

Continuing medical education

## New imaging techniques in the evaluation of joint cartilage <sup>☆</sup>

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### ABSTRACT

Magnetic resonance (MR) imaging provides an excellent spatial resolution to visualize cartilage and define its main properties. Both 1.5 and especially 3 Tesla equipments have become very efficient in showing the whole joint cartilage and classifying the degenerative damage by analyzing morphological, structural, and physical properties. MR evaluation of joint cartilage is of great clinical importance due to the prevalence of degenerative lesions and the development of new drugs and surgery-based treatments.

In this work we explain the advances in the MR quantization of the joint cartilage properties, particularly focusing on T2 and T1 relaxation times, the distribution of first-pass contrast agent (pharmacokinetic study) and late enhancement percentage. By using specific sequences and adequate measuring techniques, MR allows the evaluation of important parameters such as cartilage surface, thickness, and volume; signal intensity and the physical properties related to collagen integrity and edema; cartilage perfusion and endothelial permeability related to neovascularization; and the presence of late enhancement areas, related to proteoglycan concentrations.

This information will aid early diagnosis, establishment of the degree of degeneration, assessment of prognosis, definition of therapeutic options, and evaluation of treatment effectiveness. The study of the cartilage structural and functional alterations by MR imaging is an excellent biomarker of tissue degeneration.

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## Nuevas técnicas de imagen en la valoración del cartílago articular

### RESUMEN

La resonancia magnética (RM) brinda una excelente resolución espacial para observar el cartílago y una gran definición de sus principales propiedades. Los equipos de 1,5 teslas (T) y, principalmente, los de 3 T se demuestran muy eficaces para visualizar todo el cartílago articular, y mediante el análisis de propiedades morfológicas, estructurales y físicas estratificar el daño degenerativo. La evaluación mediante RM del cartílago articular tiene una gran relevancia clínica dada la prevalencia de lesiones degenerativas y el desarrollo de nuevos medicamentos y de tratamientos de base quirúrgica.

En este trabajo se analizan los avances de la cuantificación mediante RM de las propiedades del cartílago articular, en concreto, los tiempos de relajación T2 y T1, la distribución del primer paso de un medio de contraste (estudio farmacocinético) y el porcentaje de realce tardío. Mediante el empleo de secuencias específicas y técnicas de cuantificación adecuadas, la RM permite evaluar parámetros tan importantes como la superficie, el espesor y el volumen del cartílago; la intensidad de la señal y las propiedades físicas relacionadas con la integridad del colágeno y el edema; la perfusión del cartílago y la permeabilidad de membrana relacionada con la neovascularización y la presencia de áreas con realce tardío, relacionadas con la concentración de proteoglicanos.

Esta información puede ayudar al diagnóstico precoz de la enfermedad, establecer el grado de afectación, valorar el pronóstico, incidir en la decisión terapéutica y evaluar la eficacia del tratamiento. El estudio de las alteraciones estructurales y funcionales del cartílago mediante RM es un excelente biomarcador de la degeneración del cartílago.

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#### Palabras clave:

Cartílago

Resonancia magnética

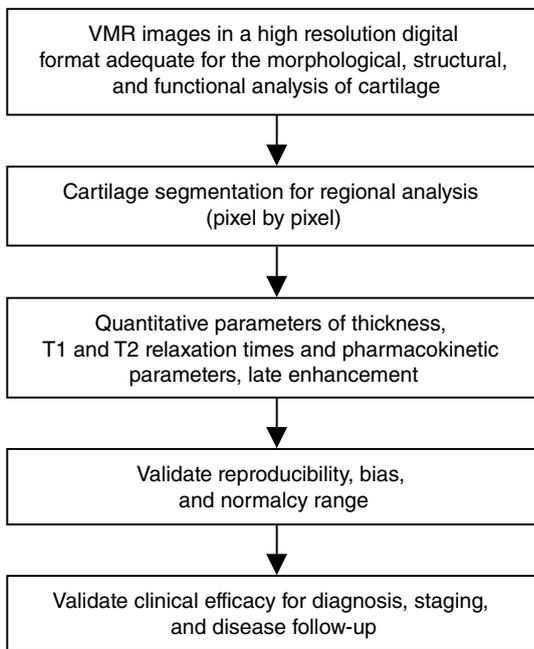
Biomarcadores

Artrosis

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**Figure 1.** Process necessary to regionally quantify variations in the different parameters obtained from magnetic resonance (MR) images of cartilage.

