

Radiographic progression of knee osteoarthritis in a Czech cohort

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Abstract

Objective

To determine the 5-year radiographic progression of osteoarthritis (OA) of the knee in a Czech cohort.

Methods

139 patients with idiopathic OA were followed for 5 years, receiving only physical therapy and non-steroidal antiinflammatory drugs as needed. Weight-bearing radiographs of both knees were performed at the initial and final evaluation by a single technician using the same instrument and a standardized procedure. Radiographs were evaluated using the Kellgren-Lawrence scale (KL). Joint space width (JSW) was determined by 2 independent trained readers, and discrepancies re-reviewed.

Results

JSW decreased 0.39 ± 0.95 mm in 5 years, or 0.078 ± 0.19 annually. The reduction of JSW was greatest in the KL grade III radiographs (0.099 ± 0.18 mm). The smallest reduction in JSW was seen in those with KL grade I (0.044 ± 0.14 mm). However, only 25% of those with KL stage II or stage III demonstrated any change in JSW over the 5-year period. The reduction in JSW was not constant, being most rapid in the first year and then much slower. The coefficient of variation (CV) of the method was good (intra- and inter-observer CV 3.6%).

Conclusion

This 5-year follow up of Czech patients with OA of the knee demonstrated a low rate of radiographic progression of JSW. The most rapid progression appeared in KL stage III. The progression was most rapid in the first year.

Key words

Knee osteoarthritis, radiographic progression, quantitative radiography.

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Introduction

Treatment of osteoarthritis (OA) has up to now been symptomatic. There is now a demand to improve the methodology and metrology in OA concomitant with the attempt to develop new agents that may alter the course of OA (1-6). The objective of structure (disease) modifying drugs (DMOAD) will be to prevent or retard progression, and to reverse or stabilize OA, thereby altering the underlying pathologic processes. At this time, the radiograph of the knee continues to be the standard surrogate marker for disease progression. Other techniques such as magnetic resonance imaging, sonography, chondroscopy and biomarkers have not been validated in longitudinal trials.

Radiographic changes in the knee include osteophytes, joint space narrowing (JSN), subchondral sclerosis, subchondral cyst formation, attrition, etc. However, change in joint space width (JSW) on a plain radiograph has evolved as the primary efficacy variable for most DMOAD trials as it is the most reproducible and sensitive measure to change (7, 8).

Several studies have attempted to determine the rate of JSN (18). Because of differences in methodology and target populations, there has been a wide variation; the rate of change has ranged from 0.60 mm/year to 0.06 mm/year. We followed a cohort of Czech patients with knee OA using radiographs taken by a standardized technique. We report on the progression of their OA over a 5-year period.

Patients and methods

Patients

As part of a 5-year, double blind, controlled, randomized study of osteoarthritis of the knee, a cohort of 139 Czech patients with OA of the knee were treated with physical therapy, nonsteroidal antiinflammatory drugs (NSAIDs), or a placebo for a 5-year period. The results for those treated with an active agent (GAGPC) will be reported elsewhere upon completion of the analysis.

The consensus of the 1988 Scientific Advisory Committee was to include patients with knee pain plus radiological evidence of JSN in at least one of the 3

knee compartments and/or osteophytes and/or subchondral sclerosis. Those with knee pain from other causes were to be excluded. Consecutive patients with OA of the knee undergoing evaluation for their arthritis at the Prague Institute of Rheumatology were screened for inclusion in the trial. Only patients with primary OA were included.

Patients were to be of either sex and over the age of 40. Demographic information included the duration of symptoms, the degree of pain and disability as measured by the Lequesne algofunctional index (11), and the Kellgren-Lawrence (KL) radiographic stage (12).

Methods

Patients were examined every 3 months for 5 years. Patients were already on a prescribed physical therapy program that was not altered during the trial. NSAIDs were permitted and their consumption monitored.

All radiographs were performed in a single radiology unit by the same radiology technician and using the same x-ray equipment. The x-ray cassette film was placed 1.15 m from the x-ray tube. Anterior-posterior and lateral weight-bearing radiographs of both knees were obtained with the patient's heels and toes together and knees fully extended. The X-ray beam was horizontal and the central X-ray beam was directed at the center of the joint space at the level of the tibial tubercle (using fluoroscopy). The repositioning of the patient was guided by the original radiograph, and the same radiographic techniques were repeated (i. e., killivolts, milliamps, and milliseconds).

