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Articular Cartilage Mapping through Novel Advances in MRI Techniques

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ABSTRACT

Background: Magnetic resonance imaging (MRI) has emerged as a useful tool for clinicians and scientists to assess the health of cartilage and other soft tissues. Conventional MRI provides sufficient tissue contrast to detect morphological changes in cartilage where radiography cannot. However, changes in cartilage physiology prior to morphological changes cannot be visualized or measured with conventional MRI. The recent advances in MR sequences together with the implementation of higher resolution MRI due to high-field MR systems as well as sophisticated coil technology have overcome existing limitations and led to promising in vivo approaches in morphological and biochemical MRI of cartilage. Recently, quantitative MRI techniques such as T2, T2*, dGEMRIC (delayed gadolinium-enhanced MRI of cartilage), sodium imaging ((23)Na), chemical exchange saturation transfer (CEST), diffusion weighted imaging (DWI) and T1rho mapping have been shown to be sensitive to biochemical changes in cartilage. Advanced magnetic resonance (MR) sequences for cartilage evaluation are focused on the assessment of articular cartilage biochemical composition, more specifically to the collagen and glycosaminoglycan content.

Aim of the Study: The aim of this work is to emphasize the role of new advances of magnetic resonance imaging in diagnosis of cartilage disease.

Conclusion: MRI provides a powerful solution for noninvasive imaging. Improvements have been made in morphologic imaging of cartilage in terms of contrast, resolution, and acquisition time. These improvements allow detailed maps of the cartilage surface to be developed that can be used to quantify both thickness and volume.

Keywords: MRI of cartilage, cartilage mapping, glycosaminoglycan, T2, T2*, dGEMRIC (delayed gadolinium-enhanced MRI of cartilage, MR sequences.

INTRODUCTION

Magnetic resonance imaging (MRI) has emerged as a useful tool for clinicians and scientists to assess the health of cartilage and other soft tissues. Conventional MRI provides sufficient tissue contrast to detect morphological changes in cartilage where radiography cannot. However, changes in cartilage physiology prior to morphological changes cannot be visualized or measured with conventional MRI [(1)].

The recent advances in MR sequences together with the implementation of higher resolution MRI due to high field MR systems as well as sophisticated coil technology have overcome existing limitations and led to promising in vivo approaches in morphological and biochemical MRI of cartilage [(2)].

Since the introduction of MRI evaluation of joints, there has been a quest for MRI sequences that optimize articular cartilage evaluation. Over time, increased signal to noise ratio (SNR), contrast to noise ratio (CNR) and acquisition speeds have become available, along with coil and scanner improvements. Despite this, there is currently no single specific sequence that allows for one stop shopping evaluation of this complex tissue. It is generally accepted that a combination of sequences is necessary for comprehensive morphologic and quantitative evaluation. Essential requirements for evaluation of hyaline cartilage include high in plane and through plane resolution and optimal SNR and CNR, thereby avoiding partial volume artifacts and allowing differentiation from surrounding fluid and tissues. To this end, utilization of high field strength scanners and dedicated coilsis strongly advised [(3)].

Significant advances have been made in characterizing, quantifying, and standardizing the specific morphological as well as biochemical changes in patients with cartilage pathologies. Besides the exact evaluation of the cartilage defect, respectively, the cartilage degeneration, also the specific therapeutical approaches, can be assessed in best possible fashion noninvasively [(2)].

As structural cartilage damage is preceded by biochemical alterations such as proteoglycan loss, or changes in the collagen matrix, there is a substantial interest in detecting such changes in the course of cartilage disease/injury or after cartilage repair [(4)]. Recently, quantitative MRI

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techniques such as T2, T2*, dGEMRIC (delayed gadolinium enhanced MRI of cartilage), sodium imaging ((23)Na), chemical exchange saturation transfer (CEST), diffusion weighted imaging (DWI) and T1rho mapping have been shown to be sensitive to biochemical changes in cartilage. Advanced magnetic resonance (MR) sequences for cartilage evaluation are focused on the assessment of articular cartilage biochemical composition, more specifically to the collagen and glycosaminoglycan content.

