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Tesi di Specializzazione

# Ultra-high-field (7 Tesla) MRI study of the articular cartilage in normal subjects: a work in progress

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## Abstract

*Objective:* The purposes of this study are to optimize cartilage-dedicated sequences for in vivo articular cartilage imaging at 7 Tesla MRI and to investigate the diagnostic potential of UHF in detecting early changes of the articular cartilage related to the physiological aging, focusing on the feasibility and the results of in vivo T2 and T2* mapping.

*Materials and methods:* Until now 12 healthy subjects of different age (<50 yrs, n=7, mean age = 37.32 ± 10.21; >50 yrs , n=5, 58.7 ± 5.14) were recruited for the study. Inclusion criteria were absence of clinical symptoms and no history of previous knee surgery or significant knee trauma. All the subjects underwent MR knee examination at 7 T whole-body system.

*Results*: The mean T2 and T2* maps values were obtained for all 12 subjects. The average T2 maps values were 26,5 ms ± 1,5 and 29,5 ms ± 1,7 respectively for under 50 years and over 50 years aged subjects. The mean T2* maps values were 21,1 ms ± 2,2 and 25,6 ms ± 1,6 for under 50 years and over 50 years aged volunteers respectively. Our preliminary data revealed a significant correlation between both the increase in the T2 and T2* maps values and subjects age (p=0,0192* and p=0,082* respectively).

*Conclusion:* The number of subjects imaged until now it is still limited but according to our project, totally 30 subjects will undergo MR examination. We cannot have precise data at the moment. However we obtained the mean T2 and T2* values for under 50 years and over 50 years aged subjects. Our preliminary data revealed the T2 and T2* values increase with the subjects age, in according to literature data. An expansion of the sample in study will be necessary to describe the extent of this correlation.

**Keywords** Magnetic resonance imaging, Cartilage imaging, Ultra-high-field technology, 7 Tesla

## Introduction

Cartilage is a connective tissue structure composed of a collagen and proteoglycan-rich matrix and a single celltype: the chondrocyte. Hyaline cartilage is the predominant type in the human body and forms all diarthrotic articular surfaces [1]. Healthy articular cartilage is ideally suited to provide the resilient load-bearing, energy-dissipating lubrication and frictional properties [2]. The cartilage matrix consists predominantly of extracellular water (66–78%) with the remaining (dry) weight composed of proteoglycans (PGs), collagen, and additional specialized proteins.

PGs are directly responsible for the high water content of cartilage; they are molecules referred to as aggrecans that consist of central protein cores with a long extended domain to which many glycosaminoglycan (GAG) side chains are attached. Chondroitin sulfate (CS) is the predominant GAG molecule found in cartilage. PGs give articular cartilage its stiffness to compression, resilience and durability.

The articular cartilage may be divided into four zones (superficial, transitional, deep, and calcified) [1,3] according to the different orientation of the collagen fibers and the different distribution of the chondrocytes. Articular cartilage undergoes significant structural, matrix composition and mechanical changes with age. Alterations in aggregating PG are among the most striking matrix changes; the size of these aggregates decreases significantly with age, perhaps in relation to the alterations in chondrocytes synthesis of PGs and the chondrocytes responsiveness to anabolic growth factors related to their progressive senescence [3,4].

Due to aging population and increasing prevalence of osteoarthritis (OA) which is set to become the 4th-highest impact condition in women and the 8th-most important in men all over the world, [5] imaging of cartilage, one of the most important biomarkers in degenerative and joint disease, has become a topic of growing interest.

MRI has been established as the standard cartilage imaging technique and it is the only modality that allows direct visualization of cartilage with sufficient contrast. It has already been recognized as the most important non-invasive diagnostic modality in particular for the assessment of anatomical and morphological cartilage status. Anyway changes in cartilage physiology prior to morphological ones, cannot be visualized or measured with conventional MRI, although detecting these subtle changes is a priority due to the importance of diagnosing and managing disease at its earliest stages [6].

To improve the MRI accuracy new-dedicated sequences have been proposed in order to obtain biochemical information about cartilage composition. Actually, quantitative MRI collects information about the tissue rather than just the anatomy, such as the amount and quality of the cartilage, evaluating matrix composition regarding PGs concentration and collagen integrity. This can allow objective evaluation of cartilage health.

New therapeutic modalities, both on surgical (cartilage repair) and pharmacological level, motivate the development of techniques to assess morphology, but also to quantify volume and to analyze biochemical composition of cartilage. For quantitative assessment of cartilage status, MR sequences have to present high (signal to noise ratio) SNR, high contrast to noise ratio (CNR) and high-spatial resolution; they should minimize image distortions and should be fast [7]. Compliance with these requirements translates into easier cartilage segmentations that also require less user interaction, yielding more accurate and precise measurements. Unfortunately, there is interdependency among these MRI parameters, so improvement of one factor results in detrimental of another. There must be sufficient SNR and CNR to accurately delineate the bone cartilage interface and the articular surface both in healthy and diseased joints. High SNR means that the cartilage signal should be considerably higher than that of the background noise. High CNR is necessary to easily distinguish cartilage from other tissues. High SNR together with high CNR facilitate the delineation of cartilage boundaries during segmentation. Further increase in SNR and CNR is accomplished by eliminating fat signal from surrounding bone structures that also helps to minimize image distortions due to the different magnetic susceptibilities of fat and cartilage, as well as to minimize the chemical shift artifact.