JSW was measured on the antero-posterior radiograph by the method of Lequesne (9), using a 10x magnifying lens marked with a 20 mm scale at 0.1 mm intervals. The site of the tibiofemoral compartment selected for interpretation was based on the site, on the final radiograph, at which the joint space was narrowest. The choice was made by mutual agreement between the two readers. If the JSW was equal in both tibiofemoral compartments, the narrowest point of the compartment adjacent to the largest osteophyte was measured. If the JSW were equal and the osteophytes were equal in

size, the medial compartment was measured at its narrowest point. If there was no narrowest point of the compartment, the midpoint of the compartment was measured (10). A drawing pencil was used to mark the radiograph for the measuring points. Each reader marked the landmark of measure using a special pencil. For marking the reader could use a reading magnifier. These marks were cleared after each measurement. The space between marked points was measured by a reading magnifier equipped with a graded scale, placed on the X-ray. The Kellgren-Lawrence grade was estimated using an atlas. Intra- and inter-observer reliability was not estimated. The Kellgren-Lawrence grading and the measurement of JSW at baseline on the final films was done at the same time; the readers were blinded to the chronology of the films (but knew that a given set of films corresponded to a single patient).

Two readers were trained to read the JSW. Readers reviewed radiographs independently. If the two JSW readings were within 0.3 mm of each other, the mean of the 2 values were recorded as the final reading. If the difference between the 2 JSW readings was greater than 0.3 mm, the radiographs were re-interpreted. This occurred in about 10% of the readings. Upon re-interpretation, if the readings were within 0.3 mm of each other, the mean was recorded. If the second readings were also over 0.3 mm apart, the average of the 4 readings was recorded.

Inter-observer error was calculated on all data. Intra-observer error was estimated on 10 randomly chosen X-rays, measured 6 times over 10 days by each reader.

Results

The 139 patients included 33 men (24%) and 106 (76%) women (ratio 1:3.3). The mean age of the group was 59.1 ± 8.0 (standard deviation) (men 60.0 ± 8.4 ; women 58.6 ± 7.9) years. The mean duration of disease symptoms was 5.8 ± 4.9 years. The Lequesne algofunctional index measured 9.2 ± 3.4 points, suggesting moderate pain and disability.

The distribution of the patients according to the Kellgren-Lawrence score is shown in Table I. The majority of pa-

tients were in stage II (20/139) or stage III (67/139), but there were also 21 patients in stage 0 or 1. There were 21 patients in stage 0-1, 20 in stage II; 67 in stage III and 31 in stage IV. Sixteen patients had JSW < 1 mm and 2 patients had JSW 0 mm. The overall progression for the whole group was 25%, being highest in the group with KL stage III (26.8%). Worsening of 2 grades was observed only in 3 patients (2.2 %). We could also see reduction of KL score in 2 patients (1.4%).

The overall change in joint space over the 5 years was a mean reduction of 0.39 ± 0.95 mm. This represents a mean change of 0.078 ± 0.19 mm/year (Table II, Figs. 1 and 2). The reduction in JSW for the KL subgroups is recorded in Table II. The greatest reduction was in KL class III; however, those with KL II and even with KL IV had a further reduction of JSW.

We analysed a subgroup of patients who had at baseline a KL score 2 and JSW 1 mm and who completed the study.

In the group were 95 patients. They lost 0.50 ± 0.81 mm in 5 years, which corresponds 0.1 mm yearly. The progression in joint space reduction was not linear, being quickest in first year ($-0.30 \text{ mm} \pm 0.32 \text{ mm}$) and much slower in next 4 years (-0.04 mm/year) (Table III).

The intra-observer reliability for JSN was as follows: Reader A intraclass correlation 0.99 and CV 2.0%; Reader B intraclass correlation 0.98 and CV 3.6%. The inter-observer reliability for JSN reflected a baseline intraclass correlation of 0.97 at baseline and 0.98 at the 5-year radiographs. This represents a CV of 6.6% (-0.06 ; $+3.03$ 95% confidence interval, CI) and 6.5% (-0.07 ; $+0.01$ CI) respectively. There was little change after the agreement process with a final CV of 3.6% ($+0.02$; 0.08 CI) for baseline

Table I. Change in the Kellgren-Lawrence score: baseline versus 5 years.

Kellgren-Lawrence	N	Kellgren-Lawrence 5-year					Progression
		0	1	2	3	4	
0	3	3				0 (0.0%)	
1	18		14	2	1	1	14 (22.2%)
2	20			15	4	1	5 (25%)
3	67			2	47	18	18 (26.8%)
4	31					31	Not applicable
Total at 5 years	139	3	14	19	52	51	27 (25.0)%

Table II. Joint space narrowing in the knees (mm, mean \pm SD).

