Modification of longitudinal relaxation time ($T1$) as a biomarker of patellar cartilage degeneration

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Abstract

Objectives: To study the viability of longitudinal relaxation time ($T1$) of patellar cartilage as a biomarker of the degree of degeneration.

Material and methods: We included 15 subjects classified into three groups according to clinical criteria (pain, functional limitation, and duration of symptoms) and imaging criteria as follows: (a) normal (3 men, 2 women; age $30 \pm 14$ years), (b) with initial degeneration of the patellar cartilage (3 men, 2 women; age $30 \pm 6$ years), or (c) with advanced degeneration (3 men, 2 women; age $57 \pm 10$ years). All underwent MRI examination using special echo-gradient sequences to segment the cartilage and calculate the $T1$ maps. We selected the entire cartilage and the regions of interest classified according to clinical and imaging criteria as normal, initial degeneration, and advanced degeneration. The $T1$ values of the cartilage were obtained pixel by pixel and were calculated as the mean for the entire cartilage or by subregions (normal, initial, advanced). Differences between groups for the entire cartilage and the regions were analyzed using Student-Newman-Keuls post-hoc ANOVA. Reproducibility was evaluated using the coefficient of variance.

Results: No significant differences in the overall analysis of the entire cartilage were found between the three groups (normal: $1003 \pm 172$ ms, initial: $1064 \pm 124$ ms, advanced: $1041 \pm 308$ ms, $p = 0.665$). However, the analysis by regions revealed significant differences (normal: $908 \pm 53$ ms, initial degeneration: $1057 \pm 157$ ms, advanced degeneration: $1133 \pm 116$ ms, $p = 0.029$). The reproducibility analysis found variations of $1.3\%$ for the overall calculation, $3.7\%$ for the regional calculation, and $8.2\%$ for the acquisition.

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Introduction

In MRI studies, proton relaxation times vary depending on tissue characteristics and the applied magnetic field. Understanding this is important for designing sequences that will enhance a specific contrast in MRI imaging. In recent years, there has been a growing interest in the clinical applications of relaxation times because calculating relaxation times can help to efficiently characterize and quantify different diseases; for example, when converting intensity readings into contrast media concentration values to determine capillary permeability and perfusion parameters through pharmacokinetic studies. In general, different techniques and sequences have been developed to measure relaxation times based on inversion recovery pulses, progressive saturation, single-shot Look-Locker, k-space direct readings and the most common spin echo multi-echo sequences and gradient echo multi-echo or multiple flip angle sequences. In general, these sequences present notable differences due to different spatial resolutions and the prolonged time period needed to quantify them. The most accurate techniques are based on inversion-recovery pulses, although they require much more time. The techniques that most reduce acquisition times for T1 values and that maintain spatial resolution are based on the repetition of gradient echo acquisitions with different flip angles.

The study of joint cartilage with MRI has traditionally been based on the modification of the system proposed by Outerbridge and applied to MRI, which allows cartilage stratification in four categories, ranging from normal

<table>
<thead>
<tr>
<th>Grade</th>
<th>MRI Image</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal cartilage</td>
</tr>
<tr>
<td>1</td>
<td>Altered intrachondral signal, normal chondral surface</td>
</tr>
<tr>
<td>2</td>
<td>Less than 50% loss of cartilage thickness (2A: focal/2B: diffuse)</td>
</tr>
<tr>
<td>3</td>
<td>More than 50% loss of cartilage thickness but without exposure of subchondral bone (3A: focal/3B: diffuse)</td>
</tr>
<tr>
<td>4</td>
<td>Complete loss of cartilage with subchondral bone exposure</td>
</tr>
</tbody>
</table>

Table 1: Modified Outerbridge classification applied to MRI

Conclusion: In this preliminary study, calculating the T1 of the cartilage enabled regions with different degrees of degeneration to be differentiated.

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cartilage to advanced degeneration (table 1). Advances in quantification techniques and the use of faster acquisition sequences permit the incorporation of different quantitative biomarkers extracted from specific images to aid in diagnosis. Some important parameters include thickness, volume and cartilage relaxation times. Since variation is caused by the direct effects of disease, less subjective evaluations can be obtained, making more reproducible analysis of the overall and regional state of the cartilage.

Some of these biomarkers are based on the biochemical properties of the cartilage, such as the collagen matrix quality and its proteoglycans, which are directly related to the initial stages of cartilage degeneration\(^1\)\(^{11,13}\). At present, it is possible to calculate \(T2\) values that relate to the presence of disease and the severity of cartilage degeneration\(^1\)\(^3\) and the \(T1\rho\) (longitudinal relaxation time in the rotating frame, obtained using spin-lock techniques) values related to the extent of collagen matrix destruction and increases in the quantity and mobility of water\(^1\)\(^4\). In this study, we propose the utilization of longitudinal relaxation \(T1\) time for cartilage evaluation.

