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Correlation between radiographic severity of knee osteoarthritis and future disease progression. Results from a 3-year prospective, placebo-controlled study evaluating the effect of glucosamine sulfate

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Summary

Objective: To investigate the relationship between baseline radiographic severity of knee osteoarthritis (OA) and the importance of long-term joint space narrowing.

Design: Sub-analysis from a three-year randomized, placebo-controlled, prospective study, of 212 patients with knee OA, recruited in an osteoarthritic outpatient clinic and having been part of a study evaluating the effect of glucosamine sulfate on symptom and structure modification in knee OA.

Material and Methods: Measurements of mean joint space width (JSW), assessed by a computer-assisted method, were performed at baseline and after 3 years, on weightbearing anteroposterior knee radiographs.

Results: In the placebo group, baseline JSW was significantly and negatively correlated with the joint space narrowing observed after 3 years ($r=-0.34$, $P=0.003$). In the lowest quartile of baseline mean JSW (<4.5 mm), the JSW increased after 3 years by (mean (S.D.)) 3.8% (23.8) in the placebo group and 6.2% (17.5) in the glucosamine sulfate group. The difference between the two groups in these patients with the most severe OA at baseline was not statistically significant ($P=0.70$). In the highest quartile of baseline mean JSW (>6.2 mm), a joint space narrowing of 14.9% (17.9) occurred in the placebo group after 3 years while patients from the glucosamine sulfate group only experienced a narrowing of 6.0% (15.1). Patients with the most severe OA at baseline had a RR of 0.42 (0.17–1.01) to experience a 0.5 mm joint space narrowing over 3 years, compared to those with the less affected joint. In patients with mild OA, i.e. in the highest quartile of baseline mean JSW, glucosamine sulfate use was associated with a trend ($P=0.10$) towards a significant reduction in joint space narrowing.

Conclusion: These results suggest that patients with the less severe radiographic knee OA will experience, over 3 years, the most dramatic disease progression in terms of joint space narrowing. Such patients may be particularly responsive to structure-modifying drugs. © 2003 OsteoArthritis Research Society International. Published by Elsevier Science Ltd. All rights reserved.

Key words: Osteoarthritis, Knee, X-rays, Progression.

Introduction

Osteoarthritis (OA) is a major cause of pain and physical disability in the elderly[1]. Since the elderly population is more in search of a pain-free active life, the management of knee OA, the location responsible for the most important pain and disability, has become a major social and economic issue in health management[2]. It is now widely recognized that the rate of structural progression of OA may significantly differ from a patient to another[3–6]. However, since the determinants of OA progression are not yet fully understood[7], it remains rather difficult to predict which individual patients will deteriorate, experience the most severe functional impairment and eventually require joint replacement surgery[2]. Several studies have aimed at the identification of predictive factors for rapid OA progression. Most of the studies focused on the predictive value of clinical factors to identify patients with the most severe osteoarthritis progression[6,8,9], but relatively few studies weighted the value of current radiological severity on future structural outcomes. The aim of the present study was to investigate whether radiographic knee OA severity, assessed by a precise joint space width (JSW) measurement, was correlated to the future structural progression of the disease, over a three-year period of follow-up.

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Patients and methods

PATIENTS

The study population, more extensively described in a previous publication[10], was constituted by 212 subjects,

Table I
Baseline characteristics of the patients in the placebo and glucosamine sulfate group stratified into quartiles of baseline joint space width (JSW)

	Placebo			Glucosamine sulfate		
	Quartile 1* (*N*=23) Mean±S.D. Frequencies (%)	Quartile 4† (*N*=26) Mean±S.D. Frequencies (%)	*P*-value	Quartile 1* (*N*=29) Mean±S.D. Frequencies (%)	Quartile 4† (*N*=27) Mean±S.D. Frequencies (%)	*P*-value
Sex						
Men	17 (74)	21 (81)	0.56	21 (72)	19 (70)	0.87
Women	5 (26)	5 (19)		8 (28)	8 (30)	
Age (years)	67.6±7.8	65.2±6.5	0.26	67.1±8.2	67.5±7.4	0.86
Height (cm)	160.5±7.2	160.0±6.9	0.78	160.3±9.5	162.4±10.9	0.44
Weight (kg)	73.0±9.5	69.0±8.6	0.13	71.5±10.3	71.3±11.5	0.94
Body mass index (kg/m^2)	28.2±2.3	26.9±2.5	0.06	27.7±2.3	26.9±2.7	0.22

