EXTENDED REPORT

Risk factors for progression of tibiofemoral osteoarthritis: an analysis based on fluoroscopically standardised knee radiography

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Objective: To evaluate risk factors for progressive radiographic changes of knee osteoarthritis using a standardised fluoroscopically assisted protocol for knee radiography.

Methods: Subjects (n=319) with unilateral or bilateral knee osteoarthritis underwent a fluoroscopically standardised x ray examination of the knees (semiflexed AP view) and assessment with the Western Ontario and McMaster Universities (WOMAC) osteoarthritis index at baseline and at 30 months. Tibiofemoral joint space narrowing and osteophytosis were graded in randomly ordered serial radiographs by consensus of two readers using standard pictorial atlases.

Results: Progression of joint space narrowing was inversely related to baseline joint space width (odds ratio (OR)=0.67/1.4 mm (95% confidence interval (CI), 0.49 to 0.91)) and positively associated with patellofemoral osteoarthritis (OR=3.36 (1.83 to 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 to 0.66)), and directly related to baseline stiffness (OR=1.39/2.1 WOMAC scale points (95% CI, 1.09 to 1.77)) and the presence of patellofemoral osteoarthritis at baseline (OR=2.31 (1.37 to 3.88)).

Conclusions: Progression of both joint space narrowing and osteophyte growth are predicted by the severity of the respective radiographic features of osteoarthritis at baseline and by the presence of patellofemoral osteoarthritis. In addition, knee stiffness is a risk factor for progressive osteophyte growth.

Osteoarthritis is the most common specific joint disease of humans. Moderate to severe osteoarthritis affects more than 22 million American adults between the ages of 25 and 74 years¹—more than 12% of the population in this age range.² Osteoarthritis 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 osteoarthritis; current guidelines for management of knee osteoarthritis emphasise control of joint pain and maintenance of function until surgery is indicated.⁷

Previous epidemiological studies, all of which have used the conventional weight bearing knee radiographs, have identified cross sectional associations between osteoarthritis 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 osteoarthritis in the population, longitudinal studies of knee osteoarthritis have failed to identify robust risk factors for the incidence and progression of radiographic changes in this disease. Spector *et al*¹² found obesity to be related to growth of osteophytes in knees with established osteoarthritis, but not to progression of joint space narrowing. In a study of incident and progressive osteoarthritis, Cooper *et al*¹³ found obesity, knee injury, and physical activity to be related to incident knee osteoarthritis 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 D¹⁵ and vitamin C¹⁶ in the Framingham cohort are related to progression of joint space narrowing but not to incident radiographic changes of osteoarthritis.

Inconsistencies in the results of previous studies of knee osteoarthritis may reflect the use of the conventional standing anteroposterior (AP) radiograph. We have shown

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 osteoarthritis; however, longitudinal changes in joint positioning in the standing AP view have a profound effect on the radiographic joint space width, on which judgments of osteoarthritis progression are made.¹⁷ In addition, concern has also been raised about the extent to which associations with joint space narrowing in the conventional standing AP radiograph may be artefactual because of concurrent increases in knee pain that can alter weight bearing and increase knee flexion, thereby reducing the interbone distance in the tibiofemoral compartment.¹⁸

The design of disease modifying osteoarthritis drug (DMOAD) trials would also be facilitated by eligibility criteria based on robust risk factors for progressive radiographic changes in osteoarthritis. To elucidate such risk factors we have undertaken a 30 month longitudinal study in a heterogeneous, community based sample of subjects with knee osteoarthritis. 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 osteoarthritis. Notably, evidence of osteophytosis and joint space narrowing was obtained using a protocol whereby the radioanatomical position of the knee in serial examinations was standardised under fluoroscopy.

Abbreviations: DMOAD, disease modifying osteoarthritis drug; GEE, generalised estimating equation; K&L, Kellgren and Lawrence; NSAID, non-steroidal anti-inflammatory drug; OARSI, Osteoarthritis Research Society International; WOMAC, Western Ontario and McMaster Universities

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 to Indiana University Purdue University, Indianapolis.