For the past 20 years, medium and high-field (1-3 Tesla) MRI have represented the standard for routine clinical applications, as well as for clinical MRI research. The clinical benefits of an approximately twofold increase in SNR of the 3T MRI technology compared to the standard ones, consist predominantly in the opportunity to put together morphological and functional methods such as metabolic, functional and diffusion-weighted imaging [8]. In the early 2000s, Ultra High Field (UHF) 7 Tesla (7T) MRI becomes available, under ethical committee permission, for human clinical research. UHF unit installations worldwide are approximately 40 to date [9], but still today the majority of studies are focused on neurological applications, while just a few 7 T sites work on whole-body clinical research [9,10]. This is mainly for the limited availability of suitable 7 T coils, which must be transmit-and-receive ones [10].

At 7 T, the larger susceptibility effect compared with 3T results in more informative images with an increased contrast between different components of the same volume [11]. Because image SNR increases approximately linearly with the magnitude of the main magnetic field, the “extra” SNR available at 7 T will guaranteed a better image spatial resolution and faster scanning speed [12]. This is beneficial for MRI of cartilage; since it has only 1–4 mm thickness and long scan times are required in order to obtain images of cartilage with high resolution. However, also disadvantages occur at UHF MRI, such as the not clinical use FDA-approval, increased B0 and B1 magnetic field inhomogeneities, greater chemical shift artifacts from fat and in particular the amplified Specific Absorption Rate (SAR), related to the increased radiofrequency (RF) power deposition that is known to increase with the square of the magnetic field [13]. Different techniques for its mitigation, such as parallel imaging or flip angle modulation, may have to be applied at the cost of the SNR [10-13].

Variations in field strength also modify tissue relaxation characteristics necessitating an adjustment of the adequate repetition time (TR) and echo time (TE) to obtain appropriate SNR and contrast. In particular, an increased T1 relaxation time and a decreased T2 relaxation time for musculoskeletal tissues occur. Anyhow, better spatial resolution may give a more accurate visualization of morphologic features such as thickness and volume, but there are more sophisticated acquisitions providing information on biochemical composition. So an ideal MRI cartilage study should evaluate its thickness, volume, and integrity, providing also details about cartilage biochemistry and physiology including collagen and proteoglycan matrices [11-14].

Due to the availability of an UHF MR system (7 Tesla – Imago 7), a work in progress study evaluating knee cartilage has been starting in our Institute in collaboration with Imago 7 team. Because the study is still in a phase in which we are optimizing the MR protocol and more sophisticated sequences useful for explore the GAG content of the cartilage are not available at the moment, we will focus on morphologic sequences and on T2 and T2* mapping in order to assess the normal values in young subjects and the possible subtle variations relate to aging.

**Purpose** The purposes of this study are to optimize cartilage-dedicated sequences for in vivo articular cartilage imaging at 7 Tesla MRI and to investigate the diagnostic potential of UHF in detecting early changes of the articular cartilage related to the physiological aging, focusing on the feasibility and the results of in vivo T2 and T2* mapping.

## Materials and methods

*Volunteer selection*

Our University ethics commission granted ethical approval for this study and written informed consent was obtained from all volunteers before enrolment into the study. Until now 12 healthy subjects of different age (< 50 yrs, n=7, median age: 37.32 ± 10.21; > 50 yrs , n=5, median age: 58.7 ± 5.14) have been recruited for the study. The group consisted of 10 male volunteers and 2 female volunteers. Inclusion criteria were absence of clinical symptoms and no history of previous knee surgery or significant knee trauma. Exclusion criteria were knee joint pain or discomfort, and contraindications to MRI.

*Imaging acquisition*

All the subjects underwent MR knee examination at 7 T whole-body system (Signa, GE Medical Systems, Waukesha, WI, USA) in the supine position with the extended knee tightly fixed.

First step: surface 2 channel coil, created by IMAGO7 team and placed anteriorly over the knee to get more signal from the femoro-patellar joint and parallel to B0.

Second step: 8-channel volume coil able to explore the whole knee.

MR protocol included: 3D bSSFP fast imaging employing steady-state acquisition (FIESTA), multiple-echo recombined GRE (MERGE), coherent oscillatory state acquisition for the manipulation of image contrast (COSMIC), GRE T2* Map using 3D T2 star-weighted angiography (SWAN), multi-echo SE T2 for T2 Mapping, 3D fast spoiled gradient echo (FSPGR) with fat saturation. We used a surface coil named “Rossella” created by Imago team at the

beginning of the study, by which 4 subjects were scanned, then the eight-channel high-resolution knee joint coil, called “Kneena” was available.

For T2 relaxation, an axial or sagittal, me-SE sequence with 8 echoes was performed, whereas T2* relaxation was obtained by an axial 3D T2 SWAN.

Technical parameters were:

- FIESTA: TR/TE of 5/2 ms; bandwidth of 41 KHz, slice thickness of 0.6 mm, NEX 1, FOV 12-15 cm, time acquisition of 2:30 min.

- FSPGR: TR/TE of 16/4ms; bandwidth of 19 KHz, slice thickness 1.2 mm, NEX 1, FOV 16 cm, acquisition time 3:45 min.

- me-SE-T2 mapping: TR 1800 ms, TEs 13, 20, 26, 39, 40, 52, 60, 80 msec, NEX 1, FOV 14-16 cm; the bandwidth of 60 KHz, slice thickness of 3 mm, acquisition time 9 min.

- SWAN: TR/TE of 48/25ms, NEX 0,69, FOV 15 cm, bandwidth 41 KHz, slice thickness 1.2 mm, acquisition time 3:30 min.

T2 maps and T2∗ maps were obtained including the entire patellar cartilage using the axial or sagittal plane.

