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CARTILAGE THICKNESS CHANGE AS AN IMAGING BIOMARKER OF KNEE OSTEOARTHRITIS PROGRESSION – DATA FROM THE FNIH OA BIOMARKERS CONSORTIUM

F. Eckstein¹, J.E. Collins², M. C. Nevitt³, J. A. Lynch³, V. Kraus⁴, J. N. Katz², E. Losina², W. Wirth¹, A. Guermazi⁵, F. W. Roemer^{5,6}, and D.J. Hunter⁷ for the FNIH OA Biomarkers Consortium

Address correspondence and reprint requests to: Univ. Prof. Dr. med. Felix Eckstein, Institute of Anatomy, Paracelsus Medical University, Strubergasse 21, A5020 Salzburg Austria; felix.eckstein@pmu.ac.at; Fon: + 43 699 144 20024; Fax: +43 662 44 2002 1249.

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AUTHOR CONTRIBUTIONS

- Study conception and design: Eckstein, Collins, Nevitt, Kraus, Katz, Losina, Guermazi, Roemer, Hunter
- Acquisition of data: Eckstein, Collins, Nevitt, Lynch, Wirth
- Analysis & interpretation of data: Eckstein, Collins, Nevitt, Kraus, Katz, Losina, Roemer, Guermazi, Hunter
- Writing of first manuscript draft: Eckstein
- Critical manuscript revision and approval of final manuscript: All authors

Jamie Collins had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

ROLE OF THE STUDY SPONSOR

The statistical analysis and writing of this article was independent from and not contingent upon approval from the study sponsors.

DISCLOSURE OF INTEREST

- Felix Eckstein is CEO/CMO and co-owner of Chondrometrics GmbH, a company providing MR image analysis services to academic researchers and to industry. He has provided consulting services to Merck Serono and Mariel Therapeutics, and has received speaker honoraria from Medtronic. Chondrometrics GmbH has received funding from the FNIH Biomarker Consortium for the quantitative analysis of cartilage data from this study.
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- Wolfgang Wirth is a part time employee and co-owner of Chondrometrics GmbH; he has provided consulting services to Merck Serono and to Ampio Pharmaceuticals
- Ali Guermazi is President of Boston Imaging Core Lab, LLC (BICL), a company providing MRI reading services to academic researchers and to industry. He has provided consulting services to Merck Serono, Genzyme, OrthoTrophix and TissueGene. BICL has received funding from the FNIH Biomarker Consortium for semi-quantitative analysis of MRI data from this study.
- Frank Roemer Frank Roemer is CMO and co-owner of BICL.
- David Hunter has received support from the FNIH OA Biomarkers Consortium.

¹Institute of Anatomy, Paracelsus Medical University Salzburg & Nuremberg, Salzburg, Austria & Chondrometrics GmbH, Ainring, Germany

²Orthopedic and Arthritis Center for Outcomes Research; Department of Orthopedics, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

³Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, CA

⁴Duke Molecular Physiology Institute and Division of Rheumatology, Duke University School of Medicine, Durham, NC, USA

⁵Quantitative Imaging Center, Department of Radiology, Boston University School of Medicine, & Boston Core Imaging Lab (BICL), Boston, MA

⁶Department of Radiology, University of Erlangen-Nuremberg, Erlangen Germany

⁷Rheumatology Department, Royal North Shore Hospital and Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Sydney, NSW Australia

Abstract

Objective—To investigate the association of cartilage thickness change by MRI (over 24 months (M)) with knee osteoarthritis (OA) progression at 24–48M.

Methods—This nested case-control study included 600 knees with baseline Kellgren Lawrence grade (KLG) 1–3 from 600 Osteoarthritis Initiative (OAI) participants. Case knees had both medial tibiofemoral radiographic joint space loss (> 0.7 mm) and a persistent increase in WOMAC pain (> 9 on a 0–100 scale) at 24–48M from baseline (n=194). Control knees (n=406) included 200 with neither radiographic nor pain progression, 103 with radiographic progression only and 103 with pain progression only. Medial and lateral femorotibial cartilages were segmented from sagittal 3Tesla baseline, 12M, and 24M MRIs. We used logistic regression to assess the association of change in cartilage thickness, with a focus on the central medial femorotibial (cMFTC) compartment, and OA progression.

