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Semi-Quantitative Imaging Biomarkers of Knee Osteoarthritis Progression: Data from the FNIH OA Biomarkers Consortium

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Abstract

Objective—To determine the association between changes in semi-quantitative knee MRI biomarkers over 24 months and radiographic and pain progression over 48 months in knees with mild to moderate osteoarthritis.

Methods—We undertook a nested case-control study as part of the Osteoarthritis Biomarkers Consortium Project. We built multivariable logistic regression models to examine the association between change over 24 months in semi-quantitative MR imaging markers and knee OA radiographic and pain progression. MRIs were read according to the MRI Osteoarthritis Knee Score (MOAKS) scoring system. We focused on changes in cartilage, osteophytes, meniscus, bone marrow lesions, Hoffa-synovitis, and synovitis-effusion.

Results—The most parsimonious model included changes in cartilage thickness and surface area, synovitis-effusion, Hoffa-synovitis, and meniscal morphology (C-statistic =0.740). Subjects with

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worsening cartilage thickness in 3+ subregions vs. no worsening had 2.8-fold (95% CI: 1.3 – 5.9) greater odds of being a case while subjects with worsening in cartilage surface area in 3+ subregions vs. no worsening had 2.4-fold (95% CI: 1.3 – 4.4) greater odds of being a case. Having worsening in any region in meniscal morphology was associated with a 2.2-fold (95%CI: 1.3 – 3.8) greater odds of being a case. Worsening synovitis-effusion (OR=2.7) and Hoffa-synovitis (OR=2.0) were also associated with greater odds of being a case.

Conclusion—Twenty-four-month change in cartilage thickness, cartilage surface area, synovitis-effusion, Hoffa-synovitis, and meniscal morphology were independently associated with OA progression, suggesting that they may serve as efficacy biomarkers in clinical trials of disease modifying interventions for knee OA.

Keywords

knee osteoarthritis; biomarkers; MRI; semi-quantitative score

Introduction

Knee osteoarthritis (OA) is a prevalent chronic medical condition, affecting an estimated 250 million adults worldwide[1]. The disease is characterized by joint pain, swelling, and stiffness and is associated with lower quality of life and higher healthcare utilization. In the USA alone, 15 million quality adjusted life years are lost due to knee OA[2–4].

Even though knee OA is highly prevalent, disabling and costly, development of therapies capable of arresting structural progression has been slow, with no disease modifying agents presently approved. One of the many purported reasons for this slow pace of drug development has been the lack of valid and responsive biomarkers to ascertain the efficacy of disease-modifying interventions.

Semi-quantitative scoring of magnetic resonance imaging (MRIs) is a valuable method for performing multi-feature assessment of the knee using conventional MRI acquisitions[5–7]. MRIs are scored for a variety of features that are currently believed to be relevant to the functional integrity of the knee and/or potentially involved in the pathophysiology of OA. These articular features include cartilage damage, subarticular bone marrow abnormalities, subchondral cysts, subarticular bone attrition, marginal and central osteophytes, medial and lateral meniscal damage, anterior and posterior cruciate ligament lesions, medial and lateral collateral ligament lesions, synovitis/effusion, intra-articular loose bodies, and periarticular cysts/bursitis. The instruments developed for scoring MRI on OA have been shown to be adequately reliable, specific, and sensitive, and have the ability to detect lesion progression over 1–2 years[8].

The goal of this study was to determine the association between semi-quantitative knee MRI biomarkers and knee OA progression over 48 months. We investigated whether baseline biomarkers and whether changes in biomarkers from baseline to 24 months predict radiographic and pain progression from baseline to 48 months in knees with mild to moderate OA. We also investigated whether multivariable modeling including biomarkers across joint features would improve the predictive ability of the models.

Methods

Study Design

This analysis was conducted as a part of OA Biomarkers Consortium Project. Details of the study design had been published elsewhere. In short, we undertook a nested case-control study using data from the Osteoarthritis Initiative (OAI)[9,10]. We selected subjects from the OAI with at least one knee with a Kellgren Lawrence grade (KLG) of 1, 2 or 3 at baseline based on the central reading of a standardized fixed-flexion radiograph and availability at baseline and 24 months of medial joint space width (JSW) from knee radiographs, knee MRI, stored serum and urine specimens and clinical data.

We selected a predetermined number of index knees, one knee per subject, in four mutually exclusive groups: 1) knees with both radiographic and pain progression (composite cases); 2) knees with radiographic but not pain progression (joint space loss (JSL) cases/pain controls); 3) knees with pain but not radiographic progression (JSL controls/pain cases); and 4) knees with neither radiographic nor pain progression (composite controls). For the purposes of this analysis we use the single contrast, comparing knees with both radiographic and pain progression (cases) vs. all other knees (controls). Radiographic progression, based on medial joint space loss, and pain progression, based on an increase in WOMAC knee pain score above a minimum clinically important difference (MCID) were determined as previously described[10]. Briefly, radiographic progression was defined as joint space width loss (JSL) of ≥0.7mm; pain progression was defined as a persistent (sustained at ≥ 2 time points) increase of ≥9 points on the WOMAC pain subscale (0–100 scale)[9,11,12]. If both of a subject's knees fell into any one group, one was randomly selected as the index knee. Knees with radiographic and pain progression by 12 month follow-up, with lateral joint space narrowing (JSN) grade 2 or 3 at baseline, and subjects with total knee or total hip replacement by 24 months were excluded.

For better covariate balance among the groups, and to the extent feasible, knees selected for the four groups were frequency matched for KLG and BMI (kg/m^2) categories (<25; 25 to <27.5; 27.5 to <30; 30 to <35; ≥35). MRIs of the selected index knees were reviewed for artifacts that would interfere with image analysis. If artifacts were present the knee and subject were excluded and a replacement selected. The sample size for the four groups was 194 (radiographic and pain progression), 103 (radiographic only), 103 (pain only) and 200 (neither radiographic nor pain progression) knees, respectively. In this analysis we compared 194 cases (radiographic and pain progression) vs. the remaining 406 subjects, whom we considered controls. Results for the secondary analysis of radiographic and pain progression separately are presented in the appendix.

Knee MRI Acquisition and Scoring

MRI acquisition was performed using a 3 Tesla MRI system (Trio, Siemens Healthcare, Erlangen, Germany) at the four OAI clinical sites. Additional parameters of the full OAI pulse sequence protocol and sequence parameters have been published in detail[13]. All these sequences were utilized for semi-quantitative assessment. The semi-quantitative scorings were done by two musculoskeletal radiologists with 15 and 13 years of experience in semi-

quantitative MRI assessment of OA (AG, FWR). MRIs were read according to the MOAKS scoring system in sequential order, and unblinded to time point of acquisition to maximize sensitivity to change [5,14]. The readers were blinded to all clinical characteristics.

Select Joint Features Assessed on MRI

This analysis focused on several joint features measured by MOAKS and described below. The features are grouped into the following domains: cartilage, osteophytes, meniscus, bone marrow lesions, Hoffa-synovitis, and synovitis-effusion. These features were selected as potentially associated with progression by consensus by the OA Biomarkers Consortium Investigative Team prior to data analysis.

Cartilage surface area and thickness—We considered separate scores for cartilage thickness and surface area at each timepoint (baseline and 24 month follow up). Separately for thickness and surface area we computed the number of subregions with cartilage damage as the number of subregions with score >0. The number of subregions with cartilage thickness or surface area score >0 has a possible range of 0 to 14. We computed the number of subregions with worsening for surface area and thickness. Change over time for surface area was computed in two ways: including within-grade changes and excluding-within grade changes. The within-grade change denotes a definite change that does not fulfill the defined criteria of a full grade change[15,16]. Within- grade scoring for cartilage refers to within grade change in area. For both thickness and surface area, worsening was grouped into 4-levels: 0, 1, 2, or 3+ areas with worsening.

Osteophytes—Across the entire knee and within each compartment (medial, lateral, and patello-femoral) we computed the number of locations affected by any osteophyte (Grade > 0) and the maximum osteophyte score across all locations at both baseline and 24 month. We computed the change in number of locations affected by any osteophyte and created categories of no change, worsening in 1 location, and worsening by 2+ locations, which were then further classified into no change vs. any worsening. Maximum worsening in score was categorized into no worsening vs. any worsening

Meniscus—Meniscal morphology was scored in the anterior horn, body segment, and posterior horn of the medial and lateral menisci from 0 to 8 taking into account intrameniscal signal changes, different types of meniscal tears and meniscal substance loss or maceration. Meniscal damage was stratified into grades 0 and 1 (reference), grades 2–5 (tears) and grades 6–8 (maceration). We computed the maximum meniscal damage grade for the medial and lateral compartment separately, and for the entire knee. We also computed the number of areas affected in both the medial and lateral compartment (range 0–6). In each of the 6 compartments we assessed whether there was any worsening in morphology from baseline to 24 months (i.e., reference to tear, reference to maceration, or tear to maceration). To describe worsening across the whole knee we categorized this worsening into number of compartments with worsening (possible range: 0 to 6) and whether any compartment had any worsening (yes/no).

Meniscal extrusion—Meniscal extrusion was scored in four areas: medial meniscus: medial extrusion, medial meniscus: anterior extrusion, lateral meniscus: lateral extrusion, lateral meniscus: anterior extrusion. Meniscal extrusion was scored from 0 to 3: Grade 0: <2mm, Grade 1: 2–2.9mm, Grade 2: 3–4.9mm, Grade 3: >5mm. We assessed changes in meniscal extrusion separately in the medial and lateral compartments and categorized change in extrusion as improvement (lower score at 24 months as compared to baseline), no change, and worsening (higher score at 24 months as compared to baseline). We further categorized change in extrusion as any worsening vs. no worsening.

Size of Bone Marrow Lesions (BML)—Across the entire knee and within each compartment (medial, lateral, and patello-femoral) we computed the number of subregions affected by any BML (BML size score > 0) and the maximum BML size score across all subregions (from 0 to 3). We categorized change in overall number of subregions affected by any BML into improvement, no change, worsening in 1 subregion and worsening in 2+ subregions. We also calculated the number of subregions with worsening and the number of subregions with improvement. In both instances we took into account within-grade changes in BMLs, meaning that within-grade worsening was categorized as worsening[17]. We further categorized these measures into any subregions with worsening vs. no subregions with worsening and any subregions with improvement vs. no subregions with improvement.

We computed maximum worsening in BML size score and created categories of worsening by <2 grades (that included improvement, within grade worsening and worsening in at most one grade in size score) vs. worsening by 2+ grades.

Hoffa-Synovitis and Effusion-Synovitis—Signal alterations in the intercondylar region of Hoffa's fat pad were scored from 0 to 3 as a surrogate for synovial thickening termed Hoffa-synovitis. We classified 24 month change as improvement, no change, or worsening.

Joint effusion (also called effusion-synovitis as it is not possible to discern joint fluid from synovial thickening on MRI) was graded from 0 to 3 in terms of the estimated maximal distention of the synovial cavity. We classified 24 month change as improvement, no change, or worsening.

Statistical Analysis

We used logistic regression to examine the association between change in each biomarker and cases, defined as radiographic and pain progression in the same knee, vs all other knees as controls We present odds ratios with associated 95% confidence intervals to evaluate the association between biomarker and case status. We evaluated adjusted logistic regression models, with adjustment for sex, race, and baseline age, BMI, KLG, WOMAC pain, pain medication use, and JSW.

Biomarkers that were statistically significantly associated with case status in univariate analysis ($p<0.05$) were advanced to multivariable modeling. We allowed more than one biomarker from the same domain to progress to multivariable modeling. In this case, we first examined the correlation between the markers and assessed multiplicative interactions

between the candidate markers. If the markers were independent predictors of case status, that is, maintained a non-trivial effect size (Odds Ratio [OR] > 1.5 or OR < 0.67) when entered into the same multivariable model, then the markers were advanced for further modeling. Supplement Table 1 lists the biomarkers and groupings that were advanced to multivariable modeling. Multivariable models were built in a hierarchical fashion, with the best performing biomarkers added to the model first based on OR and area under the receiver operating characteristic curve (AUC). The AUC, expressed by c-statistics, is the probability that for any pair of case and control, the predicted probability of being a case is higher for the case. The added impact of each new biomarker was assessed by the p-value and OR of the new marker in the multivariable model. We focus on the OR of the new marker because it has been suggested that measures of prediction performance should focus on estimation, rather than formally testing the improvement in model performance[18,19]. The c-statistic will be used to describe the overall predictive ability of the model. Models were evaluated in a stepwise manner; biomarkers that did not maintain a pre-specified effect size (OR > 1.5 or OR < 0.67) or had p>0.10 were removed from subsequent models.

Results

Baseline characteristics

Demographic characteristics—The demographic characteristics of the cohort are presented in Table 1. The average age of the cohort was 62 years, 60% were females and average BMI was 30kg/m^2. The cases and controls were well balanced on all demographic and clinical covariates, with the exception of baseline Kellgren-Lawrence grade. Thirty-three percent of the controls had baseline KLG3 compared to 44% of cases. By definition, no subjects reached case status (radiographic (JSL) and pain progression) at 12 months. Of the 194 cases, 57 (29%) reached JSL case status (JSL of ≥0.7mm) by 24 months and had a first increase in WOMAC pain (≥9 points) at 24 months.

Semi-quantitative MRI markers

Cartilage: Associations between baseline imaging features are shown in Table 2. Overall, 25% of subjects had zero subregions affected by cartilage thickness damage and 26% had 3 or more subregions affected. Number of subregions with cartilage thickness damage category was significantly associated with case status (p=0.0021): subjects with 3+ subregions affected had 2.6 times the odds of being a case compared to subjects with 0 subregions affected. The maximum thickness score across all 14 subregions was also significantly associated with case status (p=0.0120). Eight percent of subjects had 0 or 1 subregions affected by surface area damage and 13% had 8 or more subregions affected. Number of subregions with cartilage surface area damage category was significantly associated with case status (p<0.0001): subjects with 8+ subregions affected had 10.3 times the odds of being a case compared to subjects with 0–1 subregions affected. The maximum surface area score across all 14 subregions was also significantly associated with case status (p=0.0086).

Osteophytes: Sixteen percent of subjects had 0–2 locations affected by any osteophyte at baseline and 58% had 6 or more locations affected. The number of locations affected was

significantly associated with case status (p<0.0001): subjects with 6+ locations affected by osteophytes at baseline had 4.4 times the odds of being a case compared to subjects with 0–2 locations affected. Fifty-two percent of subjects had a maximum osteophyte score across all locations in the knee of 0–1 and 15% had a maximum score of three. Maximum osteophyte score category was significantly associated with case status (p=0.0181).

Meniscus: Twenty-eight percent of subjects had maceration of the meniscus in at least one location at baseline, and we did not find a statistically significant association between meniscal morphology and case status (p=0.1678). Baseline medial meniscal extrusion was associated with case status (p=0.0113): subjects with grade 3 extrusion had 3.3 times the odds of being a case compared to subjects with grade 0 extrusion.

BMLs: Eleven percent of subjects had zero subregions affected by any BML and 16% had 5 or more subregions affected. Number of subregions affected category was significantly associated with case status (p<0.0001). Eighteen percent of subjects had a maximum BML score of 3 across all subregions in the knee. Maximum BML score was significantly associated with case status (p=0.0145): subjects with a maximum BML score of 3 had 3.5 times the odds of being a case compared to those with a maximum score of zero (i.e., no BMLs).

Hoffa-synovitis and effusion: Forty-one percent of subjects had a MOAKS Hoffa-synovitis score of zero at baseline, 50% had a score of one and 9% had a score of 2+. The odds of being a case were 2.2 times higher for subjects with a synovitis score of 2+ compared to those with a score of 0 (p=0.0032). At baseline, 80.5% of subjects had a effusion-synovitis score of 0–1 and 19.5% had a score of 2+. The distributions did not vary significantly between cases and controls (p=0.2441).

Change over 24 Months

Univariate analysis

Cartilage: Associations between changes in MRI features over 24 months and case status are shown in Table 3. Forty-two percent of subjects had at least one area with worsening in thickness (Table 3). This was significantly associated with case status: the odds of being a case were higher for each increased level of worsening vs. no change: 1.9 for 1 subregion vs. no worsening, 3.2 for 2 subregions vs. no worsening, and 4.7 for 3+ subregions vs. no worsening (p<0.0001). Fifty-nine percent of subjects had at least one area with worsening in surface area. This was significantly associated with case status: the odds of being a case were higher for each increased level of worsening vs. no change: 1.6 for 1 subregion vs. no worsening, 2.7 for 2 subregions vs. no worsening, and 5.1 for 3+ subregions vs. no worsening (p<0.0001). We observed similar associations when we did not include within-grade worsening (i.e., subjects with within-grade worsening were counted as *no change*).

Osteophytes: Overall there was little change in osteophytes over 24 months. Nine percent of the cohort had at least 1 location with worsening in osteophyte score over 24 months. Across all locations, the maximum amount of worsening was 2 grades and 83% had no change in any location. Maximum amount of worsening, categorized as no worsening in any location

vs. any worsening, was significantly associated with case status (p=0.0209): subjects with worsening had 1.7 times the odds of being a case compared to subjects with no worsening.

Meniscus: The number of regions with meniscal morphology worsening ranged from 0 to 5, with 16% of subjects having worsening in at least one subregion. Meniscal morphology worsening was strongly associated with case status: the odds of being a case were 3.8 times higher for subjects with any meniscal worsening compared to no worsening (p-value <0.0001). Fourteen percent of subjects had worsening in median meniscal extrusion, 26% of cases compared to 9% of controls. The odds of being a case were 4.3 times higher for subjects with worsening in meniscal extrusion (p-value <0.0001) compared to those that did not worsen. There was only 1 subject with worsening lateral meniscal extrusion. Meniscal morphology worsening and meniscal extrusion were moderately correlated (Spearman r=0.49): of subjects with meniscal morphology worsening, 54% also had meniscal extrusion worsening, of subjects without meniscal morphology worsening, only 7% had meniscal extrusion worsening.

BMLs: Overall, 14% of subjects showed improvement in number of subregions with BMLs and 52% showed no change based on this definition. We did not find a statistically significant association between change in number of subregions and case status (p=0.2473). The number of subregions with any improvement ranged from 0 to 6, with 46% of cases and 54% of controls having no subregions with improvement. The number of subregions with worsening (including within-grade worsening) ranged from 0 to 6, with 27% of cases and 34% of controls having no subregions with worsening. Thirty-two percent of subjects had no worsening in BML score and 17% had a maximum worsening of 2 or more grades. There was a significant association with case- status (p=0.0032), with 25% of cases worsening by 2+ grades compared to 13% of controls. The odds of being a case vs. a control were higher for each category of change in BMLs as compared to the no change category: 1.3 for within-grade worsening vs. no change, 1.2 for worsening by 1 grade vs. no change, and 2.6 for worsening by 2+ grades vs. no change.

Hoffa-Synovitis and Effusion-Synovitis: Ten percent of subjects experienced worsening in Hoffa-Synovitis, with more cases than controls experiencing a worsening (17% vs. 6%). The odds of being a case were much higher for those subjects that worsened vs. had no change in Hoffa synovitis (OR=3.4, p=0.0001). Progression was similar for those subjects that improved in Hoffa-synovitis score vs. had no change (OR=1.3).

Twenty-six percent of subjects worsened in effusion over 24 months, 41% of cases compared to 19% of controls. The odds of being a case were higher for those subjects that worsened vs. had no change (OR=3.0, p<0.0001), but similar for those subjects that improved vs. had no change (OR=0.7).

Multivariable analysis

We started with markers for cartilage thickness and surface area because these had the largest ORs and C-statistics in univariate analysis (Table 3). The markers were moderately correlated (ρ=0.35) and we did not find significant multiplicative interaction between the

two markers and case status. When added to the same multivariable model, both markers were statistically significantly associated with cases status. The C-statistic for this model was 0.706 (Table 4). The most parsimonious model (Model 6) included changes in cartilage thickness and surface area, synovitis-effusion, Hoffa-synovitis, and meniscal morphology (C-statistic =0.740). Subjects with worsening in cartilage in 3+ subregions vs. no worsening had 2.8 (95% CI: 1.3 – 5.9) times the odds of being a case for cartilage thickness and a 2.4 (95% CI: 1.3 – 4.4) times the odds for cartilage surface area. Worsening in any region in meniscus morphology was associated with a 2.2 times increased odds of being a case compared to subjects with no worsening (95% CI: 1.3 – 3.8). Compared to those whose synovitis-effusion improved, those with worsening had 2.7 (95%CI: 1.4 – 5.4) times increased odds of being a case. Worsening in Hoffa-synovitis was associated with a 2.0 (95%CI: 1.1 – 3.9) increased odds of being a case compared to those that did not worsen. BMLs (p=0.4262) and osteophytes (p=0.2444) were not significantly associated with case status when added to model 6.

Discussion

All baseline joint features examined, with the exception of effusion and meniscal morphology, were predictive of 48 month case status. Similarly, we found that for all joint features examined – size of bone marrow lesions, cartilage thickness and surface area, effusion, meniscus morphology and extrusion, osteophytes size, and synovitis – change over 24 months was associated with OA progression. A multivariable model including changes in cartilage thickness and surface area, synovitis-effusion, Hoffa-synovitis, and meniscal morphology had a C-statistic of 0.740, demonstrating acceptable discrimination[20].

A number of studies have examined whether MRI measures of joint damage can predict future OA progression. Dam et al. attempted to distinguish non-progressors from early progressors in a subgroup of subjects with KLG 0 at baseline and found that quantitative cartilage markers, including measures of roughness and homogeneity, performed well[21]. Bloecker et al. reported that a quantitative measure of medial meniscal extrusion was associated with cartilage loss in specific femorotibial subregions in data from the Osteoarthritis Initiative[22]. Roemer et al. found that cross-sectional semi-quantitative measures of joint damage, including cartilage loss, BMLs, meniscal maceration, effusion, and synovitis, were associated with subsequent total knee replacement in a case-control study using subjects from the OAI[23]. Eckstein et al. undertook a nested case-control study using subjects from the OAI, and found that quantitative cartilage measures, including thickness loss in the central and total medial femorotibial compartment and the central tibia, were associated with subsequent total knee replacement[24].

To our knowledge, our study is the first to examine whether semi-quantitative changes in joint structure over 24 months can predict clinically meaningful OA progression, as defined by both loss of medial joint space width on radiograph and an increase in knee pain above MCID. In addition, we used a multivariable approach to combine the different joint structures in order to identify combinations of biomarkers that best predicted progression. We found that worsening in cartilage thickness and cartilage surface area were independently associated with OA progression; both markers remained statistically

significant when entered into the same multivariable model, and the c-statistic was 0.706. Changes in BMLs and osteophytes were not significant predictors in models that already included cartilage, meniscus, effusion-synovitis, and Hoffa-synovitis biomarkers.

Our analysis has several limitations. The time period used to define change in MRI biomarkers (baseline to 24 months) overlapped with the time period used to define case status (baseline to 48 months). With this design we are not able to distinguish between evidence for the concurrent validity of changes in the biomarkers and that for the predictive validity of changes in the biomarkers. While our ability to assess predictive validity is limited by this study design feature, a main aim of the FNIH OA Biomarkers Consortium was to evaluate the validity of efficacy of intervention markers, which would demonstrate, as we have shown in this analysis, change in biomarker and change in pain and structure occurring in a parallel fashion. In addition, knees with both radiographic and pain progression by 12 months were excluded, reducing the possibility that case status was reached prior to any change in the biomarkers. The analyses presented in this paper reflect our primary comparison of knees with both radiographic and pain progression vs all other knees. The control group in this comparison includes knees that had either radiographic or pain progression but not both. Future work will evaluate the association between these semi-quantitative biomarkers and pain and radiographic progression separately. Finally, for this analysis we focused on the whole knee. The MOAKS scoring system allows us to examine specific compartments, and future work will focus specifically on the MR imaging markers in the specific tibial-femoral compartments.

Semi-quantitative knee joint features, including cartilage thickness and surface area, meniscus, and BMLs, measured both at baseline and as change over 24 months, were significantly associated with 48 month knee OA progression. These measures were associated with clinically relevant OA progression and could be proposed as measures of efficacy in clinical trials of disease modifying interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline Characteristics of the Sample Included in the Case-Control Study

Characteristic	Control n=406	Case (radiographic and pain progression) n=194
Age	61.3 (8.9)	62.0 (8.8)
Sex		
Male	163 (40%)	84 (43%)
Female	243 (60%)	110 (57%)
BMI	30.7 (4.8)	30.7 (4.8)
History of knee injury *		
No	260 (64%)	125 (65%)
Yes	145 (36%)	68 (35%)
Baseline Kellgren Lawrence grade (KLG)		
1	51 (13%)	24 (12%)
2	222 (55%)	84 (43%)
3	133 (33%)	86 (44%)
Baseline WOMAC Pain score; mean (SD)	13.0 (16.7)	10.2 (13.0)
Baseline JSW; mean (SD)	3.9 (1.1)	3.8 (1.4)

* Ever injured knee badly enough to limit ability to walk for at least two days

Table 2

Baseline distribution of semi-quantitative MRI-based markers: Odds ratios (95% confidence intervals) from logistic regression models for baseline markers predicting case status (radiographic and pain progression).

Domain	Category	Control	Case (radiographic and pain progression)	OR* (95% CI)
CART	Cartilage morphology: max thickness score across entire knee			
	0	118 (29.1%)	32 (16.5%)	REF
	1	83 (20.4%)	44 (22.7%)	2.1 (1.2, 3.6)
	2	184 (45.3%)	106 (54.6%)	2.2 (1.4, 3.6)
	3	21 (5.2%)	12 (6.2%)	2.1 (0.9, 4.9)
	Cartilage morphology: number of subregions with thickness score>0 across entire knee			
	0	118 (29.1%)	32 (16.5%)	REF
	1–2	194 (47.8%)	98 (50.5%)	2.0 (1.2, 3.2)
	3+	94 (23.2%)	64 (33.0%)	2.6 (1.5, 4.4)
	Cartilage morphology: max surface area score across entire knee			
	0–1	34 (8.4%)	6 (3.1%)	REF
	2	297 (73.2%)	133 (68.6%)	2.6 (1.0, 6.5)
	3	75 (18.5%)	55 (28.4%)	4.2 (1.6, 11.2)
	Cartilage morphology: number of subregions with surface area score>0 across entire knee			
	0–1	40 (9.9%)	5 (2.6%)	REF
	2–4	174 (42.9%)	56 (28.9%)	2.9 (1.0, 7.8)
	5–7	153 (37.7%)	96 (49.5%)	6.4 (2.3, 18.0)
	8+	39 (9.6%)	37 (19.1%)	10.3 (3.3, 31.8)
OST	Number of locations affected by any osteophyte			
	0–2	81 (20.0%)	14 (7.2%)	REF
	3–5	120 (29.6%)	39 (20.1%)	1.8 (0.9, 3.6)
	6+	205 (50.5%)	141 (72.7%)	4.4 (2.3, 8.5)
	Max osteophyte score in knee			
	0–1	224 (55.2%)	85 (43.8%)	REF
	2	132 (32.5%)	70 (36.1%)	1.4 (0.9, 2.2)
	3	50 (12.3%)	39 (20.1%)	2.1 (1.2, 3.6)
MEN	Meniscal morphology: max grade across all locations			
	0	178 (43.8%)	75 (38.7%)	REF
	1	114 (28.1%)	65 (33.5%)	1.3 (0.9, 2.1)
	2	114 (28.1%)	54 (27.8%)	0.8 (0.5, 1.5)
	Medial meniscal extrusion - medially			
	Grade 0: < 2mm extrusion	151 (37.4%)	51 (26.3%)	REF
	Grade 1: 2–2.9mm extrusion	119 (29.5%)	57 (29.4%)	1.5 (0.9, 2.4)
	Grade 2: 3–4.9mm extrusion	106 (26.2%)	58 (29.9%)	1.8 (1.1, 3.1)

Domain	Category	Control	Case (radiographic and pain progression)	OR* (95% CI)
	Grade 3: > 5mm extrusion	28 (6.9%)	28 (14.4%)	3.3 (1.6, 6.8)
BML	Number of subregions affected by any BML			
	0	55 (13.5%)	11 (5.7%)	REF
	1	76 (18.7%)	22 (11.3%)	1.4 (0.6, 3.3)
	2	88 (21.7%)	38 (19.6%)	2.3 (1.1, 5.1)
	3	88 (21.7%)	41 (21.1%)	2.5 (1.2, 5.5)
	4	52 (12.8%)	32 (16.5%)	3.3 (1.5, 7.4)
	5+	47 (11.6%)	50 (25.8%)	6.1 (2.7, 13.7)
	Max BML score in knee			
	0	55 (13.5%)	11 (5.7%)	REF
	1	148 (36.5%)	75 (38.7%)	2.4 (1.2, 5.0)
	2	138 (34.0%)	64 (33.0%)	2.2 (1.1, 4.6)
	3	65 (16.0%)	44 (22.7%)	3.5 (1.6, 7.7)
SYN	Hoffa-Synovitis			
	0	186 (45.8%)	60 (30.9%)	REF
	1	190 (46.8%)	112 (57.7%)	1.8 (1.3, 2.7)
	2–3	30 (7.4%)	22 (11.3%)	2.2 (1.2, 4.3)
EFF	Synovitis-Effusion			
	0–1	332 (81.8%)	151 (77.8%)	REF
	2–3	74 (18.2%)	43 (22.2%)	1.3 (0.8, 2.0)

*Univariate models for each marker adjusted for sex, race, and baseline age, BMI, KLG, WOMAC pain, pain medication and min JSW.

Table 3

Change in semi-quantitative MRI-based markers over 24 months Odds ratios (95% confidence intervals): results of logistic regression models predicting case-status (radiographic and pain progression).

Domain	Category	Control	Case (radiographic and pain progression)	OR* (95% CI)
CART	Cartilage morphology: number of areas with worsening in thickness across entire knee			
	No Change	266 (65.5%)	82 (42.3%)	REF
	Worsen in 1 subregion	83 (20.4%)	49 (25.3%)	1.9 (1.2, 3.0)
	Worsen in 2 subregions	39 (9.6%)	38 (19.6%)	3.2 (1.9, 5.4)
	Worsen in 3+ subregions	18 (4.4%)	25 (12.9%)	4.7 (2.4, 9.5)
	Cartilage morphology: number of areas with worsening in surface area (include within-grade change) across entire knee			
	No Change	193 (47.5%)	53 (27.3%)	REF
	Worsen in 1 subregion	122 (30.0%)	54 (27.8%)	1.6 (1.0, 2.6)
	Worsen in 2 subregions	52 (12.8%)	39 (20.1%)	2.7 (1.6, 4.6)
	Worsen in 3+ subregions	39 (9.6%)	48 (24.7%)	5.1 (2.9, 8.8)
	Cartilage morphology: number of areas with worsening in surface area (exclude within-grade change) across entire knee			
	No Change	277 (68.2%)	105 (54.1%)	REF
	Worsen in 1 subregion	87 (21.4%)	41 (21.1%)	1.3 (0.8, 2.0)
	Worsen in 2 subregions	31 (7.6%)	25 (12.9%)	2.4 (1.3, 4.4)
	Worsen in 3+ subregions	11 (2.7%)	23 (11.9%)	7.1 (3.2, 15.8)
OST	Increase in number of locations affected by any osteophyte			
	No	371 (91.4%)	173 (89.2%)	REF
	Yes	35 (8.6%)	21 (10.8%)	1.3 (0.7, 2.3)
	Change in number of locations affected by any osteophyte			
	No Change	371 (91.4%)	173 (89.2%)	REF
	Worsen in 1 subregion	21 (5.2%)	11 (5.7%)	1.1 (0.5, 2.5)
	Worsen in 2+ subregions	14 (3.4%)	10 (5.2%)	1.5 (0.6, 3.7)
	Max change in osteophyte score >=1 across all subregions in knee			
	No	347 (85.5%)	151 (77.8%)	REF
	Yes	59 (14.5%)	43 (22.2%)	1.7 (1.1, 2.7)
MEN	Meniscal morphology: any regions with worsening			
	No	365 (90.1%)	140 (72.2%)	REF
	Yes	40 (9.9%)	54 (27.8%)	3.8 (2.4, 6.1)
	Meniscal extrusion medial: worsening			
	No	369 (91.3%)	143 (74.1%)	REF
	Yes	35 (8.7%)	50 (25.9%)	4.3 (2.6, 7.1)
BML	Change in number of subregions affected by any BML			
	Improvement	55 (13.6%)	26 (13.4%)	1.1 (0.6, 1.8)

Domain	Category	Control	Case (radiographic and pain progression)	OR* (95% CI)
	No Change	214 (52.8%)	95 (49.0%)	REF
	Worsen in 1 subregion	105 (25.9%)	49 (25.3%)	1.0 (0.7, 1.6)
	Worsen in 2+ subregions	31 (7.7%)	24 (12.4%)	1.9 (1.0, 3.4)
	Max change in BML score across all subregions in knee			
	No Change	138 (34.1%)	53 (27.3%)	REF
	With grade worsening	24 (5.9%)	12 (6.2%)	1.3 (0.6, 2.8)
	Worsening by 1 grade	192 (47.4%)	81 (41.8%)	1.2 (0.8, 1.8)
	Worsening by 2+ grades	51 (12.6%)	48 (24.7%)	2.6 (1.5, 4.4)
	Any subregions with improvement (including within changes) in BML			
	No	219 (54%)	89 (46%)	REF
	Yes	187 (46%)	105 (54%)	1.4 (1.0, 2.0)
	Any subregions with worsening (including within grade changes) in BML			
	No	138 (34%)	53 (27%)	REF
	Yes	268 (66%)	141 (73%)	1.4 (1.0, 2.1)
SYN	Change in Hoffa-synovitis			
	Improvement	7 (1.7%)	3 (1.5%)	1.3 (0.3, 5.3)
	No Change	374 (92.1%)	158 (81.4%)	REF
	Worsen	25 (6.2%)	33 (17.0%)	3.4 (1.9, 6.1)
EFF	Change in Synovitis-effusion			
	Improvement	62 (15.3%)	17 (8.8%)	0.7 (0.4, 1.4)
	No Change	269 (66.3%)	98 (50.5%)	REF
	Worsen	75 (18.5%)	79 (40.7%)	3.0 (2.0, 4.5)

*Univariate models for each marker adjusted for sex, race, and baseline age, BMI, KLG, WOMAC pain, pain medication and min JSW.

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Table 4

Change in semi-quantitative MRI-based markers over 24 months: results of multivariable regression models* predicting case-status (radiographic and pain progression).

	Model 1: **Include Cartilage**	**Model 2:** **Model 1 + Meniscal Extrusion**	**Model 3:** **Model 2 + Meniscal Morphology**	**Model 4:** **Model 3 + Synovitis-Effusion**	**Model 5:** **Model 4 − Meniscal Extrusion**	**Model 6:** **Model 5 + Hoffa-Synovitis**
C-statistic**	**0.706**	**0.715**	**0.722**	**0.734**	**0.733**	**0.740**
Cartilage: number of areas with worsening in thickness	P=0.0005	P=0.0033	P=0.0061	P=0.0222	P=0.0140	P=0.0260
None	REF	REF	REF	REF	REF	REF
1 subregion	1.7 (1.1, 2.6)	1.6 (1.0, 2.5)	1.6 (1.0, 2.5)	1.5 (0.9, 2.4)	1.5 (1.0, 2.5)	1.4 (0.9, 2.3)
2 subregions	2.5 (1.4, 4.3)	2.3 (1.3, 4.0)	2.2 (1.2, 3.9)	1.9 (1.0, 3.4)	1.9 (1.1, 3.5)	1.8 (1.0, 3.3)
3+ subregions	3.5 (1.7, 7.2)	3.0 (1.4, 6.3)	2.9 (1.4, 6.0)	2.7 (1.3, 5.8)	2.8 (1.3, 6.0)	2.8 (1.3, 5.9)
Cartilage: number of areas with worsening in surface area	P=<0.0001	P=0.0066	P=0.0199	P=0.0699	P=0.0271	P=0.0540
None	REF	REF	REF	REF	REF	REF
1 subregion	1.4 (0.9, 2.2)	1.3 (0.8, 2.1)	1.3 (0.8, 2.0)	1.2 (0.8, 2.0)	1.3 (0.8, 2.0)	1.2 (0.8, 2.0)
2 subregions	2.0 (1.1, 3.5)	1.7 (0.9, 3.0)	1.6 (0.9, 2.9)	1.5 (0.8, 2.7)	1.5 (0.9, 2.8)	1.5 (0.8, 2.6)
3+ subregions	3.8 (2.1, 6.8)	2.9 (1.6, 5.3)	2.6 (1.4, 4.8)	2.3 (1.2, 4.3)	2.5 (1.4, 4.7)	2.4 (1.3, 4.4)
Meniscal extrusion medial worsening		P=0.0015	P=0.0387	P=0.1013		
		2.4 (1.4, 4.2)	1.9 (1.0, 3.4)	1.7 (0.9, 3.1)		
Meniscal morphology: any regions with worsening			P=0.0337	P=0.0363	P=0.0027	P=0.0034
			1.8 (1.0, 3.2)	1.9 (1.0, 3.3)	2.2 (1.3, 3.8)	2.2 (1.3, 3.8)
Synovitis-Effusion : change in effusion category				P=0.0017	P=0.0008	P=0.0024
Improvement				REF	REF	REF
No change				1.4 (0.8, 2.6)	1.4 (0.8, 2.6)	1.3 (0.7, 2.5)
worsening				2.9 (1.5, 5.7)	3.0 (1.5, 5.8)	2.7 (1.4, 5.4)
Hoffa-Synovitis: change in synovitis category						P=0.0305
No change/improve						REF
Worsening						2.0 (1.1, 3.9)

* Models adjusted for sex, race, and baseline age, BMI, KLG, WOMAC pain, pain medication and min JSW and the other markers included in the model.

** C-Statistic for model with covariates only:0.608