- COSMIC: TR/TE of 5.9/1.8 ms; bandwidth of 83.3 KHz, slice thickness of 1 mm, FOV 15 cm, acquisition time of 2:40 min.

- MERGE: TR/TE of 30/12.5 ms; bandwidth of 50 KHz, slice thickness of 0.5 mm, FOV of 14 cm and acquisition time of 7 min.

The parameters used for the different sequences are reported in Table 1.

*Imaging analysis*

T2 and T2* mapping were obtained with an homemade software in Matlab.

Region of interest (ROI) analyses were manually defined for evaluation. Three ROIs were manually drawn in the patellar cartilage in its medial facet, central portion and lateral facet. The three ROI measurements were repeated in three contiguous slices in the axial plane. Both the average T2 and T2* values were calculated for each volunteer. The gray-scale maps were than converted to the color-coded maps pixel by pixel, with colours corresponding to a range of T2 and T2* relaxation times.

*Statistical analysis*

Statistical data analysis was performed using JMP version 7.0 (SAS) statistics software.

One-way Anova analysis of variance was used to compare the different distribution of T2 and T2* map values between groups. A statistical comparison of age and measurements was performed by bivariate test, and a p value of .05 or less was considered to indicate significance.

*Results*

All 12 volunteers have completed MRI examination according to our study protocol, without needing to stop it early. No significant adverse effects have been reported; in particular, no volunteer has experienced warmth feelings. Two subjects warned metallic taste during MR examination and other two ones have tried feeling dizzy in particular during the sliding of the bed inside the magnet or when it stopped.

In two subjects, cartilage visualization was affected by banding artefact in the FIESTA and COSMIC sequences.

For the cartilage segmentation, we used an open source application called ITK-SNAP (3.2 version) [15]; until now, we observed the best results with the FIESTA and the SPGR sequences.

The T2 and T2* maps mean values were obtained for all 12 subjects. The average T2 maps values were 26,5ms ± 1,5 and 29,5ms ± 1,7 respectively for under 50 years and over 50 years aged subjects. The mean T2* maps values were 21,1ms ± 2,2 and 25,6 ms ± 1,6 for the under 50 years and over 50 years aged volunteers respectively. Our preliminary data revealed a significant correlation between both the increase in the T2 and T2* maps values and subjects age (p=0,0192 and p=0,082, respectively).

## Discussion

The availability of a 7 Tesla scanner, the only one in Italy at the moment, was an intriguing opportunity for us and thus we decided to exploit the benefits of the UHF system for studying the cartilage of the knee. Although the currently available sequence protocols at 7T have not been shown to be superior to 3.0 T in the assessment of cartilage [11], we do believe that research for imaging at 7.0, after the development of adequate surface coils and optimization of new generation sequences, will improve the accuracy of MRI in this field.

The first step was to optimize an MR protocol for cartilage evaluation and to do this we started with ex vivo examinations of pig leg and human femoral heads (after prosthetic implants) using the head coil. Once the first surface coil was available we began with human subjects.

The purpose of this study, started just few months ago and still on course, is to investigate the diagnostic potential of UHF MRI in detecting early changes of the articular cartilage.

For the reason, we decided to examine the knee of volunteers of different ages with no symptoms and no history of recent traumatic event or previous surgery at the knee. Since it is a work in progress, the numbers of subjects imaged until now it is still limited but according our project, totally 30 subjects will undergo MR. Consequentially, we cannot have precise data at the moment. Another important point is the recent availability of the new 8 channel volume coil that allows the entire assessment of the knee that before was only limited to the femoro-patellar joint. This new knee joint coil, that we named “Kneena” is a birdcage eight-channel high-resolution coil and represents an important technical innovation since no knee coils are commercially available for 7T MRI at the moment.

MRI has been established as the standard cartilage imaging technique and the only modality that allows direct visualization of cartilage with sufficient contrast. Changes in cartilage physiology prior to morphological ones cannot be visualized or measured with conventional MRI. The detection of these subtle changes is a priority due to the importance of diagnosing and managing disease at its earliest stages [14]. So in this study we sought to investigate the diagnostic potential of UHF-MRI with regard to early changes of the articular cartilage.

Many techniques have been developed and optimized to assess cartilage morphology, to quantify its volume and to analyze its biochemical composition. Prevention and treatment of traumatic and degenerative diseases at their earliest stages push the research in this area.

Traditional morphological MR modalities visualize cartilage defects and volumetric MRI detects volume, loss both of which are irreversible, but it would be more beneficial to characterize cartilage biochemical composition before it is lost, identifying individuals with potentially reversible changes or those who would benefit most from preventive management. Articular cartilage features such as its anatomic location, short transverse relaxation time (T2), typical geometry and small size with a thickness of only 1-4 mm, constitute a challenge for MRI. For their suitability for quantitative assessment of cartilage status, MR sequences have to present high SNR, CNR and high-spatial resolution; they should minimize image distortions and should be fast. We thought to the study of cartilage by 7T MRI because it involves the magnification of some characteristics necessarily required for cartilage imaging. The larger susceptibility effect of UHF results in more informative images with an increased contrast between different components of the same volume; the linear SNR increase with the field strength guarantees a better spatial resolution and a faster scanning speed [12]. Variations in tissue relaxation characteristics, in particular an increased T1 relaxation time and a decreased T2 relaxation time, also occur with the field strength increase. For this reason, it is necessary an adjustment of TR and TE to obtain appropriate SNR and contrast. Some studies have already pointed out that standard FSE imaging used for cartilage is not feasible at 7.0 T given SAR issues and that gradient echo sequences may be more viable [12,17]. In terms of new imaging sequences, we followed the increasing trend to move from 2D to 3D sequences. Three-dimensional sequences have been used mainly for their potentiality to allow shortening imaging time thanks to the elimination of acquisition in multiple imaging planes and visualization of smaller defects with decreased slice thickness.

