Structural and Symptomatic Efficacy of Glucosamine and Chondroitin in Knee Osteoarthritis

A Comprehensive Meta-analysis

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Objective: To assess the structural and symptomatic efficacy of oral glucosamine sulfate and chondroitin sulfate in knee osteoarthritis through independent meta-analyses of their effects on joint space narrowing, Lequesne Index, Western Ontario MacMaster University Osteoarthritis Index (WOMAC), visual analog scale for pain, mobility, safety, and response to treatment.

Methods: An exhaustive systematic research of randomized, placebo-controlled clinical trials published or performed between January 1980 and March 2002 that assessed the efficacy of oral glucosamine or chondroitin on gonarthrosis was performed using MEDLINE, PREMEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Current Contents, BIOSIS Previews, HealthSTAR, EBM Reviews, manual review of the literature and congressional abstracts, and direct contact with the authors and manufacturers of glucosamine and chondroitin. Inclusion, quality scoring, and data abstraction were performed systematically by 2 independent reviewers who were blinded to sources and authors. Conservative approaches were used for clear assessment of potential efficacy.

Results: Our results demonstrated a highly significant efficacy of glucosamine on all outcomes, including joint space narrowing and WOMAC. Chondroitin was found to be effective on Lequesne Index, visual analog scale pain, mobility, and responding status. Safety was excellent for both compounds.

Conclusions: Our study demonstrates the structural efficacy of glucosamine and indistinguishable symptomatic efficacies for both compounds. Regarding the relatively sparse data on glucosamine and joint space narrowing and the absence of data on structural effects of chondroitin, further studies are needed to investigate the relationship among time, dose, patient baseline characteristics, and structural efficacy for an accurate, disease-modifying characterization of these 2 compounds.

Arch Intern Med. 2003;163:1514-1522

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MUSCULOSKELETAL diseases are rapidly becoming a major public health concern because of the aging of the world population and the increasing prevalence of the aging population's risk factors.[1-3] Osteoarthritis is a frequent and major cause of morbidity and disability, particularly in the second half of human life.[2] Moreover, osteoarthritis is widely recognized to interfere with social life, socioeconomic status, and psychological well-being.[4]

Medical interventions can be directed toward different stages of the disease process: patient education (eg, weight reduction), exercise, analgesics (eg, acetaminophen), nonsteroidal anti-inflammatory drugs (NSAIDs), and eventually orthopedic surgery, including joint replacement.[3] The reassessment of the central role of the NSAIDs in the treatment of osteoarthritis has favored the screening and development of drugs that could interfere directly with the disease progress, aiming at protection and regeneration of the cartilage and therefore providing clinical benefits in a more specific pattern than broad spectrum analgesics. Recent recommendations of the American College of Rheumatology and the European League Against Rheumatism[5,6] classify drugs for the treatment of osteoarthritis as either symptom-modifying or structure-modifying drugs, depending on their capacity to interfere with the disease progression. The European Agency for the Evaluation of Medicinal Products and the Food and Drug Administration defined the requirements for the registration of such drugs. The main evaluation criterion for symptom-modifying drugs is the improvement of pain and function. For structure-modifying drugs, the prospective evaluation of the radiographic changes, by analysis of the joint space narrowing (JSN), is the recommended one.[7,8]

Chondroitin 4 and 6 and glucosamine sulfates, natural compounds found in healthy cartilage, have been inves-

tigated for 20 years, and their exact slot in the therapeutic strategy of osteoarthritis remains debated. Chondroitin sulfate, a major component of the aggrecan, and glucosamine sulfate, a normal constituent of glycosaminoglycans in cartilage matrix and synovial fluid,[1] were tested in several short-, medium-, and, for glucosamine, long-term clinical trials in osteoarthritis.[9-46] Their symptomatic efficacy was recently analyzed through high-quality quantitative systematic reviews.[47-49] Since these publications, new data, obtained from long-term prospective, well-designed studies using glucosamine, have also assessed the structural activity of these compounds.[14,17,24,26] We performed the present meta-analyses to reevaluate, from the perspective of these new results, the evidence of structural efficacy (ie, a disease-modifying property) of glucosamine and of the symptomatic effects of the 2 compounds in knee and hip osteoarthritis. We based our analyses on the outcomes that are currently considered by regulatory agencies as required for the demonstration of efficacy for a drug to be used in the treatment of osteoarthritis: radiological evolution assessed by JSN; evaluation of pain by visual analog scale (VAS pain); joint mobility; Lequesne Index (LI)[50,51] and Western Ontario MacMaster University Osteoarthritis Index (WOMAC)[52] (2 Algo-functional, eg, assessing both pain and physical functioning, validated, disease-specific, self-administrated tools that assess the perceived symptomatic burden of osteoarthritis); tolerance defined as the comparison of the number of adverse effects in treated and placebo groups; and responding-to-treatment status assessed by physicians.

