Hidden osteophyte formation on plain x-ray is the predictive factor for development of knee osteoarthritis after 48 months - data from the Osteoarthritis Initiative

(単純 X 線撮像で描出困難な位置の骨棘形成は、48 ヵ月後の変形性膝関節症進行の予測因子である - OAI のデータから)

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ABSTRACT

Objective: To examine whether the detection of osteophytes anywhere in the knee could serve as a pre-radiographic biomarker for OA development.

Methods: Baseline MRIs of 132 participants in the Osteoarthritis (OA) Initiative were studied. Based on radiographs, 66 knees were assessed as osteoarthritis-free (No-osteoarthritis [NOA], or Kellgren/Lawrence [K/L] severity grade 0/1 both at baseline and 48 months), and another 66 knees were assessed as having radiographic OA changes (pre-radiographic-osteoarthritis [PROA], or with K/L grade 0/1 at baseline and grade ≥2 at 48 months). Using baseline MRI data, we examined eight sites of osteophyte formation: the medial and lateral femoral condyle (MFC and LFC, respectively); medial and lateral tibial plateau (MTP and LTP, respectively); medial and lateral facets of the patellofemoral joint (PM and PL, respectively); tibial spine (TS); and femoral intercondylar notch (IC). Knee joint osteophyte size was assessed via the 8-point marginal osteophytes item of the whole-organ magnetic resonance imaging score (WORMS). The frequencies and distributions of osteophytes were compared between groups.

Results: Mild-size osteophytes (defined as score ≥2) were observed more frequently at the MFC ($p=0.00278$), MTP ($p=0.0046$), TS ($p=0.0146$), PM ($p<0.0001$), PL ($p=0.0012$), and IC ($p<0.0001$) in PROA knees than in NOA knees. Moderate-size osteophytes (defined as score ≥4) were more frequently observed in PROA knees than in NOA knees only at the IC ($p<0.0001$).

Conclusion: Knees with osteophyte formation at the IC, even those of K/L severity grade 0/1, are at risk for the development of radiographic OA by 48 months.

Keywords

<intercondylar notch; magnetic resonance imaging; osteoarthritis; Osteoarthritis Initiative; osteophyte formation; pre-radiographic osteoarthritis>

INTRODUCTION

Osteoarthritis (OA) of the knee joint is a common musculoskeletal problem in the elderly, and it can adversely affect quality of life (QOL); it is also the most prevalent medically treated arthritic condition worldwide, affecting 3532 per 100,000 people in the United State [1, 2]. This disease is not only associated with impaired QOL, but it also generates high socio-economic costs, in the form of physician visits, medications, hospitalizations, surgeries, and transportation costs, which are representative of direct costs, and comorbid conditions and lost productivity at home and work, which are representative of indirect costs [3-6]. Unfortunately, there is no good intervention to prevent disease progression that could be called a disease-modifying anti-osteoarthritic drug (DMOAD). Early detection of preclinical OA appears to be important, because early introduction of interventions might prevent disease development and/or progression. Biomarkers for this purpose have been sought, but these searches have been unsuccessful to date. Conventional radiographs are currently the standard method for a radiographic diagnosis of knee OA [7-9]. The most common grading system for OA is the Kellgren-Lawrence (K/L) system, which classifies OA into 5 grades according to its severity [7]. Several previous studies have defined the criterion for a radiographically assessed OA change as K/L grade 2 or worse [10, 11], and this is often used in epidemiological studies. Factors that can predict the progression of OA in the knees of patients with a K/L grade of 0/1 would help identify patients at high risk for future development of OA.

When long-term follow-ups were performed on changes occurring over time based on radiographs, some knees showed worsening of the K/L-grade, but some did not. We hypothesized that if it is possible to detect a difference between those knees at baseline, then we can predict which knees have the potential for exacerbation of OA before radiographic changes become evident. However, biomarkers that fulfill this prediction have not been established.

Magnetic resonance imaging (MRI) provides high-resolution visualization of most components of the knee joint, including the articular cartilage, menisci, intra-articular ligaments, synovium, bone marrow, subchondral cysts, and other peri-articular and intra-articular lesions that are not detectable radiographically. MRI also has a greater sensitivity than radiographs to detect bone changes that are typical features of OA [12, 13]. Considering that obvious osteophyte formation is one of the criteria for OA, and that osteophyte formation anywhere in the knee joint is more easily detected with MRI, we speculated that detecting the very early formation of osteophytes could serve as a pre-radiographic biomarker for OA.