Results—cMFTC thickness loss was statistically significantly associated with case status (odds ratio (OR) 1.9; 95% confidence interval [CI] 1.6, 2.3), $p < 0.0001$), with both the central femur (OR=1.8; 95% CI 1.5, 2.2) and the central tibia (OR=1.6; 95% CI 1.3, 1.9) reaching $p < 0.05$. Lateral femorotibial compartment cartilage thickness loss, in contrast, was not significantly associated with case status. Reduction in cMFTC cartilage thickness was associated strongly with radiographic progression (OR: 4.0; 95% CI: 2.9, 5.3; $p < 0.0001$) and only weakly with pain progression (OR: 1.3; 95% CI: 1.1, 1.6; $p < 0.01$).

Conclusions—Loss in medial femorotibial cartilage thickness over 24M is associated with the combination of radiographic and pain progression in the knee; this association was stronger for radiographic progression.

Keywords

cartilage thickness; MRI; osteoarthritis; progression

Introduction

The lifetime risk of knee osteoarthritis (OA) is 14% (1), it substantially impacts quality-of-life and is responsible for elevated health care utilization and cost (2). Although risk factors have been identified (3;4), disease progression is slow, with periods of structural and symptomatic stasis interposed with periods of worsening (4). Current diagnostic methods are of limited value in predicting periods of symptomatic and radiographic progression (5).

A biomarker exhibiting near-term change that is associated with longer-term, clinically important outcomes has potential as a marker of treatment efficacy and is pivotal for evaluating disease modification in clinical trials. This study was therefore undertaken under auspices of the Foundation for the National Institutes of Health (FNIH) OA Biomarkers Consortium, to evaluate association of change of several molecular and imaging biomarkers with structural (radiographic) and symptomatic knee OA progression (5).

The specific purpose of this work was to test whether change in the central medial femorotibial compartment (cMFTC) quantitative cartilage thickness from baseline to 24 months (M) was associated with medial compartment radiographic and symptomatic progression over 48M. Exploratory questions included a) Do associations differ between radiographic and symptomatic progression, b) Do findings for baseline to 24M change hold for 12M change, prior to progression status being reached, and c). what is the associations with lateral and location-independent femorotibial cartilage loss (6).

PATIENTS AND METHODS

Study Design

We undertook a nested case-control study using data from the Osteoarthritis Initiative (OAI), a multi-center prospective observational cohort study with 4,796 participants (Suppl Fig. 1), Clinical data, imaging and serum and urine specimens were obtained annually from baseline through 48M (7). Eligible participants for the present study had 1 knee with baseline Kellgren-Lawrence grade (KLG) 1–3 from central readings and availability of baseline and 24M knee radiographs, knee magnetic resonance images (MRI), serum and urine specimens, and clinical data (5). 98.5% had 36M and 91% radiographic 48M data available; 99% had 36M, 99% 48M, and 97% 60M pain data available. Participants with knee or hip replacement up to 24M were excluded.

Non-fluoroscopic fixed flexion knee radiographs were assessed by central reading for KLG and semi-quantitative joint space narrowing (JSN) (7). Minimum joint space width (minJSW) in the MFTC was measured using automated software (7). Knees with poor radiographic positioning (defined by tibial plateau rim distance) or with lateral JSN grades 2/3 at baseline were excluded, as this may render measurement of MFTC joint space width (JSW) unreliable or result in misclassification of radiographic progression (8).

