Quantitative MRI of Osteoarthritis for Multicenter Trials: Standardization between Different Centers and Manufacturers

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Introduction: Quantitative magnetic resonance imaging (qMRI) is a powerful tool which has great promise as a potential biomarker for early detection of osteoarthritis and for evaluating cartilage response to disease-modifying OA drugs[1]. Quantitative measurement of cartilage morphometry provides information about cartilage area, thickness, and volume, while compositional parameters based on cartilage relaxation times and sodium content provide valuable information regarding degradation of the cartilage extracellular matrix [2]. A variety of sequences and coils across several manufacturers have been developed to measure these cartilage parameters, each with their own strengths as well as inherent biases. This makes evaluation of each of these tissue parameters difficult across multicenter trials. One study examined reproducibility of cartilage morphology and T_2 and T_{1rho} relaxation times across sites and platforms and found greater reproducibility of morphology as compared to T_2 and T_{1rho} [3]. Reproducibility of sodium MR has not been assessed across platforms. In this work we assess the repeatability and reproducibility of cartilage morphometry, T_2, and sodium concentration qMRI measurements intra-site and between sites and manufacturers.

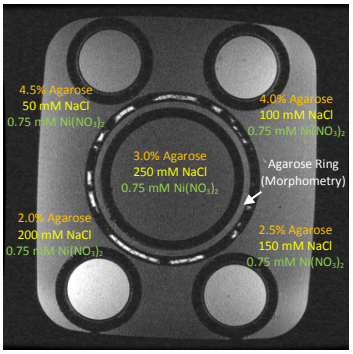

Figure 1: Imaging phantom

Methods: *MRI Scanning:* Imaging experiments were performed at two research sites on Siemens Tim Trio (Siemens Medical Systems, Erlangen, Germany) and GE MR 750 (GE Healthcare, Milwaukee, WI) 3T whole body MRI scanners. A phantom, with 5 cylindrical compartments and one cartilage-like layer, was designed in CAD and then 3D printed (figure 1). The compartments were filled with solutions of varying concentrations of sodium chloride and agarose to create variable sodium and T_2 relaxation values across compartments. The imaging protocol at each site included a 3D double echo steady-state (DESS) sequence (TR = 16.3 ms, TE = 4.7/11.3 ms, flip angle (FA) = 25°, 0.6x0.5x0.7 mm resolution) for morphometry and a multi-echo spin echo (MESE) sequence with seven echo times from 10.6 ms to 73 ms(TR = 2.7s, 0.6x0.4x3.0 mm resolution) for T2 measurement. Sodium images were obtained using a fast gradient-spoiled sequence with the 3D cones k-space trajectory[4] (TR/TE= 35/0.6 ms, FA =70°, 28 signal averages). The imaging protocol at each site consisted of 5 randomized scan blocks with phantom repositioning between each block. Each sequence was repeated twice consecutively, per scan block, giving a total of 10 scans per sequence, per site.

Analysis: T_2 relaxation times were calculated using a mono-exponential fit in OsiriX. Morphometric measurements consisted of an area calculation of each compartment. Sodium concentrations were assessed with ratiometric analysis; the compartment with the largest sodium concentration ([250 mM]) was used as the control. For consistency, each respective quantitative measure for both sites was analyzed by a single individual. The repeatability of each sequence at each site, and reproducibility of each sequence between sites, was assessed using the Bland-Altman method and calculation of the concordance correlation.

Results and Discussion: Bland-Altman plots for intra-scan differences in morphometric measurements, calculated sodium concentrations, and calculated T_2 relaxation times in each phantom compartment across the two sites showed good agreement (Figure 2). A high concordance correlation coefficient (CC) was observed between intra-site measurements of phantom morphometry, T_2 relaxation times, and sodium concentrations for each site (Table 1). This implies that within a given site, quantitative measurements of tissue morphometry, T_2, and sodium concentration are repeatable. A high concordance correlation coefficient (CC = 0.967) was also observed between the two sites for morphometric measurements suggesting that quantitative morphometric measurements can accurately be assessed between imaging sites. Sodium concentration measurements were significantly higher at site 1 compared to site 2 ($p<0.001$), leading to low reproducibility (CC=0.749). However, a high correlation coefficient (r=0.956) suggests that the difference might be readily correctable. The sequence used for sodium image acquisition was written in house and is identical between sites. Thus biases in sodium quantification may be due to MR hardware differences between sites which may be accounted for. MESE T_2 measurements were not reproducible between sites and had a very low correlation. Variations in the T_2 mapping sequences may introduce a bias in T_2 measurements[5]. This study employed manufacturers' product MESE sequences that differ in radiofrequency and gradient pulses that limited our ability to standardize the scan parameters. Along with their inherent biases, the different sequences likely have contributed to the low correlation in T_2 values between sites.

Table 1: Intra-Site Correlation

Site	N	CC	95% Confidence Interval
MESE T2			
1	30	0.998	.997-.999
2	30	1	1.00-1.00
Sodium			
1	10	0.991	.965-.998
2	10	0.995	.982-.999
Morph			
1	30	1	1.00-1.00
2	30	1	1.00-1.00

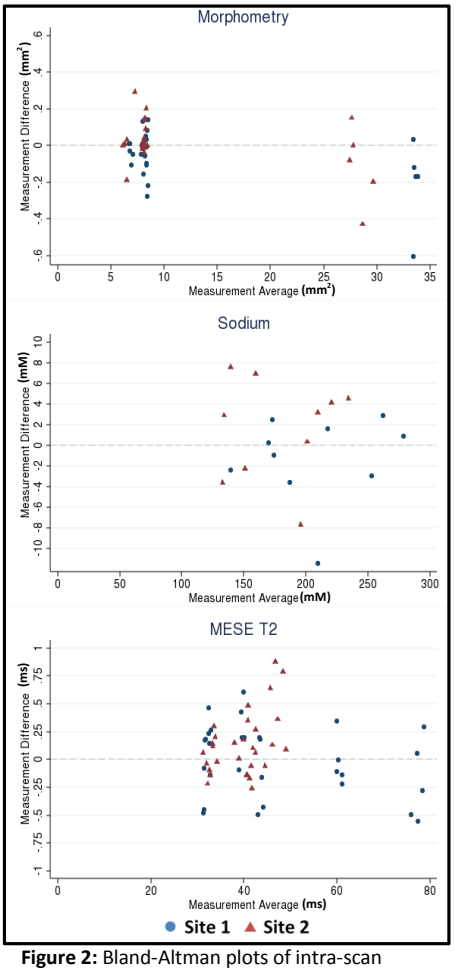

Figure 2: Bland-Altman plots of intra-scan differences across the 2 sites

Conclusion: Correlation is high for morphologic imaging between sites with different manufacturers. For sodium MR with identical imaging sequences at both sites, a correctable bias is introduced, likely due to hardware differences. However, use of different acquisition sequences on different platforms for T_2 measurements showed errors that are not easily correctable. For standardization of quantitative MRI of OA between sites, nearly identical software is likely required.

References: [1] Crema et al. *Radiographics*. 2011;31:37-61 [2] Li et al. *J Magn Reson Imaging.* 2013;38:991-1008. [3] Mosher et al. *Radiology*. 2011; 258:832-42 [4] Irarrazabal et al. *Magn Reson Med* 1995;33:656–662. [5] Liney et al. *J Magn Reson Imag.* 1996; 6:603-7

Acknowledgements: NIH EB002524, AR062068, and CA159992, Arthritis Foundation.