Hand Joint Space Narrowing and Osteophytes Are Associated with Magnetic Resonance Imaging-defined Knee Cartilage Thickness and Radiographic Knee Osteoarthritis: Data from the Osteoarthritis Initiative

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ABSTRACT. ***Objective.*** To evaluate whether features of radiographic hand osteoarthritis (OA) are associated with quantitative magnetic resonance imaging (MRI)-defined knee cartilage thickness, radiographic knee OA, and 1-year structural progression.

Methods. A total of 765 participants in Osteoarthritis Initiative (OAI; 455 women, mean age 62.5 yrs, SD 9.4) obtained hand radiographs (at baseline), knee radiographs (baseline and Year 1), and knee MRI (baseline and Year 1). Hand radiographs were scored for presence of osteophytes and joint space narrowing (JSN). Knee radiographs were scored according to the Kellgren-Lawrence (KL) scale. Cartilage thickness in the medial and lateral femorotibial compartments was measured quantitatively from coronal FLASHwe images. We examined the cross-sectional and longitudinal associations between features of hand OA (total osteophyte and JSN scores) and knee cartilage thickness, 1-year knee cartilage thinning (above smallest detectable change), presence of knee OA (KL grade ≥ 3), and progression of knee OA (KL change ≥ 1) by linear and logistic regression. Both hand OA features were included in a multivariate model (if $p \leq 0.25$) adjusted for age, sex, and body mass index (BMI).

Results. Hand JSN was associated with reduced knee cartilage thickness (ß = –0.02, 95% CI –0.03, –0.01) in the medial femorotibial compartment, while hand osteophytes were associated with the presence of radiographic knee OA (OR 1.10, 95% CI 1.03–1.18; multivariate models) with both hand OA features as independent variables adjusted for age, sex, and BMI). Radiographic features of hand OA were not associated with 1-year cartilage thinning or radiographic knee OA progression.

Conclusion. Our results support a systemic OA susceptibility and possibly different mechanisms for osteophyte formation and cartilage thinning. (First Release Nov 1 2011; J Rheumatol 2012;39:161–6; doi:10.3899/jrheum.110603)

Key Indexing Terms:
OSTEOARTHRITIS HAND KNEE CARTILAGE MAGNETIC RESONANCE IMAGING

The Osteoarthritis Initiative (OAI) is a large multicenter prospective observational study of participants with established (symptomatic and radiographic) knee osteoarthritis (OA) or at risk of incident symptomatic knee OA (Website: www.oai.ucsf.edu). The general aim of the OAI study is to identify sensitive biomarkers of knee OA, and characterize risk factors for its onset and progression.

OA is recognized to be a disease affecting the whole joint, including not only the cartilage, but also the subchondral bone, ligaments, synovium/capsule, and menisci if present[1]. OA is therefore a heterogeneous disease with multiple causes. Local factors that alter the specific biomechanical environment of a joint (e.g., meniscal or ligament injury or degeneration) are common risk factors for knee OA[2]. However, OA is

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often generalized and affects multiple joints, the hand being frequently involved[3]. Hand OA is therefore often considered a marker of generalized OA[4,5]. Studies have shown an association between hand and knee OA[6,7,8,9], and to lesser extent with hip[8,9,10] and spine OA[11], supporting the concept of an endogenous OA susceptibility. The presence of hand OA also appeared to increase the risk of knee OA after meniscectomy, suggesting a possible interaction between systemic risk factors (i.e., hand OA) and the local biomechanical environment (i.e., meniscus)[12,13]. Hence, the pathogenesis of knee OA is complex, and the classical distinction between primary and secondary OA is questionable.

No previous studies have explored the association between hand and knee OA using current imaging techniques, and none have assessed the independent role of individual hand OA features. The aims of our study were therefore to investigate (1) whether radiographic features of hand OA such as osteophytes and joint space narrowing (JSN) were associated with decreased knee cartilage thickness observed with quantitative magnetic resonance imaging (qMRI) and/or radiographic knee OA cross-sectionally; and (2) whether hand OA features at baseline could predict 1-year qMRI-defined knee cartilage thinning and/or radiographic knee OA progression.

MATERIALS AND METHODS

Subjects. The OAI is a multicenter prospective observational cohort study, designed to identify biomarkers for incident or progressive knee OA, and includes participants aged between 45 and 79 years and from a diversity of ethnic backgrounds (n = 4796). General criteria for exclusion were rheumatoid arthritis or other inflammatory arthritides, bilateral endstage knee OA, inability to walk without aids, or contraindications for MRI.