## Introduction

Magnetic resonance imaging (MR) offers excellent resolution of the contrast between soft tissue and a great definition of anatomical structures and its lesions. Equipment with 1.5 tesla (T) coils and mainly those with 3 T coils are very effective in visualizing in a non-invasive way all of the joint cartilage and performing an analysis of its structural, biochemical and physical properties.

This paper analyzes advances in MR quantification of joint cartilage, concretely T1 and T2 times of relaxation, the first step distribution of a contrast agent (pharmacokinetic study) and the late enhancement percentage. It is very likely that these forms of joint cartilage image analysis represent effective biomarkers of its deterioration.

In order for these contributions to be useful, they must be based on preliminary premises (Figure 1). Images must be of a digital nature, in standard DICOM (Digital Imaging and Communication in Medicine) and with a high resolution in order to allow their processing and quantification with specialized software. The analysis must be performed pixel by pixel in order to visualize regional alterations of the joint cartilage through parametric images in which the quantified values are represented by a color scale superimposed to the original image. Results must be reproducible and trustworthy and must be subject to averaging in order to obtain population studies and allow for the establishment of relationships to disease, prognosis and response to treatment.

## High resolution images of joint cartilage

Cartilage signal evaluation, the integrity of its surface, its thickness and volume are very important elements in its analysis. The most effective sequences are those that have a high spatial resolution (size of the small voxel) and contrast (cartilage is well differentiated from fat, effusion, and its lesions). They are based in volumetric acquisitions (tridimensional) potentiated in T1 (echo gradient [EG]) or T2 (EG or turbo spin echo). Fat signal suppression facilitates the visualization of cartilage and its separation from the rest of the structures. Separation of cartilage from neighboring structures

(tissue segmentation) can be performed semi automatically through different computer processes such as umbralization, seeding, outline models, and other algorithms.

Thickness varies in a same individual, being higher in the patella and lower in the terminal cleft of the femoral condyle and the lateral tibial plateau. A good tool with a high reproducibility is planar visualization of the thickness of cartilage represented as a parametric lesion on which, in addition, the total volume of cartilage is measured. The normalized volume in the area presents a precision of 3% in equipments with 3 T and of 14% in equipment with 1.5 T.<sup>1</sup>

Because cartilage defects are initially focal and their size is similar to the variation between the measurements of total cartilage thickness, thickness-map based techniques are necessary to diagnose, stage, and follow up the progression of these lesions.

These high resolution images and especially those with T2 potentiation allow for the visualization of rows of chondrocytes as a laminar structure related to the orientation of collagen fibers. The size and signal of these bands is dependent not only on its structure but, unfortunately, of the MR sequence employed and the orientation of each part of the cartilage with respect to the main magnetic field.<sup>2</sup>

These high resolution sequences have a very high sensitivity ( $\approx 85\%$ ) and specificity ( $\approx 95\%$ ) for the evaluation of lesions. The challenge of these techniques is to improve the visualization of lesions by delamination, break-up, fissures, and fibrillation.<sup>1,2</sup>

## Imaging in T2 relaxation time

T2 is related with the capacity of protons to move and exchange energy in the cartilage matrix. T2 vary according to the integrity of tissue. Cartilage T2 varies from the deep layer, where it is shorter, to the superficial one, which shows a greater intensity in these sequences.

