Chapter 10

MRI Mapping for Cartilage Repair Follow-up

Mars Mokhtar

Additional information is available at the end of the chapter

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Abstract

Patients, who benefit from cartilage repair surgery, need a non-invasive and high-quality imaging modality to assess the structure and the biochemical property of the repair tissue. Magnetic resonance imaging (MRI), which provides better tissue contrast and high spatial resolution, is currently the best imaging technique available for the assessment of articular cartilage pathologies. In addition to MR morphology sequences, that allow cartilage lesions detection as well as repair tissue evaluation from the articular surface of the joint to the bone-cartilage interface, MRI mapping techniques help to assess the technical success of the procedure of cartilage repair and the state of cartilage healing, as well the identification of possible complications after cartilage repair surgery. MRI mapping techniques such as T1, T2 and T2* mapping help to assess the biochemical property of the repair tissue using delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) to assess the proteoglycan content and T2/T1rho (T1ϱ) mapping to assess the collagen content and the fiber matrix arrangement. This chapter gives an overview about the MRI mapping techniques used for Cartilage Repair Tissue Follow-up.

Keywords: MRI, cartilage repair, T2 mapping, dGEMRIC, follow-up, T1rho, T2* mapping

1. Introduction

Many techniques are used to evaluate the knee articular cartilage however non-invasive conventional magnetic resonance imaging (MRI) is the method of choice for the evaluation of knee articular cartilage [1]. Imaging of articular cartilage needs MRI sequence which is able to characterize morphological alterations of cartilage as well as adjacent tissue and to measure with high accuracy the cartilage thickness [2]. Conventional MRI sequences allow the detection of degenerative cartilage lesions and the changes due to therapy response, e.g., after cartilage repair procedures.

In addition to the evaluation of cartilage morphology which is possible by MRI conventional 2D or 3D sequences, there is a need to visualize the biochemical components of the cartilage especially after cartilage repair surgery. MRI has been demonstrated to be sensitive to the variation of local water content [3], the loss of collagen content [4] and the organization of the collagen fiber [5] in the extracellular matrix. MRI parameters such as T1, T2 and T2* can serve as marker of biochemical properties of the knee articular cartilage. The most used mapping techniques are T2 and delayed gadolinium-enhanced MRI of cartilage (dGEMRIC). *T*2 mapping was reported to provide information about collagen matrix concentration and organization, whereas dGEMRIC is sensitive to proteoglycan content [6].

2. Cartilage repair surgery techniques

It is very important to know the different repair procedures and the behavior of the repair tissue in MR imaging at various postoperative intervals to evaluate the success of the surgery or to check for any complications [7]. Different methods have been used to stimulate the formation of a new articular cartilage such as microfracture, autologous chondrocyte implantation (ACI) and Osteochondral Allograft.

2.1. Microfracture

This procedure, introduced by Steadman et al., consists of removing all unstable and damaged articular cartilage till the subchondral bone plate, then making multiple small holes in it. This leads to bleeding, clot formation, as well as the introduction of marrow derived stem cells to the site [8]. The microfracture technique is generally used to repair small- to mid-sized cartilage defects in osteoarthritis (OA). It was reported that cartilage tends to deteriorate within a few years [9–11].

2.2. Autologous chondrocyte implantation (ACI)

This technique was first performed by Peterson et al. in Gothenburg in 1987. First, cartilage is harvested from a patient using arthroscopy. Second, it is grown in tissue culture medium. Then, it is reimplanted within the patient's cartilage defect beneath a periosteal patch to produce new cartilage repair tissue [12].

2.3. Osteochondral allograft

Osteochondral allografting involves the replacement of damaged articular cartilage with mature hyaline one from a suitable donor.

3. Cartilage repair surgery follow-up

The ideal cartilage repair tissue should, over time, develop a collagen network with a similar organization and concentration of normal hyaline cartilage [6]. Cartilage repair surgery

techniques require a non-invasive postoperative technique to monitor the cartilage repair tissue over time to detect complications or deviation of the normal maturation process. The normal appearance of cartilage repair tissues varies according to the applied surgical technique and the timing of postoperative follow-up.

3.1. Cartilage repair surgery follow-up parameters

Many parameters should be assessed in MR imaging examinations after cartilage repair procedure. Magnetic resonance observation of cartilage repair (MOCART) proposes the assessment of the following MR imaging parameters: the degree of defect repair and defect filling, integration to border zone, quality of repair tissue surface, structure of repair tissue, signal intensity of repair tissue, status of subchondral lamina, integrity of subchondral bone the presence of complications (adhesions and effusion) [13, 14].

This scoring system was validated in a 2-year longitudinal study of patients with matrix assisted chondrocyte implantation and correlated well with clinical scores. The evaluated parameters are the degree of defect filling, structure of repair tissue, change in subchondral bone, and signal intensity of repair tissue [15]. In another study of patients who underwent either microfracture or ACI, the following MR imaging parameters were evaluated: signal intensity relative to native cartilage; morphology with respect to native cartilage; delamination; nature of the interface with the adjacent surface; degree of defect filling; integrity of cartilage on the opposite articular surface and bony hypertrophy [16].

After microfracture and osteochondral autograft transplant sites, MRI can evaluate the degree of defect filling, the extent of integration of repair tissue with adjacent tissues, the presence or absence of proud subchondral bone formation, the characteristics of the graft substance and surface, and the appearance of the underlying bone [7]. After ACI, visualization of the biochemical properties of cartilage becomes more important, since repair tissue shows a gradual maturation over time [17, 18].

3.2. Cartilage repair surgery follow-up timing

In case of articular cartilage repair, first we need to fill the defect area with a tissue that has the same mechanical properties as normal articular cartilage; second we need to promote successful integration between the repair tissue and the native articular cartilage [19]. The parameters which determine the mechanical properties of knee articular cartilage are the content, the arrangement and the interaction between the main components such as the collagen matrix, proteoglycans (PGs), and interstitial water [20]. PGs have been shown to be the primary parameter which determines the compressive properties of cartilage and collagen was reported to responsible for the tensile property [21].

