T_2 mapping and glycosaminoglycan-dependent chemical exchange saturation transfer (gagCEST) imaging of focal lesions in knee cartilage using 3 T MRI

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Introduction:

Glycosaminoglycans (GAG) are elementary components of cartilage, responsible for their biomechanical properties [1]. Focal loss of GAG represents the earliest stages of cartilage degeneration [2]. MR techniques suggested for non-invasive assessment of cartilage GAG content are delayed gadolinium enhanced MRI of cartilage (dGEMRIC) [3], assessment of the T_1 relaxation time in the rotating frame (T_{1rho}) [4], and sodium imaging [5]. Recently, an initial study showed feasibility of GAG-dependent chemical exchange saturation transfer (gagCEST) imaging in the knee at 7 T [6]. The aim of our study was to investigate the potential of gagCEST imaging on a clinical 3 T MR scanner and assess the quality of a retrospective B_0 correction method. GagCEST results from patients with focal knee injuries were compared to T_2 mapping to assess a possible value of gagCEST imaging at 3 T.

Materials & Methods:

The study comprised 3 healthy volunteers, and 9 patients with focal cartilage defects in the knee who were referred for routine diagnostic MRI and asked if they were willing to participate in this study. All patients gave written informed consent to participate in this institutional review board approved study. Experiments were performed on a clinical 3 T MR system (Siemens Healthcare Germany) using a standard knee coil (InVivo, USA). For gagCEST imaging, a 3D RF-spoiled gradient-echo (GRE) sequence was employed (T_E=3.49 ms, T_R =7.7 ms, resolution=0.6x0.6x3.3 mm³, matrix=256x248x30, scan time: 12:48 min). Selective RF presaturation was achieved using a series of 3 Gaussian RF pulses with pulse duration τ_p=100 ms, an interpulse delay τ_d=10 ms, and a continuous-wave amplitude equivalent $B_{1\text{-}CWAE}$ of 2.6μT. In patients, mapping of the T_2 relaxation time was performed using a standard multi-echo spin-echo approach with 7 echo times from 11.9 to 71.4 ms (T_R=1200ms, resolution=0.4x0.4x3 mm³, matrix=320x320x13). In volunteers, a 2D dual echo GRE approach was used for phase mapping (ΔT_E=2.46 ms, T_R=1 s, equal resolution as gagCEST images). To calculate absolute frequency shifts ($\Delta\upsilon$) from the relative phase differences obtained by the phase mapping technique, the absolute resonance frequency was determined in a 2x2x2 mm³ volume placed in femoral cartilage using a STEAM acquisition scheme. To compensate for movement of the knee during the course of a measurement, gagCEST datasets were registered using a non-rigid approach. Z-spectra from images were interpolated with a smoothing spline method and corrected for B_0 inhomogeneities by determination of the position of the signal minimum on a pixel-by-pixel basis. The asymmetry of the magnetization transfer rate (MTR) as determined by $MTR_{asym}(\delta) = MTR(+\delta)-MTR(-\delta)$ was integrated over the offset range from 0.5 to 2ppm, which corresponds to the resonance signal distribution from exchangeable GAG –OH protons, and used as signal intensity for gagCEST images. GagCEST and phase mapping data were registered to compare the B_0 variations determined by z-spectrum analysis to the values determined by phase mapping using Pearson correlation analysis. Assessment of gagCEST values in cartilage was performed by region-of-interest (ROI) based analysis. GagCEST results were compared to T_2 maps qualitatively to rule out influences of altered local T_2 values on gagCEST results.

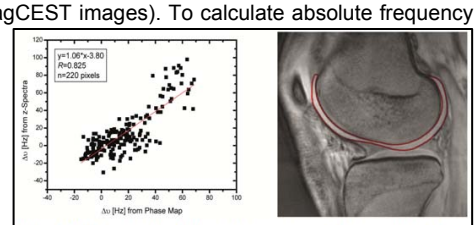

Fig. 1: Differences in bulk water resonance frequencies (Δυ) obtained by phase mapping and retrospective z-spectrum correction in the lateral femoral condyle of volunteer # 3 showing a linear correlation with *R*=0.825.

Results:

Linear correlations were found between $\Delta\upsilon$ values from phase mapping and retrospective analysis of z-spectra in corresponding ROIs placed in different morphologic cartilage regions of volunteers (Fig. 1). The average correlation coefficient obtained was R = 0.840±0.029, (mean±SD, n=12, range: 0.813 – 0.878). The average RMSE of linear fits was 6.41±2.96 Hz (Range: 2.46 – 10.89 Hz), which corresponds to δ=0.05 ppm at 3 T. The asymmetry values and distributions measured in volunteers are displayed in Fig. 2. Focal cartilage lesions with increased T_2 values tended to exhibit similar or higher gagCEST values than surrounding intact cartilage. However, in 4 out of 9 patients, significantly reduced gagCEST signals compared to normal reference tissue (NT) were found in cartilage areas, which were adjacent (AT) to apparent lesions and exhibited no increased T_2 values (Fig's. 3,4).

