Review / Pregledni članak

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Imaging of the articular cartilage repair

Oslikavanje rezultata liječenja zglobne hrskavice

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Abstract. Postoperative imaging is necessary for assessing the technical success of the procedure and state of the cartilage healing, as well as for identifying potential complication. A plenty of radiological methods are available today in assessing the articular cartilage: radiography, computed tomography and thomositesis, ultrasonography and magnetic resonance. Radiography is the most used radiological modality but with high limitations in evaluation of the articular cartilage repair. Computed tomography and tomosynthesis are useful only after intraarticular contrast media injection (arthrography) and offer the evaluation of the cartilage surface but with the harmful influence of ionizing radiation. Magnetic resonance (MR) imaging provides non-invasive assessment of the entire joint including evaluation of the cartilage changes and lesions as well as the assessment of the repair site and all other joint tissues. Using compositional MR imaging of cartilage we may get information about its molecular status, specifically in regard to its collagen and glycosaminoglycan content. This article is a review of all imaging methods, in cartilage repair evaluation stressing novel imaging methods representing their advantages and limitations in cartilage repair evaluation.

Key words: articular cartilage; cartilage repair; magnetic resonance imaging; radiology

Sažetak. U praćenju uspjeha provedenog liječenja hrskavičnih oštećenja, radiološko je oslikavanje neophodno, kako za procjenu statusa zglobne hrskavice, tako i za procjenu tehničkog uspjeha primijenjenog liječenja, ali i za otkrivanje mogućih komplikacija liječenja. Danas nam u tome na raspolaganju stoje brojne radiološke metode: radiografija, kompjutorizirana tomografija i tomosinteza, ultrasonografija i magnetska rezonancija. Radiografija je najviše korištena radiološka metoda, no ima izrazito ograničene mogućnosti u procjeni reparirane hrskavice. Kompjutorizirana tomografija i tomosinteza za prikaz reparirane hrskavice trebaju koristiti intraartikularno primijenjeno kontrastno sredstvo (artrografija), ali sve uz primjenu ionizirajućeg zračenja. Magnetska rezonancija jedina je metoda koja *in vivo* može prikazati morfologiju hrskavice: njene konture, ali i njen unutarnji izgled. To je metoda koja osim prikaza hrskavice daje informacije o stanju svih struktura u zglobu. Koristeći metode biokemijskog oslikavanja magnetskom rezonancijom možemo dobiti informaciju o kemijskom sastavu same hrskavice i hrskavičnog reparata, prvenstveno sadržaju proteoglikana i mreže kolagenih vlakana. Članak donosi pregled svih radioloških metoda s težištem na modernim metodama oslikavanja uz prikaz njihovih mogućnosti u prikazu reparirane hrskavice.

Ključne riječi: magnetska rezonancija; radiologija; repariranje hrskavice; zglobna hrskavica

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INTRODUCTION

Postoperative imaging is necessary for assessing the technical success of the procedure and state of the cartilage healing, as well as for identifying potential complication. Radiography is limited by insensitivity to cartilage imaging and gives us indirect information about cartilage existence through the narrowing of the joint space width (Figure 1). Ultrasonography is unable to show the entire articular cartilage due to limited penetration through the bone. Computed tomography and tomosynthesis are useful only after intraarticular contrast media injection (arthrography) offers evaluation of the cartilage surface but with the harmful influence of ionizing radiation. Magnetic resonance (MR) imaging provides noninvasive assessment of the entire joint including evaluation of the cartilage changes and lesions as well as assessment of the repair site and all other joint tissues. MR imaging is a less invasive method than arthroscopy, and it allows a more comprehensive evaluation of articular cartilage, from the articular surface of the joint to the bone-cartilage interface. MR imaging techniques also can be used to depict the components of the extracellular matrix and help assess the biochemical status of OA changes. MR observation of the cartilage repair tissue is a well-stablished in many semiquantitative scoring systems that has been primarly been used in clinical research studies[1-3].

