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One-Year Change in Radiographic Joint Space Width in Patients With Unilateral Joint Space Narrowing: Data From The Osteoarthritis Initiative

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Abstract

Objective—To examine the rate of joint space width (JSW) loss in both knees of patients with unilateral medial joint space narrowing (JSN) at baseline.

Methods—Cases were selected from a pool of 2,678 subjects enrolled in the Osteoarthritis Initiative cohort. Inclusion criteria for the present study were unilateral medial JSN, bilateral frequent knee pain, and body mass index (BMI) ≥ 25 kg/m². Baseline and 1-year fixed flexion radiographs of both knees were read (blinded to time point) using an automated algorithm for minimum JSW and JSW at 4 fixed locations in the medial compartment.

Results—Sixty-seven participants met the inclusion criteria: 43 women and 24 men, with mean \pm SD age 60 ± 9 years and mean \pm SD BMI 31 ± 4 kg/m². Thirty-seven subjects (55%) had ≥ 1 definite tibiofemoral osteophyte. The average progression in no-JSN knees was comparable with that in JSN knees (approximately -0.2 mm/year). However, JSW change was more variable in no-

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JSN knees, resulting in standardized response means (SRMs; the mean/SD) of approximately -0.24 in no-JSN knees versus approximately -0.41 in JSN knees on average at the 4 fixed locations, and SRMs of -0.24 and -0.35 , respectively, for minimum JSW. Young age and high BMI were associated with increased progression, especially in JSN knees.

Conclusion—JSN and no-JSN knees progressed at a comparable rate, but a wider distribution of JSW change in no-JSN knees resulted in a poorer sensitivity to change in these knees.

INTRODUCTION

Clinical development of disease-modifying osteoarthritis drugs (DMOADs) requires enrollment of a patient population with various and potentially conflicting characteristics. On the one hand, these patients should be at high risk of structural progression so that a trial with a reasonable sample size and duration would provide adequate power to detect a treatment difference between active drug and placebo. Multiple risk factors have been identified for knee osteoarthritis (OA) progression (1). Advanced OA may be one of these risk factors, being that several lines of evidence suggest that knees with baseline joint space narrowing (JSN) are at higher risk of radiographic progression than those without JSN (2-4). On the other hand, joints that already have established OA may be less responsive to pharmacologic treatment due to the overwhelming influence of biomechanical factors (altered alignment, loss of cartilage surface smoothness, ligament laxity, and meniscal damage).

The aim of this study was to assess the rate of structural progression in both knees of patients with baseline unilateral JSN as a means of evaluating the feasibility of detecting a DMOAD effect in a clinical trial enrolling this population. This specific OA population was chosen because the risk of structural progression in a given knee without baseline JSN (no-JSN knee) is higher when the contralateral knee has already lost some joint space (index knee = JSN-knee) than when the contralateral knee has not lost joint space (4). The no-JSN knee would be the target knee in a DMOAD trial, because it would be expected to have less damage than a JSN knee (and therefore less biomechanical constraints) but may have a significant progression over time due to the prevalence of a contralateral JSN, hence allowing the detection of a drug effect versus placebo.

We investigated the 1-year change in joint space width (JSW) in both knees of patients with baseline unilateral JSN who were overweight (body mass index [BMI] >25 kg/m²) and experienced frequent bilateral knee pain. High BMI increases the likelihood that the disease origin is general rather than local (5,6) and therefore increases the risk of progression in the no-JSN knee. In the same line of thought, prevalence of bilateral frequent symptoms increases the likelihood that the no-JSN knee also has OA and avoids inclusion of patients with unilateral disease who would be at low risk of progression in the no-JSN knee.

PATIENTS AND METHODS

Data for these analyses are from the public use data sets (0.2.1 and 1.2.1 clinical data sets and 0.B.1 and 1.B.1 imaging data sets) of the Osteoarthritis Initiative (OAI; online at www.oai.ucsf.edu/datarelease/DataImaging.asp), a multi-center, longitudinal cohort study designed to identify biomarkers for the development and/or progression of symptomatic knee OA.

Patient selection

The inclusion criteria for the present study were BMI >25 kg/m², bilateral chronic frequent pain, unilateral medial tibiofemoral JSN (Osteoarthritis Research Society International

[OARSI] grades 1–3), and no JSN in the lateral compartment (or less than in the medial compartment and with an OARSI JSN grade ≤ 1). The OAI protocol defined chronic frequent pain as “pain, aching, or stiffness on most days of at least a month during the previous year.”

Patients included in the present study were selected from the OAI cohort based on the above criteria and had baseline and 1-year knee radiographs and magnetic resonance images (MRIs) that were of adequate quality for review (only a few participants were excluded based on the absence of 1-year followup radiographs or the presence of metal artifacts on MRI analyses). The MRI analyses of this subgroup have been published elsewhere (7). Radiographs at baseline and 1 year were performed in fixed flexion position using a SynaFlexer Plexiglass positioning frame (Synarc) to achieve a reproducible foot fixation and knee flexion (8). The full OAI radiographic procedures manual can be downloaded from the OAI Web site after registration (online at www.oai.ucsf.edu/datarelease/OperationsManuals.asp). The screening radiographs were read at each site and these readings are available in the OAI database.

