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Do rates of femorotibial cartilage loss in Kellgren-Lawrence 2 and 3 knees differ between those with mild-moderate vs. severe patellofemoral structural damage? – Data from the FNIH and IMI-APPROACH cohorts

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ABSTRACT

Background: The aim was to assess whether rates of quantitative femorotibial (FT) cartilage loss are increased for knees with semiquantitatively (sq)-defined severe patellofemoral (PF) cartilage damage and/or large bone marrow lesions (BMLs) vs. those without over a period of 24 months.
Methods: 626 knees with Kellgren-Lawrence 2 and 3 from the FNIH and IMI-APPROACH studies were included. MRI assessment was performed using the MRI Osteoarthritis Knee Score (MOAKS) instrument. Baseline FT cartilage damage severity was defined as mild, moderate, or severe. PF cartilage damage was defined as mild-moderate vs. severe. A 2nd definition was based on the presence or absence of large BMLs. Quantitative cartilage thickness loss (defined as the difference from baseline to follow-up in mean cartilage thickness in the medial and in the lateral femorotibial joint, which were computed by summing the cartilage thickness measures observed in the respective cartilage plates) was derived from baseline and 24-month manual segmentations. Between-group comparisons were performed using analysis of covariance (ANCOVA) adjusting for age, sex and body mass index.
Results: 410 (65%) knees were categorized as mild, 92 (15%) as moderate, and 124 (20%) as severe medial FT cartilage damage. For almost all categories of FT cartilage damage, the difference in quantitative medial FT cartilage loss was not statistically significant. Only for the category of knees with moderate medial FT cartilage damage, statistically higher rates of FT cartilage loss were observed for those with large PF BMLs compared to those without (mean adjusted difference −0.128 mm, 95% confidence interval [-0.238, −0.018], p=0.023).
Conclusions: Screening for PF cartilage damage and BMLs does not appear to be required in a disease-modifying OA drug trial.

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Introduction

Assessment of the anterior-posterior knee radiograph is commonly performed at the eligibility phase of a clinical disease-modifying osteoarthritis drug (DMOAD) trial to primarily define structural severity of disease [1]. Recently, semi-quantitative MRI has been introduced as a tool to define eligibility due to its superior capability to screen out patients with X-ray-occult exclusionary findings like tumors, subchondral insufficiency fractures or complete posterior meniscal root tears that likely will not respond to pharmacologic therapy [2]. Further, the definition of a predominant structural morphotype can be achieved by semi-quantitative assessment [3]. An abbreviated MRI protocol allows for the evaluation of most of these findings and seems feasible to apply for screening purposes. Based on the Foundation for the National Institutes of Health (FNIH) consortium sample, we recently reported that the presence of baseline semi-quantitatively defined MRI features, including bone marrow lesions (BMLs), makes it possible to specifically select progressor knees suitable for inclusion in clinical trials [4].

Currently, any MRI screening efforts in the context of clinical trials focus on the femorotibial joint only [2,5]. However, patellofemoral structural damage is very common and it is currently not known whether it is important to include assessment of the patellofemoral joint in MRI-based screening efforts [6]. Rates of structural progression in the femorotibial joint may differ between knees with similar severity of femorotibial cartilage damage but with different levels of patellofemoral structural damage.

Thus, the prespecified aim of our study was to assess whether KL 2 and 3 knees with comparable baseline femorotibial cartilage damage severity and concomitant prevalent cartilage damage and/or large BMLs in the patellofemoral joint exhibit increased rates of quantitatively evaluated cartilage loss in the medial and/or lateral femorotibial joint over 24 months compared to those with only mild or moderate patellofemoral damage.

Methods

OAI/FNIH sample

The FNIH study sample, nested within the larger Osteoarthritis Initiative (OAI) study [7], was defined by symptomatic and structural progression outcomes over 48 months. [8] Knees that had both semi-quantitative assessments and quantitative cartilage thickness measurements at baseline and 24 months follow-up, and a baseline radiographic severity grade of KL 2 or 3 were included (n=523).