The purposes of our study were to examine the frequency and distribution of osteophyte formation in patients' knees using MRI and to determine the role of osteophyte detection in predicting the future development of OA versus plain radiographic examinations that may result in undetected OA pathology.

MATERIALS AND METHODS

Cohort

We used publicly available data from the Osteoarthritis Initiative (OAI), which is a longitudinal observational cohort study of the natural history of knee OA and associated risk factors. The OAI is a public-private partnership jointly sponsored by the National Institutes of Health (NIH). OAI data are a resource for identifying the most promising biomarkers associated with the development and progression of symptomatic knee OA.

A total of 4796 subjects, men and women aged 45 to 79 years, who either have or are at increased risk of developing knee OA, were enrolled in the study [14]. Annual radiography, MRI, and clinical assessments of knees and disease activity were performed for all participants over a period of 6 years [14]. Details of the cohort have been published elsewhere and can be found at the OAI website: http://oai.epi-ucsf.org/datarelease/StudyOverview.asp

As a first step towards model construction, data were obtained from OAI version E.1 (Entire cohort version 1). The right knees of all subjects were assessed, because in the OAI dataset, two MRI sequences were excluded from the left knee examination unless subjects had surgical hardware in their right knee, in which case, the two sequences were to be performed on the knee without surgical hardware [14]. So in case of later necessity using full sequence of MRI data, we selected right knees as prior materials.

In version E.1., 2110 right knees were registered at the time the baseline was established (version 0.E.1.: baseline entire cohort version 1), and 1658 right knees were followed from baseline until 48 months had elapsed (version 5.E.1.:48 months entire cohort version 1). For those 1658 knees, the following exclusion criteria were applied: 1) Knees that lacked 48-month data (156 knees did not have the central reading data for K/L grade) [15], 2) Knees treated with knee surgery between baseline and the 48-month time period (8 knees had already undergone surgery before baseline, and 14 knees underwent surgery between baseline and 48 months), and 3) K/L severity grade of 2 or worse at baseline (649 knees were grade 2 or worse). The resulting sample contained 831 right knees with K/L grade 0/1 at baseline (Fig. 1).

A second step was then performed on the knees. We divided them into two groups: knees assessed radiographically to have no OA change (NOA group), i.e., K/L grade 0/1 at baseline and 48 months later and knees radiographically determined to have an OA change (pre-radiographic-OA group [PROA group]), i.e., those with K/L grade 0/1 at baseline and grade ≥2 48 months later (Fig. 1).

The K/L grade for each knee was assessed via central reading of knee radiographs; these assessments were performed at the Boston University Clinical Epidemiology Research and Training Unit [15]. OAI investigators used an extensive adjudication process to establish the baseline knee OA diagnosis. Three central readers with extensive training and experience with the K/L classification systems served as adjudicating readers. When 2 readers agreed on independent readings, that score

was entered for the patient. When a disagreement occurred, a third expert reviewed the scores from both readers. If the third reader agreed with either the first or second reader's scoring, then the agreed-upon score was determined to be final. If the third expert reader did not agree with either of the other readers, the 3 readers attended an adjudication session in which consensus scoring was obtained. Reliability among the adjudicating readers was substantial to almost perfect, with weighted kappa (kw) coefficients ranging from 0.70 to 0.87 for repeated independent readings separated by 3 to 9 months [15]. A total of 763 knees were allocated to the NOA group, and 68 knees were assigned to the PROA group (Fig. 1).

To balance the groups and avoid bias of the demographic, historical, and clinical assessment data (i.e., age, gender, body mass index [BMI], race, and Western Ontario and McMaster Universities Arthritis Index [WOMAC]), a propensity score analysis was used [16, 17]. Propensity score matching is a statistical matching technique that attempts to estimate the effect of an intervention by accounting for the covariates that predict receiving the intervention, reducing the bias due to confounding that could affect an estimate of the effect obtained from simply comparing outcomes with controls [16]. Later in the study, we focused on whether any significant change could occur for each group related to BMI and the WOMAC total score between baseline and the 48-month time point. All data (age, gender, BMI, race, and WOMAC score) were drawn from the OAI dataset.

