Risk Factors for Progression of Tibiofemoral Osteoarthritis:
An Analysis Based on Fluoroscopically Standardized Knee Radiography

(Extended Report)

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Supported in part by NIH grants R01 AR43370, R01 AR43348 and P60 AR20582.

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Key Words: Incident OA, OA Progression, Knee Radiography, Patellofemoral OA, OA Risk Factors

COMPETING INTEREST STATEMENT: The Authors report no competing interests.

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ABSTRACT

**Objective.** An evaluation of risk factors for progressive radiographic changes of knee osteoarthritis (OA) using a standardized, fluoroscopically assisted protocol for knee radiography.

**Methods.** Subjects (N = 319) with unilateral or bilateral knee OA underwent a fluoroscopically standardized x-ray exam of the knees (semiflexed AP view) and assessment with the Western Ontario and McMaster Universities (WOMAC) OA Index at baseline and 30 months. Tibiofemoral joint space narrowing (JSN) and osteophytosis were graded in randomly ordered serial radiographs by consensus of 2 readers using standard pictorial atlases.

**Results.** Progression of JSN was inversely related to baseline joint space width (OR 0.67/1.4 mm, 95% CI 0.49 – 0.91) and positively associated with patellofemoral OA (OR 3.36, 95% CI 1.83 – 6.18). Osteophyte growth was inversely related to overall severity (number and size) of osteophytosis at baseline (OR 0.47/1.8 points on a 12-point osteophyte severity scale, 95% CI 0.33 – 0.66), and directly related to baseline stiffness (OR 1.39/2.1 WOMAC scale points, 95% CI 1.09 – 1.77) and the presence of patellofemoral OA at baseline (OR 2.31, 95% CI 1.37 – 3.88).

**Conclusions.** Progression of both JSN and osteophyte growth are predicted by the severity of the respective radiographic features of OA at baseline and by the presence of patellofemoral OA. In addition, knee stiffness is a risk factor for progressive osteophyte growth.
Osteoarthritis (OA) is the most common specific joint disease of humans. Moderate-to-severe OA affects more than 22 million American adults between the ages of 25 and 74 years [1] – more than 12% of the population in this age range [2]. OA of the knee is the most common cause of chronic disability in the elderly [3-5] and the most frequent indication for total knee arthroplasty [6]. There is no cure for OA; current guidelines for management of knee OA emphasize control of joint pain and maintenance of function until surgery is indicated [7].

Previous epidemiologic studies, all of which have used the conventional weightbearing knee radiographs, have identified cross-sectional associations between OA of the knee and increasing age, female sex, obesity and trauma [8-11]. However, while such factors explain to a great degree the prevalence of knee OA in the population, longitudinal studies knee OA have failed to identify robust risk factors for the incidence and progression of radiographic changes of this disease. Spector et al [12] found obesity to be related to growth of osteophytes in knees with established OA, but not to progression of JSN. In a study of incident and progressive OA, Cooper et al [13] found obesity, knee injury, and physical activity to be related to incident knee OA, but not to progressive changes. Zhang et al. [14] reported a similar discrepancy in predicting incident and progressive changes on the basis of bone mineral density. On the other hand, McAlindon and colleagues have shown that dietary deficiencies in vitamin D [15] and vitamin C [16] in the Framingham cohort are related to progression of JSN, but not to incident radiographic changes of OA.

Inconsistencies in the results of previous studies of knee OA may be due to use of the conventional standing anteroposterior (AP) radiograph. We have demonstrated that the lack of positioning standards for the standing AP radiograph does not limit substantially the detection of emergent osteophytes, the key indicator of incident OA; however, longitudinal changes in joint
positioning in the standing AP view have a profound effect on the radiographic joint space width (JSW), on which judgments of OA progression are made [17]. In addition, concern has been raised also about the extent to which associations with JSN in the conventional standing AP radiograph may be artifactual due to concurrent increases in knee pain that can alter weightbearing and increase knee flexion, thereby reducing the inter-bone distance in the tibiofemoral compartment [18].