The OAI (clinicaltrials.gov: NCT00080171; https://data-archive.nimh.nih.gov/oai/) was approved by the Committee on Human Research, the Institutional Review Board of the University of California, San Francisco (UCSF) and the institutional review boards of all clinical sites.

IMI-APPROACH sample

The Innovative Medicines Initiative-Applied Public–Private Research enabling OsteoArthritis Clinical Headway study (IMI-APPROACH) is an observational study at five clinical centers in Europe (https://www.imi.europa.eu/projects-results/project-factsheets/approach) [9]. Details regarding participant inclusion have been published previously [10]. As for the FNIH sample, knees that had both semi-quantitative MRI assessments and quantitative cartilage thickness measurements at baseline and 24 months follow-up, and a baseline radiographic grade of KL 2 or 3 were included (n=103).

IMI-APPROACH was conducted in compliance with the protocol, Good Clinical Practice, the Declaration of Helsinki, and the applicable ethical and legal regulatory requirements (for all countries involved), and is registered under clinicaltrials.gov identifier: NCT03883568.

Details of the two cohorts including a description of structural damage severity have been described in previous publications [11,12].

MRI acquisition

In FNIH, MRIs of both knees were acquired using 3 T systems (Siemens MAGNETOM Trio, Erlangen, Germany). The sequence protocol included a coronal intermediate-weighted 2D turbo spin echo sequence, a sagittal 3D dual-echo at steady state (DESS) sequence, a sagittal intermediate-weighted fat-suppressed turbo spin-echo sequence and a coronal T1-weighted fat suppressed 3D high resolution gradient echo sequence (fast low-angle shot -FLASH) sequence for the right knee [13].

In IMI-APPROACH, MRI of the index knee was acquired at the five clinical centers with two of the centers using 1.5 T systems, and the other centers using 3 T systems. Both field strengths have been shown to provide a similar accuracy and precision for cartilage morphometry [14,15]. The pulse sequence protocol included an axial, a sagittal, and a coronal intermediate-weighted fat-suppressed sequence and a T1-weighted coronal turbo spin echo sequence that were all used for semi-quantitative evaluation [11]. In addition, a sagittal 3D spoiled gradient echo or volume-interpolated gradient echo sequence with selective water excitation or fat-suppression was acquired for the quantitative cartilage analysis.

MRI assessment

Either two musculoskeletal radiologists with 13 (F.W.R.) and 15 (A.G.) years' experience with semi-quantitative assessment of knee OA at the time of image assessment (FNIH), or one musculoskeletal radiologist (F.W.R.) with 17 years' experience of semi-quantitative assessment of knee OA at the time of reading (IMI-APPROACH) read the baseline and 24-month MRIs according to the Magnetic resonance imaging Osteoarthritis Knee Score (MOAKS) system unblinded to time point of acquisition [16].

MOAKS uses a two-digit score for cartilage assessment (each 0–3) that incorporates both the area size per subregion and the percentage of subregion that is affected by full-thickness cartilage loss. BMLs in MOAKS are assessed in three dimensions. In this study, only the size component (graded from 0 to 3) was considered.

Quantitative cartilage thickness analysis was based on the 3D sequences as acquired in FNIH and IMI-APPROACH. Segmentation of the femorotibial cartilage plates, that is, medial and lateral tibia and weight-bearing femur, was performed by seven experienced readers with blinding to timepoint. All segmentations were quality-controlled by one of two experts before the cartilage thickness was computed from the cartilage segmentations [17]. The current study focused on the mean cartilage thickness in the medial and in the lateral femorotibial joint separately, which were derived by summing the cartilage thickness measures observed in the respective cartilage plates (medial femorotibial joint = medial tibia + central medial femur, lateral femorotibial joint = lateral tibia + central lateral femur). Quantitative cartilage thickness change on a compartmental level was computed as an absolute difference between 24 months and baseline value (mm) within a given compartment.

