

QUANTITATIVE MRI OF CARTILAGE

A FOCUS ON T2 MAPPING

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Paul Lauterbur published the very first magnetic resonance image (MRI) in 1973. Later in the 1970s, Sir Peter Mansfield, a physicist by training, developed mathematical techniques to make MRI scans more time-efficient. The 2003 Nobel Prize in Medicine of Physiology, shared by Lauterbur and Mansfield, reflected the importance of MRI. Modern day MRI plays a critical role in daily medical practice and has significantly improved evaluation of the joints by providing direct visualisation of the morphology of joint tissues including the articular cartilage, synovium, ligaments, menisci, tendons and bone.

Articular cartilage damage is common and may be seen acutely as a result of injury or appear gradually as manifestation of arthropathies including osteoarthritis (OA). OA is the most prevalent joint disease, affecting up to 27 million people in the United States and its incidence is increasing due to

an aging population and obesity pandemic. The hallmark feature of OA is cartilage degradation, which has a progressive, irreversible course. Plain radiography – still considered the reference standard for imaging of the joints – provides a crude measure for cartilage loss. The discordance between OA symptoms and radiography is well established. Additionally, radiography is not sensitive to progression of cartilage loss. Joint space narrowing on radiographs is nevertheless recommended by regulatory agencies including the United States Food and Drug Administration (FDA) as the primary imaging endpoint to establish the effectiveness of disease-modifying OA drugs (DMOADs).

Despite promising pre-clinical research, no FDA approved DMOADs are available at present. Insensitive imaging outcome measures utilised in OA research may partly be responsible for the failure to develop

effective treatments. In comparison to radiography, MRI provides vastly improved morphological evaluation of joint soft tissues. Additionally, several advanced MRI techniques have been developed to non-invasively assess the biochemical composition of cartilage. These include relaxometry measurements (T₂, T₂* and T₁rho mapping), sodium imaging, delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), glycosaminoglycan specific chemical exchange saturation transfer (gagCEST), diffusion weighted imaging (DWI) and diffusion tensor imaging (DTI). Information regarding the microarchitecture of cartilage gained using these techniques is enhancing our understanding of joint disease pathophysiology. Furthermore, compositional MRI techniques have the potential to serve both as imaging biomarkers of cartilage quality and as quantitative, reproducible and objective



endpoints for research. In this article, we provide a brief introduction to these techniques, with a focus on T2 mapping and its applications as a potential imaging biomarker for cartilage degeneration.

CARTILAGE BIOCHEMISTRY

Articular cartilage is responsible for resistance to compressive forces, distribution of load and, together with synovial fluid, frictionless movement of the articular joint components. It consists of approximately 70 to 80% fluid and 20 to 30% solid extracellular matrix (ECM)¹. The ECM is made up of a network of collagen fibrils and proteoglycan molecules. A proteoglycan unit includes a protein core and covalently attached glycosaminoglycans (GAGs). The negatively charged GAGs make up the majority of the fixed charge in the ECM and are neutralised by cations (positively charged molecules) including sodium (^{23}Na) dissolved in fluid.

Initial histological changes of cartilage degeneration involve disruption of the collagen network and loss of proteoglycan content, resulting in increased permeability to water. Compositional MRI techniques

enable detection of these biochemical changes in the cartilage ECM, even before morphological change occurs.

COMMON QUANTITATIVE MRI TECHNIQUES

Understanding even basic MRI can be a daunting task for non-radiologists, as it requires understanding multiple concepts of physics and the retention of these simultaneously. Detailing the advanced techniques used for imaging composition of cartilage is beyond the scope of this article and we will describe these techniques only briefly.

T2 mapping

Articular cartilage T2 measurements reflect the water content, collagen content and collagen fibre orientation in the extracellular matrix, with longer T2 results in early cartilage degeneration predictive of the development of macroscopically visible MR changes. The evaluated cartilage can be also subdivided into superficial and deep layers for further analysis. Laminal analysis of normal articular cartilage T2 maps has

shown that T2 values are higher at the articular level than at the bone interface. This is due to the deep zone collagen fibres being densely packed, reducing the mobility of protons. Since the superficial cartilage is progressively lost in osteoarthritis, laminal analysis may not be particularly useful when advanced degeneration is present.

T1rho mapping

T1rho values reflect changes in the cartilage ECM and proteoglycan content. T1rho has been shown to predict the development of morphological lesions in articular cartilage but does not reflect a specific macromolecular component of the ECM i.e. collagen or proteoglycan content. T1rho technique requires an MRI pulse sequence that is not widely available.

