

## Alignment of the medial tibial plateau affects the rate of joint space narrowing in the osteoarthritic knee

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### SUMMARY

**Objective:** To determine, in serial fixed-flexion (FF) radiographs of subjects with knee osteoarthritis (KOA), the importance of, and basis for, the effect of alignment of the medial tibial plateau (MTP), as determined by the inter-margin distance (IMD), on joint space narrowing (JSN).

**Methods:** Baseline and 12-month X-rays of 590 knees with Kellgren and Lawrence grade (KLG) 2/3 OA from the public-release dataset of the Osteoarthritis Initiative (OAI) were assigned to subgroups based upon IMD at baseline ( $IMD_{BL}$ ) and the difference between  $IMD_{BL}$  and  $IMD_{12mos}$ . Relationships of JSN to  $IMD_{BL}$  and to the difference between  $IMD_{BL}$  and  $IMD_{12mos}$  were evaluated.

**Results:** In all 590 knees, mean JSN was  $0.13 \pm 0.51$  mm ( $P < 0.0001$ ) and MTP alignment and replication of  $IMD_{BL}$  in the 12-month film were, in general, poor. JSN was significantly ( $P = 0.012$ ) more rapid in Subgroup A ( $IMD \leq 1.70$  mm at both time points) than in Subgroup B (both  $IMDs > 1.70$  mm):  $0.15 \pm 0.43$ ;  $0.08 \pm 0.47$ . Within Subgroup B we identified a subset, Subgroup B1, in which, although alignment was poor at both time points, the large  $IMD_{BL}$  was, by chance, highly reproduced by  $IMD_{12mos}$  (difference between the two  $IMDs = 0.01 \pm 0.27$  mm, NS). JSN in Subgroup B1 was  $0.06 \pm 0.41$  mm and did not differ from that in other knees of Subgroup B ( $P = 0.87$ ). The standardized response mean (SRM) in all 590 knees and Subgroups A, B and B1 was 0.25, 0.34, 0.17 and 0.06, respectively. Independent of  $IMD_{BL}$ , JSN correlated significantly with the difference between the  $IMDs$  in the two radiographs ( $r = 0.17$ ,  $P = 0.0001$ ).

**Conclusion:** Skewed MTP alignment in serial films and poor replication of  $IMD_{BL}$  in the follow-up exam affect JSN measurement. The magnitude of change in joint space width (JSW) related to the poor quality of alignment that is common with the FF view jeopardizes accurate evaluation of JSN.

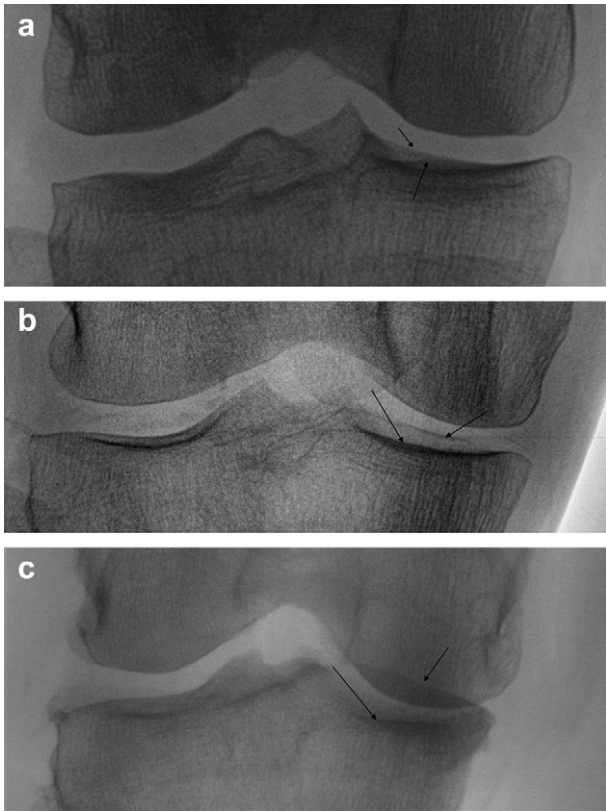
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Slowing of articular cartilage breakdown in osteoarthritis (OA) is considered to be the most relevant target in development of structure-modifying drugs (SMOADs) and can be assessed in randomized clinical trials (RCTs) by various methods. Measurement of the rate of joint space narrowing (JSN) in patients treated with the active agent, relative to placebo, is the approach favored by most investigators and regulatory agencies.

