7 Tesla Clinical applications in MSK

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This abstract provides an overview of the initial clinical results of musculoskeletal studies performed at 7 Tesla, with special focus on sodium imaging, new techniques such as chemical exchange saturation transfer (CEST) and T2* imaging, and multinuclear MR spectroscopy.

Sodium imaging

Proton MRI at ultra-high-field (7 T and above) MR systems poses various challenges, including radiofrequency power deposition, increased chemical shift, susceptibility artifacts, homogeneity of RF coils, and changes in relaxation times, compared to lower-field clinical MR systems. These problems are much less pronounced in nuclei with a low gyromagnetic ratio, such as sodium (23Na). However, a 3.8-fold smaller gyromagnetic ratio, a lower resonance frequency (23Na: 78.6 MHz vs. 1H: 297.2 MHz), a significantly shorter T2 relaxation time, and a lower concentration of sodium nuclei (23Na: 300 mM vs. 1H: 110 M) result in sodium MR signal in articular cartilage that is 1/4,000–1/5,000 smaller than the proton MR signal. In order to achieve sufficiently high SNR (SNR>15), sodium MRI requires longer measurement times (15–40 min) and results in low-resolution images. Ultra-high-field MR systems can provide higher intrinsic 23Na SNR and/or higher spatial/temporal resolution and improved contrast in the image [1,2] . Sodium MRI offers many potential clinical applications. Sodium content measured by 23Na MRI has been shown to be proportional to glycosaminoglycan (GAG) content in articular cartilage [3,4]. Sodium MRI can be used to detect early signs of cartilage degeneration or injury before morphological changes can be detected by proton MRI. Sodium MRI may enable the noninvasive in vivo evaluation of disease-modifying treatments for osteoarthritis (OA) and methods for cartilage repair. The very short T2 times of sodium in articular cartilage result in sequences with short echo times that are very effective with regard to SNR. However, radial sequences are prone to blurring and artifacts from off-resonance effects, fast components of T2* decay, and variations in gradient timing. Although the Cartesian sampled sequences are less effective in regards to the SNR, they can offer much sharper images. In an article by Trattnig et al., a Cartesian 3D gradient echo sequence was used for sodium MRI at 7 T in patients after matrix-associated autologous chondrocyte transplantation (MACT) [5]. These authors observed significant differences in sodium normalised values between repaired cartilage transplant tissue and healthy cartilage. Moreover, a strong significant correlation was found between sodium normalised values from 7 T and intravenously enhanced T1 values from another GAGspecific technique—delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) at 3 T. These findings suggest that sodium MRI can differentiate between repaired tissue and native cartilage in MACT patients and may be useful for the noninvasive evaluation of different cartilage repair techniques.

In degeneration of the Achilles tendon tendinopathy is also accompanied by disaggregation of the microfibrillar bundles due to the greater quantities of water and proteoglycan. Almost double the GAG content was observed in pathologic tendons in studies using biochemical assays [6]. In a study by Juras et al., the feasibility of sodium magnetic resonance imaging for the diagnosis of Achilles tendinopathy was investigated at ultra-high field [7]. Their cohort comprised 20 healthy volunteers with no history of pain in the Achilles tendon and 8 patients with clinical findings of chronic Achilles tendinopathy. The study found that the mean bulk sodium SNR was 4.9±2.1 in healthy control subjects and 9.3±2.3 in patients with Achilles tendinopathy, and that the difference between the means was statistically significant.

Preliminary results of sodium imaging in patients with Diabetes type 1 have shown that although morphologically normal, patellar tendon in the knee joint shows already a statistically significant increase in GAG comparable to chronic tendinits and a loss of GAG in cartilage of the same knee joint.

In another preliminary study by Juras et al normalized sodium signal was able to distinguish between the Achilles tendon before ciprofloxacin treatment and ten days after. Five month after the treatment, there was no significant change. This study showed that it may be sensitive enough to visualize macromolecular alterations which are present after ciprofloxacin treatment.