Hyaline cartilage is in fact a macromolecular network that supports mechanical loads. Three quarters of its weight is composed of water and the rest is a molecular mesh composed of collagen and proteoglycans. Collagen accounts for one fifth of its volume, with aggrecanas the most abundant proteoglycan. Proteoglycans have glycosaminoglycans (GAGs) attached as side chains that are negatively charged. The preservation of proteoglycanis directly assessed by the distribution pattern of associated positively charged sodium (Na+). Similarly, regions lacking proteoglycan cause negatively charged gadolinium based contrast (Gd DTPA2–) agents to accumulate [(5)].

The study was approved by the Ethics Board of Ain-Shams University.

CARTILAGE ARCHITECTURE

Articular cartilage zones

Based upon differences in collagen fiber orientation and biochemical composition, the articular cartilage can be divided according to into the following four zones **[(6)]**:

1. The superficial or tangential zone (10–20 % of cartilage thickness; collagen fibers running parallel to the articular surface).
2. The transitional or intermediate zone (~ 60 % of cartilage thickness; random collagen fiber orientation with collagen fibers bending to form arcades).
3. The radial or deep zone (~ 30 % of cartilage thickness; collagen fibers running perpendicular to the subchondral bone providing anchorage to the underlying calcified matrix).
4. The calcified zone (cartilage–bone interface).

Superficial Zone

The superficial zone, which is the most cellular zone, has a high collagen and water content, whereas the content of proteoglycan is low **[(5)].** It is the thinnest zone of articular cartilage, with specialized mechanical and possibly biological properties. This zone typically consists of two layers. A sheet of fine fibrils with little polysaccharide and no cells covers the joint surface. This portion corresponds lamina splendens, which can be stripped from the articular surface in some regions. Deep to this acellular sheet of chondrocytes arrange themselves so that their major axes are parallel to the articular surface. The chondrocytes synthesize a matrix that has a high concentration of collagen and a low concentration of proteoglycan relative to the other cartilage zones; Concentrations of fibronectin and water are also highest in this zone **[(7)].**

The dense matrix of collagen fibrils lying parallel to the joint surface in the superficial zone helps to determine the mechanical properties of the tissue and affect the movement of molecules in and out of the cartilage. These fibrils give this zone greater tensile stiffness and strength than the deeper zones, and they may resist shear forces generated during use of the joint **[(7)].**

II. Transitional Zone

The transitional zone has higher proteoglycan content and a lower collagen and water content than the superficial zone **[(6)].**

As the name of this zone implies, the morphology and the matrix composition of the transitional zone are intermediate between the superficial zone and the middle (radial) zone. The transitional zone usually has several times the volume of the superficial zone. Cells in the transitional zone assume a spheroidal shape and synthesize a matrix that has larger diameter collagen fibrils, a higher concentration of proteoglycan, and lower concentrations of water and collagen than does the matrix of the superficial zone **[(7)].**

III. Middle (Radial) Zone

The radial zone has a high proteoglycan content (proteoglycan content is highest in the upper sector of the radial zone) while the collagen and water content is low **[(6)].** The chondrocytes in the middle zone are spheroidal in shape and tend to align themselves in columns perpendicular to the joint surface. This zone contains the largest diameter collagen fibrils, the highest concentration of proteoglycans, and the lowest concentration of water **[(7)].**

IV. Calcified Cartilage Zone

A thin zone of calcified cartilage separates the radial zone (uncalcified cartilage) from the

subchondral bone. The cells of the zone of calcified cartilage have a smaller volume than the cells of the radial zone. In some regions, these cells appear to be surrounded completely by calcified cartilage that is, they are buried in individual "calcific sepulchers" suggesting that the cells have an extremely low level of metabolic activity. However, recent work suggests that they may have a role in the development and progression of osteoarthritis [(7)].