Follow-up MR imaging studies should be performed at 3–6 postoperative months to assess the volume and the integration of repair tissue and after 1 year to evaluate the maturation of the graft and identification of any complications [22]. The ability to evaluate the organization of the collagen matrix in repair tissue over time is important, as failure within the collagenous fiber network is considered as failure of cartilage repair procedure [6].

4. Magnetic resonance imaging (MRI)

The MRI principle can be explained by the fact that atomic nuclei of fluids in a magnetic field can be flipped off their preferred orientation parallel to a magnetic field when exposed to an electromagnetic radio frequency field (RF field). When the RF field is switched off, the atomic nuclei return to their original state and release the absorbed energy as electromagnetic radiation. During excitation, we send radio frequency energy to the hydrogen protons inside the body. Those protons will absorb this energy as a heat. When we stop excitation, the relaxation process starts and the energy introduced during excitation is transferred to the surrounding protons.

There are two types of relaxation. First, the T1 (longitudinal Relaxation) whereby there is energy transfer from the spins to the environment and the T2 (transverse Relaxation) where there is dephasing of spins. The contrast in MRI depends on many parameters mainly patient parameters, sequence type and sequences parameters. The patient related parameters are T1, T2 and proton density. By varying parameters such as repetition time (TR) and echo time (TE), we can obtain weighted sequence like T1, T2 and proton density weighted sequences.

4.1. T1 relaxation

The T1 relaxation curve which describes the relaxation speeds for any given tissue follows an exponential law. The constant T1 is defined as the time required for the longitudinal component of M0 to return to 63% of its initial value. The difference in relaxation times gives the T1 contrast. The T1 value depends on the mass and the size of the molecules constituting the tissue. It depends strongly on B0 and is a function of the micro-viscosity of the medium. For liquid, the values of T1 are greater than the second and for the most structured tissues, the T1 values are of the order of a few 100 ms.

4.2. T2 relaxation

During the T2 relaxation process, each tissue loses transverse coherence (magnetization) via an exponential decay process. T2 is defined as the time after which the transverse magnetization is decayed to 37% of its starting amplitude. T2 is a tissue specific parameter and is weakly dependent on the magnetic field B0 because it happens on a perpendicular plane to B0. In solids, which possess a rigid atomic network, T2 is extremely short, whereas in liquids where the decay of the transverse magnetization takes place slowly, T2 is longer and that is why pure water will appear as hyper signal on a T2-weighted sequence.

5. T1 mapping

The contrasts in MRI morphology sequences depend on the difference of signal intensities between tissues at the time of echo measurement. To display the T1, T2 and T2* values of each tissue, we need to calculate parametric maps. In those maps, the pixel intensities in the image provide quantitative values of the studied relaxation time.

5.1. T1 mapping calculation

To calculate T1 mapping we can use either spin echo or gradient echo sequence. With the 2D spin echo sequence, there are two methods to calculate T1 maps either based on the phase inversion or saturation of the longitudinal magnetization. In each case, at least two data sets with different parameters are needed. In case of spin echo, we need to acquire the same sequences twice with the same parameters but different repetition time (TR) and in case of inversion recovery sequence, we use the same sequence but with different inversion time (TI). The acquisition time required for the T1 mapping using spin echo technique is relatively long and often limited to a small number of slices. 3D gradient echo sequences are better alternative solution which provide high signal to noise ratio (SNR) and thin slices in relatively less acquisition time. 3D spoiled fast gradient echo (3D FLASH) sequence with two different excitation flip angles of was used to assess the T1 relaxation times [23, 24].

5.2. T1 mapping clinical applications

The measurements of T1ρ can be used to visualize interactions between the water molecules in restricted movement and local macromolecular environment. The extracellular matrix of the articular cartilage provides a limited movement environment of water molecules. The modifications of the extracellular matrix, such as loss PG, may be reflected by the change of the T1ϱ values. In one study, the normalized T1ϱ rate was strongly correlated with alterations in fixed charge density (FCD) due to depletion of PG which was confirmed by histology [23].

6. Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC)

A dGEMRIC involves intravenous administration of negatively charged contrast agent ($Gd\text{-}DTPA^{2-}$). After injection of Gd-DTPA2, the contrast agent penetrates the cartilage through both the articular surface and the subchondral bone [24]. Since the contrast agent has negative charge, it will interact with FCD which is directly related to the GAG concentration. The distribution of $Gd\text{-}DTPA^{2-}$ is inversely proportional to glycosaminoglycan (GAG) content of the tissue of interest. T1 relaxation times are inversely proportional to the concentration of $Gd\text{-}DTPA^{2-}$. The $Gd\text{-}DTPA^{2-}$ will shorten the T1 of tissues in this case the cartilage, therefore T1 can be used as a specific marker of GAG concentration. Healthy cartilage, which contains an abundance of GAG, will show a low $Gd\text{-}DTPA^{2-}$ concentration, whereas GAG-depleted degraded cartilage will show a high $Gd\text{-}DTPA^{2-}$ concentration which will result in lower T1 values compared with healthy cartilage [25] (**Figure 1**).

6.1. Exam preparation

It was recommended to inject a bolus of $Gd\text{-}DTPA^{2-}$ with a quantity of 0.2 mmol contrast agent per kilogram body weight (double dose). After injection, we ask the patient to do some exercises of the knee, for example, walking up and down stairs for about 20 minutes. Ninety minutes after IV injection, we acquire the postcontrast MRI study. This delay time of 90 minutes

allows the contrast agent to fully diffuse into the cartilage. However, since cartilage thickness is variable within the knee and between patients, the delay time to reach equilibrium has to be adjusted [26]. Moreover, after different cartilage repair surgeries, the timing to reach the equilibrium, and the exercise period are difficult to be defined and standardized [21].