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MAGNETIC RESONANCE IMAGING

MR imaging techniques used for evaluation of articular cartilage and cartilage repair tissue can be divided into two main categories according to their possibilities for morphologic or compositional evaluation. As for all cartilage imaging, 1.5-T, 3.0-T, and, for research, 7.0-T magnet systems with extremity coils are recommended. To assess the structure of cartilage the same **morphological MRI technique** are used for repair tissue and native cartilage: combination of cartilage-sensitive sequences such as fat-suppressed 3D gradient-echo (GRE) and fluid-sensitive sequences such as fat-suppressed proton-density–weighted, T2-weighted, or intermediate-weighted fast spin-echo techniques, as recommended by the International Cartilage Repair Society[4,5].

The 3D GRE sequences with fat suppression or water excitation allow the accurate depiction of the thickness and surface of cartilage, whereas the aforementioned fast spin-echo sequences outline the internal structure of cartilage and enable detection of focal cartilage defects at higher sensitivity compared with GRE sequences. These techniques allow the detection of morphologic defects in the articular cartilage and cartilage repair tissue and are commonly used for semiquantitative and quantitative assessments. Morphologic characteristics of joint cartilage are assessed in conjunction with those of other

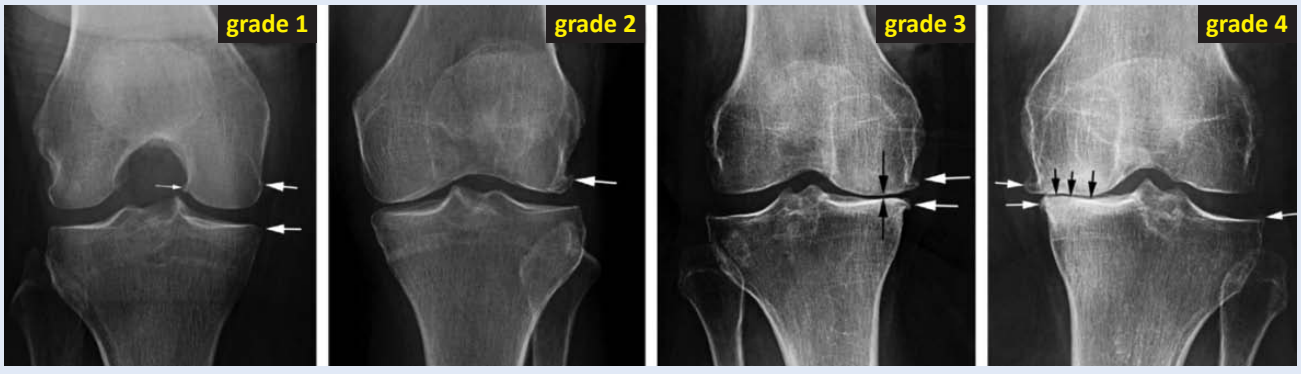

Figure 1. Radiograms of the knee show indirectly cartilage status in different Kellgren-Lawrence stage by reactive osteophytes (white arrows) and joint space narrowing in grade 3 and grade 4 (black arrows).

structures around the knee: menisci, subchondral bone, osteophytes, and synovium. The parameters that can be evaluated with MR imaging in assessment of cartilage repair include the degree of defect filling, the extent of integration of repair tissue with adjacent tissues, the presence or absence of proud subchondral bone formation (extension of repair tissue beyond the adjacent subchondral plate to include new bone formation), the characteristics of the graft substance and surface (its structure and signal intensity), and the appearance of the underlying subchondral bone (Figure 2).

Ideally, the repair tissue should have the same thickness as the adjacent native cartilage, the articular surface should be smooth, should completely fill the defect and the margins of the repair tissue should be continuous with the adjacent native articular cartilage without gaps between the repair tissue and adjacent cartilage or between the repair tissue and adjacent bone.

