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Editorial

Editorial: from theory to practice – the challenges of compositional MRI in osteoarthritis research

Compositional magnetic resonance imaging (MRI) reveals biochemical and microstructural changes in cartilage and other joint tissues well before morphologic alterations are detectable[1]. To date, compositional MRI is not in standard clinical use despite its availability for many years, but it is being used with increasing frequency in osteoarthritis (OA) research particularly for 'pre-structural' evaluation of cartilage and to assess biochemical response of joint tissue to loading through physical activity[2].

At the molecular level, cartilage consists of approximately 70–80% fluid and 20–30% solid extracellular matrix (ECM) with a sparse distribution (approximately 2%) of chondrocytes. The ECM is made up of a network of collagen fibrils and proteoglycan molecules that consist of a protein core with covalently attached glycosaminoglycans (GAGs). The biomechanical properties of cartilage are largely due to water flow within the ECM, the cartilage-joint fluid distribution of water as well as collagen and proteoglycan content and organization. Compositional MRI acquisitions provide a way to detect biochemical and microstructural changes in the cartilage ECM before gross morphological changes occur[3]. To date, many of these compositional MRI techniques have not been thoroughly validated in human patients with OA, which is one of the reasons why they are not currently used in routine clinical practice. Techniques comprise relaxometry measurements (T2, T2*, and T1rho mapping), T2* mapping with ultrashort echo times (UTE), sodium imaging, delayed gadolinium-enhanced MRI of cartilage or meniscus (dGEMRIC, dGEMRIM), magnetization transfer contrast, GAG-specific chemical exchange saturation transfer (gagCEST), diffusion-weighted imaging, and diffusion tensor imaging[3]. Compositional techniques seem to have the potential to serve as quantitative, reproducible, noninvasive, and objective endpoints for OA research, particularly in early and pre-radiographic stages of the disease. The two most commonly applied compositional MRI techniques are T2 and T1rho relaxometry.

T2 mapping, one of the oldest compositional techniques, is widely available on most clinical MRI systems and provides a calculated image with spatially localized spin–spin relaxation values. T2 relaxation time is the time constant of dephasing in the transverse plane following a radiofrequency pulse. Articular cartilage T2 reflects the water content, collagen content, and especially collagen fiber orientation in the ECM. Spin echo (SE) based sequences including standard SE, multi echo spin echo (MESE), and fast spin echo (FSE), are typically used for T2 relaxation time measurements, with MESE sequences most commonly utilized. Calculation of T2 relaxation values from cartilage regions of interest is usually performed by monoexponential curve fitting of the signal intensities of images acquired at multiple echo times (TEs) for each image voxel[4].

T2 quantification is generally considered to reflect collagen matrix integrity; however, a few studies have also reported its association with proteoglycans[5]. Native cartilage T2 relaxation measurements have been extensively used as an outcome measure to assess the biochemical impact of risk factors including metabolic syndrome and ligamentous injury on articular cartilage[6]. The earliest histological changes of OA include loss of proteoglycans, which is then followed by a disorganization of the collagen fiber network and loss of collagen fibers causing increased cartilage permeability. Therefore, longer cartilage T2 is generally consistent with more advanced cartilage degeneration and seems to be predictive for the development of morphological changes[7].

T1rho is a newer technique and evaluates the spin-lattice (T1) relaxation in the rotating frame[8]. In contrast to T2 relaxation, T1rho involves the use of an additional radiofrequency pulse applied after the magnetization is tipped into the transverse plane. The magnetization then becomes aligned or "spin-locked" with the applied radiofrequency field. The signal decay is exponential with a time constant, T1rho, and is typically calculated from multiple images by changing the duration of the spin-locking pulse. T1rho is sensitive to the interaction between motion-restricted water molecules and their environment. Alterations in the cartilage ECM and particularly proteoglycan content are reflected by T1rho values[5]. On the other hand, collagen fiber orientation also affects T1rho measurements. T1rho, like T2, has been demonstrated to predict the development of morphological lesions in articular cartilage but does not reflect a specific macromolecular component of the ECM[7]. To date T1rho is not as widely available due to a more challenging sequence implementation.