METHODS

RESEARCH QUESTION

Our global goals were to obtain an up-to-date, evidence-based document that provided a detailed view of the structural and symptomatic activity of this much debated class of agents for knee osteoarthritis. Thus, our primary objective was the analysis of the potential efficacy of the oral administration of glucosamine and chondroitin on knee JSN. Our secondary end point was the assessment of the symptomatic efficacy of these 2 compounds by subgroup analyses of the currently recommended outcomes for symptomatic efficacy based on pain and function.

TRIAL SEARCH

We searched for any randomized, placebo-controlled clinical trial on the efficacy of oral glucosamine or chondroitin for knee or hip osteoarthritis published or performed between January 1980 and March 2002. We had no limitations on language or age group. An exhaustive search of all relevant publications was performed, following a predefined protocol. We used a maximum of data sources to retrieve as many relevant publications as possible, including MEDLINE and PREMEDLINE, BIOSIS Previews, HealthSTAR, EMBASE, Cochrane Library of Randomized Controlled Trials, Current Contents, EBM Reviews, and Internet searches. The search strategy on electronic databases was based on the sensitive search strategy for randomized controlled trials recommended by the Cochrane Collaboration Musculoskeletal Group,[53] and the results were added to those provided by another validated method.[54] Generic keywords, according to the thesaurus of each individual database, were used. Since not all data are indexed on the electronic databases, we conducted a manual search of the reference section of each of the articles retrieved by the primary search. We also examined congressional abstracts of the American College of Rheumatology, British Society for Rheumatology, and Osteoarthritis Research Society International and directly contacted pharmaceutical companies and leading authors active in this particular field.

The 36 relevant publications found were reviewed by 2 independent authors (F.R. and O.B.) for methodologic standards and inclusion criteria compatibility. When divergence appeared, a third author (Y.H.) was consulted to reach consensus. To prevent desirability bias, authors' names and sources were blinded at this stage and for the quality scoring process.

SELECTION

All of the following criteria had to be fulfilled for study inclusion: (1) randomized, double-blind, placebo-controlled, parallel-group, prospective trial performed between January 1980 and March 2002, published or not; (2) assessment of the structural and/or symptomatic efficacy of oral glucosamine or chondroitin on knee or hip osteoarthritis; (3) treatment period of at least 4 weeks; (4) results expressed by one of the following outcomes: JSN; LI; WOMAC; VAS pain; VAS for mobility assessment (VAS mobility); and responders to treatment and safety; and (5) sufficient precision in design, methods, and results (authors of abstracts were invited to provide detailed information for inclusion in the meta-analysis).

QUALITY ASSESSMENT

The complete reports of these randomized controlled trials that were potentially appropriate for inclusion in the meta-analyses were blindly scored by 2 reviewers (O.E. and M.C.) for quality using a validated instrument.[55] The score was given as follows: if the study was described as randomized, 1 point; if the study was described as double masked, 1 point; and if there was a description of withdrawals and dropouts, 1 point. When random allocation and double-blinding were properly described and appropriately put into practice, each item received 1 point; if the method of randomization was not appropriate or if the method of masking was not appropriate, 1 point was deducted. Differences were resolved by consensus.

