Arthritis Care & Research
Vol. 0, No. 0, Month 2022, pp 1–7
DOI 10.1002/acr.24605

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

BRIEF REPORT

Magnetic Resonance Imaging–Defined Osteophyte Presence and Concomitant Cartilage Damage in Knees With Incident Tibiofemoral Osteoarthritis: Data From the Pivotal Osteoarthritis Initiative Magnetic Resonance Imaging Analyses Study

James MacKay,[1] Ali Guermazi,[2] C. Kent Kwoh,[3] P. L. Paul See,[4] Mohamed Jarraya,[5] Ling Li,[6] Michael J. Hannon,[7] Tomoko Fuji,[8] and Frank W. Roemer[9]

Objective. To describe compartmental frequencies of magnetic resonance image (MRI)–defined osteophytes and co-localized cartilage damage and evaluate the associations of osteophyte size with any ipsicompartmental cartilage damage in knees with incident tibiofemoral radiographic knee osteoarthritis (OA).

Methods. We evaluated knees from the Osteoarthritis Initiative without radiographic knee OA at baseline that developed radiographic knee OA during a 4-year interval. Semiquantitative MRI scoring of osteophytes and cartilage damage was performed at the time point when radiographic knee OA was diagnosed, defined as Kellgren/Lawrence grade of ≥2, using the MRI Osteoarthritis Knee Score instrument. The frequencies of maximum osteophyte size and maximum grade of ipsicompartmental (i.e., patellofemoral, medial tibiofemoral, lateral tibiofemoral, posterior femur) cartilage damage were assessed. Generalized estimating equations were used to determine the association of MRI-defined maximum osteophyte size with presence of any (excluding focal superficial defects) ipsicompartmental cartilage damage.

Results. A total of 296 knees that did not have tibiofemoral radiographic knee OA at the baseline visit but developed radiographic knee OA during the 48-month observational period were included. In the patellofemoral, medial tibiofemoral, and lateral tibiofemoral compartments, the most frequent osteophyte grade was 1 (67.6%, 59.1%, and 51.7%, respectively) and was 0 (51.7%) in the posterior femur. For all compartments except the posterior femur, a linear trend was found between increasing maximum osteophyte size and the presence of any concomitant cartilage damage.

Conclusion. In this sample of knees with incident tibiofemoral radiographic knee OA, the patellofemoral joint showed more severe cartilage damage than other compartments regardless of concomitant osteophyte size. In the posterior femur, cartilage damage was rare despite the presence or size of concomitant osteophytes.

INTRODUCTION

Radiographic diagnosis of knee osteoarthritis (OA) is determined by the presence of a definite osteophyte, equivalent to grade 2 on the Kellgren/Lawrence (K/L) scale. However, the validity of this definition remains uncertain, as radiography cannot directly visualize many intraarticular tissue changes characteristic of OA. OA is now recognized as a disease of the whole joint (1),

This article was prepared using an Osteoarthritis Initiative (OAI) public-use data set, and its contents do not necessarily reflect the opinions or views of the OAI Study Investigators, the NIH, or the private funding partners of the OAI.

The study and image acquisition was funded by the OAI, a public–private partnership between the NIH (contracts N01-AR-2-2258, N01-AR-2-2259, N01-AR-2-2260, N01-AR-2-2261, and N01-AR-2-2262) and private funding partners (Merck Research Laboratories, Novartis Pharmaceuticals, GlaxoSmithKline, and Pfizer, Inc.) and is conducted by the OAI Study Investigators. Private sector funding for the OAI is managed by the Foundation for the NIH. The authors of this article are not part of the OAI investigative team. The image analysis of this study was funded in part by Novartis Pharma AG (Basel, Switzerland), in part by a contract with the University of Pittsburgh (Pivotal OAI Magnetic Resonance Imaging Analyses [POMA]: NIH/National Heart, Lung and Blood Institute [NHLBI] grant HHSN2682010000 21C) and in part by a vendor contract from the OAI coordinating center at University of California, San Francisco (grant N01-AR-2-2258). The statistical data analysis was funded in part by a contract with the University of Pittsburgh (POMA: NIH/NHLBI grant HHSN2682010000 21C) and by the Biomarker of Early osteoArthritis of the Knee (BEAK) study (AR066601).

