T2 Mapping issues of the knee articular cartilage at 3 Tesla

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ABSTRACT

Background: Early identification of Knee Osteoarthritis (OA) is important to improve clinical decision making. MRI T2 mapping sequences were used to detect biochemical changes which happen in early stage of OA. This study was aims to compare the mean T2 relaxation time values, Signal to Noise Ratio (SNR) and Contrast between spin echo family sequences used in the evaluation of the knee articular cartilage. Materials and Methods: Thirty one subjects underwent a femoral-tibial articular knee cartilage exam at 3 Tesla Magnetic Resonance Imaging (MRI). We compared mean T2 Values, SNR and contrast between Single Echo Spin Echo (SESE), Multi Echo Spin Echo (MESE) and Fast Spin Echo (FSE) sequences. Results: The results showed a T2 average values equal to 46.6 ± 15.6% for the SEME, 40.5 ± 13.3% for SESE and 42.9± 13.8% for FSE. The SESE had the best fitting factor with $R^2_{min} = 0.999$ followed by the FSE with $R^2_{min} = 0.995$ and MESE with $R^2_{min} = 0.962$. Regarding SNR, MESE and FSE showed higher SNR in most regions compared to the SESE. MESE gave the best cartilage and bone contrast followed by the FSE and SESE. The comparison of the reference SESE sequence with other sequences using the Pearson test showed significant difference in most regions (p <0.05). Conclusions: We conclude there is a variation of mean T2 values, fitting, contrast and signal to noise ratio between sequences. Difference between sequences types and parameters lead to variation of T2 relaxation time. Care must be taken when performing T2 mapping and interpreting results.

Keywords: Cartilage, Osteoarthritis, T2 mapping, MRI sequence

INTRODUCTION

Knee Osteoarthritis (OA) is characterized by progressive loss of articular cartilage (Baum et al., 2013) which lead to disorders and functional failure of synovial joints. It is the most prevalent chronic disease which affects 75% of the population over 70 years of age and it is generally diagnosed at an advanced stage when treatment is difficult or even impossible. (Liess et al., 2002). Early identification of OA is important to improve clinical decision making, help the understanding of the disease progression and evaluate treatment options. (Braun and Gold, 2012) MRI conventional sequences are used to display anatomy and to detect morphological changes of the knee cartilage. (Nieminen et al., 2001). The T2 mapping which calculates the transverse relaxation time of any tissue is able to evaluate the cartilage matrix status and identify biochemical changes associated with the early stages of osteoarthritis (Emilio et al., 2008; Phan et al., 2006). As early degeneration of cartilage is
characterized by the variation of local water content (Lusse et al., 2000), the loss of collagen content (Nieminen et al., 2000) and the change of collagen fiber orientation (Xia, 2000) in the extracellular matrix, T2 mapping has the potential to identify cartilage degeneration in an early stage (Rubenstein et al., 1993). The decreased collagen concentration, the change of fiber orientation, and the increased cartilage water content will result in an increased T2 value (Lusse et al., 2000; Fragonas et al., 1998; Vladimir et al., 1999; Watrin et al., 2001; Lusse et al., 1995). Several recent studies have demonstrated that T2 mapping can be useful for the detection of early stages of matrix degeneration that precede morphological cartilage damage and for postoperative evaluation after arthroscopic cartilage repair (White et al., 2006; Mosher et al., 2004; Glaser, 2005). T2 relaxation time generally increase with biochemical degradation of cartilage. This phenomenon makes T2 relaxation time mapping an effective tool for tracking changes over time of cartilage status (Stephen et al., 2015). However, the specific T2 values of the knee articular cartilage vary in the literature depending on the acquisition sequences and the evaluation methods. Compared with other quantitative imaging techniques, T2 relaxation time mapping presents advantages and disadvantages. The primary advantage of T2 relaxation time mapping is that it can be performed without the use of intravenous contrast agents (Stephen et al., 2015). The primary disadvantage 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 (Xia, 2000). Regions with curved surfaces such as the femoral head and condyles are susceptible to this effect. 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 (Stephen et al., 2015). The most fundamental sequences used for T2 mapping are the stimulated echo acquisition mode (STEAM) spectroscopy and SE (Jens et al., 1969). The cartilage is thin which will lead to a very poor SNR and long scan times when using spectroscopy. The SE sequence needs to be repeated for each Echo Time (TE) resulting in an increase of scan time and this prevent the use of both sequences in clinical routine to assess the cartilage ultrastructure. To overcome these drawbacks, two other 2D sequences have been developed. They are MESE and FSE sequences. Both sequences offer a good SNR and short acquisition time. 3D approaches are also available for T2 relaxation time mapping but in our study, we were limited to 2D sequences on the purpose to compare them with morphological sequences with the same geometrical parameters.