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A variety of protocols accurately and sensitively measure JSN over time in knee radiographs. The fixed-flexion (FF) and Lyon schuss (LS) views offer greater reliability in measurement of tibio-femoral joint space width (JSW), and greater sensitivity to JSN, than a standing anteroposterior (AP) view<sup>1</sup>. In both the LS and FF views, the knee is positioned in 20–30° of flexion. However, in the LS view, the angle of the X-ray beam is adjusted under fluoroscopy to achieve parallel alignment of the beam with the medial tibial plateau (MTP), as indicated by superimposition of the anterior and posterior margins of the plateau (Fig. 1). In contrast, in the FF protocol, the beam angle is fixed at 10° caudally for each exam; parallel alignment is, therefore, fortuitous and much less common than in the LS view<sup>2</sup>.



**Fig. 1.** Radiographs of OA knees showing parallel MTP alignment (a), with superimposition of the anterior and posterior margins (arrows) of the plateau (IMD = 0 mm at the middle of the MTP); (b) skewed alignment of the MTP (IMD = 2.5 mm in the middle of the medial joint space) and (c) dramatic misalignment (IMD = 7.5 mm in the middle of the medial joint space).

When parallel alignment of the MTP was present in both members of paired films taken at a 2-year interval, FF radiographs were sensitive to JSN. However, parallel alignment occurred in less than half of the pairs<sup>3</sup>. An inter-margin distance (IMD, a measure of superimposition of anterior and posterior margins of the MTP, Fig. 1)  $\leq 1.5$  mm was achieved in only 51% of FF views<sup>2</sup>. Nevitt *et al*<sup>4</sup> reported good sensitivity of the FF view in detecting JSN in OA knees and concluded that absence of alignment did not preclude sensitivity to JSN.

In the only head-to-head comparison of LS and FF protocols<sup>2</sup>, JSN was much more rapid with the LS view, which was also much more sensitive to JSN over 12 months. Mean IMD was  $< 1$  mm with LS, but more than twice as large in the FF view. We suggested the greater sensitivity of the LS view to JSN was due to its superiority in aligning the MTP.

In another direct comparison that emphasized the importance of MTP alignment, the fluoroscopically-assisted semiflexed AP view was compared with the non-fluoroscopic metatarsophalangeal view<sup>5</sup>. In a 14-month follow-up exam, the latter showed no JSN whereas JSN with the semiflexed AP was  $0.09 \pm 0.31$  mm. An IMD  $\leq 1$  mm was achieved in  $> 90\%$  of the paired semiflexed AP views but only 29% of the baseline metatarsophalangeal views, in which it was reproduced at follow-up in only 54%.

The Osteoarthritis Initiative (OAI)<sup>6</sup> provides the largest series of subjects with knee OA (KOA) that has been assembled to improve knowledge of the disease. It makes available to investigators clinical, X-ray, magnetic resonance imaging (MRI) and biological data for the evaluation of disease progression. For technical reasons, the FF view was selected as the standardized radioanatomic

positioning protocol for the OAI. The present study was undertaken to confirm that measurements of JSW were artefactually modified in films in which the quality of alignment of the MTP with the X-ray beam was inadequate, jeopardizing the interpretation of data on JSN over time in relation to results obtained with other OAI evaluation tools.

The present work utilized baseline and 12-month FF radiographs from a subset of subjects in the OAI<sup>6</sup> and was conducted to elucidate the importance of alignment in measures of JSN by answering three questions:

1. Does good alignment of the MTP in both the baseline and 12-month follow-up X-ray result in greater sensitivity to change in JSW than a large IMD at both time points?
2. Among paired radiographs in which poor MTP alignment is present at baseline, does replication of the large IMD in the follow-up film provide good sensitivity to change?
3. Regardless of the magnitude of the baseline IMD, does a difference in MTP alignment between the baseline and follow-up radiographs modify JSN?

