MULTI-TISSUE ASSESSMENT AND 24-MONTH PROGRESSION OF SEMI-QUANTITATIVE MRI BIOMARKERS OF KNEE OSTEOARTHRITIS IN THE IMI-APPROACH COHORT

[1,2]Frank W. Roemer, [3]Anna Wisser, [3]Susanne Maschek, [1,4]Ali Guermazi, [3]Felix Eckstein, [5]Anne-Karien Marijnissen, [5]Mylène Jansen, [5]Floris Lafeber, [6]Agnes Lalande, [5]Harrie Weinans, [7]Francisco Blanco, [8]Francis Berenbaum, [9]Margreet Kloppenburg, [10]Ida K Haugen, [11]Christoph Ladel, [1]Rafael Heiss, [12]Jaume Bacardit, [9]Lotte A van de Stadt, [3]Wolfgang Wirth

[1] Universitätsklinikum Erlangen & Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany; [2]Boston Univ. Sch. of Med., Boston, MA; [3]Paracelsus Med. Univ. & Chondrometrics GmbH, Salzburg, Austria & Freilassing, Germany,Austria; [4]VA Boston Hlth.care System, West Roxbury, MA, [5]Utrecht Univ.Med. Ctr., Utrecht, Netherlands, [6] Servier, Suresne, France, [7]Grupo de Investigación de Reumatologia (GIR),INIBC-Complejo Hosp Univ de A Coruña, SERGAS, Univ. de A Coruña, A Coruña, Spain, [8] Dept. of Rheumatology, AP-HP Saint-Antoine Hosp, Sorbonne Univ., INSERM, Paris, France, [9]Dept. Of Rheumatology, Leiden Univ. Med. Ctr., Leiden, Netherlands, [10]Div. of Rheumatology and Res., Diakonhjemmet Hosp., Oslo, Norway [11] Independent Consultant, Darmstadt, Germany; [12]Newcastle University, Newcastle, UK

BACKGROUND AND PURPOSE

• The Innovative Medicines Initiative - Applied Public-Private Research enabling OsteoArthritis Clinical Headway (IMI-APPROACH) consortium is a longitudinal cohort study to combine conventional and new disease markers and to identify different OA phenotypes [1]

• Historical data were used to train machine learning models to provide a structural and pain progression score for each individual, which was used as basis for inclusion

•Study parameters used to assess structural progression include quantitative MRI of cartilage including thickness and semi-quantitative MRI scoring of cartilaginous and non-cartilaginous features of OA

• Aim was to describe baseline multi-tissue semiquantitative MRI evaluation of index knees and to describe change for different MRI features based on number of subregion-approaches and change in maximum grades over a 24-month period.

METHODS

•MRIs were acquired using clinical 1.5T or 3T MRI systems

•The clinical pulse sequence protocol included an axial, a sagittal, a coronal intermediate-weighted fat-suppressed sequence and a T1-weighted coronal turbo spin echo sequence that were all used for SQ evaluation

• MRIs were read at baseline and 24-months for cartilage damage, bone marrow lesions (BML), osteophytes, meniscal damage and extrusion, and Hoffa- and effusion-synovitis by a single trained reader (FWR) using the semi-quantitative MOAKS instrument (**Figure 1**) [2]

•In addition, within-grade changes were coded that fulfill the definition of a definite visual change but do not fulfill the definition of a full-grade change on the ordinal scales applied. Within-grade changes were applied for cartilage and BML assessment.

•For reliability assessment, 20 MRIs were randomly selected to represent the spectrum of study sites and disease severity.

•Descriptive statistics are used to report frequencies for the different features and parameters for baseline and change over time.

•Mann-Whitney-U test was applied to describe differences between knees without radiographic OA (i.e. KL 0 and 1) vs. those with radiographic OA (i.e. KL 2-4).

•For some features raw distributions were grouped into categories. In these instances, descriptive statistics are presented for both raw and categorical versions of features.

•For the longitudinal analyses, only those knees with complete and available baseline and 24-months data for the respective feature were included.

•Weighted kappa statistics were applied to determine inter- and intra-observer reliability for baseline and change over time.

RESULTS

• Of the 297 IMI-APPROACH participants, 289 had a readable baseline scan and at least one feature assessable

• There were 223 women (76.8%). Participants were on average 66.6±7.1 years old and had a body mass index (BMI) of 28.1±5.3 kg/m². A considerable proportion of the knees had no definite radiographic OA (45%, KL 0: n=52; KL1: n=77), but the majority (55.3%) of the knees had definite signs of radiographic OA (KL 2: n=65 KL 3: n=84, KL 4: n=11)

• Summarizing the intra- and inter-reader results for the baseline assessment, all of the measures showed at least substantial agreement ranging between 0.71 for maximum cartilage area extent on a knee level (intra-reader) and 1.00 for several features

• Any change in total cartilage MOAKS score was seen in 53.1% considering only full-grade changes and in 73.9% including full-grade and within-grade changes. Any medial cartilage progression was seen in 23.9% and any lateral progression in 22.1% (**Table 1**)

• While for the medial and lateral compartments numbers of subregions with improvement and worsening of BMLs were very similar, for the PFJ more improvement was observed compared to worsening (15.5% vs. 9.0%). Including within grade changes, the number of knees showing BML worsening increased from 42.2% to 55.6%.