The design of DMOAD trials would be facilitated also by eligibility criteria based on robust risk factors for progressive radiographic changes in OA. To elucidate such risk factors we have performed a 30-month longitudinal study in a heterogeneous, community-based sample of subjects with knee OA. The possible risk factors evaluated in this study represent a broad array of demographic, clinical and structural variables that have been examined, with mixed results, in previous studies of knee OA. Notably, evidence of osteophytosis and JSN was obtained using a protocol by which the radioanatomic position of the knee in serial examinations was standardized under fluoroscopy.

**METHODS**

The procedures, radiation exposure, other research risks and associated safeguards for this study were approved by the Radiation Safety Committee and the Institutional Review Board affiliated with Indiana University Purdue University Indianapolis.

**Subjects:** Subjects in the present study were derived from 2 cohorts: The first comprised 253 men and women, 45 years of age or older, with mild-to-moderate knee OA, based on radiographic evidence of a marginal tibiofemoral osteophyte in either the standing AP or semiflexed AP view and JSW \( \geq 2.0 \) mm in the semiflexed AP view [19]. The second cohort
contained 66 obese women, 45-64 years of age, with unilateral knee OA in the standing AP radiograph, based on Kellgren and Lawrence (K&L) criteria [20], who were recruited in Indianapolis and randomized to the placebo group of a concurrent clinical trial of a purported DMOAD. Subjects in the second cohort were in the upper tertile of the age-, race-, and sex-appropriate norms for body mass index (BMI) established by the Second National Health and Nutrition Examination Survey [21]. Both cohorts were recruited from a variety of community and clinical sources.

**Knee radiography.** Subjects from both cohorts were examined in the Radiology Department at Indiana University Medical Center by the same radiology technologists using the same equipment. Each subject underwent a standardized series of radiographs at baseline, including a fluoroscopically assisted semiflexed AP view of each knee [19], a supine lateral view of each knee and bilateral Hughston view of the patellofemoral compartment. Positioning for the Hughston view requires that the subject lie prone with knees flexed to 55°, with the central ray of the x-ray beam at a 45° angle, relative to the tabletop [22]. Follow-up radiographs were obtained 30 months after baseline.

Minimum JSW in the medial tibiofemoral compartment at baseline was measured manually with a digital calipers and was corrected for magnification, based on the projected diameter of a magnification marker (6.35 mm steel ball) that was affixed with tape over the lateral aspect of the head of the fibula. In addition, the severity of individual radiographic features of OA (JSN and osteophytosis in the tibiofemoral and patellofemoral compartments) was rated independently by two readers (KDB,SM) in sets of serial radiographs that were randomly ordered prior to reading. In the case of Cohort 2, readers were blinded also to treatment group. Ratings of severity (grades 0–3) were based on exemplars in standard pictorial
atlases [23,24]. Differences between the two readers were discussed until consensus was achieved; if consensus could not be reached, a musculoskeletal radiologist (KAB) was consulted and agreement was reached among the three examiners.

The overall severity of osteophytosis in the knee was expressed as the sum of the ratings of osteophyte severity at 4 locations in the semiflexed AP view: medial femur, lateral femur, medial tibia and lateral tibia. Because the individual rating scales for osteophytes ranged from 0 to 3, the overall osteophyte “score” varied from 0 to 12.

Based on repeat ratings of a random sample of 24 semiflexed AP radiographs, estimates of reproducibility (kappa) consensus ratings of the severity of medial and lateral JSN were 0.85 and 0.70, respectively. Kappas for osteophyte size in each of the four tibiofemoral locations varied from 0.52 (medial tibia) to 0.68 (medial femur) (ICC for osteophyte score = 0.72).