Subset	N	Initial JSW	5-year JSW	JSN over 5 years	Annual JSN
Kellgren 0 or I	21	4.12 ± 0.67	3.90 ± 0.72	0.22 ± 0.74	0.044 ± 0.148
Kellgren II.	20	5.72 ± 1.60	5.39 ± 1.50	0.33 ± 0.85	0.065 ± 0.170
Kellgren III.	67	4.10 ± 0.90	3.62 ± 1.20	0.49 ± 0.89	0.099 ± 0.178
Kellgren IV.	31	2.25 ± 1.45	1.89 ± 1.36	0.38 ± 1.26	0.076 ± 0.252
All patients	139	3.92 ± 1.54	3.53 ± 1.61	0.39 ± 0.95	0.078 ± 0.191

Kellgren: Kellgren Lawrence grade; N: number of patients; JSW: joint space width; JSN: joint space narrowing.

Table III. Change in knee joint space in yearly intervals (subgroup analysis, patients with initial Kellgren-Lawrence stage 2, JSW > 1 mm) completers (mm \pm SD).

	Baseline	1 year	2 years	3 years	4 years	5 years
JSW mm \pm SD	4.14 ± 1.34	3.84 ± 1.34	3.76 ± 1.38	3.72 ± 1.38	3.59 ± 1.44	3.64 ± 1.51

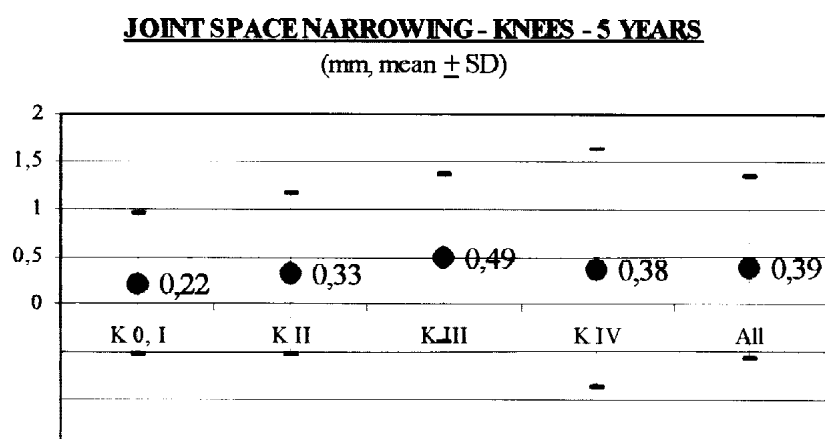


Fig. 1. Joint space narrowing in the knees at 5 years.

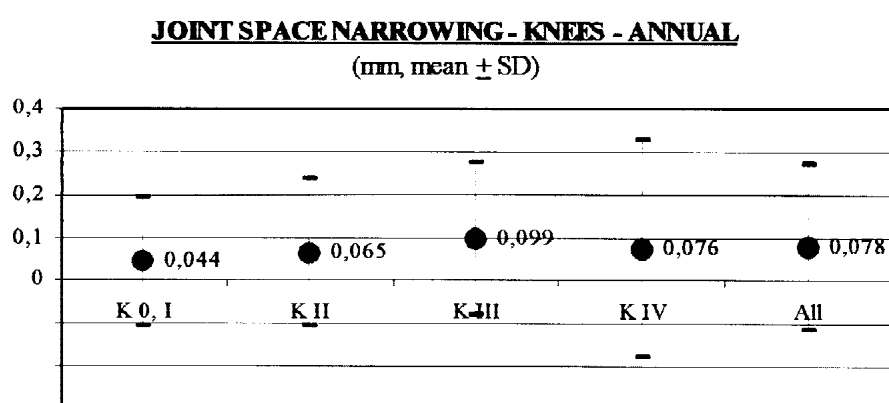


Fig. 2. Joint space narrowing in the knees - annual rate.

studies and a CV of 4.9% (-0.04; +0.05 CI) for the 5-year radiographs.

Discussion

In this 5-year prospective study of 139 Czech patients with OA of the knee, progression of OA averaged a loss of JSW of 0.39 mm or 0.078 mm yearly. In this study, standard radiography was able to demonstrate progression with the use of a trained and careful technician working under close supervision.