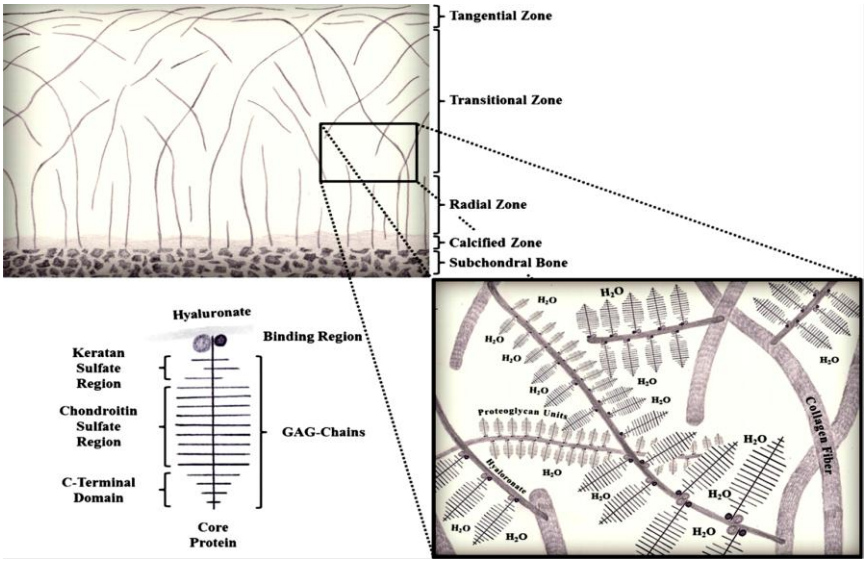


Figure (1**): illustrates:** Schematic drawing illustrating the zonal anatomy, the structure and composition of articular cartilage. The extracellular components form an interconnected lattice structure in which proteoglycan aggregates of hyaluronic acid and side units of glycosaminoglycan (GAG) chains with hydrophilic chondroitin and keratin sulfate regions bind collagen fibers and link them together. Both the high density of negatively charged GAG side chains, which attract positive ions and their surrounding fluid, and the tensile strength of the collagen network to resist this osmotic swelling, contributes to the mechanical stiffness of articular cartilage [(6)].

VARIABLE MRI TECHNIQUES USED IN EVALUATION OF CARTILAGE

In cartilage imaging high resolution MR is required due to thin cartilage layers, so it is required 1.5 Tesla MR scanner with a high performance gradient system and a dedicated extremity coil (quadrature/phased array coil) in cartilage examination. With the increasing availability of 3 Tesla clinical MR systems in routine examinations, the requirement for the best high signal to noise ratio and high resolution imaging has also been reported, 3 Tesla MR played a very significant role in musculoskeletal imaging [(8)].

Major techniques in morphological imaging of cartilage include kspin echo (SE) and gradient recalled echo (GRE) sequences, fast SE (FSE), and 3D SE and GRE. Physiological imaging techniques such as transverse relaxation time (T2) mapping, delayed gadolinium enhanced MRI of cartilage (dGEMRIC), T1rho mapping, sodium MRI, and diffusion weighted imaging (DWI), provide insight into the molecular composition of cartilage [(9)].

Differentiation between different method of morphological imaging of cartilage in comparison are demonstrated in table (1).

Table (1): Comparison between different methods of morphological imaging of cartilage [5]

