Evaluation of the dependency of glycosaminoglycan (GAG) chemical exchange saturation transfer (gagCEST) imaging on cartilage GAG content in the ankle at 3 T

Benjamin Schmitt[1], Siegfried Trattnig[2], Claudia Sallinger[2], Jochen Hofstätter[2], Reinhard Windhager[2], and Stephan Domayer[2]
[1]*Centre for High-Field MR, Medical University of Vienna, Vienna, Austria,* [2]*Medical University of Vienna*

Introduction:

MR methods for the non-invasive assessment of cartilage glycosaminoglycan (GAG) content are delayed gadolinium enhanced MRI of cartilage (dGEMRIC) [1], assessment of the T_1 relaxation time in the rotating frame (T_{1rho}) [2], sodium imaging [3] and glycosaminoglycan (GAG)-dependent chemical exchange saturation transfer (gagCEST) [4]. For the latter technique, initial investigations indicated feasibility for cartilage quality assessment in the knee at a magnetic field strength of 7 T [5]. This study was performed to evaluate the feasibility of gagCEST imaging in the ankle on a clinical MR scanner with B_0=3 T. The dependency of gagCEST signal on cartilage GAG content was investigated by comparison of MRI data with quantitative biochemical assessment of cartilage GAG content.

Materials & Methods:

The study comprised 7 ankle samples from human cadavers, which were examined on a clinical 3 T MR System (Siemens Healthcare, Germany) with a standard knee coil (InVivo, USA). PD_w were acquired with turbo spin-echo (TSE) imaging and fatsat (FS) in the sagittal plane (T_E=26ms, T_R=4000ms, resolution=0.4x0.4x3mm³, matrix=384x384x15). GagCEST imaging was performed using a segmented 3D RF-spoiled gradient-echo (GRE) sequence (T_E=3.49 ms, T_R =9.1ms, resolution=0.6x0.6x3.3mm³, matrix=248x256x22, scan time 10:30 min). Selective RF presaturation was achieved using a series of 3 Gaussian RF-Pulses with pulse duration τ_p=100ms, an interpulse delay τ_d=10ms and a continuous-wave amplitude equivalent $B_{1\text{-CWAE}}$ of 2.6µT. Z-spectra from images were corrected for B_0 inhomogeneities on a pixel-by-pixel basis by a smoothing spline method. The asymmetry of the magnetization transfer rate (MTR) as determined by MTR_{asym} (δ) = MTR(+δ)-MTR(–δ) was integrated over the offset range from 0.5 – 2ppm, which corresponds to the resonance signal distribution from exchangeable GAG –OH protons, and used as signal intensity for gagCEST images. For quantitative biochemical analysis of absolute GAG content in cartilage, as gold standard, the tibial and talar cartilage compartments were divided into three segments (lateral, central, medial) with 1cm width in the sagittal plane (Fig. 1). In each segment, 5 contiguous cartilage samples were taken, and a GAG assay (Blyscan B3000 GAG Assay) was used to determine absolute GAG content (µg/mg) and water content of the probes. The calculated GAG concentrations were expressed as the relative weight per cartilage wet weight [% GAG/mg WWt]. To compare MRI data to biochemical analysis, cartilage areas were segmented in MR images and gagCEST values were averaged in regions corresponding to the division used for biochemical analysis. The correlation coefficient (*r*) for gagCEST and biochemical essay was determined using Pearson correlation analysis. To account for individual differences in cartilage water content, which can alter chemical exchange effects, measured gagCEST signals were scaled to the fictive case of 90 % water content in cartilage.

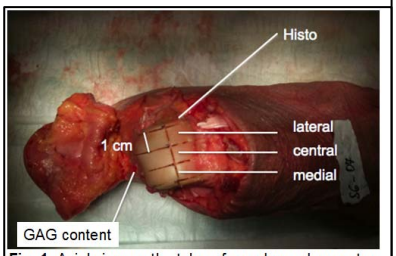

Fig. 1: Axial view on the talus of a cadaver demonstrating the segmentation of cartilage for biochemical essay.