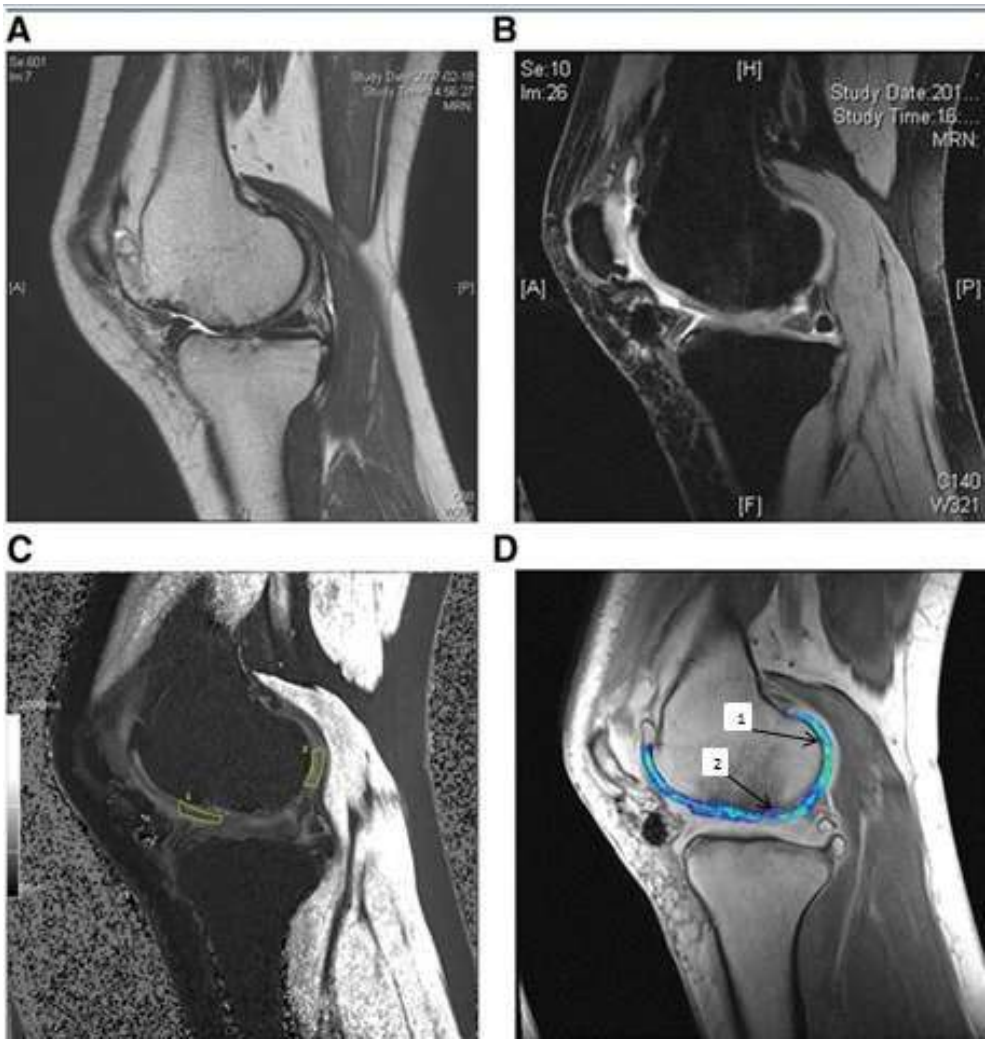

Figure 1. MRI evaluation of cartilage regeneration 3 years after transplantation. (A) Preoperative MRI showing cartilage defect at the medial femoral condyle; (B) at 3 years posttransplantation, they observed cartilage regeneration at the defect site; (C) two ROI's were drawn to calculate the change in relaxation rate (ΔR1) in regenerated cartilage and in native cartilage; (D) map by delayed gadolinium-enhanced MRI (dGMRI) of the cartilage shows high glycosaminoglycan (GAG) in the regenerated cartilage. Higher T1 values (arrow 1) reflected an increase of relative GAG content, whereas lower T1 values (arrow 2) are associated with decreased GAG content [25].

6.2. Exam protocol

To calculate proteoglycan content and fixed charge density (FCD) using dGEMRIC, it is required to acquire both precontrast and postcontrast T1 mapping for articular cartilage in addition to a known Gd-DTPA concentration [24]. It has been suggested that native articular cartilage has a relatively constant unenhanced T1 value. So, no need to acquire precontrast images to estimate FCD [26]. However, some authors have shown differences between the precontrast T1 values of ACI repair tissue and articular cartilage [27]. So, it is recommended for the study of cartilage repair tissues to acquire both precontrast and postcontrast T1 measurements when possible [21].

When evaluating cartilage repair tissue using dGEMRIC, we have to know that before contrast injection, repair tissue may show different T1 values compared to normal cartilage. In this case, the postcontrast T1 mapping may not correlate directly with GAG content. So, the solution will be to correlate the difference between precontrast and postcontrast imaging, so called "delta relaxation rate," $\Delta R1 = 1/T1$ precontrast $- 1/T1(Gd)$, which correlates well. Watanabe et al. demonstrated that on study done on 7 patients that the relative $\Delta R1$ or "$\Delta R1$ index" (Δ relaxation rate of repair tissue divided by the Δ relaxation rate of normal hyaline cartilage) correlates with the GAG concentration in ACI repair tissue, using such reference the gas chromatography which is accepted to be the gold standard for the measurement of GAG content in biopsy samples. The limitation of this study was the low number of patients which make statistics low significant [27].

6.3. Spatial resolution

Native articular cartilage and postoperative cartilage repair tissue are relatively thin structures which require very high-resolution images for an accurate assessment. In plane spatial resolution is characterized by the pixel size in both frequency and phase encoding direction. The pixel size is defined as the ratio of the field of view (FOV) over the matrix in both frequency and phase encoding direction whereas the through Plane resolution is characterized by the slice thickness. For accurate assessment of the articular cartilage, it was recommended to use slice thickness less or equal to 2 mm and a pixel size less than 0.3 mm [28] or better less than 0.2 mm [21]. Those recommendations need enough signal to noise ratio (SNR) which can be obtained at higher magnetic field (1.5 T and higher) [21]. This high resolution is recommended to assess fissures which can be developed at the area of peripheral integration as well as the development of proud subchondral bone formation which can be seen after marrow stimulation repair techniques [21].