Subjects

Subjects in the present study were derived from two cohorts: The first comprised 253 men and women, 45 years of age or older, with mild to moderate knee osteoarthritis, based on radiographic evidence of a marginal tibiofemoral osteophyte in either the standing AP or semiflexed AP view and joint space width ≥ 2.0 mm in the semiflexed AP view.¹⁹ The second cohort contained 66 obese women, 45 to 64 years of age, with unilateral knee osteoarthritis in the standing AP radiograph, based on Kellgren and Lawrence (K&L) criteria,²⁰ who were recruited in Indianapolis and randomised 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 standardised 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 views 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 table top.²² Follow up radiographs were obtained 30 months after baseline.

Minimum joint space width in the medial tibiofemoral compartment at baseline was measured manually with a digital caliper and was corrected for magnification using the projected diameter of a magnification marker (6.35 mm steel ball) that was fixed with tape over the lateral aspect of the head of the fibula. In addition, the severity of individual radiographic features of osteoarthritis (joint space narrowing and osteophytosis in the tibiofemoral and patellofemoral compartments) was rated independently by two readers (KDB, SM) in sets of serial radiographs which were randomly ordered before reading. In the case of cohort 2, readers were also blinded 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 four 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.

On the basis of repeat ratings of a random sample of 24 semiflexed AP radiographs, estimates of reproducibility (κ) consensus ratings of the severity of medial and lateral joint space narrowing were 0.85 and 0.70, respectively; κ values for osteophyte size in each of the four tibiofemoral locations varied from 0.52 (medial tibia) to 0.68 (medial femur) (intraclass correlation 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 joint space narrowing 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 joint space narrowing were designated grade 2. In the presence of osteophytes, ratings of 1 or 2 for medial/lateral joint space narrowing resulted in classification as grade 3 osteoarthritis. Grade 4 osteoarthritis required the presence of an osteophyte and a rating of 3 for joint space narrowing severity. This classification scheme did not allow discrimination between grade 0 and grade 1 osteoarthritis by K&L criteria because the OARS atlas²³ contains no example of the “minute osteophyte of doubtful significance,” which is the key feature of K&L grade 1 osteoarthritis.²⁰

Patellofemoral osteoarthritis 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 joint space narrowing, an increase in the rating of severity of medial or lateral joint space narrowing 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) osteoarthritis index (five point Likert version).²⁵ WOMAC assessment occurred after washout (five half lives) of all non-steroidal 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 undertaken on all knees with grade 2 or greater severity of osteoarthritis at baseline. Separate analyses were carried out for progression of joint space narrowing and growth of tibiofemoral osteophytes.

To screen baseline variables as possible risk factors, logistic regression models with generalised estimating equations (GEE) were run separately for three domains: general clinical (that is, age, sex, race, and BMI); osteoarthritis clinical (duration of symptoms, duration of diagnosis, and WOMAC scores for pain, stiffness, and function); and radiographic (medial tibiofemoral joint space width (mm), osteophyte score, the presence of patellofemoral osteoarthritis in the ipsilateral knee, and the presence of tibiofemoral or patellofemoral osteoarthritis in the contralateral knee). Screening within the domains identified the strongest risk factors among correlated variables.

Variables that were found to have a marginal or stronger association ($p < 0.20$) with incident or progressive changes of osteoarthritis were included as independent variables in a two step multiple logistic regression model with GEE to account for between knee correlations in subjects with bilateral knee osteoarthritis at baseline. The initial analysis entailed estimation of adjusted odds ratios (OR), 95% confidence intervals (CI), 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 values above 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 difference

Table 1 Characteristics of subjects at baseline

	Cohort 1* (n = 253)	Cohort 2† (n = 66)	Combined (n = 319)
Female sex (n (%))	201 (79%)	66 (100%)	267 (84%)
Age (years)	61.6 (9.8)	54.1 (5.5)	60.0 (9.6)
African American race (n (%))	62 (25%)	17 (26%)	79 (25%)
BMI (kg/m ²)	33.0 (7.9)	36.7 (6.0)	33.7 (7.7)
Duration of symptoms (years)‡	8.7 (9.0)	6.3 (6.4)	8.2 (8.6)
Duration of diagnosis (years)‡	3.8 (5.5)	1.2 (3.2)	3.3 (5.2)
Overall severity of tibiofemoral osteoarthritis§			
Grade 0–1 (n (%))	93 (18%)	70 (53%)	163 (26%)
Grade 2 (n (%))	71 (14%)	25 (19%)	96 (15%)
Grade 3 (n (%))	282 (56%)	34 (26%)	316 (50%)
Grade 4 (n (%))	60 (12%)	3 (2%)	63 (10%)
WOMAC osteoarthritis index			
Knee pain score, range 5 to 25**	11.4 (4.4)	11.9 (4.3)	11.5 (4.4)
Knee stiffness score, range 2 to 10**	5.4 (2.1)	5.4 (2.1)	5.4 (2.1)
Function score, range 17 to 85	40.9 (14.2)	38.1 (13.0)	40.3 (14.0)