The MOCART (MR observations of cartilage repair tissue) system has excellent interobserver reproducibility for scoring of the defined variables, and it is an effective method for standardized reporting of the imaging features of autologous chondrocyte implants. MOCART scores may be helpful in long-term follow-up of cartilage repair[6].

The morphologic appearance of cartilage repair sites evolves over time. Complete filling of the defect can take several months to years. The newly formed fibrocartilage is initially poorly organized and highly water permeable. In the early postoperative period, the repair tissue appears hyperintense to native cartilage on T2-weighted images, and, initially, the repair tissue may be difficult to differentiate from fluid or appear very thin. As the repair tissue matures, its signal intensity decreases and becomes hypointense to native cartilage. After 1 or 2 years, the repair tissue should have grown to fill the defect with a smooth and well-defined surface[7].

Bone marrow edema in subchondral bone after micro/nanofractures or within the grafts and the surrounding bone is seen during the first 12 months and may persist for 3 years, but decrease in size and signal intensity during the time. With bone incorporation, the edema in the osteochondral plugs and surrounding bone resolves and the plugs are no longer different from the recipient bone.

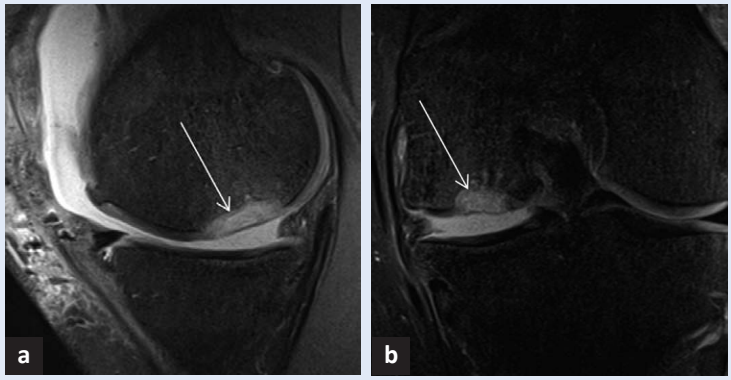

Figure 2. Sagittal (a) and coronal (b) MR images show morphological appearance of the cartilage repair after microfractures of the medial femoral condyle (arrow): chondral defect is completely fulfilled with fibrocartilaginous tissue and is aligned with the surrounding cartilage without subchondral bole edema.

Poorly filled defects and incomplete peripheral integration after 2 years are associated with poor functional outcomes. Persistent edemalike marrow signal intensity within subchondral bone beyond 18 months and subchondral cyst formation are concerning and may be signs of poor tissue integration[2,7].

Hyaline articular cartilage is composed of a fluid-filled macromolecular network that supports mechanical loads. This macromolecular network consists mainly of collagen and proteoglycans. Because collagen and proteoglycan-associated glycosaminoglycan are important to preserve the functional and structural integrity of cartilage, **compositional MR imaging** assessment of cartilage is focused on its molecular status, specifically in regard to its collagen and glycosaminoglycan content.

To evaluate the collagen network and proteoglycan content in the knee cartilage matrix, compositional assessment techniques such as T2 mapping, delayed gadolinium-enhanced MR imaging of cartilage (or dGEMRIC), T1ρ imaging, sodium imaging, and diffusion-weighted imaging are available. These techniques may be used in various combinations and at various magnetic field strengths in clinical and research settings to improve the characterization of changes in cartilage[5].