6.4. Acquisition sequence

In a previous study done on phantom, Trattnig et al. used a 3-D variable flip angle dGEMRIC technique to obtain information related to the long-term development and maturation of grafts in patients after matrix-induced ACI (MACI) surgery. There was a good correlation between variable flip angle technique and standard inversion recovery technique for T1 mapping [29]. Another study also confirmed this correlation *in vivo* [30].

6.5. Clinical dGEMRIC studies on patients with cartilage repair

dGEMRIC has been used to evaluate GAG content in repair tissue after different surgical cartilage repair techniques such as microfracture, ACI, and MACI. Two previous studies reported that MRI non-invasive dGEMRIC technique could be used to monitor the content of GAG after ACI procedure. They suggested that the GAG concentration in repair cartilage after 10 months (or longer) of ACI is comparable with the GAG concentration in the adjacent normal hyaline cartilage [31, 32].

Besides, another study based on MR examinations of 45 patients after cartilage repair surgery using precontrast and dGEMRIC postcontrast, T1 mapping technique revealed a high correlation between T1Gd and ΔR1 in all examinations with R values above −0.8 [33]. From the results, they could assume that both T1Gd and ΔR1 might be useful for evaluation of cartilage repair tissue. Since the T1(Gd) needs only one MRI scan instead of 2 in case of ΔR1, they preferred using T1(Gd) method in order to save time and costs. However, in case they need to compare GAG content of native cartilage and repair tissue within the same patient, the noncontrast T1 values of the native cartilage and repair tissue need to be similar otherwise the comparison may not be valid [21].

In a previous study, a dGEMRIC MRI of cartilage was used to evaluate the quality of the regenerated cartilage at 3 years posttransplantation. The precontrast T1 relaxation time was calculated to evaluate the change in GAG content in the repair-cartilage tissue. The T1 relaxation time was measured in the repair tissue area and the healthy native cartilage. Then, they calculated the relaxation rate R1 as 1/T1 (in 1/second). After, they calculated ΔR1 which represents the change in R1 as the difference of R1 between the precontrast and postcontrast. The ΔR1 represents the concentration of Gd-DTPA^{2-}. They defined relative index of ΔR1 as the ratio of ΔR1 in regenerated cartilage divided by ΔR1 in native cartilage. In case of perfect regeneration, this ratio will be equal to 1. The MRI evaluation of five participants after 3 years revealed that the mean relative ΔR1 index was 1.44 which indicated high GAG content of the regenerated cartilage [25, 27].

Trattnig et al. reported that biopsy studies have shown that most of the changes in cartilage implants occur in the early postoperative period. So, in order to assess the maturation of cartilage implants over time, they subdivided patients in 2 groups early postoperative (3–13 months) and late postoperative (19–42 months) groups [29]. In the early postoperative group, the mean ΔR1 (in s^{-1}) for repair tissue was 2.49 (±1.15) versus 1.04 (±0.56) at the intact control site and 1.90 (±0.97) versus with 0.81 (±0.47) in the late postoperative group. The difference in ΔR1 between repair tissue and normal hyaline cartilage in both groups was statistically significant ($P < 0.007$), whereas the difference in ΔR1 of repair tissue and normal hyaline cartilage between the groups was not statistically significant ($P = 0.205$). The mean relative ΔR1 was 2.40 in the early group compared to 2.35 in the late group. They explained this fact by the results of biopsies histological investigations which have shown that MACI may develop hyaline-like, mixed hyaline-fibrous, or fibrous tissue over time [17, 34].

A previous study was conducted on 10 patients treated with microfracture and 10 with MACI. The mean ΔR1 was 1.07 ± 0.34 for microfracture and 0.32 ± 0.20 at the control site, whereas it was 1.90 ± 0.49 for MACI compared to 0.87 ± 0.44 at the control site. Calculated

relative ΔR1 was 3.39 for microfracture and 2.18 for MACI and the difference between the cartilage repair groups was statistically significant [35]. The histology and biochemistry analyze showed that the repair tissue formed by microfracture contained less PGs and an abnormal distribution of collagen compared with normal cartilage which may explain the poor mechanical properties often exhibited by repair tissue. The T1 mapping showed a significantly higher relative ΔR1 of the repair tissue after microfracture when compared after MACI, suggesting a lower GAG content after microfracture [36, 37].

In one study, Fibrocartilage formed after microfracture, evaluated using dGEMRIC, demonstrated a greater difference between precontrast and postcontrast T1 relaxation time compared with repair tissue formed after MACI. As dGEMRIC reflects the glycosaminoglycan content, they deduced from the results that glycosaminoglycan content in fibrocartilage were lower compared to other types of cartilage repair tissue [35].

Another study conducted on nine patients (average age, 21.2 years) reported that relative ΔR1 index was 1.32 after 1 year post-ACI for focal chondral defects. In nine patients (average age, 43.2 years) postosteochondral allograft transplantation, relative ΔR1 index were 1.13 at the first year and 1.55 at the second year [38].

7. T2 mapping

During the relaxation process of MRI experiment and due to the variations of the local magnetic field, the individual magnetic moments gradually lose their phase coherence, which leads to a decrease of the net magnetization vector. This decrease of the signal is called spin-spin relaxation and noted T2 relaxation. The calculation of T2 mapping is obtained usually with a spin echo sequence using different echo times (**Figure 2**). From the signals measured with different TE's, we draw the T2 decay curve where T2 correspond to the time spent by the transverse relaxation magnetization to reach 37% from its initial value. T2 maps are usually obtained by using a pixelwise, monoexponential, non-negative least-squares fit analysis (**Figure 3**).

The T2 relaxation time is affected by the speed the spins lose phase coherence during relaxation. The presence of free water molecules in knee cartilage will slow the decay of the transverse magnetization which will make from the T2 mapping a common tool to measure the water content in the cartilage [39].

