7 Advancing Imaging of the Hip: Cartilage

Gerd Melkus and Kawan S. Rakhra

Key Learning Points

- Understanding the basic concepts of biochemical sensitive MRI methods for quantitative hip cartilage mapping.
- Learning about the currently available and applied quantitative mapping sequences for the hip cartilage.
- Getting an overview of the application of biochemical sensitive MRI in the context of hip dysplasia evaluation.
- Understanding the necessary post-processing steps from MRI data acquisition to successful data analysis.
- Learning about the necessary infrastructure to perform quantitative hip cartilage MRI.

Introduction

Hip dysplasia is one of the major causes of hip osteoarthritis (OA) [1]. Reduced contact areas and increased contact pressures lead to reduced function, pain, and degenerative changes in the cartilage [2]. Acetabular hip dysplasia is associated with a modestly increased risk of incident hip OA [3]. Joint preserving non-surgical treatments such as physiotherapy, osteopathy, chiropractic and sports medicine as well as surgical approaches, such as osteotomy, are applied to reduce symptoms [4]. In this context, it is important to evaluate the status of OA in subjects with hip dysplasia to develop and apply optimal joint-preserving procedures [5].

Currently, various imaging techniques exist to evaluate the dysplastic hip, including radiography (plain x-rays), computed tomography (CT), and magnetic resonance imaging (MRI). While these techniques can evaluate anatomical and structural changes in the dysplastic hip, it is the status of the hyaline cartilage that is a key factor in determining prognosis and optimizing the management plan [6, 7]. Traditional MRI sequences have been effective in identifying qualitative, macroscopic changes in the cartilage related to gross thickness and integrity. However, these gross structural alterations often manifest late in the OA pathway, at a point where treatment options may be limited to invasive, surgical reconstructive procedures. Consequently, advanced MRI techniques have

G. Melkus (✉) · K. S. Rakhra
Department of Radiology and Division of Orthopaedic Surgery, University of Ottawa, Ottawa, ON, Canada

Department of Medical Imaging, The Ottawa Hospital, Ottawa, ON, Canada
e-mail: gmelkus@toh.ca; krakhra@toh.ca

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been developed in the hope of detecting biochemical changes in the macromolecular matrix of cartilage before gross, morphologic damage, possibly irreversible changes, occur [8].

In OA the cartilage degeneration begins with changes in hydration and degradation of the macromolecular content in the tissue matrix, which is not detectable with classical anatomical MR sequences. Early cartilage degeneration is characterized by loss of proteoglycans (PG) within the extracellular matrix and an increased hydration [9]. With ongoing OA the collagen within the cartilage is thinning and disrupting, which leads to dehydration and loss of the cartilage in the late stage of the degenerative process [10]. In the last fifteen years, several MRI techniques were developed that are sensitive to the biochemical content of cartilage and can be used as biomarkers for early cartilage degeneration [11, 12]. These quantitative MRI methods have been evaluated in vitro, validated with correlation to histological cartilage analyses, confirming their sensitivity to biochemical changes in the cartilage [13–16]. Several human, in vivo studies have also been conducted, in various joints, but predominantly the knee followed by the hip [17–19].

Infrastructure for Cartilage Mapping

Although research studies have shown the successful application of biochemical sensitive MR methods to evaluate early cartilage changes in OA, these sequences have not fully found their way into clinical practice. The reasons for this are the availability of the advanced sequences on the MRI scanner, the complexities of running the novel MRI sequences, the post-processing procedure related to the availability of post-processing software, and expertise for segmentation and interpretation. Additionally, these sequences can add considerable scan time to the overall protocol.