DELAYED GADOLINIUM-ENHANCED MR IMAGING OF CARTILAGE (dGEMRIC)

dGEMRIC is a molecular imaging technique that has been used to study GAG loss in the articular cartilage of patients with primary OA and after cartilage repair procedure. With dGEMRIC, T1-maps of hyaline cartilage are created following the intravenous (IV) administration of an anionic gadolinium-based contrast agent [Gd(DTPA)$^{2-}$]. Since cartilage matrix is largely composed of GAG molecules with negatively-charged carboxyl and sulfate groups, it repels the negatively charged contrast ions. As a result, the gadolinium concentrations are higher in cartilage regions with low GAG concentrations, and the cartilage T1-relaxation time ($T1_{gd}$) is reduced. The Gd-DTPA^{2-} concentration per voxel is described by means of the dGEMRIC index ($T1_{gd}$) which is calculated from the five different inversion times using a curve fitting method. In areas with low GAG the calculated T1gd will be low, and *vice versa*. The resulting dGEMRIC index (the average $T1_{gd}$ in a region of interest) is related to both the GAG concentration and the time between gadolinium administration and image acquisition. Therefore, healthy cartilage containing an abundance of GAGs will have low concentrations of Gd(DTPA)$^{2-}$ whereas degraded cartilage will have high concentrations of the contrast agent in areas where GAGs have been lost (Figure 3). T1 relaxation times are inversely proportional to the concentration of Gd(DTPA)$^{2-}$, and thus provide a quantitative metric of cartilage integrity[5,8].

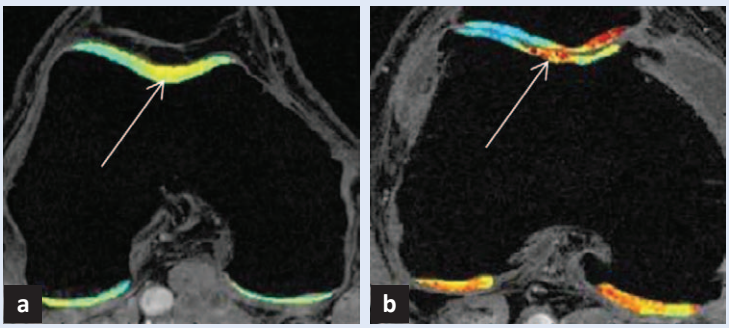

Figure 3. Axial dGEMRIC image (a) shows good postoperative result after femoral trochlea microfracture: increased dGEMRIC index in area of microfracture (arrow) represent high glycosaminoglycan content. Axial dGEMRIC image (b) shows bed postoperative result after femoral trochlea microfracture: low dGEMRIC index in area of microfracture (arrow) represent decreased glycosaminoglycan content of new fibrocartilaginous tissue.

For dGEMRIC study patient receive 0.2 mmol/Kg paramagnetic contrast media (Gd(DTPA)^{2}), administered by slow IV infusion through a catheter placed in the antecubital vein. The contrast agent injection time has to be less than 5 minutes followed by exercising by (walking up and down stairs) for approximately 10 min, starting 5 min after injection to promote delivery of the contrast agent to the joint. Post-contrast imaging of the cartilage has to be performed with a delay of at least 90 minutes after contrast injection; delay is needed for penetration of the contrast agent into the cartilage. Although the 90-minute delay is still required, this might increase the clinical applicability of the dGEMRIC technique. Drawbacks of dGEMRIC study are: the use of i. v. contrast agent administration in double dose of contrast agent, and time consuming because of at least 90 minutes delay of examination after contrast agent injection[9-14].

In a dGEMRIC study in which microfracture and matrix-assisted autologous transplantation are compared, a significantly higher relative DR1 was found in microfracture repair tissue than in matrix-assisted autologous transplantation, which suggests that the GAG content is lower in the microfracture repair tissue, most probably fibrocartilage[15].

Another dGEMRIC study found that the dGEMRIC index in matrix-assisted chondrocyte transplantation repair tissue was higher than that in microfracture repair tissue, presumably from higher extracellular matrix proteoglycan content[16].

Maturation of autologous chondrocyte implantation repair tissue has also been demonstrated with the dGEMRIC, with a lower index in early postoperative tissue that increased to values similar to that of native cartilage after 1 year. The authors concluded that the time dependent changes indicate increasing extracellular matrix proteoglycans as the repair tissue matures[17].