Newer techniques of standardization of the radiographic procedure for OA of the knee have been developed and reported elsewhere. It is expected that prospective 5-year follow-ups of patients with OA of the knee using the newer methods will validate these methods as being more sensitive to change than the method reported above. Some of these improvements include the positioning of the patient with semiflexed knees, fluoroscopy and image digitization. It appears that these changes will improve the quantifi-

cation of the disease. For example, arthroscopic findings confirm that the semiflexed view are more likely to display the region of the tibiofemoral compartment where cartilage damage in OA is most prevalent (13). Different degrees of flexion from 15°-60° have been suggested. Mesquida *et al.* did not find any improvement in reproducibility between 30° flexion and extended knees (14). Fluoroscopic positioning may better standardize the flexion position and improve the reproducibility of X-rays (15). However, prospective studies are needed to establish whether they are more sensitive to change than a carefully performed plain radiograph.

The intra-rater reliability (2% and 3.6%) in this trial was comparable to that reported by Lequesne (3.8%) (16) and less than that reported by Buckland-Wright *et al.* (6.4%) (17). Similarly, the results are comparable with the coefficient of variation reported by Buckland-Wright where he used the semiflexed position,

image computerization, and magnification correction (17). The inter-observer reliability from this trial (3.6% and 4.9%) was also comparable to the manual measurements of Buckland-Wright (6.4%), but higher than the computerized, magnified and semiflexed position radiographs (3.2%). The agreement process seemed successful as the coefficient of variation did decrease (baseline 6.5 and 6.6% reduced to 3.6 and 4.9%). These data support the credibility of conventional radiography with manual measurements in trials of disease-modifying drugs for OA of the knee.

Because of differences in methodology and target populations, the reported annual rate of JSN of the knee ranges from 0.60 mm a year to 0.06 mm a year (18) (Table III). The median annual rate of JSN was 0.26 mm. The authors of the analysis suggested that the discrepancies were due to different populations of patients, as those recruited from the community would probably have a slower rate of progression than those recruited from clinic populations. Estimates of JSN in the population-based Baltimore Longitudinal Study of Aging (20) and the Framingham Study (21) reported slower rates of progression (i. e., 0.06 - 0.10 mm yearly). Tucker *et al.* reported a loss of 0.035 to 0.053 mm per year in 104 patients followed for 8 years (19). Dieppe *et al.* also reported a loss of 0.1 mm yearly for 145 patients followed for 3 years (23). Reginster *et al.* found also yearly JSN 0.1 mm in placebo arm of drug study in cohort of 106 patients followed for 3 years (24). Our results are concordant with the community-based epidemiological studies.

However, there are studies with much greater annual rates of JSN. Ravaud *et al.* found an annual loss of 0.42 mm (25), nearly 5 times our findings. Ravaud's patient cohort was characterized by highly symptomatic patients (44% had effusions and 52% scored > 50 mm on a 100 mm visual analog scale). These values were higher than those for our population and probably than for the population-based studies listed above. The presence of synovitis may imply more rapid progression, as suggested by Amor, who reported higher annual JSN in patients with synovial effusions (26). He coined

the term 'chondrolytic episodes' to represent this group of patients with effusion and more rapid cartilage loss. Unfortunately, we were not able to calculate the exact number of patients with effusion at the beginning of the study.

Analysis of the subgroup of patients who had a KL score 2 at the beginning of the study showed slightly higher JSN (0.5 mm - 0.1 mm yearly) than for the whole group. Progression was quickest in the first year and much slower over the next 4 years. This confirms the fact that JSN is not necessarily linear but phasic. The patients included in the study were in an active phase of their disease, with greatest pain, which was replaced by a phase of stabilization.

We observed that 19% of the patients progressed in 5 years using the KL grading system. This rate of about 4% per year corresponds to the reports of the Framingham study, where a 4% progression per year in KL grade was reported over an 8-year observation period (27). However, Ravaud *et al.* observed progression in 11% of patients during a one-year follow-up (8). In this study, the JSW was more sensitive to change than the KL grading system.

At the present time patients with KL II and III are recommended for recruitment into disease modifying studies on OA. We could demonstrate that even in those target groups the yearly JSN (0.065 ± 0.17 mm; 0.099 ± 0.18 mm) is lower than expected. This is important for calculating the power of the study. The striking fact was the non-linearity of JSN. Probably the whole process of OA progression is irregular, with rapid periods of progression and periods of stabilization. This stresses the necessity of management strategies which treat the inflammation in OA.

Various aspects of our study are open to criticism. Nevertheless it should be stressed that the study was begun in 1989 and was based on the standards of that time. In fact, all long-term studies will probably fall behind the contemporary state of the art in terms of methodology. We were not able to change the inclusion criteria and radiographic technique used. We must also stress that this study was not originally designed as methodo-

logical study, but as a randomized, controlled study to demonstrate the efficacy of drug therapy. As such, it nevertheless represents one of the longest observational studies of the natural course of knee OA in a large cohort of patients and some of the data will be useful for present clinical studies in OA.

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