For advanced MR imaging and data analysis in a clinical setting, a multi-disciplinary team is needed, which covers everything from the clinical aspects to the technical components of the study. A successful team consists of an orthopedic surgeon and musculoskeletal radiologist, who evaluate the clinical status, develop the treatment strategy for the patient, and set the necessary time points for cartilage evaluation. If the MR sequences and post-processing techniques are not available, an MRI physicist with access to source code and the scanner research mode (both are necessary to modify and implement new sequences) is needed. Further, an image analyst or MRI physicist with image software programming knowledge for data post-processing is required to analyze the data. For custom programmed sequences own data processing pipelines need to be established to transform the raw data from the MR machine to quantitative maps which can be segmented and evaluated. Last but not least a knowledgeable MRI technician is recommended who is aware of performing advanced MR sequences, can interfere if image artifacts occur and has detailed knowledge of the techniques to solve difficulties related to imaging.

MRI Requirements

Quantitative MR imaging for hip cartilage evaluation can be carried out at 1.5 T [8], 3.0 T [20], and 7.0 T [21]. In clinical practice 1.5 T and 3.0 T are most commonly used, 7.0 T studies are limited to larger research centers with access to human high-field MRI. The standard hardware setup for quantitative hip cartilage imaging is a scanner built-in body coil for radio-frequency (RF) transmission and a flexible surface receive coil array wrapped around the hip (uni- or bilateral) for signal reception (Fig. 7.1). The hip of interest, if the scan is performed uni-lateral, should be positioned as close as possible into the magnet center to ensure the best homogeneity of the main magnetic field (B_0) as well as

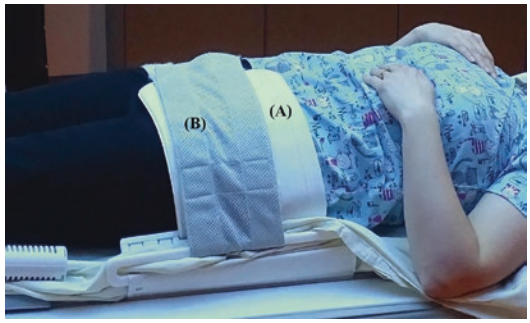

Fig. 7.1 Setup for uni-lateral hip MRI exam. The subject is lying on the scanner table, before being moved into the magnet bore. The flexible MR signal surface receiver coil array ((**A**), white color) is wrapped around the left hip. The receiver coil is fixed with a hook-and-loop tape ((**B**), gray color) wrapped around both hips and tied to the table

good homogeneity of the sending RF field (B_{1+}). Compared to quantitative knee cartilage imaging or intervertebral disc mapping, hip cartilage imaging has the challenge that the hip joint is located deeper in the body which results in a reduced signal to noise ratio (SNR). The SNR can be compensated by longer scan time and/or by a reduction of the spatial resolution. The spherical shape of the hip joint results in partial volume effects of the cartilage for any slice orientation.

MRI Cartilage Mapping Techniques

The advanced MR imaging techniques for the hip cartilage discussed in this chapter are all sensitive to the biochemical content of the cartilage, but they do not directly measure the PG or the collagen concentration within the cartilage, rather they do indirectly by analyzing the content of water in the environment. Only the later discussed dGEMRIC technique can quantify the glycosaminoglycan (GAG) concentration; however, this is clinically not straightforward [16]. The methods discussed are based on proton (^{1}H) MRI, which is almost exclusively used clinically. ^{1}H MR cartilage imaging techniques are based on the protons of the free water molecules within the tissue. It is the chemical environment around these water molecules (the content of PG and collagen within the cartilage matrix) that affect MR specific properties of the free water molecules, which can be measured using advanced techniques: a change in the biochemical content of the cartilage leads to a change of a ^{1}H MR measurable parameter of water proton signal. All the advanced techniques discussed in more detail below measure an MR-specific quantitative parameter called "relaxation time".

