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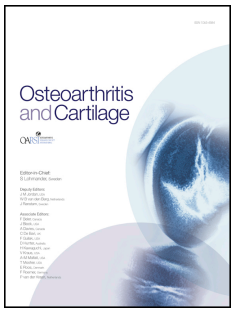

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Title

Standardized multi-vendor compositional MRI of knee cartilage: a key step towards clinical translation?

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Cartilage compositional magnetic resonance imaging (MRI) techniques are sensitive to changes in the composition of the extracellular matrix of articular cartilage. Their promise lies in the potential to detect the earliest stages of cartilage degeneration, at a stage where these changes may still be reversible. This is a considerable advantage over conventional (structural) MRI; even with the high spatial-resolution imaging offered by modern high-field (3T) MRI systems, by the time structural cartilage damage is apparent, there is (by definition) damage to the collagen matrix implying that the changes are probably already irreversible[1].

A wide variety of cartilage compositional MRI techniques have been described over the past three decades (Table 1). The most widely used of these is T_2 (transversal relaxation time) mapping, which is now available as a product (i.e., commercially available) pulse sequence from all three major MRI vendors (GE, Siemens and Phillips). $T_{1\rho}$ (longitudinal relaxation time in the presence of a radiofrequency field) mapping is an alternative which may offer improved dynamic range to T_2 mapping but is not widely available (typically requiring a research agreement to be in place with the MRI vendor). Both T_2 and $T_{1\rho}$ have considerable advantages over other cartilage compositional techniques making them the most amenable to widespread use. They do not require the administration of contrast agent, unlike delayed gadolinium enhanced MRI of cartilage (dGEMRIC), do not require specialist hardware, unlike sodium imaging, and are feasible at clinically accessible field strengths (i.e., 1.5 or 3 Tesla), unlike sodium imaging and glycosaminoglycan chemical exchange saturation transfer (gagCEST). The trade-off is that T_2 and $T_{1\rho}$ do not have the same tissue specificity as some of these other techniques, for example dGEMRIC has a stronger correlation with proteoglycan content than

does $T_{1\rho}$[2]. However, when performed correctly, they have been shown to be able to distinguish between patients with or at risk of OA from healthy controls and predict development and progression of OA (Figure 1)[3–5]. They may also offer considerably improved sensitivity to change when compared to structural MRI or plain radiography[6,7].

[FIGURE 1]

[TABLE 1]

Despite the clear promise of T_2 and $T_{1\rho}$ mapping, both technical and clinical issues have hindered the widespread uptake of these techniques. Both techniques were introduced more than 20 years ago but there have been several obstacles to clinical use and acceptance by the community. From a technical point of view, there is a lack of standardization of acquisition protocols across different sites and vendors, with a wide variety of sequences available which may or may not be commercially available. It is therefore little surprise that multi-vendor reproducibility has previously been reported as suboptimal[8]. Linked to this, in many previous studies there has been wide variance in selection of sequence parameters and a lack of understanding of the effect of signal-to-noise ratio (SNR) on data quality. This has led to poorly executed studies and thus inconclusive or difficult to interpret results. From a clinical point of view, there is no established threshold for what constitutes a normal vs abnormal value of T_2 or$T_{1\rho}$ – nor is there likely to be, given the well-characterized variation between healthy individuals and within the same individual across different cartilage subregions. Although efforts have been made to standardize cross-sectional assessment using healthy reference

cohorts and Z-scores, in our opinion the real clinical utility of these methods is likely to be the assessment of change within an individual over time and particularly in monitoring the earliest disease stages that are likely to be the ones most amenable to non-surgical therapy[9,10]. Ultimately, clinical utility is also limited by the lack of demonstrable effect on patient management, although there may be exceptions to this (e.g. suitability for and follow-up of focal cartilage repair treatments such as autologous chondrocyte implantation) and this is a limitation applicable to all advanced imaging of OA.

The article in the present issue by Kim and colleagues[14] represents an important step in addressing the suboptimal multi-site reproducibility of T_2 and $T_{1\rho}$ mapping. The key innovation is the implementation of the same pulse sequence structure (3D magnetization-prepared angle-modulated partitioned k-space spoiled gradient echo snapshots, or MAPSS) across all three major MRI vendor platforms. This vendor-neutrality is a significant advance over previous multi-site standardization efforts which have used vendor-specific pulse sequences (Table 2). They demonstrate excellent intra-site repeatability for both T_2 and $T_{1\rho}$, in agreement with previous studies and confirming the ability of these methods to detect relatively small longitudinal changes in this setting. Inter-site reproducibility was not as good (as would be expected), but as mentioned above the utility of these methods is likely to be for the detection of longitudinal changes. Therefore, intra-site repeatability is of most interest, assuming an individual is imaged on the same platform at baseline and follow-up visits. As alluded to above, interpretability of many existent studies using T_2 and $T_{1\rho}$ is limited by the lack of acquisition and analysis expertise. In particular, the quality of data used to generate the T_2 and $T_{1\rho}$ maps is often hampered by low

SNR and suboptimal parameter selection. The contribution of this study in providing a reproducible set of parameters suitable to generate images of sufficient quality for valid cartilage T_2 and $T_{1\rho}$ quantification across all major MRI vendor platforms is therefore to be welcomed. An important extension of the current work would be an evaluation of inter-site and inter-vendor variability of longitudinal changes in T_2 and $T_{1\rho}$.

