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Worsening of Articular Tissue Damage as Defined by Semi-Quantitative MRI Is Associated With Concurrent Quantitative Cartilage Loss Over 24 Months

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Abstract

Objective. To assess the association of worsening of magnetic resonance imaging (MRI) semi-quantitative (SQ) tissue features with concurrent change in quantitative (Q) cartilage thickness measurements over 24 months within the Foundation for the National Institutes of Health (FNIH) Biomarker Consortium study. *Methods.* In all, 599 participants were included. SQ assessment included cartilage damage, meniscal extrusion and damage, osteophytes, bone marrow lesions (BMLs), and effusion- and Hoffa-synovitis. Change in medial compartment Q cartilage thickness was stratified by concurrent ipsicompartmental SQ changes. Between-group comparisons were performed using analysis of covariance (ANCOVA) with adjustment for age, sex, and body mass index (BMI). Results were presented as adjusted mean difference. *Results.* Knees with any increase in SQ cartilage scores in the medial compartment ($n = 268$) showed more Q cartilage loss compared to knees that remained stable (mean adjusted difference [MAD] = -0.16 mm, 95% confidence interval [CI]: [-0.19, -0.13] mm). Knees with any increase in meniscal extrusion in the medial compartment (n = 98) showed more Q cartilage loss than knees without (MAD = -0.18 mm, 95% CI: [-0.22, -0.14] mm. Comparable findings were seen for meniscal damage worsening. Regarding BMLs, an increase by one subregion resulted in a MAD of Q cartilage loss of -0.10 mm, 95% CI: [-0.14, -0.06] mm, while this effect almost tripled for change in two or more subregions. Increase in either effusion- and/or Hoffa-synovitis by one grade resulted in a MAD of -0.07 mm, 95% CI: [-0.10, -0.03] mm. *Conclusion.* Worsening of SQ cartilage damage, meniscal extrusion and 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.

Keywords
cartilage, MRI, knee, osteoarthritis

Introduction

The Foundation for the National Institutes of Health (FNIH) Osteoarthritis Biomarkers Consortium is a nested case-control study based within the larger Osteoarthritis Initiative (OAI) study. One goal of this study was to determine the association between baseline presence and change in semi-quantitative (SQ) magnetic resonance imaging (MRI) biomarkers and knee osteoarthritis (OA) progression as defined by pre-determined radiographic, clinical or combined outcomes. The results of this study showed that worsening of several structural MRI features, as defined by semiquantitative assessment, from baseline to 24 months was associated with increased odds of progression defined as worsening of radiographic OA and worsening of pain at 48 months.[1]

However, to date there is a gap in knowledge whether worsening of cartilage and non-cartilaginous SQ features is not only associated with radiographic and pain progression but also with concurrent progression in cartilage loss as defined by quantitative (Q) assessment. While two studies have previously evaluated baseline SQ features and subsequent Q defined cartilage loss (thickness or volume),[2,3]

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no data are available on concurrent change of SQ features with Q cartilage loss over time. Q evaluation of cartilage is commonly used as an outcome measure in disease modifying osteoarthritis drug (DMOAD) clinical trials.[4,5] While SQ and Q MRI assessment of cartilage are complementary, SQ scoring by experts is considered less sensitive to change compared to Q approaches based on cartilage segmentation, particularly regarding subtle widespread cartilage loss.[6] On the other hand, focal cartilage defects cannot be assessed using common Q approaches that measure cartilage volume or thickness across entire joint subregions but are morphologically detectable and can be described using SQ measures. It has been shown previously that prevalent focal cartilage defects, regardless of defect depth, in the tibiofemoral joint increase the risk of developing new cartilage damage in other subregions of the same compartment for persons with or at high risk of knee OA.[7] In order to increase sensitivity to change, so-called within-grade changes have been introduced to SQ scoring instruments particularly for assessing changes in cartilage morphology and subchondral bone marrow lesions (BMLs).[8] While the clinical validity of this approach has been shown in the past,[8] it is unknown whether within-grade worsening of cartilage damage is associated with concurrent Q cartilage loss. Knowledge on concurrent progression of cartilaginous and non-cartilaginous tissues would help in understanding the potential role of ordinal grading approaches to be potentially used as outcome measures, for example, when Q assessment is not available. Furthermore, such insights would add to our understanding of knee OA as a whole joint disease as reflected on MRI affecting both Q evaluated cartilage measures and visually assessed joint tissues, including the relevance of so-called within-grade changes.