Patients were selected in this study using 2 different processes (Figure 1). In the first process, after patients were selected based on the above inclusion criteria (according to the information available in the OAI database), their baseline radiographs were re-read centrally and adjudicated (in case of disagreement between site reading and central reading) for the presence and scoring of JSN and osteophytes in each compartment of both knees. Patients were included in the present study only if they fulfilled the above radiographic inclusion criteria based on central reading and, when necessary, the adjudicated reading. Of the 2,678 patients for whom radiographic data were already available in the OAI database at the time of this analysis, 48 patients were included based on this process.

In the second process, files for 160 patients with symptomatic OA who had previously been selected from the OAI database for other published analyses (9-11) were screened for the current study. Radiographs for these patients had already been centrally re-read and, if needed, adjudicated for the presence of osteophytes and JSN. Of these 160 subjects, 19 fulfilled the present study inclusion criteria.

Image analysis methods

Measurement of medial JSW was facilitated by the use of automated software that delineated the femoral and tibial margins of the joint (12). JSW(x) was measured at 4 fixed locations ($x = 0.2$, $x = 0.225$, $x = 0.25$, and $x = 0.275$) (Figure 2). These measures of medial JSW(x) were defined as the distance from the tibial margin to the femur margin at each fixed location on the x-coordinate system (13). Measurement of minimum JSW was made by the software at the location of the smallest distance between the femur and tibia margins in the medial compartment. Readings of baseline and 1-year radiographs were paired but blinded to time point.

Statistical analysis

Change from baseline significance was assessed with 1-sample *t*-tests and *P* values calculated separately for JSN knees and no-JSN knees. Paired *t*-tests were used to compare change from baseline between JSN knees and no-JSN knees. Comparison of the variability in change from baseline in JSN and no-JSN knees was performed with an adaptation of Levene’s test for paired data, based on a paired *t*-test of the absolute value of the difference between each patient’s change and the mean change. Comparisons of change from baseline between subgroups (e.g., presence of osteophytes) were performed with 2-sample *t*-tests. Spearman’s correlations and partial correlations (adjusting for age) were used to evaluate

univariate correlations of baseline characteristics with change from baseline measures. Comparisons between age groups for BMI (Wilcoxon's rank sum test) and presence of osteophytes (chi-square test) were also performed. Multiple stepwise regression analysis was performed to assess the impact of baseline variables (age, sex, BMI, osteophytes, baseline JSW, and history of traumatic knee injury) on change in JSW from baseline to 1 year. Variables such as BMI and age were analyzed as continuous variables. Regression coefficients (β) plus or minus their SEs are presented.

The standardized response means (SRMs) comparing the baseline and 1-year radiographs were defined as the mean change divided by the SD of the change. Bootstrap resampling was performed to generate 1,000 SRMs for JSN knees and no-JSN knees, and the distribution of the difference between knees was used to compute P values.

Summary statistics for continuous variables were expressed as mean \pm SDs. Two-tailed P values less than 0.05 were considered significant, and calculations were performed using SAS, version 9.1 (SAS Institute).

RESULTS

Baseline characteristics

Of 2,678 subjects for whom data were available in the OAI database, 67 were included in the present analyses (Figure 1). There were 43 women and 24 men with an average \pm SD age of 60 ± 9 years (range 45–78 years). Mean \pm SD BMI was 31 ± 4 kg/m² at inclusion (range 25–42 kg/m²). A history of knee injury was reported in 27 patients (40%). All subjects had bilateral frequent chronic knee pain. The baseline radiographic characteristics of these 67 patients are presented in Table 1.

Mean changes in JSW over 1 year in both JSN and no-JSN knees and distribution of change

The average progression in no-JSN knees was comparable with that in JSN knees at the 4 fixed locations, with JSW reductions of ~ 0.2 mm over 1 year. The change in minimum JSW was slightly less, numerically, in JSN knees than in no-JSN knees (-0.14 mm and -0.18 mm, respectively), but this difference was far from statistically significant ($P = 0.62$).

Variability of structural progression was higher in the no-JSN knees, as can be seen from the consistently higher SDs observed in these knees (e.g., for minimum JSW, $P = 0.008$) (Table 2) and the visually wider distribution of change (Figure 3). This is reflected in the P values, which were generally smaller for progression within the JSN knees compared with progression within the no-JSN knees. As a result, the sensitivity to change of JSW, as assessed by SRMs, tended to be greater in JSN knees than in no-JSN knees (Table 2), with $x = 0.225$ having significantly different SRMs ($P = 0.04$). Overall, SRMs for the change in JSW at fixed locations were approximately -0.41 in JSN knees versus -0.24 in no-JSN knees (Table 2).

