ACRIN-PA 4001: Reproducibility of Cartilage MRI Biomarkers in a Multi-Center Trial

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Introduction: The purpose of this study is to determine reproducibility of quantitative MRI biomarkers of knee cartilage morphometry (volume, mean thickness, surface area) and composition (T1rho, T2) in a multi-center/multi-vendor trial.

Methods: 53 participants were recruited into the study at 5 centers in the ACRIN-PA Network (University of Pennsylvania, Thomas Jefferson University, Fox Chase Cancer Center, Penn State University, and University of Pittsburgh). Participants were divided into 3 cohorts: normal, minimal osteoarthritis and moderate osteoarthritis based on Kellgren and Lawrence scoring of knee radiographs. Cartilage volume, mean thickness, and surface area was determined from manual segmentation of axial and coronal images of the target knee obtained using a water excited 3D T1-weighted spoiled gradient echo sequence at 3.0 T with an in-plane resolution of 0.30 mm and section thickness of 1mm. T1rho magnetization was prepared using a 3 pulse cluster consisting of two 90^o hard pulses and a low power spin lock pulse, and imaged with coronal and axial 3D balanced fast field echo sequences at 3.0T. A series of 5 T1rho weighted images was obtained by varying the duration of the spin lock (TSL: 1ms, 10ms, 20 ms, 30 ms, 40 ms). Cartilage T2 was measured using coronal and axial 7 echo train 2D MSME sequences with TR/TE of 1500ms/16ms to 112 ms. Both T1rho and T2 MSME images were obtain with a section thickness of 4 mm and in-plane resolution of 0.55 mm for T1rho and 0.36 mm for T2 source images. T1rho and T2 maps were calculated by fitting the signal intensity of the source images on a pixel by pixel basis. Cartilage regions of interest (ROI) were segmented by location in the joint (medial femoral, lateral femoral, medial tibial, lateral tibial and patella) as well as zones based on distance from the articular surface (deep, middle and surface zone).

Each participant underwent 4 sequential MRI evaluations within a 4 week period to calculate precision error. Intraclass correlation coefficient (ICC) was calculated for each parameter (cartilage volume, mean thickness, surface area, T1rho and T2), stratified by cohort (normal, minimal OA and moderate OA) and location (medial femoral, lateral femoral, medial tibial, lateral tibial and patella) yielding 15 sites. For T1rho and T2 additional sub regional analysis was performed based on distance from articular surface (deep, middle and surface zone) resulting in 45 sites. ICC values were interpreted as follows: *poor reproducibility* ICC = 0.00 to 0.40, *moderate* ICC= 0.40 to 0.59, *substantial* ICC 0.60 to 0.74, *excellent* ICC 0.75 to 0.84, *almost perfect* 0.85 to 1.00.

Results: As indicated in *Table 1*, morphometric biomarkers had almost perfect reproducibility for all 15 sites analyzed. The range of ICC values was 0.989 to 0.999. Reproducibility of T1rho was lowest of the biomarkers evaluated and varied based on location. The best reproducibility of T1rho was observed in the patella with an ICC> 0.85 for all zones and cohorts. Lowest reproducibility was observed in medial tibial cartilage with ICC values ranging from 0.20 to 0.74. Better reproducibility was observed in cartilage T2 where 31 of 45 sites (68%) had near perfect or excellent reproducibility. Pooling the depth dependent zones substantially improved reproducibility for compositional biomarkers. When T1rho zones were pooled all but the medial tibial zone demonstrated ICC values > 0.65. Pooled cartilage T2 values had ICC values > 0.85 for all but the lateral femoral condyle.

Table 1: Reproducibility of cartilage MRI biomarkers

	Volume		Thickness		Area		T1rho		T2	
Reproducibility	#†	%	#†	%	#†	%	#‡	%	#‡	%
Near perfect	15	100%	15	100%	15	100%	1	2%	20	44%
Excellent	0	0%	0	0%	0	0%	4	9%	11	24%
Substantial	0	0%	0	0%	0	0%	8	18%	8	18%
Moderate	0	0%	0	0%	0	0%	14	31%	4	9%
Poor	0	0%	0	0%	0	0%	18	40%	2	4%

† 15 sites evaluated for cartilage morphology: 3 cohorts (normal, minimal OA and moderate OA) and 5 locations (medial femoral, lateral femoral, medial tibial, lateral tibial and patella)

‡ 45 sites evaluated for T1rho and T2: 3 cohorts (normal, minimal OA and moderate OA), 5 locations (medial femoral, lateral femoral, medial tibial, lateral tibial and patella), and 3 zones (deep, middle and surface zone)

Conclusion: MRI measurements of cartilage morphometry are highly reproducible in a multi-center/multi-vendor trial. Subregional T1rho analysis should not be performed based on depth from the articular surface. Improved reliability is obtained when T1rho analysis is performed using data obtained using the full thickness of the cartilage, allowing analysis at the level of the cartilage plate. Cartilage T2 mapping is sufficiently reproducible to allow for subregional analysis based on depth from articular surface.

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