*Baseline JSW <4.5 mm.
†Baseline JSW >6.2 mm.

from both genders aged from at least 50 years, with primary knee OA. They were issued from a double-blind, placebo-controlled study evaluating, over a period of 3 years, the symptomatic and structural effects of glucosamine sulfate in OA. Knee OA was diagnosed according to the clinical and radiological criteria of the American College of Rheumatology[11]. 106 patients were randomized to both the placebo and the treated groups from whom 71 and 68 completed the 3-year study, respectively.

METHODS

X-rays acquisition

Standard radiographs were taken for each knee at baseline and after 3 years. The patients stood with their knees fully extended and the posterior aspect of the knees in contact with a vertical cassette in a cassette holder. The lower limbs were internally rotated until the patella was centralized over the lower end of the femur. The feet were parallel and positioned a small distance apart. Foot maps were used for repositioning the patient at the time of subsequent X-rays. The X-ray beam was centered on the joint space and parallel to the tibial plateau. Fluoroscopy was used to correct lower limb positioning and X-ray beam alignment. The focus film distance was 110 cm.

JSW measurement

Radiographs were digitized and image analysis was performed according to a validated technique[12], 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 (S.D.) 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].

Statistical analysis

Quantitative variables were expressed as mean±S.D. and qualitative variables were reported as absolute or relative frequencies. The association between baseline JSW and 3-year joint space narrowing was assessed by the Pearson coefficient of correlation, in the placebo and the glucosamine sufate groups separately, to avoid any interaction of the treatment effect. We also performed, in the placebo group, a multivariate analysis in which the dependant variable was the 3-year changes in JSW and the independent variables include the patient's characteristics (age, BMI), the symptoms (pain, function and stiffness subscales of the WOMAC) and baseline JSW. In order to investigate the real progression of the disease, the analysis has been performed only in the 3-year completers and not in intention-to-treat. In order to evaluate whether the baseline levels of JSW affect the structural response to glucosamine sulfate, we compared the 3-year joint space narrowing in the placebo and in the glucosamine sulfate group, in the highest and the lowest quartiles of baseline JSW. The differences between quartiles were assessed by ANOVA. In each quartile we looked at the number of patients who experienced a relevant joint space narrowing over a 3-year period. Based on the literature, any loss above 0.5 mm was considered as relevant[13]. We eventually calculated the relative risk [RR (95% CI)] of having a joint space narrowing over 3 years greater than 0.5 mm in the lowest as compared to the highest quartile. This arbitrary cut-off of 0.5 mm in JSW was based on the paper by Lequesne *et al.*[13] in which a difference of 0.5 mm in joint space narrowing between an active drug and a comparator, was suggested to be a relevant primary endpoint in a study looking at disease modifying drugs in OA. The results were considered significant at the 5% level (P<0.05). Statistical calculations were carried out with the SAS software (SAS Institute, Cary, NC, U.S.A.).

Results

No statistically significant differences for age (P=0.31), BMI (P=0.46) or sex (P=0.64) were observed between the patients who completed the 3-year study and those who prematurely discontinued. We also did not find any significant difference between the baseline demographics of the patients from the highest and the lowest quartiles of baseline JSW (Table I), most likely because of the small size of our sample. We found no statistically significant differences between the baseline characteristics of the glucosamine sulfate group and the placebo group, nor in the lowest quartile neither the highest quartile of OA severity. From the

Table II
*Multivariate analysis results for the prediction of 3-year changes in JSW (*N=*71)*

Variable	Parameter estimate	S.E.	*P*-value
Age	−0.003	0.003	0.36
BMI	0.012	0.009	0.18
JSW at baseline	−0.048	0.026	0.07
Pain subscale of the WOMAC	−0.00008	0.0003	0.81
Stiffness subscale of the WOMAC	0.0005	0.0005	0.29
Function subscale of the WOMAC	0.00006	0.00009	0.51