MRI sequence

Images were acquired on a 3 Tesla MRI scanner (Siemens MAGNETOM Trio, Erlangen, Germany) and a quadrature transmit-receive knee coil (USA Instruments, Aurora, OH). The acquisition for morphological cartilage analysis was a double oblique coronal T1 3D FLASH sequence with water excitation (coronal FLASH WE) with a slice thickness of 1.5 mm, an in-plane resolution of 0.31 mm x 0.31 mm, and an acquisition time of 8 minutes and 30 seconds. The sagittal 3D DESS WE images (sagittal DESS WE) were prescribed orthogonal to the coronal FLASH WE with a slice thickness of 0.7 mm and 0.37 mm x 0.46 mm in-plane resolution (acquisition time 10 minutes 23 seconds) [18]. To directly compare DESS WE with coronal FLASH WE, DESS WE underwent MPR to create 64 double oblique coronal images with 1.5 mm slice thickness (coronal MPR DESS WE), oriented in the same way as the coronal FLASH WE.

When examining each site for osteophyte formation, we searched using the axial MPR 3D DESS WE sequence for assessing the intercondylar fossa and patellofemoral joint initially, and then used the coronal MPR 3D DESS WE and T1 3D FLASH sequence to assess the edge of the condyle and the intercondylar eminence and fossa again. Finally, a sagittal 3D DESS WE sequence was used to check that no osteophytes were overlooked.

Image analysis

A single orthopedic knee surgeon who had 5 years of experience in musculoskeletal image reading analyzed the images. The reader analyzed 8 sites of interest in terms of occurrence of osteophyte formation; that is, at the medial and lateral femoral condyle (MFC and LFC, respectively), medial and lateral tibial plateau (MTP and LTP, respectively), medial and lateral facets of the patellofemoral joint (PM and PL, respectively), tibial spine (TS), and femoral intercondylar notch (IC), and the sizes of the osteophytes in the knee joint were assessed and compared between the two groups (Fig. 2).

Osteophyte size was assessed using a semiquantitative whole-organ magnetic resonance imaging score (WORMS) that included an 8-point scale for scoring marginal osteophytes [19]. With this system, osteophytes at each site were graded from 0 to 7 on the following scale: 0=none; 1=equivocal; 2=mild; 3=mild-moderate; 4=moderate; 5=moderate-large; 6=large; 7=very large by comparing the images to be assessed with the published schema [19]. Osteophyte size at the IC was assessed by the largest size at either the medial or lateral side.

After WORMS were assessed for osteophyte size at each site, we calculated the prevalence of the osteophytes based on the WORMS classification: 2 points or more defined a mild-size osteophyte and 4 points or more defined a moderate-size osteophyte.

Intra-observer reliability was assessed by reading 30 sets of randomly selected images with an interval of 3 weeks. A musculoskeletal radiologist with 15 years of experience in the field read the

same sets of images, and inter-observer reliability was assessed.

Statistical analysis

For the baseline variables, we constructed summary statistics, with frequencies and proportions for categorical data, and means and SDs for continuous variables. We compared patient characteristics using the chi-square test for categorical outcomes and t tests or the Wilcoxon rank sum test for continuous variables, as appropriate. Patient selection was performed employing the propensity score matching method with a Greedy 5-to-1 digit-matching algorithm for clinical factors, i.e., age, sex, race, and WOMAC score.

Patient selection was performed employing the propensity score matching method for clinical factors, i.e., age, sex, race, and WOMAC score. Our applied algorithm performed one to one nearest neighbor within-caliper matching; therefore, matches were made within a caliper width of 0.00001, then caliper width decreased incrementally for unmatched cases to 0.1[20-22]. At each stage, control subject with closest propensity score was selected as the match to the case. The sampling was done without replacement. After all of the propensity-score matches had been performed, we compared baseline covariates between the two groups.

The primary endpoint for osteophyte prevalence was evaluated by Fisher's exact test and estimated by odds ratios (OR) with 95% confidence intervals (95% CI). Additionally, intra-observer

reliability was assessed by Kendall's coefficient of concordance and inter-observer reliability was evaluated with the Kappa coefficient of concordance.

All comparisons were planned, and the tests were two-sided. A p-value of less than 0.05 was considered to be statistically significant. All statistical analyses were performed with SAS software version 9.3 (SAS Institute, Cary, NC).

RESULTS

Demography, BMI, and WOMAC scores of the NOA and PROA groups

The demographic, historical, and clinical assessment data and K/L grade (both at baseline and 48 months) before the propensity analysis are shown in Table 1. In the NOA and PROA groups, BMI at baseline (27.2+/-4.3 vs. 28.5+/-4.4, respectively) and 48 months (27.4+/-4.5 vs. 28.7+/-4.6, respectively), as well as WOMAC total score at baseline (6.3+/-10.2 vs. 9.4+/-12.7 respectively), were statistically significantly higher in the PROA group than in the NOA group.