The morphologic sequences we used (FSPGR, FIESTA, MERGE) needed to be optimized during the time; for example we changed the flip angle of the FIESTA from 12 to 20°, getting a better contrast between cartilage and fat. Probably, the sequences of the protocol will change again during time.

FSPGR are thin section fat-saturated T1-weighted spoiled gradient echo sequences, with fat suppression so bone displays background signal, while cartilage and joint fluid show bright and

low signal, respectively facilitating segmentation of the cartilage; on FIESTA imaging cartilage, displays intermediate signal while fluid is bright; it has been stated that FIESTA has an higher SNR efficiency than FSPGR, with contrast dependent on the ratio of the longitudinal and transverse relaxation times of a given tissue [16,17-20].

Thickness and volume are the most important morphologic features considered in quantified MRI, since cartilage thinning and loss are common pathophysiological elements of OA [6,18]. However, before performing any morphological measurement, cartilage must be isolated from the rest of the image, a process called image segmentation. Cartilage segmentation is usually performed by manually delineating its boundaries; consequently, it is a time consuming process. Up to date, there is no fully automatic cartilage segmentation technique published in the scientific literature that works well for patients with knee OA. However, scientific literature is vast with respect to semiautomatic cartilage segmentation techniques. The main goals of these techniques aim to reduce user interaction while preserving accuracy and precision.

Automatic technique and high reproducibility have to be guaranteed for segmentation clinical significance. For the segmentation of the cartilage, a dedicated software (ITK-SNAP version 3.2) [15] has been used and we are now evaluating the best sequence to be segmented to get the cartilage volume. Until now, we observed the best results with the FIESTA and SPGR sequences mainly for their high SNR and CNR and the higher cartilage signal compared to adjacent tissues, but we are still working on it. Anyhow, a better spatial resolution may give a more accurate visualization of morphologic features such as thickness and volume, but there are more sophisticated acquisitions providing information on biochemical cartilage composition.

Among the numerous features of the UHF that are seen as advantageous for the cartilage imaging, the increased strength of the B0 has led to some problems, the most important of which is the amplified SAR, related to the increased RF power deposition that is known to increase with the square of the magnetic field [10,12]. For this reason, we fix one hour as the limit examination time. Other drawbacks are greater chemical shift artifacts and B1 magnetic field inhomogeneities. The latter in particular was responsible of the banding artifacts that occurred mostly in FIESTA and COSMIC sequences of some of our cases.

Between the various techniques of quantitative biochemical imaging, great interest in the literature is focused on T2 mapping, particularly, for detecting early changes in cartilage [18-19, 21-22]. Also in this case, we changed the protocol during time switching from the Fast SE to the me-SE sequence, because the better results of the mapping. T2 relaxation times of the first 3 volunteers were performed with FSE; for the second 3 subjects we tried both me-SE and FSE, than we preferred the me-SE. The first three subjects so were scanned again to obtain me-SE sequences. In order to keep the SAR rate acceptable, we had to manually lower the transmit gain (140-150).

T2* relaxation was obtained by an axial T2 star-weighted angiography (SWAN) performed with 3-dimensional (3D) imaging.

T2 is constant for a given tissue at a given MR field strength and it is a measurable MRI time constant that is sensitive to slow molecular motions of water protons and anisotropy of the tissue matrix. The limited mobility of cartilage water within a highly anisotropic matrix is responsible of relatively short T2 values for such a highly hydrated tissue (range 15 - 60 ms) [18-21]. T2 relaxation time relates with the speed of the coherence phase loss of the hydrogen nuclei after the RF impulse. This loss of coherence determines an exponential decay of the transversal magnetization and of the MR signal. The speed of this signal decay is related to the amount of free water molecules that slow the transversal magnetization loss. Thanks to this relationship between T2 relaxation time and free water molecules, T2 mapping is a precious tool to evaluate the amount of cartilage water content and the orientation of collagen fibrils, which are important early OA, and to analyze its changes through physiological aging [18-19,23-24]. Collagen fibrils in superficial regions, closest to the synovial fluid, are oriented parallel to the articular surface to reduce friction and shear stress. In contrast, collagen in deep regions of cartilage is oriented perpendicular to the bone surface in order to anchor itself to the subchondral bone. PGs, with GAG side-chains that are rich in negatively charged carboxyl and sulfate groups present a fixed charged density (FCD) that attracts cations, such as sodium, and generates an osmotic pressure that draws water into the cartilage [1-3]. Because of this osmotic pull, water constitutes 65–85 % of the total weight of healthy cartilage [3-5]. The collagen matrix of health cartilage traps and immobilizes water protons, so signal intensity on T2w images is low. In the earliest stages of OA, prior to cartilage loss, the biochemical composition of cartilage breaks down. The concentration of PGs and GAGs decreases, leading to decreased FCD. Additionally, the structure

of the collagen matrix breaks down, and becomes more permeable to water, with water molecules content and motion increase and the subsequent degeneration and loss of cartilage tissue, causing an elevation in T2 relaxation times and an increase signal intensity on T2-weighted images [18-25]. By measuring the spatial distribution of T2-relaxation time throughout articular cartilage, areas of increased or decreased water content, which correlate with cartilage damage, can be identified. T2 mapping is a powerful tool because it provides information regarding cartilage health without the need for contrast. It is proportional to the distribution of cartilage water, inversely proportional to the distribution of PGs and sensitive to small water content changes. Thus measurement of the spatial distribution of the T2, reflecting areas of increased and decreased water content, can quantify cartilage degeneration before morphologic changes are evident. In particular, aging is associated with an asymptomatic increase in T2 of the transitional zone of articular cartilage [21-25].