Compared to clinical MRI sequences the biochemical sensitive techniques for hip cartilage evaluation demand higher spatial resolution from about 0.4×0.4 mm^2 to 0.5×0.5 mm^2 in-plane and a slice thickness of 2–3 mm. A higher resolution is necessary to avoid partial volume effects due to the spherical shape of the cartilage at femoral head and acetabulum. While such a resolution may still enable a separated analysis of femoral head and acetabulum cartilage in healthy subjects, such differentiation can be difficult if the subject has considerable OA and thin cartilage or the imaging is performed at a lower magnetic field strength (1.5 T) [22]. While the above-mentioned resolution is the typical accomplishable resolution for T2 and T1ρ mapping dGEMRIC ($T1_{GD}$) and T2∗ mapping techniques are able to achieve isotropic resolutions of 0.8–1 mm^3 in clinically acceptable scan times (< 20 min) (see overview Table 7.1).

MR Image Post-Processing and Data Analysis

For cartilage data analysis several post-processing steps are required. Some of the quantitative sequences that are available on commercial scanners might have part of the processing steps already implemented, for others establishment or programming of the post-processing steps are necessary. Four main steps are required to process data from the MRI machine

Table 7.1 Summary of quantitative cartilage mapping parameters used in the hip

	dGEMRIC	T2	T2*	T1ρ
Contrast agent needed?	Yes	No	No	No
Commercial sequence availability?	Not from all vendors	Yes	Yes	No
Additional post-processing necessary?	Yes	Yes	Yes	Yes
Biochemical sensitivity	Directly related to GAG content	Water content; Correlation with collagen content and fibril orientation	Water content; Correlation with collagen content and fibril orientation	Water content; Correlation with proteoglycan content
Typical resolution	0.8–1 mm^3 isotropic	0.5 × 0.5 × 3 mm^3	0.8–1 mm^3 isotropic	0.5 × 0.5 × 3 mm^3
Typical scan time (3D acquisition)	~10 min	~15 min	~5 min	~15 min
Advantages	Established technique; Sensitivity to GAG content; High-resolution imaging	Established technique; Sequence availability	Short acquisition time; High-resolution imaging; Sequence availability	Sensitivity to PG content
Disadvantages	Contrast agent needed; Application of the contrast agent 60–90 min before the actual scan	Less sensitivity to early cartilage degeneration; Sensitivity to magic angle effect; Long acquisition time	Sensitivity to global magnetic field inhomogeneities and shim	Sequence availability; Long acquisition time
Relaxation time change with cartilage degeneration	dGEMRIC index (T_{GD}) ↓	T2 ↑	T2* ↓	T1ρ ↑

and retrieve quantitative results. In the following the processing for T1ρ mapping is outlined (Fig. 7.2), but these steps are also applicable to the other relaxation time mapping techniques such as T2, T2∗, and dGEMRIC. For the first step image re-alignment might be necessary as the datasets acquired at different spin-lock times (TSL) could be misaligned due to subject movement. Image alignment is essential for the second processing step, where the signal decay of each pixel of the dataset is fitted to a mono-exponential decay function to generate the quantitative relaxation time map. In the third step, hip cartilage segmentation is performed. The segmentation can be carried out on the first T1ρ-weighted dataset. If additional high-resolution anatomical data is available, a co-registration can be applied to register the high-resolution data to the first T1ρ-weighted dataset [20]. From the cartilage segmentation a binary mask is generated which is applied on the T1ρ map to retrieve the hip cartilage T1ρ values. The hip cartilage segmentation can be performed manually or semi-automatically [23, 24]. Recently, more fully automatic hip cartilage segmentation methods were proposed, which greatly reduce the post-processing time [25]. The last step typically involves a sub-division of the hip cartilage into different regions of interest, which can be analyzed and compared between study subjects. Methods need to be established which standardize the location of regions toward reproducibility comparisons across centers and longitudinal follow-up of individual subjects. A technical study by Surowiec et al. evaluated hip cartilage T2 maps from 3 mix-type FAI patients and subdivided the cartilage into 12 regions (6 on the acetabular side, 6 on the femoral side) to estab-