Delayed gadolinium-enhanced MRI of cartilage

dGEMRIC is a technique which uses the negative ionic charge of gadopentetate dimeglumine (Gd-DTPA²⁻) contrast to map the density of cartilage GAGs. Gd-DTPA²⁻ is repelled by the negatively charged GAGs and

therefore distributed in inverse proportion to the local proteoglycan concentration. Gd-DTPA²⁻ accumulates in areas of low GAG content. Implementation of dGEMRIC is limited by the 90-minute delay necessary to allow diffusion and contrast agent equilibration within the cartilage, which may be inconvenient for the patient.

Sodium (²³Na) imaging

²³Na⁺ ions in the ECM neutralise the negative fixed charge density of GAGs and therefore their distribution reflects the local GAG concentration. Degenerated cartilage with lower GAG content will have a lower concentration of positively charged ²³Na⁺ ions than normal cartilage. The advantage of ²³Na imaging is that it can estimate GAG content without intravenous contrast administration. However, complex hardware requirements, including special coils, is a limitation for the implementation of this type of imaging.

Diffusion-weighted imaging

Intra- and extracellular barriers determine the molecular motion of water. DWI provides the ability to map diffusion of water and therefore enables analysis of cartilage ECM microarchitecture. Increased mobility of water is seen in degenerated cartilage.

DTI is a DWI-based technique which evaluates the direction of water mobility in the ECM. The microarchitecture of normal cartilage causes anisotropic (directionally dependent) water diffusion. A change in anisotropy can indicate changes in collagen architecture. DTI has been shown to be able to detect and grade early cartilage damage. A limitation of DTI is that it is time-consuming to acquire and process data.

Magnetisation transfer contrast (MTC) and gagCEST

Magnetisation transfer contrast and gagCEST are techniques which can quantify GAG content while avoiding the practical limitations of dGEMRIC and ²³Na imaging. Limitations of gagCEST include requirement of ultra-high field MR systems and complex postprocessing.



Figure 1: Sagittal image of the knee demonstrating segmentation of the patella.

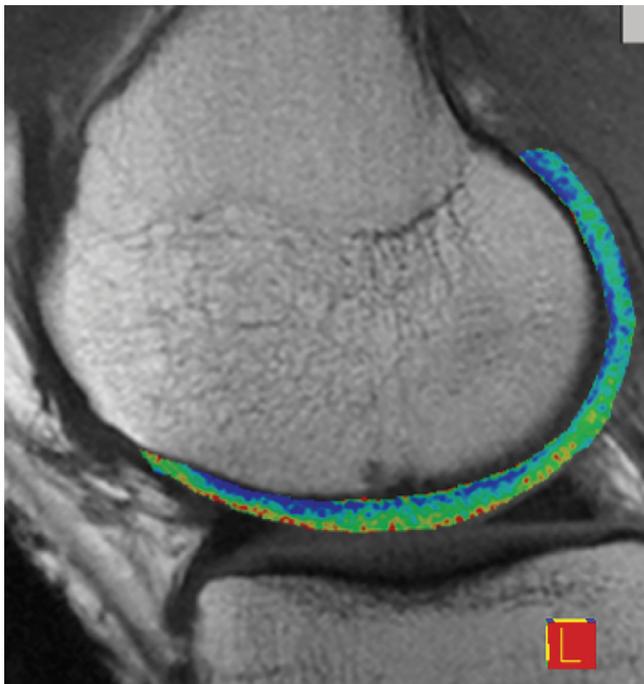


Figure 2: 35-year-old male patient, 24 months after matrix-associated autologous chondrocyte transplantation of the medial femoral condyle. Quantitative multi-echo spin-echo T2 map of the repair tissue shows comparable zonal T2 values in the repair tissue and the surrounding cartilage.

SPOTLIGHT ON T2 MAPPING

Image processing

After acquisition of T2 mapping images, cartilage is segmented using one of the several available proprietary or open-source software. This software is used to draw regions of interest around the cartilage compartments to be evaluated (Figure 1). The following compartments of articular cartilage are usually investigated: patella, trochlea, medial femur, lateral

femur, medial tibia and lateral tibia. This post-acquisition image processing requires a time of 30 to 60 minutes. For the mathematically inclined, calculation of T2 relaxation values from cartilage regions of interest is performed using mono-exponential curve fitting of the signal intensity of each echo-time for each voxel². For the rest of us, the intensity of the signal in each pixel within the regions of interest contributes to the final T2 values; the more

intense (brighter) the pixels, the higher the T2 measurement in milliseconds (ms).