In a study comparing effects of B0 field strength, Duewell et al. obtained a bulk T2 value of 39 ms at 1.5 T compared with 25 ms at 4.0 T. Kaufman and others reported in vivo values of human patellar cartilage of 35 ms at 1.5 T and 29 ms at 4.0 T[16]. Several studies from many investigators sustain that cartilage T2 value is dependent on many extracellular cartilage matrix properties, in particular on the tissue anisotropy as characterized by orientation of the collagen matrix, on collagen fibrils concentration and water content compared to its insensitivity to PGs concentration changes. Gold and colleagues obtained in vivo human patellar T2 relaxation time of 31.7 ± 3.4 ms at 7 T, with a decrease of 18.9% compared to the 3T T2 values [16].

However, one drawback is the susceptibility of T2 relaxation to the magic angle effect. Collagen fibers at certain orientations to the B0 field influence the estimation of T2 relaxation and render T2 mapping inaccurate for these regions of cartilage. Additionally, PGs depletion is believed to occur prior to degradation of the collagen matrix in OA progression, so T2 mapping may not detect changes as early as techniques sensitive to GAG content [26,27].

Other imaging techniques which offer the possibility to provide a quantitative understanding of the physiological articular cartilage content, its early damage and breakdown process include Sodium MRI, gag-CEST, delayed gadolinium-enhanced MR imaging of cartilage (dGEMRIC), T1rho mapping and diffusion-weighted imaging (DWI) [23-27].

The high magnetic field scanners, together with novel ultra short echo time pulse sequences and RF have great potential for improving the performance of multinuclear imaging.

Sodium MR imaging has been shown to strongly correlate with the GAG concentration in the cartilage and can potentially be used as a marker of cartilage health [28]. Sodium cations are attracted to negatively charged GAGs and are so distributed in accordance with their content. Like $^{1}H$, $^{23}Na$ has an odd number of protons or neutrons and therefore possesses a net nuclear spin. Imaging of cartilage in vivo using sodium MRI at high field strength has been challenging due to hardware and software requirements. Sodium exhibits a short, bi-exponential T2 relaxation, with a fast component of 0.7–3.0 msec and a slow component of 16–30 msec and a Larmor frequency much lower than the $^{1}H$ one (11262 v 42575 MHz/T) [29,30]. Additionally, the sodium concentration in the body is approximately 700 times lower than the proton concentration. Together, these properties make sodium very difficult to image with adequate SNR. Despite these challenges, sodium is the second most MR-visible naturally occurring nucleus in the body after hydrogen and Na imaging is a promising technique for cartilage evaluation. In healthy cartilage, high concentrations of positively charged $^{23}Na$ are associated with the negatively charged GAG side chains, which contain a plethora of negatively charged carboxyl and sulfate groups. When proteoglycan depletion occurs in cartilage damage, GAGs are damaged and sodium signals decline [28-30].

The GAG-chemical exchange saturation transfer (CEST), based on the magnetization transfer contrast (MTC) principle, enables to create endogenous contrast sensitive to in vivo PG and collagen content. CEST of labile –OH protons on GAG with bulk water leads to a significant reduction of bulk water magnetization creating “gag-CEST”[31]. MTC involves an off-resonance preparatory pulse that excites in a selective way and saturates immobile protons bound to macromolecules. Some of this induced transverse magnetization transfers to nearby free water protons, resulting in faster dephasing and reduced signal in free water. This creates contrast between regions with variable rates of magnetization transfer. CEST is a similar technique that saturates exchangeable protons that move from macromolecules to free water, rather than transferring magnetization to free water. In articular cartilage, hydroxyl residues on GAGs are selectively excited to provide contrast between regions of high and low GAG content.

Gag-CEST thus provides a direct measurement of GAG content, expressed as a magnetization transfer asymmetry value/percentage. Regions of low GAG content have low magnetization transfer and low asymmetry value [31,33].

d-GEMRIC provides an assessment of GAG concentration through the use of the intravenous contrast agent Gd (DTPA). Ions in the extracellular fluid are distributed in relation to the negatively charged GAGs concentration, which is a reflection of PG content. The images are obtained after 10 min of exercise and almost 90 min delay from Gd (DTPA) injection to allow for cartilage penetration. Within cartilage, Gd (DTPA) molecules encounter repulsive electrostatic forces from the negatively charged GAGs, so they are in high concentration in areas lacking in GAG and in low concentration in GAG-rich regions. Important drawbacks are the injection of a contrast agent and the added time necessary to allow the contrast to diffuse into the joint [32].

T1rho mapping is a technique sensitive to GAG content within cartilage. With this technique, a spin-lock RF pulse follows the initial RF pulse to lock protons in phase. Protons then relax in the presence of a B1 field with the time constant T1ρ, and this decay can be sampled similar to that of T2 decay to obtain quantitative measurements. Water protons that are associated with large macromolecules such as PGs dissipate energy faster than free water protons. Thus, regions of cartilage with more free water as a result of GAG depletion have longer T1ρ relaxation compared to physiologically normal regions with an inverse relationship between GAG content and T1ρ relaxation times [19,22]. As with T2 relaxation time mapping, findings suggest that increased heterogeneity of T1ρ relaxation times within regions of cartilage is indicative of degenerative changes. T1ρ relaxation time mapping has the benefit that it provides an assessment of GAG content without the need for invasive contrast agent or specialized hardware. However, this method is not as specific for GAG content as other MR methods.