We used a subsample of participants (n = 1003) from the progression and incidence cohorts with available knee MRI data from baseline and 1-year followup (0.E.1 and 1.E.1 datasets), as described[14]. Additional inclusion criteria for the current analyses were the availability of Fast Low Angle SHot (FLASH) images of the right or left knee, risk of or established knee OA, and available hand radiographs. In total, 765 participants (455 women) fulfilled these combined criteria and were included for the current analyses.

Our study was conducted in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with the local institutional review board, informed consent regulations, and International Conference on Harmonization Good Clinical Practices Guidelines.

Hand radiographs. Posteroanterior hand radiographs of dominant (n = 467) or both hands (n = 298) were obtained at baseline (n = 760; 0.E.1 dataset) or 1-year followup (n = 5; 1.E.1 dataset). One investigator (IKH) scored the distal and proximal interphalangeal, metacarpophalangeal, and first carpometacarpal joints for osteophytes (grade 0–3) and JSN (grade 0–3) according to the OsteoArthritis Research Society International (OARSI) atlas[15]. The same investigator rescored 30 randomly selected radiographs (60 hands) after 6 weeks, and the intrareader reliability was excellent (intraclass correlation coefficients ≥ 0.90).

When bilateral radiographs were present, the hand with the highest total score for each feature was selected for analyses. For estimation of hand OA severity, we calculated the total scores for osteophytes (range 0–45) and JSN (range 0–45) by summing the values for all 15 joints.

Knee radiographs. Bilateral posteroanterior knee radiographs (SynaFlexer; fixed flexion) were performed at baseline and 1-year followup. Centrally trained radiologists at the clinical sites scored all baseline radiographs according to the OARSI atlas (0.2.2 dataset)[15]. A calculated Kellgren-Lawrence grade (cKLG) was assigned according to a predefined algorithm as described[14].

Two central readers scored 372 paired knee radiographs from baseline and 1 year (0.3 and 1.3 datasets), blinded to chronological order, according to Kellgren-Lawrence[16]. Adjudication of discrepancies was performed if the readers did not agree on the absence/presence of knee OA at either timepoint or knee OA progression. Test-retest reliability was good for cross-sectional and longitudinal readings (kappa ≥ 0.82). These central longitudinal readings were used for analyses on knee OA presence/progression.

Knee MRI. Double oblique coronal 3-D FLASH images with water excitation (slice thickness 1.5 mm, in-plane resolution 0.31 mm) of the right (n = 759) or left knee (n = 6) were available from baseline and 1-year followup (0.E.1 and 1.E.1 datasets)[17]. The MR images were acquired with a 3.0 Tesla system (Siemens Magnetom Trio, Siemens, Erlangen, Germany) using dedicated quadrature transmit-receive knee coils (USA Instruments, Aurora, OH, USA)[17,18].

Seven trained operators at Chondrometrics GmbH (Ainring, Germany) manually segmented the total area of subchondral bone and cartilage surface in the medial and lateral tibiae and in the weight-bearing central part of the medial and lateral femoral condyles from the paired MR images. The segmentation was performed blinded to the order of acquisition and radiographic status[19]. The mean cartilage thickness over the total area of subchondral bone (including denuded areas but excluding osteophytes) was determined. Aggregated values for the medial femorotibial compartment were obtained from medial tibia and central medial femoral condyle and for the lateral femorotibial compartment from lateral tibia and central lateral femoral condyle. The test-retest precision for segmentations of 3.0 Tesla FLASH images has been reported[19].

Statistics. We examined cross-sectional associations between radiographic features of hand OA (i.e., hand osteophytes sum score and hand JSN sum score as predictor variables) and knee cartilage thickness (n = 765) and severe radiographic knee OA (KL grade ≥ 3 in 1 or both knees; n = 372) by linear and logistic regression, respectively.

Logistic regression was used for the associations between baseline hand OA features and knee cartilage thinning (above the smallest detectable change; n = 765) and radiographic knee OA progression (KL grade change ≥ 1 in 1 or 2 knees with baseline KL grade = 2–3; n = 267 at risk). The smallest detectable change of cartilage thinning was 102 μm and 92 μm in the medial and lateral femorotibial compartments, respectively[20].