## Subjects and methods

Subjects in this analysis are a subset of the 4796 participants in the OAI, an ongoing 4-year, multi-center, longitudinal, prospective observational cohort study focusing primarily on KOA. The study protocol, amendments, and informed consent documentation were reviewed and approved by the institutional review boards at the participating clinical centers. Data used in this manuscript were obtained from the public use database for the OAI Progression subcohort available at <http://www.oai.ucsf.edu/><sup>6</sup>. Subjects in the Progression subcohort had an age range of 45–79 years and at least one knee with symptomatic (pain, aching or stiffness on most days of a month in the past year) and radiographic OA (grade 1–3 osteophyte)<sup>7</sup>. The data for the subsample used in this analysis are from Clinical Datasets 0.1.1 and 1.2.1 and Image Release 0.C.1 and 1.C.1<sup>8</sup>.

Among 956 knees from 523 cases, 113 were eliminated because of the presence of a lateral OA (i.e., a lateral compartment JSW less than medial compartment JSW) and six were eliminated because the baseline or 12-month X-ray was missing or technically unsatisfactory for measurement. Among the 837 remaining knees, Kellgren and Lawrence grade (KLG) zero, one and four changes, respectively, were found in 32, 116 and 99 knees. This report is based on an analysis of 590 paired baseline and follow-up knee radiographs from the 417 patients (both knees from 173 patients and one knee from 244 patients) who had KLG two or three OA in the baseline exam. KLG was determined either from independent readings of a musculoskeletal radiologist and a rheumatologist (DH), with discrepancies resolved by consensus, or from independent readings of the investigator in the Clinical Center and the musculoskeletal radiologist, with discrepancies adjudicated by DH. The protocol for the FF view has been described<sup>9</sup>. Measurements of IMD and JSW were performed exactly as described previously<sup>2</sup>. The rate of JSN was calculated as  $JSW_{BL} - JSW_{12mos}$ .

In each pair of films we analyzed the difference in IMD, in mm, in the follow-up film ( $IMD_{12mos}$ ), relative to IMD at baseline ( $IMD_{BL}$ ). A positive value signifies an  $IMD_{12mos}$  that was larger than  $IMD_{BL}$ . A negative value signifies an  $IMD_{12mos}$  smaller than  $IMD_{BL}$ .

## Composition of subgroups

To answer Question 1, Subgroup A, which had good alignment at both time points, was compared with Subgroup B, in which the IMD

was large in both films. Subgroup A was constituted of 256 knees (43.4% of all knees) in which  $IMD_{BL}$  and  $IMD_{12mos}$  were both  $\leq 1.70$  mm. Subgroup B contained 182 knees (30.8%) in which  $IMD_{BL}$  and  $IMD_{12mos}$  were both  $> 1.70$  mm. The threshold of 1.70 mm was selected specifically because it approximated that in a recent study of JSN in LS radiographs<sup>2</sup>.

To explore whether JSN is affected by a large  $IMD_{BL}$  even if the latter is replicated in the follow-up film (Question 2), we identified 80 knees in Subgroup B (designated Subgroup B1) in which the difference between  $IMD_{BL}$  and  $IMD_{12mos}$  was minimal ( $\pm 0.50$  mm) and was similar to that in Subgroup A ( $\pm 0.50$  mm).

In answering Question 3 we evaluated the difference in JSN between subgroups that differed markedly with respect to whether the difference between  $IMD_{12mos}$  and  $IMD_{BL}$  was positive or negative. Accordingly, we analyzed 12-month JSN in the 152 knees that did not fall into Subgroup A or B by constructing two additional subgroups: in Subgroup C (79 knees),  $IMD_{BL}$  was  $\leq 1.70$  mm and was smaller than  $IMD_{12mos}$ . In Subgroup D (73 knees), the relationship was reversed: i.e.,  $IMD_{BL}$  was  $\geq 1.70$  mm and was larger than  $IMD_{12mos}$  (Table 1).