Values are mean (SD) unless stated otherwise.

*Community based longitudinal cohort.

†Subjects from the placebo group of a randomised controlled trial of doxycycline in knee osteoarthritis.

‡Knee with the longer duration of symptoms/diagnosis.

§Based on grading of joint space narrowing and osteophyte size in the semiflexed anteroposterior view.

Percentages reflect the total number of knees (n = 506 for cohort 1, n = 132 for cohort 2, n = 638 for combined cohorts).

**Knee with the more severe pain/stiffness.

BMI, body mass index; WOMAC, Western Ontario and McMaster Universities.

between subjects in the independent variable. Knees with grade 4 tibiofemoral osteoarthritis at baseline were excluded from analyses to predict progression of joint space narrowing.

RESULTS

Demographic, clinical, and radiographic characteristics of subjects in the two 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 osteoarthritis and mean duration of diagnosis were significantly greater in cohort 1 than in cohort 2 ($p < 0.05$ for each). However, the cohorts did not differ at baseline with respect to pain, stiffness, or function scores on the WOMAC osteoarthritis 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 osteoarthritis in the semiflexed AP radiograph (that is, they had bilateral grade 0–1 osteoarthritis in the latter view). These subjects were excluded from the analysis. In all, 101 subjects with unilateral knee osteoarthritis in the semiflexed AP view and 187 with bilateral knee osteoarthritis at baseline contributed data to analyses of risk factors for progression of osteoarthritis. Patellofemoral osteoarthritis was present in

41% of knees with grade 0–1 tibiofemoral osteoarthritis and 73% of knees with grade 2–4 ($p < 0.0001$).

Follow up radiographs (30 months) were obtained from 207 subjects in the longitudinal research cohort and 60 from the placebo group of the DMOAD trial (overall retention = 84%). The frequencies with which knees showed progression of individual radiographic features of knee osteoarthritis are shown in table 2. Progression of joint space narrowing was observed in 32% of knees with grade 2 osteoarthritis at baseline and 30% of knees with grade 3 osteoarthritis. Joint space narrowing was far more likely to occur in the medial compartment (86%) than in the lateral compartment. Osteophyte growth (that is, 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 osteoarthritis. Subjects in the two cohorts did not differ with respect to the frequency of or progression of joint space narrowing or osteophyte growth.

Risk factors for progression of joint space narrowing

Preliminary analyses identified five clinical and radiographic variables as potential risk factors: age, WOMAC function score, the presence of contralateral knee osteoarthritis, baseline joint space width, and the presence of patellofemoral osteoarthritis in the ipsilateral knee. Of these, only baseline

Table 2 Knees showing progressive radiographic changes of tibiofemoral knee osteoarthritis (joint space narrowing and osteophytosis) over 30 months by grade of radiographic severity at baseline

Radiographic feature of progressive osteoarthritis	Radiographic severity of knee osteoarthritis at baseline*			
	Grade 2 (n = 85)	Grade 3 (n = 265)	Grade 4 (n = 38)	Combined
Medial or lateral joint space narrowing	27 (32)	80 (30)	N/A	107 (31)
Osteophyte growth	23 (27)	95 (36)	11 (29)	129 (34)

Values are n (%).

*Based on Kellgren and Lawrence criteria applied to consensus ratings of osteophyte size and joint space narrowing (OARS atlas) in the baseline semiflexed anteroposterior view.

N/A, not applicable.