In our study, we used the SESE sequence which is composed of two radio frequency pulses, a 90° pulse followed by a 180° pulse. Maximum signal will be measured at the Echo Time (TE). With this sequence, we measure one echo in each Repetition Time (TR). It is well known that maps generated with a series of SESE images suffer from steady state effects (i.e., different T1 weightings) in the images. To prevent this, long TR times are necessary. In addition, we have to repeat the sequence for different TEs which make the scan even longer compared to the MESE and this will limit its use in routine clinical applications (Jens et al., 1969). Second, we used the MESE sequence; where many echoes can be measured in one TR. It is important to know that Multi Slice MESE sequences cause stimulated echo contributions to the measured signal which causes an overestimation of T2 values. Excluding the first echo from the calculation reduce the effects from stimulated echo signal contribution in the calculated T2 values (Nieminen et al., 2000; Watrin et al., 2001). The last sequence is the FSE which is composed of a 90° pulse followed by a series of 180° pulses with different phase encoding amplitude. The problem with this sequence is that the image is reconstructed using different TE which will result in mixed weighting. Since the centre lines of the K-space are responsible for the image contrast, this weighting mixing problem is minimized when positioned at the centre of the Fourier plane (contrast) the signals corresponding to the desired echo time.

The purpose of this study was to compare the T2 relaxation time of the knee articular cartilage between spin echo sequences family as well as the SNR and Contrast.

MATERIALS AND METHODS

Patients

This study was approved by the ethics commission of the Mohamed Kassab Hospital, verbal and written consent was obtained from all patients prior to exam. Thirty patients (5 females, 25 males) with a mean age of 33.1 years (range 14 to 66 years) underwent a knee MRI examination on a 3 Tesla system. Phantoms For T2 maps comparison, we have designed a phantom from a sodium chloride solution. To this solution, we added different concentrations of contrast agent (Dotarem) to obtain a range of T2 values similar to that found in the articular cartilage of the knee (20-70ms).

Acquisition Protocol

MR examinations were performed on 3 Tesla Scanner (Magnetom Verio, Siemens Erlangen, Germany) with 8 elements knee coil. Special attention was paid to ensure that all patients were well fixed with the joint space in the middle of the coil and the knee extended in the coil. To avoid possible differences in T2 relaxation times due to
loading/weight bearing of cartilage before the examination. Parametric mappings were performed after around half an hour of rest and after the acquisition of the morphological protocol. To minimize the T1 contribution in the image contrast, it was better to use a higher TR value compared to the T1 value of the articular cartilage. We know that the T1 relaxation time correspond to the 67% of the amplitude of the longitudinal magnetization and after 5x T1, the longitudinal magnetization will recover 100% of its value. If we assume the T1 of the cartilage is around 600ms, we have chosen a TR of 1500ms which we think will reduce the T1 effect on the T2 images contrast compared to TR of 1000ms used in other studies (Liney et al., 1996). Due to the shorter value of cartilage T2 relaxation time, short echo time (TE) and short echo spacing are required to accurately characterize the T2 decay curve. Since the expected T2 values of articular cartilage are in the range between 20ms and 70ms, we used in our study echo time between 12ms and 75ms. It is evident that the use of more echoes give a better fit of the curve and more accuracy of the calculated value of T2.

We have chosen the sagittal plane as acquisition plane because it allows the evaluation of articular cartilage in a direction perpendicular to the majority of the weight forces acting on the joint. TE values and the echo spacing time are two parameters which limits the number of slices and the number of echo train in case of a FSE sequence. In our protocol, we have chosen a TR value equal to 1500ms which allowed us to acquire 11 slices. In a previous study, they reported a drop in T2 values when obtained with the multi-slice compared to the single slice acquisition (Lusse et al., 1995).