DATA ABSTRACTION

Predefined outcomes were extracted blindly by 2 authors (F.R. and O.B.) according to a standardized form. In case of disagreement, a third reviewer (Y.H.) helped reach a consensus after separately reviewing the report. Demographic baselines, study duration, dosage, dropout rates, and report of intention-to-treat analysis were first extracted. The core data in each study consisted of the sample size in both the placebo and treated groups, the number of events in each group, the values of relevant continuous outcomes and their SDs at the beginning and end of the study, and the SD of the mean difference between groups at the study end. When not available, we extracted the absolute value and the corresponding *P* value of the statistical test used to estimate the standardized mean difference. *P* values mentioned as less than .05 were encoded as .049 and so on. This favored trustworthiness of the results and reduced type I error. Responders to treatment were defined on the basis of dichotomization by the investigators or on the basis of their global assessment. Very good and good results were consequently classified as responders.

QUANTITATIVE DATA SYNTHESIS

The continuous and dichotomous data of the remaining publications were then used for meta-analyses. Dichotomous out-

Table 1. Progress Through the Stages of Meta-analysis for RCTs

Stage	No. of Studies	References
Raw hits from all sources	>500	
RCTs reviewed for inclusion criteria	36	
Insufficient data	–3	11, 30-32
Active comparator	–7	9, 10, 23, 33-36
Other compounds	–3	37-39
Neither knee osteoarthritis nor hip osteoarthritis	–2	40, 41
Administration path is IA or IM	–5	22, 42-45
Open trial	–1	46
RCTs matching inclusion criteria	15	
Usable outcomes		
Joint space narrowing	2 (Glucosamine sulfate)	24, 26
Lequesne index	10 (3 Glucosamine sulfate and 7 chondroitin sulfate)	12-16, 18, 19, 21, 26, 27
WOMAC	2 (Glucosamine sulfate)	24, 26
VAS pain	12 (4 Glucosamine sulfate and 8 chondroitin sulfate)	12-19, 25, 27-29
VAS mobility	3 (2 Glucosamine sulfate and 1 chondroitin sulfate)	17, 25
Responder's rate	9 (4 Glucosamine sulfate and 5 chondroitin sulfate)	12, 13, 16, 18, 19, 21, 24, 25, 29
Adverse events	11 (7 Glucosamine sulfate and 5 chondroitin sulfate)	12, 15-19, 21, 24-29

Abbreviations: IA, intra-arterial; IM, intramuscular; RCT, randomized controlled trial; VAS, visual analog scale; WOMAC, Western Ontario MacMaster University Osteoarthritis Index.

comes were combined using methods based on multiplicative and additive models. The result kept was the one for which the homogeneity among individual trials was the highest. Meta-analysis on continuous outcomes (eg, VAS pain, VAS mobility) was performed using a combination model able to take into account the outcome variability of both placebo and treated groups' mean differences before and after treatment (standardized mean difference, effect size), for example, the difference between the treated and placebo outcomes variations standardized by the SD of this difference.[56] This is considered a more conservative model than Glass scores. We calculated 95% confidence intervals (CIs) for the calculated individual and global effect sizes. The association between treatment and improvement in an outcome was assessed by a 2-tailed, unpaired *t* test of null at $\alpha = .05$. We investigated whether the differences among individual trials' effect sizes could be higher than expected, by a matter of chance only, using the Cochran Q test for heterogeneity.[57,58] The α risk for this analysis was set at .10. When heterogeneity was significant and remained so after removing the trial, which seemed to induce heterogeneity, a specific combination model (random-effects model) was applied. Publication bias was investigated in 2 ways: graphically by drawing a funnel plot graph and statistically by regressing linearly the standard normal deviates of the estimators against their precisions. In absence of publication bias, the intercept on the y-axis would be different than 0 at $\alpha = .10$.[59,60] Guidelines from the QUOROM (Quality of Reports of Meta-analyses of Randomized Controlled Trials) statement were used for improving the quality of reports of our meta-analysis.[61] All analyses were performed by a skilled analyst (F.R.), using registered copies of Comprehensive Meta-Analysis statistical software (version 1.0.25; Biostat, Englewood, NJ) and Statistica 5.5 statistical software (Statsoft, Maisons-Alfort, France).