We performed crude analyses with each hand OA feature in separate models. If both hand OA features were associated with the knee outcome ($p \leq 0.25$) in the crude analyses, both were included in the same multivariate model together with age, sex, and body mass index (BMI). Second, the analyses on qMRI-defined cartilage thickness/thinning were stratified for cKLG status (cKLG = 0–2 vs cKLG = 3–4, because of few participants with cKLG = 0–1). Finally, we also adjusted for risk factors used as selection criteria in the OAI (frequent/infrequent knee pain, frequent pain medication, previous knee injury, previous knee surgery, family history, and repetitive knee bending).

The analyses were performed using SPSS version 17.0, and a p value ≤ 0.05 was considered statistically significant.

RESULTS

The 765 participants (455 women) had a mean age of 62.5 (SD 9.4) years, significantly higher than the remaining 4031 OAI participants, who had a mean age of 60.9 (SD 9.1) years ($p < 0.001$; no significant difference in the proportion of women, $p = 0.54$). The participants had a wide range of radiographic hand OA severity, although the majority had mild disease (Table 1). The number of hand OA features was similar in the right and left hands. Of those with bilateral hand radiographs (n = 298), the median (interquartile range; IQR) JSN

Table 1. Demographic and clinical data for the total sample (n = 765) and the subsample with central reading of knee radiographs (n = 372).

Characteristic	Total Sample, n = 765	Subsample, n = 372
Sex, n (%) female	455 (59.5)	204 (54.8)
Age, mean (SD), yrs	62.5 (9.4)	61.0 (9.5)
Body mass index, mean (SD), kg/m^2	29.6 (4.7)	30.2 (4.7)
Race, n (%) white	649 (84.8)	309 (83.1)
Radiographic hand OA features, median (minimum, maximum)		
Total osteophyte score (range 0–45)	3 (0, 31)	2 (0, 31)
Total JSN score (range 0–45)	8 (0, 30)	8 (0, 30)
Hand OA (≥ 1 OA joint)*, n (%)	596 (77.9)	283 (76.1)
Erosive hand OA (≥ 1 joint with radiographic erosion), n (%)	131 (17.1)	50 (13.4)
Knee OA severity (total sample: cKLG, subsample: KLG)**, n (%)		
0	32 (4.2)	44 (11.8)
1	36 (4.7)	36 (9.7)
2	296 (38.7)	92 (24.7)
3	294 (38.4)	136 (36.6)
4	107 (14.0)	64 (17.2)
Cartilage thickness, mm, in MFTC, median (quartiles)	3.44 (2.98, 3.85)	NA
Cartilage thickness, mm, in LFTC, median (quartiles)	3.77 (3.35, 4.17)	NA
Cartilage thinning above smallest detectable change (102 µm) in MFTC, n (%)	145 (19.0)	NA
Cartilage thinning above smallest detectable change (92 µm) in LFTC, n (%)	133 (7.4)	NA
Radiographic knee OA progression (n = 267 at risk)***, n (%)	NA	36 (13.5)

* OA defined as sum of osteophyte score and JSN score ≥ 2. ** cKLG (calculated Kellgren-Lawrence grade) in the total sample refers to the knee examined by MRI; KLG for the subsample refers to the knee with highest Kellgren-Lawrence score. *** KLG change ≥ 1 in one/2 knees with baseline KLG = 2–3. JSN: joint space narrowing; MFTC: medial femorotibial compartment; LFTC: lateral femorotibial compartment; NA: not applicable; total sample not used for analyses of radiographic knee OA progression, subsample not used for analyses of cartilage thickness/thinning; OA: osteoarthritis.

sum score was 8 (IQR 5–11) and 8 (IQR 5–12) in the right and left hand, respectively. The median osteophyte sum score was 2 (IQR 1–6) and 2 (IQR 1–4) in the right and left hand, respectively. Radiographic knee OA was frequent, and 401 knees (52%) had moderate/severe disease (cKLG 3–4; Table 1). Of those with moderate/severe radiographic knee OA, 57% had medial JSN, 29% had lateral JSN, and 14% displayed bicompartmental JSN[15].

Hand JSN was associated with reduced cartilage thickness in the medial femorotibial compartment independent of hand osteophytes (Table 2). Significant associations were found in cKLG = 0–2 (ß = –0.01, 95% CI –0.02, –0.004; adjusted for age, sex, and BMI) and cKLG = 3–4 knees (ß = –0.03, 95% CI –0.04, –0.01; adjusted for age, sex, BMI, and osteophytes). We found a similar tendency in the lateral compartment (Table 2), but this was significant only in cKLG = 0–2 knees (ß = –0.01, 95% CI –0.02, –0.001; adjusted for age, sex, and BMI).