• While for some features 24-months change was rare, frequency of change was much more common in the ROA compared to the non-ROA subgroup (e.g. worsening of total MOAKS score cartilage in 68.4% of ROA knees vs. 36.7% of no-ROA knees, and 60.7% vs. 21.8% for an increase in maximum BML score per knee)

Table 1. Cartilage damage change – any MOAKS worsening (baseline to 24 months)

	N=226		All knees		No ROA		ROA		P-value
			Frequency	Percent	Frequency	Percent	Frequency	Percent	
Worsening - total MOAKS cartilage score (only full-grade worsening)									
Knee	None vs. any	0	106	46.9	69	63.3	37	31.6	0.0000
		≥1	120	53.1	43	36.7	80	68.4	
	Number of regions	1	60	26.5	26	23.9	34	29.1	
		2	35	15.5	9	8.3	26	22.2	
		3	17	7.5	3	2.8	14	12.0	
		4	6	2.7	2	1.8	4	3.4	
		5	2	0.9	0	0.0	2	1.7	
MFTJ	None vs. any	0	172	76.1	96	88.1	76	65.0	0.0000
		≥1	54	23.9	13	11.9	41	35.0	
	Number of regions	1	40	17.7	11	10.1	29	24.8	
		2	12	5.3	1	0.9	11	9.4	
		3	2	0.9	1	0.9	1	0.9	
LFTJ	None vs. any	0	176	77.9	99	90.8	77	65.8	0.0000
		≥1	50	22.1	10	9.2	40	34.2	
	Number of regions	1	35	15.5	8	7.3	27	23.1	
		2	11	4.9	2	1.8	9	7.7	
		3	3	1.3	0	0.0	3	2.6	
		4	1	0.4	0	0.0	1	0.9	
PFJ	None vs. any	0	168	74.3	83	76.1	85	72.6	0.5176
		≥1	58	25.7	26	23.9	32	27.4	
	Number of regions	1	43	19.0	20	18.3	23	19.7	
		2	13	5.8	5	4.6	8	6.8	
		3	2	0.9	1	0.9	1	0.9	
Worsening - total score including within-grade worsening									
Knee	None vs. any	0	85	37.6	61	56.0	24	20.5	0.0000
		≥1	141	73.9	48	44.0	93	79.5	
	Number of regions	1	59	26.1	30	27.5	29	24.8	
		2	43	19.0	12	11.0	31	26.5	
		3	29	12.8	4	3.7	25	21.4	
		4	7	3.1	2	1.8	5	4.3	
		5	3	1.3	0	0.0	3	2.6	
MFTJ	None vs. any	0	154	68.1	93	85.3	61	52.1	0.0000
		≥1	72	31.9	16	14.7	56	47.9	
	Number of regions	1	50	22.1	13	11.9	37	31.6	
		2	16	7.1	2	1.8	14	12.0	
		3	6	2.7	1	0.9	5	4.3	
LFTJ	None vs. any	0	168	74.3	97	89.0	71	60.7	0.0000
		≥1	58	25.7	12	11.0	46	39.3	
	Number of regions	1	38	16.8	10	9.2	28	23.9	
		2	16	7.1	2	1.8	14	12.0	
		3	3	1.3	0	0.0	3	2.6	
		4	1	0.4	0	0.0	1	0.9	
PFJ	None vs. any	0	154	68.1	77	70.6	77	65.8	0.3948
		≥1	72	31.9	32	29.4	40	34.2	
	Number of regions	1	54	23.9	25	22.9	29	24.8	
		2	16	7.1	6	5.5	10	8.5	
		3	2	0.9	1	0.9	1	0.9	

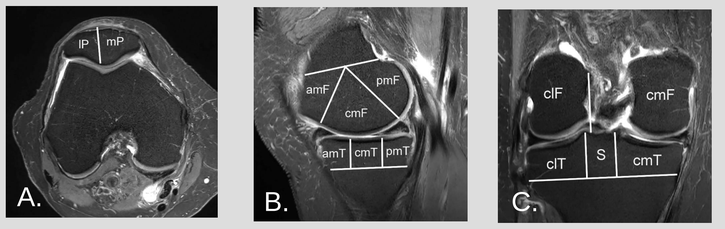

Figure 1. Subregional division for cartilage and bone marrow lesion assessment using the MOAKS instrument. Both features are assessed in 14 articular subregions. A. Axial intermediate-weighted fat suppressed image shows subregional division of the patella into the medial (mP) and lateral patella (lP). B. Sagittal intermediate-weighted fat suppressed image of the medial compartment shows the three femoral and three tibial subregions. The femur is subdivided into the anterior (amF), central (cmF) and posterior (pmF) subregions. The tibia is subdivided into the anterior (amT), central (cmT) and posterior (pmT) subregions. The lateral compartment is subdivided in corresponding fashion in the sagittal plane (not shown). C. Coronal intermediate-weighted fat suppressed image shows the central femoral and tibial subregions. The tibial S region (subspinous – adjacent to the tibial spines) is not considered for BML and cartilage evaluation.

CONCLUSION

• A wide range of MRI-detected structural pathologies was present in the APPROACH cohort

• More severe changes over time were detected primarily among the ROA group suggesting that once disease is structurally established it progresses more likely than pre-radiographic OA

• The role of structural predictors of progression that are also potential therapeutic targets for cartilage-anabolic or anti-catabolic approaches, anti-inflammatory agents or compounds targeting subchondral bone changes should be the focus of further evaluation

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