

# #255: FLUCTUATION IN BONE MARROW LESIONS AND INFLAMMATORY MRI MARKERS AND CONCURRENT ASSOCIATIONS WITH QUANTITATIVE CARTILAGE LOSS: DATA FROM THE IMI-APPROACH COHORT

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## BACKGROUND AND PURPOSE

- The Innovative Medicines Initiative - Applied Public-Private Research enabling OsteoArthritis Clinical Headway (IMI-APPROACH) consortium is a longitudinal cohort study designed to combine conventional and new disease markers, and to identify different OA phenotypes <sup>1,2</sup>
- Measures used to assess structural progression encompassed quantitative MRI of cartilage including thickness and semi-quantitative MRI scoring of cartilaginous and non-cartilaginous features of knee OA
- While for a long time OA was understood as a one-way road to joint failure, in recent years symptom fluctuation has been linked to concomitant fluctuation of structural changes in the same direction <sup>3</sup>
- Particularly subchondral bone marrow lesions (BMLs) and inflammatory markers of disease (effusion-synovitis and Hoffa-synovitis) show fluctuation and have been considered as potential treatment targets <sup>4</sup>
- Several studies have shown that worsening or improvement in these features may also have impact on structural progression, which is frequently used as an outcome measure in clinical DMOAD trials <sup>5</sup>
- We aimed to assess whether worsening of BMLs and MRI-defined signs of inflammation is associated with increased rates of femorotibial (FTJ) and ipsicompartamental cartilage loss over 24 months when compared to those compartments without change of these features and whether improvement in those parameters is associated with less cartilage loss in the same compartment

## METHODS

- MRIs were acquired at 5 sites using clinical 1.5T or 3T MRI systems
- MRI assessment was performed using the semi-quantitative MOAKS instrument including assessment of BMLs in 10 subregions of the FTJ joint, effusion-synovitis and Hoffa-synovitis by a single trained reader (FWR, Boston Imaging Core Lab)
- Quantitative cartilage thickness measurements were performed by experienced readers with quality control by an expert reader (Chondrometrics)
- Change in overall number of subregions affected by any BML was defined as the difference between the number of subregions affected by any BML at 24 months (size>0) and the number of subregions affected by any BML at baseline. A positive number means more subregions had BMLs at 24 months compared to baseline (=worsening), while a negative number means that less subregions had BMLs at FU compared to BL (=improvement)
- 24-months changes in Hoffa-synovitis and effusion-synovitis were assessed separately and categorized as improvement, no change, or worsening
- The medial and lateral tibio-femoral joint compartments (MFTJ and LFTJ) and the entire FTJ was considered for analyses
- Between-group comparisons regarding cartilage loss in the medial and lateral compartment were performed using ANOVA
- Results were presented as mean difference and 95% confidence intervals.