### Statistical analysis

The unit of analysis unit was the knee. Differences between  $JSW_{BL}$  and  $JSW_{12mos}$  and between  $IMD_{BL}$  and  $IMD_{12mos}$  (overall and within subgroups) were tested with a Pairwise *t* test or a Pairwise Wilcoxon rank sum tests (skewed distribution). Associations between baseline and 1 year values were evaluated, using Pearson's product moment correlation coefficient or Spearman's rho (if distribution was skewed). Correlation between the rate of JSN and the difference between  $IMD_{BL}$  and  $IMD_{12mos}$  was estimated in the same manner.

The effects of the difference between  $IMD_{BL}$  and  $IMD_{12mos}$  and of the various subgroups on JSN were tested as fixed effects in a mixed model of regression, where the subject was considered as a random effect to take into account the within-subject correlation (two knees for the same subject). The mixed model was also applied on ranks because of the skewed distribution of JSN. Also, sensitivity to change in JSN in paired radiographs with differing alignment characteristics was expressed by the standardized response mean (SRM), i.e., the mean difference in JSN between baseline and 12-month radiographs divided by the standard deviation (SD) of that difference.

## Results

### Characterization of paired radiographs

Based upon differences in JSW in the paired baseline and follow-up radiographs, 12-month JSN for all 590 knees was  $0.13 \pm 0.51$  mm ( $P < 0.0001$ ) and SRM was 0.25.

**Table 1**  
Subgroups and overall characteristics

Subgroup	n	KL2/3	$IMD_{BL}$ , mm Mean (SD)	$IMD_{12mos}$ , mm Mean (SD)	$IMD_{12mos}-BL$ , mm Mean (SD)	JSN, mm Mean (SD)	JSN SRM
All	590	299/291	1.81 (1.29)	1.86 (1.39)	0.05 (1.16)	0.13 (0.51)	0.25
A	256	119/137	0.92 (0.44)	0.84 (0.47)	-0.08 (0.50)	0.15 (0.43)	0.34
B	182	98/84	3.14 (1.21)	3.23 (1.22)	0.09 (1.09)	0.08 (0.47)	0.17
B1	80	49/31	2.74 (0.92)	2.75 (0.97)	0.01 (0.27)	0.06 (0.41)	0.06
B2	102	49/53	3.45 (1.32)	3.60 (1.27)	0.15 (1.43)	0.10 (0.52)	0.19
C	79	43/36	1.02 (0.44)	2.74 (1.05)	1.72 (1.02)	-0.06 (0.43)	-0.14
D	73	39/34	2.51 (0.71)	1.09 (0.42)	-1.43 (0.79)	0.33 (0.80)	0.41
C+D	152	82/70	1.74 (0.95)	1.95 (1.16)	0.21 (1.82)	0.13 (0.66)	0.20

A:  $IMD_{BL}$  and  $IMD_{12mos}$  both  $\leq 1.70$  mm.

B:  $IMD_{BL}$  and  $IMD_{12mos}$  both  $> 1.70$  mm.

B1: Subgroup B, with differences between  $IMD_{BL}$  and  $IMD_{12mos}$  both  $< \pm 0.5$  mm.

B2: Knees from Subgroup B that did not meet criteria for Subgroup B1.

C:  $IMD_{BL} \leq 1.70$  mm and smaller than  $IMD_{12mos}$ .

D:  $IMD_{BL} > 1.70$  mm and greater than  $IMD_{12mos}$ .

For all 590 knees, the IMD was large in both the baseline and follow-up X-rays ( $1.81 \pm 1.29$  mm;  $1.86 \pm 1.39$  mm, respectively) and in both the range of values for IMD was very large (0.00–7.93 mm, 0.00–7.22 mm, respectively). Reproducibility of  $IMD_{BL}$  in the follow-up X-ray was marginal; i.e., the SD of the mean difference in  $IMD_{12mos} - IMD_{BL}$  was 1.16 mm, with a broad range of (-) 3.70 mm to (+) 5.65 mm.  $IMD_{12mos}$  was somewhat larger than  $IMD_{BL}$  and the mean difference between  $IMD_{12mos}$  and  $IMD_{BL}$  ( $0.05 \pm 1.16$  mm) was not significant ( $P = 0.3$ ).

