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Authors

Roemer, Frank W
Kwoh, C Kent
Hannon, Michael J
et al.

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Can Structural Joint Damage Measured with MR Imaging Be Used to Predict Knee Replacement in the Following Year?[1]

Frank W. Roemer, MD
C. Kent Kwoh, MD
Michael J. Hannon, MA
David J. Hunter, MBBS, PhD
Felix Eckstein, MD
Zhijie Wang, MS
Robert M. Boudreau, PhD
Markus R. John, MD
Michael C. Nevitt, PhD
Ali Guermazi, PhD

Purpose: To assess whether magnetic resonance (MR) imaging–based cross-sectional measures of structural joint damage can be used to predict knee replacement during the following year.

Materials and Methods: Participants were drawn from the Osteoarthritis Initiative, a longitudinal observational study that includes 4796 participants who have knee osteoarthritis or are at risk. The HIPAA-compliant protocol was approved by the institutional review boards of all participating centers, and written informed consent was obtained from all participants. During the 5 years of follow-up, 199 knees underwent knee replacement and were matched with 199 control knees that did not undergo knee replacement. Knees were matched according to radiographic disease stage and patient sex and age. All knees that underwent knee replacement and had MR images available from the year before surgery were included. MR images were assessed for cartilage damage, bone marrow lesions, meniscal damage, meniscal extrusion, synovitis, and effusion prior to reported knee replacement. Conditional logistic regression was applied to assess the risk of knee replacement. Analyses were performed on a compartmental and knee level.

Results: Participants had a mean age ± standard deviation of 64.2 years ± 8.4 (range, 47–82 years) and were predominantly women (232 of 398 participants, 58.3%). Risk for knee replacement was significantly increased for knees that exhibited two or more subregions with severe cartilage loss (odds ratio [OR], 16.5; 95% confidence interval [CI]: 3.96, 68.76), more than two subregions with bone marrow lesions (OR, 4.00; 95% CI: 1.75, 9.16), medial meniscal maceration (OR, 1.84; 95% CI: 1.13, 2.99), effusion (OR, 4.75; 95% CI: 2.55, 8.85), or synovitis (OR, 2.17; 95% CI: 1.33, 3.56), but not extrusion (OR, 1.00; 95% CI: 0.60,1.67), when compared with knees that did not exhibit these features as the reference standard.

Conclusion: Apart from meniscal extrusion, all features of tissue abnormalities at MR imaging were related to clinical prognosis and could be used to predict knee replacement in the following year.

Online supplemental material is available for this article.

[1] From the Quantitative Imaging Center, Department of Radiology, Boston University School of Medicine, FGH Building, 3rd Floor, 820 Harrison Ave, Boston, MA 02118 (F.W.R., A.G.); Department of Radiology, University of Erlangen-Nuremberg, Erlangen, Germany (F.W.R.); University of Arizona Arthritis Center & University of Arizona College of Medicine, Tucson, Ariz (C.K.K.); Division of Rheumatology and Clinical Immunology, University of Pittsburgh School of Medicine, Pittsburgh, Pa (M.J.H., Z.W.); Department of Rheumatology, Royal North Shore Hospital and Kolling Institute, University of Sydney, St Leonards, NSW, Australia (D.J.H.); Institute of Anatomy, Paracelsus Medical University, Salzburg, Austria (F.E.); Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pa (R.M.B.); Novartis Pharma AG, Basel, Switzerland (M.R.J.); and Department of Epidemiology and Biostatistics, University of California at San Francisco, San Francisco, Calif (M.C.N.). Received April 28, 2014; revision requested June 13; revision received July 27; accepted July 30; final version accepted August 13. A full disclosure of the support for this research appears in the Acknowledgments. **Address correspondence to** F.W.R. (e-mail: *froemer@bu.edu*).

Osteoarthritis (OA) is a complex, heterogeneous condition that is the most common cause of disability in the aging population (1). The hallmarks of the pathophysiology of OA are the breakdown of cartilage and associated changes in adjacent soft tissue and subchondral bone that lead to debilitating joint symptoms, including pain and disability, accompanied by structural deformity (1). Not surprisingly, prognosis of disease progression on an individual level is complex.

Rates of knee replacement have more than doubled in the United States from 1999 to 2008 (2). In the absence of disease-modifying OA drugs, further increase in total knee replacement volume is projected to continue into the future, owing to an aging population, the obesity epidemic, the growing prevalence of sports-related knee injuries, expanded indications for knee replacement, and other factors (3,4). Preoperative decision making is a complex process for both clinician and patient, taking into account structural radiographic disease severity, preoperative symptoms, obesity, age, and sex, in addition to other factors, such as patient willingness, comorbidities, and socioeconomic status (5–8). Despite the large numbers of knee replacements undertaken, to our knowledge, there is no clear consensus on indications or appropriateness criteria for surgery (9).

So far, imaging markers have been used as indirect surrogate measures of disease status and activity with variable plausibility and success (10,11). While radiography only depicts osseous tissue alterations and only in advanced stages of the disease, magnetic resonance (MR) imaging provides insights concerning all involved joint tissues that are clinically relevant and associated with pain, such as bone marrow alterations, synovitis, effusion, periarticular cystic lesions, and meniscal tears (12–14).

Since joint preservation represents the ultimate clinical goal of any therapeutic attempt, imaging biomarkers that allow prediction of joint replacement may serve as prognostic markers, may aid in the decision-making process for surgery, and may eventually replace radiographic joint space assessment in disease modification trials as an intervention effectiveness marker (14,15).

