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Authors

Crema, MD
Nevitt, MC
Guermazi, A
et al.

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Progression of cartilage damage and meniscal pathology over 30 months is associated with an increase in radiographic tibiofemoral joint space narrowing in persons with knee OA - The MOST study. (Original Research - Brief Report)

M. D. Crema[1,2], **M. C. Nevitt**[3], **A. Guermazi**[1], **D. T. Felson**[4], **K. Wang**[4], **J. A. Lynch**[3], **M. D. Marra**[1], **J. Torner**[5], **C. E. Lewis**[6], and **F. W. Roemer**[1,7]

[1]Department of Radiology, Quantitative Imaging Center, Boston University School of Medicine, Boston, MA, USA

[2]Department of Radiology, Hospital do Coração (HCor) and Teleimagem, Sao Paulo, SP, Brazil

[3]Department of Epidemiology and Biostatistics, University of California at San Francisco, San Francisco, CA, USA

[4]Clinical Epidemiology Research Unit, Boston University School of Medicine, Boston, MA

[5]University of Iowa, Iowa City, IA, USA

[6]University of Alabama, Birmingham, AL, USA

[7]Department of Radiology, University of Erlangen, Erlangen, Germany

Abstract

Purpose—To determine the association of MRI-assessed worsening of tibiofemoral cartilage damage, meniscal damage, meniscal extrusion, separately and together, with progression of radiographic joint space narrowing (JSN).

Method and Materials—The Multicenter Osteoarthritis (MOST) Study is a cohort study of subjects with or at risk for knee osteoarthritis (OA). Knees with radiographic OA Kellgren-Lawrence grade 2 at baseline and with baseline and 30 month 1.0T MRIs were selected for

Corresponding author: Michel D. Crema, MD, Department of Radiology, Quantitative Imaging Center, Boston University School of Medicine, 820 Harrison Avenue, FGH Building, 3rd Floor, Boston, MA 02118, USA. michelcrema@gmail.com. Tel: +1 617-414-3893; Fax: +1 617-638-6616.

AUTHORS CONTRIBUTIONS

Conception and design: all authors; Analysis and interpretation of the data: MDC, MCN, AG, DTF, KW, MDM, JAL, FWR; Drafting of the article: all authors; Critical revision of the article for important intellectual content: all authors; Final approval of the article: all authors; Provision of study materials or patients: DTF, MCN, JT, CEL; Statistical expertise: DTF, KW, JAL, MCN; Obtaining of funding: DTF, MCN, JT, CEL.

CONFLICT OF INTERST

Michel D. Crema, Frank W. Roemer, and Monica D. Marra are stockholders of Boston Imaging Core Lab (BICL), LLC. Ali Guermazi is president of BICL, LLC. He is also a consultant for MerckSerono, Genzyme, Novartis, Stryker, and AstraZeneca.

reading using the WORMS system for cartilage damage, meniscal damage, and meniscal extrusion. The association of worsening of cartilage damage, meniscal damage, and/or meniscal extrusion with increases in the JSN was performed using logistic regression.

Results—A total of 276 knees (one per subject) were included (women 68.5%, mean age 62.9 ± 7.8, mean BMI 30.2 ± 5.0). Worsening of each MRI feature was associated with any increase in JSN ($p < 0.01$). Worsening of cartilage damage was more frequently observed than worsening of meniscal damage and extrusion, and was significantly associated with both slow and fast progression of JSN. An increasing risk of JSN worsening was associated with increasing number of worsening MRI features (p for trend <.0001).

Conclusion—Worsening of tibiofemoral cartilage damage, meniscal damage, and meniscal extrusion are independent predictors of JSN progression in the same compartment. Worsening of cartilage damage is more frequently observed in JSN when compared to meniscal worsening. A strong cumulative effect on JSN progression is observed for worsening of more than one MRI feature.

Keywords

osteoarthritis; knee; joint space narrowing; magnetic resonance imaging; cartilage

INTRODUCTION

Radiographically-assessed tibiofemoral joint space narrowing (JSN) is the recommended structural endpoint for disease-modifying osteoarthritis drugs in clinical trials of knee osteoarthritis (OA) [1]. Current standards of the U.S. and European regulatory authorities for demonstrating the efficacy of these drugs require that they: 1) Normalize the radiograph (reverse progression); 2) Improve the radiograph (halt progression); and 3) slow JSN by at least a pre-specified amount [2,3]. Progression of JSN is considered a surrogate for longitudinal cartilage loss in a given articular compartment[4-6].