MR Imaging Technique	Characteristics	Strengths	Drawbacks
2D fast SE	Standard imaging technique used in clinical and research settings; includes T1, T2, intermediate, and proton density weighted sequences	T2 and intermediate weighted sequences provide excellent contrast between fluid and cartilage	Anisotropic voxels, section gaps, partial volume effects
3D fast SE	Relies on flip angle modulation to reduce blurring, parallel imaging to reduce time for acquisition of inter mediate weighted or proton density weighted images	Isotropic voxels allow multiplanar reformatting of image data, decrease in partial volume artifacts	Has not yet replaced 2D fast SE in clinical practice
3D SPGR	Spoils the transverse steady state by semi randomly changing the phase of the radiofrequency pulse; provides T1 or proton density weighted contrast	Standard technique for 3D morphologic imaging, has higher sensitivity than routine 2D fast SE; isotropic voxels allow multi planar reformatting, decrease in partial volume artifacts	Long acquisition times, lack of reliable contrast between fluid and cartilage, vulnerability to susceptibility artifacts
3D DESS	Two or more gradient echoes, each pair separated by a refocusing pulse, are acquired, and data from both are combined in image reconstructions; higher flip angles may be used	Allows shorter acquisition times than SPGR, high SNR, and high cartilage to fluid contrast; isotropic voxels allow multiplanar reformatting, decreased partial volume artifacts	Unreliable depiction of signal intensity changes within cartilage, vulnerability to susceptibility artifacts
3D bSSFP	Steady state sequence similar to DESS but with different parameters; may be combined with a 3D radial *k space* acquisition (VIPR)	High SNR and cartilage to fluid contrast; isotropic voxels allow multiplanar reformatting, decreased partial volume artifacts	Long TR leads to banding artifacts, especially when high field strength (3.0 T) is used
3D DEFT	Active return of magnetization to the z axis after each excitation enhances the signal intensity of fluid while preserving that of cartilage	Allows diagnostic performance comparable to that obtained with 2D fast SE and SPGR techniques	Long acquisition times, frequently insufficient fat saturation
3D fast SE SPACE	Large eligible turbo factors are used with a restore pulse and variable flip angle distribution to achieve a pseudo steady state	Allows acquisition of isotropic voxels for multiplanar reformatting; has good SNR and high SNR efficiency	Long acquisition times; insufficiently validated for clinical use

NEW TECHNIQUE OF BIOCHEMICAL MAGNETIC RESONANCE IMAGING

Hyaline articular cartilage is consist of a fluid filled macromolecular network which backing mechanical loads. Through joint loading, the electrolyte consist of interstitial fluid, which represents about 75% of cartilage volume by weight, get to be pressurized to the extent where its movement is limited by the macromolecular network that dispense and backing the mechanical load. This macromolecular network composed mainly of collagen and proteoglycans. Collagen is the most copious macromolecule represent about 20% of cartilage volume by weight and aggrecan, a large aggregating proteoglycan is the second most copious. In normal joints, the collagen network acting like the structural framework for tissue supplying the main source of its shear and tensile strength. The arranged collagen network and its correlated water content cause both magic angle artifacts and magnetization transfer.

Proteoglycans have glycosaminoglycans which are covalently connected as side chains, with negatively charged carboxyl and sulfate groups. Glycosaminoglycans provide the cartilage with a massive compressive strength. Since proteoglycans have a significant net negative charge, mobile ions as sodium (Na+) and charged gadolinium based MR imaging contrast agents as gadolinium diethylene triamine penta acetic acid $(Gd\ DTPA)^{2-}$ are dispenserelated to the proteoglycan concentration in cartilage [(10)].

Since collagen and proteoglycan related glycosaminoglycan's are important to maintain the structural and functional integrity of cartilage, compositional MR imaging evaluation of cartilage is focused on its molecular status, particularly with regard to its collagen and glycosaminoglycan content [(11)]. Newer techniques to evaluate articular cartilage often depend on quantitative techniques which directly measuring the relaxation times in native cartilage or repair tissue. These techniques are guided toward an evaluation of a particular component of articular cartilage biochemistry [(12)].

Compositional evaluation includes techniques as T1*ρ*, T2 mapping, sodium imaging, delayed gadolinium enhanced MRI of cartilage (dGEMRIC) and diffusion weighted imaging. These techniques permits 'molecular' or 'biochemical' imaging of cartilage and used to detect 'premorphologic' changes within cartilage [(13)].

CURRENT APPLICATIONS OF MRI CARTILAGE MAPPING

Aging

Several investigators have studied the age dependency of cartilage T2 maps. Most studies evaluated changes in cartilage T2 in animal models during the period of skeletal maturation. In a longitudinal study of Dunkin Hartley guinea pigs, Watson and coworkers demonstrated increasing bulk cartilage T2 values from age 18 weeks to age 1 year [(13)].