The purpose of our study was therefore to find out whether the presence and/or severity of MR imaging–based measures of structural joint tissue damage, including cartilage, subchondral bone, menisci, and synovium, differ between knees undergoing joint replacement in the following year and matched control knees not undergoing joint replacement.

Advances in Knowledge

- In a matched case-control design, participants who underwent knee replacement exhibited MR imaging findings of joint abnormalities to a much higher degree than control subjects, including cartilage damage, subchondral bone alterations, meniscal abnormalities, and inflammatory manifestations of disease.
- MR images that demonstrate structural damage can allow prediction of whether a patient is likely to undergo joint replacement, compared with images that do not exhibit these structural changes or exhibit them to a lesser degree.

Implications for Patient Care

- Since the indications for joint replacement are not uniform and are commonly based on clinical and radiographic disease manifestations, MR imaging may potentially help in the decision-making process for joint replacement in a symptomatic, treatment-refractory patient.
- If images have negative findings with regard to relevant predictors, further optimization of symptomatic therapy might yield at least a delay of knee replacement, as clinical improvement might still potentially be possible.

Materials and Methods

The image assessments and statistical analyses were partially funded by Novartis.

The Osteoarthritis Initiative

The Osteoarthritis Initiative (OAI) is an ongoing longitudinal cohort study designed to identify biomarkers of the onset and/or progression of knee OA. Both knees of 4796 participants were studied by using 3-T MR imaging and fixed-flexion radiography at baseline and at 1, 2, 3, 4, and 5 years of follow-up (16). OAI participants were 45–79 years of age at baseline, with symptomatic knee OA in at least one knee or risk of developing symptomatic knee OA. General exclusion criteria were presence of rheumatoid or other inflammatory arthritis, bilateral end-stage knee OA, inability to walk without aids, and MR imaging

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Abbreviations:
BML = bone marrow lesion
CI = confidence interval
OA = osteoarthritis
OAI = Osteoarthritis Initiative
OR = odds ratio

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Conflicts of interest are listed at the end of this article.

contraindications. Patients were recruited at four clinical sites in the United States. The institutional review boards at each of the sites approved the study, and all participants gave informed consent.

Case and Control Knee Selection

OAI participants were interviewed yearly and asked about knee replacement in the preceding 12 months. For the current analysis, case knees were selected if *(a)* a knee replacement was reported after baseline and up to the 5-year follow-up visit, which was confirmed with radiography and/or review of medical records; *(b)* central radiographic readings were available; and *(c)* MR imaging measurements were available at the time point prior to the visit where knee replacement was reported.

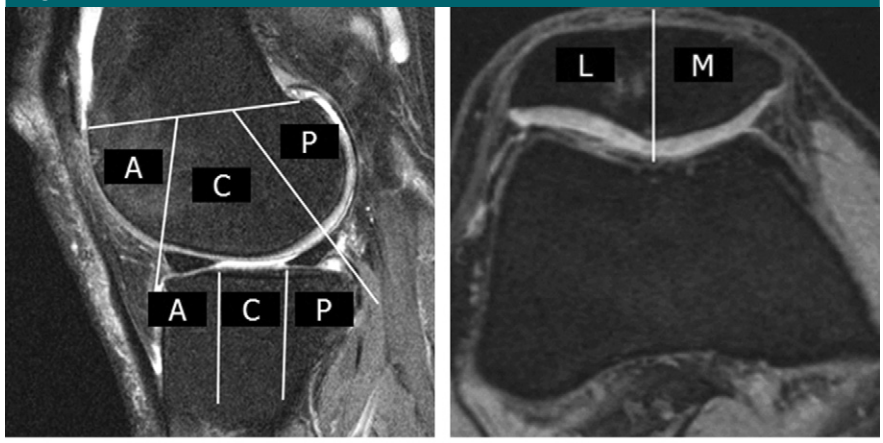
Control knees were matched to case knees from all available OAI participants on a 1:1 basis, according to the same sex, age within 5 years, and same radiographic disease stage at study enrollment (ie, radiographic disease status assessed by using the Kellgren-Lawrence grading system, stratified as grades 0, 1, 2, 3, and 4) (10). The Kellgren-Lawrence grade was determined by means of central readings (OAI public data sets release version 0.4) of baseline serial fixed-flexion knee radiographs. The same time points were used for both control knees and matched knee-replacement knees.

Physical activity levels were measured by using the Physical Activity Scale for the Elderly, and clinical symptoms were assessed with the Western Ontario and McMaster Universities Arthritis questionnaire at MR imaging at the time point prior to the visit where knee replacement was reported (17,18).

MR Imaging Acquisition

MR imaging of both knees was performed with 3-T systems (Trio; Siemens, Erlangen, Germany) at the four OAI clinical sites. MR images were acquired with a dedicated quadrature transmit-receive knee coil by using a coronal intermediate-weighted two-dimensional turbo spin-echo sequence (section thickness of 3.0 mm with no gap; repetition time msec/cho time msec, 3700/29; 180° flip angle; 140-mm field of view; 384 × 307-pixel matrix; echo train length of seven; number of sections acquired, 35; 352-Hz/pixel bandwidth; and one signal acquired), a sagittal three-dimensional dual-echo at steady state sequence (section thickness of 0.7 mm with no gap; 16.3/4.7; 25° flip angle, 140-mm field of view; 384 × 307-pixel matrix; echo train length of one; number of sections acquired, 35; 185-Hz/pixel bandwidth; and one signal acquired), coronal and axial multiplanar reformations of the three-dimensional dual-echo at steady state sequence, and a sagittal intermediate-weighted fat-saturated fast spin-echo sequence (section thickness of 3 mm with no gap, 30/3200, 180° flip angle, 160-mm field of view, 313 × 448-pixel matrix, echo train length of five, 37 sections acquired, 248 Hz/pixel bandwidth, and one signal acquired). Additionally, sagittal T2 mapping (multiecho spin-echo) and coronal three-dimensional T1-weighted fast low-angle shot imaging with water excitation sequences were performed, but these images were not used for assessment. Additional parameters of the full OAI pulse sequence protocol and the sequence parameters have been published in detail (16).