Overall grades of radiographic severity (grades 0-1, 2, 3 and 4), similar to those defined by Kellgren and Lawrence in the standing AP radiograph [20], were assigned to each knee at baseline, according to the presence and severity of tibiofemoral osteophytes and of JSN in consensus ratings of the semiflexed AP view. Knees with no tibiofemoral osteophytes at baseline were classified as grade 0-1. Knees with a sum of osteophyte ratings ≥ 1 that were rated 0 for medial and lateral JSN were designated grade 2. In the presence of osteophytes, ratings of 1 or 2 for medial/lateral JSN resulted in classification as grade 3 OA. Grade 4 OA required the presence of osteophyte(s) and a rating of 3 for JSN severity. This classification scheme did not permit discrimination between grade 0 and grade 1 OA by K&L criteria because the OARSI atlas [23] contains no example of the “minute osteophyte of doubtful significance” that is the key feature of K&L grade 1 OA [20].
Patellofemoral OA was judged to be present if a definite patellar or trochlear osteophyte \( \geq \) grade 2 was seen in the lateral or Hughston view [23,24].

Progressive osteophytosis was defined by an increase in the sum of atlas-based ratings of osteophyte severity across the four margins of the tibiofemoral compartment (see above). For JSN, an increase in the rating of severity of medial or lateral JSN was considered a progressive change.

**Clinical assessment.** Knee pain, stiffness and functional limitation (disability) at baseline was measured with the Western Ontario and McMaster Universities (WOMAC) OA Index (5-point Likert version) [25]. WOMAC assessment occurred after washout (5 half-lives) of all nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics taken by the subject for knee pain or other reasons. Pain and stiffness were assessed separately in left and right knees.

**Statistical analysis.** Analyses were performed on all knees with grade 2 or greater severity of OA at baseline. Separate analyses were performed for progression of JSN and growth of tibiofemoral osteophytes.

To screen baseline variables as possible risk factors, logistic regression models with generalized estimating equations (GEE) were run separately for 3 domains: general clinical (i.e., age, sex, race and BMI); OA clinical (i.e., duration of symptoms, duration of diagnosis and WOMAC scores for pain, stiffness and function); radiographic (medial tibiofemoral JSW (in mm), osteophyte score, the presence of patellofemoral OA in the ipsilateral knee and the presence of tibiofemoral or patellofemoral OA in the contralateral knee). Screening within the domains identified the strongest risk factors amongst correlated variables.

Variables that were found to have a marginal or stronger association \( (P<0.20) \) with incident or progressive changes of OA were included as independent variables in a 2-step
multiple logistic regression model with GEE to account for between-knee correlation in subjects with bilateral knee OA at baseline: The initial analysis entailed estimation of adjusted odds ratios, 95% confidence intervals and $P$-values for each variable that passed the preliminary screening for each domain. In the final model, backward selection removed variables with multivariate $P>0.05$ until all remaining independent variables were statistically significant. All odds ratios for continuous variables were expressed as the change in odds of progression for every standard deviation (SD) difference between subjects in the independent variable. Knees with grade 4 tibiofemoral OA at baseline were excluded from analyses to predict progression of JSN.

**RESULTS**

Demographic, clinical and radiographic characteristics of subjects in the 2 research cohorts are shown in Table 1. Subjects from the longitudinal research cohort (Cohort 1) were significantly older and less obese at baseline than subjects from the placebo group of the DMOAD trial (Cohort 1) ($P<0.001$ for each). The mean duration of symptoms of knee OA and mean duration of diagnosis was significantly greater in Cohort 1 than in Cohort 2 ($P<0.05$ for each). However, the cohorts did not differ significantly at baseline with respect to pain, stiffness or function scores on the WOMAC OA Index.

