

MENISCAL DAMAGE AND BONE MARROW LESIONS ARE ASSOCIATED WITH CONCURRENT QUANTITATIVELY DEFINED CARTILAGE THICKNESS LOSS OVER TWO YEARS: THE FNIH BIOMARKERS CONSORTIUM STUDY

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BACKGROUND AND PURPOSE

- The Foundation for the National Institutes of Health (FNIH) OA Biomarkers Consortium is a nested case-control study based within the larger OAI study
- One goal of this study was to determine the association between semiquantitative MRI biomarkers and knee OA progression over 48 months
- The results showed that worsening of several structural MRI features from baseline to 24 months was associated with increased odds of being a 'case' at 48 months (defined as worsening of radiographic OA and worsening of pain) ¹
- There is a gap in knowledge whether change of non-cartilaginous features such as meniscus extrusion and damage, bone marrow lesions (BML) or inflammatory features are also associated with short term concurrent progression in cartilage loss as defined by quantitative (Q) measures
- Aim of this study was to assess whether worsening of meniscal damage, BMLs and MRI-defined signs of inflammation (effusion-synovitis and Hoffa-synovitis) is associated with concurrent increased rates of cartilage loss over 24 months when compared to those compartments without worsening of these features

METHODS

- Of the 600 participants from the OAI FNIH study, 599 had MOAKS ² assessments of meniscal extrusion, meniscal damage, BMLs, and effusion-synovitis and Hoffa-synovitis as well as Q cartilage thickness measurements (**Figure 1**)
- MOAKS grades meniscal extrusion from 0 to 3 in the coronal plane. Meniscal damage is assessed on an 8-point scale and was collapsed to either normal (including normal and meniscal signal=grade 0), any tear (including horizontal, vertical, radial and complex=grade 1) and any maceration (including partial and complete maceration=grade 2)
- BMLs are evaluated on a three-dimensional scale. For this study only the size portion was considered
- Effusion-synovitis and Hoffa-synovitis are scored from 0-3 each
- Change was defined as an any increase in 1 or 2 grades in meniscal damage scores and in similar fashion and separately for meniscal extrusion in a compartment
- For BMLs, change was defined as ipsicompartamental change in maximum BML size or change in number of subregions affected by BMLs in a compartment
- Worsening by 1 or 2 grades in either effusion- or Hoffa-synovitis was considered change
- Two-year change in medial compartment cartilage thickness (MFTC) change was stratified by concurrent ipsicompartamental change in meniscus extrusion, meniscus damage, BML (size and number of subregions) and inflammation score
- Between-group comparisons were performed using ANCOVA with adjustment for age, sex, and BMI
- Results were presented as adjusted mean difference and 95% confidence intervals
- Change in the lateral compartment was assessed in identical fashion

RESULTS

- Knees with 1 grade increase in extrusion in the MFTC (n=71) showed more MFTC cartilage loss than knees that remained stable (mean adjusted difference (MAD) -0.15 mm, 95% CI: [-0.20, -0.10] mm), which was even more pronounced for combined 2/3 grade increase (MAD -0.26 mm, 95% CI: [-0.33, -0.18]mm)
- Comparable findings were seen for 1 and 2 grade meniscal damage worsening
- Regarding BMLs, an increase in 1 subregion affected by BMLs resulted in a MAD of cartilage loss of -0.10 mm, 95% CI: [-0.14, -0.06] mm, while this effect almost tripled for change in 2 or more subregions (MAD -0.31 mm, 95% CI: [-0.37, -0.24]mm)
- Similar findings were observed for increase in maximum BML size per subregion
- Increase in either effusion- and/or Hoffa-synovitis by 1 grade resulted in a MAD of -0.07 mm, 95% CI: [-0.10, -0.03] mm and an increase of 2 grades in -0.25 mm, 95% CI: [-0.33, -0.17] mm.
- Table 1** shows these results in detail
- Less change was observed in the lateral compartment and the associations were not as strong as for the medial compartment (data not shown).

Table 1. Change of non cartilaginous tissue features (MOAKS) over 24 months and concurrent mean change in cartilage thickness in the medial femoro-tibial compartment

Δ	N	Mean	SD	(95% CI)	Mean adj. diff.	(95% CI)
Increase in MOAKS MFTC meniscus extrusion scores ¹						
0	500	-0.07	0.18	(-0.09, -0.05)	(Reference)	
1	71	-0.22	0.26	(-0.28, -0.16)	-0.15	(-0.20, -0.10)
2/3	27 (25/2)	-0.32	0.26	(-0.42, -0.22)	-0.26	(-0.33, -0.18)
Any	98	-0.25	0.27	(-0.30, -0.20)	-0.18	(-0.22, -0.14)
Increase in MOAKS MFTC meniscus damage scores ²						
0	530	-0.08	0.20	(-0.10, -0.07)	(Reference)	
1	48	-0.18	0.24	(-0.25, -0.11)	-0.10	(-0.16, -0.04)
2	17	-0.36	0.25	(-0.49, -0.24)	-0.28	(-0.37, -0.18)
Any	65	-0.23	0.25	(-0.29, -0.17)	-0.14	(-0.20, -0.09)
Increase in MOAKS MFTC osteophyte scores						
0	540	-0.08	0.18	(0.09, -0.06)	(Reference)	
1	54	-0.30	0.31	(-0.39, -0.21)	-0.23	(-0.28, -0.18)
2	3			n/a (too few knees)		
Increase in number of MFTC subregions with BMLs ³						
0	414	-0.06	0.17	(-0.08, -0.04)	(Reference)	
1	103	-0.16	0.23	(-0.21, -0.12)	-0.10	(-0.14, -0.06)
2-4	35 (31/3/1)	-0.38	0.33	(-0.49, -0.26)	-0.31	(-0.37, -0.24)
Any	138	-0.22	0.27	(-0.26, -0.17)	-0.15	(-0.19, -0.11)
Increase in maximum MOAKS MFTC BML size scores						
0.0	427	-0.05	0.16	(-0.07, -0.04)	(Reference)	
0.5 ⁴	7	-0.10	0.10	(-0.20, -0.01)	-0.01	(-0.16, 0.13)
1.0	109	-0.17	0.21	(-0.21, -0.13)	-0.11	(-0.15, -0.07)
2.0	39	-0.29	0.32	(-0.39, -0.18)	-0.23	(-0.29, -0.17)
3.0	16	-0.37	0.34	(-0.55, -0.19)	-0.31	(-0.40, -0.21)
Any	171	-0.21	0.26	(-0.25, -0.17)	-0.15	(-0.19, -0.12)
Increase in MOAKS effusion-synovitis and/or Hoffa-synovitis scores ⁵						
0	414	-0.07	0.18	(-0.09, -0.05)	(Reference)	
1	157	-0.14	0.24	(-0.18, -0.10)	-0.07	(-0.10, -0.03)
2	23	-0.32	0.27	(-0.43, -0.20)	-0.25	(-0.33, -0.17)
Any	180	-0.16	0.25	(-0.20, -0.12)	-0.15	(-0.19, -0.12)