Definitions of radiographic and symptomatic progression

(Medial) radiographic progression was defined by loss in minJSW of 0.7 mm from baseline to 24, 36 or 48M. This threshold was set based on the distribution of 12 month change in

minJSW in normal knees of OAI healthy reference participants and was estimated to involve a 10% probability of change due to measurement error (5;9). For repeat minJSW measurements on identical radiographs in the OAI, the ICC was 0.98 cross-sectionally and 0.96 for change from baseline to 36M (<http://www.oai.ucsf.edu/datarelease/>)

Knee pain was assessed using the Western Ontario McMasters (WOMAC) pain subscale. Progression was defined as a *persistent* increase of 9 points on a 0–100 normalized score from baseline to 24, 36, 48 or 60 months, based on previous reports for a minimum clinically important difference (MCID) (10). Persistence required the pain level to stay above the MCID at 2 time points from 24–60M (5). If a subject reached the pain progression threshold at 24, 36 or 48M, and data were lacking to confirm whether pain was maintained later, the subject was excluded.

For measurement of imaging biomarkers, index knees (one per subject) were selected in the following outcome groups (5) (Suppl. Fig. 1): 1) Primary cases were knees that had both radiographic and pain progression; control knees did not have this combination, and included 2) knees with radiographic but not pain progression, 3) knees with pain but not radiographic progression, and 4) knees with neither radiographic nor pain progression. If both knees of a participant were in any one group, one was randomly selected as index knee. Participants in whom one knee displayed only radiographic progression and the other only pain progression were excluded. Knees with radiographic and pain progression by 12M were also excluded, as this provided opportunity to study biomarker change before the progression criterion was met. Those with an index knee selected for group 4 could not have radiographic progression, including worsening of lateral compartment JSN, or pain progression in the contralateral knee.

The sample size goal was 200 primary cases and 2 controls for each case (Suppl Fig. 1). For better covariate balance among the groups, the knees selected for the four groups were frequency matched to the extent feasible, using KLG strata 1–3 and BMI strata <25, 25–27.5, 27.5–30, 30–35 and ≥35 kg/m².

Cartilage thickness measurement by MRI

The MRI acquisition protocol of the OAI was described previously (7). Cartilage thickness analysis for this study relied on sagittal double-echo steady-state (DESS) imaging (7). Reading IDs that precluded access to information on the OAI ID and on the time point of acquisition were assigned by the OAI coordinating center and the data sent to one analysis centre (Chondrometrics GmbH). Segmentation of the femorotibial cartilage surfaces, i.e. medial and lateral tibia and weight-bearing femur, was performed by 7 readers who had received continuous training for 5 years. All time-points of one knee (baseline, 12M and 24M) were processed as triplets by the same reader. The analysis center was blinded to case/control status and image acquisition order, so that an unbiased rate of change could be determined in each group. All segmentations were quality control checked by one of two experts (S.M.; F.E). The reliability of these measurements in the OAI (7;11) and their feasibility in clinical trials has been reported previously (12).

The mean cartilage thickness (ThCtAB.Me) was computed in MFTC and in the lateral compartment (LFTC), and in 5 tibial (central, external, internal, anterior, posterior) and 3 femoral subregions (central, external, internal) (8). Cartilage thickness change was computed as an absolute difference between 12M or 24M versus baseline value (mm). Based on longitudinal changes in the above 16 subregions (8 medial and 8 lateral), location-independent cartilage thickness change was determined using the ordered value (OV) approach (6). OV1 represents the subregion with the greatest rate of cartilage thinning in each knee, and OV16 the subregion with the least thinning or greatest thickening (6). Further, summary measures of subregional cartilage thinning (ThnScore) were determined; i.e. the sum of all negative thickness changes across all of the 16 subregions in which cartilage loss occurred, as well as the subregional thickening score (ThkScore), i.e. the sum of all positive thickness changes.

