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Baseline radiographic osteoarthritis and semi-quantitatively assessed meniscal damage and extrusion and cartilage damage on MRI is related to quantitatively defined cartilage thickness loss in knee osteoarthritis: The Multicenter Osteoarthritis Study

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Abstract

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Competing Interests

Ali Guermazi is the president of Boston Imaging Core Lab, LLC (BICL), Boston, MA, a company providing radiological image assessment services. He is a consultant to MerckSerono, TissueGene and Ortho-Trophix. Frank Roemer is a shareholder and CMO of BICL. Felix Eckstein is CEO and co-owner of Chondrometrics GmbH and provides consulting services to Merck and Synarc. Wolfgang Wirth is a co-owner of Chondrometrics GmbH. None of the other authors have declared any possible conflict of interest.

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Objectives—To provide a comprehensive simultaneous relation of various semiquantitative knee OA MRI features as well as the presence of baseline radiographic OA to quantitative longitudinal cartilage loss.

Methods—We studied Multicenter OA Study (MOST) participants from a longitudinal observational study that included quantitative MRI measurement of cartilage thickness. These subjects also had Whole Organ MRI Score (WORMS) scoring of cartilage damage, bone marrow lesions (BMLs), meniscal pathology, and synovitis, as well as baseline radiographic evaluation for Kellgren and Lawrence (KL) grading. Knee compartments were classified as progressors when exceeding thresholds of measurement variability in normal knees. All potential risk factors of cartilage loss were dichotomized into “present” (score ≥2 for cartilage, ≥1 for others) or “absent”. Differences in baseline scores of ipsi-compartmental risk factors were compared between progressor and non-progressor knees by multivariable logistic regression, adjusting for age, sex, body mass index, alignment axis (degrees) and baseline KL grade. Odds ratios (OR) and 95% CIs were calculated for medial (MFTC) and lateral (LFTC) cartilage loss. Cartilage loss across both compartments was studied using Generalized Estimating Equations.

Results—196 knees of 196 participants were included (age 59.8±6.3 years [mean±SD], BMI 29.5±4.6, 62% women). For combined analyses of MFTC and LFTC, baseline factors related to cartilage loss were radiographic OA (KL grade ≥2: aOR 4.8 [2.4-9.5], cartilage damage (aOR 2.3 [1.2-4.4]), meniscal damage (aOR 3.9 [2.1-7.4]) and extrusion (aOR 2.9 [1.6-5.3]), all in the ipsilateral compartment, but not BMLs or synovitis.

Conclusion—Baseline radiographic OA and semiquantitatively assessed MRI-detected cartilage damage, meniscal damage and extrusion, but not BMLs or synovitis is related to quantitatively measured ipsicompartmental cartilage thinning over 30 months.

Keywords

meniscus; effusion; synovitis; cartilage; semiquantitative; quantitative

Introduction

Several studies have shown that structural features of knee OA that can be graded semiquantitatively (SQ) with MRI, are associated with subsequent SQ determined structural progression. These include meniscal pathology [1,2], bone marrow lesions [3,4], and cartilage damage [5,6]. In addition Hoffa-synovitis and effusion-synovitis are commonly assessed using SQ scoring methods, but the relation of synovitis and subsequent cartilage loss is debated [5,7,8,9,10].

Evaluating both cartilage loss, the outcome, and structural features, i.e. factors that relate to this outcome, in the same images at the same time, may theoretically introduce bias. Quantitatively measured cartilage loss is commonly used as an outcome measure in longitudinal studies of structural change in knee OA and the process is done by readers who are not involved in semiquantitative assessment of baseline features, enabling evaluation of outcome measures totally independent of baseline readings without the risk of biasing the outcome assessment.

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The purpose of this study was to provide a comprehensive simultaneous relation of various SQ knee OA MRI features as well as the presence of baseline radiographic OA to quantitative longitudinal cartilage loss, either in the medial or lateral compartments, or in the whole tibiofemoral knee joint.

PATIENTS AND METHODS

Study Design and Subjects

Subjects were participants in the Multicenter Osteoarthritis Study (MOST), a prospective study of 3,026 persons aged 50-79 years with a goal of identifying risk factors for incident and progressive knee OA in a sample either with OA or at high risk of developing disease. Participants from two US communities, Birmingham, Alabama and Iowa City, Iowa were enrolled in the study over a 22 month period. Details of subject inclusion, exclusion and recruitment have been described previously [7,11]. The study protocol was approved by the institutional review boards at the University of Iowa, University of Alabama, Birmingham, University of California, San Francisco and Boston University Medical Campus, and written informed consent was obtained from all participants.

At baseline, all participants without contraindications for 1.0T extremity MRI and whose knees were not too large for the extremity scanner had 1.0 T MR images acquired on both knees. At the baseline and 30 month clinic visits serial 1.5 T large bore MRI scans were also acquired on a subset of participants to obtain quantitative measures of cartilage loss. During a 12 month period during the baseline visit every third person at the Alabama site and every fourth person at the Iowa site was asked to participate, and those who agreed and did not have knee MRI contraindications had 1.5T scans of both knees. Baseline 1.5T MRIs were obtained in 426 subjects and 30 month 1.5T scans in 300 subjects. Of these subjects, 196 knees (one knee per subject) had longitudinal measurements of quantitative cartilage loss as well as semiquantitative WORMS assessment at baseline and at 30 months. The dominant or the right (if dominance was unknown) knee was measured. If images for this knee had poor orientation, only tibial cartilage thickness was measured. If images for this knee had poor quality (e.g. due to fat saturation failure, or motion artifact), then the contralateral knee was measured. These 196 knees were included in our study (Figure 1).

Radiographs

At baseline, all subjects underwent weight-bearing posteroanterior (PA) fixed flexion knee radiographs using a plexiglass positioning frame (SynaFlexer™). Radiographs were read by a team of three readers including one author (DTF), blinded to clinical data, who graded radiographs according to Kellgren-Lawrence (KL) grade, followed by an adjudication process [7,11]. KL grade 2 or above was considered to have radiographic OA. The weighted kappa coefficient of inter-observer reliability for the KL readings was 0.79.

Full-limb radiographs of both legs were obtained at baseline using a 14-in × 51-in cassette. The mechanical axis was defined as the angle formed by the intersection of a line from the center of the head of the femur to the center of the tibial spines and a line from the center of the talus to the center of the tibial spines. The interobserver intraclass correlation coefficient

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for the mechanical axis was 0.99 ($P < 0.0001$). Varus alignment was defined as a hip-knee-ankle (HKA) angle <179°; 179-181° was considered neutral and valgus alignment was defined as an HKA angle >181°.

MRI Acquisition

In the MOST parent study, MR imaging was performed using a 1.0 T extremity-based OrthOne scanner (Oni MSK Extreme, GE Healthcare, Waukesha, WI). Images were acquired using a circumferential extremity coil using fat-suppressed, fast spin echo, proton density-weighted sequence in two planes, sagittal (TR=4800 ms, TE=35 ms, 3.0mm slice thickness, 0mm interslice gap, FOV 14×14cm, matrix 288×192, NEX2); and axial (TR=4700 ms, TE=13.2 ms, 3.0mm slice thickness, 0mm interslice gap, FOV 14cm, matrix 288×192, NEX2) and a short tau inversion recovery sequence (STIR) in the coronal plane (TR=7820 ms, TE=14 ms, TI=100 ms, 3.0mm slice thickness, 0mm interslice gap, FOV 14cm, matrix 256×256, NEX2).

Coronal T1-weighted fast low-angle shot (FLASH) MRI with water excitation (TR=17 or 18.6 ms, TE=4.2 – 9.3 ms, 1.5 mm slice thickness, 0 mm interslice gap, FOV 0.3125×0.3125 mm in-plane resolution) was obtained at baseline and 30-month follow-up using a 1.5 T MRI (Siemens, Erlangen, Germany) in the participants, who volunteered for the longitudinal substudy, in which MRI measurement of cartilage thickness and volume were performed.

MRI Interpretation

MRI readings were performed independently by two musculoskeletal radiologists (AG, FWR), with 14 and 12 years of experience respectively in semiquantitative MR assessment of knee OA using the WORMS grading scheme. These readers were blinded to all other data [12]. Cartilage signal intensity and morphology were scored according to WORMS from 0 to 6 (depending upon depth and extent of cartilage loss) in five subregions each in the medial and lateral tibiofemoral compartments, for a total of 10 tibiofemoral subregions. Meniscal status was graded from 0 to 4 in the anterior horn, body, and posterior horn of each meniscus, defining tear as a WORMS score ≥1 in one or more segment. In addition, extrusion of each meniscal body was scored on the coronal image from 0 to 2, defining the presence of extrusion as a score ≥1 [2]. MR images were assessed using eFilm^{TM} software (Version 2.0.0, Merge Healthcare, Milwaukee, WI). In addition, bone marrow lesions (BMLs) and meniscal damage were assessed according to the WORMS system at baseline. BML size was scored from 0–3 based on the extent of regional involvement.

Signal alterations in the infrapatellar and intercondylar regions of Hoffa's fat pad were scored from 0 to 3 as a surrogate for synovial thickening according to the literature as this feature is not part of the original WORMS system [8,9,13]. We will refer to these scores as 'Hoffa-synovitis' in the following sections, although acknowledging that these signal changes also include non-specific alterations not necessarily related to synovitis [10,14]. WORMS uses a combined measure of joint effusion and synovitis based on the amount of intraarticular fluid-equivalent signal. This composite score is graded from 0 to 3 according to the estimated maximal distention of the synovial cavity. and was applied in addition to mentioned signal changes in Hoffa's fat pad [15].We will refer to this scoring measure as

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'effusion-synovitis' in the following sections to acknowledge both constituents of the composite score [10]. All semiquantitative MR assessments were dichotomized into "present" (score ≥2 for cartilage since score of 1 represents a hyperintensity of the cartilage of unknown significance, ≥1 for others) or "absent" for the purpose of statistical analysis.

Quantification of Cartilage Thickness Loss on MRI

Segmentation of the tibial and femoral cartilage involved manual tracing of the total subchondral bone area (tAB) and the cartilage surface area (AC) of the medial tibia, lateral tibia, central (weight-bearing) medial femoral condyle, and central (weight-bearing) lateral femoral condyle using custom software (Chondrometrics GmbH, Ainring, Germany). Segmentation was performed by trained readers with several years of experience in cartilage segmentation. Baseline and follow-up images were displayed simultaneously but with blinding to the acquisition order or date, to allow a consistent selection of the number of slices and peripheral edges. Quality control of all segmentations was performed by one expert (F.E.). The cartilage thickness was computed from the cartilage surfaces (tAB and AC) as described previously [16]. The reliability of the technique has been published before [17].

The mean cartilage thickness (considering denuded areas as "0") in the medial femorotibial compartment (MFTC) was obtained by adding the cartilage thickness measured in the medial tibia and the central, weight-bearing part of the medial femoral condyle. The cartilage thickness in the LFTC was similarly computed as the sum of the cartilage thickness observed in the lateral tibia and the central, weight-bearing part of the lateral femoral condyle.

Outcome Definition

The classification of knees as progressors (defined as loss above a certain threshold in cartilage thickness – see below) and non-progressors (loss below the threshold or increase in cartilage thickness) was based on one-year measurement variability observed in the medial (MFTC) and lateral (LFTC) femorotibial compartment of participants from the healthy reference cohort of the OA Initiative [18] [http://oai.epi-ucsf.org/datarelease/]. These were not expected to show a change in cartilage thickness other than measurement variability, biological variability, and aging, given the absence of radiographic or symptomatic OA and the non-exposure to risk factors for the onset of OA. The change observed in that cohort in the MFTC and the LFTC using a coronal FLASH 3D MRI sequence had a mean value close to zero (MFTC: 2μm, LFTC: 7μm) [18]. The thresholds of progression / non-progression were chosen so that 95% of the knees analyzed in the OAI healthy reference cohort would be classified as non-progressors, with 2.5% of these knees at each end of the range showing cartilage thinning or thickening, respectively. Hence, knees from the MOST cohort were classified as progressors (cartilage thinning) when exceeding a thresholds of -162μm in the MFTC, and/or -145μm in the LFTC.

Statistical Analysis

Differences in baseline scores of ipsi-compartmental independent variables were compared between progressor and non-progressor knees by multivariable logistic regression, adjusting

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for age, sex, body mass index, mechanical alignment axis (degrees) and baseline KL grade. Given the literature evidence that BMLs and effusion-synovitis/Hoffa-synovitis can fluctuate over time, to evaluate the effect of transient vs. persistent BMLs and synovitis, we performed additional analyses by stratifying subjects based on the following criteria for the analysis using these three baseline MRI features: score ≥1 at baseline and disappears (score 0) at follow up vs. score ≥1 at baseline and stays ≥1 at follow up. Odds ratios (OR) and 95% CIs were calculated for MFTC and LFTC cartilage loss, respectively. We further combined MFTC and LFTC to calculate an OR of ipsi-compartmental cartilage loss across compartments, using Generalized Estimating Equations. As a secondary analysis, we did logistic regression model of step-wise selection, including MRI features (meniscal damage, meniscal extrusion, cartilage damage, BMLs, effusion synovitis, and Hoffa synovitis) and KL grade, with entry level =0.2 and stay level =0.1. The aforementioned baseline demographic characteristics were forced in the model. All statistical analyses were performed using SAS 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

196 knees from 196 participants were included (Table 1) and their mean age was 59.8±6.3 years, mean BMI was 29.5±4.6, and 62% were women. 46 knees had radiographic knee OA (KL grade 2 or above) at baseline.

In the MFTC (Table 2), there were 35 progressors and 161 non-progressors. The only baseline factor related to cartilage thickness loss was baseline radiographic OA (aOR 2.51, [95%CI 1.03-6.09]). None of the MRI-based OA features in the MFTC is related to subsequent cartilage thickness loss in the same compartment.

In the LFTC (Table 3), there were 29 progressors and 167 non-progressors. Baseline factors related to cartilage thickness loss were baseline radiographic OA (aOR 8.50 [1.97-36.63], prevalent lateral cartilage damage (aOR 3.08 [1.14-8.29]) and lateral meniscal damage (aOR 12.16 [2.64-56.00]).

For analysis combining MFTC and LFTC, baseline factors related to cartilage thickness loss in the ipsilateral compartment were (Table 4) baseline radiographic OA (aOR 4.79 [2.41-9.53], cartilage damage (aOR 2.27 [1.18-4.37]), meniscal damage (aOR 3.94 [2.09-7.43]) and meniscal extrusion (aOR 2.92 [1.62-5.26]).

In all analyses (MFTC, LFTC and combined), stratification of subjects according transient vs. persistent BMLs and synovitis did not alter our results (i.e. BMLs and effusion-synovitis/ Hoffa-synovitis were not associated with subsequent cartilage thickness loss regardless of whether they were transient or persistent).

DISCUSSION

The aim of our study was to determine, which SQ MRI-detected OA features are related to quantitative cartilage thinning over a 30-month period. We demonstrated that the baseline factors related to cartilage thinning were baseline radiographic OA, prevalent SQ cartilage damage, meniscal damage and extrusion in the same femorotibial compartment. Of these

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features, meniscal damage and extrusion were most strongly associated with cartilage thinning. We did not find a statistically significant association of baseline SQ BMLs, effusion-synovitis or Hoffa-synovitis with subsequent quantitative cartilage loss. Lack of statistically significant results for these semiquantitative MRI features may be related to the fact that most of our study knees (150 of 196 knees) did not have radiographic OA. It has been shown previously that prevalent SQ cartilage damage is related to further SQ cartilage loss over time [5,7]. Recent studies based on data from the Joints on Glucosamine Study [5] and the MOST study [7] showed that SQ cartilage damage at baseline was associated with SQ cartilage loss (i.e. worsening of SQ cartilage scores) over 6 months [5] and 30 months [7], respectively. Moreover, prevalent SQ cartilage damage has also been shown to be related to quantitative cartilage volume loss over a longer than 2-year period [19,20] in Tasmanian Older Adult Cohort Study. It is interesting to note that cartilage damage was not statistically significant associated with cartilage thinning in the analysis of MFTC, while it was in the analyses of LFTC and the combined analysis. The reason for this result is unclear. However, perhaps it would be more important to focus on the results of combined analysis rather than individual medial and lateral compartmental analyses, since the knee OA pathologic process involves the whole FT joint. An important implication of our findings for the future knee OA clinical trials is that investigators may wish to preferentially include persons with baseline SQ cartilage damage to assess efficacy of a new therapy targeting articular cartilage, outcome of which is measured quantitatively.

In our study, the presence of BMLs at the baseline or its fluctuation was not associated with cartilage thickness loss over time. Our finding is discordant with the available literature evidence showing BMLs related to SQ cartilage loss [5, 21-24] as well as quantitatively measured cartilage volume loss [21-24]. However, to the best of our knowledge, our study is the first to examine baseline BMLs as well as it changes as potential risk factors for quantitative cartilage thickness loss. When calculating aORs for BMLs, statistical significance was lost when we adjusted our model for baseline KL grade. This implies that the presence or fluctuation of BMLs may be closely related to the severity of radiographic OA, which is an indirect marker for cartilage thinning (i.e. higher KL grade means more joint space narrowing). BMLs and cartilage thinning may be closely related to each other in knee OA pathogenesis, and one may cause the other or vice versa. It remains difficult to determine ‘which comes first’, however.

SQ meniscal damage and extrusion were the two strongest factors related to quantitative cartilage loss in our study. Several studies have reported associations between baseline meniscal damage and cartilage loss over time. Chang et al. showed SQ medial meniscal body tear was associated with quantitatively measured thickness loss of meniscus-covered portion of femorotibial cartilage over two years [25]. Berthiaume et al. showed SQ medial meniscal tear or extrusion are strongly related to medial compartment cartilage volume loss over two years [26]. In a study by Crema et al, the risk of quantitative medial femorotibial cartilage thickness loss over two years increased significantly in knees with SQ medial meniscal tears or macerations [27]. Specifically, cartilage loss in the external medial tibia was associated with tears of the posterior horn of the medial meniscus. Hunter et al demonstrated baseline SQ medial meniscal damage and malpositioning were associated with increased risk of SQ cartilage score worsening within the medial femorotibial compartment

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over 30 months based on the WORMS [2]. Findings of our study further support the strong relationship between SQ meniscal pathology and quantitative cartilage loss over time.

Our study showed effusion-synovitis or Hoffa synovitis were not associated with quantitative cartilage thinning over time. Studies examining this issue using semiquantitative cartilage loss data have not been consistent in their findings [5,7,8,9,10]. A study based on the MOST study showed longitudinal fluctuation in synovitis has borderline association with SQ cartilage loss [9]. In that study, MRI signal changes within Hoffa fat pad, suprapatellar and intercondylar regions on a non-enhanced sequence were used as a surrogate for synovitis, similar to the way we assessed Hoffa synovitis. Another study using the MOST data showed effusion-synovitis had a borderline association with SQ cartilage loss over 30 months in the femorotibial joint [7]. Data from the Joints on Glucosamine study demonstrated that baseline effusion (= “effusion synovitis” in the current study) was a strong risk factor for patellofemoral cartilage loss over a 6-month period [5]. Moreover, one arthroscopic study showed synovitis was related to progression of cartilage damage over one year assessed by repeat arthroscopy, although adjustment was not performed to take into account other structural features that might have caused both the synovitis and cartilage loss [28]. Possible reasons for these discrepancies between our study and previous publications are unclear. Even though synovitis may be a prominent component of disease in some knees with OA, unlike meniscal factors and cartilage defects, it appeared to have only mild association with cartilage loss. However, it should be noted that no studies have been reported to show if synovitis as detected by contrast-enhanced MRI is associated with cartilage loss over time. Considering that synovitis is more accurately assessed with contrast-enhanced MRI, further studies are needed to determine the relationship between CE-MRI-assessed baseline synovitis and future cartilage loss. A strength of our study is the fact that the odds ratio for cartilage loss over time remained statistically significant after adjustment for alignment as well as the demographic characteristics, implying our findings hold true regardless of the alignment status. Another notable strength of our study is that we examined quantitative cartilage thickness loss, while all MRI-based assessments were semiquantitatively assessed by readers who were not involved in quantitative outcome analysis. This avoided potential bias in reading. Since readers are usually blinded to the research questions asked at the time of reading, and in large scale multicenter epidemiological studies, analyses are often designed after the reading is completed, reader bias due to simultaneous assessment may be unlikely. However, if there were bias in examination of the progression of cartilage lesions, for example, our data is not vulnerable to the bias associated with grading independent and outcome variables together in the same session by the same readers. The semiquantative MR measurements and OA status were not included in one model since the order of MRI features and the causal relationship among them are not clearly understood yet. If some baseline factors are potential confounders to the association of a specific factor and the outcome, the results we observed would be biased. On the other hand, if some baseline factors are on the path way from a specific factor to the outcome, i.e., mediators, adjusting them in the model is not appropriate. As we did not have enough knowledge to separate the potential confounders and mediators, we chose to assess the relation of each baseline factor without controlling for other factors.

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Limitations of our study include the fact that synovitis, in the form of effusion synovitis and Hoffa synovitis, was assessed using non-contrast enhanced MRI. MRI assessment of synovitis in knee OA should ideally be performed using contrast-enhanced sequence [29]. However, the cohort of patients included in our study did not undergo contrast-enhanced MRI examination and such data could not be collected.

In conclusion, baseline radiographic OA and the baseline presence of MRI-detected cartilage damage, meniscal damage and extrusion in the ipsilateral FTC were associated with quantitatively assessed cartilage thickness loss over 30-months, but not BMLs, effusion-synovitis or Hoffa-synovitis.

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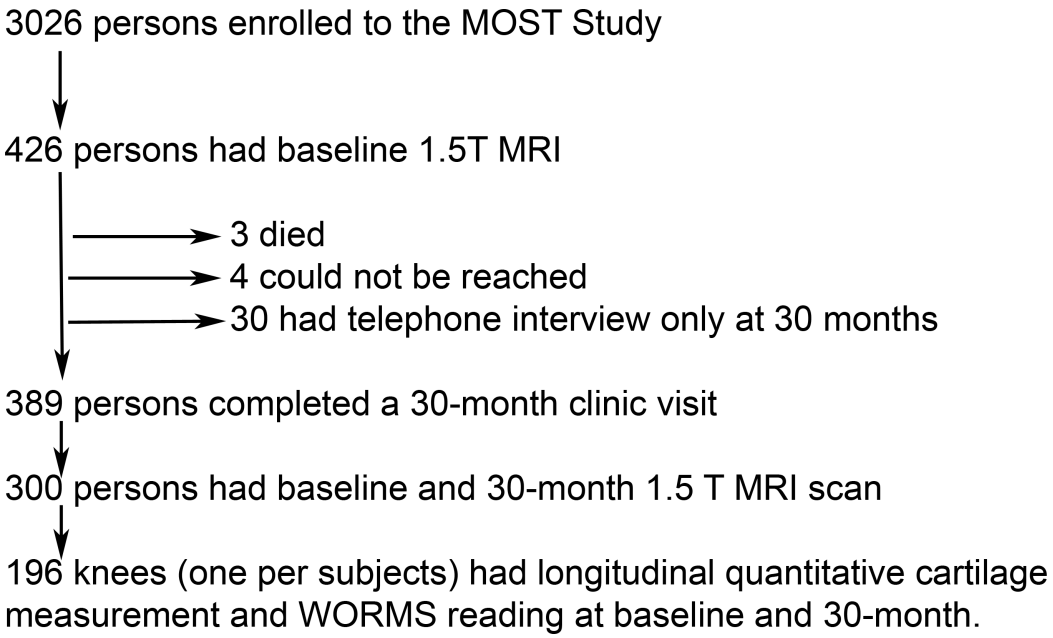

Figure 1.
Flowchart summarizing the subject inclusion/exclusion process.

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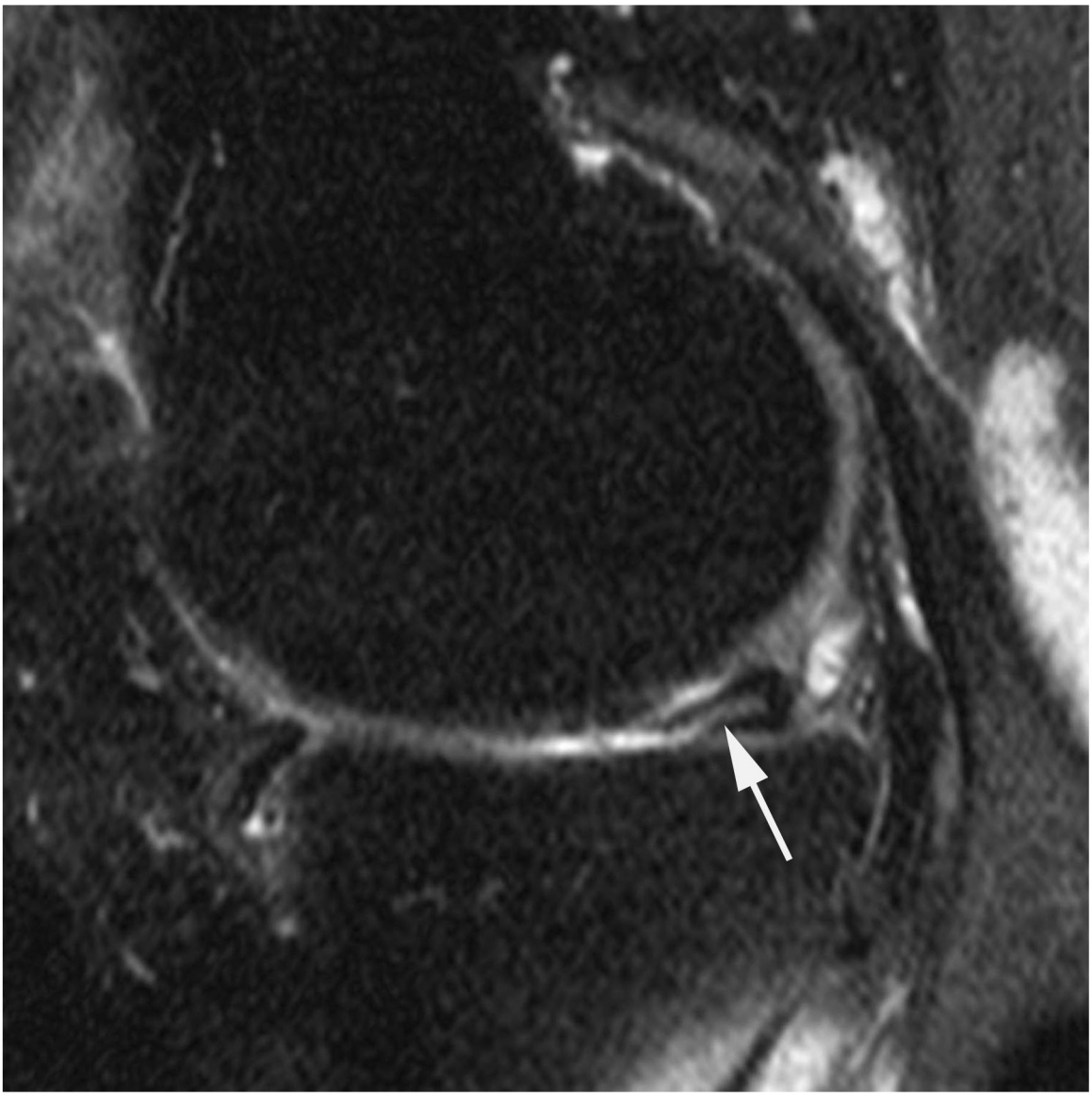

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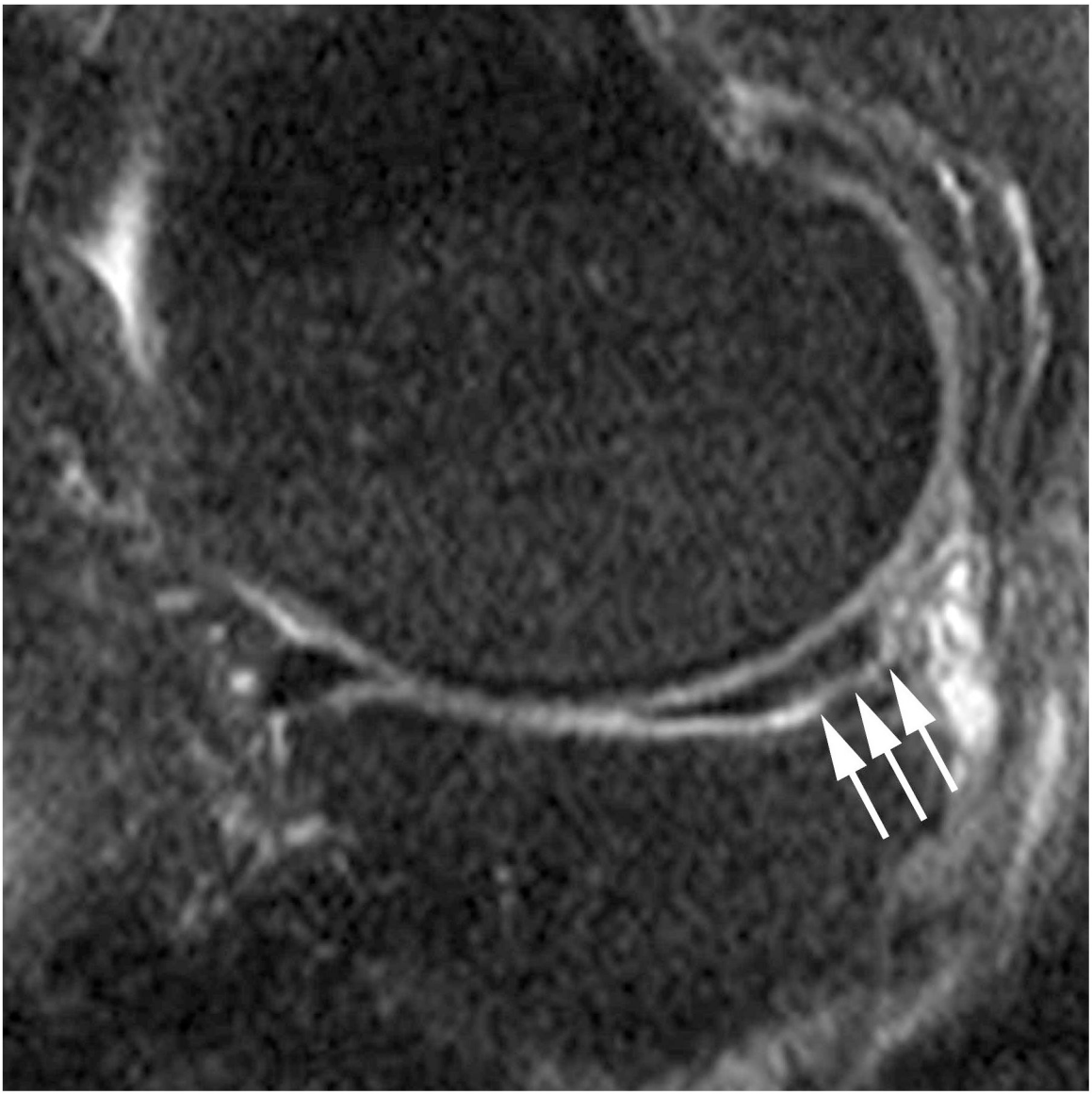

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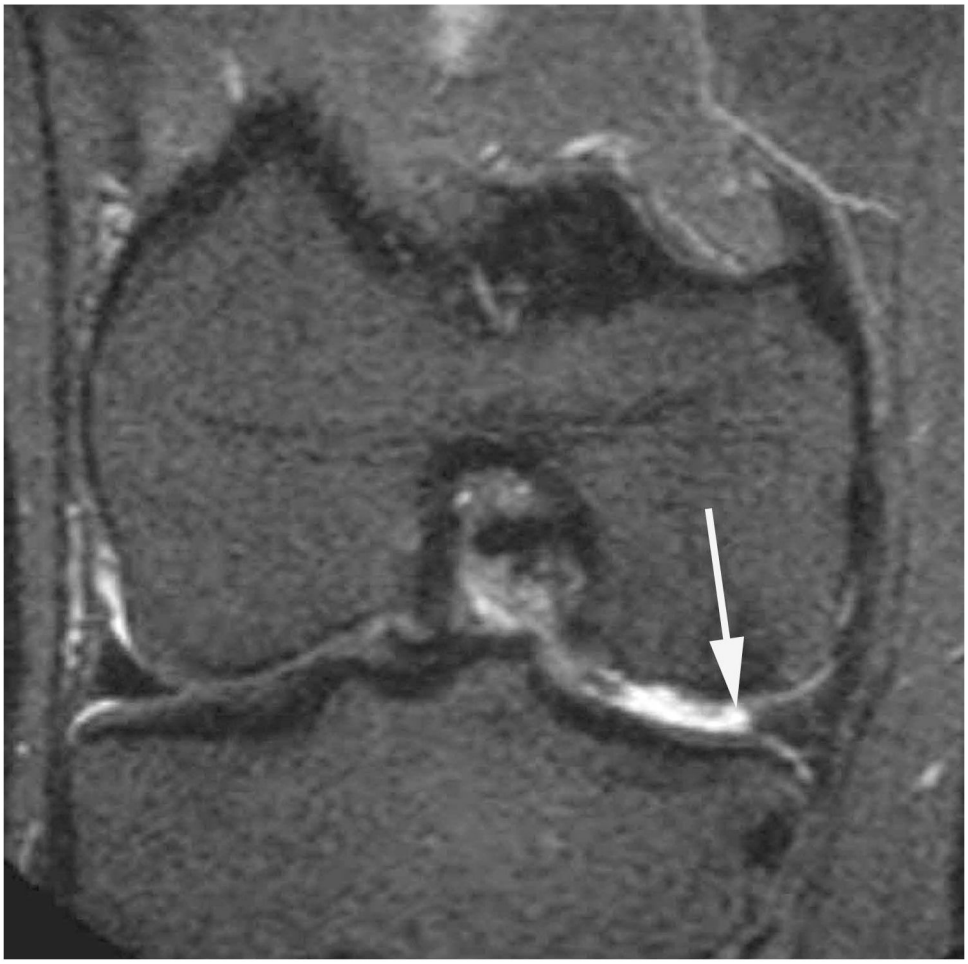

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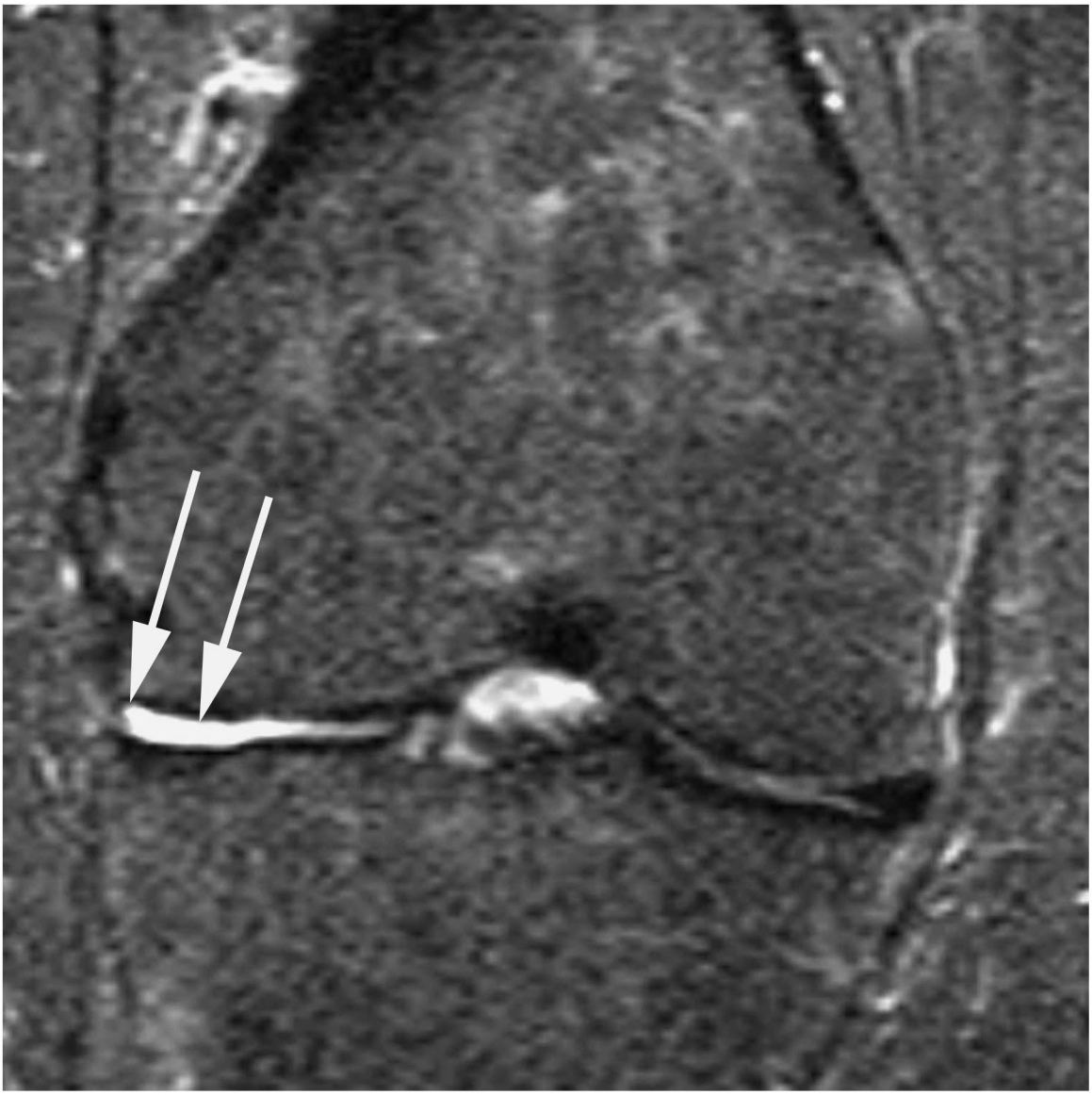

Figure 2.

Sagittal proton density-weighted fat suppressed MRI shows (a) a parrot-beak tear of the posterior horn of the medial meniscus reaching the inferior surface of the meniscus (arrow). This lesion would be scored as a grade 1 lesion in WORMS; (b) a non-displaced horizontal-oblique tear of the posterior horn of the medial meniscus reaching both, the superior and inferior surfaces of the meniscus (arrows). This tear type would be assessed as a grade 2 lesion in WORMS. Coronal STIR MRI shows (c) partial maceration (i.e. substance loss) of the meniscal body with an amputated triangular appearance (arrow). This finding represents a grade 3 lesion in the WORMS system; (d) complete maceration or substance loss of the lateral meniscal body. No meniscus is seen in the weight-bearing central subregions of the lateral femorotibial compartment (arrows). This finding represents a grade 4 lesion in WORMS.