Figure 1



a. b.

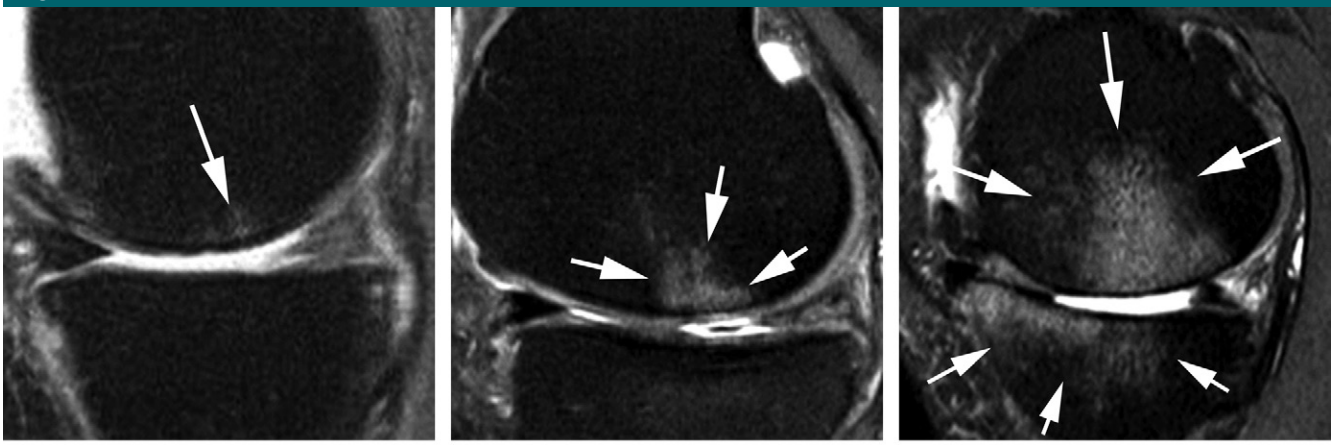
Figure 1: MR images demonstrate subregional joint division by using the MRI Osteoarthritis Knee Score, or MOAKS. **(a)** Sagittal MR image demonstrates the anatomic delineation of the femur into the anterior *(A),* central *(C),* and posterior *(P)* subregions. The tibia is subdivided into anterior, central, and posterior subregions, which are separated by equal thirds. **(b)** Axial proton density–weighted MR image shows the subdivision of the patella into the medial *(M)* and lateral *(L)* facets (ie, subregions). The patella apex is part of the medial subregion.

MR Imaging Assessment

Two musculoskeletal radiologists with 10 (F.W.R.) and 13 (A.G.) years of experience with semiquantitative assessment of knee OA, who were blinded to clinical data and case-control status, interpreted the MR images according to a validated scoring system (19). Each radiologist scored half of the cases that were randomly assigned with regard to case or control status. The following joint structures were assessed: cartilage morphology, subchondral bone marrow lesions (BMLs), meniscal status, meniscal extrusion, synovitis, and effusion. Illustrative examples of the subregional joint division by using the MRI Osteoarthritis Knee Score, or MOAKS, that was used for assessment is presented in Figure 1.

Cartilage was scored in 14 articular subregions (five subregions in the medial and lateral tibiofemoral compartments

Figure 2



a. b. c.

Figure 2: MR images demonstrate BML assessment according to lesion size. **(a)** Sagittal intermediate-weighted fat-saturated MR image shows a small grade 1 subchondral BML in the central subregion of the medial femur (arrow). **(b)** Sagittal MR image demonstrates a grade 2 BML (arrows). **(c)** Sagittal fat-saturated MR image depicts a large grade 3 lesion as diffuse hyperintensity (large arrows). Note the additional diffuse bone marrow changes, also in the anterior and central part of the medial tibia (small arrows).

and four subregions in the patellofemoral compartment), incorporating area size per subregion (scored 0–3) and percentage of subregion that was affected by full-thickness cartilage loss (scored 0–3). Severe cartilage damage was defined as cartilage damage involving 10%–75% of the area of a specific subregion, with 10%–75% of that same subregion affected by full-thickness cartilage damage (ie, grade 2 and higher for both the area of the lesion and the area affected by full-thickness loss).

BMLs were graded 0–3 in the same 14 subregions by taking into account the percentage of a subregion that was affected by BML. The different grades of BML assessment are presented in Figure 2. Meniscal status was scored in the anterior horn, body segment, and posterior horn of the medial and lateral menisci from 0 to 8, taking into account intrameniscal signal intensity changes and different types of meniscal tears and meniscal maceration—that is, substance loss. Signal intensity alterations in the intercondylar region of the Hoffa fat pad were scored from 0 to 3 as a surrogate for synovial thickening, termed *Hoffa synovitis*. Joint effusion (also called effusion synovitis, as it is not possible to discern joint fluid from synovial thickening on MR images) was graded from 0 to 3 in terms of the estimated maximal distention of the synovial cavity.