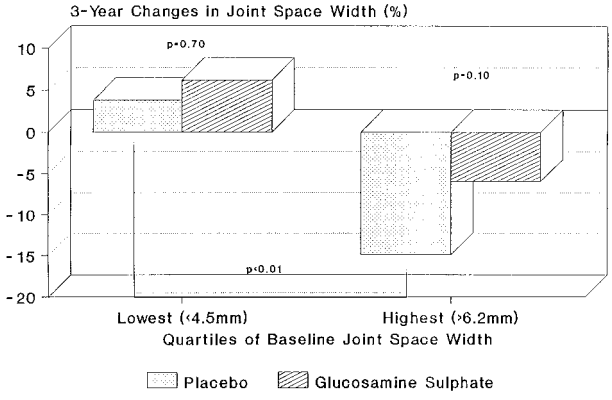

Fig. 1. 3-year changes in JSW stratified for quartiles of baseline JSW in the placebo and the glucosamine sulfate group.

212 patients enrolled in the study, 139 completed the 3-year study: 71 in the placebo group (14 and 19 in quartile 1 and 4, respectively) and 68 in the glucosamine sulfate group (16 and 19 in quartile 1 and 4, respectively).

In the placebo group, baseline JSW was significantly and negatively correlated with the 3-year joint space narrowing ($r=-0.34$, $P=0.003$). In the placebo group ($N=71$), a multivariate analysis including demographics (age, BMI) and symptoms (pain, function and stiffness of the WOMAC), showed baseline JSW to be the only variable borderline significant ($P=0.07$) for the prediction of the structural progression observed after 3 years (Table II). In the lowest quartile of baseline JSW (<4.5 mm), mean (S.D.) JSW increased after 3 years by 3.8% (23.8) while a joint space narrowing of 14.9% (17.9) was observed in the highest quartile (baseline mean JSW >6.2 mm). The joint space variations observed in the two quartile are statistically different ($P=0.01$) (Fig. 1). The increase in JSW reached 0.13 (0.81) mm in the lowest quartile and for a decrease of 1.05 (1.28) mm in the highest quartile. In the lowest quartile, 4/14 patients (28.6%) experienced a joint space narrowing greater than 0.5 mm over 3 years compared to 13/19 (68.4%) in the highest quartile. The relative risk of having a joint space loss over 0.5 mm, in patients with the less severe OA at baseline (highest quartile of JSW) was 2.39 (95% CI: 0.99–5.79) compared to those from the lowest quartile of JSW at baseline.

In the glucosamine sulfate-treated patients, baseline JSW was significantly and negatively correlated with the 3-year joint space narrowing ($r=-0.28$, $P=0.019$). JSW increased by 6.2% (17.5) over 3 years in the lowest quartile (baseline JSW <4.5 mm), i.e. almost twice the value observed in the placebo group and decreased by only 6.0% (15.1) in the highest quartile (baseline JSW >6.2 mm), i.e. more than 50% less than in the placebo group (Fig. 1). In absolute value, the increase in JSW was 0.22 (0.66) mm in the lowest quartile and the decrease of 0.45 (1.04) mm in the highest quartile. In the lowest quartile, 1/16 patients (6.3%) experienced a joint space narrowing greater than 0.5 mm over 3 years compared to 9/19 (47.4%) in the highest quartile. In the most severely affected patients, the 3-year joint space narrowing observed in the placebo group was not statistically different from the one observed in the glucosamine sulfate-treated group ($P=0.70$). However, in patients with the lowest initial degree of OA, i.e. in the highest quartile of baseline mean JSW, glucosamine sulfate use was linked to a trend ($P=0.10$) towards a reduction in joint space narrowing (Fig. 1). The number of patients needed to treat (NNT) with glucosamine sulfate, to prevent one joint space narrowing of at least 0.5 mm over 3 years is 4.48 in the lowest quartile and 4.75 in the highest quartile.