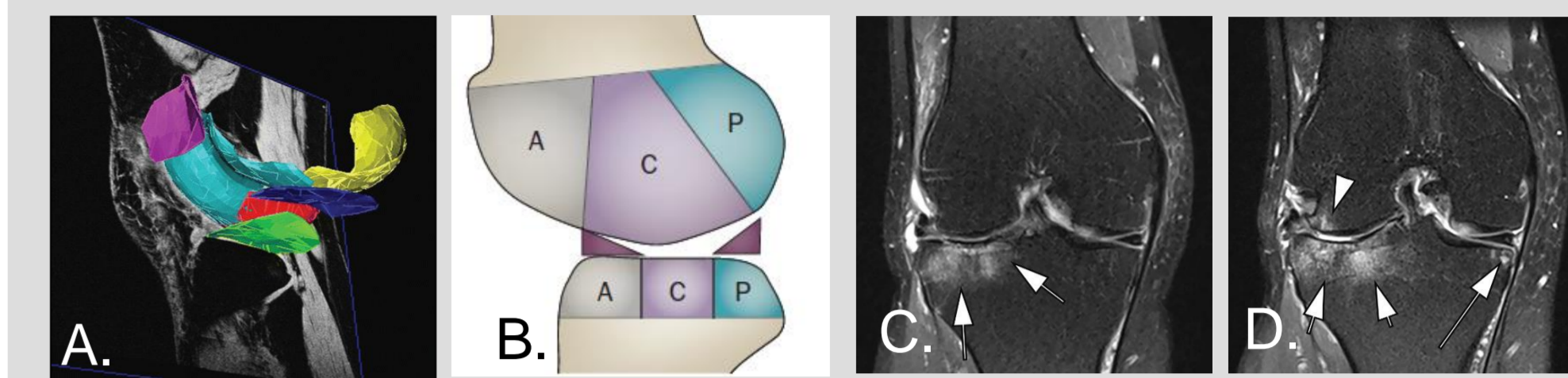
## RESULTS

- Complete baseline and 24 month follow-up MRI data was available for 224 of the 289 participants
- Regarding structural disease severity at baseline, 129 (44.5%) participants did not have radiographic OA, 65 (22.5%) had KL2, 84 (29.1%) KL3 and 11 (4%) KL4
- Mean age was 66.7 ( $\pm 7.2$ ) years, mean BMI 27.8 ( $\pm 5.1$ ) kg/m<sup>2</sup>
- For the entire FTJ, 34 (15.1%) knees showed improvement, 161 (71.9%) no change and 29 (12.9%) knees showed worsening regarding number of subregions with BMLs. For the MFTJ, these numbers were 22 (6.7%), 181 (80.8%) and 21 (9.4%); for the LFTJ 17 (7.6%), 194 (86.6%) and 13 (5.8%), respectively
- Hoffa-synovitis improvement was observed in 15 (14.7%), no change in 189 (84.4%) and worsening in 18 (8.0%) knees
- Effusion-synovitis improvement was seen in 22 (9.8%), no change in 150 (67.0%) and worsening in 51 (22.8%) knees
- Knees with worsening of BMLs in the FTJ had more than twice the rates of cartilage loss compared to those with no change (mean change -0.31 mm, 95% CI [-0.43, -0.18] vs. -0.13 mm [-0.16, -0.10]; p=0.001). Similar findings were observed for the MFTJ (mean change -0.18 mm, 95% CI [-0.26, -0.09] vs. -0.09 mm [-0.11, -0.07]; p=0.04) and the LFTJ (mean change -0.16 mm, 95% CI [-0.31, -0.01] vs. -0.06 mm [-0.08, -0.04]; p=0.10)
- Change in Hoffa- or effusion-synovitis, or the combination of both features, did not show any differences in rates of cartilage loss compared to those without change
- Table 1** shows the delta values of thickness change for knees with improvement or worsening compared to those without change
- Figure 1** shows examples of image assessment of fluctuation of BMLs over 24 months

**Table 1. Change of BMLs and inflammatory markers over 24 months and concurrent mean change in FTJ or ipsicompartamental cartilage thickness (delta compared to no change, in mm)**

	N	Mean <sup>1</sup>	95% CI	p	N	Mean <sup>1</sup>	95% CI	p
<b>Cartilage thickness change stratified by BML number of region change compared to those without change (delta)</b>								
		<b>Improvement</b>				<b>Worsening</b>		
FTJ	34	-0.145	-0.255; -0.035	0.005	29	-0.176	-0.293; -0.058	<b>0.001*</b>
MFTJ	22	-0.063	-0.145; 0.018	0.18	21	-0.087	-0.170; -0.004	<b>0.04*</b>
LFTJ	17	-0.048	-0.142; 0.046	0.65	13	-0.094	-0.200; 0.012	0.10
<b>Cartilage thickness change stratified by Hoffa-synovitis change compared to those without change (delta)</b>								
		<b>Improvement</b>				<b>Worsening</b>		
FTJ	15	0.055	-0.108; 0.217	1.00	18	-0.043	-0.192; 0.106	1.00
MFTJ	15	0.037	-0.062; 0.135	1.00	18	-0.036	-0.126; 0.055	1.00
LFTJ	15	0.018	-0.082; 0.118	1.00	18	-0.008	-0.100; 0.084	1.00
<b>Cartilage thickness change stratified by type of effusion-synovitis change compared to those without change (delta)</b>								
		<b>Improvement</b>				<b>Worsening</b>		
FTJ	22	0.062	-0.076; 0.200	0.84	51	0.000	-0.098; 0.098	1.00
MFTJ	22	0.013	-0.071; 0.096	1.00	51	-0.033	-0.092; 0.027	0.55
LFTJ	22	0.049	-0.035; 0.134	0.49	51	0.033	0.027; 0.093	0.57
<b>Cartilage thickness change stratified by combined inflammatory marker change compared to those without change (delta)</b>								
		<b>Improvement</b>				<b>Worsening</b>		
FTJ	33	0.080	-0.037; 0.197	0.31	57	0.016	-0.080; 0.111	1.00
MFTJ	33	0.031	-0.040; 0.102	0.89	57	-0.016	-0.074; 0.042	1.00
LFTJ	33	0.049	-0.023; 0.121	0.31	57	0.032	-0.027; 0.090	0.59

N – number of knees; 95% CI – 95% confidence interval; FTJ – femorotibial joint; MFTJ – medial femorotibial joint; LFTJ – lateral femorotibial joint  
<sup>1</sup> Delta of thickness change in mm compared to those with stable BMLs or stable inflammatory markers; positive numbers indicate more change compared to those with stable features  
 \*statistically significant at p<0.05



**Figure 1.** A. The outcome of this study was Q cartilage loss based on tissue segmentation of 3D high resolution MRI. B. Drawing (from Ref. 4) shows sagittal representation of the subregional division of SQ MOAKS assessment of the lateral TFJ. C. Coronal intermediate-weighted fat suppressed image shows a large (grade 3) bone marrow lesion at the central subregion of the lateral tibia (arrows). No additional bone marrow lesions are seen. D. At the follow-up visit, in addition to the tibial bone marrow lesion that was already present at baseline (short arrows), incident bone marrow lesions are observed at the central subregion of the lateral femur (arrowhead) and the central medial tibia (long arrow). This knee would be categorized as having worsened regarding bone marrow lesions as change from one to three subregions affected was observed.

## CONCLUSION

- Knees with worsening of the number of subregions affected by BMLs show almost twice the rates of cartilage thickness loss in the FTJ over 24 months compared to those with stable BMLs
- No significant differences were observed between knees with improvement in BMLs compared with those with stable BMLs
- No differences were seen for change in inflammatory markers and concomitant rates of cartilage loss compared to those with stable MRI markers of inflammation.
- Therapeutic approaches resulting in decreased worsening of BMLs may have protective effects on quantitative cartilage loss.

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## FUNDING

**Funding:** This work was supported by the Innovative Medicines Initiative Joint Undertaking under grant agreement no 115770, resources of which are composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA companies' in kind contribution. See [www.imi.europa.eu](http://www.imi.europa.eu) and [www.approachproject.eu](http://www.approachproject.eu).