One radiologist (F.W.R.) rescored 20 randomly chosen MR imaging examinations in random order for the same features after a 4-week interval to determine intrareader reliability. Interobserver reliability between the two readers was assessed by using the same 20 cases.

Statistical Analysis

Analyses were performed on a compartmental (medial tibiofemoral, lateral tibiofemoral, patellofemoral) and whole-knee level. Conditional logistic regression was used to assess the risk of knee replacement related to several structural parameters at the time point prior to the visit of reported knee replacement: *(a)* Maximum grade of cartilage damage per compartment and knee and number of subregions affected by severe cartilage in knees were assessed by using knees with no subregions or one subregion affected as the reference. *(b)* Number of subregions affected by any BML was assessed by using compartments and knees, with no subregions or one subregion affected as the reference, and maximum BML grade per knee was evaluated by using knees with a maximum grade of 0 in all subregions as a reference. *(c)* Meniscal damage was stratified into grades 0 and 1 (reference), grades 2–5 (tears), and grades 6–8 (maceration and/or substance loss). The maximum grade for the medial and lateral compartment, the number of subregions affected in the compartment, and the presence of meniscal extrusion in the coronal plane were assessed as risk factors. *(d)* Hoffa synovitis and effusion synovitis were evaluated by using knees with grade 0 as the reference. Odds ratios (ORs) were calculated separately for each level of the stratifications outlined earlier.

Additionally, to test for trends, the models were run with structural predictors used as linear variables. Because some features were tested up to three ways in the same compartment and/or knee, we considered a two-tailed Bonferroni P value of less than .017 to indicate a significant difference. Weighted κ statistics were applied to determine inter- and intraobserver reliability. Paired t tests were applied to assess differences in Western Ontario and McMaster Universities Arthritis questionnaire scores and Physical Activity Scale for the Elderly scores between cases and controls at the time point prior to the

visit where knee replacement was reported. All statistical calculations were performed by using Stata/IC software version 11.2 for Windows (StataCorp, College Station, Tex).

Results

Altogether, 398 knees were included. Participants had a mean age ± standard deviation of 64.2 years ± 8.4 and were predominantly women (232 of 398, 58.3%) and were predominantly overweight (mean body mass index, 29.6 ± 4.8). The baseline Kellgren-Lawrence grades for the matched pairs were 17 knee pairs of grade 0 or 1, 39 knee pairs of grade 2, 75 knee pairs of grade 3, and 68 knee pairs of grade 4. The case-defining visit of reported knee replacement was 12 months for 26 knees (13.1%), 24 months for 34 knees (17.1%), 36 months for 49 knees (24.6%), 48 months for 39 knees (19.6%), and 60 months for 51 knees (25.6%). Most patients underwent total knee arthroplasty (n = 191, 96%). Of those with a partial knee replacement, seven participants underwent partial medial replacements, and one participant underwent patellofemoral replacement.

With regard to total Western Ontario and McMaster Universities Arthritis questionnaire scores, cases differed significantly from controls (33.5 ± 17.0 vs 18.8 ± 16.0, $P < .001$). The same was found for Physical Activity Scale for the Elderly scores (10.8 ± 72.7 vs 144.9 ± 72.4, $P < .001$). Oral medication of chondroitin sulfate was taken by 44% of the subjects (n = 175), and glucosamine was taken by 41% (n = 163), while 8% (n = 32) received a hyaluronic acid 14% steroid injection (51 cases and five controls, $P < .0001$). All of these were more common in cases compared with controls and were significant for all but chondroitin sulfate.

Summarizing the intra- and interobserver reliability results, all of the measures showed at least substantial agreement (20). Table E1 (online) gives a detailed overview of the reliability results.

Table 1

Knee Replacement Risk with Regard to Presence and Severity of Prevalent Cartilage Damage (Area Extent) at the Time Point Prior to the Visit Where Knee Replacement Was Reported

Risk Factor and Grade	No. of Cases (n = 199)	No. of Controls (n = 199)	Risk for Total Knee Replacement	
			Crude OR*	P Value
Maximum grade for area extent of cartilage damage in the medial tibiofemoral joint†				
0	25 (12.6)	38 (19.1)	Reference	…
1	4 (2.0)	7 (3.5)	1.11 (0.29, 4.27)	.89
2	67 (33.7)	86 (43.2)	1.37 (0.75, 2.53)	.31
3	103 (51.8)	68 (34.2)	3.01 (1.52, 5.95)	.002‡
Maximum grade for area extent of cartilage damage in the lateral tibiofemoral joint§				
0	61 (30.6)	79 (39.7)	Reference	…
1	11 (5.5)	11 (5.5)	1.41 (0.55, 3.60)	.48
2	83 (41.7)	73 (66.7)	1.58 (0.96, 2.61)	.07
3	44 (22.1)	36 (18.1)	1.69 (0.94, 3.02)	.08
Maximum grade for area extent of cartilage damage in the patellofemoral joint‖				
0	12 (6.0)	22 (11.0)	Reference (0–1 combined)	…
1	2 (1.0)	4 (2.0)	Reference (0–1 combined)	…
2	122 (61.3)	118 (59.3)	1.87 (0.95, 3.68)	.07
3	62 (31.2)	55 (27.6)	2.22 (1.02, 4.83)	.04‡
Maximum grade for area extent of cartilage damage in the whole knee				
0	0 (0.0)	3 (1.5)	Reference (0–2 combined)	…
1	0 (0.0)	2 (1.0)	Reference (0–2 combined)	…
2	27 (13.6)	64 (32.2)	Reference (0–2 combined)	…
3	172 (86.4)	130 (65.3)	4.00 (2.23, 7.18)	<.001‡

Note.—Numbers in parentheses are percentages, unless indicated otherwise. "Reference" indicates the reference group to which the other groups were compared with regard to risk. Per definition, the risk for the reference group is 1.0.