T2 value is also affected mostly by collagen network structure of cartilage [19]. It depends on both water [16, 17] and collagen content [18]. The concentration of collagen and proteoglycans is responsible for the water movements in the extracellular matrix and the appearance of the cartilage in T2-weighted images. Quantitative T2 MR mapping of articular cartilage is a non-invasive imaging technique that has the potential to characterize hyaline articular cartilage and repair tissue. The T2 relaxation time has been significantly correlated with collagen orientation in cartilage repair models using either polarized light microscopy or Fourier transform infrared imaging spectroscopy [40–42] where as it showed a poor correlation with collagen content in several repair models [42, 43].

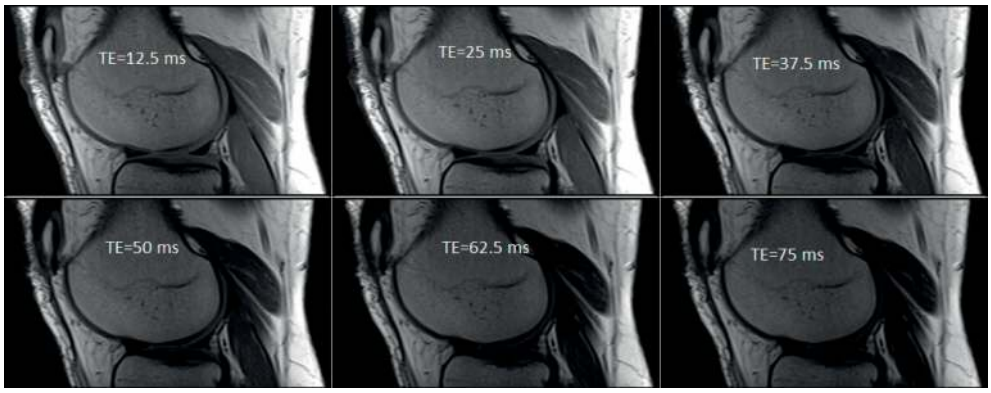

Figure 2. Images acquired using multi echo spin echo (MESE) sequence with different TE's in the range of 12.5–75 ms.

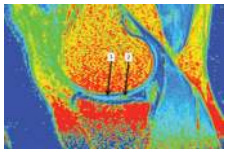

Figure 3. T2 mapping image calculated using a MESE sequence. Arrow 2 indicates higher T2 whereas arrow 1 indicates lower T2 values.

7.1. Spatial variation of T2 values

The T2 relaxation time is affected by the organization of the extracellular matrix of native articular cartilage [6]. In native hyaline cartilage, the T2 relaxation times is varying over depth when going from deepest layers to superficial layers with shorter T2 values in the deeper, radial zone, where the collagen is highly ordered and the collagen fiber matrix has a preferred orientation perpendicular to the cartilage surface, and longer values in the transitional zone because of less organization of the collagen where the collagen fiber matrix has an oblique orientation. The superficial zone may not be visualized on morphological imaging and quantitative T2 mapping because it is too thin [44].

When doing quantitative MR T2 mapping in the knee articular cartilage to compare different cartilage repair surgeries, we can either evaluate mean global T2 value throughout the thickness of the repair or a zonal assessment in the deep versus the superficial half of the repair tissue. Cartilage repair tissue with a lack of zonal organization of collagen would not be expected to demonstrate a similar of T2 values from the deep to superficial aspects of the tissue compared to normal cartilage. Alteration in this orderly transition in T2 values within cartilage has been shown to correlate to changes in water content and changes in collagen structure and organization associated with hyaline articular cartilage degradation [45].

7.2. T2 mapping sequences

The common point between the sequences used for T2 mapping calculation is the acquisition of multiechoes to describe the T2 decay curve and to allow the calculation of T2 value. Among those sequences we found spin echo single echo sequence (SESE), multiecho spin echo sequence (MESE), dual echo steady state sequence (DESS) and turbo gradient spin echo (TGSE).

7.2.1. Spin echo single echo sequence (SESE)

The SESE Sequence uses two RF pulses, 90 and 180° pulses. The 90° pulse will tilt the longitudinal magnetization vector M0 to the measurement plane which is the transverse plane. The spins start dephasing. Then we apply the 180° pulse to rephase spins. At a certain time called echo time (TE) when the spins are totally rephased we measure the signal. Then we repeat the pulse sequence many times as much as the phase encoding matrix. The Time which separates two consecutive 90° pulses is called repetition time (TR). In this sequence, we measure a single echo in each repetition time (TR). To calculate the T2 relaxation time, we need to repeat the sequence many times in order to collect different TE's. The main advantage of this type of sequence is that it is not contaminated by the stimulated echo. Also, this sequence, by the use of 180° refocusing pulses is less sensitive to artifacts in case of postoperative imaging [21]. The disadvantages are that the exam duration will be longer adding to that the risk of patient's movement.

7.2.2. Multiecho spin echo sequence (MESE)

The MESE sequence uses the same preparation radio frequency (RF) pulses as the SESE. The difference is that in SESE sequence we measure only one echo in a TR where as in the MESE sequence, we can measure many echoes. The biggest advantage is that we measure all the TE's on one scan which will save time with less movement artifact. In addition, this sequence gives the possibility to measure the T2 using the inline calculation method. The only disadvantage is the presence of the stimulated echo which can be reduced by the elimination of the first echo from the calculation.

7.2.3. Dual echo steady state sequence (DESS)

T2 can be calculated using dual echo steady state sequence (DESS) which demonstrated to provide results as comparable with the standard multiecho spin echo T2 [2]. In both 2D fat suppressed turbo spin echo proton density and 3D DESS sequence, hyaline cartilage has intermediate signal and synovial fluid has high signal. 3D DESS has the advantage to use thinner slices which make this sequence to me sensitive to detect smaller cartilage defects better than the 2D sequence.

7.2.4. Turbo gradient spin echo

This sequence combines a gradient echo and a spin echo imaging. It generates additional gradient echo before and after each spin echo. The spin echo gives the T2 contrast and the gradient

echo determines the image resolution. The main advantage of the sequence is that it is fast and provides high resolution images. The TGSE sequence combines the TSE and echo-planar imaging method. It provides T2-weighted images. There are technical differences between TSE and TGSE sequences that could make the contrast and signal-to-noise ratio potentially different.