To reduce the effect of the chemical shift artifact between water and fat in the cartilage, we have chosen a bandwidth of ~ 220 Hz / pixel corresponding to a chemical shift of 0.5 pixel on an imaging system 3 Tesla. Practical issues have to be considered for T2 acquisition. Significant differences between cartilage T2 values 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. In our study, we start our exam with the routine protocol and the mapping scanning is done at the end of the exam which is around half hour after positioning the patient on the table.

The imaging protocol included morphological (sagittal T1-weighted fast-spine-echo as well as sagittal, axial and coronal PD-weighted fast-spine-echo) and biochemical sequences. To compare the sequences in an efficient way, we used the same geometrical parameters, the same Repetition Time and almost the same bandwidth (same chemical shift) when it's possible. For the geometrical parameters, we used a square field of view (FOV) of 160mm x 160mm, a slice thickness of 3mm, a number of slices equal to 11, a gap of 3mm between slices and the acquisition matrix was 192 x 256. The TR was 1500ms.

The other parameters for the SESE were: TE: 12-24-36-50-60-70ms with a bandwidth of 222 Hz / pixel which correspond to a chemical shift less than 1 pixel and the acquisition time was 2min 56sec. For MESE, the TE values were 12.5-25-37.5-50-62.5-75ms, the bandwidth was 219 Hz / pixel and the acquisition time was 2min 50sec. The additional parameters for the FSE sequence were: TE 20-50-70ms, the Turbo Factor was 3, the partial Fourier was 4/8, the bandwidth was 201 Hz / pixel and the acquisition time was 1min 47sec.

For each subject, two sagittal images through the center of the lateral and medial femoral condyle were obtained. Femoral cartilage was segmented into anterior, mid, and posterior. The inner margin of the meniscus was used as a marker for determining the anterior and posterior borders of the weight-bearing cartilage on the sagittal MR images (Maier et al., 2003). In this imaging plane, the femoral and tibial articular cartilage in the weight-bearing area consisted on cartilage covered by the anterior meniscus, cartilage in contact with the opposing articular cartilage, and cartilage covered by the posterior meniscus (Gha et al., 2012). ROIs were drawn in the internal and external part of the knee. In each location, three ROIs were drawn. Total of six ROIs were obtained. Three ROI's were drawn in each internal and external sagittal image [Figure 1].

We didn't include the superficial zone to avoid the chemical shift artifact. When movement of the knee between scans is noticed, ROI's were manually moved and adjusted visually. A few cases with big movement between scans were excluded.

**Signal to noise ratio**

As the MR signal depends on many parameters such as sequence type and sequence parameters and to compare the T2 values from different sequences in an efficient way, we used a common TE value of 50ms then we performed a normalization step in order to compare the T2 relaxation curve of each sequence. ROIs were placed in the different cartilage regions to measure the signal and in the background of the image to measure the Standard Deviation (SD). Afterwards, the signal to noise ratio were calculated by the ratio of the Mean Cartilage Region Signal divided by the SD of Background, with Mean Cartilage Region Signal being the mean signal in the individual cartilage regions (Anterior, Mid, Posterior) and SD of Background being the average noise of the background. Then, we compared the Signal to Noise Ratio value in each region between the three sequences.
Contrast ratio

To compare the contrast from different sequences in an efficient way, we used a common TE value of 50ms and we calculated the Contrast Ratio based on the absolute value of signals difference between cartilage in three ROIs (Anterior, Mid, Posterior) and bone or meniscus divided by the sum of both signals. Then we compared the mean value in each region between the three sequences.

Statistical analysis

We compared the MESE and the FSE sequences to the reference SESE sequence. We calculated the mean T2 values and their standard deviations from different sequences for phantom and patients. Then, we calculated the average of differences and the percent differences between the SESE reference sequence and the other sequences. By drawing the plots of all sequences compared to the SESE, we performed linear regressions on each of the plots to determine the regression line equations and coefficients of determination. The slope of each regression line was used as an indicator of the dynamic range of T2 relaxation time in each sequence.

