echo steady state (DESS) sequence is shorter in imaging time than FLASH or SPGR techniques and for the discrimination of cartilage, DESS appears to be the superior technique over FLASH [68]. The additional ability

to offer high cartilage to fluid contrast [69], delineate osteophytes, display cysts and bone attrition [68] makes DESS a promising diagnostic tool for imaging of OA and it is already in regular use in scientific assessment of cartilage morphology [70].

Analysis of cartilage morphometry in severe OA can hold high diagnostic value [71], but for early OA, morphological changes can be nonexistent [17]. Additionally, cartilage morphology can highly alternate even between healthy individuals [17].

8.2 Relaxation time mapping

Relaxation time mapping is a process of fitting a relaxation function to the acquired signal. In quantitative MRI, same slice is acquired multiple times and a specific imaging parameter, e.g. acquisition time or flip angle, is alternated between acquisitions. Fitting is generally done to each pixel separately using specific optimization method, e.g. derivative-free method [72].

8.2.1 T₂ relaxation time mapping

In T₂ relaxation time mapping, equation (9) is fitted pixel-by-pixel and the T₂ values acquired from the fittings will form a relaxation time map (Figure 6). T₂ relaxation time mapping is arguably one of the best known methods of assessing ECM composition [73]. Increase in transverse relaxation rate is associated with increase in water content [74] and changes in the molecular structure of tissue. T₂ relaxation rate is not only sensitive to molecular structure and concentration of the tissue, but also sensitive to changes in the structure of the collagen network [75-78]. As the changes in cartilage during the early stage of OA occur in a molecular level [37, 38], the ability of T₂ to assess molecular ECM composition makes it a candidate for the detection of early OA and longitudinal analysis of OA progression.

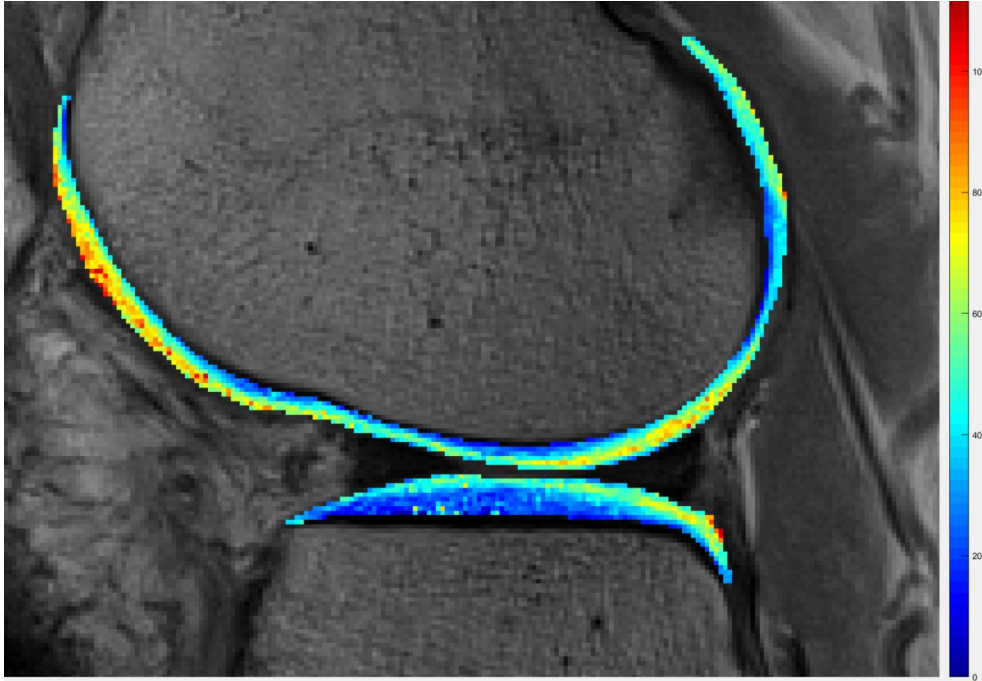


Figure 6. T_2 relaxation time mapping can reflect the ECM structure and changes in water content.

8.2.2 T_1 relaxation time mapping

In the case of longitudinal relaxation time mapping, equation (6b) is solved with the appropriate initial condition, which is dependent on the pulse sequence. In the case of inversion recovery experiment, relaxation function is equation (7). The solved equation is then fitted to the acquired data, from which a T_1 map of the slice can be formed.

T_1 , in the absence of contrast agents, is not considered to be a sensitive method for the study of cartilage degeneration [79]. However, another study concluded that T_1 reflects the water content in articular cartilage [80]. With the use of a charged contrast agent, specifically gadopentetate dimeglumine ($GdTPA^{2-}$), molecular contents of cartilage can be studied with longitudinal relaxation time mapping.

Glycosaminoglycan (GAG) concentration decreases during early OA [81-83]. Delayed gadolinium enhanced MRI contrast (dGEMRIC) is based on the different distributional properties of $GdTPA^{2-}$ with respect to GAG concentration. In healthy tissue, $GdTPA^{2-}$ cannot diffuse due to the high concentration of negatively charged GAGs. The distributional dependence of

GdTPA²⁻ can be used to indirectly quantify the GAG concentration and distribution in cartilage. Studies have shown, that the measured GAG concentrations in dGEMRIC correlate with the histologically and biochemically measured GAG concentrations [84, 85].

8.2.3 T_{1ρ} relaxation time mapping

T_{1ρ} relaxation time constant can be measured by acquiring signal after the spin lock and changing the duration of the spin lock field (TSL) and fitting the signal to equation (10). T_{1ρ} can be used to study the interaction between water molecules within the ECM and their local macromolecular environment [86]. Cartilage degradation and decrease in PG concentration, is associated with increase in T_{1ρ} values. Some studies have concluded T_{1ρ} to be the superior method to T₂ in depicting cartilage degeneration [87, 88].

9. Conclusion

Morphological assessment of cartilage is a common clinical routine, but usually shows damage in cartilage when the tissue is irreversibly lost [55]. As different relaxation time analysis techniques can depict changes in water content of cartilage, the structure of the ECM and possibly the initiation of OA, they are preferable biomarkers for early OA.

As established in this review, different quantitative relaxation time analysis techniques have already been able to indicate both the early stage OA and the progression of the disease. Future research on these methods will show how useful they are on the clinical side.

Morphological evaluation of cartilage, on the other hand, has not asserted itself to be as a promising method to screen the earliest stage of OA as relaxation time analysis has. As a tool for longitudinal analysis, however, morphological analysis methods can be beneficial, because they can be used as a precise indicator of the rate of cartilage loss [89, 90].

10. References

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