Thirty-one subjects who qualified for the study because of the presence of tibiofemoral osteophytes in one or both knees in the standing AP view showed no such evidence of OA in the semiflexed AP radiograph (i.e., they had bilateral grade 0-1 OA in the latter view). These subjects were excluded from the analysis. One hundred one subjects with unilateral knee OA in the semiflexed AP view and 187 subjects with bilateral knee OA at baseline contributed data to
analyses of risk factors for progression of OA. Patellofemoral OA was present in 41% knees with grade 0-1 tibiofemoral OA and 73% of knees with grade 2-4 tibiofemoral OA ($P<0.0001$).

Follow-up (30-month) radiographs were obtained from 207 subjects in the longitudinal research cohort and 60 subjects from the placebo group of the DMOAD trial (overall retention = 84%). The frequencies with which knees exhibited progression of individual radiographic features of knee OA are shown in Table 2. Progression of JSN was observed in 32% of knees with grade 2 OA at baseline and 30% of knees with grade 3 OA. JSN was far more likely to occur in the medial compartment (86%) than in the lateral compartment. Osteophyte growth (i.e., an increase in the number or size of definite tibiofemoral osteophytes) occurred in 34% of knees. The frequency of osteophyte growth was unrelated to baseline severity of knee OA.

Subjects in the two cohorts did not differ with respect to the frequency of progression of JSN or osteophyte growth.

**Risk factors for progression of JSN.** Preliminary analyses identified 5 clinical and radiographic variables as potential risk factors: age, WOMAC function score, the presence of contralateral knee OA, baseline JSW and the presence of patellofemoral OA in the ipsilateral knee. Of these, only baseline JSW and patellofemoral OA were significantly related to disease progression (Table 3). The odds of progression of JSN were 3-fold greater in knees of subjects with concomitant patellofemoral OA in the ipsilateral knee at baseline ($P<0.001$). However, they were inversely related to baseline JSW (OR 0.67/1.4 mm, $P=0.001$). These findings were essentially unchanged after backward selection of non-significant predictors in the final model (Table 4).

**Risk factors for progression of osteophyte growth.** Three variables were identified as potential risk factors for osteophyte growth: the baseline osteophyte score, WOMAC stiffness
score and the presence of patellofemoral OA in the ipsilateral knee (Table 4). The odds of osteophyte growth were >2-fold greater in knees in which patellofemoral OA was present at baseline ($P=0.002$) and increased 39% for every SD (2.1-point) increase in the baseline WOMAC stiffness score ($P=0.008$). In addition, for each SD (1.8-point) increase in baseline osteophyte scores, the odds of progressive osteophyte growth decreased 53% ($P<0.0001$). Because all variables in the initial model were statistically significant ($P<0.05$), the final model was obviated.

**DISCUSSION**

The present study represents one of the first examinations of the risk factors of knee OA to utilize fluoroscopically standardized positioning of the knee in serial examinations. Fluoroscopic positioning affords reproducible alignment of the medial tibial plateau and x-ray beam, which effectively eliminates position-related [17] and symptom-related [18] changes in radiographic JSW in serial x-ray examinations. The elimination of these sources of error in estimates of JSW results in increases sensitivity to JSN (i.e., decreased between-subject variability in JSN, relative to the mean) [17,26]. For this reason, fluoroscopically standardized knee radiography has been lauded as an advance that will lead to new insights into disease progression and structure modification in knee OA [27].

In the present study, we found that the progression of both tibiofemoral JSN and osteophytosis was significantly more frequent in knees in which concomitant patellofemoral OA was present than in knees in which patellofemoral OA was absent. Despite the primary focus on the tibiofemoral compartment in many previous studies of knee OA, patellofemoral OA is highly prevalent. Davies et al [28] found significant patellofemoral OA in 33% of men and 36% of
women in a clinical population of patients older than 60 years of age; 37-47% of these cases represented isolated patellofemoral disease. In a population-based sample, McAlindon et al [29] found patellofemoral OA in 30% of women and 18% of men; moreover, they showed that pain and disability were attributable as much to patellofemoral OA as to tibiofemoral OA. In fact, structural changes in the patellofemoral joint may provide a better explanation of knee pain than changes in the tibiofemoral compartment [30,31]. More recently, patellofemoral OA has been shown to be related cross-sectionally to varus-valgus malalignment [32] and quadriceps weakness [33], known risk factors for tibiofemoral OA [31-36].