* Numbers in parentheses are 95% CIs.

† P for trend = .001.

‡ $P < .017$ was considered to indicate a significant difference.

§ P for trend = .047.

‖ P for trend = .045.

With regard to prevalent cartilage damage at the time point prior to the visit where knee replacement was reported, knees with a maximum area involvement of more than 75% of a subregion affected (ie, grade 3) and/or more than 75% of a subregion affected by full-thickness damage (ie, grade 3) in the whole knee had increased odds for knee replacement compared with knees with a maximum grade of 0, 1, or 2 (OR of 4.00 and 95% confidence interval [CI]: 2.23, 7.18; OR of 3.45 and 95% CI: 2.15, 5.55, respectively). In addition, knees with two or more subregions affected by severe cartilage loss had a markedly increased risk for knee replacement when compared with the ones without (OR, 16.5; 95% CI: 3.96, 68.76). The detailed cartilage results, including the compartmental analyses for maximum grades, are presented in Tables 1–3.

Table 2

Knee Replacement Risk with Regard to Presence and Severity of Prevalent Cartilage Damage (Full-Thickness Damage) at the Time Point Prior to the Visit Where Knee Replacement Was Reported

Risk Factor and Grade	No. of Cases (n = 199)	No. of Controls (n = 199)	Risk for Total Knee Replacement	
			Crude OR*	P Value
Maximum grade for full-thickness damage in the medial tibiofemoral joint†				
0	64 (32.2)	82 (41.2)	Reference	…
0.1	5 (2.5)	15 (7.5)	0.41 (0.13, 1.29)	.13
0.2	79 (39.7)	84 (42.2)	1.49 (0.86, 2.58)	.15
0.3	51 (25.6)	18 (9.0)	5.79 (2.56, 13.05)	<.001‡
Maximum grade for full-thickness damage in the lateral tibiofemoral joint§				
0	117 (58.8)	109 (54.8)	Reference	…
0.1	15 (7.5)	18 (9.1)	0.79 (0.39, 1.61)	.52
0.2	41 (20.6)	53 (26.6)	0.73 (0.46, 1.18)	.20
0.3	26 (13.1)	19 (9.6)	1.34 (0.67, 2.69)	.41
Maximum grade for full-thickness damage in the patellofemoral joint‖				
0	80 (40.2)	92 (46.2)	Reference	…
0.1	5 (2.5)	14 (7.0)	0.48 (0.17, 1.38)	.17
0.2	78 (39.2)	75 (37.7)	1.33 (0.80, 2.21)	.27
0.3	35 (17.6)	18 (9.1)	2.39 (1.21, 4.71)	.01‡
Maximum grade for full-thickness damage in the whole knee†				
0	1 (0.5)	17 (8.5)	Reference (0–0.2 combined)	…
0.1	1 (0.5)	8 (4.0)	Reference (0–0.2 combined)	…
0.2	91 (45.7)	122 (61.3)	Reference (0–0.2 combined)	…
0.3	106 (53.3)	52 (26.1)	3.45 (2.15, 5.55)	<.001‡

Note.—Numbers in parentheses are percentages, unless indicated otherwise. "Reference" indicates the reference group to which the other groups were compared with regard to risk. Per definition, the risk for the reference group is 1.0.

* Numbers in parentheses are 95% CIs.

† P for trend < .001.

‡ P < .017 was considered to indicate a significant difference.

§ P for trend = .782.

‖ P for trend = .019.

Knees with two or more subregions affected by subchondral BMLs at the time point prior to the visit of reported knee replacement had an increased risk for knee replacement compared with knees that had no or only one subregion affected (OR, 4.00; 95% CI: 1.75, 9.16). An increasing risk for knee replacement was observed for increasing numbers of subregions involved in the medial tibiofemoral compartment (P for trend = .001) but not the lateral (P for trend = .173) or the patellofemoral (P for trend = .875) compartment. A maximum BML grade of 3 (ie, more than 66% of subregional involvement) in any of the 14 subregions also increased risk for knee replacement (OR, 5.53; 95% CI: 1.13, 27.06). Table 4 gives a detailed summary of the BML results.

Presence of maceration in the medial compartment (OR, 1.84; 95% CI: 1.16, 2.92) led to an increased risk for knee replacement compared with compartments or knees with grade 0 or 1 meniscal damage as the reference, and knees with one or more subregions affected by any meniscal damage (grades 2–8) in the medial compartment had an increased risk for knee replacement compared with knees without (OR, 1.63; 95% CI: 1.04, 2.57), as shown in Table 5.

As presented in Table 6, knees with any Hoffa synovitis or effusion synovitis at the time point prior to the visit of reported knee replacement exhibited a markedly increased risk for knee replacement compared with knees without Hoffa synovitis or effusion synovitis (OR of 2.17 and 95% CI: 1.33, 3.56; OR of 4.75 and 95% CI: 2.55, 8.85, respectively).