Future Application: Identifying ''Cartilage at Risk''

In development of chondroprotective therapy it will be desirable to develop MRI techniques that can identify cartilage that is capable of restoration. A simila approach is currently used in evaluation of neuroprotective agents in the treatment of stroke, where a combination of perfusion and diffusion weighted imaging are used to differentiate ''brain at risk'' in the peri infarct penumbra from irreversible tissue damage. Potentially a similar multispectral approach could be developed to identify ''cartilage at risk.'' For example, using a combination of cartilage T2 mapping with proteoglycan sensitive MRI techniques such as dGEMRIC71 or T1 rho imaging, it may be possible to categorize cartilage according to proteoglycan content and collagen matrix integrity.

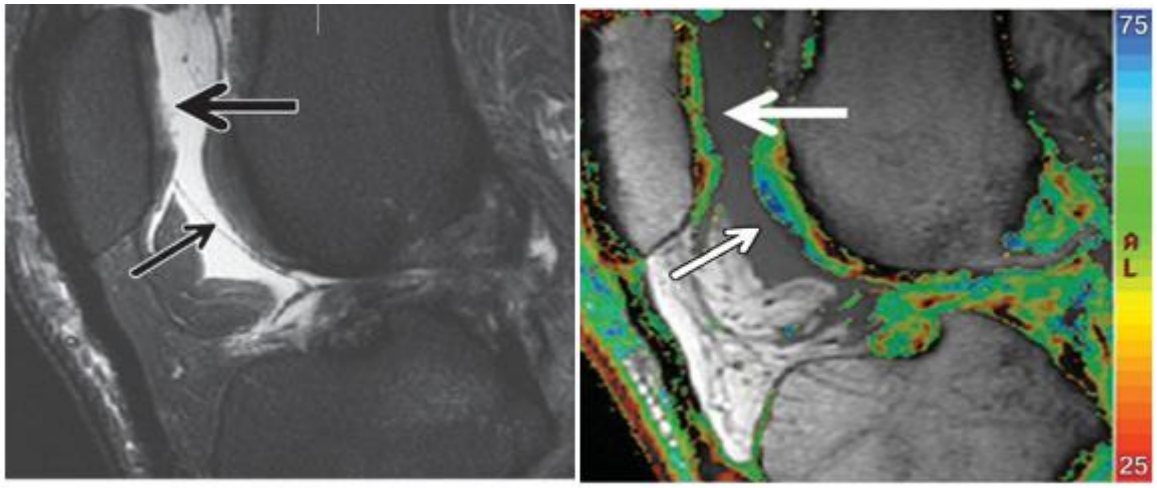
In theory, cartilage with isolated proteoglycan depletion and an intact collagen framework is less able to restrict water movement and thus ''at risk'' due to greater stress on the solid matrix; yet may be capable of functional recovery if proteoglycan synthesis is increased. Cartilage with substantial damage to the collagen matrix is unlikely to recover the fiber content and structural organization necessary for normal biomechanical function. using a combination of cartilage T2 mapping and proteoglycan sensitive parametric mapping it may be possible to identify cartilage in which there is irreversible damage to the collagen matrix (elevated T2) from that in which the collagen matrix is intact but proteoglycan concentration is low (normal cartilage T2, low proteoglycan score) [(14)].

Table (2): Summary of MR Imaging Compositional Techniques [15]

Compositional MR Imaging Technique	Cartilage Component Assessed	Strengths	Reported Applications for Cartilage Repair Imaging	Limitations
T2 mapping	Collagen network, water content	Well validated, compatible with most MR systems, does not require contrast material administration.	Evaluation of cartilage repair tissue after microfracture. Osteochondral grafting and matrix assisted autologous transplantation evaluation of graft maturation after autologous chondrocyte implantation.	Long acquisition times with multiecho spin echo sequence, cannot assess calcified cartilage at osteochondral junction
T2* mapping	Collagen network, water content	Faster acquisition than T2 mapping,does not require contrast material administration.	Used with ultrashort echo times to assess calcified cartilage at osteochondral junction evaluation of cartilage repair tissue after microfracture.	Not fully validated; susceptible to postoperative magnetic field inhomogeneities and magic angle effects
Sodium imaging	GAG	Correlates directly with GAG content, does not require contrast material administration.	Differentiation between normal articular cartilage and matrix assisted autologous transplantation repair tissue	Requires specialized hardware; long examination times; low spatial resolution
dGEMRIC	GAG	Indirect assessment of GAG content, well validated, clinically useful.	Evaluation of cartilage repair tissue after microfracture and matrix assisted autologous transplantation evaluation of graft maturation after autologous chondrocyte implantation	Requires intravenous administration of contrast material and delay between injection and imaging
Ultrashort echo time imaging	Collagen network, water content, GAG	Can be used to assess tissue with intrinsic short T2 such as cartilage near osteochondral junction; can demonstrate the calcified cartilage as curvilinear increased signal intensity just superficial to the subchondral bone.	Evaluation of the calcified cartilage layer in osteochondral allografts	Special pulse sequences only available at a few academic institutions