The apparent diffusion coefficient (ADC) is a value which measures the translational motion of water protons. This is obtained by the application of diffusion-sensitizing gradients that break down phase coherence amongst mobile protons, reducing the MR signal from regions with mobile water [14,22]. Higher ADC values relate with more translational protons movement. The collagen matrix structure and orientation of articular cartilage influence movement of protons. When the matrix

breaks down, the movements of water increase. Thanks to this, elevated values of ADC are believed to be indicative of early changes related to the cartilage degeneration [11,14].

## Conclusion

7 T MRI gives the opportunity to study in vivo articular cartilage with better SNR and CNR than lower field strength systems; it might become an alternative to histology in defining early cartilage changes aging related, and in estimating the water and collagen cartilage content.

Since our study is a work in progress, the numbers of subjects imaged until now it is still limited but according to our project, totally 30 subjects will undergo MR examination. Consequentially, we cannot have precise data at the moment. However, we obtained the mean T2 and T2* maps values for under and over 50 years aged healthy subjects and based on our preliminary data, both T2 and T2* maps values show an increase with the subjects age. Of course, the study group need to be increase to confirm the results.

**Table 1:** Sequences parameters

| | FIESTA | FSPGR | Me-SE T2 | SWAN | COSMIC | MERGE |
|---|---|---|---|---|---|---|
| TR [ms] | 5 | 16 | 1800 | 48 | 5.9 | 30 |
| TE [ms] | 2 | 4 | 13,20,26,39,40,52,60,80 | 25 | 1.8 | 12.5 |
| BW [KHz] | 41 | 19 | 60 | 41.7 | 83.3 | 50 |
| Slice thickness [mm] | 0.6 | 1.2 | 3 | 1.2 | 1 | 0.5 |
| NEX | 1 | 1 | 1 | 0.69 | 0.7 | 0.7 |
| FOV [cm] | 12-15 | 16 | 14-16 | 15 | 15 | 14 |
| TA [min:sec] | 2:30 | 3:45 | 9 | 3:30 | 2:40 | 7:40 |

TR repetition time, TE echo time, BW bandwidth, NEX number of exitations, FOV field of view, TA acquisition time