By using propensity score analysis on the two groups, we identified 66 knees from both groups, and the differences between the demographic, historical and clinical assessment data extracted were all non-significant between the NOA and PROA groups. Further out, there were no statistically significant changes for BMI (28.2+/-3.8 vs. 28.4+/-4.4) and the WOMAC total score (9.7+/-14.2 vs. 9.2+/-12.6) between baseline and the 48-month time point for the NOA and PROA groups (Table 2).

Reliability

Kendall's coefficient of concordance for intra-observer reliability was 0.92, 0.91, 0.91, 0.86, 0.94, 0.90, 0.92, and 0.92 for the MFC, MTP, LFC, LTP, TS, PM, PL, and IC respectively. The kappa coefficient of concordance for inter-observer reliability was 0.65, 1.00, N.A. (not available), 1.00, 0.86, 0.83, 0.76, and 0.87, respectively.

Number of osteophyte formations

The number of knees positive for osteophytes at each site was assessed, and the odds ratio of the number of knees between the NOA group and PROA group was calculated, when defining no less than mild or no less than moderate-size osteophytes as positive for osteophyte formation (Table 3).

The number of knees that had no less than mild-size osteophytes was 56, and the odds ratio in the PROA group for intercondylar notch osteophyte formation was 9.41, (Table 3); when defining no less than moderate as positive, these values were 21 and 9.8, respectively (Table 3). IC osteophytes were relatively high compared to other sites on both criteria (Table 3).

No smaller than mild-size osteophytes were more frequently observed at the MFC (p=0.00278), MTP (p=0.0046), TS (p=0.0146), PM (p<0.0001), PL (p=0.0012), and IC (p<0.0001) in PROA knees than in NOA knees. No smaller than moderate-size osteophytes were more frequently

observed only at the IC (p<0.0001) in PROA knees compared to NOA knees.

Co-existence of osteophyte formation was assessed. Defining no smaller than mild-size osteophytes as positive, 6 knees had isolated osteophytes at the IC, 22 had isolated osteophytes at both the IC and another site, and 6 had isolated osteophytes at another site in the NOA group. Thus, 28 knees had IC osteophytes among the 34 knees that had osteophytes at any site. Defining no smaller than moderate-size osteophytes as positive, 3 knees had isolated osteophytes at the IC, no knee had isolated osteophytes at both the IC and another site, and no knee had isolated osteophytes at another site in the NOA group (Table 4(a)). Defining no smaller than mild-size osteophytes as positive, 7 knees had isolated osteophytes at the IC, 49 (28+17+4) had isolated osteophytes at both the IC and another site, and 5 had isolated osteophytes at another site in the PROA group. Thus, 56 knees had IC osteophytes among the 61 knees that had osteophytes at any site. Defining no smaller than moderate-size osteophytes as positive, 17 knees had isolated osteophytes at the IC, 4 had isolated osteophytes at both the IC and another site, and no knee had isolated osteophytes at another site in the PROA group (Table 4(b)).

DISCUSSION

In this study, we showed the possibility that osteophyte formation detected via MRI at baseline, but not on conventional radiographs, could serve as a biomarker for predicting radiographic OA

development. MRI examinations are costly, but this finding would enable an early detection of knees at risk. Thus, it can lead to very early interventions, a situation that has not been achieved as yet.

Diagnostic value of osteophytes in OA

Osteophyte formation is one of the typical features of OA, and detection is an important aspect of the diagnosis of knee OA [23]. The size and extent of osteophyte formation is used for classifying the stage of OA [7]. Osteophytes are strongly associated with radiographic detection of joint space narrowing, subchondral sclerosis, and cartilage defects both in tibiofemoral and patellofemoral joints [24-26]. Roemer et al reported that the risk of severe cartilage damage increased markedly with increasing osteophyte size in the majority of patients in a population-based cohort study and that an atrophic or a hypertrophic phenotype of OA, in which cartilage damage and osteophyte formation were not in accordance with each other, accounted for only the mild subjects [27]. Thus, we consider that the early detection of osteophyte formation would likely be of diagnostic value.