The standard parameter of cartilage T2 mapping used in statistical analysis is mean T2 of all pixels included in the segmented compartment². As previously touched on, further analysis may include an evaluation of the spatial distribution of T2 relaxation times, via either laminar or texture analysis. These are more sophisticated techniques, which provide additional information regarding changes in cartilage microarchitecture. Laminar analysis can be automatically performed and subdivides the segmented compartment into – for example – a superficial and deeper cartilage layer. Carballido-Gamio et al have reported significantly greater T2 relaxation times in the superficial compared to the deep cartilage layer, suggesting that laminar analysis could lead earlier identification of cartilage matrix changes³. Texture analysis evaluates the spatial distribution of T2 relaxation time values by analysing their co-occurrences at a certain orientation and inter-pixel distance⁴. An example of one of the many parameters of texture analysis contrast is a measure of the differences in neighbouring pixel T2 values. High T2 contrast signifies that many pixels with different T2 values are neighbouring.

Correlation of T2 relaxation time with histological and biochemical properties of cartilage

Multiple studies have assessed the potential role T2 mapping as an imaging biomarker for cartilage quality. A study by Dardzinski et al showed increasing T2 values proportional to the known spatial variation in cartilage water and inversely proportional to the GAG distribution⁵. Another study by Mosher et al reported elevated T2 relaxation times in damaged compared to healthy articular cartilage⁶.

Reproducibility of T2 measurements

Multiple studies have shown T2 measurements to have good reproducibility. Mosher et al showed moderate to excellent reproducibility of T2 measurements for subjects – without as well as with – mild and severe radiographic OA in a clinical trial network (ACRIN-PA 4001 multicenter trial)⁷.

T2 texture parameters showed greater reproducibility errors compared to mean T2⁸. Different MRI scanners and radiofrequency coils may impact reproducibility of T2 mapping⁷.

T2 and OA risk factors

Several studies have found association between risk factors for OA and T2 relaxation

times. Age, female gender, increased body mass index (BMI) and knee malalignment are known risk factors for knee OA.

A study by Mosher et al reported significantly higher T2 values in the superficial cartilage in a subgroup of asymptomatic 46 to 65 year old subjects⁹. Additionally, this study found T2 values to be significantly higher in the entire cartilage in an older subgroup aged 66 to 86. A younger asymptomatic sub-group aged 18 to 30 years old was used for comparison in this study. These suggest that senescent changes of the cartilage matrix begin near the articular surface and progress to the deeper cartilage with advancing age.

Mosher et al observed no significant differences in mean T2 and spatial variation of T2 values between men and women in a study of young, healthy, asymptomatic subjects¹⁰. The predisposition for OA in the female gender is well known. Further studies using T2 mapping in older populations are needed to evaluate this known association.

Baum et al studied the association of cartilage T2 measurements with BMI¹¹. In this study, cartilage T2 measurements were performed in 267 subjects aged 45 to 55 years, including subjects with normal weight (n=78), overweight (n=84) and obesity (n=69). They found the highest



Although currently utilised mostly in the research setting, these quantitative MRI techniques seem to have great potential for eventual translation into clinical practice



T2 values and the most heterogeneous cartilage as assessed by T2 texture analysis in obese subjects. The normal controls in this study had the lowest mean T2 values and the most homogeneous cartilage at baseline. These results suggest advanced cartilage degeneration is associated with increased BMI, underlining the risk of OA due to obesity.

Knee malalignment is considered a potential risk factor for OA. A study by Friedrich et al observed greater T2 values in subjects with medial knee OA and varus compared to those with valgus malalignment in all compartments of the femoro-tibial joint¹². Longitudinal studies are needed to further investigate this relationship.

T2 and physical activity

The effect of physical activity on T2 values is different for acute and for chronic joint loading. Acute loading of the knee results in a decrease in T2 relaxation times¹³, while temporary non-weight bearing is associated with elevated T2 relaxation times¹⁴. Further studies are needed to establish whether these changes are completely reversible or whether irreversible changes may result from acute loading events.

A few studies have evaluated the effect of chronic loading of knee joints on T2 relaxation times. All of these studies used the Physical Activity Scale for the Elderly (PASE) to assess activity levels. Stehling et al found subjects with high PASE scores to have higher prevalence and severity of meniscal and cartilage lesions and significantly higher patellar T2 values, when compared to the subjects with low PASE scores¹⁵. Hovis et al reported that light exercise was associated with low T2 values, whereas moderate/strenuous exercise in women with OA risk factors was associated with high T2 values¹⁶. A study by Lin et al evaluated the effects of physical activity on T2 relaxation times over a period of 4 years¹⁷. High and very low PASE scores were associated with greater progression of cartilage T2 measurements in asymptomatic, middle-aged individuals. This suggests that there is an optimal activity level for cartilage maintenance, with high and low activity resulting in cartilage degeneration.