[1]James MacKay, MD, PhD: Norwich Medical School, University of East Anglia, Norwich, UK, and University of Cambridge School of Clinical Medicine, Cambridge, UK; [2]Ali Guermazi, MD, PhD: Boston University School of Medicine, Boston, Massachusetts, and VA Boston Healthcare System, West Roxbury, Massachusetts; [3]C. Kent Kwoh, MD: University of Arizona College of Medicine, Tucson; [4]P. L. Paul See, MBBS, FRCR (UK): Boston University School of Medicine, Boston, Massachusetts, and Khoo Teck Puat Hospital, Singapore,

SIGNIFICANCE & INNOVATIONS

- Prior studies have evaluated the presence of osteophytes and any cartilage damage in the same knee, but whether the relationship was compartment-specific was not known.
- In the present study, we show that the presence of magnetic resonance imaging–defined osteophytes is, in general, associated with cartilage damage in the same compartment in knees with incident radiographic osteoarthritis.
- The patellofemoral joint commonly demonstrated high-grade cartilage damage regardless of concomitant osteophyte presence or size.
- Despite the presence or size of concomitant osteophytes, cartilage damage in the posterior femur was rare.

including cartilage damage and other bone and soft tissue pathology that is common in pre–radiographic OA (2). While the K/L scale is based on a composite measure of presence or absence of osteophytes and joint space narrowing without differentiating which knee compartment is involved, the Osteoarthritis Research Society International (OARSI) atlas grading system takes into account the compartmental location of both osteophytes and joint space narrowing (3). However, the OARSI system cannot differentiate whether joint space narrowing is based on cartilage loss, meniscal damage/extrusion, or both (4). Radiographic presence of a definite osteophyte, particularly when there is no joint space narrowing (i.e., K/L grade 2), does not allow extrapolation on whether concomitant ipsicompartmental cartilage damage is present or not. It has previously been demonstrated that on a whole knee basis, osteophytes detected by radiography and magnetic resonance imaging (MRI) are associated with cartilage damage (detected by MRI) and that osteophyte size correlates with degree of cartilage damage in most cases for all K/L grades (5,6). However, the compartmental relationship between osteophytes and cartilage damage has not previously been characterized, which makes it difficult to understand whether the presence of an osteophyte can be regarded as a reliable surrogate of cartilage damage in the same compartment. This relationship may also have implications for interventional approaches targeting early OA. Given the known high prevalence of MRI-detected tissue alterations in pre–radiographic OA, our hypothesis was that MRI-detected osteophytes are an indicator of ipsicompartmental cartilage damage in knees with incident tibiofemoral radiographic OA (ROA).

Therefore, the purpose of this study was to describe cross-sectionally MRI-defined maximum osteophyte size and maximum grade of co-localized cartilage damage by compartment and to analyze the association of maximum osteophyte size with concomitant presence of any cartilage damage in the same compartment on MRI for knees that had recently developed tibiofemoral radiographic OA.

MATERIALS AND METHODS

Participants. Participants were drawn from the Osteoarthritis Initiative (OAI), a prospective cohort study of 4,976 adults with or at risk of developing knee OA. The OAI was approved by the institutional review boards of the University of California, San Francisco and the 4 OAI clinical centers. Informed consent was given by all participants. We included knees from the Pivotal OAI MRI Analyses (POMA) substudy (7). Participants in POMA had at least 1 knee that did not have radiographic knee OA at baseline but developed radiographic knee OA prior to or at the 48-month OAI visit. The time point of incident radiographic knee OA was defined as the first visit with a radiographic K/L grade ≥2 (P0). Our sample was limited to knees within the POMA study who had MRI available for grading at P0 and the year prior.

Image acquisition. OAI knee radiograph acquisition has been described in detail (8). Radiographs were acquired on an annual basis using a posteroanterior fixed flexion weight-bearing protocol with a Plexiglas positioning frame (SynaFlexer; BioClinica). K/L grades were determined by central readings of the fixed flexion knee radiographs.