The tibiofemoral radiographic joint space includes the meniscus as well as articular cartilage[5,7]. Previous studies have shown that as damage to the meniscus progresses—including meniscal extrusion—JSN also worsens [4,5]. However, the cumulative effect of worsening of all three MRI features with respect to JSN progression is not known. In addition, the contribution of the different MRI changes to fast vs. slow JSN progression is also unknown. Some types of meniscal damage may involve rapid loss of meniscal substance and/or displacement of meniscal fragments while degenerative cartilage damage is believed to occur relatively slowly.

To address these unknowns we studied the compartment-specific association of worsening of cartilage and meniscus pathology assessed by MRI with medial and lateral tibiofemoral JSN progression in knees with mild radiographic OA, which are likely to exhibit a range of both slow and fast JSN progression.

METHOD AND MATERIALS

Study Design and Subjects

Subjects were participants in the Multicenter Osteoarthritis Study (MOST), a prospective epidemiological study of 3,026 people with the goal of identifying risk factors for incident and progressive knee OA in a population with or at high risk of developing OA[8,9]. The Health Insurance Portability and Accountability Act-compliant study protocol was approved by the Institutional Review Boards at the University of Iowa, University of Alabama at Birmingham, University of California at San Francisco and Boston University School of Medicine, and we obtained written informed consent from all patients. Subjects included in the present study were selected from the cohort study of risk factors for radiographic OA progression consisting of randomly selected knees with tibiofemoral OA. In the present study, we analyzed a random sample of 297 knees. The knees had been given Kellgren-Lawrence (KL) grades of 2 at baseline, and in addition to radiographs, MRIs were also acquired at baseline and at 30 months.

Radiographs

Subjects underwent weight-bearing postero-anterior fixed-flexion knee radiographs using a Plexiglas positioning frame (SynaFlexer™, Synarc Inc., San Francisco, CA)[10]. A musculoskeletal radiologist and a rheumatologist (non-authors), each with over 10 years of experience, independently graded the baseline x-rays according to the KL scale [11]. As previously described [12], medial and lateral tibiofemoral compartments on radiographs were evaluated at both baseline and 30 months for JSN according to the OARSI atlas [13], and for increases in JSN, including within-grade changes (the joint space narrowed but by less than a full grade) [12].

MRI Acquisition

Knee MRIs were acquired at baseline and at 30-month follow-up with a 1.0 T dedicated extremity unit (OrthOne™, ONI Inc., Wilmington, MA) using sagittal and axial fat-suppressed fast spin-echo proton density-weighted sequences, and a short tau inversion-recovery-STIR sequence in the coronal plane [8,9].

MRI Interpretation

MRIs were read using the WORMS grading system[14] by two musculoskeletal radiologists (FWR and AG), with 11 and 13 years experience in semiquantitative MRI assessment of knee OA, and were blind to the radiographic and clinical data.

Cartilage morphology was scored from 0 to 6 in each of the five subregions in the medial and lateral tibiofemoral compartments (total of 10 subregions per knee), including within-grade assessments, which has been shown to increase sensitivity to change [15]. Worsening of cartilage loss in the tibiofemoral compartments was defined as a within-grade or greater change in at least one of five subregions in each compartment.

The anterior horn, body, and posterior horn of the medial and lateral menisci were graded separately from 0 to 4. The maximum grade of damage in a compartment's meniscal regions

was used to evaluate change overtime. A change from grade 0-2 (no loss of meniscal substance) to 3 or higher, or from 3 to 4 was considered worsening of meniscal damage.

Extrusion of the medial and lateral meniscal body was assessed from grade 0 to 2 using coronal STIR images [8,9]. Any increase of extrusion from baseline to follow-up was considered worsening of extrusion.

The weighted kappa coefficients of inter-observer reliability (30 knees randomly selected and read by both readers) were 0.80 for meniscal morphology, 0.65 for meniscal extrusion, and 0.78 for cartilage morphology.

Statistical analysis

In compartment-specific analyses using one knee per person, we assessed the association of worsening of the MRI features with any increase in JSN and with the speed of the change in JSN. When assessing JSN progression at the medial tibiofemoral compartment, only changes in the medial tibiofemoral structures (cartilage and meniscus) were taken into account for the performed analyses. Similarly, when assessing JSN progression at the lateral tibiofemoral compartment, only changes in the lateral tibiofemoral structures were taken into account for the analyses. We defined slow progression as an increase of up to one grade and fast progression as an increase of more than one grade. We used logistic regression with generalized estimated equations to account for correlations between a knee's compartments. Logistic models simultaneously included all three MRI features adjusted for age, gender, and body mass index (BMI). All statistical calculations were performed using SAS® software (Version 9.1 for Windows; SAS Institute; Cary, NC).

RESULTS

A total of 276 knees (one knee per subject) with complete data for 260 medial and 268 lateral tibiofemoral compartments were included, for a total of 528 tibiofemoral compartments (Figure 1). The mean age was 62.9 (± 7.8 standard deviation – SD; range 50-79), the mean BMI was 30.2 (± 5.0 SD; range 18-55.8), and the majority were women (n=189, 68.5%). Sixty-five (12.3%) compartments had any progression of JSN (46 medial/19 lateral), while 51 (9.7%) showed slow progression of JSN (36 medial/15 lateral), and 14 (2.6%) showed fast progression of JSN (10 medial/4 lateral). Of 528 compartments, worsening of cartilage damage was seen in 134 (25.4%), meniscal damage in 33 (6.3%) and meniscal extrusion in 20 (3.8%). Of 65 compartments with any progression of JSN, worsening of cartilage damage was seen in 43 (66.1%), meniscal damage in 19 (29.2%) and meniscal extrusion in 14 (21.5%). There were no significant differences in age, gender, or BMI among subjects according to JSN progression status (data not shown). However, a significant difference in gender was found when comparing the sample included in this study (N=276) with the cohort study of risk factors (N=1,644) previously mentioned (68.5% vs. 61% females, respectively; $p<0.05$).

In analyses combining medial and lateral compartments, as each MRI feature worsened, the risk for progression of JSN increased in the same compartment (Table 1) Results were similar when considering medial and lateral compartments separately, although the trends

were not significant for worsening of meniscal extrusion (Table 1). In general, odds ratios were higher for the lateral than medial compartment.

In analyses combining medial and lateral compartments, progression of cartilage damage was associated with both slow (OR 4.6 (95%CI 2.3, 9.1);p<0.0001), and fast JSN progression (OR 7.9 (95%CI 1.5, 42.4);p=0.01). There was an almost significant association between worsening of meniscal damage and slow JSN (OR 2.9 (95%CI 0.9, 9.4);p=0.07), and a significant association between worsening of meniscal damage and fast JSN (OR 20.3 (95%CI 3.0, 135.2);p=0.002). Worsening of meniscal extrusion was associated with slow JSN (OR 4.7 (95%CI 1.2, 17.6);p=0.02), and there was an almost significant association with fast JSN (OR 5.8 (95%CI 0.9, 34.2);p=0.05).

In medial compartments, progression of cartilage damage was associated with slow JSN progression (OR 2.5 (95%CI 1.1, 5.7);p=0.04) and there was a non-significant trend for fast JSN progression (OR 8.6 (95%CI 0.9, 82.6);p=0.06). Worsening of meniscal damage had a non-significant association with slow (OR 2.6 (95%CI 0.8, 8.7);p=0.11) and a significant association with fast JSN progression (OR 8.5 (95%CI 1.6, 46.9);p=0.01). Worsening of meniscal extrusion was not significantly associated with slow (OR 2.9 (95%CI 0.5, 16.0);p=0.22) but there was a trend for fast JSN progression (OR 5.0 (95%CI 0.9, 26.2);p=0.06).

In the lateral compartment, worsening of cartilage loss was significantly associated with slow JSN (OR 16.9 (95%CI 4.2, 67.7);p<0.0001), with trends also seen for both worsening of meniscal damage (OR 7.6 (95%CI 0.8, 68.9);p=0.07) and worsening of meniscal extrusion (OR 11.6 (95%CI 0.8, 159.9);p=0.07). Due to small numbers, we could not assess the associations with fast lateral compartment JSN.

An increase in the number of cartilage and meniscus features that worsened was associated with a steady increase in the odds of JSN progression (p for trend <.0001) (Table 2). In three of every four compartments with JSN progression, at least one MRI-identified feature also worsened.

DISCUSSION

Our study demonstrated that progression of cartilage damage, meniscal damage, and meniscal extrusion are each independently associated with progression of tibiofemoral JSN in the same compartment and that the likelihood of progression increased substantially with the number of MRI features that worsened. Results were similar for medial and lateral compartments analyzed individually, though the associations appeared to be stronger in the lateral compartment. Worsening of each feature was also associated with both slow and fast JSN progression, with slightly higher odds ratios for fast progression. Similar associations were also found for fast and slow JSN in the medial and slow progression in the lateral compartments separately, although the 95% confidence intervals for ORs were wide due to small numbers.