Influence of baseline characteristics on radiographic progression

BMI had a univariate association with radiographic progression, especially in JSN knees. The average rate of progression and sensitivity to change were higher in participants with a baseline BMI ≥ 30 kg/m² than in those with a BMI between 25 and 30 kg/m², but interestingly, the differences were significant only for the JSN knees. Univariate Spearman's correlation coefficients between baseline BMI and JSW change were significant for all 5 locations in JSN knees, but generally decreased when adjusting for age (data not shown).

Although the age cutoff of 60 years was not associated with statistically significant differences in radiographic progression (Table 3), age as a continuous variable was significantly correlated with progression for all locations in JSN knees and for 2 locations in no-JSN knees. Younger age was associated with greater JSW decreases and therefore with more progression.

Radiographic progression, as assessed by 1-year change in JSW, tended to be faster in JSN knees with ≥ 1 definite osteophyte versus those without, but these differences were not statistically significant (Table 3).

Multivariate analyses were performed to determine which demographic factors were most related to JSW change. Both age ($\beta = 0.01 \pm 0.006$ mm per year of age; $P = 0.03$) and BMI ($\beta = -0.03 \pm 0.01$ mm per kg/m^2 ; $P = 0.03$) as continuous variables were significantly related to the average change of the 4 fixed locations in analyses of JSN knees. Age as a continuous measure was the only variable significantly selected using stepwise regression for both minimum JSW of JSN knees ($\beta = 0.01 \pm 0.005$ mm per year of age; $P = 0.01$) and for the average change of the 4 fixed locations ($\beta = 0.02 \pm 0.01$ mm per year of age; $P = 0.049$) in analyses of no-JSN knees. No variables were selected at the $P < 0.05$ cutoff for the minimum JSW measure of the no-JSN knees; however, when the cutoff was raised to $P < 0.10$, age was the only selected measure ($\beta = 0.02 \pm 0.01$ mm per year of age; $P = 0.09$).

Older patients in this population tended to have lower BMI (age ≥ 60 years: BMI 30.4 ± 3.9 kg/m^2 , age < 60 years: BMI 32 ± 3.8 kg/m^2 ; $P = 0.10$) and a higher prevalence of osteophytes in the JSN knee (age ≥ 60 years: 64% with ≥ 1 osteophyte, age < 60 years: 41% with ≥ 1 osteophyte; $P = 0.07$), but these differences were not statistically significant.

DISCUSSION

This study is the first to our knowledge to explore the rate of progression in the population with the specified characteristics. Participants with unilateral OA have previously been studied in either an observational or a clinical trial setting (6,14). In these studies, inclusion was based on the Kellgren/Lawrence (K/L) grading system, with OA defined as a definite tibiofemoral osteophyte (with or without JSN). In the current study, we focused on JSN as an inclusion criterion rather than the presence of osteophytes. The additional inclusion criteria (bilateral frequent pain and BMI > 25 kg/m^2) were aimed at increasing the risk of progression in the no-JSN knee. The relatively small proportion of patients eligible for this study (67 of 2,678 subjects in this subset of the OAI database) suggests that a clinical trial aimed at enrolling this population would require significant recruitment efforts, especially if screening radiographs are not read centrally.

In our target population, no-JSN knees progressed radiographically as rapidly as JSN knees, with an annual rate of progression of ~ 0.2 mm. However, progression was more variable in no-JSN knees, with an SD of 0.7–0.8 mm (versus ~ 0.5 in JSN knees), which accounts for the relatively low SRMs observed in these knees. Two outlier knees with fast progression are shown in Figure 3. Removing them reduced 1-year progression in no-JSN knees by approximately half on average, suggesting that progression in no-JSN knees was largely driven by a few patients (although most differences between JSN and no-JSN knees remained not significant; data not shown).

Measures performed with the x-coordinate system tended to be more responsive than the measure of minimum JSW in JSN knees (nonsignificant), whereas both analysis methods were comparable in no-JSN knees. This agrees with a previously published report that used the same positioning protocol for radiographs collected at baseline and 36-month followup: the Dynamics of Health, Aging, and Body Composition study (13).

Studying JSN knees in this population provides an improved sensitivity to change versus studying no-JSN knees. Targeting no-JSN knees in a similar population, a placebo-controlled DMOAD trial would require ~800 patients per group over 1 year in order to detect a 50% difference between an active drug and placebo (80% power, 1-sided, $\alpha = 0.05$, average for 4 fixed locations). The higher sensitivity to change observed in JSN knees in this population would translate into a sample size of ~270 patients per group in a DMOAD trial intended to detect a similar difference between active compound and placebo in the JSN knees. This raises questions as to whether this patient population and their no-JSN knees represent an appropriate target for a DMOAD trial. SRMs for change in cartilage thickness measured quantitatively with MRI in the same population (7) were also higher in JSN knees than in no-JSN knees, suggesting that regardless of the methodology used (radiography or MRI), a larger sample size would be required if the target knees for such a trial were the no-JSN knees.

Some of our data confirm previously published findings. Byers-Kraus et al have reported that patients recruited based on familial hand OA had a remarkably symmetric annual medial JSW change, although knee OA was not among the inclusion criteria of this study (15).