Statistical analysis

The statistical analysis plan was developed and discussed between the first and the last author, considering study samples, analytic approach and possible future interpretation of the data. Knees were categorized by baseline femorotibial semi-quantitative cartilage damage severity, as (1) those without or only superficial

damage (i.e. grades 0.0, 1.0, 2.0 and 3.0, defined as “mild”), (2) those with superficial damage and minor focal full-thickness involvement (i.e. grades 1.1, 2.1 and 3.1, defined as “moderate”), and (3) those with widespread full-thickness damage (i.e. grades 2.2, 3.2 and 3.3, defined as “severe”), because ipsi-compartmental cartilage damage is a strong predictor of subsequent cartilage loss [18,19]. Image examples for the different femorotibial cartilage damage categories are shown in Fig. 1. Patellofemoral joint cartilage damage severity was defined as mild-moderate (grades 0, 1.0, 1.1, 2.0, 2.1, 3.0 or 3.1 in all four patellofemoral subregions) vs. severe (2.2, 3.2 and 3.3 in at least one subregion). A second definition of patellofemoral disease severity was based on the presence or absence of at least one of four subregions 8with a grade 3 BML. Fig. 2 illustrates these different patellofemoral damage categories.

Between-group comparisons were performed for the medial and lateral femorotibial joint separately using analysis of covariance (ANCOVA) and were adjusted for demographic variables (age, sex, and BMI). Results were presented as adjusted least squares means, standard deviations, and 95% confidence intervals. The between group differences (primary endpoints) were presented as adjusted least squares mean differences and 95% confidence intervals. The analyses were based on all knees with complete MRI and demographic data and assumed that missing data are ‘Missing Completely At Random’.

Results

Baseline and follow-up MRI data were available for 626 participants (62% women). 351 (56%) knees were KL 2 and 275 (44%) KL 3. Mean age was 62.6 (± 8.8, range: 44–82) years and mean BMI was 30.5 (± 5.0, range: 19–48) kg/m [2].

Regarding medial femorotibial cartilage damage, 410 (65.5%) knees were categorized as mild, 92 (14.7%) as moderate and 124 (19.8%) as severe. Laterally, these numbers were 488 (78.0%), 70 (11.2%) and 68 (10.9%). In the patellofemoral joint, 350 (55.9%) had mild-moderate cartilage damage, and 276 (44.1%) severe cartilage damage; 221 (35.3%) knees had large BMLs in at least one of four patellofemoral subregions. Demographic data stratified by patellofemoral severity are reported in Supplementary Table 1.

The longitudinal cartilage thickness loss was not observed to differ between knees with severe vs. mild-moderate patellofemoral cartilage damage for both the medial (mean adjusted difference of longitudinal changes [95% confidence intervals]: medial femorotibial mild: −0.011 [-0.042, 0.019] mm, medial femorotibial moderate: −0.031 [-0.144, 0.083] mm, medial femorotibial severe: 0.025 [-0.061, 0.112] mm) and the lateral compartment (lateral femorotibial mild: −0.004 [-0.025, 0.017] mm, lateral femorotibial moderate: 0.003 [-0.60, 0.065] mm, lateral femorotibial severe: 0.058 [-0.027, 0.143] mm). These results are presented in detail in Table 1.

Concerning stratification based on presence of large BMLs, those with moderate medial femorotibial disease and large BMLs in the patellofemoral joint had higher rates of cartilage loss compared to those with moderate medial femorotibial disease but without large BMLs (mean adjusted difference −0.128 mm, 95% confidence interval [-0.238, −0.018], p=0.023). No statistically significant differences were seen for those knees with no/mild (-0.026 [-0.058, 0.005]mm) and severe (0.030 [-0.059, 0.118]mm) medial tibiofemoral cartilage damage. Furthermore, no statistically significant differences were observed for all three femorotibial categories in the lateral compartment with or without large BMLs in the patellofemoral joint (mild: −0.016 [-0.038, 0.005]mm, moderate: −0.002 [-0.070, 0.066] mm, severe: 0.027[-0.065, 0.119]mm). Details are shown in Table 2.

Results adjusted for magnetic field strength (1.5 T vs. 3 T) are shown in Supplementary Tables 2 and 3.