RESULTS

TRIAL FLOW AND STUDY CHARACTERISTICS

More than 500 studies were identified by the search strategy. After removing studies with false-positive results, a restricted set of articles was reviewed for inclusion. Of these 36 primary hits, we eventually kept 15 studies[12-19,21,24-29] (**Tables 1**, **2**, and **3**) that fulfilled the inclusion criteria. Four studies provided information on JSN assessment. Two articles[14,17] contained information that was too restricted for inclusion; therefore, these articles were dropped from this analysis and conclusions for this outcome are applicable to glucosamine alone. Indeed, these 2 articles were abstracts or preliminary results and therefore did not report sufficiently detailed data for proper analysis. Ten trials reported data on the LI, 2 on WOMAC, 12 on pain assessed by VAS, 3 on joint mobility, 9 on responders rates, and 11 on adverse events (Table 2 and Table 3).

BASIC ANALYSIS

The data of 1775 patients (1020 glucosamine patients and 755 chondroitin patients) were analyzed in the 15 studies. Quality scores ranged from 60% to 100%, with a mean (SD) of 78.4% (17.2%). The mean quality of glucosamine trials (90%) was significantly higher than in chondroitin trials (68.4%) (Mann-Whitney *U* test, adjusted $z = 2.27$, $P = .02$). Individual demographic baselines were well matched in each study. Furthermore, no statistical difference was observed for age, sex, body mass index (calculated as weight in kilograms divided by the square of height in meters), and radiologic score at inclusion among the trials. The patients enrolled in glucosamine or chondroitin studies were not statistically different regarding mean age (62.1 years), radiologic score (1.96), and body mass index (27.6). The homogeneity of the sample can be attributable to the restrictive inclusion criteria used. Each study showed a well-balanced number of patients receiving active drug or matched placebo. After adjustment for study duration and sample size and regarding dropout rates, no statistical difference was observed, except in the study by Pujalte et al.[25] Because this study was the smallest in terms of sample size and individual estimator weight, we decided to use its information, since it could not generate a bias in the global effect size.

We first double-checked that the 2 compounds had the same efficacy for all outcomes, except the analysis

Table 2. Data From the 7 Trials of Glucosamine Sulfate for Osteoarthritis*

Source	Inclusion Criteria	Sample Size (Randomization Dosage)	Treatment Period	Variables Analyzed	Dropout Rate, %	ITT Analysis	Quality Score (of 5)
Noack et al,[21] 1994	Gonarthrosis, Weseloh (I→III), symptoms >180 j	252 (1500 mg/d)	4 wk	LI, responders, adverse events	4.3	Yes	4
Pujalte et al,[25] 1980	Osteoarthritis	24 (750 mg/d)	6-8 wk	VAS pain, responders, adverse events	16	No	4
Reginster et al,[24] 2001	Age >50 y, gonarthrosis (ACR)	212 (1500 mg/d)	3 y	JSN, WOMAC, adverse events	34	Yes	5
Pavelka et al,[26] 2002	Age >50 y, gonarthrosis (ACR)	202 (1500 mg/d)	3 y	JSN, WOMAC, LI, adverse events	42.5	Yes	5
Rovati,[27] 1997	Gonarthrosis (ACR)	319 (1500 mg/d)	3 mo	LI, VAS pain, adverse events	16.3	Yes	4
Rindone et al,[28] 2000	Gonarthrosis (ACR), Kellgren >I	114 (1500 mg/d)	2 mo	VAS pain, adverse events	14	No	5
Hughes and Carr,[29] 2002	Age >40 y, gonarthrosis, pain on most days for the previous 3 mo	80 (1500 mg/d)	6 mo	VAS pain, mobility, responders (OARSI), adverse events	6.2	Yes	5

Abbreviations: ACR, American College of Rheumatology; ITT, intention to treat; JSN, joint space narrowing; Kellgren, Kellgren and Lawrence radiological scale for osteoarthritis severity assessment; LI, Lequesne Index; OARSI, OsteoArthritis Research Society International; VAS, visual analog scale; WOMAC, Western Ontario MacMaster University Osteoarthritis Index.
*The design for all trials was double-blind, randomized, and parallel, except for Noack et al, which was also a multicenter trial.