Hand osteophytes were associated with radiographic knee OA (KLG ≥ 3) independent of hand JSN (Table 2). We found similar but weaker associations when defining knee OA as KLG ≥ 2 (data not shown).

Hand JSN was associated with less severe longitudinal cartilage thinning in the lateral femorotibial compartment (Table 3). The association was significant in cKLG = 0–2 knees only (OR 0.92, 95% CI 0.86–1.00; adjusted for age, sex, and BMI). No significant association was found for the medial femorotibial compartment or for radiographic knee OA progression (Table 3).

Multivariate cross-sectional/longitudinal analyses with additional adjustment for risk factors used as inclusion criteria in the OAI (as described in Materials and Methods) yielded similar results (data not shown).

DISCUSSION

Our study of OAI participants with either risk of or prevalent knee OA is the first, to our knowledge, to demonstrate an association between radiographic features of hand OA and knee OA assessed by both conventional radiography and qMRI. Hand JSN (but not osteophytes) was associated with knee cartilage thickness, while hand osteophytes (but not JSN) were associated with radiographic knee OA. However, we did not find evidence for an association between hand OA and higher risk of 1-year qMRI-defined knee cartilage thinning or radiographic knee OA progression.

Our results extend previous cross-sectional studies, which showed a significant association between hand OA and radiographic knee OA[3,6,8,21]. Our main focus was on qMRI-defined knee cartilage thickness. We found that hand JSN was strong-

Table 2. The cross-sectional associations between radiographic hand osteoarthritis (OA) features and quantitative magnetic resonance imaging (qMRI)-defined knee cartilage thickness and radiographic knee OA.

Variable	Crude Estimates (95% CI); Separate Models	Adjusted Estimates (95% CI); Separate Models†	Adjusted Estimates (95% CI); Combined Model††
Cartilage thickness in the medial femorotibial compartment			
Total hand JSN	ß = –0.03 (–0.04, –0.02)**	ß = –0.02 (–0.03, –0.01)**	ß = –0.02 (–0.03, –0.01)**
Total hand osteophytes	ß = –0.02 (–0.03, –0.01)**	ß = –0.01 (–0.02, 0.00)*	ß = $4*10^{-4}$ (–0.01, 0.01)
Cartilage thickness in the lateral femorotibial compartment			
Total hand JSN	ß = –0.03 (–0.04, –0.02)**	ß = –0.006 (–0.02, 0.003)	NA
Total hand osteophytes	ß = –0.02 (–0.03, –0.007)**	ß = 0.002 (–0.01, 0.01)	NA
Severe radiographic knee OA (Kellgren-Lawrence grade ≥ 3)			
Total hand JSN	OR 1.04 (1.00, 1.08)*	OR 1.03 (0.98, 1.08)	OR 1.00 (0.95, 1.05)
Total hand osteophytes	OR 1.12 (1.06, 1.19)**	OR 1.10 (1.03, 1.17)*	OR 1.10 (1.03, 1.18)*

† Adjusted for age, sex, and body mass index (BMI); each hand OA feature as independent variables in separate models.†† Adjusted for age, sex, and BMI; both hand OA features as independent variables in the same multivariate model. * $p < 0.05$; ** $p < 0.001$. NA: not applicable (multivariate regression model not performed due to $p > 0.25$ for 1 or both hand OA variables); ß: regression coefficient (linear regression); OR: odds ratio (logistic regression); JSN: joint space narrowing.

Table 3. The associations between radiographic hand osteoarthritis (OA) features and 1-year quantitative magnetic resonance imaging (qMRI)-defined knee cartilage thinning and radiographic knee OA progression.