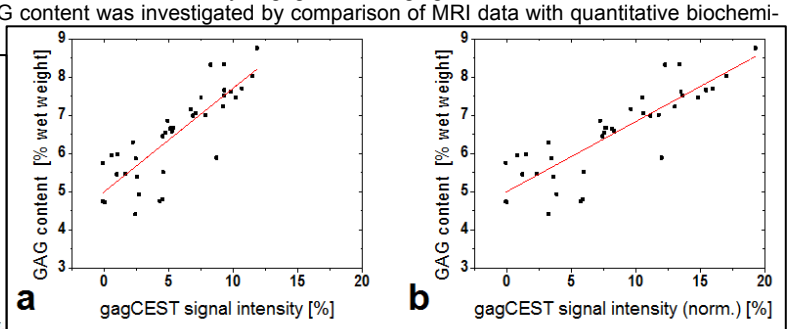

Fig. 2: Biochemically determined cartilage GAG content compared to (**a**) gagCEST signal intensities measured in segmented cartilage, and (**b**) measured gagCEST signal intensities normalized to a fictive case of 90 % relative water content in cartilage. The values in (a) show a linear correlation with *r* = 0.797, which is distinctly increased for the normalized signal values (*r* =0.859) indicating the importance of this correction.

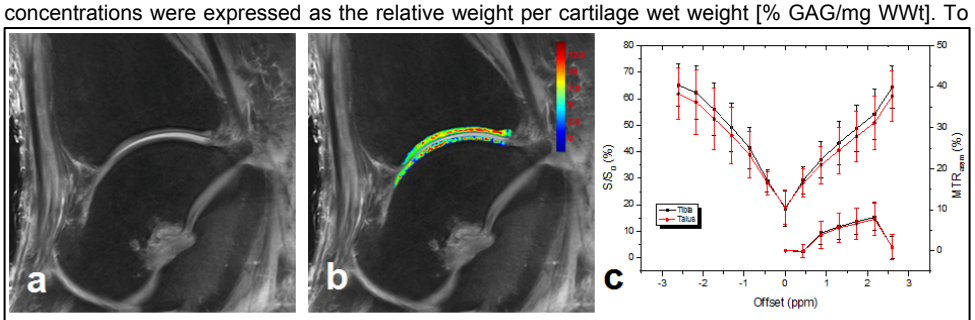

Fig. 3: (**a**) Morphologic PD_w image, (**b**) segmented cartilage with gagCEST signals, (**c**) corresponding z-spectra and analysis of MTR asymmetry (MTR_{asym}) in tibial and talar cartilage. The morphological intact cartilage shows evenly distributed gagCEST values in the tibial cartilage. The signal losses in the posterior part of talar cartilage are attributed to partial volume effects owing to thin cartilage in combination with insufficient spatial resolution. The asymmetry is throughout positive in the range of resonance signals from exchangeable GAG –OH protons (0.5 – 2.0 ppm).

Results:

All examined ankles showed morphologically intact cartilage on PD_w MR images. From the 42 available cartilage samples (7 patients x 2 cartilage surfaces x 3 cartilage segments = 42), 4 samples from ankle # 6 were excluded from analysis due to extremely thin (<< 0.8 mm) cartilage in the medial and lateral segments. The remaining 38 data points showed a linear correlation between gagCEST signal intensities and GAG concentrations with *r* = 0.797 if differences in water contents were neglected (Fig. 2a). If these differences were accounted for, a higher correlation coefficient of *r* =0.859 was obtained (Fig. 2b). The average measured gagCEST signal intensity (Fig. 3) was 5.47±3.52 % (mean±SD), and 8.11±5.32 % with normalized water content. The average GAG content as determined by biochemical analysis was 6.49±1.14 % GAG/mg WWt. The relative water content in cartilage had a mean of 68.85±4.54 %.

Discussion and Conclusion:

The linear correlation between gagCEST signal intensities and cartilage GAG content is in agreement with CEST theory, which yields that CEST effects scale linearly with the concentration of exchanging protons in bulk water if further exchange parameters, such as pH or temperature as well as relaxation times are stable. Thus, our results indicate that gagCEST imaging at 3 T is sensitive to cartilage GAG content in intact tissue samples. However, it seems indispensable to account for the relative water content in cartilage to discriminate changes of gagCEST signal intensities due to actual variations in concentrations of exchangeable GAG protons from misleading effects owing to differences in relative water content. Although the initial results from this study suggest a potential of gagCEST imaging for clinical assessment of cartilage GAG content, further studies, involving larger numbers of patients and a larger variance of cartilage GAG content are needed to evaluate the clinical relevance of the technique, also in comparison to other PG sensitive imaging techniques.

References: [1] Trattnig S *et al*. J. Magn. Reson. Imaging. 2007;26(4). [2] Li X *et al*. Osteoarthritis Cartilage. 2007 ; 15(7). [3] Wheaton AJ *et al*. Radiology. 2004;231(3). [4] Ling W *et al*. PNAS 2008;105(7). [5] Schmitt B *et al*. Radiology. 2011;260(1). [6] Zhou J and van Zijl PCM. Prog. Nucl. Magn. Reson. Spectrosc. 2006; 48.