Thus, the aims of our study were twofold: First, we wished to study the association of change in SQ-defined cartilage worsening with concurrent ipsicompartmental change in Q cartilage thickness measurements over 24 months. For this end, full-grade-only changes, within-grade-only changes and full-grade plus within-grade worsening were considered. As a second aim, we wanted to evaluate whether SQ worsening of non-cartilaginous tissue damage is associated with concurrent ipsicompartmental increased rates of Q cartilage loss over 24 months when compared to those compartments without worsening of these features.

Materials and Methods

Study Design

The OAI is a multi-center prospective observational cohort study of knee OA that enrolled 4,796 participants aged 45 to 79 years at four clinical centers. Clinical data, MRI scans, radiographs and serum and urine specimens were obtained at baseline, 12, 24, 36, 48, 72 and 96 months follow-up. A subset of patients with Kellgren-Lawrence 0 at baseline were also examined at 120/132 months but no MRI was acquired at those time points.[9] Informed consent was obtained from all subjects and the study was Health Insurance Portability and Accountability Act (HIPAA) compliant. The study protocol, amendments, and informed consent documentation were reviewed and approved by the local Institutional Review Boards of all participating centers: Memorial Hospital of Rhode Island Institutional Review Board, The Ohio State University's Biomedical Sciences Institutional Review Board, University of Pittsburgh Institutional Review Board, and University of Maryland Baltimore–Institutional Review Board, and the OAI coordinating center (Committee on Human Research at University of California, San Francisco).

FNIH Study Sample

The FNIH study sample was defined by symptomatic and structural progression outcomes over 48 months (1). A predetermined number of index knees was selected in the following outcome groups, for measurement of imaging biomarkers: (1) case knees had both radiographic and pain progression; control knees did not have this combination, and included (2) knees with radiographic but not pain progression, (3) knees with pain but not radiographic progression, and (4) knees with neither radiographic nor pain progression. Of the total 600 participants from the OAI FNIH study, 599 had both SQ assessments and quantitative cartilage thickness measurements and were included.

MRI Acquisition

MRIs of both knees were acquired using 3T systems (Siemens MAGNETOM Trio, Erlangen, Germany) at the four OAI clinical sites. The sequence protocol included a coronal intermediate-weighted 2-dimensional turbo spin echo sequence, a sagittal 3-dimensional dual-echo steady-state (DESS) sequence, and a sagittal intermediate-weighted fat-suppressed turbo spin-echo sequence.[10]

Quantitative Assessment

Cartilage thickness analysis for this study relied on the sagittal DESS sequence. Segmentation of the femorotibial cartilage plates, that is, medial and lateral tibia and weight-bearing femur, was performed by seven readers. The analysis center was blinded with regard to case–control status and image acquisition order, so that an unbiased rate of change could be determined in each group. All segmentations were quality-controlled by one of two experts (F. E. or S. M.). The reliability of these measurements in the OAI and their feasibility in clinical trials has been reported

previously with average precision errors across plates being 1.8% for fast low angle shot (FLASH), 2.6% for dual echo at steady state (DESS) and 3.0% for multiplanar reformations (MPR) of DESS. At year 2, the average change across the femorotibial cartilage plates was −1.7% for FLASH, −2.8% for DESS, and −0.3% for MPR-DESS.[11,12] The current study focused on the mean cartilage thickness in the medial (MFTC) and in the lateral femorotibial compartment (LFTC), which were derived from the cartilage thickness measures observed in the respective cartilage plates (e.g., MFTC = medial tibia +central medial femur). Q cartilage thickness loss was computed as an absolute difference between 24 months and baseline value (mm).