Variable	Crude Estimates (95% CI); Separate Models	Adjusted Estimates (95% CI); Separate Models†
Cartilage thinning in the medial femorotibial compartment		
Total hand JSN	OR 0.98 (0.96, 1.03)	OR 1.00 (0.96, 1.04)
Total hand osteophytes	OR 1.03 (0.99, 1.07)	OR 1.03 (0.99, 1.08)
Cartilage thinning in the lateral femorotibial compartment		
Total hand JSN	OR 0.98 (0.94, 1.01)	OR 0.96 (0.92, 1.00)*
Total hand osteophytes	OR 1.01 (0.97, 1.05)	OR 0.99 (0.95, 1.04)
Radiographic knee OA progression		
Total hand JSN	OR 1.02 (0.96, 1.09)	OR 1.00 (0.93, 1.08)
Total hand osteophytes	OR 0.97 (0.89, 1.06)	OR 0.96 (0.87, 1.06)

† Adjusted for age, sex, and body mass index (each hand OA feature as independent variables in separate models). * $p < 0.05$. JSN: joint space narrowing.

ly associated with reduced qMRI-defined knee cartilage thickness, independent of other key radiographic hand OA features such as osteophytes. The opposite was found for radiographic knee OA; i.e., hand osteophytes were associated with severe radiographic knee OA, as defined by Kellgren-Lawrence. Although KL is a global score of OA, it has been criticized for an emphasis on osteophytes[22]. Our results indicate first that there may exist a systemic susceptibility to OA, which could be due to a common genetic risk profile[23], hormonal factors[24,25], autoimmune mechanisms[26], metabolic factors[27], or other unknown systemic risk factors. However, local biomechanical factors are also important for the development of hand OA[28,29,30,31], and we cannot completely rule out that the observed association is due to a common environmental risk factor for hand and knee OA. Our results also indicate that mechanisms of bone modeling involved in osteophyte formation are different from mechanisms involved in cartilage thinning. This is also supported by studies showing that bony enlargement of the finger joints is related to knee osteophytes, but not JSN[32], and possibly different risk factors for osteophytes and JSN in radiographic knee OA[7,32].

We found no convincing association between hand OA and 1-year knee cartilage thinning or progression of radiographic knee OA, in contrast to other studies demonstrating an increased risk of incident[7,9,32] and progressive radiographic knee OA[7,32,33] associated with hand OA. Given the precision errors of qMRI[20] and limited 1-year progression, we may be unable to detect such a relationship. Further, Zhang, *et al* recently described the methodological challenges in studying risk factors for progression of knee OA[34]. Several observational studies have shown discrepancies between risk factors for incident and progressive disease. This paradoxical phenomenon may be a result of several risk factors that are no longer independent when they are conditioning of a common effect (here, decreased cartilage thickness or radiographic knee OA), and may tend to bias the effect of the risk factor on progression toward the null unless the analyses adjust properly for all risk factors. Our results remained similar after adjust-

ment for all risk factors used as selection criteria in the OAI, suggesting that there are risk factors that are unknown or unmeasured.

In contrast to our expectations, we found that hand JSN was associated with lower risk of cartilage thinning in the lateral compartment in knees with no/mild radiographic knee OA at baseline. Lateral OA was less common than medial OA, and the lateral compartment may therefore be more prone to development of early OA (i.e., cartilage swelling or hypertrophy) during followup[35]. Alternatively, knees with medial OA and potential varus malalignment may lead to less loading of the lateral compartment due to alterations in the biomechanical environment, and may therefore decrease the risk of cartilage thinning in the lateral compartment during followup.

The strengths of our study are the large sample of both women and men, and the independent assessment of exposure and outcome variables. However, there are several limitations that are noteworthy. Most participants had radiographs of the dominant hand only, and we may therefore have underestimated the burden of hand JSN and osteophytes. However, hand OA usually shows polyarticular and symmetrical involvement, and the amount of hand JSN and osteophytes was similar in the right and left hand in those with bilateral radiographs. Contrarily, flexion deformities of the joints may possibly lead to false or more severe appearance of radiographic JSN. The analyses were not adjusted for occupation or hand activity, and we can therefore not rule out the presence of common environmental risk factors for hand and knee OA. The short period of followup and the methodological challenges associated with unknown or unmeasured risk factors in the analyses of progression represent further limitations of the longitudinal analyses. Finally, the study sample consisted of participants with either risk of or prevalent knee OA, and the external validity regarding the general population is uncertain.

We found that radiographic hand JSN and osteophytes were significantly associated with reduced knee cartilage thickness assessed by qMRI and radiographic knee OA, respectively. Our results support an endogenous and generalized susceptibility for OA (or alternatively, common environmental risk factors). Further, the results might indicate that cartilage loss and osteophyte formation are separate systemic processes. In contrast, we found no evidence for an association between hand OA and 1-year knee cartilage thinning or progression of knee OA, and reevaluation of the sample after a longer period of followup is warranted.

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