Compared to patients treated with placebo, patients on glucosamine sulfate had a RR of experiencing a joint space narrowing greater than 0.5 mm over 3 years of 0.69 (95% CI: 0.39–1.22) in the lowest quartile of baseline JSW and of 0.22 (95% CI: 0.03–1.73) in the highest quartile.

Discussion

It is now widely recognized that the rate of clinical and radiological progression of OA may significantly differ between patients[2]. In order to identify patients who will suffer from a rapid progression, several studies aimed at selecting the most predictive risk factors for the progression of OA. Some studies were mainly focused on demographic characteristics and symptoms changes. In the Bristol 'OA500' study[3], the 3-year clinical progression of OA, defined as a self-reported worsening of the overall condition, was more severe in women, older patients and those with severe pain at entry.

Other studies also investigated which clinical or demographical baseline features were related to the structural progression of OA. In 508 patients aged between 50 and 75 years[9], the parameters predictive of the one-year radiological progression of hip OA (i.e. a change of a least 0.6 mm in JSW) were a Lequesne's functional index >10 [OR: 2.66 (95% CI: 1.46–4.83)], age at entry >65 years [OR 1.90 (95% CI: 1.18–3.08)] and to be a women [OR, 2.51 (95% CI: 1.49–4.23)]. In a 5-year study, 354 men and women aged >55 years were followed for their knee OA[8]. Structural progression, assessed by the changes in the Kellgren and Lawrence scale[14], was significantly increased among subjects with higher baseline body mass index [OR: 18.3 (95% CI: 5.1–65.1)], previous knee injury [OR: 4.8 (95% CI: 1.0–24.1)] and history of regular sports participation [OR: 3.2 (95% CI: 1.1–9.1)]. Knee pain at baseline [OR 2.4 (95% CI: 0.7–8.0] and Heberden's nodes [OR 2.0 (95% CI 0.7–5.7)] were weakly associated with progression. Another study, with 12 years of follow-up of patients with knee OA[6], reported the same prognostic factors for a decrease in JSW between two radiographs: higher body mass index, older age, presence of Heberden's nodes but also other factors like clinical diagnosis of generalized osteoarthritis or previous bow legs or knock knees.

Few studies investigated whether baseline radiographic severity of OA was related to radiological long-term progression. When considering the predictors of whole body OA progression in a follow-up of 1 to 9 years of a cohort of elderly women[15], using the grading method of Kellgren and Lawrence on 10 joint groups, an increased length of

follow-up and a lower baseline OA score were associated with greater OA progression. In another trial[5], 63 subjects were followed for a mean of 11 years and knee radiographs were read and scored with the Kellgren and Lawrence scale. At baseline, 35.5% of knees were radiologically normal while grade 1 to 4 corresponded respectively to 17.5%, 24.5%, 9% and 1.6% of the population. During this follow-up period, only one-third of the patients worsened, maybe because of the relatively poor sensitivity to changes of the OA grading score[16]. Nevertheless, the proportion of knees deteriorating of at least one Kellgren and Lawrence grade was 48% in knee scored 0 at baseline, 45% for knee scored 1, 38% for knee scored 2 and 16% for knee scored 3. Theses results are consistent with the present study where patients with the less affected knee OA, assessed by the medial femoro-tibial JSW measurement, with a computer-assisted method, do experience, over 3 years, the most severe structural progression. Our results obtained from a longitudinal study investigating the exact weight of radiological features on structural outcomes, with changes in JSW assessed with a precise and sensitive method, confirm therefore data obtained in previous observational studies. However, in hip OA, discrepant results were reported, with progression being significantly increased, after one year of follow-up, if baseline radiological joint space width was <2 mm[9]. While the explanation for this discrepancy remains unclear, this might re-emphasize the different pathogenesis processes underlying the progression of the disease at different locations. In our study, data were pooled for men and women. However, some studies suggested that the age-related morphology of knee joint cartilage[17] or the onset of knee OA[18] could differ between genders. Similarly, the rate of progression could have been different between the 3-year completers and the premature withdrawals with a significant impact on the overall results. However, the baseline characteristics of the two populations were not significantly different and only eight patients (five in the placebo group and three in the glucosamine sulfate group) withdrew from the study because of a lack in efficacy.