The mean rate of JSN was significantly ( $P = 0.006$ ) larger in the 291 KLG three knees than in the 299 KLG two knees ( $0.35 \pm 0.59$  mm;  $0.16 \pm 0.42$  mm, respectively). Mean JSN was larger for males than for females ( $0.15 \pm 0.42$  mm;  $0.11 \pm 0.56$  mm, respectively,  $P = 0.008$ ), and was weakly correlated with age ( $\rho = 0.08$ ,  $P = 0.023$ ) but not with Body Mass Index (BMI) ( $r = 0.01$ ,  $P = 0.4$ ). After taking into account the within-patient correlation (model on ranks only), the effects on JSN of sex ( $P = 0.02$ ) and KLG ( $P = 0.0065$ ), but not those of age ( $P = 0.22$ ) or BMI ( $P = 0.78$ ), remained significant.

### Question 1

Does good alignment of the MTP in both the baseline and 12-month follow-up X-ray result in greater sensitivity to change in JSW than a large IMD at both time points?

Twelve-month JSN was greater ( $P = 0.012$ ) in Subgroup A (good alignment at both time points) than in Subgroup B (poor alignment at both time points),  $0.15 \pm 0.43$  mm and  $0.08 \pm 0.47$  mm, respectively (Table 1). The difference between these two subgroups remained significant ( $P = 0.046$ ) in the mixed model on ranks after adjustment for sex and KLG. SRM was also clearly greater in Subgroup A than in Subgroup B (0.34, 0.17, respectively) (Table 1).

### Question 2

Among paired radiographs in which poor MTP alignment is present at baseline, does replication of the large IMD in the follow-up film provide good sensitivity to change?

In Subgroup B1 (difference between  $IMD_{12mos}$  and  $IMD_{BL} = \pm 0.50$  mm) the mean difference between  $IMD_{12mos}$  and  $IMD_{BL}$  was only  $0.01 \pm 0.27$  mm and mean JSN was  $0.06 \pm 0.41$  mm, i.e., comparable to that of Subgroup B2 (knees from Subgroup B that did not meet criteria for Subgroup B1) in which mean JSN was  $0.10 \pm 0.52$  mm (Table 1). The mixed model on ranks indicated that, after adjustment for sex and KLG, the mean JSN in Subgroups B1 and B2 did not differ significantly ( $P = 0.87$ ). SRM was not larger in subgroup B1 than in Subgroup B (0.06 vs 0.17).

### Question 3

Regardless of the magnitude of the baseline IMD, does a difference in MTP alignment between the baseline and follow-up

radiograph with respect to MTP alignment artefactually modify JSN?

Among all 590 knees, 12-month JSN correlated with the difference in IMDs ( $r = -0.17$ ,  $\rho = -0.22$ ). An  $IMD_{12mos}$  that was larger than the corresponding  $IMD_{BL}$  was associated with a slower rate of JSN whereas an  $IMD_{12mos}$  that was smaller than the corresponding  $IMD_{BL}$  was associated with more rapid JSN. According to the regression slope, a 1.0 mm difference in  $IMD_{12mos}$ , relative to  $IMD_{BL}$ , was associated with a  $-0.07$  mm change in JSN ( $P = 0.0001$ ).

The difference in JSN between subgroups that differed markedly, depending upon whether the difference between  $IMD_{BL}$  and  $IMD_{12mos}$ , was positive or negative (Subgroups C and D, respectively, Table 1) was notable. In Subgroup C,  $IMD_{12mos}$  was significantly larger ( $P < 0.0001$ ) than  $IMD_{BL}$  [ $(+) 1.72 \pm 1.02$  mm]. In Subgroup D, in contrast,  $IMD_{12mos}$  was significantly smaller ( $P = 0.0001$ ) than  $IMD_{BL}$  [ $(-) 1.43 \pm 0.79$  mm]. JSN was much more rapid in Subgroup D than in Subgroup C [ $0.33 \pm 0.80$  mm;  $-0.06 \pm 0.43$  mm respectively]. Consistent with the difference between Subgroups C and D with respect to the direction [i.e.,  $(+)$  or  $(-)$ ] of  $IMD_{12mos} - IMD_{BL}$  (Table 1), their SRMs differed greatly (0.14, 0.41, respectively). In the paired films, an  $IMD_{12mos}$  that was larger than the corresponding  $IMD_{BL}$  had no influence on JSN ( $P = 0.96$ ), but an  $IMD_{12mos}$  that was smaller than the corresponding  $IMD_{BL}$  was associated with a significant increase in the rate of JSN ( $P = 0.042$ ).