Discussion

In a sample largely representative of a clinical trial study population, we found that for the large majority of semi-quantitatively defined femorotibial cartilage damage categories, no statistically significant differences in medial or lateral femorotibial rates of quantitative cartilage loss were observed over 24 months, when stratifying knees based on presence or absence of severe cartilage damage or large BMLs in the patellofemoral joint. Only the presence of large BMLs seemed to be relevant regarding medial femorotibial cartilage loss in those knees with moderate medial femorotibial cartilage damage at baseline but not for those with mild or severe femorotibial cartilage damage. This finding is difficult to interpret particularly as it was only found in the “moderate” cartilage damage group and may be due to other factors, including the possibility of a finding by chance.

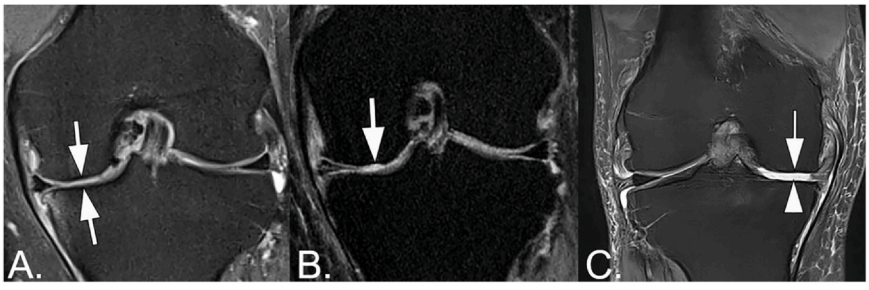

Fig. 1

Osteoarthritis and Cartilage

Categories of femorotibial cartilage damage. A. Coronal intermediate-weighted fat-suppressed image (3 mm slice thickness, 256x256 matrix, 150 mm field of view) shows diffuse superficial cartilage thinning at the medial femur and tibia (arrows). There is no full-thickness component defining this knee as being in the “mild” category. B. The “moderate” cartilage damage category includes those with focal full thickness damage as shown here for the medial femur (coronal T1-weighted fat suppressed 3D high resolution gradient echo sequence (fast low-angle shot -FLASH) image; 0.7 mm slice thickness, 512x512 matrix, 140 mm field of view). There is diffuse cartilage thinning and an additional small full thickness lesion (arrow). C. Diffuse full thickness cartilage damage is shown in this example (intermediate-weighted fat-suppressed coronal image, 3 mm slice thickness, 256x256 matrix, 150 mm field of view) for the medial femur (arrow) and tibia (arrowhead) fulfilling the criteria for “severe”.