Progressive osteophyte growth was related also to the degree of joint stiffness reported by the patient at baseline. Joint stiffness is a heretofore unrecognized risk factor of knee OA. Knee stiffness may have been a surrogate for the presence of radiolucent chondrophytes that buttressed the joint and restricted mobility but had not yet ossified sufficiently to be apparent radiographically. Alternatively, knee stiffness may have reflected synovitis. The washout of NSAIDs and analgesics that preceded clinical assessments in the present study was employed to increase the sensitivity of stiffness scores and pain scores to synovial inflammation, compared to that which is possible when symptoms are masked by OA medications. However, inflammation is not the only source of pain in knee OA. Myers et al [37] have reported that only 55% of symptomatic OA knees exhibit arthroscopic evidence of synovitis.

It should be acknowledged that the high prevalence of obesity in the present sample (mean BMI = 33.7 kg/m²) may have precluded the variability in BMI required for it to serve as a useful risk factor for progression of knee OA. For this reason, the generalizability of results from the present study to populations in which obesity is less prevalent may be limited.
In conclusion, we have conjectured that inconsistencies in the results of previous studies of risk factors for incident and progressive knee OA may be due to the lack of positioning standards for the conventional standing AP knee radiograph, on which previous investigations have relied. In the present study, radiographic changes of OA were documented in images in which flexion and rotation of the knee was standardized under fluoroscopy. The results of the present study indicate that the progression of both JSN and osteophyte growth are predicted by the severity of the respective radiographic features of OA at baseline and by the presence of patellofemoral OA. In addition, knee stiffness is a risk factor for progressive osteophyte growth. Future investigations into the roles of patellofemoral OA and joint stiffness as risk factors for progression of tibiofemoral OA should focus on the systemic and local influences at play that these ostensible risk factors represent.
REFERENCES


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outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee.


### Table 1. Characteristics of subjects at baseline

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1* (N = 253)</th>
<th>Cohort 2† (N = 66)</th>
<th>Combined (N = 319)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, N (%) female</strong></td>
<td>201 (79)</td>
<td>66 (100)</td>
<td>267 (84)</td>
</tr>
<tr>
<td><strong>Age, years (mean ± SD)</strong></td>
<td>61.6 ± 9.8</td>
<td>54.1 ± 5.5</td>
<td>60.0 ± 9.6</td>
</tr>
<tr>
<td><strong>Race, % African American</strong></td>
<td>62 (25)</td>
<td>17 (26)</td>
<td>79 (25)</td>
</tr>
<tr>
<td><strong>Body mass index (BMI), kg/m² (mean ± SD)</strong></td>
<td>33.0 ± 7.9</td>
<td>36.7 ± 6.0</td>
<td>33.7 ± 7.7</td>
</tr>
<tr>
<td><strong>Duration of symptoms, years (mean ± SD) ‡</strong></td>
<td>8.7 ± 9.0</td>
<td>6.3 ± 6.4</td>
<td>8.2 ± 8.6</td>
</tr>
<tr>
<td><strong>Duration of diagnosis, years (mean ± SD) ‡</strong></td>
<td>3.8 ± 5.5</td>
<td>1.2 ± 3.2</td>
<td>3.3 ± 5.2</td>
</tr>
<tr>
<td><strong>Overall severity of tibiofemoral OA§</strong></td>
<td>93 (18)</td>
<td>70 (53)</td>
<td>163 (26)</td>
</tr>
<tr>
<td>Grade 0-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>71 (14)</td>
<td>25 (19)</td>
<td>96 (15)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>282 (56)</td>
<td>34 (26)</td>
<td>316 (50)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>60 (12)</td>
<td>3 (2)</td>
<td>63 (10)</td>
</tr>
<tr>
<td><strong>WOMAC OA Index</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knee pain score, range 5-25 (mean ± SD)#</td>
<td>11.4 ± 4.4</td>
<td>11.9 ± 4.3</td>
<td>11.5 ± 4.4</td>
</tr>
<tr>
<td>Knee stiffness score, range 2-10 (mean ± SD)#</td>
<td>5.4 ± 2.1</td>
<td>5.4 ± 2.1</td>
<td>5.4 ± 2.1</td>
</tr>
<tr>
<td>Function score, range 17-85 (mean ± SD)</td>
<td>40.9 ± 14.2</td>
<td>38.1 ± 13.0</td>
<td>40.3 ± 14.0</td>
</tr>
</tbody>
</table>