In the doxycycline trial, which included obese women with unilateral knee OA as assessed on standing anteroposterior knee radiographs, JSW reduction was 0.24 ± 0.54 mm and 0.23 ± 0.59 mm over 16 months in the index (knees with a definite tibiofemoral osteophyte) and contralateral knees, respectively (14). These figures would result in SRMs of -0.44 and -0.43 , respectively, over 1 year, although only 42% of the patients included in the doxycycline trial had baseline JSN in the index knee. One of the differences between the methodology of these 2 studies lies in the knee positioning technique: the OAI study used a frame-assisted fixed flexion, whereas the doxycycline trial used a fluoroscopic-assisted alignment of radiograph beam and medial tibial plateau in a semiflexed position.

Several recent articles have suggested that the fluoroscopic-assisted positioning leads to better alignment of the tibial margin and the radiograph beam, and therefore allows less variability and more sensitivity in detecting progression than the fixed flexion (3,16-18). One of these reported the results of an observational study that compared, in the same patients (obese women with radiographic knee OA), radiographic progression over 1 year as assessed on radiographs performed in Lyon schuss and fixed flexion positions (3). Sensitivity to change of JSW showed a striking difference, with SRMs of -0.34 and -0.65 for K/L grade 2 and 3 knees, respectively, with the Lyon schuss, versus -0.01 and -0.01 for the same knees with fixed flexion.

In the present study, we did not exclude radiographs with poor or inconsistent tibial rim alignment. The software method functioned by delineating the structures of interest (femur margin and bright band associated with the tibial plateau) and made no attempt to correct for imperfect alignment. This may partially explain the relatively poor sensitivity to change of the minimum JSN measurements as compared with measurements at fixed locations in the present study.

Despite the technical limitations described above, the present study was able to detect radiographic progression over 1 year in this specific population, although sensitivity to change was modest. The relatively high variability and low SRMs observed might have improved with Lyon schuss positioning, or with the recently described modified Lyon schuss positioning (19), which also allows precise alignment of the tibial plateau without requiring fluoroscopic equipment.

Another limitation of this study is that 30 of 67 patients did not have a definite (OARSI grade ≥ 2) tibiofemoral osteophyte at baseline in either knee. However, all but 6 of these 30 patients had a grade 1 osteophyte in at least 1 knee. In addition, all patients had bilateral frequent chronic pain. Finally, the OAI study eligibility criteria were designed to specifically exclude patients in whom knee symptoms were likely to result from a disease process other than OA (OAI protocol, online at www.oai.ucsf.edu/datarelease/docs/StudyDesignProtocol.pdf).

The inclusion criteria used here preclude evaluation of risk factors for progression such as unilateral JSN, bilateral pain, and BMI >25 kg/m². For instance, it is not possible to infer from our data whether JSN in 1 knee predicts future progression in the contralateral knee, or whether a BMI >25 kg/m² predicts progression. This study was not designed to address these questions, although it does allow assessment of other potential risk factors in this population, such as age, BMI within the limits of eligibility (>25 kg/m²), and tibiofemoral osteophytes. It appeared that both age and obesity were associated with future progression and significantly improved the sensitivity to change of JSW (especially in JSN knees). Whether or not a future DMOAD trial should have inclusion criteria such as age or obesity in addition to those defining the population enrolled in the present study is debatable, being that the smaller the target population is, the more difficult it is to enroll.

In conclusion, sensitivity to change of JSW (on radiographs performed in fixed flexion) in no-JSN knees of patients with unilateral JSN is such that a placebo-controlled proof of concept DMOAD trial using the same technique would require close to 800 patients per arm over 1 year. This sample size might be decreased by the use of a positioning technique that reduces the variability of JSW change (19), although this technique adds some complexity to the procedure.

Refining inclusion criteria may also help obtain a higher sensitivity to change, especially requiring patients to be <60 years of age or to have a BMI of ≥ 30 kg/m². Such highly-targeted strategies involve significant recruitment challenges and would require careful thought concerning recruitment tactics.