[TABLE 2]

This work builds on existing efforts by the authors and others to develop T_2 and $T_{1\rho}$ as quantitative imaging biomarkers suitable for use in clinical trials and clinical practice. It provides further evidence of the excellent intra-site repeatability of these methods and highlights the challenges associated with multi-site and multi-vendor implementation. The Quantitative Imaging Biomarkers Alliance (QIBA), an initiative endorsed by the Radiologic Society of North America (RSNA) with the aim to foster collaboration to identify needs, barriers and solutions to create consistent, reliable, valid and achievable quantitative imaging results across imaging platforms, clinical sites, and timepoints, recently published a statement regarding the application of compositional MRI in degenerative joint disease (https://qibawiki.rsna.org/images/2/20/QIBA_Profile_MSK-Cartilage-Stage1_Profile.pdf). QIBA aims to promote quantitative imaging in clinical trials and clinical practice, with profile statements to improve method standardization. As part of this, options for accessing the 3D MAPSS pulse sequence used in this study are provided for all three major MRI vendors. The

profile is open for public comment through 29 September 2020 and we would encourage any interested party to review and contribute.

What does all this mean for the general OA researcher? First, there are ongoing international efforts to improve the accessibility and utility of T_2 and $T_{1\rho}$ to non-imaging specialist researchers. This involves work both on standardization of image acquisition (exemplified by the work of Kim and colleagues in this issue) but also on standardization of image analysis. The latter often involves automated approaches built on AI algorithms which should reduce time burden taken for analysis (particularly segmentation), improve integration into clinical workflow and reduce variability associated with the use of different analysis pipelines[11,12]. Second, the pathway to routine clinical use of T_2 and $T_{1\rho}$ for cartilage assessment in OA cannot be followed by the imaging community alone; technical validation and improvement in data quality must be accompanied by clinical validation (demonstration of how is patient care influenced, for example assisting clinicians in assessing response to therapy) and demonstration of cost effectiveness in order to achieve clinical translation[13]. Therefore, in order for the potential of these powerful techniques to be realized, it will be important to have support from the wider OA research community.

Author contributions

1. All authors were involved in the conception and design of this editorial.
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.

Responsibility for the integrity of the work as a whole is taken by James MacKay, MB BChir PhD (first author; james.w.mackay@uea.ac.uk).

Competing interests

JM, FK have no competing interests.

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Figure legends

Figure 1. $T_{1\rho}$ mapping predicts onset of focal morphological cartilage lesions. $T_{1\rho}$ mapping overlaid on morphological MRI (3D fat-suppressed spoiled gradient echo) of patient undergoing arthroscopic meniscectomy, performed pre-procedure (A) and at 6 months (B) and 1 year (C) follow-up. Note development of focal region of elevated $T_{1\rho}$ (single arrow) at 6 months which develops into an area of more diffuse partial thickness loss (double arrows) at 1 year (1 year image shown without overlaid $T_{1\rho}$ map for clarity).

Table 1. Overview of commonly used cartilage compositional MRI techniques

Technique	Cartilage component assessed	Pros	Cons
T_2 mapping	Collagen orientation, collagen content, water content	Easily accessible Feasible at 3T	Commercially available pulse sequences not optimized for cartilage
$T_{1\rho}$ mapping	Macromolecular content, water content	Improved dynamic range c.f. T_2 Feasible at 3T	Not readily available Similar information to T_2 at clinically feasible spin-lock frequencies
T_2* mapping	Collagen orientation, collagen content, water content	Potentially faster acquisition c.f. T_2 Can be combined with UTE imaging to assess deepest layers of cartilage Feasible at 3T	Similar information to T_2 mapping but less well-validated UTE requires specialist non-Cartesian pulse sequences
dGEMRIC	GAG	GAG specificity	Requires IV contrast administration Complicated scan protocol
Sodium	GAG	GAG specificity	Difficult at < 7T Requires multinuclear capability
gagCEST	GAG	GAG specificity	Currently not feasible at < 7T
DWI/DTI	Proteoglycan content, collagen orientation	Combined proteoglycan/collagen assessment	Typically limited spatial resolution & SNR with standard DWI sequences

Abbreviations: UTE – ultrashort echo time, GAG – glycosaminoglycan, DWI – diffusion-weighted imaging, DTI – diffusion tensor imaging, SNR – signal-to-noise ratio.

Table 2. Comparison of standard T_2 and $T_{1\rho}$ MRI and MAPSS pulse sequence

Drawbacks of commercially available pulse sequence (i.e., spin echo-based)	**Advantage conferred by MAPSS pulse sequence**
Slow readout so TEs not optimized for cartilage, TE dependent on hardware considerations	Magnetization prepared so TE can be short, optimized for cartilage and standardized
First TE often has to be discarded due to stimulated echo effects	Stimulated echo not an issue as T2/T1p magnetization preparation is utilized
Poor SNR efficiency, often 2D readout - so spatial resolution limited	3D readout with improved SNR efficiency
Multiple vendor-specific implementations	Single implementation available across multiple vendors

Abbreviations: SNR – signal-to-noise ratio, TE – echo time