T2 mapping

Value of T2 in hyaline articular cartilage reflects interactions between water molecules and surrounding macromolecules and is highly sensitive to alterations of the cartilage matrix.

In normal cartilage, differences in density and organization of the collagen matrix appear as variations in T2 values. A multiecho-SE technique is currently used to measure T2 values – quantitative T2 mapping provides objective data by generating either a color or a gray-scale map representing the variations in relaxation time within cartilage[18]. There is good evidence that T2 mapping is useful for identifying sites of early-stage degeneration (early disruption of the collagen matrix) in cartilage, which appear as areas with T2 higher than that of normal cartilage. Compared with the T2 values mapped in normal hyaline cartilage, those found in osteoarthritic cartilage are more heterogeneous[19]. Increased T2 is most commonly associated with cartilage damage; however, low-signal-intensity lesions that may be due to increased water interaction with molecular fragments in cartilage are seen in some cases. Although T2 maps can be used to differentiate normal areas of cartilage from areas of degeneration (Figure 4), there does not appear to be any linear relationship between T2 and osteoarthritis grade that could aid differentiation between mild and more severe disease[20]. T2 maps may be used to monitor the effectiveness of cartilage repair over time, with eventual success signaled by the emergence of a collagen network that has a shape and overall and zonal organization similar to those seen in normal cartilage[21]. In several studies laminar analysis with T2 mapping has shown differences between healthy cartilage and cartilage repair tissue in subjects after matrix-associated autologous chondrocyte transplantation. While healthy cartilage showed a significant increase from deep to superficial cartilage zones, cartilage repair tissue did not show a significant stratification of T2 values[22].

T2 measurements have also been shown to detect differences in cartilage repair tissue following different repair procedures. It is expected that after repair procedure, cartilage repair tissue develops a collagen network with a zonal organisation similar to normal hyaline cartilage over time. Welsch et al compared cartilage T2 values after microfracture therapy and matrix-associated autologous chondrocyte transplantation.

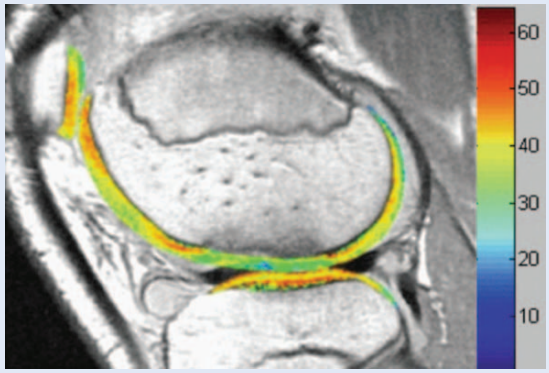

Figure 4. T2 mapping image of the knee in sagittal plane shows increased water content in fibrocartilaginous tissue at the place of microfracture (arrow) than water content in surrounding cartilage as a sign of collagen matrix loos.

The global mean T2 in the cartilage repair area was significantly lower in patients after microfracture, compared to matrix-associated autologous chondrocyte transplantation. Repair tissue after matrix-associated autologous chondrocyte transplantation showed a significant increase in T2 values from deep to superficial zones, however no such zonal variation was seen in repair tissue after microfracture. These findings corelated with histologic evaluation of repair tissue after microfracture and matrix-associated autologous chondrocyte transplantation, which have described a disorganised fibrocartilage after microfracture, while repair tissue after matrix-associated autologous chondrocyte transplantation being normal zonal collagen organisation.

Studies have suggested that zonal T2 mapping may be able to visualise the maturation process of cartilage repair tissue. T2 mapping showed promise for longitudinal monitoring of changes in cartilage[21].