MRI examination of both knees was performed on identical 3T magnets (Siemens Magnetom Trio) at the 4 OAI clinical sites according to the OAI MRI acquisition protocol. The full MRI protocol has been described in detail (9). In brief, MRIs included 2-dimensional (2D) coronal intermediate-weighted (IW) turbo spin echo (TSE), 2D sagittal IW fat-suppressed TSE, and 3D sagittal

Singapore; [5]Mohamed Jarraya, MD: Massachusetts General Hospital and Harvard Medical School, Boston; [6]Ling Li, MSPH: Pfizer, New York, New York; [7]Michael J. Hannon, MA: University of Pittsburgh School of Medicine, and Pinney Associates, Pittsburgh, Pennsylvania; [8]Tomoko Fujii, MD, PhD: The University of Tokyo Hospital, Tokyo, Japan; [9]Frank W. Roemer, MD: Boston University School of Medicine, Boston, Massachusetts, and Friedrich-Alexander University Erlangen-Nürnberg & Universitätsklinikum Erlangen, Erlangen, Germany.

Dr. MacKay has received consulting fees, speaking fees, and/or honoraria from GlaxoSmithKline, GE Healthcare, and Moximed (less than $10,000 each). Dr. Guermazi has received consulting fees, speaking fees, and/or honoraria from Pfizer, MerckSerono, and Kolon TissueGene (less than $10,000 each) and Novartis, Regeneron, and AstraZeneca (more than $10,000 each) and owns stock or stock options in Boston Imaging Core Lab (BICL). Dr. Kwoh has received consulting fees, speaking fees, and/or honoraria from EMD Serono, Thusane, Regeneron, Kolon TissueGene, TaiwanLiposome Company, Amzell, and LG Chem (less than $10,000 each) and Express Scripts (more than $10,000). Mr. Hannon has received consulting fees, speaking fees, and/or honoraria from EMD Serono (less than $10,000). Dr. Roemer has received consulting fees, speaking fees, and/or honoraria from the California Institute for Biomedical Research – Calibr (less than $10,000) and owns stock or stock options in BICL. No other disclosures relevant to this article were reported.

Address correspondence to James MacKay, MD, PhD, Department of Radiology, Norwich Medical School, University of East Anglia, Norwich NR4 7UQ, UK. Email: james.w.mackay@uea.ac.uk.

Submitted for publication July 16, 2020; accepted in revised form March 23, 2021.

dual echo in steady-state sequences with axial and coronal reformats.

Image analysis. Two musculoskeletal radiologists (AG and FWR, with 14 and 12 years of experience in semiquantitative assessment of knee MRI at time of analysis, respectively) read the MRIs at P0 according to the validated MRI Osteoarthritis Knee Score (MOAKS) system (1). Osteophytes were scored at 12 locations, including 6 patellofemoral locations (superior and inferior, medial and lateral patella, medial and lateral anterior femur), 2 medial tibiofemoral (central medial femur and central medial tibia), 2 lateral tibiofemoral (central lateral femur and central lateral tibia), and 2 posterior femoral locations (posterior medial femur and posterior lateral femur). Osteophytes were graded on a 4-point ordinal scale based on size (0 = none, 1 = small, 2 = medium, 3 = large). Locations of osteophyte assessment are shown in Figure 1.

Corresponding subregions for cartilage damage were patella (medial and lateral patella) and anterior femur (medial and lateral), medial tibiofemoral (anterior, central, posterior medial tibia, central medial femur), lateral tibiofemoral (anterior, medial, posterior lateral tibia, central lateral femur), and posterior femur (posterior medial and posterior lateral femur). MOAKS cartilage grading is performed in a 2-digit manner, taking into account the percentage of area in each subregion affected by any cartilage damage and the percentage of area of each subregion affected by full thickness cartilage damage (both scored from 0 to 3; 0 = none, 1 = <10%, 2 = 10–75%, 3 = >75%). Intraobserver and interobserver reliability results for these readers in this cohort have previously been reported, with all MOAKS features demonstrating substantial or almost perfect agreement (7).

Statistical analysis. We performed a cross-sectional analysis at the time point when radiographic knee OA was diagnosed