7.3. Technical aspects

When optimizing a T2 mapping acquisition protocol, we need to take into account many technical considerations.

7.3.1. Repetition time (TR)

To minimize the T1 contribution in the image contrast of T2 images, it is recommended to use longer TR value compared to the T1 value of the articular cartilage. A TR of 1500 ms or longer is preferred.

7.3.2. Echo time (TE)

Due to the shorter value of the T2 relaxation time of the knee articular cartilage, short TE and short echo spacing (ES) in case of multiecho sequences are required to accurately characterize the T2 decay curve. Since the expected T2 values of articular cartilage are in the range between 20 and 70 ms, we recommend using many echoes for better curve fitting. The greater the number of data sets, that is the number of TE values, the greater the accuracy of the T2 measurements but without using a higher TE which is susceptible to greater noises and errors.

7.3.3. Stimulated echo

It is important to know that multi-slice multiecho spin echo sequences (MS MESE) uses a slice-selective refocusing pulses. In case of bad calibration or inhomogeneities of the radio frequency pulse, slice-selective refocusing pulses do not result in rectangular slice profiles causing stimulated echo contributions to the measured signal. The T2 relaxation time based on multiecho sequence is subject of measurement errors because of the stimulated echo which may increase artificially the T2 value [46]. This error may be avoided by ignoring the first echo when using a multiecho sequence or by using single echo acquisitions instead of multiecho acquisition.

7.3.4. Bandwidth (BW)

To reduce the chemical shift artifact between water and fat in the cartilage, we advise to use a higher bandwidth of ~217 Hz/pixel corresponding to a chemical shift of 1 pixel on 1.5 T system and 0.5 pixel at 3 T.

7.3.5. Magnetic field

MR morphology imaging of cartilage repair tissue has significantly improved in recent years by the use of high-field MR systems like 3 T, the use of higher gradient strengths and the dedicated coils. This improvement increased the signal to noise ratio (SNR) which allows

high-resolution imaging of cartilage within reasonable scan time [6]. To further decrease the scan time while maintaining high-resolution, most of the new systems used a dedicated multi-elements coil which enables the use of parallel acquisition techniques with high acceleration factor [21].

High-field MRI system also allows the use of 3-D acquisition sequences with the advantage of isotropic high resolution where dimensions are equal in all 3 axes (frequency, phase and slice) while maintaining high SNR and high contrast-to-noise ratios (CNR). This permits multi-planar reconstruction (MPR) in any plane with the same resolution. Biochemical imaging techniques, such as sodium MR imaging, which is limited by low signal-to-noise ratio at standard clinical field strength can be used at ultra–high magnetic field [12].

Care must be taken when performing T2 mapping and interpreting the results since T2 may depend on Bo, with shorter T2 values found at higher field strengths.

7.3.6. Magic angle effect

One of the disadvantages of T2 relaxation time mapping is its susceptibility to the magic angle effect, in which T2 values may be artificially elevated in certain regions according to the orientation of cartilage in relation to the main magnetic field [5]. The magic angle effect may complicate evaluation of curved articular surfaces, such as the femoral condyle [47], and should not be misinterpreted as degeneration. However, a recent report has found that OA may affect T2 values to a greater degree than the magic angle effect [48]. This finding may enable utilization of magic angle T2 mapping data with the understanding that only regions of interest from similar anatomic locations may be compared. However, the magic angle effect should not impact results tracking changes over time or between study populations as long as the subjects are positioned in the same manner in the magnet [49].

7.3.7. Exam timing

Significant differences between cartilage T2 values were obtained at the beginning and at the end of the MRI examination resulting from the different states of unloading of the knee in the course of the MRI examination due to the supine position of the patient. Therefore, the time point of T2 acquisition has to be considered in the MRI protocol. Apprich et al. recommended to measure T2 after unloading, i.e., at the end of the MRI examination [46].

7.3.8. Question to be answered

The following questions have to be answered in case of cartilage repair follow-up: (1) are there different *T*2 relaxation times between repair tissues and adjacent native cartilage? (2) Are these differences reduced over time? (3) Is there a difference between a global assessment and line profile assessment? [6].

7.4. Clinical application of T2 mapping in cartilage repair surgery

In a previous study conducted by Welsch et al., they calculated the mean and the zonal T2 values within the repair tissue and hyaline native cartilage on twenty patients who

underwent MFX or MACT (10 in each group) with minimum 2-year follow-up. They compared cartilage T2 values after microfracture therapy (MFX) and matrix-associated autologous chondrocyte transplantation (MACT) repair procedures. They reported that in normal native hyaline cartilage, T2 values showed similar values for all patients with a significant increase of T2 values from deep to superficial zones ($P < 0.05$). In cartilage repair areas after MFX, global mean T2 was significantly decreased ($P < 0.05$), whereas cartilage repair areas after MACT showed no decrease of mean T2 ($P \geq 0.05$). For zonal variation, repair tissue after MFX showed no significant trend between different depths ($P \geq 0.05$), in contrast to repair tissue after MACT which showed a significant increase of T2 values from deep to superficial zones ($P < 0.05$) [50] (**Figure 4**).

In another study, Welsch et al. compared T2 mapping of 17 patients who underwent MACT over the patella versus 17 patients who underwent MACT in the medial femoral condyle. They reported an increase of T2 values over the condyle compared to the patella repair tissue. They conclude that differential maturation of the repair tissue depends on its environment [51].

Welsch and colleagues reported in another study that T2 mapping can be used to distinguish between MACI performed using a collagen-based scaffold and a hyaluronan-based scaffold (higher T2 values in collagen-based scaffolds) [52].

Quantitative T2 mapping has been used to assess the interface between transplanted and native cartilage. A clinical study of patellar autologous osteochondral transplantation reported progressive T2 increase at the offset of the tidemark that occurred between the thicker native cartilage over the patella and the thinner cartilage over the autologous plug [53].