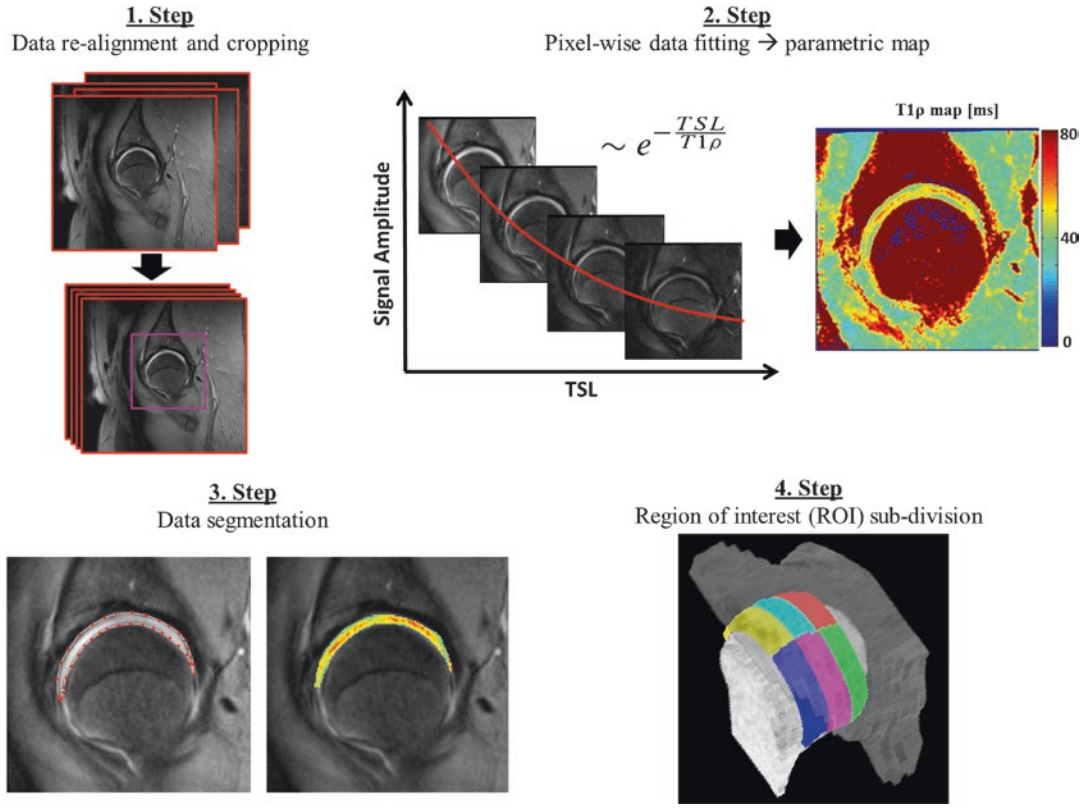

Fig. 7.2 Post-processing steps for quantitative hip cartilage analysis (shown for T1ρ mapping). In the first step raw data re-alignment and cropping is performed. The data is fitted in the second step to an exponential signal decay model to generate the quantitative T1ρ relaxation time map (shown here as a color-coded map). In the third step the cartilage is segmented on the first T1ρ-weighted dataset and the segmentation mask is applied on the T1ρ map to obtain the cartilage T1ρ values. In the fourth step the cartilage is subdivided into regions of interest (ROI) to investigate local T1ρ differences (exemplarily shown for six color-coded cartilage ROIs on the femoral head)

lish a standardized system to locate and describe quantitative mapping values [26]. A study by Anwander et al. researched and compared different approaches to subdivide the superior part of the hip cartilage into regions, which were was used to evaluate in T1ρ values of cam-FAI subjects and controls [24]. Studies at 1.5 T and 3 T on healthy volunteers have shown that T1ρ is not uniform over the hip [20, 27].