CASES

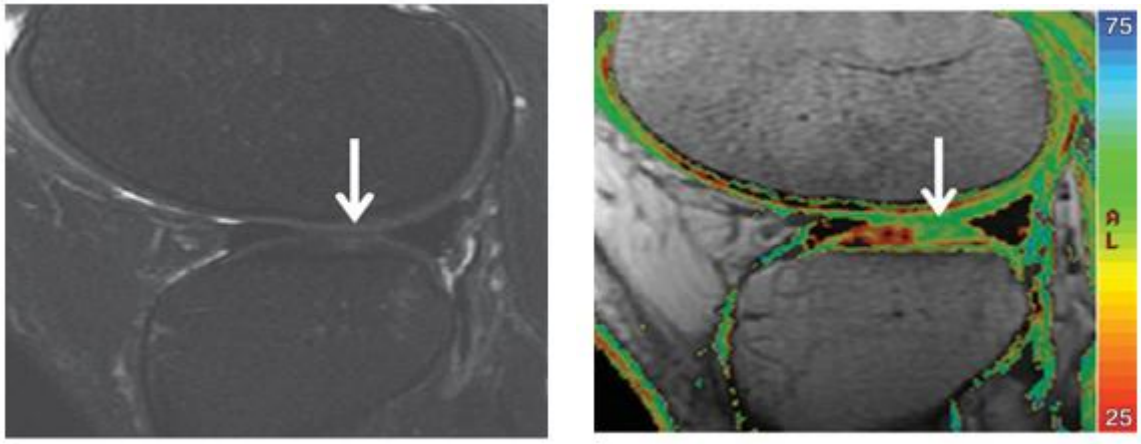
CASE (1)



a. b.

Case (1): Shows images in 46-year-old woman with surgically confirmed grade 2B cartilage lesion on patella (classified as MR grade 2B cartilage lesion) and surgically confirmed grade 1A cartilage lesion on trochlea (classified as MR grade 1A cartilage lesion). (a) Sagittal fat-suppressed T2-weighted fast spin-echo image shows partial-thickness cartilage lesion on patella (large arrow) but normal-appearing articular cartilage on trochlea (small arrow). (b) Corresponding sagittal T2 map shows areas of increased T2 relaxation time on patella (large arrow) and trochlea (small arrow) [(1)].

CASE (2)



a. b.

Case (2): Shows images in 40-year-old man with arthroscopically normal articular cartilage on lateral femoral condyle (classified as MR grade 1A cartilage lesion). (a) Sagittal fat-suppressed T2-weighted fast spin-echo image shows normal-appearing articular cartilage on lateral femoral condyle (arrow). (b) Cor- responding sagittal T2 map shows area of increased T2 relaxation time on lateral femoral condyle (arrow) [(3)].

CONCLUSION

MRI provides a powerful tool for the imaging as it is noninvasive, painless, do not involve exposure to radiation. They are particularly useful for showing soft tissue structures so it is play an important role in understanding of the cartilage. Improvements have been made in morphologic imaging of cartilage in terms of contrast, resolution, and acquisition time. These improvements allow detailed maps of the cartilage surface to be developed that can be used to quantify both thickness and volume. Recent advances in biochemical imaging of cartilage used in detecting early changes in biochemical

composition of cartilage as proteoglycan content and collagen ultrastructure.

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