Statistical analysis

The association of change in femorotibial cartilage thickness, including OVs and change scores, with knee OA progression status was examined using logistic regression, adjusting for baseline age, sex, BMI, race, KLG, WOMAC pain, pain medication and min JSW. Frequency matching was used for some, but not all key variables, and these variables were therefore included in the adjusted analysis to prevent potential confounding. Knee alignment data (i.e. the femorotibial angle on 590 participants) became available after completion of the initial analysis, and a sensitivity analysis was conducted including alignment in adjusted models. Associations were expressed as the increase in odds of being a progressor knee for each 1 standard deviation difference in longitudinal change in cartilage thickness over 12 or 24M. First, in our primary pre-specified analysis we compared cartilage thickness change in primary case knees that had both radiographic and pain progression (hereafter Group 1) with the three groups of control knees combined, i.e. radiographic progression only (Group 2), pain progression only (Group 3) and knees with neither radiographic or pain progression (Group 4). The sum of the central medial tibia (cMT) and central weight-bearing femoral (ccMF) cartilage thickness from baseline to 24M follow-up (cMFTC) was chosen as the primary analytic focus, as this was previously shown to represent the most responsive region in OAI participants (7). Change in cMT and ccMF, lateral femorotibial cartilage thickness measures, and location-independent measures of change were also evaluated as independent variables. We also analyzed change in all cartilage thickness measures from baseline to 12M to determine whether a shorter observation period, which preceded the time points at which progression status was reached, provides a sufficiently strong signal for predicting progression. Additional analyses compared association of cartilage thickness change with various combinations of progression outcomes: Multinomial logistic regression with generalized logits was used to compare each of groups 1, 2 and 3 with group 4 knees that showed no progression. In addition, the three groups of knees that progressed (groups 1–3) were combined for comparison to group 4 knees. Finally, all knees with radiographic progression (groups 1 and 2) were compared with all those not showing radiographic progression (groups 3 and 4), and all knees with pain progression (groups 1 and 3) were compared to those without pain progression (groups 2 and 4).

Results

Baseline characteristics are reported in Table 1, and longitudinal cartilage loss over 24 months in Table 2. By definition, none of the cases reached progression status by JSW and pain at 12M; 12% reached radiographic progression status by 12M, 36% by 24M, 28% at 36M, and 24% at 48M; 56% had the first increase in pain 9/100 at 24M, 34% at 36M, and 10% at 48M. Table 2 shows the crude and adjusted ORs for the association of cartilage thickness loss with combined radiographic and pain progression compared to controls that did not have this combination. cMFTC thickness loss was statistically significantly associated with progression (adjusted odds ratio (aOR) per 1 SD 1.9; 95% confidence interval [CI] 1.6,2.3), with cartilage loss in both the central femur and tibia reaching $p < 0.05$ (Table 2). There also was a significant association of total MFTC cartilage loss with case status (Table 2), and no subregion displayed a greater OR than cMFTC (data not shown). Additional adjustment for alignment had only minimal effects on the findings for cMFTC (aOR 1.9 [95%CI 1.5, 2.3] or other measures (data not shown). There was no significant association with any lateral femorotibial cartilage thickness measure (Table 2) and only the internal lateral tibia tended to show greater cartilage loss in case than control knees. Location-independent measures of cartilage loss (OV1, ThnScore) had ORs similar to cMFTC. There was no significant difference in cartilage thickening (OV16, ThkScore) between case and control knees (Table 2). Crude ORs were very similar to adjusted ORs (Table 2, Suppl. Table 1).

Results for the secondary comparisons are shown in Table 3. cMFTC cartilage thickness loss was associated strongly with radiographic progression (aOR: 4.0; 95%CI: 2.9, 5.3;) and only weakly with pain progression (aOR:1.3; 95%CI: 1.1, 1.6).

ORs for baseline to 12M medial thickness change were smaller than for 24M, but were still statistically significant (Suppl. Table 1). Also, the relative performance of different measures was consistent between both observation periods (Suppl. Table 1).

Discussion

This study shows that loss in medial femorotibial cartilage thickness over the first two years of observation is associated with greater likelihood of combined structural and symptomatic progression over 4 years. Secondary analyses suggest that the association with radiographic progression was stronger than that with pain progression. These findings confirm change in cartilage thickness to be a useful and robust imaging biomarker for knee OA progression, and hence a strong potential candidate for use as an outcome in clinical trials. The result can serve as a reference for other imaging, molecular or genetic markers to be tested as potential predictors of disease progression in a biomarker “qualification” or “validation” process.