Table 3. Data From the 8 Trials of Chondroitin Sulfate for Osteoarthritis*

Source	Inclusion Criteria	Sample Size (Dosage)	Duration	Variables Analyzed	Dropout Rate, %	ITT	Quality Score (of 5)
Bourgeois et al,[12] 1998	Gonarthrosis (ACR), Kellgren I-III, NSAID	127 (1200 or 3 × 400 mg/d)	90 d	LI, VAS pain, NSAID, responders, adverse events	10.4	Yes	3
Bucsi and Poor,[13] 1998	Gonarthrosis, Kellgren I-III	85 (2 × 400 mg/d)	180 d	LI, VAS pain, NSAID, responders, adverse events	12.2	Yes	3
Conrozier,[14] 1998	Gonarthrosis, Kellgren I-III	104 (800 mg/d)	1 y	LI, VAS pain, JSN	Missing data	Yes	Nonscored due to insufficient details in publication
Mazieres et al,[15] 1992	Gonarthrosis, coxarthrosis, Kellgren I-III, VAS pain >40 mm	114 (2000 mg/d)	90 d	NSAID, VAS pain, LI, adverse events	2.6	No	4
Mazieres et al,[16] 2001	Gonarthrosis (ACR), 4<LI<11, VAS pain >30 mm, NSAID, Kellgren II, III	114 (1000 mg/d)	90 d	LI, VAS pain, responders	10.6	Yes	3
Uebelhart et al,[17] 1998	Gonarthrosis, symptoms, 25% of the joint space remaining	46 (2 × 400 mg/d)	1 y	VAS pain, VAS mobility, JSN	8.6	No	3
L'Hirondel,[18] 1992	Gonarthrosis, joint space present	125 (3 × 400 mg/d)	180 d	VAS pain, LI, NSAID, responders, adverse events	3.1	No	3
Pavelka et al,[19] 1999	Gonarthrosis (ACR), LI >8 points, joint space present, age >30 y	140 (1200 or 800 or 200 mg/d)	90 d	LI, VAS pain, responders, adverse events	2.1	Yes	5

Abbreviations: ACR, American College of Rheumatology; ITT, intention to treat; JSN, joint space narrowing; Kellgren, Kellgren and Lawrence radiological scale for osteoarthritis severity assessment; LI, Lequesne Index; NSAID, nonsteroidal anti-inflammatory drug; VAS, visual analog scale.
*The design for all trials was multicenter, double-blind, randomized, and parallel, except for Uebelhart et al, which was not a multicenter trial.

of the structural effects of chondroitin on osteoarthritis, for which the available data were too restricted and thus prone to small study effect. We consequently provide the results of the 2 relevant studies[14,17] for this outcome for information. The obtained global estimators were not statistically different regarding glucosamine or chondroitin for all common outcomes.

QUANTITATIVE DATA SYNTHESIS

Our data provide highly significant ($P<.001$) evidence of a structural efficacy of glucosamine on minimum JSN (**Figure 1**). The global effect size found was 0.41 (95% CI, 0.21-0.60), with the results of the 2 large studies being consistent (P for heterogeneity=.95). According to the

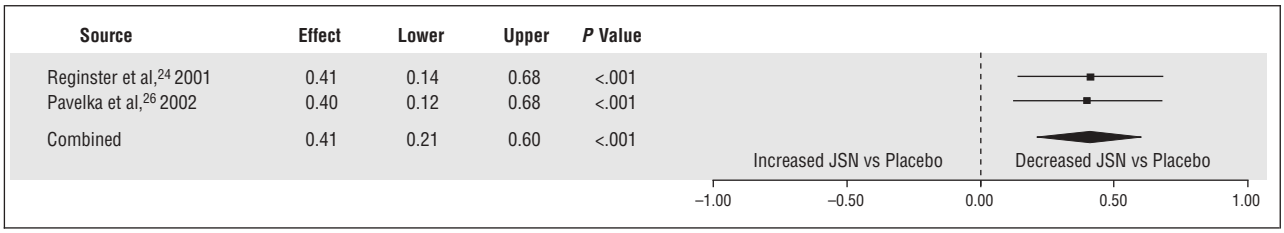

Figure 1. Effect sizes of joint space narrowing (JSN).

effect sizes scale by Cohen,[62] this activity can be rated as low to medium. Understanding that an effect size is a rather subjective unit, we converted it into natural units. The potential minimal JSN difference (SD) between placebo and active allocated drug groups would be 0.27 mm (95% CI, 0.13-0.41 mm) after 3 years of daily administration of 1500 mg of glucosamine sulfate. The 2 chondroitin studies tended to be able to produce comparable results, but high-quality, detailed articles were missing and this analysis was withdrawn.