Delayed Gadolinium-Enhanced MRI of Cartilage (dGEMRIC)

Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) is a technique that indirectly measures PG content within hyaline cartilage. The technique is sensitive to the negative charge of the extracellular GAG of the PG within the cartilage tissue [16]. The technique is based on the intravenous or intra-articular injection of a negatively charged T1 changing contrast agent (based on Gadolinium – Gd), which can diffuse into the cartilage matrix. The degree of Gd accumulation in hyaline cartilage is proportional to the GAG concentration. GAG is negatively charged, and thus loss of GAG results in a relatively positively charged environment attracting the negatively charged Gd. Therefore, regions with degenerative cartilage and reduced GAG content will have a larger amount of Gd absorbed. On the other hand, regions of healthy cartilage will have lower levels of Gd. The local presence of Gd in the cartilage reduces the relaxation time T1,

which can be measured and mapped using MRI techniques. Therefore, a shorter T1 relaxation time after administration of Gd will be observed in degrading cartilage, whereas longer T1 values will be measured in healthy cartilage.

For dGEMRIC the suggested contrast agent dose is 0.2 mmol/kg body weight, twice the recommended clinical dose [28]. In a dGEMRIC study the Gd-contrast agent is injected intravenously (or intra-articularly), outside the scanner, typically 45–90 min before the scan [29] [30]. After the injection subjects are required to perform an exercise (walk for 10–20 min) and wait typically 30–90 min before the dGEMRIC ($T1_{GD}$ mapping) scan is performed as the agent is distributed in the cartilage by diffusion [28]. The conversion of the T1 relaxation time to absolute GAG concentration is difficult, therefore the majority of clinical studies report the $T1_{GD}$ relaxation time also called the 'dGEMRIC index', which is inversely proportional to the GAG content. The dGEMRIC index map shows the cartilage $T1_{GD}$ values, where a decreased $T1_{GD}$ is equivalent to a decreased dGEMRIC index and a lower content of GAG.

dGEMRIC in Hip Dysplasia

The dGEMRIC cartilage mapping technique is the most widely studied and applied in the context of hip dysplasia. The technique has advanced knowledge of the degree and distribution of cartilage disease. The dGEMRIC index, a metric used to quantify cartilage health, has been shown to correlate with clinical pain scores [6] and can predict outcomes of surgical procedures for hip dysplasia, namely the periacetabular osteotomy [7]. Most importantly, dGEMRIC can detect early biochemical GAG depletion in the cartilage, prior to gross cartilage thinning occurs [6]. Increased OA on radiographs and a lower dGEMRIC index was found in hips where osteotomy failed. Focused analyses on the weight-bearing zone of the joint have demonstrated that the dGEMRIC index correlates with the severity of dysplasia. Additionally, the early microscopic changes in cartilage have been found to occur globally in the joint, showing that OA in the dysplastic hip affects the whole joint [31]. A study by Jessel et al. investigated ninety-six dysplastic hips using the dGEMRIC technique and found that the mean dGEMRIC index (473 ± 104 ms) was significantly lower than that of morphologically normal hips (570 ± 90 ms, $p < 0.001$). OA was associated with increasing age and the severity of dysplasia, where dGEMRIC was able to detect the severity of OA [32]. An investigation of the radial distribution patterns of cartilage degeneration in dysplastic hips at different stages of secondary OA found regional decreased dGEMRIC index in the anterosuperior to superior sub-regions in the hips with mild OA compared to the group without OA. The subgroup with moderate to severe OA was observed with a significant overall decrease in the dGEMRIC index [33].

As an example imaging results and diagnostic findings of a 27-year-old female with chronic left hip pain and mild dysplasia of the left hip are shown in Fig. 7.3a–e. The oblique sagittal orientated color-coded dGEMRIC index map of the hip cartilage on an anatomical background image is shown in Fig. 7.3f. The patient was injected 45 min before the dGEMRIC scan at 3 T with Gd-DOTA (i.v., 0.4 mL/kg, 0.2 mmol Gd/kg, Dotarem (Guerbet), Metapharm Inc., Brantford, ON, Canada) and was asked to walk 15 min after the administration of the contrast agent. The lower $T1_{GD}$ relaxation times on the map indicate a higher concentration of the Gd-based contrast agent caused by a reduced GAG content. The global dGEMRIC index of the hip was $T1_{GD} = 670 \pm 122$ ms. Decreased $T1_{GD}$ was found in the anterior and posterior areas of the hip cartilage ($T1_{GD} = 453 \pm 57$ ms).