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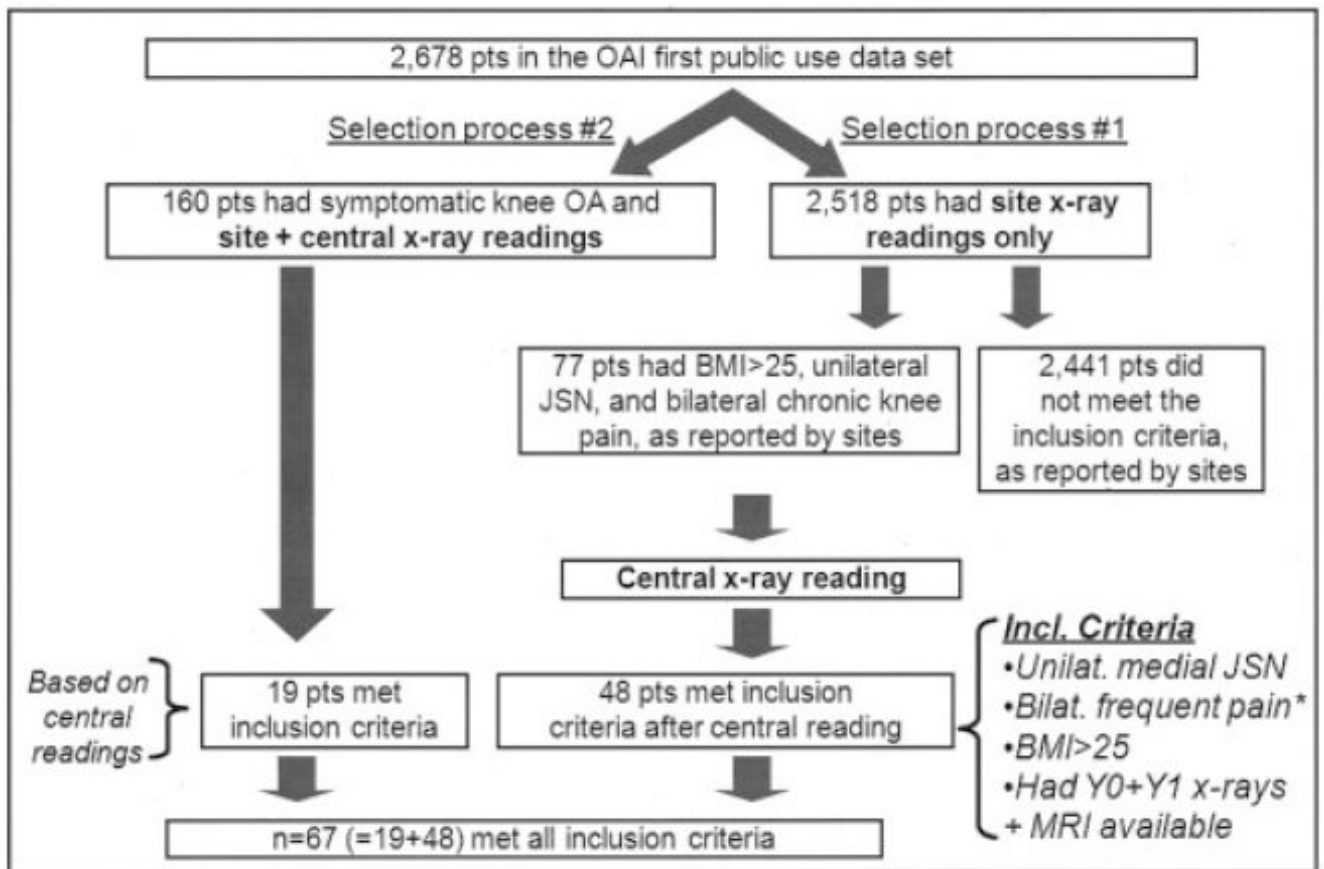


Figure 1. Patient selection process. pts = patients; OAI = Osteoarthritis Initiative; OA = osteoarthritis; BMI = body mass index; JSN = joint space narrowing; MRI = magnetic resonance imaging.

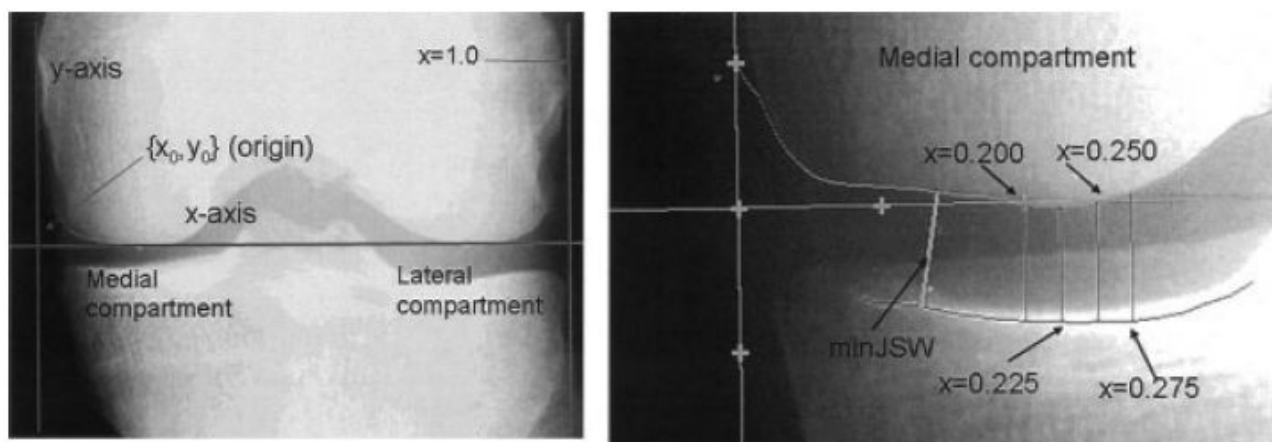


Figure 2. Method for measurement of joint space width (JSW). Baseline (Y_0) and year 1 (Y_1) fixed flexion radiographs of both knees were used. The x-axis is tangent to the femur (software placement). The y-axis and the ($x = 1.0$) line were placed manually, perpendicular to the x-axis. Medial JSW was measured at the location of the minimum distance between the femur and tibia margins (minimum JSW) and at 4 fixed locations ($x = 0.200, 0.225, 0.250,$ and 0.275) in a previously described coordinate system adjusted on lower femur epiphysis width (13).