Concerning the effects on symptoms, significant changes compared with baseline were observed in the chondroitin- and glucosamine-treated patients, whereas no placebo group showed significant improvement (**Figure 2**). The minimal time reported for the onset of a significant action was 2 weeks for either glucosamine[27] or chondroitin.[12] The combination of the available data for the LI (Figure 2) did not reveal any difference between the glucosamine and chondroitin trials (*P* for heterogeneity = .68), the global effect size being 0.43 (95% CI, 0.32-0.54; *P* for association <.001). In all studies included, 2 trials[24,26] on glucosamine sulfate at the same dose (1500 mg/d) and at the same duration (3 years) used the WOMAC as their primary outcome, including the 3 WOMAC subscales (articular pain, stiffness, and function). The common effect size was 0.30 (95% CI, 0.11-0.49; *P* for association = .002 and *P* for heterogeneity = .83). Of 15 studies, 12 provided information about pain reduction assessed by a VAS. The global effect size (random effects) was 0.49 (95% CI, 0.31-0.67; *P* for association < .001). The intrinsic analgesic activity of glucosamine and chondroitin could not be evaluated on a quantitative basis, since investigators allowed patients to use rescue medications (eg, acetaminophen or NSAIDs). Three trials[17,25,29] provided results of joint mobility evaluation. The global effect size was 0.59 (95% CI, 0.25-0.92; *P* for association = .001; *P* for heterogeneity = .73). The relative risk of being a responder (**Figure 3**) when allocated to glucosamine or chondroitin or placebo was 1.60 (95% CI, 1.38-1.82). This particular meta-analysis was also performed using an additive combination model. The associated absolute risk difference was 20% (95% CI, 15%-26%), and the number needed to treat was 4.9. The overall safety of the 2 treatments (**Figure 4**) has been investigated by comparing the number of adverse events in glucosamine or chondroitin and placebo groups in all studies. The global relative risk (random effects) for presenting an adverse reaction when being allocated to the glucosamine or chondroitin group compared with the placebo group was 0.80 (95% CI, 0.59-1.08; *P* for association = .15), which confirms that the safety profile of glucosamine and chondroitin can be considered excellent. Furthermore, in the 4 major studies that provided details on serious adverse events,[19,24,26,27] the observed rates were low and statistically identical between treated groups and placebo groups.

COMMENT

Several clinical trials assessed the effects of chondroitin and glucosamine on the symptoms of osteoarthritis.[46,47] Furthermore, recent studies[24,26] have also suggested that glucosamine efficiently prevents the long-term progression of osteoarthritis. To assess clearly and with detail the symptomatic and structural effects of these molecules, we planned individual meta-analyses on the outcomes currently requested by both the Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products for the registration of drugs to be used in the treatment of osteoarthritis. The inclusion criteria led to the selection of 15 randomized controlled trials, representative of the pragmatic effects of chondroitin or glucosamine (ie, their efficacy on osteoarthritis in a self-administrated, long-term treatment). From this perspective, we excluded studies in which the chondroitin or glucosamine administration route was intra-articular or intravenous. This led to the selection of a homogeneous sample of trials that considered baseline demographics and outcomes. The mean body mass index in chondroitin and glucosamine patients was 27.6, which exceeds the World Health Organization recommendations (20<BMI<25). This is compatible with the fact that overweight is a major risk factor for osteoarthritis.[1,2]

We only worked on complete data sets of published and unpublished studies. Abstracts often request the extrapolation of graphs or have values missing and so are more likely to produce biased estimators. They were therefore rejected even when fulfilling inclusion criteria. