

EXTENDED REPORT

Three year joint space narrowing predicts long term incidence of knee surgery in patients with osteoarthritis: an eight year prospective follow up study

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Objective: To assess the clinical relevance of mean and minimum femorotibial joint space narrowing (JSN) for predicting future osteoarthritis related surgery in patients with knee osteoarthritis.

Methods: 126 subjects with primary knee osteoarthritis were followed prospectively for a mean eight years. Minimum and mean joint space width (JSW) were assessed from standard x rays at baseline and after a follow up of three years. The rate of knee osteoarthritis related surgery was recorded for the following five years.

Results: After a mean follow up of eight years, 16 patients (12.7%) had received osteoarthritis related joint surgery. The areas under the curves (AUC) resulting from the receiver operating characteristic curve analyses for predicting osteoarthritis surgery were 0.73 ($p=0.006$) for minimum JSN and 0.55 ($p=0.54$) for mean JSN. The cut off for minimum JSN maximising sensitivity and specificity for predicting future surgery was a change of 0.7 mm or more in minimum joint space width over a period of three years. However, no meaningful differences were observed for cut off values between 0.5 and 0.8 mm. The relative risk (adjusted for age, body mass index, baseline symptoms, and baseline JSW) of experiencing osteoarthritis related surgery during the eight year of follow up was 5.15 (95% confidence interval, 1.70 to 15.60) ($p=0.004$) in patients with a minimum joint space narrowing of 0.7 mm or more during the first three years of the study.

Conclusions: A cut off of 0.5 to 0.8 mm in minimum JSN, measured on standard x rays, reflects a clinically relevant progression in patients with knee osteoarthritis.

During the last few years, major advances have been made in the treatment of osteoarthritis.¹ The current management includes non-pharmacological and non-surgical measures, the use of pharmacological agents, and surgery.^{2,3} According to recommendations from expert panels and regulatory authorities, drugs used for the treatment of osteoarthritis can be classified as symptom modifying or structure modifying agents, depending on their ability to control the symptoms of the disease or the progression of joint structural changes.^{2–5} Structural modification of the joint is considered to be the most important determinant of disease progression. Structure modifying agents have thus been assimilated into disease modifying agents. Change in joint space width, measured on standard x rays, is currently the recommended primary end point in trials assessing new chemical agents for treating osteoarthritis, for both scientific organisations^{5,6} and regulatory agencies in the USA and Europe.^{2,3}

However, to date, very few prospective long term studies have confirmed the surrogacy of joint space narrowing for relevant hard clinical end points—that is, the long term incidence of osteoarthritis related joint surgery. Subsequently, the exact clinical relevance of the results obtained in studies showing the ability of an anti-osteoarthritis drugs to delay, reduce, or prevent joint space narrowing remains equivocal. Knee surgery is widely recognised as the single most relevant outcome in knee osteoarthritis. The need for such a procedure usually reflects the failure of non-surgical treatment and it is only undertaken in patients with painful and debilitating disease.^{7,8}

Our aim in the present study was to confirm prospectively the long term clinical relevance of joint space narrowing—that is, the ability of this radiological feature to predict the risk of future knee surgery.

METHODS

Patients

The study population comprised 139 subjects, of both sexes, aged from at least 50 years, with primary knee osteoarthritis diagnosed according to the clinical and radiological criteria of the American College of Rheumatology.⁹ They correspond to the patients who completed a previously described three year prospective double blind, placebo controlled study.¹⁰ These subjects were contacted for a follow up survey, up to eight years (mean duration 5.0 years) after the end of the three year intervention period. At that time, the incidence of knee surgery, including total knee arthroplasty and knee joint debridement/menisectomy, was recorded.

Acquisition of x rays

Standard radiographs were taken for each knee at baseline and after three years. The signal joint was used for radiographic assessment. Radiographs were obtained according to the gold standard technique available at the time of study design—that is, in the standing (weight bearing) anteroposterior fully extended knee view. The posterior aspect of the knee was in contact with the x ray cassette in order to avoid variation in the distance between the knee and

Abbreviations: AUC, area under the curve; JSN, joint space narrowing

the cassette through the study. Fluoroscopy was used to direct the x ray beam to the centre of the joint space, to control for joint rotation and thus maintain the same degree of alignment with the tibial plateau in subsequent radiographs. Patient repositioning was guided by the baseline film and aided by foot maps.

Mean joint space width assessment

Radiographs were digitised and image analysis was carried out according to a validated technique¹¹ which located the proximal and distal joint margins, excluding outlier points, and calculated the mean joint space width (JSW) of the medial compartment of the tibiofemoral joint. The mean (SD) short term and long term coefficient of variation of this system for reproducing measurements was 1.82 (1.29)% and 1.62 (1.31)%, respectively.¹⁰

Minimum joint space width assessment

The minimum joint space width—that is, the narrowest point of the medial compartment of the femorotibial joint—was assessed by visual determination using a 0.1 mm graduated magnifying lens, as described previously.¹²

Statistical analysis

The areas under receiver operating characteristic (ROC) curves measuring the respective value of mean and minimal JSN for the prediction of the incidence of knee surgery were calculated. For various cut off points of mean or minimum JSN, the relative risk of undergoing knee surgery, and the specificity, sensitivity, and positive and negative predictive values were also determined. At the least, we assessed the overall efficiency of various cut off points of JSN for the prediction of knee surgery over the subsequent five years.

RESULTS

Of 139 patients who completed the three year initial trial, 13 (9.3%) could not be reached at the time of the follow up evaluation. Their baseline demographic characteristics did not differ from those of the overall cohort (table 1). This left a total of 126 patients (90.7%) assessable in the present study. During a median follow up of 5.0 years (mean 3.8, maximum 8.0) after the end of the original study, 16 patients (12.7%) had received knee surgery. These surgical procedures included 11 total knee replacements (68.8%) and five joint debridement/meniscectomies (31.2%). While some patients had surgery in both knees, this intervention occurred more often (in over 60%) in the target knee in the initial study.

The areas under ROC curves measuring the respective value of mean and minimum JSN for the prediction of the incidence of knee surgery are reported in fig 1. Minimum ($p = 0.006$), but not mean ($p = 0.51$), JSN after three years was highly predictive of the risk of requiring osteoarthritis related knee surgery within a further period of five years.

The relative risk of undergoing knee surgery, and the specificity, sensitivity, and positive and negative predictive values for various cut off points of mean or minimum JSN,

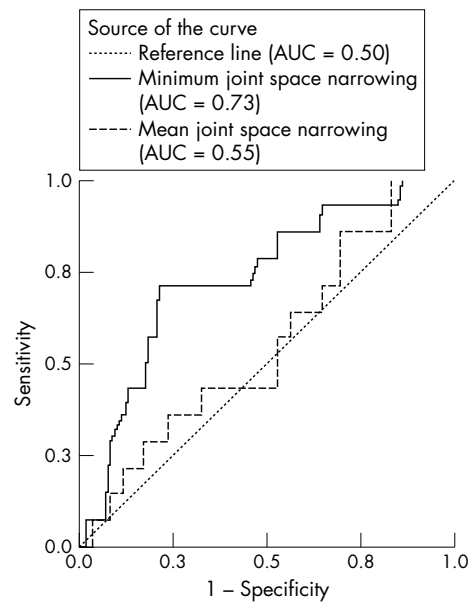


Figure 1 Area under the receiver operating characteristic (ROC) curves evaluating the predictive value of mean and minimum joint space narrowing over three years for future knee surgery within five more years.

are presented in tables 2 and 3. While a cut off value of 0.7 mm for minimum JSN after three years provides the best numerical overall efficiency for predicting the incidence of future knee surgery, no meaningful differences were observed for cut off values between 0.5 and 0.8 mm (relative risks for future surgery all above 4.5, and all overall efficiencies above 70%).