Although the relaxation mechanism is longitudinal in both cases, the magnitudes of these mechanisms differ. The \(T1\) value was calculated considering the principal magnetic field effect (\(B_0\)) and using multiple flip angles. On the other hand, to calculate \(T1\rho\), \(B_0\) is not considered as radiofrequency pulses are used to create a magnetic environment in the tissue independent from \(B_0\). In this manner, proton relaxation is also produced by spin-surroundings interactions modified by small magnetic fields so that the tissue is independent from \(B_0\). Spin-lock techniques can achieve a better sensitivity for evaluating differences among different macromolecular environments using the \(T1\rho\), however they require a longer acquisition time and a more complex acquisition technique in comparison to the gradient-echo techniques used in this article to calculate \(T1\).

As we told before, we can calculate \(T2\) values that correlate with the presence and severity of degenerative cartilage disease\(^1\)\(^3\) and \(T1\rho\) values that are related to collagen matrix destruction and increases in water quantity and mobility\(^1\)\(^4\). In addition, the use of contrast agents with late-uptake analysis (dGEMRIC) allows the detection of differences in the proteoglycan concentration by calculating the \(T1\) of the cartilage. These differences are caused by the polarization coupling that the contrast media undergoes when the proteoglycans concentration decreases\(^1\)\(^5\).

To date, existing work has focused mainly on the study of the \(T2\), \(T1\rho\) and \(T1\) after the injection of intravenous contrast media (dGEMRIC). The purpose of this study is to determine the native \(T1\) parameter (without previous intravenous contrast injection) and validate its utility as a biomarker of the degree of patellar cartilage degeneration.

Materials and methods

Patients

We included 15 patients who presented pain or functional knee limitations of a possible degenerative etiology and with a long duration of symptoms, all of whom were evaluated by orthopedic surgeons with expertise in degenerative joint disease.

Joint cartilage was assessed with MRI using signal intensity criteria, surface integrity, alteration of the subchondral bone and changes in its perfusion and analyzed with pharmacokinetic models after administration of contrast agent\(^1\)\(^6\). We used the Outerbridge classification for MRI\(^1\)\(^0\) (table 1) combined with the perfusion criteria for capillary permeability\(^1\)\(^6\).

The patellar cartilage status was classified using the following criteria: normal (grade I; 3 men, 2 women, aged 30 ± 14 years), initial degeneration (grade II; 3 men, 2 women, aged 30 ± 6 years) or advanced degeneration (grades III and IV; 3 men, 2 women, aged 57 ± 10 years).

Image acquisition

Images were acquired on a 3.0 T MRI equipment (Philips Healthcare, Best, Netherlands). Along with the usual standard knee sequence (sagittal T1, coronal DP, transverse T2, sagittal T2), we acquired two additional 3D gradient echo sequences (table 2).

The first of these two sequences, which had a high spatial resolution, was used to segment the cartilage by suppression of the adipose tissue signal, based on the maximization of its contrast with bone, synovial fluid and ligaments. The second gradient echo sequence was used to calculate \(T1\) values; to achieve this, the same volume was repeated with destruction of the residual magnetization, keeping the values of \(TR\) and \(TE\) constant but gradually changing the flip angle. The total acquisition time was approximately 17 min for the complete study.

Image analysis

In the first gradient echo images, the cartilage was selected by using a partially automatic segmentation based on intensity thresholding to minimize the variability caused by the user\(^1\)\(^7\). After identifying the cartilage, manual correction adjustments were made for the cases where the method did not automatically split the patellar cartilage from the femoral cartilage. Once the complete segmentation of the patellar cartilage was complete, it was used as a mask for the \(T1\) calculation. Since the resulting images had a lower spatial resolution, it was necessary to perform a bicubic interpolation to ensure spatial coherence. Figure 1 shows an example of patellar cartilage segmentation using this methodology.

The calculation of the \(T1\) value for each pixel was made based on the equation that relates the intensity to the flip angle and the \(TR\) and \(T1\) times for a spoiled gradient echo sequence, assuming that \(TE ≪ T2^*\):

\[
S(α,x,y) = M_0(x,y)\sin α \frac{1 - \exp[-TR/T1(x,y)]}{1 - \cos α \exp[-TR/T1(x,y)]}
\]

In this equation, \(S(α,x,y)\) is the signal for a pixel located at coordinates \((x,y)\), \(M_0(x,y)\) corresponds to the thermal
equilibrium magnetization and $T1(x, y)$ is the value of the native $T1$ that has to be calculated. From this formula, we obtain $S$ values for individual pixels, as well as flip angle values and $TR$, which does not vary through the sequence. It is therefore possible to calculate $M_0$ and $T1$ values for each pixel in the cartilage. We used a least squares curve-fitting method. Thus, when fitting a curve to the signal variation with the flip angle, we obtained the $T1$ value for each pixel (fig. 2). After adjustment for each pixel, a parametric color map was automatically generated, showing regional variations in the $T1$ values for patellar cartilage.

$T1$ measurements were obtained for all the cartilage (overall averaged $T1$) and also for those areas labeled as normal, early or advanced degeneration, according to the modified criteria of Outerbridge for MRI ($T1$-specific areas). These specific areas were manually selected by an experienced radiologist on previously segmented cartilage. All image analyses were performed using a software tool for quantification.