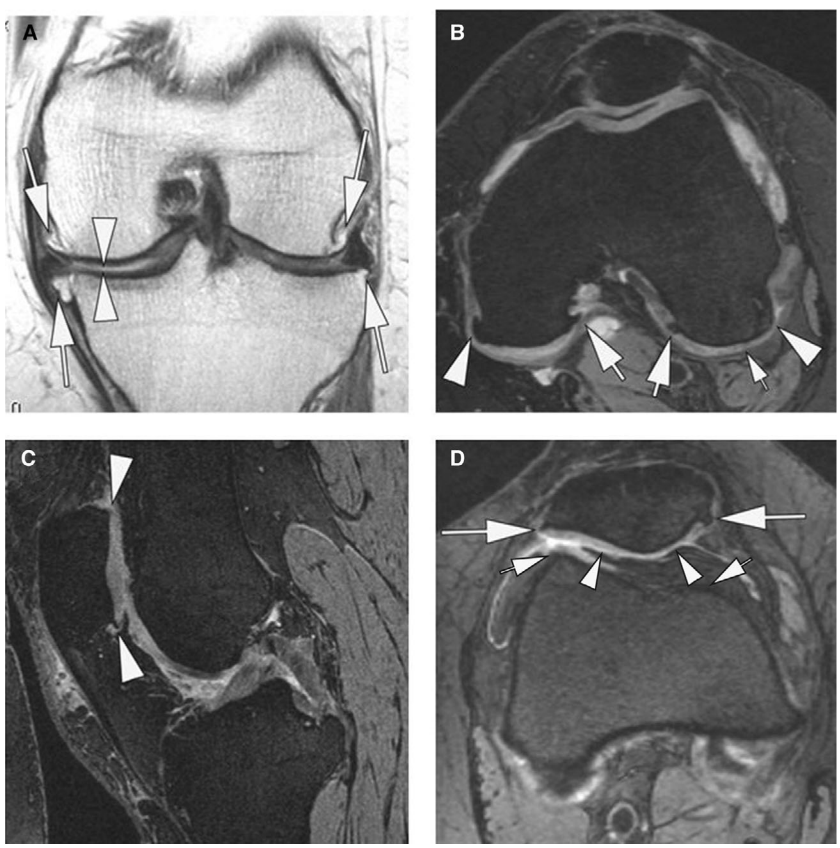

Figure 1. Locations for osteophyte assessment in the current study according to the Magnetic Resonance Imaging (MRI) Osteoarthritis Knee Score (MOAKS) scoring system. **A**, MRI locations best reflecting the Kellgren-Lawrence radiographic approach without projectional radiography issues are the medial and lateral femoral and tibial locations (**arrows**) (diffuse superficial cartilage damage at the medial femur and tibia [**arrowheads**]). **B**, Axial reformatted image of the sagittal 3-dimensional double-echo steady-state (DESS) sequence shows the posterior femoral locations for osteophyte scoring. Osteophytes were scored medially and laterally either at the intercondylar location (**long arrows**) or at the more marginal locations medially and laterally (**arrowheads**). The larger of the two sites were considered as the MOAKS grade for the posterior femur (superficial cartilage damage at the lateral posterior femur [**short arrow**]). **C**, Sagittal DESS image depicting the 2 osteophyte locations at the superior and inferior patella (**arrowheads**). **D**, Axial DESS image showing the medial and lateral patellar locations for osteophyte assessment (**long arrows**). Osteophytes are also assessed at the medial and lateral anterior femur (**short arrows**). In addition, there is superficial medial and lateral cartilage thinning (**arrowheads**).

(P0). We used descriptive statistics to describe the frequencies of maximum osteophyte size and maximum grade of co-localized cartilage damage by compartment. Due to the focus on matching osteophyte presence/size with ipsicompartmental cartilage damage/severity, we defined "compartments" as follows: patellofemoral (6 osteophyte locations, 4 cartilage locations), medial tibiofemoral (2 osteophyte locations, 4 cartilage locations), lateral tibiofemoral (2 osteophyte locations, 4 cartilage locations), and posterior femur (2 osteophyte locations, 2 cartilage locations). For grading of cartilage damage, we grouped area and full thickness assessments into 4 categories, including 0 (none), 1.0–1.1 (focal superficial or full-thickness defects), 2.0–2.2 (medium to large superficial or full thickness damage), or >2.2 (extensive full thickness cartilage damage). We used generalized estimating equations (GEE) adjusted for the correlation of 2 knees within an individual to determine the association between MRI-defined maximum osteophyte size (independent variable) in a given compartment with the presence of any ipsicompartmental cartilage damage (dependent variable, defined as grade 1.0 or higher). For the GEE analyses, we presented the results for crude (unadjusted) models and adjusted for potential confounders (i.e., age, sex, body mass index, race, and contralateral knee K/L grade status). Due to low numbers of compartments with large osteophytes, we grouped knees with maximum osteophyte size of 2 and 3 together. All statistical calculations were performed with SAS software (version 9.4).