Semiquantitative Assessment and Definition of Change

Two musculoskeletal radiologists with 13 (F. W. R.) and 15 (A. G.) years' experience of semi-quantitative assessment of knee OA at the time of image assessment, blinded to clinical data and case-control status, read the baseline and 24-month MRIs according to the Magnetic resonance imaging Osteoarthritis Knee Score (MOAKS) scoring system,[13] with knowledge of the chronological order of the scans. The following joint structures were assessed and considered for the analysis: cartilage damage, osteophytes, BMLs, meniscal damage and meniscal extrusion, Hoffa-synovitis, and effusion-synovitis. For the current analysis, only the weight-bearing medial and lateral femorotibial joint was considered to align semi-quantitative with quantitative regions of interest.

Cartilage. MOAKS uses a two-digit score for cartilage assessment that incorporates both area size per subregion and percentage of subregion affected by full thickness cartilage damage. In this analysis, separate scores for cartilage full thickness (MOAKSft) and surface area involvement (MOAKSext) were considered. In addition, within-grade changes were coded for changes that fulfill the definition of a definite visual change but do not fulfill the definition of a full grade change on the ordinal scale.[5] Within-grade changes were coded for either change in the area extent dimension or the full-thickness dimension of the MOAKS scale, but the two were not differentiated. Change over time for surface area and full thickness change was computed in two ways: including within-grade changes and excluding-within grade changes. Within-grade scoring for cartilage refers to within grade change in area or thickness.

Bone marrow lesions (BMLs). BMLs are evaluated on a three-dimensional scale including size (0-3), percentage of BML that is cystic (0-3) and number of BMLs per subregion. For this study, only the size portion was considered. For BMLs, change was defined as ipsicompartmental change in maximum BML size or change in number of subregions affected by BMLs in a compartment (for a maximum of 4 subregions medial and 4 lateral). Improvement in BMLs was considered as no change.

Meniscus. Meniscal damage is assessed on an 8-point scale in 3 anatomical subregions for the medial and lateral compartment, including meniscal signal, different tear types and meniscal substance loss defined as partial or complete maceration. Meniscal damage was collapsed to either normal (including normal and meniscal signal = grade 0), any tear (including horizontal, vertical, radial and complex tears = grade 1) and any maceration (including partial and complete maceration = grade 2). Meniscal extrusion is scored from 0 to 3 in the coronal plane. Ipsicompartmental change in meniscal damage was defined as increase from 0 to 1, 1 to 2 or 0 to 2. Any increase in extrusion was defined as change.

Osteophytes. Osteophytes are assessed from 0 to 3 in 4 locations in the coronal plane. Any ipsicompartmental increase in osteophyte size was considered change.

Hoffa-synovitis and effusion-synovitis. As MRI markers of whole-knee inflammation so-called effusion- and Hoffa-synovitis were evaluated. Effusion-synovitis is scored from 0 to 3 according to the distention of the joint capsule. Hoffa-synovitis is scored based on the amount of hyperintensity signal in Hoffa's fat pad on sagittal fat suppressed intermediate-weighted sequences from 0 to 3. Worsening by 1 or 2 grades in either effusion or Hoffa-synovitis was considered change.

Statistical Analysis

For aim 1, medial and lateral compartment cartilage thickness change over the subsequent 2 years were stratified by ipsicompartmental change in MOAKSext, and MOAKSft score. Within-grade changes were assessed in knees without full-grade change in comparison to knees without any change. Knees with full grade changes only, with within-grade changes only and with any (either full-grade change, within-grade change or both) change in MOAKSext and MOAKSft were considered separately and compared. A "number of subregion-approach" considering subregions with change was used in addition. For aim 2, two-year change in medial compartment cartilage thickness change was stratified by concurrent ipsicompartmental change in meniscus extrusion, meniscus damage, BML (size and number of subregions, including within-grade changes), osteophyte, and inflammation scores. Change in the lateral compartment was assessed in an identical fashion. For all features, knees with an improvement of scores were regarded as no change. Between-group comparisons were performed using analysis of covariance (ANCOVA) with

adjustment for age, sex, and body mass index (BMI). Results were presented as mean adjusted difference (MAD) and 95% confidence intervals.