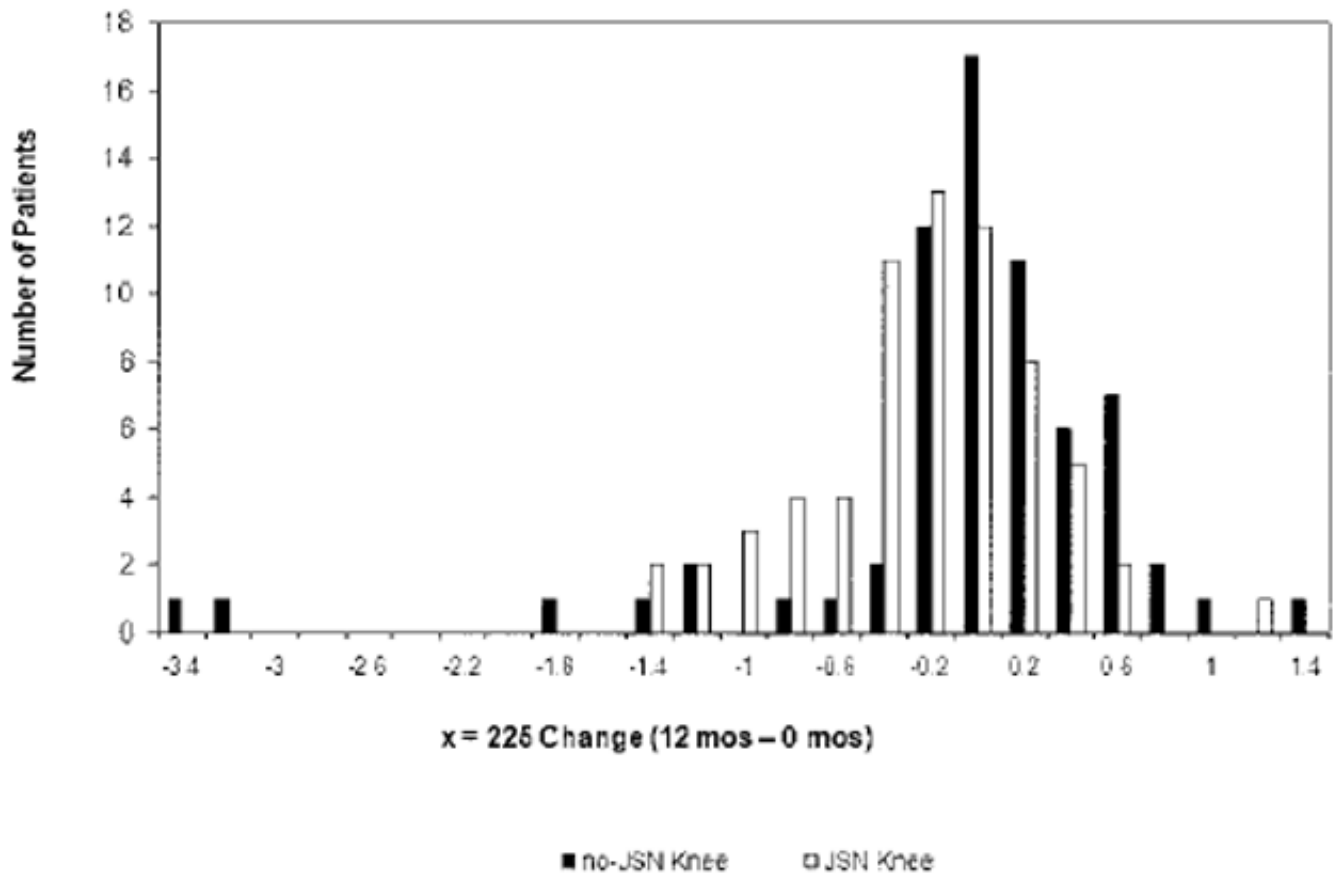


Figure 3. Distribution of 1-year joint space width (JSW) change (at location $x = 0.225$). Similar distributions of JSW change were observed at other fixed locations ($x = 0.200, 0.250,$ and 0.275) and for minimum JSW (data not shown). Open bars = joint space narrowing (JSN) knee; solid bars = no-JSN knee.

Table 1

Radiographic characteristics at baseline*

	JSN knees (n = 67)	No-JSN knees (n = 67)
JSN OARSI grade, no. (%) [†]		
0	0	67 (100)
1	42 (63)	0
2	18 (27)	0
3	7 (10)	0
Knees with ≥ 1 definite tibiofemoral osteophyte, %	52	19
Minimal JSW, mean \pm SD mm	2.9 \pm 1.2	4.7 \pm 0.9
JSW location, mean \pm SD mm		
x = 0.200	3.9 \pm 1.5	5.7 \pm 1.2
x = 0.225	4.2 \pm 1.6	6.0 \pm 1.2
x = 0.250	4.6 \pm 1.6	6.4 \pm 1.3
x = 0.275	5.1 \pm 1.7	6.9 \pm 1.3

* JSN = joint space narrowing; OARSI = Osteoarthritis Research Society International; JSW = joint space width.