## Discussion

This report is based on an analysis of 590 paired baseline and 12-month follow-up radiographs from 417 subjects (both knees from 173 patients and one knee from 244 patients) with KLG two or three OA in the baseline film. The results indicate clearly the important artefactual effect that MTP alignment exerts on the determination of JSN.

Buckland-Wright<sup>10</sup> defined good MTP alignment on the basis of an  $IMD < 1$  mm. In the present study a threshold of only 1 mm would have been far too stringent insofar as an  $IMD < 1$  mm at both time points was present in only 11% of knees. We selected the more generous threshold of  $\leq 1.70$  mm in order to afford larger subgroups for analysis and because it provided a mean  $IMD_{BL}$  that was roughly comparable to that in our recent study of JSN in LS radiographs ( $0.92$  mm)<sup>2</sup>. Nonetheless, with this pragmatic definition of acceptable alignment, parallel MTP alignment at both time points was achieved with the FF protocol in only 30% of the knee films we analyzed. The large differences between  $IMD_{BL}$  and  $IMD_{12mos}$  that we observed in paired films provide further confirmation that the FF protocol did not often offer good replication of  $IMD_{BL}$  in the follow-up film<sup>2,4</sup>.

The present work extends our previous observation<sup>2</sup> that the magnitude and the direction of a difference in the IMDs in serial knee radiographs are important determinants of JSN. The effect of a change in IMD on JSN was independent of the quality of alignment in the baseline radiograph, because 12-month JSN was not correlated with the  $IMD_{BL}$ . The impact of the change in IMD, however, was clearly an important determinant of the mean JSN ( $0.13$  mm) insofar as a 1.0 mm difference between  $IMD_{BL}$  and  $IMD_{12mos}$  modified 12-month JSN by 0.07 mm.

Furthermore, depending upon the direction of the change in IMD, the measured rate of JSN was either increased or decreased. This is illustrated by the slow rate of JSN in Subgroup C ( $-0.06$  mm), which was characterized by a large increase in  $IMD_{12mos}$ , relative to  $IMD_{BL}$  (Table 1). The absence of JSN in Subgroup C contrasted sharply with the high rate of JSN ( $0.33$  mm) in Subgroup D, which was characterized by an  $IMD_{12mos}$  that was much smaller than the corresponding  $IMD_{BL}$ . The difference between  $IMD_{BL}$  and  $IMD_{12mos}$

also had a considerable impact on sensitivity to change, as reflected by the fact that the SRMs in Subgroups C and D were 0.14 and 0.41, respectively.

Independent of reproducibility of the  $IMD_{BL}$  in the follow-up X-ray, the importance of good MTP alignment in determining the sensitivity to change in JSN is also demonstrated by the present study. For example, Subgroup A, which was defined by the presence of good alignment at both time points, demonstrated a  $0.15$  mm JSN and a SRM of 0.34. Conversely, in Subgroup B, which was defined by the presence of skewed alignment at both time points, JSN was only  $0.08$  mm and SRM was 0.17 (Table 1). Importantly, the sizeable difference in JSN between Subgroups A and B ( $0.15 \pm 0.43$  mm vs  $0.08 \pm 0.47$  mm), was statistically significant ( $P = 0.012$ ).

The fact that good replication in the follow-up radiograph of a large IMD in the baseline film did not provide good sensitivity to change was also obvious. Comparison of Subgroups B1 and B2 (knees from Subgroup B that did not meet criteria for Subgroup B1), which differed mainly with respect to the degree to which poor alignment in the  $IMD_{BL}$  was, by chance, reproduced in the follow-up X-ray, clearly showed that in paired radiographs in which alignment was poor at both time points, fortuitous reproducibility of the skewed  $IMD_{BL}$  in the follow-up film was not associated with more rapid JSN or a greater SRM.