RESULTS

We included 296 knees from 273 OAI participants who developed radiographic knee OA during the 48-month observational period. The mean ± SD age of participants was 60.4 ± 8.5 years, and participants were predominantly female (67.4%) and overweight (mean ± SD body mass index 28.8 ± 4.4). The radiographic status for knees in the cohort and contralateral knees at baseline was K/L grade 0/0 for 57 knees (19.3%), K/L grade 0/1 for 59 knees (19.9%), K/L grade 1/1 for 67 knees (22.6%), K/L grade 0/≥2 for 56 knees (18.9%), and K/L grade 1/≥2 for 57 knees (19.3%). At time point P0, radiographic knee OA status was K/L grade 2 for 237 knees (80.1%), K/L grade 3 for 57 knees (19.3%), and K/L grade 4 for 2 knees (0.7%). The case-defining visit of radiographic OA incidence was 12 months after the baseline visit for 119 knees (33.5%), 24 months for 83 knees (23.4%), 36 months for 103 knees (29.0%), and 48 months for 50 knees (14.1%).

As shown in detail in Table 1, in the patellofemoral compartment, 45, 200, and 51 knees demonstrated grades 0, 1, and 2–3 osteophytes, respectively, compared with 93, 175, and 28 knees in the medial compartment; 78, 153, and 65 knees in the lateral compartment; and 153, 121, and 22 knees in the posterior femur. In the patellofemoral compartment, 40, 33, 210, and 13 knees demonstrated grades 0, 1.0–1.1, 2.0–2.2, and >2.2 cartilage defects, respectively, compared with 108, 45, 140, and 3 knees in the medial compartment; 148, 45, 98, and 5 knees in the lateral compartment; and 217, 23, 56, and 0 knees in the posterior femur. Only 21 knees (7.1%) showed extensive full thickness cartilage loss (>2.2) in any compartment.

A linear trend was observed for all compartments for increased odds of any cartilage damage with increasing osteophyte grade, except for the posterior femur. For the patellofemoral compartment, compared to those with no osteophytes, the adjusted odds ratio (OR_{adj}) for any cartilage damage and a

Table 1. Frequencies of osteophytes and ipsicompartmental cartilage damage on magnetic resonance imaging

	Maximum osteophyte grade		Maximum cartilage damage grade, no. (%)			
Compartment	Grade	No. (%)	0	1.0–1.1	2.0–2.2*	>2.2
Patellofemoral†	0	45 (15.2)	10 (22.2)	3 (6.7)	31 (68.9)	1 (2.2)
	1	200 (67.6)	29 (14.5)	26 (13.0)	142 (71.0)	3 (1.5)
	2 and 3	51 (17.2)	1 (2.0)	4 (7.8)	37 (72.6)	9 (17.7)
Medial tibiofemoral‡	0	93 (31.4)	49 (52.7)	13 (14.0)	30 (32.3)	1 (1.1)
	1	175 (59.1)	53 (30.3)	27 (15.4)	93 (53.1)	2 (1.1)
	2 and 3	28 (9.5)	6 (21.4)	5 (17.9)	17 (60.7)	0
Lateral tibiofemoral§	0	78 (26.4)	57 (73.1)	8 (10.3)	13 (16.7)	0
	1	153 (51.7)	69 (45.1)	24 (15.7)	56 (36.6)	4 (2.6)
	2 and 3	65 (22.0)	22 (33.9)	13 (20.0)	29 (44.6)	1 (1.5)
Posterior femur¶	0	153 (51.7)	115 (75.2)	9 (5.9)	29 (19.0)	0
	1	121 (40.9)	89 (73.6)	11 (9.1)	21 (17.4)	0
	2 and 3	22 (7.4)	13 (59.1)	3 (13.6)	6 (27.3)	0

* Maximum cartilage damage grade included 2.0/2.1/2.2 (medium to large superficial or full thickness damage).
† The definition of the patellofemoral compartment was 4 subregions for cartilage (medial and lateral patella, medial and lateral anterior femur) and 6 locations for osteophytes (superior, inferior, medial, lateral patella, medial and lateral anterior femur).
‡ The definition of the medial tibiofemoral compartment was 4 subregions for cartilage (anterior, central, posterior medial tibia, central medial femur) and 2 locations for osteophytes (central medial femur, central medial tibia).
§ The definition of the lateral tibiofemoral compartment was 4 subregions for cartilage (anterior, central, posterior lateral tibia, central medial femur) and 2 locations for osteophytes (central lateral femur, central lateral tibia).
¶ The definition of the posterior femur compartment was 2 subregions for cartilage (medial and lateral posterior femur) and 2 locations for osteophytes (medial and lateral posterior femur).