Results

In all, 331 knees had no change in cartilage SQ scores, 41 knees had only within-grade changes, 170 knees had only full-grade changes, and 57 knees had both within-grade and full-grade changes. Knees with any increase in MOAKS cartilage scores (MOAKSext and/or MOAKSft) in the medial compartment (n = 268) showed more ipsicompartmental cartilage thickness loss compared to knees that remained stable (MAD = -0.16 mm, 95% CI: [-0.19,-0.13] mm). Cartilage thickness loss increased with higher-grade MOAKSext cartilage change. Similar findings were observed for an increase in MOAKSft dimension. While knees with SQ within-grade-only changes showed markedly less cartilage thickness loss compared to knees with SQ full grade-only changes, the amount of loss was still three times higher than for those without any change. The number of knees with any change in MOAKS cartilage (full-grade, within-grade or both) was markedly higher (n = 268) compared to knees with full grade changes only (n = 170) while the MAD of cartilage loss was similar. The MAD increased linearly with increase in the number of subregions showing any change. **Table 1** shows these results in detail.

Knees with one grade increase in meniscal extrusion in the medial compartment (n = 71) showed more ipsicompartmental cartilage thickness loss than knees that remained stable (MAD = -0.15 mm, 95% CI: [-0.20, -0.10] mm), which was even more pronounced for combined grade 2 or 3 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 one subregion affected by BMLs resulted in a MAD of cartilage thickness loss of -0.10 mm, 95% CI: [-0.14, -0.06] mm, while this effect almost tripled for change in two 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 with the largest difference observed for grade three change of maximum BML size. SQ increase in either effusion- and/or Hoffa-synovitis by one grade resulted in a MAD of -0.07 mm, 95% CI: [-0.10, -0.03] mm and an increase of two grades in a MAD = -0.25 mm, 95% CI: [-0.33, -0.17] mm. When looking at those features separately, any change in effusion-synovitis resulted in a MAD of -0.08 mm, 95% CI: [-0.12, -0.05] mm, and any change in Hoffa-synovitis in a MAD of -0.12 mm, 95% CI: [-0.17, -0.06] mm. **Table 2** shows these results in detail.

Due to the focus on participants with medial compartment structural progression in the OAI FNIH project, less change was observed in the lateral compartment and the associations were not as strong as for the medial compartment (**Tables 3** and **4**).

Discussion

Both full-grade and within-grade worsening in MOAKS cartilage scores corresponded with ipsicompartmental Q cartilage thickness loss confirming the validity of within-grade SQ assessment. The number of knees exhibiting change is markedly increased including within-grade changes emphasizing the benefit of including within-grade scoring when applying the MOAKS ordinal scoring instrument. Regarding worsening of SQ non-cartilaginous tissue damage, worsening of meniscal extrusion, meniscal damage, number of subregions affected by BML, maximum size of BMLs and of effusion- and/or Hoffa synovitis was associated with increase in Q cartilage loss compared to those medial compartments that do not show worsening of these features. The associations were stronger for higher-grade changes for all features.

In the same cohort focusing on SQ features, we showed previously that 24-month changes in cartilage thickness, cartilage surface area, effusion-synovitis, Hoffa-synovitis, and meniscal morphology were independently associated with OA case status, suggesting that these factors may serve as efficacy biomarkers in clinical DMOAD trials.[1] In an additional analysis using multivariable logistic regression models including Q and SQ MRI, bone shape and area, radiographic trabecular bone texture, and serum and/or urine biochemical markers, we found that the 24-month change in biomarkers that predicted pain and radiographic progression in all models were worsening in SQ effusion-synovitis, increase in the number of knee regions with worsening in SQ meniscal damage and horizontal trabecular bone texture confirming the relevance of SQ MRI for structural and symptomatic progression.[14]

Focusing on KLG 2 and 3 knees in the FNIH cohort and stratifying these into distinct structural phenotypes based on SQ assessment at baseline,[15] we could show that the bone phenotype was associated with an increased risk of having both radiographic and pain progression. This work emphasized that phenotypic stratification may be useful when selecting patients for inclusion in clinical trials. Another study tested different models to predict moderate to severe OA development (clinical and/or radiographic) over 8 years and found that adding MRI significantly improved the prognostic ability of the model compared to clinical and radiographic characteristics only.[16]

Several previous studies have examined whether MRI measures of joint damage can predict future OA progression. As an example, Bloecker *et al.*[17] reported that a quantitative measure of medial meniscal extrusion was associated with Q cartilage loss in specific femorotibial subregions. Roemer *et al.*[18] reported that cross-sectional SQ measures

Table 1. Change of Cartilage Damage (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
Mean change in MFTC cartilage thickness in knees with vs. without any[a] change in MFTC cartilage damage scores						
No	331	–0.02	0.12	(–0.04, –0.01)	(Reference)	
Yes	268	–0.19	0.25	(–0.22, –0.16)	–0.16	(–0.19, –0.13)
Any[b] increase in area dimension MOAKSext MFTC cartilage scores						
0	470	–0.06	0.16	(–0.08, –0.05)	(Reference)	
1	60	–0.19	0.25	(–0.26, –0.12)	–0.13	(–0.18, –0.08)
2	68	–0.28	0.29	(–0.35, –0.21)	–0.22	(–0.27, –0.17)
3	1			n/a (too few knees)		
Any[b] increase in full thickness dimension MOAKSft MFTC cartilage damage scores						
0	435	–0.05	0.14	(–0.06, –0.03)	(Reference)	
1	91	–0.18	0.23	(–0.22, –0.13)	–0.12	(–0.16, –0.08)
2	73	–0.33	0.32	(–0.40, –0.25)	–0.28	(–0.32, –0.23)
Full-grade only increase in any (MOAKSext and MOAKSft) MFTC MOAKS cartilage scores[c]						
No	331	–0.02	0.12	(–0.04, –0.01)	(Reference)	
Yes	170	–0.20	0.26	(–0.24, –0.17)	–0.17	(–0.21, –0.14)
Within-grade only increase in any (MOAKSext and MOAKSft) MFTC MOAKS cartilage scores[d]						
No	331	–0.02	0.12	(–0.04, –0.01)	(Reference)	
Yes	41	–0.06	0.12	(–0.09, –0.02)	–0.03	(–0.07, 0.01)
Number of subregions with any (full-grade, within-grade, both) increase in any (MOAKSext/MOAKSft) MOAKS cartilage damage scores						
0	331	–0.02	0.12	(–0.04, –0.01)	(Reference)	
1	135	–0.10	0.17	(–0.13, –0.07)	–0.07	(–0.10, –0.03)
2	86	–0.23	0.24	(–0.28, –0.18)	–0.20	(–0.24, –0.16)
3	47	–0.40	0.31	(–0.50, –0.31)	–0.37	(–0.42, –0.32)
Number of subregions with full-grade only increase in any MOAKS cartilage damage scores						
0	331	–0.02	0.12	(–0.04, –0.01)	(Reference)	
1	87	–0.12	0.19	(–0.16, –0.08)	–0.09	(–0.12, –0.05)
2	59	–0.22	0.24	(–0.28, –0.16)	–0.19	(–0.24, –0.15)
3	24	–0.48	0.31	(–0.61, –0.36)	–0.45	(–0.52, –0.38)
Number of subregions with within-grade only increase in any MOAKS cartilage damage scores						
0	332	–0.02	0.12	(–0.04, –0.01)	(Reference)	
1	37	–0.05	0.12	(–0.09, –0.01)	–0.02	(–0.06, 0.02)
2	4			n/a (too few knees)		