**Figures:**

Fig. 1: FIESTA 7 T

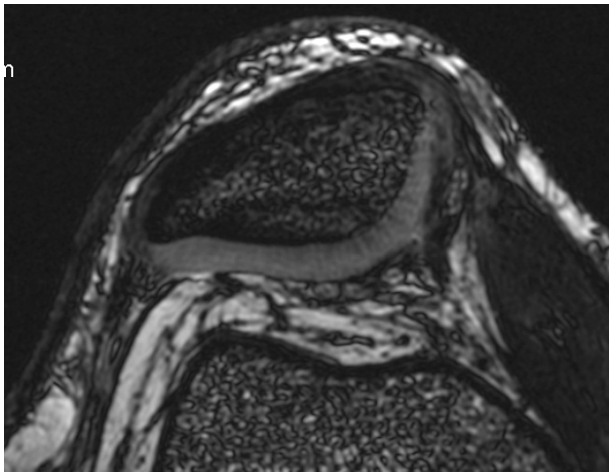


Fig. 2: MERGE 7 T

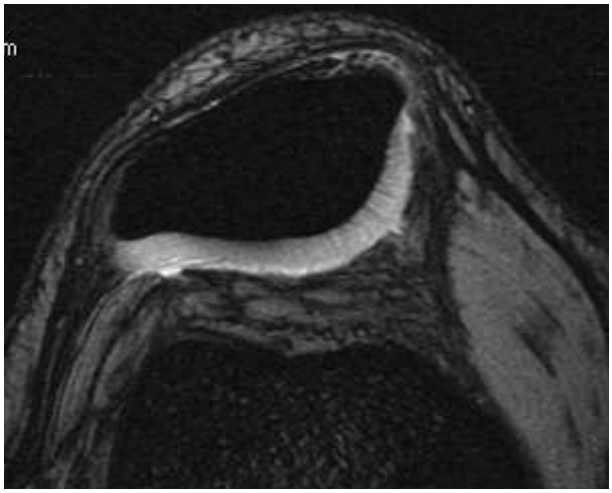


Fig. 3: COSMIC 7 T

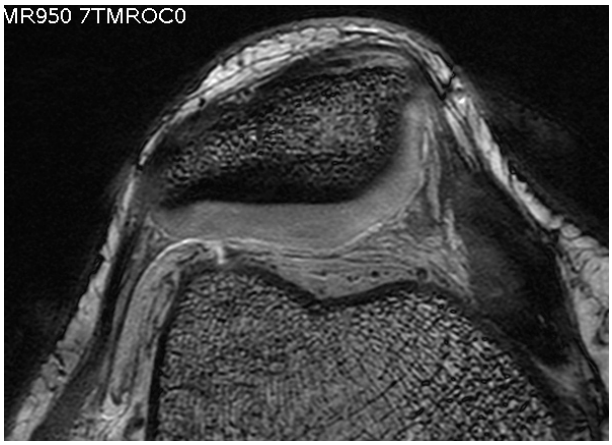



Fig. 4: FSPGR 7 T

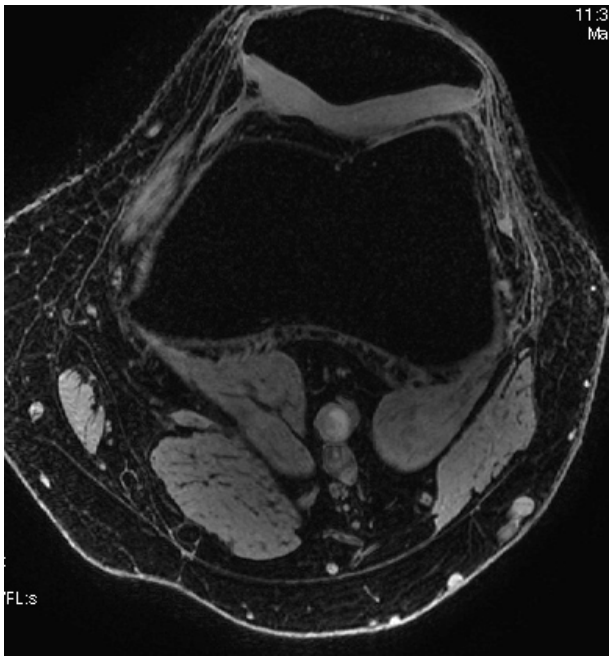


Fig. 5: an example of cartilage segmentation; ITK-SNAP (3.2 version)