Where it to be considered in isolation, the finding that JSN and SRM in Subgroup A were not markedly greater than those in all 590 OA knees ( $0.15$  vs  $0.13$  mm;  $0.34$  vs  $0.25$ , respectively) might lead to underestimation of the importance of MTP alignment in determination of JSN<sup>4</sup>. However, the measurement of JSN obviously depends upon accurate measurement of the difference between the JSN measurements at baseline and follow-up which are, to an extent, modified by the error of measurement of the method employed. We have shown that reliability of JSN measurement is high (Intra- and interobserver SD of the mean difference between test – retest =  $0.02$  mm) and that the measurement error is due mainly to the difference in replication of the image of the knee<sup>2</sup>. Because replication of MTP alignment was the main cause of measurement error and was poor in a majority of knees, the determination of mean JSN of the 590 knees was clearly not accurate in the present study. That JSN for all 590 knees approximated that for Subgroup A in this analysis is due to chance, and can be attributed to the relatively high proportion of knees in which JSN was artefactually rapid because  $IMD_{12mos}$  was much smaller than the paired  $IMD_{BL}$ . As indicated by the analyses of Subgroup C and D, JSN for the entire group of 590 knees could have been much more rapid or much less rapid if the proportion of knees in which a positive or a negative change in IMD in the paired films had differed from that which we observed.

In an observational study employing the FF view, the artefactual modification of JSN resulting from the frequent difference in size of the IMD among serial radiographs demonstrated herein may lead to erroneous conclusions concerning the relation between JSN and results obtained with evaluation tools used to assess risk factors for OA progression (e.g., BMI, quadriceps strength, varus–valgus malalignment).

These findings may have additional clinical implications: As noted below, in an RCT of an SMOAD, use of the FF protocol to detect a significant difference in JSN between treatment groups would require a much larger sample size than a radiographic positioning protocol that assures parallel alignment of the MTP in baseline and follow-up exams<sup>2</sup>, thus exposing a larger number of subjects to possible adverse effects of the test drug and increasing the cost of the study. The findings also raise a concern that in an RCT that used an X-ray protocol which did not assure small IMDs, although randomization might result in the IMD artefact affecting the active treatment arm and placebo arm similarly, because of the variability

in positioning of the knee from exam to exam and practical limits of sample size and treatment duration, an artefactually slow rate of JSN in the active treatment group, relative to the placebo group, could be erroneously attributed to a pharmacodynamic effect or an artefactually high rate could mask a “chondroprotective” effect of treatment. Furthermore, in a replicate, confirmatory RCT, alignment artefact could produce a mix of constituent IMD subcohorts that was different from that in the initial trial, producing different rates of JSN.

In support of the above, the doxycycline clinical trial<sup>11</sup> employed the semiflexed AP radiograph with fluoroscopically-assisted MTP alignment<sup>10</sup>. Analysis of a subset of films from that study showed that an IMD < 0.5 mm – an alignment criterion >3 times more stringent than that in the present study – was achieved in 68%<sup>12</sup>. With only about 215 patients per treatment arm, doxycycline treatment was shown to significantly slow JSN, relative to placebo, at 16 months and 30 months. Also, in a head-to-head comparison of the FF view and fluoroscopically-aided LS view<sup>2</sup> in which an IMD < 1.5 mm was achieved in 92% of the LS views but only 51% of the FF views, JSN among OA knees was  $0.22 \pm 0.43$  mm with the LS view but only  $(-) 0.01 \pm 0.46$  mm with the FF view ( $P = 0.0002$ ,  $P = 0.92$ , respectively). SRMs for JSN in KLG two knees were 0.34 and 0.01 for LS and FF views, respectively, and those for KLG three knees were 0.65 and 0.01, respectively. Thus, good alignment of the MTP in serial films was associated with much greater sensitivity to JSN. As a consequence, demonstration of, e.g., a 50% effect size of an SMOAD in an RCT using the FF view would require a much larger sample size than that required with use of the semiflexed AP or LS view, both of which achieve a small IMD that is highly reproducible on a follow-up exam. Given the significant limitation imposed by fluoroscopy in a multi-center RCT, it is notable that a modification of the LS protocol in which alignment is achieved without fluoroscopy may afford sensitivity to JSN comparable to that achieved with the original LS protocol<sup>13</sup>. Further experience with the modified protocol is needed.