Table 2. Association of maximum osteophyte grade and odds of ipsicompartmental cartilage damage*

Joint	Any (≥1.0) cartilage damage in 4 subregions	Crude model, OR (95% CI)	Adjusted model OR (95% CI)†
Patellofemoral			
Maximum osteophyte grade (6 locations)			
0 (ref.)	35/45 (77.8)	1.0 (ref.)	1.0 (ref.)
1	171/200 (85.5)	1.68 (0.77–3.67)	1.50 (0.62–3.63)
2 and 3	50/51 (98.0)	14.29 (1.75–116.46)	11.36 (1.46–88.22)
P for linear trend	–	0.0008	0.0042
Medial tibiofemoral			
Maximum osteophyte grade (2 locations)			
0 (ref.)	44/93 (47.3)	1.0 (ref.)	1.0 (ref.)
1	122/175 (69.7)	2.57 (1.53–4.32)	2.60 (1.45–4.66)
2 and 3	22/28 (78.5)	4.09 (1.52–11.01)	4.46 (1.55–12.85)
P for linear trend	–	0.0002	0.0007
Lateral tibiofemoral			
Maximum osteophyte grade (2 locations)			
0 (ref.)	21/78 (26.9)	1.0 (ref.)	1.0 (ref.)
1	84/153 (54.9)	2.61 (1.59–4.28)	3.39 (1.89–6.08)
2 and 3	43/65 (66.2)	4.89 (2.50–9.57)	5.27 (2.44–11.37)
P for linear trend	–	<0.0001	<0.0001
Posterior femoral			
Maximum osteophyte grade (2 locations)			
0 (ref.)	38/153 (24.8)	1.0 (ref.)	1.0 (ref.)
1	32/121 (26.4)	1.08 (0.64–1.82)	1.06 (0.64–1.76)
2 and 3	9/22 (40.9)	2.03 (0.77–5.34)	1.55 (0.44–5.49)
P for linear trend	–	0.2375	0.4849

* Values are the number/total number (%) unless indicated otherwise. 95% CI = 95% confidence interval; OR = odds ratio.
† Model adjusted for age, sex, body mass index, race, and contralateral knee Kellgren/Lawrence grade status.

maximum osteophyte grade of 1 was 1.50 (95% confidence interval [95% CI] 0.62–3.63), and for osteophyte grades 2 and 3 combined, it was 11.36 (95% CI 1.46–88.22), with *P* for trend = 0.0042. In the medial tibiofemoral compartment, the OR_{adj} for concomitant presence of any cartilage damage was 2.60 (95% CI 1.45–4.66) for a maximum osteophyte grade of 1, and 4.46 (95% CI 1.55–12.85) for maximum osteophyte grades 2 and 3, with *P* for trend <0.001. For the lateral tibiofemoral compartment, compared to those with no osteophytes, the OR_{adj} for co-locational presence of any cartilage damage for a maximum osteophyte grade of 1 was 3.39 (95% CI 1.89–6.08), and was 5.27 (95% CI 2.44–11.37) for grades 2 and 3 (*P* for trend <0.001). No statistically significant associations between cartilage damage categories and osteophyte grade were observed for the posterior femur. Full results of GEE analyses are provided in Table 2.

DISCUSSION

In this study of knees that had recently developed tibiofemoral radiographic knee OA, we found a strong association between the maximum grade of osteophyte within a compartment and the presence of ipsicompartmental cartilage damage, with the exception of the posterior femur. In general, the odds for ipsicompartmental cartilage damage increased with increasing size of osteophytes. In the patellofemoral compartment, higher grade cartilage loss was common regardless of osteophyte grade. In the posterior femur, higher grade cartilage loss was rare regardless of osteophyte size, and <50% of knees demonstrated any osteophytes in this region.

The radiography-based K/L scale is based on the assumption that osteophytes and cartilage loss appear in a sequential fashion, i.e., cartilage damage follows osteophytes. However, taking into account previous studies on prevalence of cartilage damage in knees that do not exhibit radiographic osteophytes, it must be assumed that cartilage damage is also highly prevalent in early radiographic knee OA knees (i.e., K/L grade 2) despite the fact that no joint space narrowing is observed (2).