T1ρ imaging

The interactions between motion-restricted water molecules and their local macromolecular environment can be monitored by measuring T1ρ values. Changes to the extracellular matrix, such as proteoglycan reduction, may alter T1ρ values measured in cartilage. In the osteoarthritic knee, damaged hyaline cartilage demonstrates higher T1ρ values than normal cartilage, and T1ρ imaging has higher sensitivity than T2-weighted imaging

for differentiating between normal cartilage and early-stage osteoarthritis. Some other factors other than proteoglycan reduction may contribute to variations in T1ρ values; these factors include collagen fiber orientation and concentration and the concentration of other macromolecules[23,24].

T1ρ has been studied for longitudinal evaluation of microfracture repair tissue. T1ρ and T2 values in repair tissue were longer than those in native cartilage 3–6 months after surgery. After 1 year, however, the difference between native cartilage and repair tissue decreased and remained significant only for the T1ρ measurements. A zonal distribution with higher T1ρ and T2 values in the superficial layers of repair tissue was demonstrated in this study, with the difference maintained after 1 year only with T1ρ measurements. The authors concluded that T1ρ might complement T2 relaxation time in the assessment of repair tissue maturation [2,25,26].

Magnetic resonance (MR) imaging provides non-invasive assessment of the entire joint including evaluation of the cartilage changes and lesions as well as assessment of the repair site and all other joint tissues. This article is review of all imaging methods in cartilage repair evaluation stressing novel imaging methods representing their advantages and limitation in in cartilage repair evaluation.

Sodium (23Na) imaging

Normal hyaline cartilage that is glycosaminoglycan-rich has high concentrations of sodium, and areas of cartilage with glycosaminoglycan depletion have lower concentrations. Because sodium possesses a nuclear spin momentum, it has a specific resonance frequency that is measurable at MR imaging without intravenous contrast administration.

Sodium MR imaging has shown promising results in the compositional assessment of articular cartilage. The advantages of the technique are that sodium occurs naturally in the cartilage matrix, that the signal intensity of cartilage is high in comparison with that of the background, and that sodium MR imaging can depict regions of proteoglycan depletion, which exhibit lower signal intensity than do areas of normal cartilage. Therefore, sodium imaging may be useful for differentiating between early-stage degenerated cartilage and normal cartilage.

Sodium MRI has limited clinical applicability because it requires dedicated coils, and, because of limited signal-to-noise ratio, requires 3T or higher MR field strength. While sodium MRI has shown great promise, further technical improvements are necessary to incorporation sodium MRI into a clinical feasible method[27].

A study involving long-term follow-up (7.9 years) of autologous osteochondral transplantation showed that sodium imaging with 7.0-T MR imaging could help differentiate between repair tissue and the native cartilage. However, results of sodium imaging with 7.0-T MR imaging did not correlate with clinical outcomes determined with Lysholm and Visual Analogue Scale scores[28].

In a study following matrix-assisted chondrocyte transplantation, sodium imaging showed differences between normal articular cartilage and matrix-assisted chondrocyte transplantation repair tissue (Figure 5) and good correlation with dGEMRIC, which indicates that both methods are similarly GAG specific[29].

A pilot study that evaluated microfracture and matrix-assisted chondrocyte transplantation with sodium imaging found higher GAG content after matrix-assisted chondrocyte transplantation, which is suggestive of better-quality repair tissue[30].

DIFFUSION-WEIGHTED IMAGING

Diffusion-weighted imaging (DWI) provides the ability to map diffusion of water and therefore enables analysis of cartilage extracellular matrix microarchitecture. Increased mobility of water is seen in degenerated cartilage and repair cartilage tissue.