* Community-based longitudinal cohort

† Subjects from the placebo group of a randomized controlled trial of doxycycline in knee OA.

‡ Knee with the longer duration of symptoms/diagnosis

§ Based on grading of JSN and osteophyte size in the semiflexed AP view. Percentages reflect the total number of knees (N = 638).

# Knee with the more severe pain/stiffness
Table 2. Number (%) of knees exhibiting progressive radiographic changes of tibiofemoral knee OA (JSN and osteophytosis) over 30 months by grade of radiographic severity at baseline

<table>
<thead>
<tr>
<th>Radiographic Feature of Progressive OA</th>
<th>Grade 2 (N = 85)</th>
<th>Grade 3 (N = 265)</th>
<th>Grade 4 (N = 38)</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial or lateral JSN</td>
<td>27 (32)</td>
<td>80 (30)</td>
<td>n/a</td>
<td>107 (31)</td>
</tr>
<tr>
<td>Osteophyte growth</td>
<td>23 (27)</td>
<td>95 (36)</td>
<td>11 (29)</td>
<td>129 (34)</td>
</tr>
</tbody>
</table>

* Based on Kellgren and Lawrence criteria applied to consensus ratings of osteophyte size and JSN (OARSI atlas) in the baseline semiflexed AP view.
Table 3. Risk factors for progression of radiographic features of knee OA

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Independent Variable</th>
<th>Initial Model*</th>
<th>Final Model†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Odds Ratio‡</td>
<td>95% CI</td>
</tr>
<tr>
<td>Progression of</td>
<td>Age</td>
<td>1.13</td>
<td>0.87 – 1.48</td>
</tr>
<tr>
<td>JSN</td>
<td>WOMAC function score</td>
<td>1.16</td>
<td>0.92 – 1.47</td>
</tr>
<tr>
<td></td>
<td>Contralateral knee OA (1 = present)</td>
<td>1.53</td>
<td>0.82 – 2.85</td>
</tr>
<tr>
<td></td>
<td>Baseline JSW</td>
<td>0.67</td>
<td>0.49 – 0.91</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral PF OA (1 = present)</td>
<td>3.01</td>
<td>1.63 – 5.57</td>
</tr>
<tr>
<td>Osteophyte growth</td>
<td>Osteophyte score</td>
<td>0.47</td>
<td>0.33 – 0.66</td>
</tr>
<tr>
<td></td>
<td>WOMAC stiffness score</td>
<td>1.39</td>
<td>1.09 – 1.77</td>
</tr>
<tr>
<td></td>
<td>Ipsilateral PF OA (1 = present)</td>
<td>2.31</td>
<td>1.37 – 3.88</td>
</tr>
</tbody>
</table>

* The initial model included all variables within 3 domains (general clinical, OA clinical, radiographic) associated with the dependent variable ($P\leq0.20$).

† Backward selection of independent variables with $P>0.05$ until all remaining predictors were statistically significant ($P<0.05$). There were no significant interactions.

‡ Odds ratios for continuous independent variables are scaled to reflect the change in odds of progression for each standard deviation increase in the independent variable.