Interpreting our findings in the context of interventional approaches focusing on cartilage restoration or anticatabolic effects on cartilage, knees with incident radiographic knee OA as analyzed in our study commonly exhibit superficial and full thickness cartilage damage, with highest prevalence in the patella and medial tibiofemoral compartment. Extensive widespread full thickness damage was rare, however, making these knees potentially ideal targets for cartilage preservation or restoration approaches, assuming that widespread full thickness damage is less amenable to such approaches (10). However, it should be acknowledged that there was a high prevalence of contralateral knee radiographic knee OA in our sample, which may preclude eligibility for therapies targeting a single symptomatic joint.

Katsuragi and colleagues compared a small subgroup from the OAI that developed radiographic knee OA (K/L grade ≥2) with a larger non–OA control using the Whole Organ Magnetic Resonance Imaging Score (WORMS) MRI-based scoring system focusing on osteophytes. They analyzed the baseline visit and found that mild-size osteophytes (grade 2 of 7 on the WORMS scale) are more frequently observed at the medial femur, medial tibia, tibial spines, patella, and intercondylar notch in knees that will develop radiographic knee OA as compared to those that do not (11). The authors concluded that knees with intercondylar osteophytes are at increased risk for radiographic knee OA development. Longitudinal prediction based on osteophyte location or size is not possible using our data, which is a limitation of the present study. While we could show that the posterior femur (the intercondylar region in Katsuragi and colleagues' study) shows osteophytes in about half of the cases, moderate or severe cartilage damage seems to be less common than in other locations. It is possible that the lack of association seen in the posterior femur region reflects the difference between weight-bearing and non–weight-bearing regions (although this would not explain the strong associations seen in the patellofemoral region) or the fact that the drivers of osteophyte development and cartilage damage differentially affect different compartments.

Our findings agree with the results of multiple prior studies that have demonstrated a close relationship between bone and cartilage pathology in OA (12). We have shown previously using MRI data that knees with moderate-to-large osteophytes exhibit markedly increased odds for severe cartilage damage, with increasing likelihood of having severe cartilage damage with increasing osteophyte size (6). In the current study, the odds of any cartilage damage increased with osteophyte grade consistently across all compartments (with the exception of the posterior femur), suggesting that osteophyte size is a marker of concomitant or co-locational cartilage damage in these K/L grade 2 knees. We observed the greatest magnitude of association between osteophyte size and ipsicompartmental cartilage damage in the lateral tibiofemoral compartment, complementing the findings of a previous study that found that isolated lateral tibiofemoral OA was associated with a greater severity of MRI lesions, including osteophytes and cartilage damage (13). We did not assess the role of osteophytes for longitudinal progression, but previous longitudinal studies have demonstrated associations between the presence of osteophytes at baseline with both prevalent and incident cartilage damage and radiographic progression (14).

Our sample included only knees that had recently developed tibiofemoral radiographic knee OA (i.e., knees with K/L grade ≥2), due to the relative homogeneity of this sample and the availability of MOAKS grades in this group. However, this homogeneity limits the wider interpretation of our results in other OA populations and the entire spectrum of radiographic OA severity. In addition, it should be acknowledged that contralateral knee tibiofemoral radiographic OA was common at baseline in this sample, making this a cohort biased toward individuals at high risk of progression. An additional limitation of our study is the absence of information on symptomatic OA. We do not know if subjects who developed radiographic OA also developed symptoms or if subjects developed symptoms prior to the diagnosis of OA. Inclusion of these clinical parameters would have gone beyond the scope of this study, although they are highly important and need to be explored further. For example, given the variable previously reported associations between osteophytes and pain, it would be interesting to evaluate whether the strengths of compartmental association between osteophytes and cartilage damage differed between symptomatic and asymptomatic subjects. Finally, we used an uncommon definition for "compartments" in our study. Commonly the patellofemoral and the medial and lateral tibiofemoral compartments are differentiated in imaging research. As our focus was on co-localization of osteophytes and cartilage damage, we matched these as much as possible. The posterior femur was assessed for both osteophytes and cartilage but did not contribute to the features commonly assessed on posterior-anterior radiography and, thus, was considered a separate compartment.