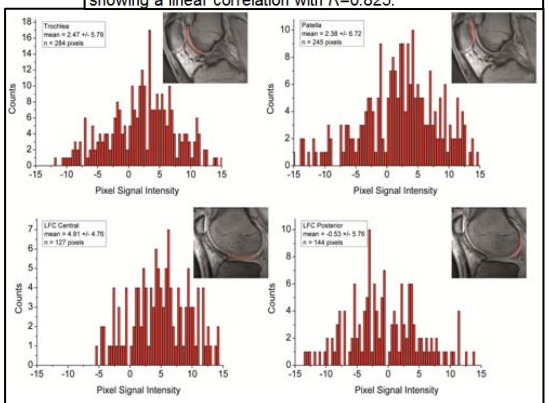

Figure 2: Histogram of gagCEST signal intensities in ROIs (red margins in inserts) from different cartilage areas of volunteers. All regions exhibit normally distributed values. The distribution with the highest mean value was found in the central, weight bearing area of the LFC.

Discussion and Conclusion:

The correlations found between the retrospective B_0 correction method and phase mapping as a reference suggest that this technique is applicable to in vivo gagCEST measurements. Retrospective correction can save scan time and registration of data to a reference scan would not be necessary. Additionally, no systematic tendency for either over- or underestimation of frequency shifts was found for the retrospective correction method. The gagCEST values measured in volunteers followed normal distributions. This indicates that actual effects were detected although measured values were considerably lower compared to values reported for 7 T [6]. This could be explained by stronger RF spillover and shorter lifetime of saturation at 3 T compared to 7 T. The results of this study suggest that gagCEST might be of limited use for assessment of cartilage GAG content in lesions with acute T_2 changes. However, it is indicated that gagCEST may have higher sensitivity to early cartilage changes than T_2 given the differences found between NT and AT. Additionally, the technique could be used in subacute or chronic GAG loss such as in osteoarthritis.

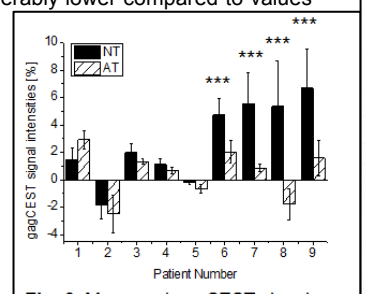

Fig. 3: Measured gagCEST signal intensities from ROIs in lesion-adjacent tissue (AT) and normal reference tissue (NT) of patients. Significant differences between AT and NT were found in patients # 6 to 9 (***: p< 0.01).

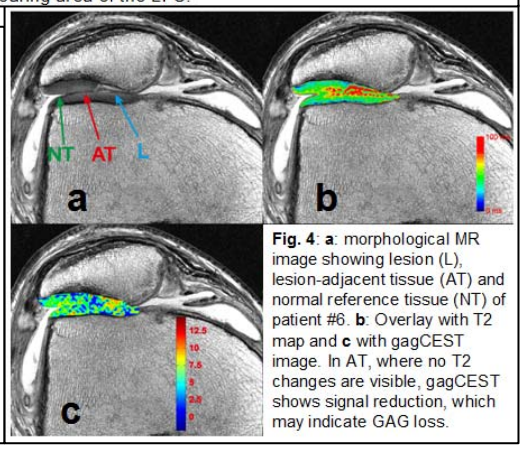

Fig. 4: **a**: morphological MR image showing lesion (L), lesion-adjacent tissue (AT) and normal reference tissue (NT) of patient #6. **b**: Overlay with T2 map and **c** with gagCEST image. In AT, where no T2 changes are visible, gagCEST shows signal reduction, which may indicate GAG loss.

References:

[1] Roughley PJ & Lee ER. Micros Res Tech 1994;28(5). [2] Buckwalter JA *et al.* J Bone Joint Surg Am Vol. 1997;79A. [3] Bashir A *et al.* MRM. 1996;36(5). [4] Li X *et al.* Osteoarthritis Cartilage. 2007;15(7). [5] Wheaton AJ *et al.* Radiology. 2004;231(3). [6] Schmitt B *et al.* Radiology. 2011;260(1).