The use of MRI to detect osteophytes and the advantages of this method over radiographs have been discussed previously. Guermazi et al. reported that osteophytes were the most common abnormality found on MRI among 710 people over 50 years of age with K/L grade 0 knees (74%, 524/710) [28]. Hayashi et al reported a high prevalence of osteophyte formation detected with MRI in K/L grade 0 knees. They identified one of the reasons for discrepancies between radiographs and

MRI in detecting osteophyte as overlap between the normal bony margin and the osteophytes [29]. Osteophytes at the IC region were not detectable with AP and lateral radiography, presumably nor with coronal and sagittal MR images. We used axial images to assess IC osteophytes, but a three-dimensionally reconstructed model might be better to visualize all of the osteophytes that might be overlooked in the previous studies and in the present study.

Osteophytes and symptoms

Although IC osteophyte formation predicted the future development of radiographic OA, our data showed no difference between the NOA and PROA groups at 48 months in terms of WOMAC total score. Correlations between symptom and radiographic severity have been discussed. Some authors found positive associations between them, but others found discrepancies. Cho et al found that in community residents, K/L grade 2 knees had higher WOMAC scores compared to K/L grade 0 or 1 knees. Link et al and Barker et al reported a discordance between K/L grades and WOMAC scores [30, 31]. These controversial results might be attributable to the fact that knees in a variety of states are included in the same grade. Cotofana reported using OAI data that denuded areas of subchondral bone (dABs) correlated with pain and that K/L grade 2 knees exhibited a variety of dABs, whereas 65% of knees had no dABs [32]. Thus, by incorporating factors other than K/L grade, the likelihood of identifying symptomatic OA might have been greater; however, we believe our findings are still

important for the purpose of detecting OA in asymptomatic patients as early as possible. Therefore, the threshold that we adopted in the present study of K/L grade 2 or worse as having OA is generally accepted, and we felt it was adequate.

Osteophyte readings of MRI

Recently, there have been advocates of several MRI-based semi-quantitative knee assessment systems [19, 33, 34]. These systems all incorporated osteophyte formation as a scoring item. Peterfy et al reported a high inter-reader agreement (ICC) of 0.97 in osteophyte assessment with the WORMS system with two readers [19]. With the Knee Osteoarthritis Scoring System (KOOS), the ICC for inter-observer and intra-observer reproducibility was 0.71 and 0.76, respectively [33]. With the Boston-Leeds Osteoarthritis Knee Score (BLOKS) system, the weighted kappa for inter-observer reliability reached 0.65 [34]. We employed the WORMS system for the current study, because it is the most widely used [27, 35, 36], and our data for reproducibility were thought to be acceptable. Guermazi et al reported inconsistency in reading osteophyte formation among investigators in reading radiographs (K/L grading) [10], so we used central readers for K/L grading assessment [15], so that we did not need to take our own reading bias into account.

Detection of osteophytes at the inter-condylar notch

The use of MRI in diagnosis of or for research purposes for OA of the knee has enabled detailed osteophyte assessment. Hayashi assessed 16 sites for osteophyte formation in K/L grade 0 knees and reported that as many as 60.8% (423/696) of knees had grade ≥2 osteophytes on the WORMS scale in the medial femoral posterior subregion [29]. In the other 15 sites, 2.0% to 33.1% of knees had osteophytes [29], which was somewhat similar to our data when combining the NOA and PROA groups. We reported that the highest prevalence was in the IC region, which reached 63.6% (28+56/66+66) prevalence, and osteophytes were seen in 4.5% to 34.8% of knees in the other 7 subregions (Table 3). Some of the osteophytes at the medial femoral posterior subregion reported by Hayashi et al and at the IC region reported in the present study might be identical if they had some three-dimensional expansion, but presumably not all of them would be identical [29], because the former were usually assessed by sagittal images, and the latter were assessed by axial images. Thus, we stress the importance of axial image analysis to detect IC osteophytes.

For the formation of osteophytes, transforming growth factor beta (TGF-beta) plays an important role [37]. The TGF-beta expression level in the synovium increased with OA progression [38], and the commonest sites of definite synovitis were posterior to the PCL [39], where IC osteophytes locate closely, which might account for the preference of osteophyte formation at the IC.