While worsening of cartilage damage, by virtue of its strong independent effect and greater frequency compared to meniscal worsening, is clearly a key determinant of JSN, the fact

that worsening of both meniscal damage and extrusion had effects on JSN progression that were independent of one another and of cartilage worsening further underscores the importance of meniscal changes for interpreting studies that use JSN as the structural outcome. The strong cumulative effect of MRI-identified changes further supports the idea that the interaction of the different joint tissues contributes to JSN.

A strength of this study is the large sample of knees with mild radiographic OA (KL grade 2). Grade 2 knees show more variation in the speed of JSN progression than either KL 0-1 or KL 3-4 knees, permitting us to assess both slow and fast radiographic progression. These knees are also at a high enough risk for progressive OA that we can detect both the independent and cumulative effects of worsening cartilage damage and meniscal damage and meniscal extrusion. Nonetheless, despite the large number of knees, the fast and slow JSN subsets were too small to allow us to draw any conclusions about the effects of the MRI features on the speed of JSN progression. Our results are also limited in that they may not apply to pre-radiographic OA (KL 0-1) or more advanced radiographic OA (KL 3-4). In addition, MRIs were read in pairs and in known chronological order, which increases sensitivity to change but may also introduce a bias toward scoring change compared to reading with the order unknown. However, readers were blind to radiographic JSN results, so it is unlikely that the associations with JSN are biased by the reading method. The image quality of 1.0T MRI is inferior to 1.5T systems, especially for cartilage assessment. However, it has been shown that WORMS scoring is comparable for MRIs obtained with a 1.0T dedicated extremity scanner and 1.5T whole body scanners [6].

In conclusion, tibiofemoral JSN over time is strongly and independently influenced by progressive worsening of cartilage damage, meniscal damage and meniscal extrusion. Although the risks for progression of JSN for each MRI predictor tested were equivalent in the applied models, worsening of cartilage damage was more frequently observed in knees with JSN than meniscal worsening. Tibiofemoral JSN is a result of complex multi-tissue articular degeneration. Untangling and understanding this complexity is distinctly relevant to patient treatment and to the interpretation of radiographic assessment as a structural outcome in clinical trials and longitudinal OA studies.

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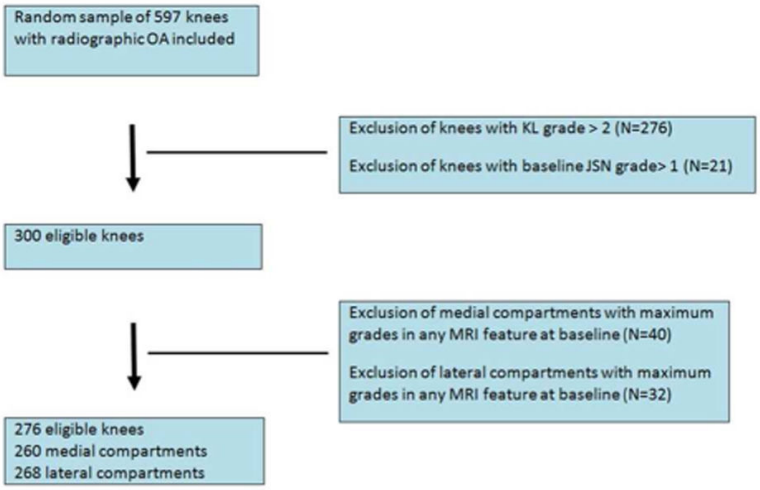

Figure 1.

This flow chart offers a graphic description of the selection process for the knees we studied. Tibiofemoral compartments with maximum grades in all subregions of any baseline MRI feature (cartilage damage, meniscal damage, or meniscal extrusion) were excluded since they cannot progress. Knees with a KL grade of 3 or higher at baseline were excluded from the analysis to avoid ceiling effects in regard to JSN increase.