DISCUSSION

Whereas clinical outcomes for the assessment of symptomatic improvement in osteoarthritis of the lower limb (that is, the Western Ontario and McMaster Universities index, the Lequesne algo-functional index, and so on) are well established, there is still debate over the most appropriate way of assessing a drug aimed at reducing, delaying, or preventing the structural progression of osteoarthritis. There is a large consensus that the incidence of lower limb surgery is the most relevant clinical outcome, but on practical grounds the assessment of this particular end point would request studies involving massive cohorts of patients over several years.⁶ Furthermore, the decision process for osteoarthritis related surgery may be affected by various non-medical conditions, including sex, race, and socioeconomic status.¹³ In fact, there are no widely accepted guidelines defining the exact profile of a patient undergoing osteoarthritis related surgery.¹⁴ All these elements make the design of a clinical trial to assess a potential structure modifying agent in osteoarthritis on the basis of the

Table 1 Baseline demographics of the study population

Variable	All patients who completed the initial 3 y study (n = 139)	Patients lost during the 5 y follow up (n = 13)	Patients included in the 5 y follow up analysis (n = 126)
Women	97 (70%)	9 (69%)	88 (70%)
Age (years)	64.5 (6.9)	69.4 (8.0)	64.7 (7.0)
Body mass index (kg/m ²)	27.3 (2.8)	26.5 (2.5)	27.3 (2.8)
Mean joint space width (mm)	5.4 (1.3)	5.4 (1.3)	5.4 (1.3)
Minimum joint space width (mm)	3.9 (1.2)	3.9 (1.3)	4.0 (1.2)

Values are mean (SD) or n (%).
y, years.

Table 2 Relative risk* of various cut off points of joint space narrowing after three years for the prediction of knee surgery within five subsequent years

3 Year JSN	RR for patients with JSN above the specified threshold after 3 y, compared with lower rates of JSN			
	Mean JSN	p Value	Minimum JSN	p Value
Above 0.2 mm	1.44 (0.49 to 4.16)	0.49	3.01 (1.09 to 8.26)	0.03
Above 0.3 mm	1.98 (0.68 to 5.78)	0.20	3.43 (1.24 to 9.53)	0.017
Above 0.4 mm	1.82 (0.58 to 5.68)	0.30	3.88 (1.39 to 10.86)	0.009
Above 0.5 mm	2.26 (0.71 to 7.21)	0.16	4.61 (1.65 to 12.84)	0.003
Above 0.6 mm	2.64 (0.83 to 8.39)	0.09	5.16 (1.76 to 15.12)	0.003
Above 0.7 mm	2.34 (0.68 to 8.06)	0.17	5.15 (1.70 to 15.60)	0.004
Above 0.8 mm	2.88 (0.83 to 9.97)	0.09	4.83 (1.64 to 14.20)	0.004

Values are relative risks and 95% confidence intervals.
 *Adjusted for age, body mass index, total baseline WOMAC score, and baseline joint space width.
 JSN, joint space narrowing; RR, relative risk; WOMAC, Western Ontario and McMaster Universities osteoarthritis index; y, years.

incidence of lower limb osteoarthritis surgery at least hazardous, and at any rate impractical.

There is now a consensus within scientific organisations and regulatory authorities for using radiographic changes—that is, JSN over a period of two to three years—as a surrogate for a hard clinical end point.^{2,3,6} However, as of today no long term prospective clinical study has ever unequivocally confirmed the surrogacy of JSN at the knee for lower limb surgery. To be fully validated, a surrogate end point should show a natural course closely related to that of the relevant end point (thus a decrease in JSW would be linked to an increase in the incidence of joint surgery). The magnitude of the change in the surrogate responsible for a subsequent increase or decrease in the end point should be clearly defined (for example, a 0.5 mm decrease in JSW would be linked to a twofold increase in the risk of joint surgery). Eventually, this numerical relation should also be validated following an external intervention, such as a reduction in JSN by 50% resulting in a 25% decrease in the incidence of joint surgery. In the present study, we show for the first time from a long term prospective study that the assessment of minimum JSN fulfils the two first requirements of the validation of this particular surrogate end point.