Limitations and Strengths

The present study has several limitations. First, we did not compare other imaging markers, such as cartilage, bone marrow lesions (BMLs), etc. This would be of interest, but our focus was on osteophytes, because our next goal is to establish a screening system to detect knees at risk at a mass level; thus, an imaging marker that could be detected with conventional radiographs had priority. It would be of help clinically to establish a method to detect osteophytes at the IC with conventional radiographs by modulating the knee position and the direction of the x-ray beam, which has yet to be established. Wolfe et al reported a comparison among three radiographs in terms of the ability to detect osteophytes. They concluded that little difference in osteophyte detection was present among semiflexed, schuss-tunnel, and weight bearing anteroposterior views [40], but we speculate that there would be more to be explored.

Second, we selected five items for the analysis of the propensity score; age, gender, BMI, race, and WOMAC score; among them, the WOMAC score before propensity analysis differed between the NOA and PROA groups, which indicated that the PROA groups had unidentified symptoms at baseline. It would be of interest if we could incorporate items related to symptoms for the detection of PROA groups of knees, because it might increase the sensitivity for detecting PROA knees. Our data showed that 10 out of 66 knees were neglected simply due to no IC osteophyte formation.

Third, we dealt only with the incident cohort data of the OAI; studies dealing with other cohorts will enhance these findings. While a number of cross-sectional studies have reported the association

of osteophytes to the progression of knee OA [41], as far as we could determine, no longitudinal study results have yet reported the association of osteophytes of the intercondylar notch to the progression of knee OA, so this study might be the first to assess the relationship between osteophytes and the progression of knee OA.

CONTRIBUTIONS

JK, TS, KT contributed to the conception and design of the study.

SY, RA, YM contributed to the acquisition, collection, assembly of data and provision of study materials.

YS, AW, SM, YA, TF, JE, HH, YY, TS contributed to the analysis and interpretation of data, technical support, statistical expertise.

JK, TS, SY, YS, AW contributed to drafting the article.

RA, YM, SM, YA, TF, JE, HH, YY, TS, KT contributed to revising it critically for important intellectual content.

All authors contributed to final approval of the version.

TS and JK take responsibility for the integrity of the work.

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COMPETING INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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Table 1. Demographic, historical, and clinical assessment of the data, including K/L grade prior to propensity analysis

Abbreviations: K/L = Kellgren/Lawrence; max = maximum; min = minimum; n = number in group; NOA = no-osteoarthritis; PROA = pre-radiographic-osteoarthritis; WOMAC = Western Ontario and McMaster Universities Arthritis Index; Δ = change.

* All p-values determined via t-tests, unless otherwise noted.

† Chi-square test.

Bold *p*-values indicate a statistically significant difference (<0.05)

	NOA n=763	PROA n=68	*p*-value*
Age, years			
Mean (SD)	58.5 (8.8)	60.1 (8.4)	0.1393
Range (min – max)	(45 – 79)	(45 – 78)	
Gender†			
Female/male	369/394	40/28	0.0982 †
Race†			
White or Caucasian	631	53	0.4467 †
Black or African American	120	13	0.3758 †
Hispanic or Latino	7	0	0.4276 †
Asian	5	1	0.3335 †
Other Non-white	4	1	0.7651 †
Undisclosed	1	0	0.3244 †
Mean BMI, kg/cm^2			
Baseline (SD)	27.2 (4.3)	28.5 (4.4)	**0.0177**
Range (min – max)	(17.2 – 42.4)	(19.1 – 40.3)	
48 months (SD)	27.4 (4.5)	28.7 (4.6)	**0.0217**
Range (min – max)	(16.8 – 44.2)	(19.2 – 41.2)	
Δ Baseline – 48 months (SD)	-0.2 (1.7)	-0.3 (2.2)	0.7871
Range (min – max)	(-7.8 – 7.1)	(-7 – 5.9)	
Mean WOMAC total score			
Baseline (SD)	6.3 (10.2)	9.4 (12.7)	**0.0174**
Range (min – max)	(0 – 81)	(0–54)	
48 months (SD)	6.1 (11.5)	8.6 (12.1)	0.0812
Range (min – max)	(0 – 96)	(0 – 61)	
Δ Baseline – 48 months (SD)	0.2 (9.9)	0.7 (12.2)	0.7100

Range (min – max)	(-96 – 40)	(-44 – 48)
K/L grade, baseline > 48 months (%)		
0 > 0	514 (67.4)	
0 > 1	20 (2.6)	
1 > 1	229 (30.0)	
0 > 2		19 (27.9)
0 > 3		6 (9.1)
0 > 4		0 (0)
1 > 2		28 (42.4)
1 > 3		12 (18.2)
1 > 4		3 (4.5)

Table 2. Demographic, historical, and clinical assessment of the data and K/L grade following propensity analysis

Abbreviations: K/L = Kellgren/Lawrence; max = maximum; min = minimum; n = number in group; NOA = no-osteoarthritis; PROA = pre-radiographic-osteoarthritis; WOMAC = Western Ontario and McMaster Universities Arthritis Index; Δ = change.