T2 Mapping

T2 mapping is a well-investigated biomarker for cartilage evaluation [34, 35]. T2 mapping does not need the application of an exogenous contrast agent and the imaging sequence is available as a standard sequence on most commercial clinical MRI scanners. The T2 relaxation time is sensi-

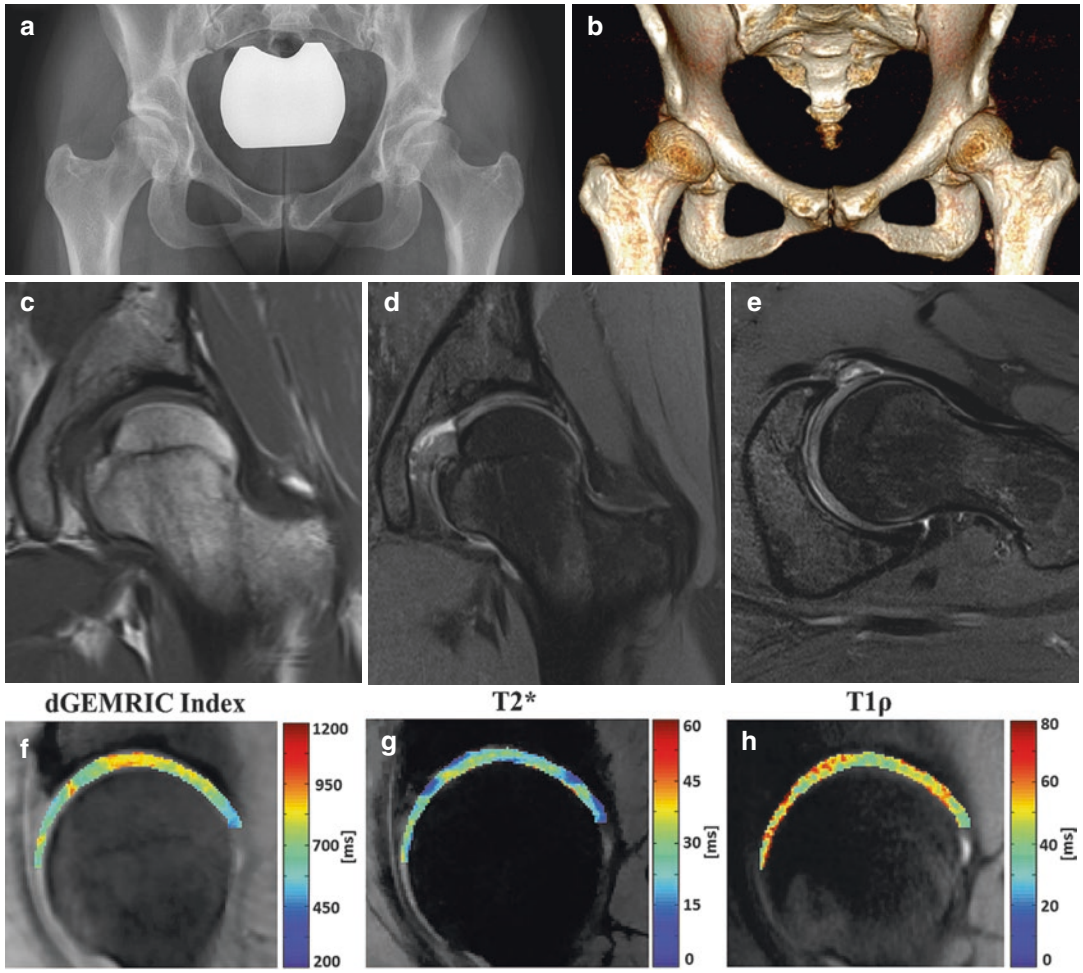

Fig. 7.3 Hip imaging results and diagnostic findings of a 27-year-old female with chronic left hip pain. (**a**) AP pelvis demonstrates mild dysplasia of the left hip with increased acetabular roof index and mild undercoverage of the femoral head. (**b**) Surface rendered CT reconstruction demonstrates undercoverage of the left anterosuperior femoral head. (**c**–**e**) Oblique coronal T1, proton-density weighted fat-saturated (PD-FS) and oblique axial PD-FS MRI images demonstrate mild superior labral hypertrophy with tear and paralabral cyst formation. (**f**–**h**) Oblique sagittal color-coded quantitative cartilage MRI maps on anatomical background images: (**f**) dGEMRIC index map, (**g**) T2∗ map, and (**h**) T1ρ map. (Note: see details in text)

tive to early cartilage changes, including water content and collagen fiber orientation. In an early stage of OA, a loss of collagen anisotropy and an increase of water content lead to an increase of the T2 relaxation time within the cartilage [36, 37].

Therefore, the T2 map represents a visual assessment of water and collagen content as well as the fiber orientation [34]. Increased cartilage T2 values indicate increased water content as well as collagen breakdown and/or structural collagen transformations. Topographic variation of hip cartilage T2 values were observed in a study of young, healthy volunteers [35]. T2 mapping is affected by the magic angle effect, which causes a prolongation of T2 in regions where the collagen fibrils are aligned 54.7° to the direction of the main magnetic field, a condtion which needs to be considered when T2 maps are evaluated [38]. Closer to the subchondral plate T2 relaxation times are shorter due to the high order of the collagen in the radial zone.

T2 Mapping in Hip Dysplasia

T2 cartilage mapping has been conducted for hip dysplasia, demonstrating significantly altered profile in the cartilage of dysplastic hips when compared to normal controls [39]. Recently T2 mapping has also been used to detect and monitor changes in the T2 profile of dysplastic hip hyaline cartilage after corrective surgery. Preoperative T2 values show correlations with postoperative functional scores and thus may also have prognostic value [40].