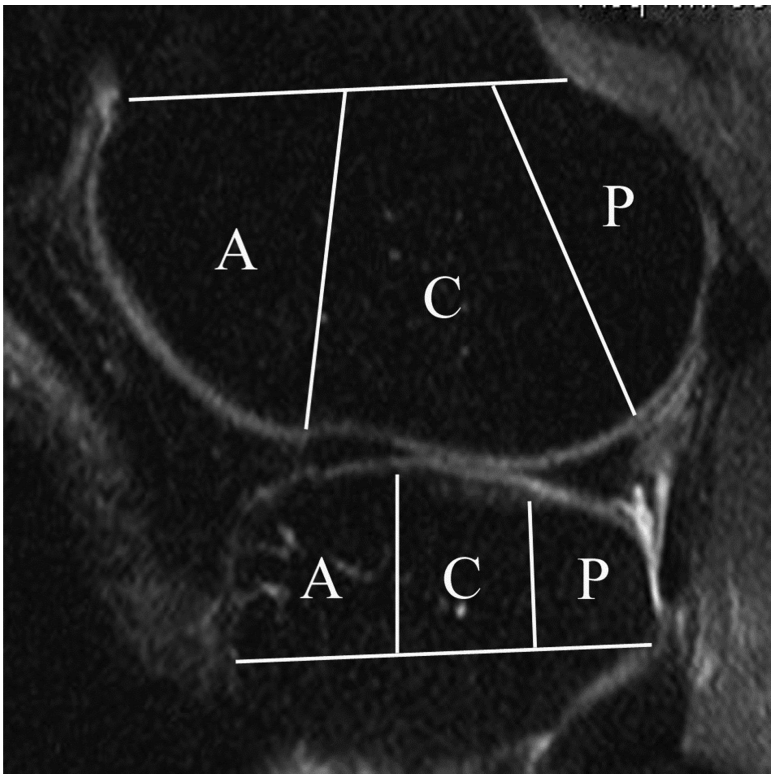

Figure 2.

Subregional division in WORMS. Ten tibiofemoral subregions are defined for cartilage assessment: the central (C) and posterior (P) femur medially and laterally, as well as the anterior (A), central (C), and posterior (P) tibia medially and laterally. The anterior (A) femur subregion is part of the patellofemoral compartment.

Table 1

The associations of worsening of MRI features with progression of radiographic joint space narrowing (JSN) from baseline to 30-month follow-up.

MRI Feature	Any progression of JSN (all compartments combined); N=528		Adjusted OR* (95% confidence intervals) Overall	Any progression of JSN (medial compartments); N=260		Adjusted OR* (95% confidence intervals) Medial	Any progression of JSN (lateral compartments); N=268		Adjusted OR* (95% confidence intervals) Lateral
	Absence	Presence		Absence	Presence		Absence	Presence	
Worsening of cartilage loss									
Absence	372 (70.4%)	22 (4.2%)	**1.0 (reference)**	162 (62.3%)	18 (7%)	**1.0 (reference)**	210 (78.4%)	4 (1.5%)	**1.0 (reference)**
Presence	91 (17.3%)	43 (8.1%)	4.9 (2.6, 9.3) p<.0001	52 (20%)	28 (10.7%)	2.8 (1.3, 6.2) p=.009	39 (14.6%)	15 (5.5%)	19.7 (4.9, 79.1) p<.0001
Worsening of meniscal damage									
Absence	449 (85%)	46 (8.7%)	**1.0 (reference)**	201 (77.3%)	30 (11.5%)	**1.0 (reference)**	248 (92.5%)	16 (6%)	**1.0 (reference)**
Presence	14 (2.7%)	19 (3.6%)	4.8 (1.8, 13.0) p=.002	13 (5%)	16 (6.2%)	3.4 (1.2, 9.7) p=.02	1 (0.4%)	3 (1.1%)	80.6 (6.5, 1000.5) p=.0007
Worsening of meniscal extrusion									
Absence	457 (86.5%)	51 (9.7%)	**1.0 (reference)**	209 (80.4%)	36 (13.8%)	**1.0 (reference)**	248 (92.5%)	15 (5.6%)	**1.0 (reference)**
Presence	6 (1.1%)	14 (2.7%)	5.1 (1.5, 17.0) p=.0008	5 (1.9%)	10 (3.9%)	3.7 (0.9, 15.3) p=.07	1 (0.4%)	4 (1.5%)	13.4 (0.9, 194.6) p=.06

OR = odds ratio.

*Adjusted for age, gender and body mass index, and the other MRI features simultaneously in the model.

Table 2

The associations of combinations of MRI features that became worse with progression of radiographic JSN from baseline to 30-month follow-up. The percentages presented refer to the total of 528 tibiofemoral compartments included in the analysis.

MRI feature	Any progression of JSN		Adjusted OR** (95% confidence intervals)
	Absence	Presence	
Number of features showing worsening*			
No worsening of all 3 MRI features	366 (69.3%)	18 (3.4%)	**1.0 (reference)**
Worsening of 1 of the 3 MRI features	85 (16.1%)	27 (5.1%)	6.5 (3.4, 12.2) p<.0001
Worsening of 2 of the 3 MRI features	10 (1.9%)	11 (2.1%)	22.5 (8.8, 57.5) p<.0001
Worsening of all 3 MRI features	2 (0.4%)	9 (1.7%)	92.6 (18.7, 457.4) p<.0001