A limitation of the study is that the observation interval used for assessing imaging biomarker changes partially overlapped with that of the outcome, limiting our ability to make strong inferences about predictive validity of the changes. However, about 50% of the cases reached progressor status by 24M and the other 50% later. Further, BL to 12M cartilage thickness results confirmed the findings of the 24M analysis while reducing the

overlap in observation periods, since none of the participant knees met the primary case status at 12M per exclusion criteria. Post hoc analysis showed the mean JSW change in cases over 12M to be only 0.24mm, a value much lower than the threshold of 0.7mm required to reach the pre-defined threshold for radiographic progression. Together, these findings support the use of cartilage thickness loss over 24, or even 12 months, as a marker that is associated with clinically important outcomes over a longer time frame. The association reported reflects a combination of concurrent and predictive validity, rendering the biomarker valuable as a potential indicator of treatment response. These findings extend previous ones on concurrent correlation of radiographic JSW and cartilage thickness loss by MRI (7)(12) and the results may be used as a benchmark against which other molecular and imaging biomarkers explored in the FNIH OA biomarker consortium can be evaluated. We acknowledge that the study involved a number of cartilage measures and secondary analyses; however, the primary analysis and cartilage measure were clearly identified in an a priori analysis plan, whereas other analyses were defined as exploratory.

cMFTC was selected as the primary analytic focus, because being previously shown the most sensitive region in OAI participants (7). Structural progression in the present study was defined by loss of medial radiographic minJSW, and knees with predominantly lateral compartment JSN were excluded. Therefore, it is not surprising that lateral cartilage measures were not associated with progression (8). This may also help explain why location-independent measures (i.e. ordered values) performed similar to the best region-specific measures (i.e. cMFTC) despite superior performance of the former in some previous studies (8). Yet, location-independent measures of cartilage loss may be useful in populations including a mix of medial and lateral disease (8).

Previous reports showed knees with more frequent baseline pain exhibit significantly greater medial cartilage loss than those without pain (13), even after adjustment for radiographic status. Further, medial cartilage loss has been shown to be a significant predictor of knee replacement, a hard clinical outcome closely related to pain status (14). The secondary analyses of this study suggest that reduction in medial cartilage thickness was associated more strongly with radiographic progression than with pain progression, potentially because cartilage tissue is aneural and not directly responsible for nociception. Previous work showed that cross-sectionally, radiographic status is associated with knee pain status (15). In the current study, we find that loss in cartilage thickness was not significantly associated with pain progression when radiographic progression was actively ruled out. However, in an unselected population it is probable that radiographic and pain progression would often coincide and therefore risk of progression might be detectable in advance by cartilage loss.

In conclusion, loss in medial femorotibial cartilage thickness over 24 and 12 months was found to be associated with the combination of radiographic and pain progression in knee OA over 48 months, a longer-term and clinically important outcome. The association appears to be stronger for radiographic than for pain progression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline demographic data, structural and pain characteristics (mean±standard deviation),

	Primary cases Group 1 (n=194)	Controls Groups 2–4 (n=406)
Age	62.0±8.8	61.3±8.9
Sex	57% female	60% female
BMI	30.7 ±4.8	30.7 ±4.8
White	80%	79%
KLG1/2/3	12% / 43% / 44%	13% / 55% / 33%
BL WOMAC	10.2 ±13.0	13.0 ±16.7
BL minJSW	3.8 ±1.4	3.9±1.1
BL cMFTC	3.9±1.0	4.0±0.8

Primary cases: Knees with radiographic and pain progression (Group 1). Controls: Knees with radiographic but not pain progression (Group 2), knees with pain but not radiographic progression (Group 3), and knees without radiographic or pain progression (Group 4). BMI = body mass index; BL = baseline; WOMAC = Western Ontario McMasters; minJSW = minimum medial radiographic joint space width; cMFTC = central medial femorotibial compartment.

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Table 2

24 month longitudinal cartilage loss from baseline to 24 months (in mm) in case and control knees as well as crude and adjusted odds ratios (OR) with 95% confidence interval (CI) of being a case for a 1 SD greater change in cartilage thickness.