#### Author contributions

E. Vignon performed measurements and redaction of manuscript.

K.D. Brandt performed the study plan and redaction of manuscript.

C. Mercier performed statistical analysis:

M. Hochberg performed manuscript review for the OAI publications committee.

D. Hunter performed manuscript review for the OAI publications committee.

S. Mazzuca revised the manuscript:

K. Powell was in charge of radiographs management.

B. Wyman revised the manuscript.

M.-P. Hellio Le Graverand performed the study plan and revised the manuscript.

#### Conflict of interest

The authors have no conflict of interest in the work presented.

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#### References

1. Brandt KD, Mazzuca SA, Conrozier T, Dacre JE, Peterfy CG, Provvedini D, *et al.* Which is the best radiographic protocol for a clinical trial of a structure-modifying drug in patients with knee osteoarthritis? Proceedings of January 17–18, 2002 Workshop in Toussus-le-Noble, France. *J Rheumatol* 2002;29:1308–20.
2. Hellio Le Graverand M-P, Vignon E, Brandt KD, Mazzuca SA, Piperno M, Buck R, *et al.* Head-to-head comparison of the Lyon schuss and fixed flexion radiographic techniques. Long-term reproducibility in normal knees and sensitivity to change in osteoarthritic knees. *Ann Rheum Dis* 2008;67:1562–7.
3. Botha-Scheepers S, Kloppenburg M, Kroon HM, Hellio Le Graverand MP, Breedveld FC, Ravaud P, *et al.* Fixed-flexion knee radiography: the sensitivity to detect knee joint space narrowing in osteoarthritis. *Osteoarthritis Cartilage* 2007;15:350–3.
4. Nevitt MC, Peterfy C, Guermazi A, Felson DT, Duryea J, Woodworth T, *et al.* Longitudinal performance evaluation and validation of fixed-flexion radiography of the knee for detection of joint space loss. *Arthritis Rheum* 2007;56:1512–20.
5. Mazzuca SA, Brandt KD, Buckwalter KA. Detection of radiographic joint space narrowing in subjects with knee osteoarthritis. Longitudinal comparison of the metatarsophalangeal and semiflexed anteroposterior views. *Arthritis Rheum* 2003;48:385–90.
6. <http://www.oai.ucsf.edu/>; 2003
7. Altman RD, Hochberg M, Murphy Jr WA, Wolfe F, Lequesne M. Atlas of individual radiographic features in osteoarthritis. *Osteoarthritis Cartilage* 1995;3:3–70.
8. <http://www.oai.ucsf.edu/datarelease/>; 1995
9. Peterfy C, Li J, Zaim S, Duryea J, Lynch J, Miaux Y, *et al.* Comparison of fixed-flexion positioning with fluoroscopic semi-flexed positioning for quantifying radiographic joint-space width in the knee: test-retest reproducibility. *Skeletal Radiol* 2003;32:128–32.
10. Buckland-Wright JC, Macfarlane DG, Williams SA, Ward RJ. Accuracy and precision of joint space width measurements in standard and macroradiographs of osteoarthritic knees. *Ann Rheum Dis* 1995;54:872–80.
11. Brandt KD, Mazzuca SA, Katz BP, Lane KA, Buckwalter KA, Yocum DE, *et al.* Effects of doxycycline on progression of osteoarthritis. Results of a randomized, placebo-controlled, double-blind trial. *Arthritis Rheum* 2005;52:2015–25.
12. Hellio Le Graverand MP, Mazzuca S, Lassere M, Guermazi A, Pickering E, Brandt K, *et al.* Assessment of the radioanatomic positioning of the osteoarthritic knee in serial radiographs: comparison of three acquisition techniques. *Osteoarthritis Cartilage* 2006;14(Suppl A):32–6.
13. Mazzuca SA, Hellio Le Graverand M-P, Vignon E, Hunter DJ, Jackson CG, Kraus VB, *et al.* Performance of a non-fluoroscopically assisted substitute for the Lyon schuss knee radiograph: quality and reproducibility of positioning and sensitivity to joint space narrowing in osteoarthritic knees. *Osteoarthritis Cartilage* 2008;16:1555–9.