T2* mapping of the Achilles tendon at 7 Tesla

Standard MRI was successfully employed to detect partial or total tendon rupture or even the degenerative processes in the tendon tissue. Most imaging findings are related to the pathologic processes of tendon degeneration and repair progression. In addition to the morphological MRI evaluation (imaged predominantly by T2*-weighted sequences), the quantitative MRI analysis of tendon tissue may be helpful in identifying the early pathological changes in the tissue. Using spectroscopic methods, it was shown that the T2* decay in the Achilles tendon is a multicomponent process [8]. However, with clinical sequences, it is difficult to acquire signal from the second, third, and fourth components, since these have a small component ratio. The first component has the largest ratio, but it is in the submillisecond range, and thus, can barely be acquired with conventional echo times. In general, MR imaging of rapidly relaxing tissues, such as tendons, menisci, ligaments, and bones, is rather difficult with clinical sequences. Recent developments in new hardware and sequence design allow the

acquisition of a signal directly from these tissues. Moreover, ultra-high field provides a substantial increase in SNR. The 3D-UTE sequence provides the ability to detect MR signal from a large variety of rapidly relaxing tissues and materials, including tendons. Juras et al. used a 3D-UTE sequence at 7 T to estimate T2* in tendons in order to investigate the potential feasibility of using this parameter as a marker for Achilles tendinopathy [9]. The SNR increase between 3 and 7 T was validated by this study as well. Ten volunteers with no history of pain in the AT and five patients with chronic Achilles tendinopathy were recruited. T2* was acquired by fitting bi-component exponential functions, and both short (T2*s) and long (T2*l) were evaluated. With regard to the comparison of patients and volunteers at 7 T, the bulk T2*s was significantly higher in patients, although the bulk T2*l difference was not statistically significant. It seems that ultra-short bi-component T2* measurements in the human Achilles tendon in vivo are feasible using a 3DUTE sequence. Higher SNR at 7 T allows the calculation of both T2* components very accurately. The observed differences between T2*s in healthy and abnormal tendons suggest that advanced quantitative imaging of the human AT may provide additional information beyond standard clinical imaging in reasonably short MR data acquisition times. T2* may be a promising marker for the diagnosis of early tendinopathy in the AT.

gagCEST imaging

Saturation transfer (ST) is a commonly used technique in nuclear magnetic resonance (NMR) [10] and has been proposed as a method for the direct detection of chemical exchange between bulk water protons and protons bound to solutes [11]. The resultant MR imaging scheme is referred to as CEST MRI [12,13]. The basic principle of CEST imaging is a reduction in bulk water MR signal after off-resonant spins are selectively pre-saturated by radiofrequency (RF) irradiation and then undergo chemical exchange with bulk water protons [14]. The hydroxyl and amide protons of glycosaminoglycans (GAG) provide exchange properties that render them principally suited for CEST experiments [15]. In vitro experiments at 11.7 T demonstrated that CEST imaging can be used as a biomarker for cartilage GAG content (gagCEST) in bovine cartilage samples [16].
From the initial studies, the key requirements for in vivo gagCEST examinations can be derived: For accurate quantification of gagCEST effects, it is essential to account for inhomogeneities of the static magnetic field B0 in a sample. For this purpose, fitting of the absorption curve and a separate reference MR data acquisition have been proposed as possible methods. Furthermore, compensation for sample movement during the course of a measurement is crucial for accurate assignment of signal evolution to a certain location. Data from a separate B0 reference also have to be aligned with the measurement data, which induces a greater registration effort. Despite the requirements mentioned above, gagCEST imaging is a valuable tool for the non-invasive assessment of GAG content in vivo. A recent study demonstrated that gagCEST can be used to reliably detect GAG in the knee cartilage of patients who had undergone cartilage repair surgery [17]. This study was conducted at 7.0 T with a 3D GRE-based measurement technique, and 23Na MRI was used as a reference for GAG measurements. The main strength of gagCEST compared to other GAG-sensitive imaging techniques, such as dGEMRIC and sodium imaging, is the relatively short acquisition time, which covers the entire volume of a knee joint in about 10 min, and gagCEST does not require administration of contrast agent and can easily be implemented into a standard imaging protocol.