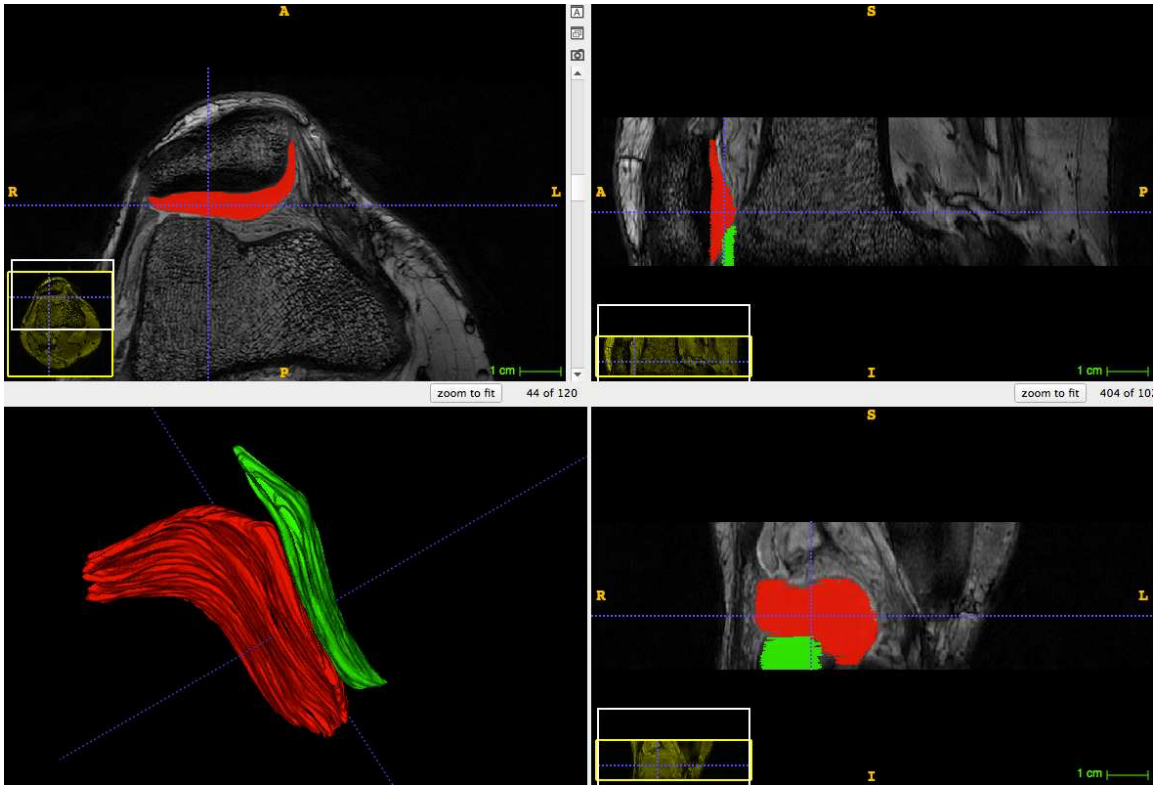


Fig. 6: mean values of T2 maps in over 50 and under 50 years aged subjects

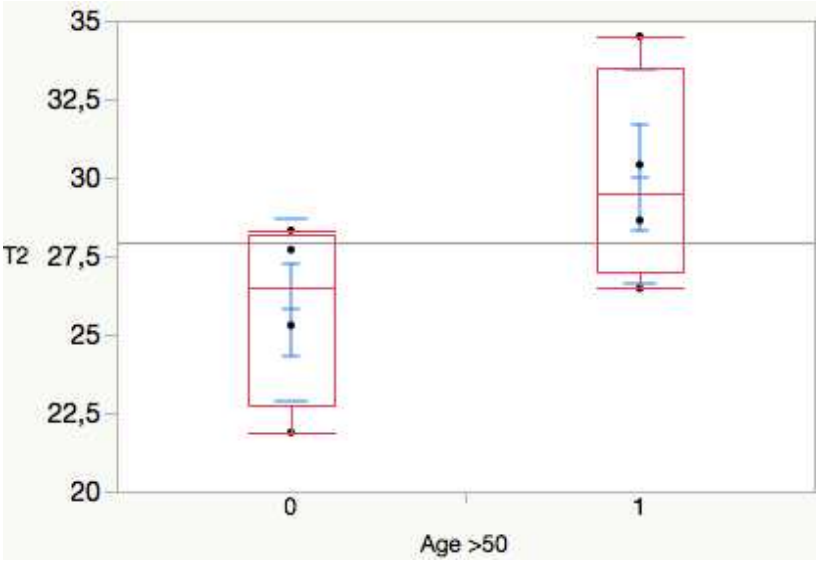



Fig. 7: mean values of T2* maps in over 50 and under 50 years aged subjects

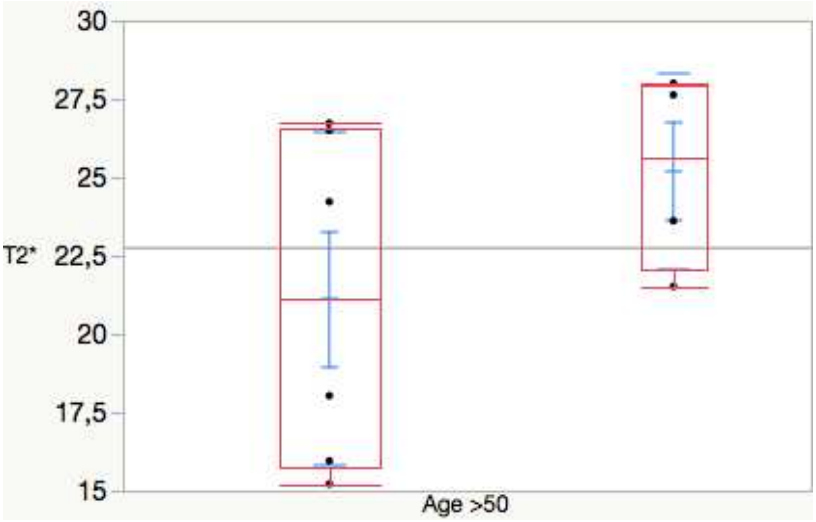
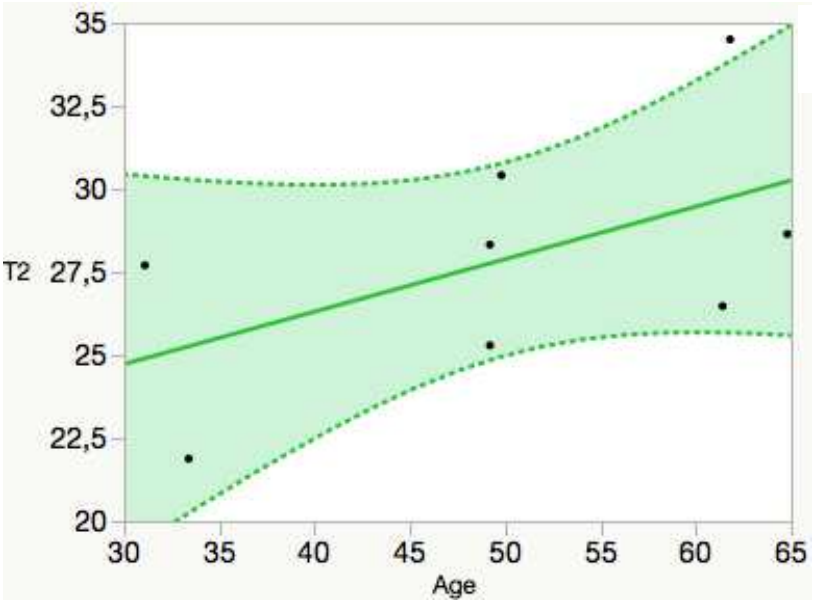
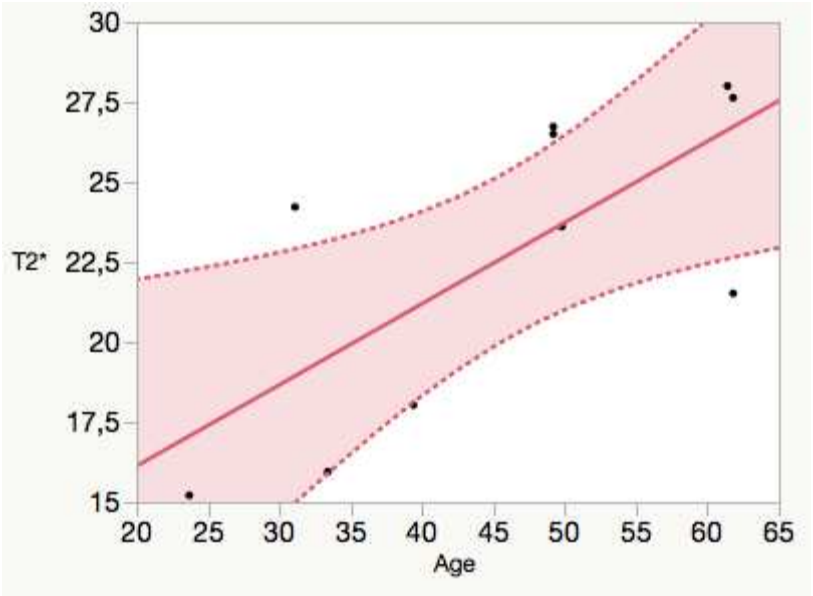


Fig. 8.a: correlation between the increase T2 map values and subjects age




a

Fig. 8.b: correlation between the increase in T2* map values and subjects age




b

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