T2∗ Mapping

T2∗ mapping may prove similar information as T2 with regards to collagen status, although it is more sensitive to other compositional changes such as cartilage calcification [41]. T2∗ is related to T2 and therefore it also reflects the water and collagen content as well as the fiber orientation. The difference of T2∗ to T2 is its sensitivity to microscopic susceptibility differences, which leads to decreased T2∗ values with cartilage degeneration. Reduced T2∗ values indicate the degeneration of the cartilage tissue and the T2∗ relaxation time is decreased in OA-affected cartilage [42, 43]. T2∗ mapping is a fast and high-resulting imaging technique and available on most commercial available MRI machines.

T2∗ Mapping in Hip Dysplasia

To date, there is no published data on the applications of T2∗ mapping in hip dysplasia.

T2∗ cartilage mapping has been carried out in the hip, although limited to the normal and femoroacetabular impingement hip status. T2∗ measured in the acetabulofemoral cartilage of 10 healthy adult controls ranged from 23.06 ms to 29.83 ms [44]. A study investigating the hip cartilage T2* of 47 healthy asymptomatic volunteers found higher T2* values in the anterior part of the hip joint compared to posterior regions [45]. T2∗ mapping in symptomatic femoroacetabular impingement patients revealed decreased T2∗ values with increasing morphologically apparent damage ($p < 0.001$) [43]. The dysplastic hip, however, would also be amenable to cartilage mapping with these techniques. Further studies using the non-contrast-based T2∗ MRI cartilage mapping are required to determine their efficacy in investigation hip dysplasia, and to compare to the more researched dGEMRIC technique. A color-coded hip cartilage T2∗ map of a patient with dysplasia hip is shown in Fig. 7.3g. T2∗ mapping was performed with a 3D multi-gradient echo sequence at 3 T and a spatial in-plane resolution of 0.5×0.5 mm^2 (3 mm slice thickness). The global T2∗ value (T2∗ for the whole cartilage) was 25.5 ± 8.5 ms, where decreased T2∗ relaxation times were detected in anterior and posterior regions (T2∗ = 18.3 ± 4.1 ms). The decreased T2∗ relaxation indicates changes in collagen/macromolecular content and/or collagen fiber orientation.