[†] Based on central reading (with or without adjudication).

Table 2

Mean JSW change (in millimeters) over 1 year at 5 locations ($x = 0.200, 0.225, 0.250, 0.275$, and minimum JSW)*

OARSI grade of JSN and location	JSN knee (n = 67)			No-JSN knee (n = 67)			JSN versus no-JSN knees [†]		
	JSW change, mean ± SD	SRM	P within knee	JSW change, mean ± SD	SRM	P within knee	P for mean	P for SD	P for SRM
All (n = 67)									
x = 0.200	-0.18 ± 0.44	-0.42	0.001	-0.20 ± 0.81	-0.24	0.051	0.89	0.07	0.15
x = 0.225	-0.22 ± 0.48	-0.45	0.0005	-0.16 ± 0.76	-0.21	0.09	0.53	0.20	0.04
x = 0.250	-0.21 ± 0.53	-0.41	0.002	-0.17 ± 0.75	-0.23	0.07	0.64	0.38	0.19
x = 0.275	-0.20 ± 0.55	-0.36	0.005	-0.21 ± 0.74	-0.29	0.02	0.86	0.44	0.56
Minimum JSW	-0.14 ± 0.40	-0.35	0.0006	-0.18 ± 0.76	-0.24	0.059	0.62	0.008	0.28
Grade 1 (n = 42)									
x = 0.200	-0.18 ± 0.43	-0.42	0.009	-0.11 ± 0.49	-0.22	0.16	0.32	0.59	0.16
x = 0.225	-0.21 ± 0.48	-0.43	0.007	-0.10 ± 0.50	-0.20	0.20	0.19	0.73	0.13
x = 0.250	-0.18 ± 0.52	-0.34	0.04	-0.09 ± 0.49	-0.19	0.23	0.37	0.61	0.37
x = 0.275	-0.14 ± 0.49	-0.28	0.08	-0.16 ± 0.52	-0.32	0.047	0.75	0.81	0.59
Minimum JSW	-0.09 ± 0.38	-0.25	0.12	-0.10 ± 0.54	-0.18	0.26	0.98	0.23	0.32
Grade 2 (n = 18)									
x = 0.200	-0.25 ± 0.48	-0.51	0.046	-0.24 ± 1.05	-0.23	0.34	0.99	0.27	0.18
x = 0.225	-0.29 ± 0.53	-0.55	0.03	-0.18 ± 0.98	-0.18	0.46	0.55	0.51	0.05
x = 0.250	-0.31 ± 0.51	-0.60	0.02	-0.24 ± 0.95	-0.25	0.31	0.74	0.52	0.14
x = 0.275	-0.28 ± 0.62	-0.45	0.08	-0.20 ± 0.93	-0.22	0.37	0.69	0.74	0.28
Minimum JSW	-0.25 ± 0.46	-0.54	0.03	-0.22 ± 0.97	-0.23	0.34	0.89	0.08	0.06
Grade 3 (n = 7)									
x = 0.200	-0.03 ± 0.38	-0.08	0.85	-0.61 ± 1.46	-0.41	0.31	0.35	0.18	0.54
x = 0.225	-0.08 ± 0.41	-0.20	0.62	-0.49 ± 1.36	-0.36	0.38	0.48	0.21	0.78
x = 0.250	-0.20 ± 0.64	-0.31	0.44	-0.44 ± 1.32	-0.34	0.41	0.67	0.40	1.00
x = 0.275	-0.34 ± 0.69	-0.50	0.24	-0.52 ± 1.24	-0.42	0.31	0.75	0.54	0.93
Minimum JSW	-0.11 ± 0.27	-0.41	0.32	-0.56 ± 1.21	-0.46	0.27	0.34	0.16	0.65

* JSW = joint space width; JSN = joint space narrowing; OARSI = Osteoarthritis Research Society International; SRM = standardized response of the mean (the mean divided by the SD).

[†] P values for within-patient comparisons of mean JSW change and SD of change.

Table 3

Influence of age, sex, BMI, and definite tibiofemoral osteophyte on JSW change at 5 locations ($x = 0.200, 0.225, 0.250, 0.275$, and minimum JSW)*