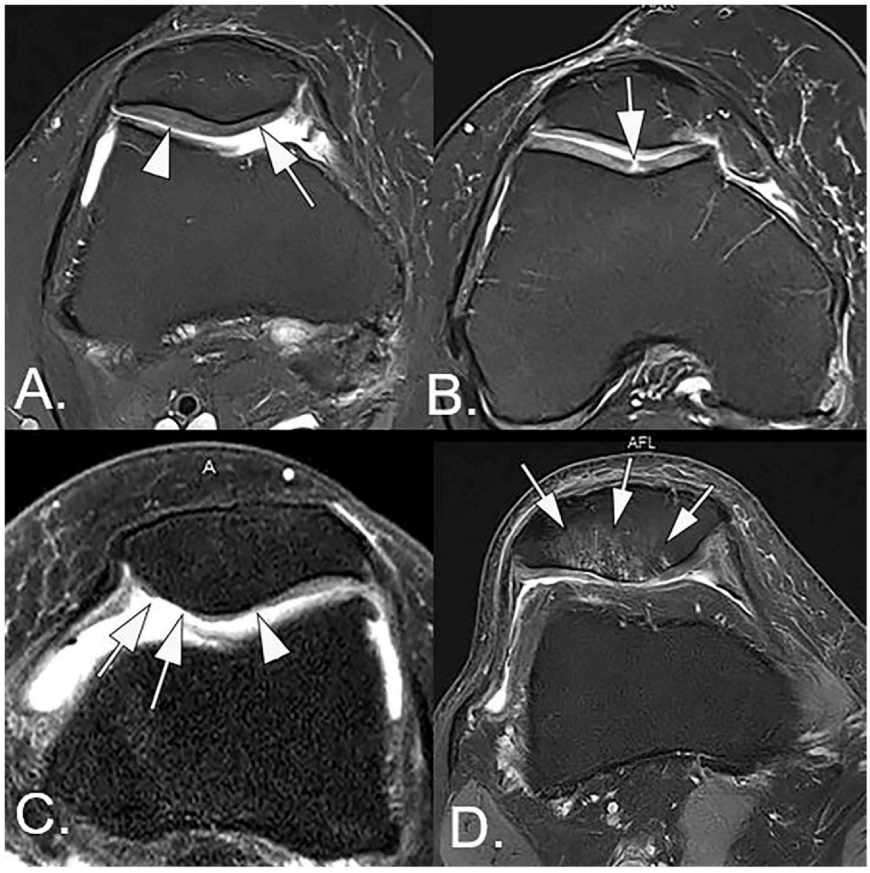

Fig. 2

Osteoarthritis and Cartilage

For the patellofemoral joint two categories of structural damage severity were considered, i.e. those with mild-moderate and those with severe damage. A. Axial intermediate-weighted fat-suppressed image (3 mm slice thickness, 256x256 matrix, 150 mm field of view) shows diffuse superficial thinning of cartilage at the medial patella (arrow) while there is no cartilage damage at the lateral patella facet (arrowhead), defining this knee as being in the mild-moderate category of patellofemoral damage. B. Another example (axial intermediate-weighted fat-suppressed image (3 mm slice thickness, 256x256 matrix, 150 mm field of view) of mild-moderate cartilage damage shows a fissure-like full thickness cartilage lesion at the medial trochlea (arrow). C. The severe damage category is defined by diffuse full-thickness cartilage damage as shown in this axial image for the medial patella facet (arrows). The lateral patella shows diffuse superficial thinning in addition. (Axial intermediate-weighted fat-suppressed image (3 mm slice thickness, 256x256 matrix, 150 mm field of view). D. A second definition of severe patellofemoral damage includes those knees with large grade 3 bone marrow lesions, as shown here for the lateral patella (arrows). (Axial intermediate-weighted fat-suppressed image (3 mm slice thickness, 256x256 matrix, 150 mm field of view).

While conventional radiography is still the most commonly used imaging modality for the evaluation of OA in clinical DMOAD trials, limitations include but are not limited to a lack of reproducibility of radiographic joint space measurements, a weak association of radiographic structural damage and pain, an inability to allow stratification based on structural morphotypes (e.g., inflammatory, subchondral bone, meniscus-cartilage and possibly others), and incapability to depict diagnoses of exclusion [20–23]. In order to overcome these shortcomings, instruments have been introduced that enable rapid screening using MRI in an eligibility context [2]. However, MRI-based screening efforts focus on the femorotibial joint only and only the femorotibial joint is considered to determine positive effects on structure of a given DMOAD candidate [1,2]. Thus, to date it is unclear whether the patellofemoral joint should be considered in an eligibility context or can be ignored. Whether patellofemoral structural damage is relevant in regard to femorotibial outcomes is not clear. In our study, we could show that for most categories of femorotibial cartilage damage, patellofemoral damage did not seem to have an impact on femorotibial cartilage thickness loss. In addition, most of the mean differences observed between groups fell far below thresholds such as the smallest detectable change (DSC) that have been established for detecting progression within knees in both the OAI and IMI-APPROACH cohorts and range between -0.103 mm and -0.125 mm for medial and lateral femorotibial cartilage loss [15,24]. This is an important finding in the light of future DMOAD trials using MRI as a screening tool.