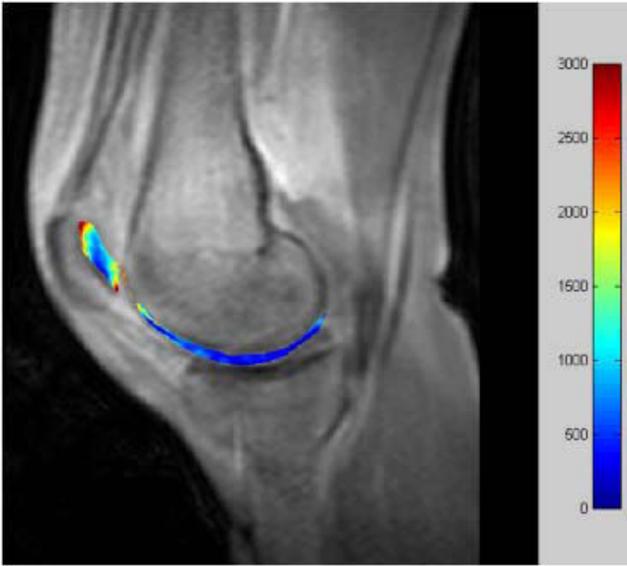
Joint cartilage is mainly influenced by the relative content of water in the pixel and, to a lesser degree, also by the integrity of the collagen matrix.<sup>3,4</sup> There are some clinical studies that calculate T2 images with parametric maps characterizing the presence and severity of cartilage degenerative disease.<sup>5,6</sup> It must be taken into account that this parameter increases with age in the subjects, making local changes more relevant than global changes. Unfortunately, this T2 value is also influenced by the orientation of the collagen fibers due to the magical angle effect, which discreetly reduces its specificity.<sup>7</sup>

Parametric maps of the cartilage T2 values permit collagen's regional composition evaluation and the proportion of water. Both factors are altered in cartilage lesions.

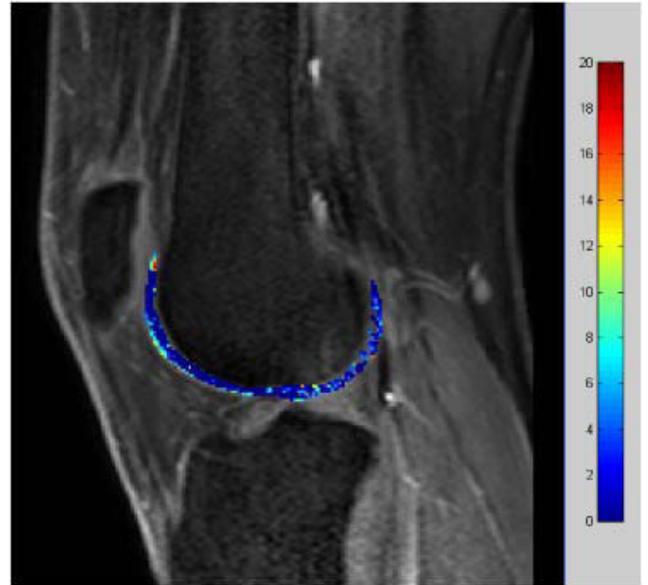
## Images in T1 relaxation time

There are studies that have shown that cartilage T1 varies with the disease and are prolonged. These values can be calculated with adequate sequences and techniques, mainly through the use of consecutive images of the same region with the variation of the angle of the EG sequence. Parametric maps of T1 values represent an excellent approach to the molecular basis of cartilage degeneration (Figure 2).

T1 has been demonstrated as predictor of degeneration, even before morphologic changes and cartilage signal alterations are present in T2 potentiated images.<sup>8</sup> Its variations are probably related with different proteoglycan concentration and properties of the disease,<sup>6</sup> because they have been shown to slowly increase with the subjects' age.<sup>8</sup> In addition, they are also necessary for the resulting calculation of other later parameters in the process that will now be explained (such as pharmacokinetics and late uptake).



**Figure 2.** Parametric image of the T1 relaxation time of cartilage with a 3 tesla coil.



**Figure 3.** Image of the pharmacokinetic parameters of capillary permeability of cartilage in a normal subject studied with a 3 tesla coil

### First contrast pass images: pharmacokinetic analysis

Pharmacokinetic analysis is based on bi-compartment models (vascular and extracellular extravascular space) to study the properties of tissue microvascularization.<sup>9</sup>

Of the serial images obtained after the rapid administration of bolus contrast, the tissue uptake compartment is analyzed from arterial entry. Through mathematical calculations and adjustment, the tissue pharmacokinetic parameters of vascular permeability are obtained from the vessel ( $K^{\text{trans}}$ ) (Figure 3), the interstitial exchange volume fraction ( $v_e$ ), the interstitium to vessel extraction coefficient, and the interchangeable blood volume fraction.

Some studies suggest that the relationship between the increase in these parameters and a larger degree of joint cartilage degeneration exists. Therefore, it has been demonstrated that there are statistically significant differences between normal cartilage, chondromalacia and osteoarthritis for  $K^{\text{trans}}$  and  $v_e$ , with very significant increases as the disease progresses (Figure 4). The values are, in addition, reproducible with less than 15% variation between equipment with 1.5 T<sup>10</sup> and even for equipment with less field intensity.<sup>11</sup>

### Late enhancement images

In MR performed after the administration of contrast, this is slowly distributed into cartilage. After approximately 2 hours and with patient having walked for at least 10 minutes, its distribution in cartilage is proportionally inverse to the concentration of proteoglycan and glucosaminoglycan.

Known as dGEMRIC (delayed gadolinium-enhanced MRI of cartilage), it is based on the fact that negatively charged contrast will distribute in regions with less concentrations of proteoglycan and glucosaminoglycan, or in regions that have been damaged.<sup>13,14</sup> It is because of this that T1 parametric images, directly proportional to the local amount of contrast, can be considered as indications of the concentration of these macromolecules. Because proteoglycans are critical for maintaining the mechanical properties of the cartilage matrix and are affected early on in degeneration, this technique is an

early and effective biomarker to diagnose the disease and follow up on the efficacy of a therapeutic process.

Because contrast is negatively charged, it will be rejected by the also negatively charged proteoglycans. Those areas with less proportion of proteoglycans retain this contrast longer and its distribution can be seen with precision by quantifying lineal T1 cartilage. It has been shown that in cartilage degeneration, earlier damage to the cartilage matrix is produced.<sup>12</sup>

### Other techniques

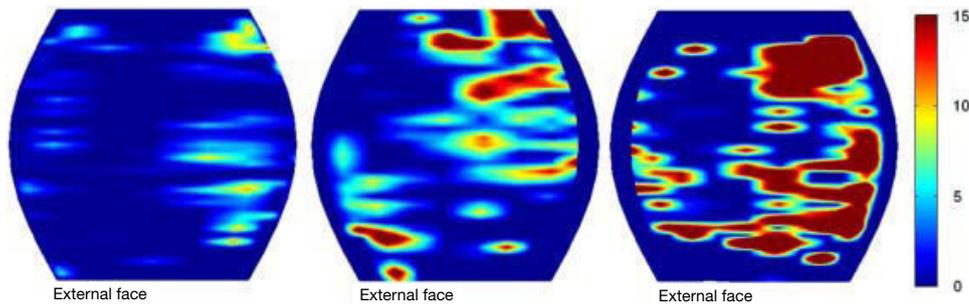
One of the MR techniques that has been more important in the early evaluation of cartilage damage has been the transference of magnetization. The intensity of this sequence is sensitive to collagen concentrations and alterations in other macromolecules. Unfortunately, these changes are small and their quantification varies with the pulse sequence and the MR equipment employed.

Other techniques that may result effective in the short term are sequences that use a very short sampling time (echo time). Because joint cartilage has a relatively short T2 time (10 to 40 ms), the use of sequences with ultra-short echo times (less than 1 ms) produces images in which macromolecule bound water and collagen present individual signals.

### Conclusions

Evaluation through MR imaging of joint cartilage is of great relevance given the prevalence of degenerative lesions and the development of new drugs and surgical treatments.

Through MR and the use of specific sequences and adequate quantification techniques, the surface, thickness, volume, signal intensity and physical properties (related with the integrity of collagen and edema), perfusion and membrane permeability (related with neovascularization), and the presence of areas of late enhancement (related to proteoglycans) can be evaluated. The adequate use of this information can help in an early diagnosis of the disease, establishing



**Figure 4.** Progression of capillary permeability with a degree of cartilage degeneration (normal, initial cartilage disease, and advanced cartilage disease).

the degree of affection, evaluating prognosis, influencing therapeutic decisions and evaluating the efficacy of treatment. The study of structural and functional alterations of the cartilage through MR is an excellent biomarker of cartilage degeneration.

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