	JSW knees				No-JSW knees			
	No. patients	Mean \pm SD	SRM	P^{\dagger}	No. patients	Mean \pm SD	SRM	P^{\dagger}
Age								
<60 years	34				34			
x = 0.200		-0.24 \pm 0.42	-0.58			-0.36 \pm 0.94	-0.38	
x = 0.225		-0.31 \pm 0.49	-0.64			-0.31 \pm 0.89	-0.35	
x = 0.250		-0.31 \pm 0.54	-0.57			-0.30 \pm 0.86	-0.35	
x = 0.275		-0.32 \pm 0.61	-0.53			-0.34 \pm 0.86	-0.39	
Minimum JSW		-0.23 \pm 0.41	-0.56			-0.29 \pm 0.85	-0.34	
≥ 60 years	33				33			
x = 0.200		-0.12 \pm 0.45	-0.27	0.26		-0.03 \pm 0.60	-0.04	0.09
x = 0.225		-0.12 \pm 0.46	-0.26	0.10		0.00 \pm 0.58	0.00	0.09
x = 0.250		-0.12 \pm 0.51	-0.23	0.14		-0.03 \pm 0.59	-0.05	0.14
x = 0.275		-0.07 \pm 0.45	-0.15	0.054		-0.08 \pm 0.57	-0.15	0.16
Minimum JSW		-0.05 \pm 0.37	-0.12	0.06		-0.06 \pm 0.64	-0.09	0.21
Sex								
Male	24				24			
x = 0.200		-0.19 \pm 0.35	-0.53			-0.02 \pm 0.50	-0.03	
x = 0.225		-0.24 \pm 0.42	-0.57			-0.02 \pm 0.53	-0.04	
x = 0.250		-0.25 \pm 0.46	-0.54			-0.02 \pm 0.60	-0.04	
x = 0.275		-0.18 \pm 0.53	-0.34			-0.07 \pm 0.63	-0.12	
Minimum JSW		-0.21 \pm 0.32	-0.66			-0.01 \pm 0.41	-0.02	
Female	43				43			
x = 0.200		-0.18 \pm 0.48	-0.37	0.94		-0.30 \pm 0.92	-0.32	0.12
x = 0.225		-0.21 \pm 0.52	-0.40	0.81		-0.24 \pm 0.87	-0.27	0.21
x = 0.250		-0.20 \pm 0.57	-0.34	0.71		-0.25 \pm 0.81	-0.31	0.24
x = 0.275		-0.20 \pm 0.56	-0.36	0.87		-0.29 \pm 0.78	-0.37	0.26
Minimum JSW		-0.10 \pm 0.43	-0.22	0.25		-0.27 \pm 0.89	-0.31	0.10
BMI								

	JSN knees			No-JSN knees				
	No. patients	Mean ± SD	SRM	<i>P</i> [†]	No. patients	Mean ± SD	SRM	<i>P</i> [†]
<30 kg/m ²	23				23			
x = 0.200		0.08 ± 0.33	0.23			-0.16 ± 0.85	-0.19	
x = 0.225		0.05 ± 0.39	0.13			-0.15 ± 0.80	-0.19	
x = 0.250		0.00 ± 0.44	-0.01			-0.10 ± 0.76	-0.13	
x = 0.275		-0.01 ± 0.41	-0.02			-0.15 ± 0.72	-0.20	
Minimum JSW		0.02 ± 0.28	0.08			-0.10 ± 0.73	-0.13	
≥30 kg/m ²	44				44			
x = 0.200		-0.32 ± 0.43	-0.75	0.0003		-0.21 ± 0.79	-0.27	0.81
x = 0.225		-0.36 ± 0.47	-0.76	0.0007		-0.16 ± 0.75	-0.22	0.96
x = 0.250		-0.32 ± 0.54	-0.60	0.02		-0.21 ± 0.74	-0.28	0.58
x = 0.275		-0.29 ± 0.59	-0.50	0.04		-0.25 ± 0.75	-0.33	0.60
Minimum JSW		-0.22 ± 0.42	-0.52	0.007		-0.22 ± 0.78	-0.28	0.53
Osteophytes [‡]								
None	32				54			
x = 0.200		-0.15 ± 0.44	-0.34			-0.19 ± 0.71	-0.27	
x = 0.225		-0.16 ± 0.49	-0.34			-0.16 ± 0.68	-0.23	
x = 0.250		-0.16 ± 0.50	-0.33			-0.18 ± 0.65	-0.27	
x = 0.275		-0.10 ± 0.50	-0.21			-0.22 ± 0.64	-0.34	
Minimum JSW		-0.08 ± 0.40	-0.20			-0.17 ± 0.66	-0.25	
≥1	35				13			
x = 0.200		-0.21 ± 0.44	-0.49	0.55		-0.20 ± 1.16	-0.17	0.98
x = 0.225		-0.27 ± 0.48	-0.55	0.39		-0.18 ± 1.09	-0.16	0.94
x = 0.250		-0.26 ± 0.56	-0.47	0.45		-0.13 ± 1.08	-0.12	0.83
x = 0.275		-0.28 ± 0.58	-0.48	0.19		-0.19 ± 1.07	-0.17	0.89
Minimum JSW		-0.19 ± 0.40	-0.48	0.26		-0.23 ± 1.11	-0.21	0.77

* BMI = body mass index; JSW = joint space width; JSN = joint space narrowing; SRM = standardized response mean.

[†] From 2-tailed 2-sample Student's *t*-test comparing age <60 years versus ≥60 years, male versus female, body mass index <30 kg/m² versus ≥30 kg/m², and osteophyte versus no osteophyte.

[‡] Definite tibiofemoral osteophytes.