Previous work has addressed associations between patellofemoral and femorotibial involvement in knee OA. Pishgar and colleagues showed that medial patellofemoral OA might play a role as a risk factor for symptomatic worsening and radiographic medial femorotibial OA progression, beyond the impact of common risk factors of patellofemoral and femorotibial OA [25]. In contrast to our study, the authors did not use quantitative MRI to evaluate progression. In another study, authors analyzed whether patellofemoral morphology is associated with the presence and longitudinal worsening of femorotibial OA and found that patellofemoral morphology

Without adjustment for field strength	PFJ Cartilage: Mild - moderate[a]			PFJ Cartilage: Severe[b]			Severe vs. Mild - moderate		
	N	Mean ± SD	[95% CI]	N	Mean ± SD	[95% CI]	Adj. mean diff	[95% CI]	P-value
Medial FTJ Change [μm]:									
MFTJ group mild: 0.0 / 1.0 / 2.0 / 3.0	226	-0.051 ± 0.154	[-0.071, -0.031]	182	-0.062 ± 0.154	[-0.085, -0.040]	-0.011	[-0.042, 0.019]	0.466
MFTJ group moderate: 1.1 / 2.1 / 3.1	49	-0.164 ± 0.267	[-0.240, -0.088]	43	-0.195 ± 0.268	[-0.276, -0.114]	-0.031	[-0.144, 0.082]	0.583
MFTJ group severe: 2.2 / 3.2 / 3.3	73	-0.226 ± 0.226	[-0.278, -0.173]	51	-0.200 ± 0.230	[-0.264, -0.136]	0.025	[-0.061, 0.112]	0.560
Lateral FTJ Change [μm]:									
LFTJ group mild: 0.0 / 1.0 / 2.0 / 3.0	270	-0.020 ± 0.116	[-0.034, -0.006]	217	-0.023 ± 0.116	[-0.039, -0.008]	-0.004	[-0.025, 0.017]	0.734
LFTJ group moderate: 1.1 / 2.1 / 3.1	40	-0.035 ± 0.125	[-0.074, 0.005]	29	-0.032 ± 0.126	[-0.079, 0.015]	0.003	[-0.060, 0.065]	0.931
LFTJ group severe: 2.2 / 3.2 / 3.3	38	-0.130 ± 0.171	[-0.186, -0.075]	30	-0.072 ± 0.172	[-0.135, -0.010]	0.058	[-0.027, 0.143]	0.179

PFJ –patello-femoral joint, MFTJ - medial femoro-tibial joint, LFTJ- lateral femoro-tibial joint, SD- standard deviation, 95% CI – 95% confidence interval, Mean Diff – mean difference

[a] Maximum MOAKS cartilage grade in all 4 PFJ subregions: 0.0.1.0, 1.1, 2.0,2.1, 3.0, 3.1

[b] Maximum MOAKS cartilage grade of 2.2, 3.2 or 3.3 in at least 1 of 4 PFJ subregions

Table 1

Osteoarthritis and Cartilage

Change in medial and lateral cartilage thickness over 24 months stratified by PFJ cartilage damage severity – without adjustment for field strength.

Without adjustment for field strength	PFJ BML: Mild - moderate[a]			PFJ BML: Severe[b]			Severe vs. Mild - moderate		
	N	Mean ± SD	[95% CI]	N	Mean ± SD	[95% CI]	Adj. mean diff	[95% CI]	P-value
Medial FTJ Change [μm]:									
MFTJ group mild: 0.0 / 1.0 / 2.0 / 3.0	258	-0.046 ± 0.154	[-0.065, -0.028]	150	-0.073 ± 0.155	[-0.098, -0.048]	-0.026	[-0.058, 0.005]	0.104
MFTJ group moderate: 1.1 / 2.1 / 3.1	55	-0.127 ± 0.258	[-0.196, -0.058]	37	-0.255 ± 0.259	[-0.340, -0.171]	-0.128	[-0.238, -0.018]	0.023*
MFTJ group severe: 2.2 / 3.2 / 3.3	90	-0.223 ± 0.219	[-0.269, -0.178]	34	-0.194 ± 0.221	[-0.269, -0.119]	0.030	[-0.059, 0.118]	0.507
Lateral FTJ Change [μm]:									
LFTJ group mild: 0.0 / 1.0 / 2.0 / 3.0	306	-0.015 ± 0.115	[-0.028, -0.002]	181	-0.032 ± 0.116	[-0.048, -0.015]	-0.016	[-0.038, 0.005]	0.141
LFTJ group moderate: 1.1 / 2.1 / 3.1	49	-0.033 ± 0.124	[-0.069, 0.002]	20	-0.035 ± 0.127	[-0.092, 0.022]	-0.002	[-0.070, 0.066]	0.955
LFTJ group severe: 2.2 / 3.2 / 3.3	48	-0.113 ± 0.171	[-0.162, -0.063]	20	-0.086 ± 0.172	[-0.163, -0.009]	0.027	[-0.065, 0.119]	0.561