There are limitations of compositional MRI techniques that need to be overcome before they can be applied in larger clinical trials. First, it is currently difficult to duplicate the exact sequence longitudinally due to frequent changes in equipment, making long term follow up studies challenging. In addition, it is challenging to compare sequences obtained with different scanners as well as sequences. Rigorous calibration standards are needed to compare T1rho and T2 obtained with different scanners and sequences. Second, it is difficult to define a threshold of "pathologic value" for indices of cartilage biochemical composition (e.g., T2, dGEMRIC index) and a universally applicable threshold to define "pathological" value of cartilage composition has not yet been defined. In order to overcome some of these challenges subregional standardization of compositional measurements have

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been suggested including the application of Z-scores to enable better prediction of an individual's risk for progressive degenerative changes comparable to the role of T-scores for bone mineral density in osteoporosis[9]. The application of standardized cartilage T2 (or T1rho) Z-scores will potentially enable clinicians to understand the significance of a specific value compared to a reference population without cartilage degeneration. Third, although compositional imaging techniques have been explored in other fields such as imaging of cartilage repair and rheumatoid arthritis, no clinical indication for compositional MRI could be established to date despite availability of these techniques for more than two decades. This may be a reflection of the aforementioned limitations and perhaps due in part to technical difficulties and limited availability of advanced MRI scanners[4]. At least one study, however, reported moderate to excellent reproducibility for T1rho and T2 mapping in a multicenter setting. The study included large differences, with intraclass correlation coefficients ranging from 0.61 to 0.98 and root-mean-square coefficients of variation ranging from 4% to 14%, which seems promising in regard to future multicenter investigations[10].

In this issue of *Osteoarthritis and Cartilage* Shao and colleagues are presenting intriguing data on an MRI phenomenon referred to as the "magic angle" effect, which has marked impact on our understanding of compositional tissue changes[11]. In initial studies with clinical MRI, the effect was seen principally in tendons that underwent a change of direction along their course such as the supraspinatus tendon near its insertion resulting in fiber orientation of parts of the tendon at or near 55° to the main magnetic field, also referred to as B0. The high signal resulting from the increase in T2 in the part of the tendon at 55° to B0 simulated an increase in T2 suggesting pathology, and consequently was regarded as an artifact, which was to be avoided if possible[12]. The main method of avoiding magic angle effects was to increase the TE of the pulse sequences used to image tendons and ligaments. With use of a longer TE, the increase in T2 produced by the magic angle effect did not result in an increase in signal in the tendon or ligament, whereas diseases that increased tissue T2 more than the magic angle effect did, resulting in an increase in signal that could be correctly attributed to disease. T2 magic angle effects are also relevant for other tissues oriented in the 55° direction to B0 such as the trochlear cartilage (Fig. 1)[13].

While the magic angle effect in T2 relaxation is well understood, the literature regarding T1rho relaxation mechanisms is somewhat inconsistent. In their current study presented in this issue, Shao *et al.* investigated magic angle effects in histologically confirmed normal and abnormal regions using a clinical whole-body 3T scanner, providing information on the angular dependence of T1rho and T2 in clinical imaging[11]. The authors found strong magic angle effects for both T1rho and T2 relaxation in articular cartilage, especially in the deeper layers. The deeper layers of cartilage are more susceptible to magic angle effects due to the highly ordered collagen fibers oriented perpendicular to the bone-cartilage interface as opposed to the more random orientation of collagen fibers in the more superficial layers of cartilage. On average T2 values were increased by more than 200%, while T1rho values were increased almost by 100% near the magic angle. Both normal and abnormal cartilage showed similar T1rho and T2 magic angle effects. The authors concluded that changes in T1rho and T2 values due to the magic angle effect can be several times more than that caused by real chondral degeneration, which may pose a significant challenge in applying T1rho and T2 as an early surrogate marker for cartilage degeneration. However, understanding the normal regional dependent variations in T2 and T1rho of articular cartilage may allow use of these quantitative MRI techniques for detecting early cartilage degeneration in clinical practice[14]. Furthermore, regional analysis of T2 and T1rho of articular cartilage between groups of subjects can be used to account for magic angle effects in OA research studies as increases in T2 and T1rho due to a combination of disease and magic angle effects in individuals with cartilage degeneration would be greater than increases in T2 and T1rho due to magic angle effects alone in healthy subjects. The feasibility of implementing T2 quantification in multi-vendor studies remains to be established. While some studies reported good reproducibility[10,15,16], another has shown significant inter-scanner differences[17]. There seems to be need for cross-validation studies of multi-vendor and multi-site T2 and T1rho quantification to better understand reproducibility across systems and sites, which will be critical for future large-scale multicenter trials.