T1ρ Mapping

T1ρ (T1-Rho) mapping is another non-contrast-based technique providing information on PG content of hyaline cartilage. It, too, does not require the administration of intravenous gadolinium contrast. The T1ρ relaxation time provides an intrinsic contrast mechanism which is sensitive to low-frequency motional processes and chemical exchange in biological tissues. It has been shown that T1ρ is more sensitive to changes in PG loss at the early stages of cartilage degeneration [10].

T1ρ mapping of the hip cartilage was successfully performed using different MR imaging techniques [8, 20, 23]. Most applications for T1ρ mapping of the hip cartilage use a B_1 spin lock field strength of 400 Hz to 500 Hz [8, 23]. Increasing B_1 is associated with increased energy deposition into the tissue and elevated specific absorption rates (SAR – measure of energy/heat accumulation within tissues), which can cause patient/tissue heating [46].

The cartilage T1ρ map visualizes the distribution of water and PG content, where increased T1ρ values are related to a reduced PG content and indicate degenerated cartilage tissue. Lower T1ρ values on the other side are related to healthier cartilage tissue.

T1ρ Mapping in Hip Dysplasia

An example of a color-coded cartilage T1ρ map can be seen in Fig. 7.3h. T1ρ imaging was performed at 3 T using a 3D turbo-spin echo sequence with T1ρ preparation pulse at B_1 = 500 Hz (CUBE QUANT, spatial resolution = 0.5 × 0.5 mm^2, slice thickness = 3 mm), similar to the protocol by Nemeth et al. [23]. The increased T1ρ relaxation times are related to a loss of PG content, indicating the cartilage degeneration. The global T1ρ value of the cartilage was T1ρ = 48.8 ± 5.9 ms, with higher local T1ρ relaxation times in the anterior and posterior regions (T1ρ = 57.1 ± 6.3 ms). Control T1ρ values from healthy subjects using this MR sequence at 3 T are reported with T1ρ = 50.1–53.0 ms [23], although lower T1ρ relaxation times were measured in healthy controls using gradient echo-based acquisition techniques [20, 47, 48]. Li et al., who investigated and compared T1ρ mapping at different sites and MR machines, observed significant differences in T1ρ values between different models of MR systems and coils [49].

T1ρ mapping has mainly been carried out on the normal/healthy and the femoroacetabular impingement hip [8, 20, 50–52]. T1ρ hip cartilage mapping protocols at 1.5 T and 3 T showed intermediate to good reproducibility [23, 24]. A study at 3 T comparing the cartilage in the hip joint of 30 volunteers found statistically significant higher T1ρ values in women than in men but no significant influence of age, body mass index (BMI), or sports activity [23].

Conclusion and Outlook

Quantitative MRI cartilage mapping methods are promising tools for clinical researchers to examine structural and biochemical changes in the cartilage that occur in hip dysplasia. However, further studies with larger sample sizes of using biochemical sensitive MR methods to characterize the cartilage status in hip dysplasia are required. Correlations of the mapping parameters with clinical joint functions and post-surgical outcomes are needed, similar to what has been done in knee OA studies or with the FAI hip. Quantitative MRI cartilage mapping may be able to fulfill the rapidly growing medical demand for a reliable, objective, non-invasive, and quantitative investigation of cartilage status in hip dysplasia. The advanced biochemical imaging techniques can detect changes much earlier and might be used as a marker for cartilage changes and health after physiotherapy or surgical corrections. Quantitative MRI protocols may serve as a future tool in monitoring the progression of cartilage changes and the responses to therapy, in both the clinical and research environments.

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