Discussion

This is the first study, to our knowledge, in which a matched case-control design was used to describe several structural predictors of knee

Table 3

Knee Replacement Risk with Regard to Presence and Severity of Prevalent Cartilage Damage (Number of Subregions Affected) at the Time Point Prior to the Visit Where Knee Replacement Was Reported

No. of Subregions Affected by Severe Cartilage Damage (≥2.2) in the Whole Knee	No. of Cases (n = 199)	No. of Controls (n = 199)	Risk for Total Knee Replacement	
			Crude OR*	P Value†
0 or 1	7 (3.5)	38 (19.1)	Reference	…
2	16 (8.0)	35 (17.6)	5.72 (1.22, 26.8)	.03
3	37 (18.6)	43 (21.6)	11.26 (2.52, 50.4)	.002‡
4	56 (28.1)	36 (18.1)	19.94 (4.45, 89.29)	<.001‡
5	45 (22.6)	23 (11.6)	27.70 (5.94, 129.30)	<.001‡
6	24 (12.1)	12 (6.0)	26.89 (5.37, 134.62)	<.001‡
7 or more	14 (7.0)	12 (6.0)	17.94 (3.34, 96.25)	<.001‡
≥2 (vs 0 or 1 as reference)	192 (96.5)	161 (80.9)	16.5 (3.96, 68.76)	<.001‡

Note.—Numbers in parentheses are percentages, unless indicated otherwise. "Reference" indicates the reference group to which the other groups were compared with regard to risk. Per definition, the risk for the reference group is 1.0.

* Numbers in parentheses are 95% CIs.

† P for trend < .001.

‡ P < .017 was considered to indicate a significant difference.

replacement 1 year later. We found that knees that exhibited multiple subregions with severe cartilage loss and with severe superficial or full-thickness cartilage damage are at increased risk for knee replacement in the subsequent year. Further, knees with three or more subregions affected by BMLs and with large BMLs had an increased risk for knee replacement. Finally, knees with medial meniscal maceration and any medial meniscal damage, as well as knees that exhibit any joint effusion synovitis or Hoffa synovitis, have a worse prognosis than knees without these features.

Our study was nested within the large OAI cohort, with participants being examined on a yearly basis over a 60-month period, which included MR imaging. This allowed a 1:1 matched case-control design with regard to patient sex, age, and radiographic disease status, which was paramount to ensure maximum comparability between cases and controls, as previous investigators had reported that knees with advanced radiographic disease have a higher likelihood for knee replacement (21,22). Of note is the fact that cases differed significantly from controls with regard to symptoms and physical activity at the time point prior to the visit where knee replacement was reported. Since knee replacement is primarily an intervention performed to alleviate symptoms, we expected to find higher levels of pain and disability in the subgroup undergoing knee replacement during the following year (5,6).

We acknowledge that we were not able to compare the MR imaging findings with a reference standard, such as arthroscopy or histologic findings. In comparison, arthroscopy demonstrates only the articular surface and does not allow evaluation of other important tissues, such as the subchondral bone, and it is not feasible to invasively assess knee joints in an observational study over several time points. By using a similar case-control design but a quantitative MR imaging approach that allows assessment of different cartilage metrics, we have recently shown that cartilage thickness in the central medial tibiofemoral compartment is diminished in knees undergoing knee replacement compared with those that do not (15).

The discordance between symptoms and structural damage in OA has long remained enigmatic, although more recent data have shown that there seems to be a stronger association than previously thought, a conclusion also reflected in our data (23,24). Our study is the first, to our knowledge, to show that participants undergoing knee replacement not only experience higher levels of symptoms and reduced physical activity but also exhibit more frequently relevant structural damage that leads to an increased risk of knee replacement, even after adjusting for radiographic structural disease stage. It has been shown that BMLs, meniscal damage, synovitis, and effusion are associated with pain and are therefore potentially responsible for differences in pain levels between the two groups (12).

We applied a validated scoring system that was developed on the basis of long-standing experience with other semiquantitative scoring instruments to assess structural joint damage in OA (19). The readers were highly experienced in MR imaging assessment, and the reliability of the readings was excellent.

BMLs are a strong predictor of cartilage loss in OA, and both subregional BML load and maximum grade play an important role in predicting knee replacement (25–27). Meniscal damage,

a common, albeit often asymptomatic finding in the general population, seems to play an important role in disease progression and, ultimately, outcome—defined as knee replacement (28). The finding that presence of knee effusions and synovitis markedly increase risk for subsequent knee replacement is noteworthy and stresses the importance of inflammation in advanced disease with regard to clinical outcomes (29). Whether aggressive treatment of inflammation reduces the risk for knee replacement will have to be shown in subsequent randomized studies. We acknowledge that assessment of Hoffa signal intensity changes as a surrogate for synovitis is an inferior measure when compared with contrast material–enhanced imaging, especially owing to its nonspecificity (30,31).

Knee OA is a major public health concern, with a lifetime risk of primary total knee replacement of 7.0% for men and 9.5% for women, as estimated in a recent report (32). More than half of the adults in the United States who receive a diagnosis of symptomatic knee OA will potentially undergo a total knee replacement during their life (32). The ultimate goal in any interventional approaches must be a reduction of these numbers in light of aging populations. We believe the presented data may be clinically relevant in the following three aspects.