* All p-values determined via t-tests, unless otherwise noted.

† Chi-square test.

	NOA n=66	PROA n=66	*p*-value*
Age, years			
Mean (SD)	60.7 (10.1)	60.2 (8.4)	0.7584
Range (min – max)	(47 – 78)	(45 – 78)	
Gender†			
Female/male	35/31	39/27	0.4830 †
Race†			
White or Caucasian	55	52	0.5051 †
Black or African American	10	13	0.4912 †
Hispanic or Latino	0	0	
Asian	1	1	1.0000 †
Other Non-white	0	0	
Undisclosed	0	0	
Mean BMI, kg/cm^2			
Baseline (SD)	28.2 (3.8)	28.4 (4.4)	0.6323
Range (min – max)	(19.6 – 37.9)	(19.1 – 40.3)	
48 months (SD)	28.5 (3.9)	28.8 (4.6)	0.7035
Range (min – max)	(20.4 – 38.3)	(19.2 – 41.2)	
Δ Baseline – 48 months (SD)	-0.3 (1.4)	-0.3 (2.2)	0.8624
Range (min – max)	(-4 – 2.9)	(-7 – 5.9)	
Mean WOMAC total score			
Baseline (SD)	9.7 (14.2)	9.2 (12.6)	0.8168
Range (min – max)	(0 – 81)	(0 – 54)	
48 months (SD)	9.2 (14.1)	8.6 (12.2)	0.7938
Range (min – max)	(0 - 73)	(0 - 61)	
Δ Baseline – 48 months (SD)	0.5 (11.3)	0.5 (12.3)	0.9133
Range (min – max)	(-32.6 – 40)	(-43.6 – 47.9)	

K/L grade, baseline > 48 months (%)		
0 > 0	41 (62.1)	
0 > 1	0 (0)	
1 > 1	25 (37.9)	
0 > 2		19 (27.9)
0 > 3		6 (9.1)
0 > 4		0 (0)
1 > 2		26 (39.4)
1 > 3		12 (18.2)
1 > 4		3 (4.5)

Table 3. Number of positive osteophyte formation sites

* All p-values determined via Fisher's exact test

Abbreviations: NOA = no-osteoarthritis; PROA = pre-radiographic-osteoarthritis; MFC = medial femoral condyle; MTP = medial tibia plateau; NS=not significant; LFC = lateral femoral condyle; LTP = lateral tibia plateau; TS = tibial spine; PM = medial facet of the patella-femoral joint; PL = lateral facet of the patella-femoral joint; IC = intracondylar notch of the femur

Bold p-values indicate a statistically significant difference (<0.05)

Sites	MFC	MTP	LFC	LTP	TS	PM	PL	IC
NOA group	0	2	2	1	14	12	2	28
PROA group	6	13	8	5	28	34	15	56
p-value	**0.0278**	**0.0046**	0.0960	0.2079	**0.0146**	**<0.0001**	**0.0012**	**<0.0001**
Odds ratio (95% confidence interval limit)	NS	7.85 1.7 - 36.34	4.41 0.9 - 21.64	5.33 0.61 - 46.91	2.74 1.27 - 5.89	4.78 2.17 - 10.54	7.6 3.31 - 17.45	9.41 2.06 - 43.06
NOA group	0	0	0	0	0	0	0	3
PROA group	0	0	0	0	1	4	0	21
p-value	-	-	-	-	1.0000	0.1193	-	**<0.0001**
Odds ratio (95% confidence interval limit)	NS	NS	NS	NS	NS	NS	NS	9.8 2.76 - 4.85

Table 4(a). Co-existence of osteophytes between the IC and other sites in the NOA group

Abbreviations: NOA = no-osteoarthritis; PROA = pre-radiographic-osteoarthritis

NOA group

		Intercondylar notch			
		none	mild	moderate or worse	total
Other sites	none	32	6	0	38
	mild	6	19	3	28
	moderate or worse	0	0	0	0
	total	38	25	3	66

Table 4(b). Co-existence of osteophytes between the IC and other sites in the PROA group

Abbreviations: NOA = no-osteoarthritis; PROA = pre-radiographic-osteoarthritis

PROA group

		Intercondylar notch			
		none	mild	moderate or worse	total
Other sites	none	5	7	0	12
	mild	5	28	17	50
	moderate or worse	0	0	4	4
	total	10	35	21	66

FIGURE LEGENDS

Fig. 1. Flow diagram showing the extraction of subject data for the current study from the Osteoarthritis Initiative (OAI) database.

Abbreviations: K/L = Kellgren/Lawrence; NOA = no-osteoarthritis; PROA = pre-radiographic-osteoarthritis

Fig. 2. Sites at which osteophytes were assessed. MRI showing a coronal view of the knee and the following locations: LFC = lateral femoral condyle; LTP = lateral tibia plateau; MFC = medial femoral condyle; MTP = medial tibia plateau; TS = tibial spine. (B) MRI showing an axial view of the femoral condyle and pinpointing the following locations: PL = lateral facet of the patellofemoral joint; PM = medial facet of the patellofemoral joint; IC = intracondylar notch of the femur

Fig. 1

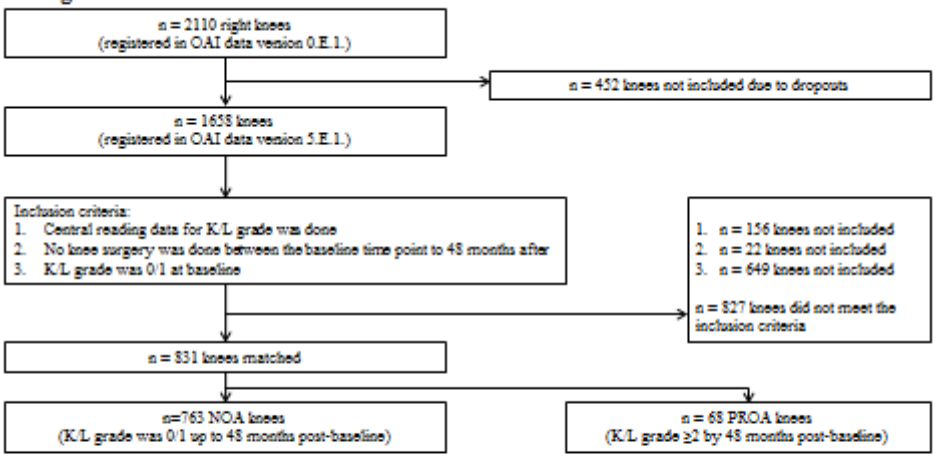
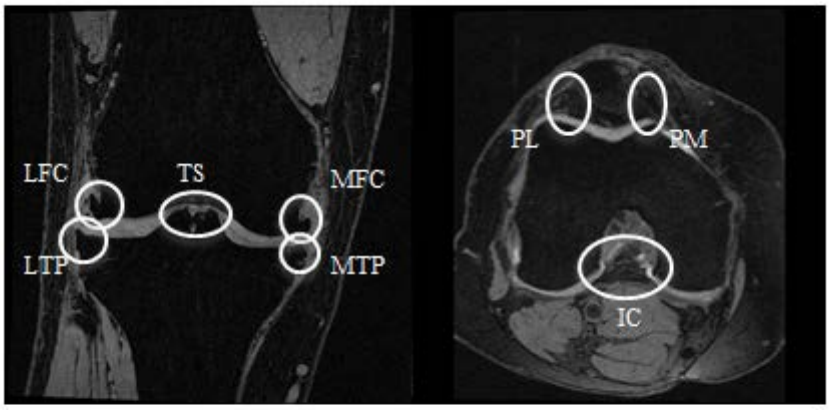

n = 2110 right knees
(registered in OAI data version 0.E.1.)
n = 452 knees not included due to dropouts
n = 1658 knees
(registered in OAI data version 5.E.1.)
Inclusion criteria:
1. Central reading data for K/L grade was done
2. No knee surgery was done between the baseline time point to 48 months after
3. K/L grade was 0/1 at baseline
1. n = 156 knees not included
2. n = 22 knees not included
3. n = 649 knees not included
n = 827 knees did not meet the inclusion criteria
n = 831 knees matched
n=763 NOA knees
(K/L grade was 0/1 up to 48 months post-baseline)
n = 68 PROA knees
(K/L grade ≥2 by 48 months post-baseline)

Fig. 2



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