The example of compositional MRI illustrates why the field can only advance if different subspecialties move on together to help understanding challenges and implement solutions on how to overcome these problems. Only imaging experts including subspecialty trained MRI physicists, musculoskeletal radiologists, clinicians, epidemiologists, and basic science researchers together will help understanding the complexities of MRI to eventually entangle the conundrum of initiation and progression of disease and particularly early cartilage degeneration.

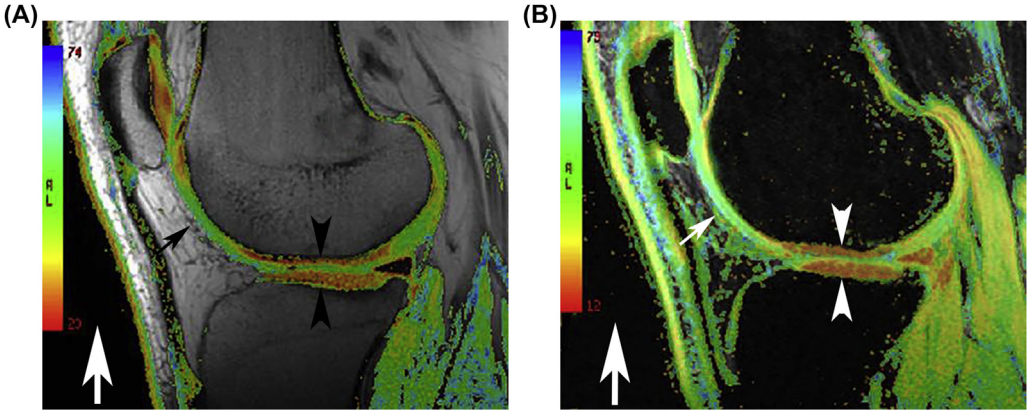

Fig. 1. (A) Non-fat-suppressed T2 map and (B) fat-suppressed T1rho map of the knee joint in a healthy subject shows increases in T2 and T1rho in the trochlea (small arrows) when compared to the femoral condyle and tibia plateau (arrowheads). The increase in cartilage T2 and T1rho is due to the magic angle effect as the trochlear articular surface is oriented 55° relative to the main magnetic field (large arrows).

Authors contributions

(1) All authors were involved in the conception and design of the study, or acquisition of data, or analysis and interpretation of data.
(2) All authors contributed to drafting the article or revising it critically for important intellectual content.
(3) All authors gave their final approval of the manuscript to be submitted.

Additional contributions

- Analysis and interpretation of the data: FWR, RK, AG
- Drafting of the article: FWR, RK, AG
- Provision of study materials or patients: N/A
- Collection and assembly of data: N/A

Responsibility for the integrity of the work as a whole, from inception to finished article, is taken by F. Roemer, MD (first author; frank.roemer@uk-erlangen.de; froemer@bu.edu).

Competing interests

F.W.R. is Chief Medical Officer and shareholder of Boston Imaging Core Lab (BICL), LLC a company providing image assessment services.

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