A study of T2 mapping performed in 53 sites reported a perfect agreement between organized T2 and histologic findings of hyaline cartilage and between disorganized T2 and histologic findings of fibrous reparative tissue (k = 1.0). Mean T2 values were 53.3, 58.6, and 54.9 ms at the deep, middle, and superficial cartilage, respectively, at reparative fibrous tissue, whereas T2 mean values were 40.7, 53.6, and 61.6 ms at hyaline cartilage. A significant increase of T2 values (from deep to superficial) was found in hyaline cartilage ($P < 0.01$). Fibrous tissue sites showed no significant change with depth ($P > 0.59$) [45].

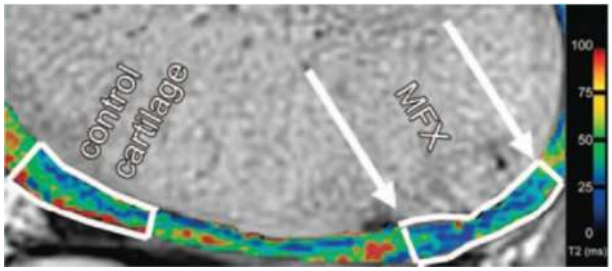

Figure 4. Enlarged section of sagittal cartilage T2 map. ROI of cartilage repair (between two arrows) shows no zonal variation and low T2 values, whereas control cartilage shows visible zonal variation from deep to superficial areas, with higher T2 values in superficial area [50].

Two previous studies evaluated the status of reparative fibrocartilage induced by microfracture using T2 mapping. They reported that spatial variation of T2 values in fibrocartilage and native hyaline cartilage were not the same (hyaline cartilage is characterized by higher T2 values near the articular surface and lower T2 values near subchondral bone) [41, 50]. Also, the overall global T2 value for fibrocartilage repair tissue was lower compared to native hyaline cartilage [50].

MACI has been studied using T2 mapping. The results showed similar spatial variation in the T2 values of repair cartilage like seen in native hyaline cartilage (although the increase in mean T2 values from deep to superficial layers of cartilage is less pronounced) [41].

T2 mapping of patients after MACT surgery at different postoperative intervals Quantitative *T*2 mapping was performed in 15 patients after MACT surgery at different postoperative intervals. With respect to the postoperative time interval, patients were subdivided into two groups: group I, 3–13 months (6 patients); group II, 19–42 months (9 patients). In group I, the mean global *T*2 values in cartilage repair tissue was 65.8 ± 16.6 compared with 50.0 ± 7.0 for native cartilage; this difference was statistically significant ($P = 0.013$). In group II, the mean *T*2 values of repair tissue were 56.5 ± 12.0 compared with 57.7 ± 9.2 for native cartilage. These differences were not statistically significant ($P = 0.784$). Results showed significantly higher *T*2 values, in cartilage repair tissue, in the early stage (3–13 months) compared with native hyaline cartilage. Over time, there was a decrease in repair tissue *T*2 values which became similar to native healthy cartilage [6]. This finding is in agreement with a study by Kurkijarvi et al. [54] who, in 1.5 T, reported *T*2 values in the repair tissue and normal hyaline cartilage with 60 ± 10 ms and 50 ± 7 ms, respectively, in 10 patients 10–15 months after ACI surgery.

Domayer et al. introduced a T2 index defined as the ratio of the mean global repair tissue T2 divided the mean global normal cartilage expressed as a percentage. They reported that this T2 index correlated with clinical measurements [55].

8. T2* mapping

In addition to the phase shift of the individual spins, there is also the additional phase shift caused by field inhomogeneities that increase the phase shift of the spins and thus accelerates the decay. The total relaxation time (T2*) is a consequence of these terms.

8.1. T2* mapping principle

The physical difference between T2* and T2 is that magnetic gradients, and not a 180° RF pulse, are used to rephase the spins at a user defined TE. T2* and T2 values are related by the equation (Eq. (1)):

$$\frac{1}{T2^*} = \frac{1}{T2} + \gamma \Delta B0 \quad (1)$$

Where γ is the gyromagnetic ratio of the observed nucleus and $\Delta B0$ is the magnetic field inhomogeneity. If we assume that the applied static magnetic field B0 is uniform then $\gamma \Delta B0$

is only influenced by local magnetic susceptibility fields. In the case of knee articular cartilage, this susceptibility will be present at the cartilage bone interface or within the cartilage microstructure.

T2* mapping is similar to T2 mapping [56]: multiple echo images at a single slice location are generated, and a mono- or bi-exponential decay equation [57] (**Figure 5**) is used to fit the signal intensity to the corresponding echo time data. The difference between T2 and T2* mapping is that T2 mapping is calculated using a spin echo sequence however T2* mapping is obtained using a gradient echo sequence (**Figure 6**). T2* mapping has the advantage of shorter scan time compared to T2 mapping. Also, with T2*, we can acquire shorter TE compared to T2 which is very important for short T2 components. In addition, with T2* mapping using 3D gradient echo sequence, we have the possibility of isotropic three-dimensional reconstruction, which seems to offer a potential alternative and reliable results in cartilage imaging [58].