In conclusion, in this sample of knees with early radiographic tibiofemoral OA, the patellofemoral joint more frequently demonstrated severe cartilage damage regardless of concomitant osteophyte size than other compartments; in the posterior femur, cartilage damage was rare despite concomitant osteophyte presence and size. An increased risk for concomitant cartilage damage was observed with increase in osteophyte size for all locations except the posterior femur. This suggests that in early TF radiographic knee OA, osteophytes are a marker of co-locational cartilage damage, and the presence of larger osteophytes increases odds for concomitant ipsicompartmental cartilage damage.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. MacKay 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.

Study conception and design. Guermazi, Kwoh, Hannon, Fujii, Roemer.

Acquisition of data. Guermazi, Kwoh, See, Roemer.

Analysis and interpretation of data. MacKay, Guermazi, Kwoh, Jarraya, Li, Hannon, Fujii, Roemer.

ADDITIONAL DISCLOSURES

Author Li is an employee of Pfizer.

REFERENCES

1. Hunter DJ, Guermazi A, Lo GH, Grainger AJ, Conaghan PG, Boudreau RM, et al. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). Osteoarthritis Cartilage 2011;19:990–1002.
2. Guermazi A, Niu J, Hayashi D, Roemer FW, Englund M, Neogi T, et al. Prevalence of abnormalities in knees detected by MRI in adults without knee osteoarthritis: population based observational study (Framingham Osteoarthritis Study). BMJ 2012;345:e5339.
3. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis Cartilage 2007;15:A1–56.
4. Crema MD, Nevitt MC, Guermazi A, Felson DT, Wang K, Lynch JA, et al. 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. Osteoarthritis Cartilage 2014;22:1743–7.
5. Boegard T, Rudling O, Petersson IF, Jonsson K. Correlation between radiographically diagnosed osteophytes and magnetic resonance detected cartilage defects in the tibiofemoral joint. Ann Rheum Dis 1998;57:401–7.
6. Roemer FW, Guermazi A, Niu J, Zhang Y, Mohr A, Felson DT. Prevalence of magnetic resonance imaging-defined atrophic and hypertrophic phenotypes of knee osteoarthritis in a population-based cohort. Arthritis Rheum 2012;64:429–37.
7. Roemer FW, Kwoh CK, Hannon MJ, Hunter DJ, Eckstein F, Fujii T, et al. What comes first? Multitissue involvement leading to radiographic osteoarthritis: magnetic resonance imaging-based trajectory analysis over four years in the osteoarthritis initiative. Arthritis Rheumatol 2015;67:2085–96.
8. Osteoarthritis Initiative. Central reading of knee x-rays for Kellgren & Lawrence grade and individual radiographic features of tibiofemoral knee OA. 2016. URL: https://oai.epi-ucsf.org/datarelease/SASDocs/kXR_SQ_BU_descrip.pdf.
9. Peterfy CG, Schneider E, Nevitt M. The Osteoarthritis Initiative: report on the design rationale for the magnetic resonance imaging protocol for the knee. Osteoarthritis Cartilage 2008;16:1433–41.
10. Oo WM, Yu SP, Daniel MS, Hunter DJ. Disease-modifying drugs in osteoarthritis: current understanding and future therapeutics. Expert Opin Emerg Drugs 2018;23:331–47.
11. Katsuragi J, Sasho T, Yamaguchi S, Sato Y, Watanabe A, Akagi R, et al. Hidden osteophyte formation on plain X-ray is the predictive factor for development of knee osteoarthritis after 48 months – data from the Osteoarthritis Initiative. Osteoarthritis Cartilage 2015;23:383–90.
12. Eckstein F, Guermazi A, Gold G, Duryea J, Hellio Le Graverand MP, Wirth W, et al. Imaging of cartilage and bone: promises and pitfalls in clinical trials of osteoarthritis. Osteoarthritis Cartilage 2014;22:1516–32.
13. Wise BL, Niu J, Guermazi A, Liu F, Heilmeier U, Ku E, et al. Magnetic resonance imaging lesions are more severe and cartilage T2 relaxation time measurements are higher in isolated lateral compartment radiographic knee osteoarthritis than in isolated medial compartment disease - data from the Osteoarthritis Initiative. Osteoarthritis Cartilage 2017;25:85–93.
14. Zhu Z, Laslett LL, Jin X, Han W, Antony B, Wang X, et al. Association between MRI-detected osteophytes and changes in knee structures and pain in older adults: a cohort study. Osteoarthritis Cartilage 2017;25:1084–92.