The presence of identified MR imaging risk features in a symptomatic, treatment-refractory patient may help in the decision-making process about whether a knee replacement should be performed. If negative with regard to relevant predictors, further optimization of symptomatic therapy might yield at least a delay of knee replacement. Since the identified imaging parameters appear to correlate with increased risk for knee replacement, it seems logical to direct efforts to identify new structure-modifying drugs toward mechanisms that aim to prevent or heal the underlying abnormalities of the observed imaging tissue markers. Finally, on the basis of the data presented, additional

Table 4

Knee Replacement Risk with Regard to Presence and Severity of BMLs at the Time Point Prior to the Visit Where Knee Replacement Was Reported

Risk Factor and No. of Subregions or Grade	No. of Cases (n = 199)	No. of Controls (n = 199)	Risk for Total Knee Replacement	
			Crude OR*	P Value
No. of subregions with any BML (≥1) in the medial tibiofemoral joint†				
0	48 (24.1)	65 (32.7)	Reference	…
1	24 (12.1)	42 (21.1)	0.81 (0.42, 1.55)	.52
2	31 (15.6)	29 (14.6)	1.66 (0.86, 3.21)	.13
3	37 (18.6)	26 (13.1)	2.42 (1.19, 4.91)	.02
4	42 (21.1)	24 (12.1)	2.98 (1.45, 6.10)	.003‡
5	16 (8.0)	13 (6.5)	1.95 (0.84, 4.55)	.12
No. of subregions with any BML (≥1) in the lateral tibiofemoral joint§				
0	105 (52.8)	127 (63.8)	Reference	…
1	42 (21.1)	26 (13.1)	2.17 (1.19, 3.94)	.01‡
2	16 (8.0)	15 (7.5)	1.28 (0.59, 2.76)	.54
3	13 (6.5)	13 (6.5)	1.27 (0.56, 2.88)	.57
4	9 (4.5)	12 (6.0)	0.94 (0.36, 2.45)	.89
5	12 (6.0)	6 (3.0)	2.65 (0.89, 7.90)	.08
No. of subregions with any BML (≥1) in the patellofemoral joint‖				
0	80 (40.4)	79 (39.7)	Reference	…
1	45 (22.7)	52 (26.1)	0.87 (0.52, 1.48)	.62
2	56 (28.3)	44 (22.1)	1.24 (0.73, 2.11)	.43
3 or 4	17 (8.6)	24 (12.1)	0.75 (0.37, 1.51)	.42
No. of subregions with any BML (≥1) in the whole knee#				
0 or 1	8 (4.0)	29 (14.6)	Reference	…
2	13 (6.5)	35 (17.6)	1.37 (0.51, 3.68)	.53
3	40 (20.1)	36 (18.1)	9.04 (2.89, 28.27)	<.001‡
4	57 (28.6)	34 (17.1)	12.97 (4.22, 39.86)	<.001‡
5	29 (14.6)	26 (13.1)	8.25 (2.60, 26.14)	<.001‡
6	31 (15.6)	22 (11.0)	10.87 (3.37, 35.04)	<.001‡
7	12 (6.0)	11 (5.5)	6.84 (1.83, 25.54)	<.004‡
≥8	8 (4.0)	6 (3.0)	7.61 (1.73, 33.54)	<.007‡
≥2 (vs reference)	190 (47.7)	170 (42.7)	4.00 (1.75, 9.16)	.001‡
Maximum-grade BML (of 14 subregions) in the whole knee#				
0	2 (1.0)	8 (4.0)	Reference	…
1	25 (12.6)	48 (24.1)	1.79 (0.35, 9.30)	.48
2	72 (36.2)	76 (38.2)	3.56 (0.73, 17.36)	.12
3	99 (49.7)	67 (33.7)	5.53 (1.13, 27.06)	.04
≥1 (vs reference)	196 (49.2)	199 (50.0)	4.00 (0.85, 18.84)	.08

Note.—Numbers in parentheses are percentages, unless indicated otherwise. "Reference" indicates the reference group to which the other groups were compared with regard to risk. Per definition, the risk for the reference group is 1.0.

* Numbers in parentheses are 95% CIs.

† P for trend = .001.

‡ $P < .017$ was considered to indicate a significant difference.

§ P for trend = .173.

‖ P for trend = .875.

P for trend < .001.

Table 5

Knee Replacement Risk with Regard to Presence and Severity of Meniscal Damage and Extrusion at the Time Point Prior to the Visit Where Knee Replacement Was Reported