Table 3 Risk factors for progression of radiographic features of knee osteoarthritis

Dependent variable	Independent variable	Initial model*		Final model†	
		OR‡	95% CI	OR‡	95% CI
Progression of joint space narrowing	Age	1.13	0.87 to 1.48	–	–
	WOMAC function score	1.16	0.92 to 1.47	–	–
	Contralateral knee osteoarthritis (1 = present)	1.53	0.82 to 2.85	–	–
	Baseline joint space width	0.67	0.49 to 0.91	0.63	0.47 to 0.86
	Ipsilateral patellofemoral osteoarthritis (1 = present)	3.01	1.63 to 5.57	3.36	1.83 to 6.18
Osteophyte growth	Osteophyte score	0.47	0.33 to 0.66	Not necessary	
	WOMAC stiffness score	1.39	1.09 to 1.77		
	Ipsilateral patellofemoral osteoarthritis (1 = present)	2.31	1.37 to 3.88		

*The initial model included all variables within three domains (general clinical, osteoarthritis clinical, radiographic) associated with the dependent variable ($p \leq 0.20$).

†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.

CI, confidence interval; OR, odds ratio; WOMAC, Western Ontario and McMaster Universities.

joint space width and patellofemoral osteoarthritis were significantly related to disease progression (table 3). The odds of progression of joint space narrowing were threefold greater in knees of subjects with concomitant patellofemoral osteoarthritis in the ipsilateral knee at baseline ($p < 0.001$). However, they were inversely related to baseline joint space width (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 3).

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 osteoarthritis in the ipsilateral knee (table 3). The odds of osteophyte growth were more than twofold greater in knees in which patellofemoral osteoarthritis 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 by 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 osteoarthritis to use fluoroscopically standardised 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 related¹⁷ and symptom related¹⁸ changes in radiographic joint space width in serial x ray examinations. The elimination of these sources of error in estimates of joint space width results in an increase in sensitivity to joint space narrowing (that is, decreased between subject variability relative to the mean).^{17–26} For this reason, fluoroscopically standardised knee radiography has been lauded as an advance that will lead to new insights into disease progression and structure modification in knee osteoarthritis.²⁷

In the present study, we found that the progression of both tibiofemoral joint space narrowing and osteophytosis was significantly more frequent in knees in which concomitant patellofemoral osteoarthritis was present than in those in which it was absent. Despite the primary focus on the tibiofemoral compartment in many previous studies of knee osteoarthritis, patellofemoral osteoarthritis is highly prevalent. Davies *et al*²⁸ found significant patellofemoral

osteoarthritis in 33% of men and 36% of women in a clinical population of patients older than 60 years; 37–47% of these cases represented isolated patellofemoral disease. In a population based sample, McAlindon *et al*²⁹ found patellofemoral osteoarthritis in 30% of women and 18% of men; moreover, they showed that pain and disability were attributable as much to patellofemoral as to tibiofemoral osteoarthritis. In fact, structural changes in the patellofemoral joint may provide a better explanation for knee pain than changes in the tibiofemoral compartment.^{30–31} More recently, patellofemoral osteoarthritis has been shown to be related cross sectionally to varus–valgus malalignment³² and quadriceps weakness,³³ known risk factors for tibiofemoral osteoarthritis.^{31–36}

Progressive osteophyte growth was also related to the degree of joint stiffness reported by the patient at baseline. Joint stiffness is a heretofore unrecognised risk factor for knee osteoarthritis. Knee stiffness may have been a surrogate for the presence of radiolucent chondrocytes 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 with what is possible when symptoms are masked by osteoarthritis drugs. However, inflammation is not the only source of pain in knee osteoarthritis. Myers *et al*³⁷ have reported that only 55% of symptomatic osteoarthritic knees show 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 osteoarthritis. For this reason, the generalisability 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 osteoarthritis may reflect 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 osteoarthritis were documented in images in which flexion and rotation of the knee was standardised under fluoroscopy. The results of our study indicate that the progression of both joint space narrowing and osteophyte growth are predicted by the severity of the respective radiographic features of osteoarthritis at baseline and by the presence of patellofemoral

osteoarthritis. In addition, knee stiffness is a risk factor for progressive osteophyte growth. Future investigations into the roles of patellofemoral osteoarthritis and joint stiffness as risk factors for progression of tibiofemoral osteoarthritis should focus on the systemic and local influences at play that these ostensible risk factors represent.

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