MOAKS = Magnetic resonance imaging Osteoarthritis Knee Score; 95% CI = 95% confidence interval; mean adj. diff. = mean adjusted difference in mm; MFTC = medial femorotibial compartment; MOAKSext = area dimension-component of the MOAKS two-digit cartilage score; MOAKSft = full thickness-component of the MOAKS two-digit cartilage score; n/a = not applicable.

[a]Any: any full grade change, within-grade change or both in either MOAKSext and/or MOAKSft.

[b]Any: full grade change, within-grade change or both.

[c]Within-grade change knees counted as no change.

[d]41 knees with within-grade change only. 170 knees with full-grade-only changes and 57 knees with both within-grade and full-grade changes not considered.

of joint damage, including cartilage loss, BMLs, meniscal maceration, effusion, and synovitis, were associated with subsequent total knee replacement as an outcome in a case-control study. In light of these previous studies, the results of the current study add to our understanding of disease progression as we particularly focused on Q cartilage loss, which is the commonly used structural outcome measure in clinical DMOAD trials.

However, biomarkers that predict progression may vary depending upon whether baseline or their changes over 24 months are evaluated for their ability to predict longer-term outcomes. Both biomarker types may be useful in a clinical trial scenario, i.e. for eligibility assessment at inclusion, and for enrichment regarding structural or symptomatic progression. Both could be particularly important in enhancing the efficiency and shortening the duration of phase 2 and 3 clinical trials by reducing costs, and increasing the likelihood of drug approval.

Our study has limitations that need mentioning. The FNIH study is a nested case-control study with cases selected based on a specific outcome, which may hinder generalization of our findings. We focused on the femorotibial joint

Table 2. Change of Non-Cartilaginous OA Features Over 24 Months and Concurrent 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[a]						
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[b]						
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[c]						
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[d]	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[e]						
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)	–0.09	(–0.13, –0.06)
Increase in MOAKS effusion-synovitis scores[f]						
0	366	–0.08	0.18	(–0.10, –0.06)	(Reference)	
1	133	–0.13	0.24	(–0.17, –0.09)	–0.05	(–0.09, –0.01)
2	21	–0.36	0.24	(–0.47, –0.25)	–0.28	(–0.37, –0.19)
Any	154	–0.16	0.25	(–0.20, –0.12)	–0.08	(–0.12, –0.05)
Increase in MOAKS Hoffa-synovitis scores[g]						
0	531	–0.09	0.20	(–0.10, –0.07)	(Reference)	
1	55	–0.21	0.25	(–0.28, –0.14)	–0.13	(–0.18, –0.07)
2	3	0.00	0.26	(–0.65, 0.65)	0.03	(–0.20, 0.26)
Any	58	–0.20	0.26	(–0.27, –0.13)	–0.12	(–0.17, –0.06)

OA = osteoarthritis; CI = confidence interval; mean adj. diff. = mean adjusted difference in mm; MOAKS = Magnetic resonance imaging Osteoarthritis Knee Score; MFTC = medialemoro-tibial compartment;; BML = bone marrow lesions.

[a] *N* = 1 with improvement.

[b] *N* = 4 with improvement.

[c] *N* = 46 with improvement.

[d] 0.5 = within-grade change.

[e] *N* = 5 with improvement.

[f] *N* = 79 with improvement.

[g] *N* = 10 with improvement.

Table 3. Change of Cartilage Damage (MOAKS) Over 24 Months and Concurrent Mean Change in Cartilage Thickness in the Lateral Femoro-Tibial Compartment.