Diffusion tensor imaging (DTI) is a DWI-based technique which evaluates the direction of water mobility in the extracellular matrix (Figure 6). The microarchitecture of normal cartilage causes anisotropic (directionally dependent) water diffusion. A change in anisotropy can indicate changes in collagen architecture, seen in degenrated and

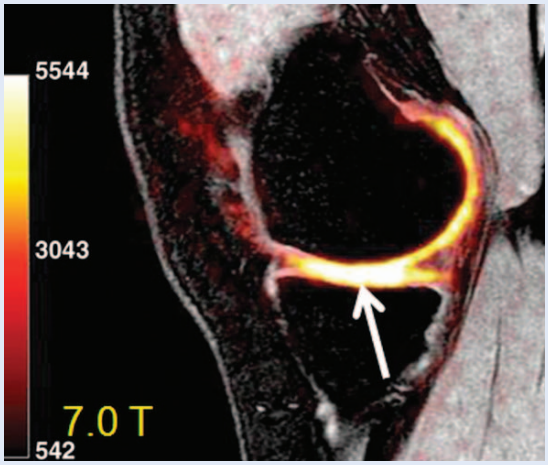

Figure 5. Sodium image of the knee in sagittal plane shows area of cartilage with glycosaminoglycan depletion (arrow) which exhibit lower signal intensity than do areas of normal cartilage (courtesy of Mihra Taljanovic, Tucson Arizona, USA).

repair cartilage tissue. DTI has been shown to be able to detect and grade early cartilage damage, too. Measurement of diffusion anisotropy also provides information on mechanical function of articular cartilage and on the transport of nutrients to the chondrocytes and for the removal of their metabolic waste product. A limitation of DTI is that it is time-consuming to acquire and process data[31-33].

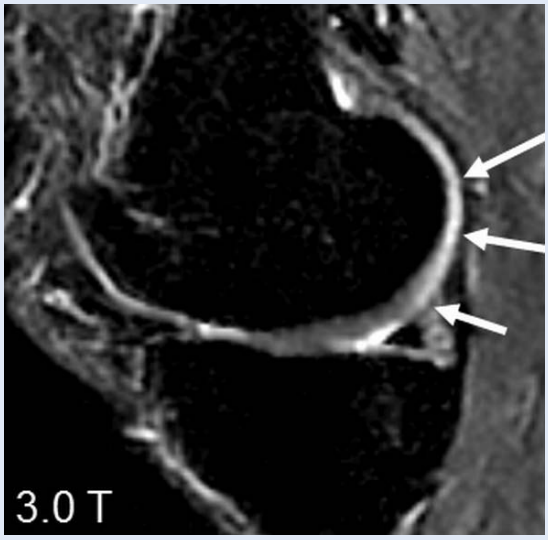

Figure 6. DW image of the knee in sagittal plane shows disruption of the cartilage matrix results in enhanced water mobility, which increases the ADC of cartilage (arrow) (courtesy of Mihra Taljanovic, Tucson Arizona, USA).

A study which compare DWI of the ankle in patients after matrix-associated autologous chondrocyte transplantation and ficrofracturing of the talar dome found that DWI showed revealed significant differences between both study groups what indicate that these two repair procedures resulted in different cartilage repair tissue quality, as described previously in histological studies, although the morphological scoring and the clinical scoring was nearly identical between those two groups of patients[34].

GLYCOSAMINOGLYCAN CEST

Chemical exchange dependent saturation transfer (CEST) imaging is the newest compositional cartilage imaging technique. The glycosaminoglycan (GAG) chemical exchange saturation transfer (CEST) imaging method (gagCEST) makes it possible to assess and quantify the GAG concentration in human cartilage. This biochemical imaging technique facilitates detection of the loss of GAG in the course of osteoarthritis. The gagCEST technique was used to analyse the perilesional zone (PLZ) adjacent to repair tissue after cartilage repair surgery, to determine whether there are biochemical changes present in the sense of degeneration.

Some publications suggested that gagCEST does not lead to accurate quantification of glycosaminoglycan content in healthy or degenerated cartilage at 3T. This may limit the clinical applicability of this technology to 7T MRI, which is a research tool and not clinically feasible[35,36]. Long-term results 8 years after autologous osteochondral transplantation[28] show that GagCEST imaging indicated reduced GAG content in repair sites compared to native cartilage, which is confirmed by a correlation between the results from other imaging methods.

Conflict of interest: Authors declare no conflicts of interest.

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