**Statistical analysis**

To analyze differences, an ANOVA test was used with the Student-Newman-Keuls post-hoc analysis to evaluate the differences from group to group (normal-initial-advanced). We considered $p$ values $< 0.05$ to be statistically significant.
To study the reproducibility of $T1$ calculations, we evaluated the images corresponding to five cases selected at random (2 normal, 2 initial and 1 advanced), with two measurements one week apart. To obtain variability, a coefficient of variation was used, and was calculated as follows:

$$\text{RMS}_\text{CoV} = \sqrt{\frac{\sum_{i=1}^{N} (\sigma_i - \mu_i)^2}{N}}$$

where $\sigma_i$ is the standard deviation, $\mu_i$ is the median for each pair of measurements and $N$ is the number of cases. Low values for this parameter correspond to a high reproducibility.

We also analyzed the variability associated with the MRI acquisition, so that for five subjects (two normal, one initial and two advanced), we acquired, in each study, two times the images with the sequence for $T1$ acquisition, calculating the mean $T1$ values for each acquisition and obtaining the associated coefficients of variation.

### Results

Table 3 shows the results for the distributions studied (overall analysis and regional analysis). We found significant differences between groups (ANOVA, $p = 0.029$) in the regional but not in the global analysis.

The Student-Newman-Keuls post-hoc test showed that statistically significant differences occurred between the normal and initial degeneration groups and the group of advanced degeneration (Fig. 3).

In the reproducibility analysis, a variation coefficient for $T1$ of 1.3% for the global analysis methodology, 3.7% for the methodology of analysis by region and 8.2% for acquisition can be considered indicators of high reproducibility.

### Discussion

This study has demonstrated the usefulness of calculating the longitudinal relaxation time $T1$ as a biomarker to evaluate differences among the various degrees of patellar cartilage degeneration. $T1$ parametric maps allow visualization of regional anomalies (fig. 4) and objective measurements using regions of interest on the most affected areas. The utility is greater when analyzing $T1$ data regionally.

The studies that have been published in recent years on the quantitative parameters of cartilage derived from MRI have focused primarily on calculating the $T2$ and $T1rho$ values. This information, along with volumetric quantification of cartilage, has complemented conventional radiological assessments based on the grading system proposed by Outerbridge.

However, to date there have been no studies on the viability of native $T1$ as a biomarker of cartilage degeneration. This deficiency is probably due to the excessive length of traditional MRI sequences necessary for its calculation, requiring multiple inversion-recovery times on the order of seconds, which has prevented its use in studies with a large population of subjects.

Fortunately, improvements in equipment and MRI sequences have allowed more rapid acquisition techniques based on spoiled gradient-echo sequences. This advantage, coupled with knowledge of the associated physical basis and with an adequate methodology design, has allowed the calculation of $T1$ maps in the order of minutes.

The possibility of calculating regional $T1$ values of cartilage provides an opportunity to gain greater knowledge about the molecular composition of tissues and to apply new methodologies to obtain additional biomarkers (e.g., for converting signal intensity values to contrast media concentration values in order to calculate pharmacokinetic parameters that characterize the tissue microvasculature). Another added value of knowing the $T1$ values of tissues is to optimize the acquisition of MRI sequences based on those times.

In this paper, we have studied only 15 patients with different degrees of patellar cartilage degeneration. This sample is relatively low for such a high-prevalence disease.

| Table 3 T1 values in milliseconds obtained by global and regional analysis for each group of subjects |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Normal                          | Initial degeneration            | Advanced degeneration           | p                               |
| Global analysis                 | 1,003 ± 172                     | 1,064 ± 124                     | 1,041 ± 308                     | 0.665                           |
| Regional analysis               | 908 ± 53                        | 1,057 ± 157                     | 1,133 ± 116                     | 0.029                           |

Values are expressed as mean ± standard deviation.
and we recommend that future studies include a larger sample size. Moreover, the classification of patients in each group has been established following conventional criteria, including clinical and imaging criteria, because none of the patients had an arthroscopic examination, which is considered the standard technique for the clinical assessment of cartilage joint degeneration. The representation of $T_1$ maps as colored parametric images (fig. 4) permits the study of the cartilage in a regional form and helps to obtain a more precise and localized characterization of cartilage degeneration. This study demonstrated that the use of traditional statistical measures (means and standard deviations) is not adequate to characterize the cartilage in a global manner. In these cases, the effect of the mean masks any variation in the values that would indicate a greater degree of cartilage degeneration. The use of these parametric maps is therefore recommended in order to evaluate the cartilage at the global level and to promptly identify any severely affected areas.

In conclusion, this preliminary study has shown that the longitudinal relaxation time ($T_1$) of the cartilage allows discriminating between normal or initially degenerated cartilages and cartilages with advanced degeneration. These results must be validated in future studies that include larger numbers of patients.

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Authors Roberto Sanz Requena and Luis Martí Bonmatí designed the study and drafted the manuscript; Vicente Hervás and María Vega contributed to the clinical analysis and diagnoses via images; José Miguel Carot contributed to the statistical section, and Angel Alberich Bayarri and Gracián García Martí contributed their critical reviews. All authors have read and approved the final version of the article.

Conflicts of interest

The authors declare no conflict of interest.

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