	Medial				Lateral			
			Risk for Total Knee Replacement				Risk for Total Knee Replacement	
Risk Factor and Grade	No. of Cases (n = 199)	No. of Controls (n = 199)	Crude OR*	P Value	No. of Cases (n = 199)	No. of Controls (n = 199)	Crude OR*	P Value
Anterior horn†								
0 and 1	173 (86.9)	180 (90.4)	Reference	…	158 (79.4)	163 (81.9)	Reference	…
2–5 (tear)	6 (3.0)	4 (2.0)	1.50 (0.42, 5.32)	.53	7 (3.5)	10 (5.0)	0.67 (0.22, 2.06)	.48
6–8 (maceration)	20 (10.0)	15 (7.5)	1.42 (0.68, 2.97)	.36	33 (16.6)	26 (13.1)	1.33 (0.73, 2.42)	.34
Body‡								
0 and 1	97 (48.7)	120 (60.3)	Reference	…	152 (76.4)	156 (78.4)	Reference	…
2–5 (tear)	6 (3.0)	7 (3.5)	1.13 (0.37, 3.48)	.83	11 (5.5)	13 (6.5)	0.89 (0.39, 2.00)	.77
6–8 (maceration)	96 (48.2)	72 (36.2)	1.84 (1.16, 2.92)	.01§	36 (18.1)	30 (15.1)	1.26 (0.72, 2.21)	.43
Posterior horn‖								
0 and 1	83 (41.7)	95 (47.7)	Reference	…	155 (77.9)	158 (79.4)	Reference	…
2–5 (tear)	40 (20.1)	42 (21.1)	1.11 (0.64, 1.91)	.71	17 (8.5)	11 (5.5)	1.62 (0.69, 3.78)	.27
6–8 (maceration)	76 (38.2)	62 (31.2)	1.59 (0.94, 2.70)	.08	26 (13.1)	30 (15.1)	0.91 (0.51, 1.64)	.77
No. of subregions affected by tear and/or maceration#								
None	69 (34.7)	88 (44.2)	Reference	…	137 (68.8)	140 (70.4)	Reference	…
One of three subregions affected (grade 2–8)	38 (19.1)	39 (19.6)	1.30 (0.73, 2.32)	.37	16 (8.0)	20 (10.0)	0.84 (0.43, 1.63)	.60
Two of three subregions (grade 2–8)	70 (35.2)	53 (26.6)	1.89 (1.12, 3.20)	.02	24 (12.1)	17 (8.5)	1.51 (74, 3.06)	.25
Three of three subregions (grade 2–8)	22 (11.0)	19 (9.5)	1.87 (0.86, 4.05)	.11	22 (11.0)	22 (11.1)	1.02 (0.50, 2.11)	.95
≥1 subregion versus no subregion affected as reference	130 (65.3)	111 (55.8)	1.63 (1.04, 2.57)	.03	62 (31.2)	59 (29.6)	1.08 (0.69, 1.68)	.74
Maximum grade in any of three locations**								
0 and 1	69 (34.7)	88 (44.2)	Reference	…	137 (68.8)	140 (70.4)	Reference	…
2–5 (tear)	23 (11.6)	27 (13.6)	1.15 (0.59, 2.24)	.69	14 (7.0)	14 (7.0)	1.03 (0.48, 2.20)	.94
6–8 (maceration	107 (53.8)	84 (42.2)	1.84 (1.13, 2.99)	.01§	48 (24.1)	45 (22.6)	1.10 (0.68, 1.77)	.71
Meniscal extrusion								
No meniscal extrusion and extrusion < 5 mm	163 (81.9)	162 (81.4)	Reference	…	186 (93.5)	189 (95.0)	Reference	…
Mensical extrusion ≥ 5 mm	72 (36.2)	36 (18.1)	1.00 (0.60, 1.67)	>.99	12 (6.0)	9 (4.5)	1.42 (0.54, 3.75)	.47

Note.—Numbers in parentheses are percentages, unless indicated otherwise. "Reference" indicates the reference group to which the other groups were compared with regard to risk. Per definition, the risk for the reference group is 1.0.

* Numbers in parentheses are 95% CIs.

† Medial P for trend = .288; lateral P for trend = .415.

‡ Medial P for trend = .01; lateral P for trend = .484.

§ $P < .017$ was considered to indicate a significant difference.

‖ Medial P for trend = .093; lateral P for trend = .883.

Medial P for trend = .022; lateral P for trend = .602.

** Medial P for trend = .014; lateral P for trend = .714.

Table 6

Knee Replacement Risk with Regard to Presence and Severity of Hoffa Synovitis and Effusion Synovitis at the Time Point Prior to the Visit Where Knee Replacement Was Reported

Risk Factor and Grade	No. of Cases ($n = 199$)	No. of Controls ($n = 199$)	Risk for Total Knee Replacement	
			Crude OR*	*P* Value
Hoffa synovitis†				
0	31 (15.6)	58 (29.1)	Reference	…
1	95 (47.7)	103 (51.8)	1.68 (1.00, 2.82)	.05
2	68 (34.2)	35 (17.6)	4.08 (2.12, 7.83)	<.001‡
3	5 (2.5)	3 (1.5)	4.25 (0.90, 20.15)	.07
Any (1–3)	168 (84.4)	141 (70.8)	2.17 (1.33, 3.56)	.002‡
Effusion synovitis†				
0	25 (12.6)	70 (35.2)	Reference	…
1	45 (22.6)	60 (30.2)	2.42 (1.18, 8.85)	.02
2	77 (38.7)	46 (23.1)	5.78 (2.86, 11.69)	<.001‡
3	52 (26.1)	23 (11.6)	7.80 (3.56, 17.1)	<.001‡
Any (1–3)	174 (87.4)	129 (64.8)	4.75 (2.55, 8.85)	<.001‡

Note.—Numbers in parentheses are percentages, unless indicated otherwise. "Reference" indicates the reference group to which the other groups were compared with regard to risk. Per definition, the risk for the reference group is 1.0.

* Numbers in parentheses are 95% CIs.

† *P* for trend < .001.

‡ $P < .017$ was considered to indicate a significant difference.

studies are warranted that potentially permit identification of predictors at much earlier time points to initiate intervention strategies before irreversible damage has occurred. Our identified population of patients undergoing knee replacement was unlikely to have benefited from a pharmacologic structure-modifying intervention at the time point examined, as the structural damage appeared to be advanced.

To summarize our findings, we demonstrated that knees that exhibited multiple subregions with severe cartilage damage, multiple subregions with bone marrow lesions, medial meniscal damage, and synovitis and effusion were at increased risk for knee replacement compared with matched knees that did not exhibit these features.

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