	Primary Cases: Group 1 (n=194)	Controls: Groups 2–4 (n=406)	Crude (non-adjusted) ORs (95% CI)	Adjusted ORs (95% CI)
cMFTC	-0.32±0.40	-0.12±0.28	1.8 (1.5, 2.2) #	1.9 (1.6, 2.3) #
cMT	-0.12±0.19	-0.05±0.13	1.5 (1.3, 1.9) #	1.6 (1.3, 1.9) #
ccMF	-0.21±0.28	-0.08±0.20	1.7 (1.4, 2.1) #	1.8 (1.5, 2.2) #
MFTC	-0.18±0.24	-0.06±0.18	1.8 (1.5, 2.2) #	1.9 (1.6, 2.4) #
cLFTC	-0.03±0.17	-0.03±0.18	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)
cLT	-0.04±0.11	-0.04±0.13	1.0 (0.9, 1.2)	1.1 (0.9, 1.3)
ccLF	0.01±0.11	-0.00±0.10	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)
LFTC	-0.02±0.13	-0.02±0.11	1.0 (0.8, 1.2)	1.0 (0.9, 1.2)
OV 1	-0.34±0.25	-0.22±0.17	1.7 (1.4, 2.1) #	1.9 (1.5, 2.3) #
ThnScore	-1.26±0.93	-0.84±0.65	1.7 (1.4, 2.1) #	1.8 (1.5, 2.3) #
OV 16	0.15±0.09	0.15±0.09	1.0 (0.8, 1.1)	1.0 (0.8, 1.1)
ThkScore	0.48±0.37	0.51±0.38	1.1 (0.9, 1.3)	1.1 (0.9, 1.4)

Primary cases: Knees with radiographic and pain progression (Group 1). Controls: Knees with radiographic but not pain progression (Group 2), knees with pain but not radiographic progression (Group 3), and knees without radiographic or pain progression (Group 4).

* p<0.01;

§ p< 0.001;

p<0.0001;

= change between baseline and follow-up; cMFTC = central medial femorotibial compartment; cMT = central medial tibia; ccMF = central medial weight-bearing femur; MFTC = total medial femorotibial compartment; cLFTC = central lateral femorotibial compartment; cLT = central lateral tibia; ccLF = central lateral weight-bearing femur; LFTC = total lateral femorotibial compartment; OV = ordered value; ThnScore = total subregion thinning score; ; ThKnScore = total subregion thickening score

Table 3

Secondary analyses comparing cartilage thickness loss between knees in four radiographic and pain progression groups[&]: Adjusted odds ratios (aOR) and 95% confidence interval (CI) for a 1 SD greater change in cMFTC cartilage thickness over 24 months and 12 months.

Group comparison ^{&}		Cartilage thickness change	
		BL→24M aOR (95% CI)	BL→12M aOR (95% CI)
1 vs. 4	Xray + pain vs. control	3.8 (2.7, 5.3) #	1.8 (1.4, 2.3) #
2 vs. 4	Xray vs. control	3.8 (2.7, 5.5) #	2.0 (1.5, 2.6) #
3 vs. 4	Pain vs. control	0.9 (0.6, 1.3)	1.2 (0.9, 1.5)
1+2+3 vs. 4	Xray or pain. vs. control	2.5 (1.9, 3.3) #	1.6 (1.3, 2.0) #
1+2 vs. 3+4	Xray vs non-Xray	4.0 (2.9, 5.3) #	1.8 (1.4, 2.1) #
1+3 vs. 2+4	Pain vs. Non-Pain	1.3 (1.1, 1.6) §	1.2 (1.0, 1.4)

* p<0.01;

§ p<0.001;

p<0.001;

& group 1 = knees with both radiographic (Xray) and pain progression (primary cases); group 2 = knees with radiographic progression but not pain progression; group 3 = knees with pain progression but not radiographic progression; group 4 = knees with neither radiographic nor pain progression (super controls).