¹N=1 with improvement, ²N=4 with improvement, ³N=46 with improvement, ⁴0.5 = within-grade change, ⁵N=5 with improvement.

•MFTC = medial femoro-tibial compartment; SD = standard deviation, mean adj. diff. = mean adjusted difference in mm

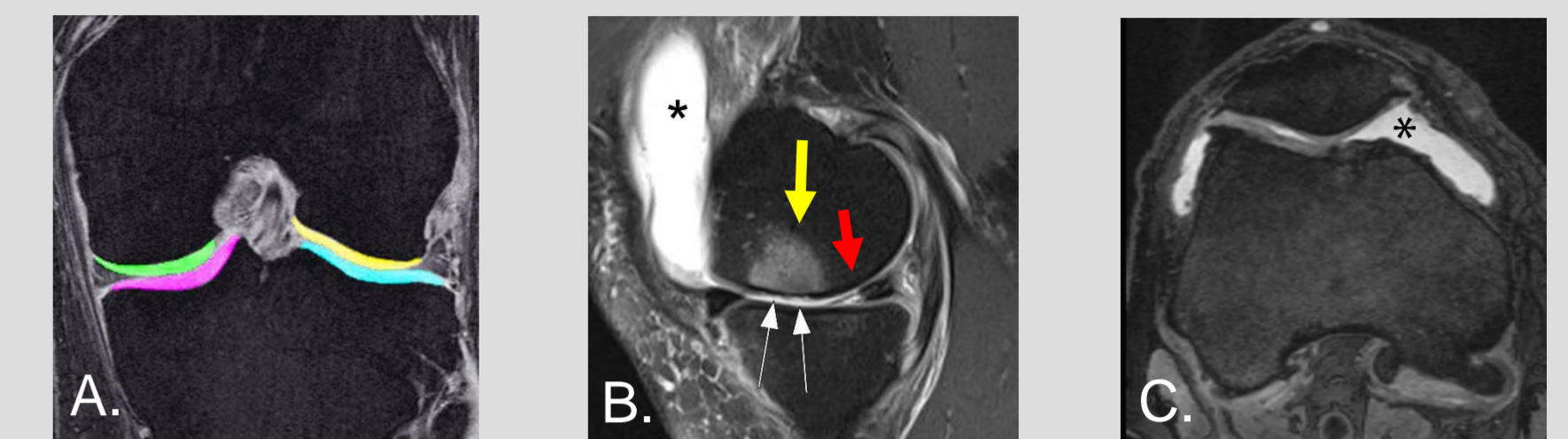


Figure 1. Q and SQ assessment in the FNIH Study. A. Coronal FLASH sequence with water excitation that was used for Q MRI and segmentation. Medial tibial cartilage marked (i.e. segmented) in purple, medial femoral cartilage marked in green, lateral tibial cartilage marked in light blue, and lateral femoral cartilage marked in yellow. B. Sagittal intermediate-weighted fat suppressed sequence shows diffuse cartilage loss at the central femur (white arrows), large femoral BML (yellow arrow) and meniscal maceration (red arrow). In addition, there is marked effusion-synovitis (asterisk) C. Corresponding axial DESS image confirms effusion-synovitis (asterisk).

CONCLUSION

- Worsening of meniscal extrusion, meniscal damage, number of subregions affected by BML, maximum size of BMLs and worsening of Effusion- and/or Hoffa-synovitis is associated with increased Q cartilage loss
- The associations are stronger for higher-grade changes for all features
- In the FNIH cohort, change in SQ MRI features are not only associated with case status but also with quantitatively assessed cartilage loss confirming the relevance of non-cartilaginous tissue changes for knee OA progression

REFERENCES

¹ Collins JE, Losina E, Nevitt MC, Roemer FW, Guermazi A, Lynch JA, et al. Semiquantitative Imaging Biomarkers of Knee Osteoarthritis Progression: Data From the Foundation for the National Institutes of Health Osteoarthritis Biomarkers Consortium. *Arthritis Rheumatol.* 2016;68(10):2422-31.

² Hunter DJ, Guermazi A, Lo GH, Grainger AJ, Conaghan PG, Boudreau RM, et al. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). *Osteoarthritis Cartilage.* 2011;19(8):990-1002

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