Previous studies have suggested that a 0.5 mm threshold of JSN at the hip would be an appropriate cut off value, mainly because this value corresponded to the smallest difference between two measurements of JSW that exceeded the measurement error.^{15,16} A decrease of 0.2 mm and 0.4 mm in hip JSW after one or two years has also been significantly associated with an increased risk of further hip arthroplasty after five years, with corresponding ranges of sensitivity and specificity of 68–75% and 67–78%, respectively.¹⁷ The figures reported in the present study for a minimum JSN of the knee between 0.5 and 0.8 mm after three years (overall efficiency

of between 73% and 75% for predicting the occurrence of knee surgery five years later) compare favourably with these results. On an individual basis, the negative predictive values of our suggested thresholds (that is, the probability of surgery in a patient with JSN below the cut off value) are high (92–94%), but the positive predictive values (the probability of surgery in a patient with JSN above the cut off value) remains marginal (25–30%). When we look only at total knee replacement, the negative and positive predictive values of our suggested thresholds are 94–95% and 13–18%, respectively. Thus our results re-emphasise the fact that clinical considerations may be more important than radiological features in the discussion process to undergo surgery.

We also, for the first time, provide a head to head comparison of the respective value of mean and minimum JSN assessment as predictor for the risk of future knee surgery. While cut off values of minimum JSN between 0.5 and 0.8 mm after three years are all linked to a four- to fivefold increase in the risk of future knee surgery (p = 0.003 to 0.004), none of the selected thresholds of mean JSN (0.2 to 0.8 mm) was significantly related to the clinical outcome (p values between 0.09 and 0.49). We have no definite explanation for such a finding. It has previously been reported that although the minimum joint space width could be more sensitive for identifying changes in cartilage than the mean joint space width, the latter is less sensitive to the influence of variations in radiographic procedures and patient positioning. Recently, the rate of tibial cartilage loss over two years—assessed by magnetic resonance imaging—has been found to be an independent predictor of knee replacement at four years.¹⁸ We suggest that minimum joint space width changes are significantly correlated with tibial cartilage volume changes. However, more studies are needed to confirm these particular findings.

Table 3 Sensitivity, specificity, positive predictive value, negative predictive value, and overall efficiency of various cut off points of joint space narrowing after three years for predicting knee surgery within five years

3 Year JSN	Sensitivity		Specificity		PPV		NPV		Overall efficiency	
	Mean JSN	Minimum JSN	Mean JSN	Minimum JSN	Mean JSN	Minimum JSN	Mean JSN	Minimum JSN	Mean JSN	Minimum JSN
Above 0.2 mm	47	63	57	60	13	19	89	92	57	62
Above 0.3 mm	47	63	64	64	15	20	90	92	63	66
Above 0.4 mm	40	63	67	67	14	22	89	93	65	69
Above 0.5 mm	40	63	72	73	16	25	90	93	69	73
Above 0.6 mm	40	63	74	76	18	28	90	93	71	77
Above 0.7 mm	33	63	76	79	16	30	89	94	72	79
Above 0.8 mm	33	50	80	80	19	27	90	92	75	78

JSN, joint space narrowing; NPV, negative predictive value; PPV, positive predictive value.

We also show in the present study that, even though other radiographic views of the knee joint might be more appropriate today than the fully extended approach, this particular view remains of significant interest as the radiographic changes observed with this technique after three years are significantly predictive of future knee surgery.

Conclusions

We conclude that, on the basis of a cohort of patients initially followed over three years in a randomised controlled trial for which standardised and digitally analysed x rays of the signal joint were available, minimum JSN is highly predictive of the risk of undergoing osteoarthritis related joint surgery during the ensuing five years. These data form a piece of evidence in the validation process of minimum JSN assessment as a surrogate for a hard clinical end point in knee osteoarthritis.

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