Δ	*N*	Mean	SD	95% CI	Mean adj. diff	95% CI
Mean change in LFTC cartilage thickness in knees with vs. without any[a] change in LFTC cartilage damage scores						
No	513	–0.01	0.11	(–0.02, 0.00)	(Reference)	
Yes	86	–0.06	0.13	(–0.09, –0.03)	–0.05	(–0.08, –0.03)
Mean change in LFTC cartilage thickness stratified by max change in MOAKS LFTC size of cartilage area cartilage scores (MOAKSext)						
0	551	–0.02	0.11	(–0.03, –0.01)	(Reference)	
1	42	–0.04	0.13	(–0.08, 0.00)	–0.02	(–0.06,0.01)
2	6	–0.11	0.12	(–0.23,0.02)	–0.09	(–0 –18,0.00)
Full-grade only increase in any (MOAKSext and MOAKSft) LFTC MOAKS cartilage scores[b]						
No	513	–0.01	0.11	(–0.02, 0.00)	(Reference)	
Yes	68	–0.06	0.12	(–0.09, –0.03)	–0.05	(–0.08, –0.03)
Mean change in LFTC cartilage thickness in knees with vs without within-grade change in LFTC cartilage damage scores (knees with full-grade changes only or full-grade AND within-grade changes excluded):						
No	513	–0.01	0.11	(–0.02, 0.00)	(Reference)	
Yes	12	–0.04	0.11	(–0.10, 0.03)	–0.02	(–0.09, 0.04)
Number of subregions with any (full-grade, within-grade, both) increase in any (MOAKSext/MOAKSft) MOAKS cartilage damage scores						
0	520	–0.01	0.11	(–0.02, 0.00)	(Reference)	
1	71	–0.06	0.14	(–0.09, –0.03)	–0.04	(–0.07, –0.02)
2	8	–0.13	0.10	(–0.22, –0.05)	–0.13	(–0.21, –0.05)
Number of subregions with full-grade only increase in any MOAKS cartilage damage scores						
0	513	–0.01	0.11	(–0.02, 0.00)	(Reference)	
1	61	–0.06	0.12	(–0.09, –0.02)	–0.04	(–0.07, –0.01)
2	7	–0.15	0.10	(–0.24, –0.06)	–0.15	(–0.23, –0.06)
Number of subregions with within-grade only increase in any MOAKS cartilage damage scores						
0	513	–0.01	0.11	(–0.02, –0.00)	(Reference)	
1	11	–0.03	0.11	(–0.10, 0.04)	–0.02	(–0.08, 0.05)
2	1			n/a (too few knees)		

MOAKS = Magnetic resonance imaging Osteoarthritis Knee Score; 95% CI = 95% confidence interval; mean adj. diff. = mean adjusted difference in mm; LFTC = lateral femoro-tibial compartment; MFTC = medial femorotibial compartment; MOAKSext = area dimension-component of the MOAKS two-digit cartilage score; MOAKSft = full thickness-component of the MOAKS two-digit cartilage score; n/a = not applicable.
[a]Any: any full-grade change, within-grade change or both in MOAKSext and/or MOAKSft.
[b]Within-grade change knees counted as no change.

only but acknowledge the potential importance of the patellofemoral joint regarding progression also in the femorotibial joint, particularly in the lateral compartment.[19] Whether Q cartilage loss is translating into clinical progression or vice versa, that is, increase in cartilage thickness resulting in clinical improvement, is currently under debate.[4,20]

The MRIs were presented sequentially, and readers were aware of the chronological order of images. This might result in a slight tendency to read more change in comparison to a blinded reading. However, it has been shown that scoring without knowing the chronological sequence substantially decreases sensitivity in the detection of clinically relevant changes in comparison to scoring in chronological order and that it does not introduce false positive changes.[21,22] These studies showed that blinding to time point can lead to misclassification of the longitudinal change in a feature and that it may compromise the assessment of the relation of that feature and its outcome.[23] Within-grade scoring is only feasible when the chronological order is known as coding refers specifically to the previous time point.