T2 and morphologic findings of OA

Mean T2 and T2 texture analysis of the articular cartilage can differentiate subjects with radiographic OA and normal controls. Early degenerative changes may be seen

using T2 mapping even in subjects with normal radiographs. A study by Joseph et al found higher and more heterogeneous knee cartilage T2 in subjects with OA risk factors, compared to normal controls, even when both groups had normal radiographs⁴. A longitudinal study by Baum et al showed similar findings¹⁸.

Furthermore, Baum et al¹⁸ also found significantly higher T2 values in subjects with cartilage lesions, meniscal lesions and alterations of the subchondral bone.

Longitudinal studies have shown that cartilage T2 measurements at baseline predicted progression of focal knee lesions over 36 months⁸. These results show that T2 may be an early biomarker for future morphologic degeneration associated with OA.

T2 and knee pain

Bone marrow oedema, meniscal tears, synovitis and joint effusion have been associated with pain severity in subjects with radiographic OA. Baum et al studied the association between focal knee lesions and cartilage T2 with knee pain status in subjects without radiographic OA, but with OA risk factors. Only cartilage lesions were significantly associated with knee pain



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status¹⁹. However, elevated cartilage T2 values were observed in subjects with knee pain compared to asymptomatic subjects.

Since cartilage is aneural, it cannot itself generate pain. Any association between articular cartilage T2 measurements and pain may be secondary to concomitant early morphological changes. The association between T2 mapping and knee pain needs to be further evaluated in longitudinal studies.

T2 and cartilage repair tissue

In the long-term, focal cartilage defects resulting from injury may predispose the patient to development of premature OA. The aim of surgical treatment strategies for focal cartilage defects is to reduce symptoms, promote cartilage healing and ultimately prevent or delay onset of OA.

Several studies have tested the hypothesis that T2 measurements provide additional information about the outcome of cartilage repair procedures. T2 mapping has been shown to differentiate between normal and cartilage repair tissue. Lamellar analysis has shown differences between healthy cartilage and cartilage repair tissue in subjects after matrix-associated autologous chondrocyte transplantation (MACT)²⁰. While healthy cartilage showed a significant increase from deep to superficial cartilage zones, cartilage repair tissue did not show a significant stratification of T2 values.

T2 measurements have also been shown to detect differences in cartilage repair tissue following different repair procedures. Welsch et al compared cartilage T2 values after microfracture therapy (MFX) and MACT²¹. The global mean T2 in the cartilage repair area was significantly lower in patients after MFX, compared to MACT. Furthermore, repair tissue after MACT showed a significant increase in T2 values from deep to superficial zones, however no such zonal variation was seen in repair tissue after MFX. These findings are consistent with histologic evaluation of repair tissue after MFX and MACT, which have described a disorganised fibrocartilage after MFX, while repair tissue after MACT being normal zonal collagen organisation.

Ideally, cartilage repair tissue develops a collagen network with a zonal organisation

similar to normal hyaline cartilage over time. Studies have suggested that zonal T2 mapping may be able to visualise the maturation process of cartilage repair tissue.

Limitations

A number of limitations hinder the implementation of cartilage T2 mapping in the routine clinical setting. The most significant limitation is the need for standardisation of the obtained measurements. T2 values obtained with different acquisition methods and at different MRI scanners show substantial variations. Quality assurance methods like those used in large clinical studies such as the Osteoarthritis Initiative may help provide regulatory measures necessary for implementation of the technique in clinical practice.

Different states of joint loading may impact T2 values. The time-point of T2 acquisition therefore has to be considered in an MRI protocol. For example a resting period of 30 minutes may be required for all patients before image acquisition.

Fully automated segmentation algorithms for T2 maps may help improve reproducibility and make post-processing time-efficient. These would further help with implementation of the technique in a clinical setting. Alternatively, T2 maps may be inspected visually to detect elevated cartilage T2 values. In a study by Kijowski et al the addition of T2 mapping to the routine MRI protocol improved detection of surgically confirmed cartilage lesions²².

CONCLUSIONS

Multiple studies have shown the ability of T2 relaxation time measurements to non-invasively assess biochemical changes of early cartilage degeneration. Cartilage T2 mapping has been shown to predict longitudinal morphologic degeneration in the cartilage and also monitor subtle changes due to therapy response after cartilage repair procedures.

The limitations of radiography and conventional MRI in their ability to detect early pre-morphologic stages of cartilage degeneration and subtle changes after cartilage repair procedures have been well described. The initial degenerative changes in the cartilage include proteoglycan loss

and deterioration of the collagen network within the cartilage and menisci, which cause increased mobility of water and consequentially increased water content. Quantitative MRI techniques including cartilage T2 relaxation time measurements reflect these pathophysiological changes. Although currently utilised mostly in the research setting, these quantitative MRI techniques seem to have great potential for eventual translation into clinical practice.

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