PFJ –patello-femoral joint, MFTJ - medial femoro-tibial joint, LFTJ- lateral femoro-tibial joint, SD- standard deviation, 95% CI – 95% confidence interval, Mean Diff – mean difference, BML – bone marrow lesion

[a] Maximum MOAKS BML grade in all 4 PFJ subregions: 0, 1, 2

[b] Maximum MOAKS BML grade of 3 in at least 1 of 4 PFJ subregions; * statistically significant at $p < 0.05$

Table 2

Osteoarthritis and Cartilage

Change in medial and lateral cartilage thickness over 24 months stratified by PFJ BML damage severity – without adjustment for field strength.

measurements were not associated with radiographically determined longitudinal joint space loss in the medial femorotibial joint or MOAKS determinants [26]. No associations were detected between patellofemoral morphology measurements and medial femorotibial OA progression, which is in line with our results [26].

Our study has limitations. We did not consider clinical variables like function or pain. As an example, structure may be modified in a positive manner in the femorotibial joint but symptoms may be unaffected by that improvement due to the concomitant presence of patellofemoral disease. Further, we used a simulated clinical trial population based on KL 2 and 3 knees from two large epidemiological studies but not from real-world clinical trials. We used cartilage damage and BMLs to define patellofemoral structural disease severity [27], but did not look at other features than quantitative cartilage loss as the outcome in the femorotibial joint. The cut-offs for our definitions of mild-moderate vs. severe cartilage damage in the patellofemoral joint were defined a priori and different definitions may yield slightly different results. Finally, the statistical analyses were not adjusted for multiple parallel comparisons, because the purpose of this analysis was to estimate the impact of patellofemoral disease severity on the change in femorotibial cartilage thickness loss.

In summary, MRI screening at the eligibility phase of a clinical trial covers the different faces of structural OA in much more detail than radiography and seems feasible based on technological advances and rapid MRI screening tools. Radiography has several limitations highlighting the need for MRI-based assessment. These limitations include poor reproducibility of joint space width measurements when imaging is not standardized, inadequate characterization of disease severity, and a weak correlation between radiographic findings and patient-reported pain. Additionally, radiography is unable to capture the full spectrum of OA tissue damage, does not support phenotypic stratification, and cannot reliably identify exclusionary diagnoses. In contrast, MRI addresses these deficiencies by providing comprehensive, reproducible, and multifaceted joint assessment. While there are practical challenges to the routine use of MRI during eligibility screening, these can be mitigated through technological advancements and streamlined imaging protocols. From a structural perspective, screening for patellofemoral disease to exclude knees with advanced patellofemoral

cartilage damage or large BMLs does not appear to be relevant in a DMOAD trial of 24 months duration in regard to quantitative femorotibial cartilage loss, whenever change in cartilage thickness in the medial or lateral femorotibial joint is the compartment of relevance in regard to structural endpoints.

Author contributions

(1) All authors were involved in the conception and design of the study, or acquisition of data, or analysis and interpretation of data.
(2) All authors contributed to drafting the article or revising it critically for important intellectual content.
(3) All authors gave their final approval of the manuscript to be submitted.

Additional contributions

Analysis and interpretation of the data: FWR, MJ, AG, RH, SM, AL, FJB, FB, LAS, MK, IKH, CHL, JB, AW, FPJGL, HHW, WW. Critical revision of the article for important intellectual content: all authors. Provision of study materials or patients: FJB, IKH, FB, HHW, MK, DJH. Statistical expertise: WW, DJH, FWR; FE. Obtaining of funding: FJB, IKH, FB, HHW, MK, DJH. Administrative, technical, or logistic support: MJ, SM, AW. Collection and assembly of data: FWR, AG, WW, SM, AW

Responsibility for the integrity of the work as a whole, from inception to finished article, is taken by F. Roemer, MD (first author; frank.roemer@uk-erlangen.de; froemer@bu.edu).