T2 maps were obtained using a mono-exponentially fitting to the equation: S(t)=S0*e (−t/T2). Statistical calculation using Pearson correlation coefficients was used to evaluate if the T2 values were significantly different between sequences. All statistical calculations were performed in SPSS version 16.0 (SPSS Inc., Chicago, IL) and a P <0.05 was considered statistically significant.

RESULTS

Phantom

In the phantom study, we applied our protocols to six samples with different concentrations. The T2 value obtained from different TEs for SESE sequence, SEME and FSE are displayed in (Table 1). The obtained results
showed that the SESE had the best fitting factor with $R^2_{\text{min}} = 0.999$ followed by the FSE with $R^2_{\text{min}} = 0.995$ and MESE with $R^2_{\text{min}} = 0.962$. Using the Linear Regression plot lines comparison between MESE, FSE and the reference SESE sequence, we have noticed that all sequences demonstrated strong fits. The Regression coefficients $R^2$ were equal to 0.999; and 0.989 for FSE and SEME respectively as shown in [Figure 2] and [Figure 3]. The slopes of the plot lines were 1.03 and 1.16 for FSE and SEME respectively compared to SESE.

The results show an average value equal to 46.6 ±15.6% for the SEME, 40.5 ± 13.3% for SESE, 42.9± 13.8% for FSE. Our results showed also that the average percent difference of the SEME were higher by 12.8 ± 3% with a maximum difference of 8.9ms. For the FSE, the difference was also higher by 5.8% ± 1% with a maximum difference of 3ms. The comparison of the reference SESE sequence with other sequences using the Paired sample test correlation showed no significant value of 0.99, 0.99 for SESE and FSE respectively. So, we can conclude that there is a statistically no significant difference between the sequences ($p > 0.05$). The Pearson correlation test gave the same result for all sequences of 0.99. The comparison between sequences using the same TE of 50ms is displayed in the [Figure 4]. We have noticed that the MR signal change from sequence to sequence. After that, we normalized all values using the TE of 50ms as a reference as shown in [Figure 5]. All curves cross the normalized value of 50 ms as TE.

**Patient study**

Table 2 represents the comparison of the Coefficient determination $R^2$ between the SESE reference sequence
and the SEME, FSE. Regarding values of $R^2$, all values were very low when comparing T2 values acquired from FSE and SEME sequences compared to SESE respectively. The FSE showed the deepest slope in the Internal Medial Region with a value of 0.816 and MESE showed the minimum slope with a value of 0.03. All values are listed in (Table 3). In (Table 4), all mean T2 values are tabulated for different sequences. For the MESE, the mean T2 value were higher in the Anterior, then goes downs in the Medial and then back higher in the Posterior for both Internal and External regions. For the FSE, the mean T2 values were higher in the Anterior and then go downs in the Medial in the Internal and External regions. In the Internal, it decreases in the Internal and almost the same in the Posterior region. For the SESE, the mean T2 values were lower in the Anterior and then increase in the Medial in both Internal and External regions in the Internal and then decrease in the Internal and External Posterior regions. The maximum percent difference between all sequences is shown in (Table 5). Results showed that the calculated T2 values using SEME sequence were higher than T2 values calculated from SESE sequence in most regions of interest with a maximum percent of difference range between 45 ± 51% and -26 ± 17%. While values of T2 using FSE compared to SESE being higher for almost values in different region of interest by a maximum percent difference that range between 88 ± 54% and -39 ± 11%.

The statistic result of Pearson correlation coefficient shown in (Table 6) between all sequences. The statistical results using the Pearson Test show a significant difference between MESE and SESE in most regions (p<0.05) except in the Anterior External region and a significant difference between FSE and SESE in most region except in the Posterior Internal, Anterior External and Posterior External regions.

**Contrast ratio**

The Contrast Ratio Graph shows a comparison of Cartilage- Bone Contrast between all sequences in different regions. From the figure, we can notice that the MESE sequence gave the best contrast between cartilage and bone followed by the FSE and SESE [Figure 6].