MR-Spectroscopy at 7T

Another MR method that has the potential to become increasingly important in clinical musculoskeletal MR at 7 T is metabolic imaging or MR spectroscopy (MRS). MRS is a powerful noninvasive tool for the investigation of metabolite concentrations and studies of bioenergetics that could otherwise only be assessed by invasive muscle biopsies [18]. MRS provides information on a cellular level beyond the anatomical information assessed by standard imaging methods and aids in the understanding of various lesions, clinical diagnosis, and treatment monitoring. The improvements in data quality for MRS techniques resulting from the higher B0 (i.e., 7 T) are larger than for standard MR imaging methods [19]. In addition to SNR improvements, 7 T MRS also offers higher spectral resolution. SNR and spectral resolution together contribute to more reliable quantification ofMRS data (i.e., more than three times higher than at 3 T and enable a significantly more rapid acquisition time for MRS experiments [19,20,22]. Based on the detected nuclei, MRS techniques can be classified as 1H-MRS, 31P-MRS, or 13C-MRS. Multinuclear MRS (i.e., 31P-MRS and 13C-MRS), in particular, improves significantly at 7 T [60, 62–66]. 1H-MRS provides insights into both lipid metabolism by quantification of intramyocellular (IMCL)/extramyocellular lipids (EMCL) [23]. Recent reports on studies of lipid metabolism of the calf muscle at 7 T show more accurate and reliable results due to improved separation of individual IMCL and EMCL resonances by both 1D [24,25] and 2D [25] correlated 1H-MRS. This can aid in clinical investigations of pathologic or training-related alterations in lipid muscle metabolism. The 13C-MRS technique allows the in vivo measurement of glycogen, which is one of the major energy sources in the skeletal muscle besides IMCL/EMCL [26,27]. One preliminary study at 7 T provides evidence of the significantly improved spectral quality along with a reproducibility that is more than three times better than that at 3 T. Although 13C-MRS is not likely to enter clinical use, even with these improvements, 13C-MRS can nevertheless improve the understanding of pathological changes in glucose metabolism in muscle disease and could be applied in clinical trials that are designed to evaluate new drugs and therapies.

31P-MRS is a popular tool that reveals the major factors of muscle metabolism noninvasively in a resting state and during muscle exercise [28]. It allows the quantification of temporal changes in high-energy phosphates, intracellular pH, and fluxes of creatine kinase and ATPase reactions, which are important indicators of muscle metabolism. Several groups use 31P-MRS regularly for the investigation of muscle diseases in basic and clinical research. In addition to SNR and spectral resolution improvements, T1 relaxation of 31P metabolites at 7 T is twice as fast as at 3 T (note that 31P is the only nucleus with decreasing T1. This improves the measurement speed, allowing acquisition of high quality data within a few minutes and improved spatial specificity. In addition, at 7 T, there was an 3 times higher reproducibility of 31P-MRS experiments than at 3 T. Apart from improved quantification of known metabolites, the availability of fast and robust MRS methods at 7 T will provide new opportunities for imaging a large clinical spectrum of musculoskeletal diseases, such as mitochondrial disorders, glycolytic defects, systemic diseases affecting muscle metabolism, muscle injury, or diabetes.

In conclusion, these initial clinical studies demonstrate the potential of ultra-high-field MR at 7 T, with the advantage of significantly improved sensitivity for other nuclei, such as 23Na (sodium) and 31P (phosphorus). This will provide new insights into normal and abnormal physiology of musculoskeletal tissues and the metabolism of muscle, and will, therefore, provide new in vivo clinical applications.

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