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Declaration of Competing Interest

FWR is shareholder and Chief Medical Officer of Boston Imaging Core Lab (BICL), LLC, a company providing image assessment services to academia and the pharmaceutical industry. He is consultant to Grünenthal, GmbH. He is Editor in Chief of *Osteoarthritis Imaging*.

MPJ has not declared any conflict of interest. SM is an employee and co-owner of Chondrometrics GmbH. SCM has received research grants from the Dutch Rheumatology Society and ZonMW. AW is an employee of Chondrometrics GmbH. RH has not declared any conflict of interest.

HHW has received grant support from EU-IMI (Approach project) to employer (UMC Utrecht) and additional grants from intereg grant Properos 2 (EU-Dutch government), Kansen voor West grant (EFRO), OA-inject NWO (Dutch government), 3DHip project (Eurostars), DartbacNWA (Dutch government, NWO) and Porospin (LSH, Dutch Governement). He holds patent with the following numbers: WO/2020/002301, WO2017209605A1, US20080262618 A1 and WO 2007053022 A3. He is minority shareholder of Replasia BV and Presurgeo BV.

FJB reports payment to the institution from Gedeon Richter Plc., Bristol-Myers Squibb International corporation (BMSIC), Sun Pharma Global FZE, Celgene Corporation, Janssen Cilag International N.V, Janssen Research & Development, Viela Bio, Inc., Astrazeneca AB, UCB BIOSCIENCES GMBH, UCB BIOPHARMA SPRL, AbbVie Deutschland GmbH & Co.KG, Merck KGaA, Amgen, Inc., Novartis Farmacéutica, S.A., Boehringer Ingelheim España, S.A, CSL Behring, LLC, Glaxosmithkline Research & Development Limited, Pfizer Inc, Lilly S.A., Corbus Pharmaceuticals Inc., Biohope Scientific Solutions for Human Health S.L., Centrexion Therapeutics Corp., Sanofi, MEIJI FARMA S.A., Kiniksa Pharmaceuticals, Ltd, Fundación para la Investigación Biomédica Del Hospital Clínico San Carlos, outside the current manuscript.

FB reports consutlancy to Grünenthal, GSK, EliLIlly, Novartis, Pfizer and Servier. He has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Viatris and Pfizer. He has received support for attending meetings and/or travel from Nordic Pharma. He is member of a Data Safety Monitoring Board or Advisory Board for AstraZeneca, Sun Pharma, Nordic Bioscience. He is shareholder of 4 P Pharma and 4Moving Biotech.

MK has received grant support from IMI-APPRAOCH (paid to institution). In addition she holds grants from the Dutch Arthritis Society (among which LPP-24 2018–2023; 21–1–203). Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Galapagos and Jansen (to institution). She is was Member of the OARSI board (2017–2022), Member EULAR council (member Advocacy Committee EULAR, since June 2023 chair elect, is President of the Dutch Society for Rheumatology.

IKH reports consultancy to Novartis, GSK and Grünenthal. She has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Abbvie.

DJH is the editor of the osteoarthritis section for UpToDate and co-Editor in Chief of Osteoarthritis and Cartilage. He provides consulting advice on scientific advisory boards for TLCBio, Novartis, Tissuegene, Biobone, Sanofi, Enlivex.

AG has provided consulting services to Pfizer, TissueGene, Coval, Medipost, TrialSpark, Novartis, ICM. He is shareholder of Boston Imaging Core Lab (BICL), LLC. He is president of the International Society of Osteoarthritis Imaging (unpaid). WW is an employee and co-owner of Chondrometrics GmbH.

Declaration of Generative AI and AI-assisted technologies in the writing process

No generative AI was used in the data collection, interpretation or writing of the manuscript.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.joca.2025.10.003.

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