Figure 7 shows a comparison of Cartilage-Meniscus Contrast between all sequences in different regions. We can notice that almost all sequences gave the same signal differentiation between cartilage and bone.

**Signal to noise ratio**

The SNR Graph shows a comparison of Signal to Noise Ration between all sequences in different regions. The MESE showed the best SNR in most regions followed by the FSE and then SESE [Figure 8 above].

**DISCUSSION**

**Phantom study**

For T2 maps comparison, we have designed a phantom composed of sodium chloride solution and contrast agent (Dotarem) with different concentrations. T2 relaxation times of our phantom was in the range between 24.7 to 62.7ms. Measurements from MESE sequences were 15% higher than those from SESE, while FSE measurements were an average of 6% higher than those from SESE. Measurements with SESE showed the highest coefficients of determination with $R^2_{\text{min}} = 0.999$ followed by FSE with $R^2_{\text{min}} = 0.995$ and MESE with $R^2_{\text{min}} = 0.964$. In a previous study, a phantom was made in-house by immersing six cylindrical vials of agar gel into a
larger container of water. T2 relaxation times of vials within the phantom ranged from 23 to 64ms. Measurements from MESE sequences were 30% lower than those from SESE, while FSE measurements were an average of 40% higher than those from SESE. Measurements from each sequence with SE measurements allowed for high coefficients of determination (R²=0.8; P<0.05 for all sequences) (Glaser, 2005). Another study reported that the T2 relaxation times have been shown to vary up to 42% between MESE and FSE sequences in agar phantoms (Gha et al., 2012). This variation between the T2 relaxation time can be explained by the difference between used sequences types and parameters as well as the phantom composition and scanning conditions.

**Patient study**

In patient study, measurements with FSE showed the highest coefficients of determination with R² mean=0.995 followed by SESE with R² mean = 0.980 and MESE with R² mean =0.972. In our patient study, The FSE sequence showed the highest slope (0.816) in the Mid Internal region and the lowest slope (0.02) in the Anterior and Posterior External region. The MESE sequence showed the highest slope (0.816) in the Mid Internal region and the lowest slope (0.03) in the Anterior External region. In a previous study, The FSE sequence showed the steepest trendline slopes (1.31), while MESE demonstrated the shallowest slopes (0.42). This phenomenon can be explained by the presence of stimulated echoes throughout the echo train that result from imperfect 180° refocusing pulses. Residual longitudinal magnetization between echoes results in partial T1-weighting, leading to an elevation in T2 relaxation time estimation (Glaser, 2005). In our study, we obtained differences of up to 77% between FSE and SESE in Anterior External Region and differences of up to 37% between MESE and SESE in Anterior Internal and External regions. In vivo studies of patellar cartilage in the axial plane, differences of up to 48% between FSE and SE sequences have been reported (Liney et al., 1996; Cynthia et al., 2003). Another study reported that measurements from the FSE sequence were 25–38% higher than those from all other sequences (Glaser, 2005). Also, FSE has been reported to yield an average of 62% higher T2 relaxation times compared with SE measurements (Mendlik et al., 2004) also, Fast spin-echo sequences have shown high sensitivity (87%), specificity (94%), and accuracy (92%) for detection of chondral lesions in the knee joint, as validated with direct arthroscopy (Potter et al., 1998). In our study, we obtained a maximum percent difference up to 88% ± 54% between FSE and SESE in Anterior External Region and a maximum percent difference of up to 45 ± 51% between MESE and SESE in the same Anterior External region. A study reported that the standard deviations exceed the corresponding average percentage differences in all comparisons except when FSE. This observation suggests it would be difficult to apply one of these average percent differences to predict a regional T2 outcome from one sequence based on the results of another (Glaser, 2005). The statistical results using the Pearson Test showed a significant difference between MESE and SESE in most regions (p<0.05) except in the Anterior External region and a significant difference between FSE and SESE in most region except in the Posterior Internal, Anterior External and Posterior External regions.