Our results suggest that OA should be diagnosed at the early stages of the disease, in order to initiate therapy when the potential for progression of the disease is high and when structural treatments appear to be the most effective. As a consequence, more accurate techniques for the early diagnosis of the disease should be validated. Magnetic resonance imaging, while potentially more accurate and precise than conventional X-rays, still suffers from a clear lack of accessibility[17]. Other imaging techniques, like computer tomography, ultrasonography and bone scanning have not been fully validated for this specific purpose[19]. Biochemical markers of bone, cartilage and synovium are actually studied and could be potentially useful[20]. Furthermore, patients with mild to moderate knee OA should be treated not only for their symptoms but also to prevent cartilage loss. The risk in treating such patients only for symptoms (pure analgesics, NSAIDs, etc.) is that structural alteration may progress rapidly. In our study, we assessed the effect of glucosamine sulfate, a structure modifying OA drug, on cartilage loss in patients with knee OA. The compound was effective in reducing joint space narrowing and symptoms over a 3-year period[10], as recently confirmed in another trial[21]. In the present secondary analysis, albeit not statistically significant between the two groups, mainly because of the low statistical power due to the low number of patients in each quartile of JSW (there were 212 patients in the initial study[10]), glucosamine was found to reduce joint space loss by 50% compared to the placebo, with a strong trend towards a statistical significance ($P=0.1$), in patients with the less affected joints. Conversely, our results show that patients with the most severe cartilage alteration at baseline did not experience an apparent disease progression over 3 years in terms of joint space narrowing. This may represent a burnout effect after reaching a certain level of OA, as previously reported in a longitudinal study of the hand[22]. An hypothesis for a stabilization or even an increase in JSW over 3 years could involve: the repair of chondral defects, occurring early after the cartilage loss, and characterized by chondrocytes clustering (mitosis and/or migration) cartilage hypertrophy, an increase in glycosaminoglycans, fibronectin and water content in the cartilage as a result of an increased glycosaminoglycan and collagen synthesis by chondrocytes[23]. At the more severe structural stage of OA, with no detectable progression over time, glucosamine sulfate was not able to induce a statistically significant difference compared with placebo, notwithstanding the magnitude of the increase in JSW was twice higher than in the placebo group, i.e. an observation that would deserve further investigations in an appropriately powered study. Glucosamine was reported to act, at least partly, by being a precursor of proteoglycans synthesis[24]. Proteoglycans are instrumental in helping cartilage to capture water and in promoting formation of an elastic layer, factors which may improve the functional characteristics of cartilage[25]. In patients with less damage in their cartilage structure, cartilage could thus be more responsive to the effects of glucosamine sulfate. Conversely, in patients with a more advanced structural damage at baseline, radiographic severity was associated to a high degree of pain[26,27] and physical impairment[28] resulting in a decreased health-related quality of life. It can thus be reasonably assumed that short or mid term outcomes for these patients with severe knee OA are likely to include joint prosthesis replacement. Severe radiological joint space narrowing at diagnosis was previously reported[29] to be a predictor of the need for total hip replacement in patients with OA of the hip. In order to delay the joint replacement, patients with a high severity of OA could then be treated preferentially with the aim to reduce symptoms. Nevertheless, it could be interesting to investigate whether glucosamine sulfate or another structure-modifying OA drug is able to delay the need for joint replacement as compared to purely symptomatic medications. Our results allow also reconsideration of the inclusion and exclusion criteria used for trials assessing the efficacy of disease modifying drugs in OA. The structure-modifying effect of a drug should be more easily demonstrated in a population with a high risk of progression over time, hence excluding OA patients with severe radiologic lesions who are less likely to experience severe progression. Moreover, when including patients with mild to moderate OA, the difference between the treated and placebo groups could be investigated at a lower cost because of a significant decrease either in the number of patients included or in the duration of the trials.

From this sub-analysis of a 3-year randomized, placebo-controlled, prospective study evaluating the effects of glucosamine sulfate, our results suggest that patients with the less severe structural knee OA at baseline will experience, over 3 years, the most severe radiographical progression. Such patients may be particularly responsive to structure-modifying drugs.

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