8.2. Clinical application of T2* mapping in cartilage repair surgery

Goetz H. and al performed MRI examinations on 30 patients after MACT at a follow-up period of 28.1 ± 18.8 months. T2* values are given in milliseconds (ms). In healthy control cartilage, T2* mean value of all patients was 30.9 ± 6.6 with a significant increase of T2* values from deep (27.9 ± 7.2) to superficial (33.9 ± 6.9) cartilage aspects. The cartilage repair tissue after MACT showed a mean (full-thickness) T2* value of 24.5 ± 8.1 with a significant increase

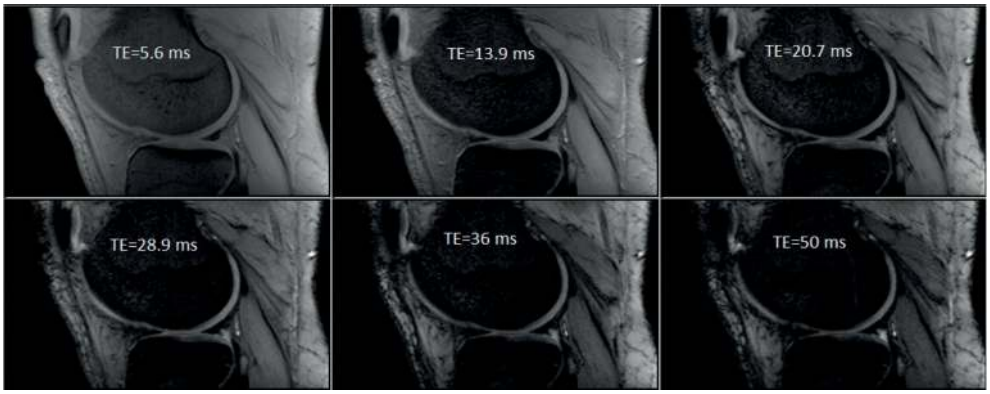

Figure 5. Images acquired using multiecho gradient echo (MEGE) sequence with different TE's in the range of 5.1–50 ms.

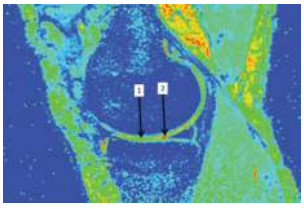

Figure 6. T2* mapping image calculated using a MEGE sequence. Arrow 2 indicates higher T2* whereas arrow 1 indicates lower T2* values.

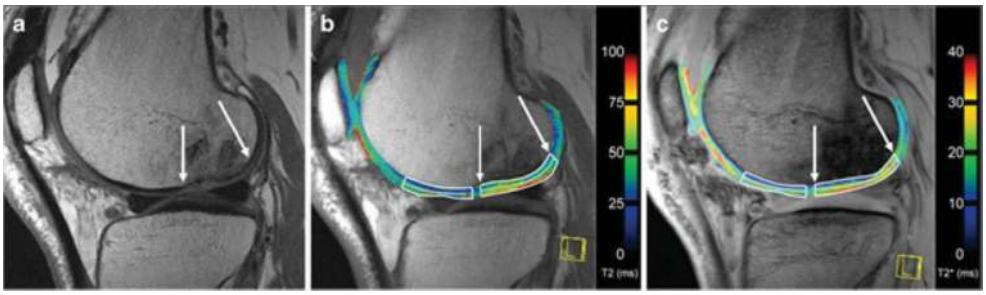

Figure 7. Depiction of cartilage in a patient 6 months after MACT of the lateral femoral condyle. Morphological PD-TSE sequence (a), matched quantitative T2 (b), and T2* (c) maps. Arrows mark the area of cartilage repair. ROIs, considering a possible zonal variation, provide information on the mean (full-thickness) as well as the deep and superficial aspect of control cartilage (left) and cartilage repair tissue (right, arrows). Zonal stratification is visible for both T2 and T2* images in most parts of the cartilage. A possible "magic angle" effect is visible within the trochlea. Higher T2/T2* values are apparent in the cartilage repair tissue, compared with the adjacent cartilage [59].

from deep (21.6 ± 7.3) to superficial (27.5 ± 9.4) ($P < 0.001$). When comparing T2* values of the healthy control cartilage with those of the cartilage repair tissue, the mean T2* values and the T2* values in deep and superficial cartilages were significantly lower in the cartilage repair tissue ($P < 0.001$) [59] (**Figure 7**).

The comparison of the mean (full-thickness) T2* values over different postoperative intervals revealed a stability of T2* values over time with T2* value of 31.4 ± 6.2 for the short-term interval, 31.0 ± 6.7 for the mid-term interval and 30.4 ± 7.0 for the long-term interval. However, the cartilage repair tissue showed significantly higher T2* values at the short-term follow-up (31.0 ± 8.1) than at the mid-term follow-up (20.7 ± 6.1) ($P < 0.001$), and stable values between the mid-term and long-term (22.2 ± 6.0) follow-up ($P = 0.232$). The difference between the short-term and long-term follow-up was also significant ($P < 0.001$) [59].

The comparison of mean (full-thickness) T2* values for healthy control cartilage and cartilage repair tissue at the different postoperative follow-up time points revealed comparable values at the short-term follow-up (0.793), significantly lower mean (full-thickness) T2* values in cartilage repair tissue compared to healthy control cartilage for the mid-term ($P < 0.001$) and long-term ($P < 0.001$) postoperative intervals [59].

Goetz H. Welsch and al reported that mean T2* values (ms) were lower at 7 T (18.3 ± 4.9) compared with 3 T (22.2 ± 4.3). Regarding zonal variation, T2* relaxation times (ms) were significantly lower at 7 T (deep: 15.5 ± 3.7; superficial: 21.0 ± 4.5) ($P < 0.001$) compared with 3 T (mean: deep: 17.6 ± 3.7; superficial: 26.9 ± 5.4) [60].

9. Conclusion

The validation of cartilage repair techniques needs short, medium and long term follow-up. The follow-up periods remain a problem for cartilage repair because of the slow progression of cartilage degeneration over time. Choosing the best technique that addresses the individual

defect is a challenge for the orthopedic surgeon. T2 mapping could provide information about collagen matrix concentration and organization, whereas dGEMRIC is sensitive to proteoglycan content. T2* mapping has the advantage of shorter scan time with the possibility to acquire shorter TE compared to T2 which is very important for shorter T2 components. The modifications of the extracellular matrix, such as loss PG, may be reflected by the change of the $T1_{\rho}$ values. Each MRI parameter can characterize certain features of the articular cartilage properties. All together may provide complementary information's about cartilage repair tissue properties.

Author details

Mars Mokhtar

Address all correspondence to: mokhtar.mars-mms@topnet.tn

Biophysics and Medical Technologies Laboratory, Institut Supérieur des Technologies Médicales de Tunis, Université de Tunis El Manar, Tunis, Tunisia

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