**Signal to noise radio assessments**

Compared to SESE, the MESE showed higher Signal to noise Ratio in Internal Interior (IN A), External Anterior (EXT A), and Internal Medial (IM), External Medial (EXTM), Internal Posterior (IN P) regions and lower value in External posterior (EXT P) Region. The FSE showed higher Signal to noise Ratio compared to SESE in IN A, OUT A, IN M, OUT M regions and lower in the IN P and OUT P. In a previous study, they reported that the reason of the T2 relaxation time variation may have resulted from differences in SNR between sequences, particularly in deep regions of cartilage (Glaser, 2005). MRI at 7 Tesla (T), with its higher signal-to-noise ratio compared to clinical field strengths of 1.5 Tor 3 T, allows to obtain images of thin layers of knee articular cartilage with a high spatial resolution which is expected to improve diagnostic accuracy. Imaging at ultra-high-field strengths (UHF, ≥7 T) remains challenging because of the increased power deposition in the examined tissue, characterized by the specific absorption rate (SAR) (Potter et al., 1998), and the B1 field heterogeneity, resulting in the need for dedicated RF shims to achieve homogenous excitation in the region of interest (Hoult and Phil, 2000; Mao et al., 2006).

**Contrast assessments**

For cartilage-bone contrast, the contrast obtained with the MESE sequence compared to the SESE was higher in IN A, OUT A, IN M, OUT M, IN P regions and lower in OUT P Region while measurements of contrast in FSE showed a higher values in all regions of interest compared to SESE sequence. In case of Cartilage-Meniscus contrast, the contrast was lower in the MESE sequence compared to SESE in all regions. The contrast for FSE values was higher in IN A, OUT A, IN M, OUT M, IN P regions and lower value in OUT P Region compared to SESE.
Magic angle

The magic angle effect may complicate evaluation of curved articular surfaces, such as the femoral condyle (Pierre et al., 2005), 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 (Mosher et al., 2001). 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. So, care must be taken when performing T2 mapping and interpreting the results since T2 may depend on Bo (Ligong and Regatte, 2015; Duewell et al., 1995), the sequence type (Borthakur et al., 2000) and the coil architecture (Matzat et al., 2015; Li et al., 2015) and the calculation method of T2 Mapping (Pachowsky et al., 2013; Koff et al., 2008).

Limitations of our study included the relative small number of patients. Additionally, the variation of T2 values because of the location of the cartilage site with respect to the main magnetic field and this has to be discussed as we know that the T2 measurements of cartilage may vary depending on the anatomic region of cartilage and its orientation relative to the main magnetic field. Another limitation of our study was the possible partial volume effects. This was reduced in our study by not including the superficial zone in when drawing the ROIs. This could be solved by increasing the acquisition matrix to obtain a good in-plane spatial resolution but this will increase the scan time which remains challenging for in vivo cartilage imaging. So, Scan Time, spatial resolution and the accuracy of the curve fit are very important to consider when reporting T2 relaxation times (Glaser, 2005). Also, we didn’t subdividethe cartilage into additional sub-compartments to examine site-specific cartilage T2 value changes because; this would require the use of small ROI which will compromise the level of precision and reproducibility of the evaluation.

CONCLUSION

The results showed an average value equal to 46.6 ± 15.6% for the SEME, 40.5 ± 13.3% for SESE, 42.9±13.8% for FSE. It showed also that the SESE had the best fitting factor with R² min=0.999 followed by the FSE with R² min = 0.995 and MESE with R² min = 0.962. Regarding SNR, MESE and FSE showed higher SNR in most regions compared to the SESE. For the scan Time, the FSE showed the minimum scan time followed by the MESE and the SESE. Almost all sequences gave the same signal differentiation between cartilage and bone where as for cartilage and bone contrast, MESE gave the best contrast followed by the FSE and SESE. The comparison of the reference SESE sequence with other sequences using the Pearson correlation coefficient showed significant difference in most regions (p < 0.05).

This study evaluate the effect of sequence type on the T2 relaxation time in phantoms and in patient knee cartilage using single echo SESE as a reference standard and MESE and FSE sequences. Variation between sequences results was observed in terms of average T2 value, fitting, contrast, Acquisition Time and Signal to Noise Ratio. Care must be taken when performing T2 mapping and interpreting the results since T2 may depend on Bo, the sequence type, the coil architecture and the calculation method of T2 Mapping.

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