While analysis of the entire OAI MRI dataset would be desirable and permit a more robust description of concurrent change over time, unfortunately such extended MRI analyses are not available. The FNIH subsample, however, is roughly comparable to an enriched clinical trial population regarding predefined progression outcomes.[14]

Finally, we only included SQ MRI parameters to assess concurrent change in Q cartilage thickness but did not consider change in other biomarkers that are available in the FNIH cohort, including serum or other imaging modalities.

In summary, we could show that both full-grade and within-grade changes in MOAKS cartilage scores correspond with ipsicompartmental Q cartilage thickness loss confirming the validity of SQ full-grade and within-grade assessment. In addition, worsening of SQ meniscal extrusion, meniscal damage, number of subregions affected by BMLs, maximum size of BMLs, and worsening of effusion- and/or Hoffa synovitis is associated with increase in Q cartilage thickness loss compared to those medial compartments that do not show worsening of these features. Thus, in the FNIH cohort, longitudinal

Table 4. Change of Non-Cartilaginous OA Features Over 24 Months and Concurrent Change in Cartilage Thickness in the Lateral Femoro-Tibial Compartment.

Δ	*N*	Mean	SD	(95% CI)	Mean adj. diff.	(95% CI)
Increase in MOAKS LFTC meniscus extrusion scores						
0	598	–0.02	0.11	(–0.03, –0.01)	(Reference)	
1	1			(too few knees)		
Increase in MOAKS LFTC meniscus damage scores[a]						
0	590	–0.02	0.11	(–0.03, –0.01)	(Reference)	
1	8[a]	–0.13	0.19	(–0.29, –0.03)	–0.11	(–0.19, –0.03)
Increase in MOAKS LFTC osteophyte scores[b]						
0	563	–0.02	0.11	(–0.03, –0.01)	(Reference)	
1	35	0.03	0.13	(–0.01, 0.07)	0.05	(0.01, 0.09)
2	1			n/a (too few knees)		
Increase in number of LFTC subregions with BMLs[b]						
0	563	–0.01	0.11	(–0.02, –0.01)	(Reference)	
1	21	–0.07	0.11	(–0.12, –0.02)	–0.05	(–0.10, –0.01)
2	6	–0.14	0.24	(–0.39, 0.11)	–0.12	(–0.21, –0.03)
Increase in maximum MOAKS LFTC BML size scores						
0.0	561	–0.01	0.11	(–0.02, –0.01)	(Reference)	
0.5[c]	3			n/a (too few knees)		
1.0	28	–0.07	0.15	(–0.12, –0.01)	–0.11	(–0.15, –0.07)
2.0	4			n/a (too few knees)		
3.0	2			n/a (too few knees)		
Increase in MOAKS effusion-synovitis and/or Hoffa-synovitis scores[d]						
0	414	–0.02	0.11	(–0.03, –0.01)	(Reference)	
1	157	–0.02	0.12	(–0.04, 0.00)	0.00	(–0.02, 0.03)
2	23	0.01	0.13	(–0.05, 0.07)	0.03	(–0.02, 0.08)

OA = osteoarthritis; 95% CI = 95% confidence interval; mean adj.diff. = mean adjusted difference in mm; MOAKS = Magnetic resonance imaging Osteoarthritis Knee Score; LFTC = lateral femoro-tibial compartment; BML = bone marrow lesion; n/a – not applicable.
[a]*N* = 1 with improvement.
[b]*N* = 8 with improvement.
[c]0.5 = within-grade change
[d]*N* = 5 with improvement.

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 and clinical trial design.

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Ethical Approval

The study protocol, amendments, and informed consent documentation were reviewed and approved by the local Institutional Review Boards of all participating centers: Memorial Hospital of Rhode Island Institutional Review Board, The Ohio State University's Biomedical Sciences Institutional Review Board, University of Pittsburgh Institutional Review Board, and University of Maryland Baltimore–Institutional Review Board, and the OAI coordinating center (Committee on Human Research at University of California, San Francisco).

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