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Table 1

Demographic characteristics (Knee-based data: N=196 knees)

Baseline data		
Age (years): Mean (standard deviation)		59.8 (6.3)
BMI (kg/m^{-2}): Mean (standard deviation)		29.5 (4.6)
Sex	Female: n (%)	122 (62.2)
	Male: n (%)	74 (37.8)
Clinical site	Alabama: n (%)	108 (55.1)
	Iowa: n (%)	88 (44.9)
Malalignment	Varus (<179°): n (%)	86 (43.9)
	Neutral (179-181°): n (%)	73 (37.2)
	Valgus (>181°): n (%)	37 (18.9)
Kellgren and Lawrence grade	0	108 (55.1)
	1	42 (21.4)
	2	25 (12.8)
	3	18 (9.2)
	4	3 (1.5)
Longitudinal data		
Change in lateral tibial and femoral mean cartilage thickness (μm)		-25.10 (140.54)
Change in medial tibial and femoral mean cartilage thickness (μm)		-63.01 (184.11)

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Table 2

Prognostic value of semiquantitative MRI-based risk factors in the medial TF compartment

Risk factor at baseline	Non-progressors (N=161) n (%)	Progressors: cartilage thickness decrease >162μm (N=35) n (%)	aOR (95% CI)	P-value
Meniscal damage WORMS score ≥1 *	42 26.58	17 50.00	2.07 *** (0.87, 4.90)	0.0978
Meniscal extrusion (present) **	49 31.21	21 61.76	2.13 *** (0.90, 5.03)	0.0839
Cartilage WORMS score ≥2 *	109 68.99	27 79.41	1.56 *** (0.56, 4.30)	0.3947
BML WORMS score ≥1 *	45 28.48	16 47.06	1.51 *** (0.64, 3.56)	0.3463
Effusion synovitis WORMS score ≥1 *	108 68.35	27 79.41	2.29 *** (0.85, 6.16)	0.1013
Hoffa synovitis WORMS score ≥1 *	92 58.23	19 55.88	0.84 *** (0.36, 1.93)	0.6731
Radiographic OA (KL grade ≥2)	40 24.84	16 45.71	**2.51 **** **(1.03, 6.09)**	**0.0418**

* 4 subjects had missing WORMS reading for this feature and were excluded from analysis

** 5 subjects had missing WORMS reading for this feature and were excluded from analysis

*** Adjusted for age, BMI, gender, clinic site, alignment and KL grade

**** Adjusted for age, BMI, gender, clinic site, and alignment

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Table 3

Prognostic value of semiquantitative MRI-based risk factors in the lateral TF compartment

Risk factor at baseline	Non-progressors (N=167) n (%)	Progressors: cartilage thickness decrease >147 μm (N=29) n (%)	aOR (95% CI)	P-value
Meniscal damage WORMS score ≥1 *	7 4.29	8 27.59	**12.16 *** (2.64, 56.00)**	**0.0013**
Meniscal extrusion (present) **	10 6.17	7 24.14	1.43 *** (0.52, 3.92)	0.4889
Cartilage WORMS score ≥2 *	74 45.40	21 72.41	**3.08 *** (1.14, 8.29)**	**0.0259**
BML WORMS score ≥1 *	40 24.54	10 34.48	1.46 *** (0.50, 4.21)	0.4865
Effusion synovitis WORMS score ≥1 *	116 71.17	19 65.52	1.43 *** (0.52, 3.92)	0.4889
Hoffa synovitis WORMS score ≥1 *	95 58.28	16 55.17	0.74 *** (0.29, 1.86)	0.5198
Radiographic OA (KL grade ≥2)	5 2.99	7 24.14	**8.50 **** (1.97, 36.63)**	**0.0041**

* 4 subjects had missing WORMS reading for this feature and were excluded from analysis

** 5 subjects had missing WORMS reading for this feature and were excluded from analysis

*** Adjusted for age, BMI, gender, clinic site, alignment and KL grade

**** Adjusted for age, BMI, gender, clinic site, and alignment

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Table 4

Odds ratios of having ipsi-compartmental cartilage loss due to risk factors in the same compartment (i.e. medial cartilage thinning with medial risk factors, and lateral cartilage thinning with lateral risk factors)

Risk factor at baseline	No. of compartments without cartilage loss (medial + lateral) (N=321) n (%)	No. of compartments with cartilage loss (medial +lateral): (N=64) n (%)	aOR (95% CI)	p-value **
Meniscal damage WORMS score ≥1 *	49 15.26	25 39.68	**3.94 *** (2.09, 7.43)**	**<0.0001**
Meniscal extrusion (present) *	59 18.50	28 44.44	**2.92 *** (1.62, 5.26)**	**0.0004**
Cartilage WORMS score ≥2 *	183 57.01	48 76.19	**2.27 *** (1.18, 4.37)**	**0.0136**
BML WORMS score ≥1 *	85 26.48	26 41.27	1.53 *** (0.85, 2.74)	0.1523
Effusion synovitis WORMS score ≥1 *	224 69.78	46 73.02	1.71 *** (0.82, 3.53)	0.1499
Hoffa synovitis WORMS score ≥1 *	187 58.26	35 55.56	0.79 *** (0.43, 1.47)	0.4640
Radiographic OA (KL grade ≥2)	45 13.72	23 35.94	**4.79 **** (2.41, 9.53)**	**<0.0001**

* 4 subjects had missing WORMS reading for this feature and were excluded from analysis

** p<0.023 is considered statistically significant, after Bonferroni correction for multiple comparisons

*** Adjusted for age, BMI, gender, clinic site, alignment and KL grade

**** Adjusted for age, BMI, gender, clinic site, and alignment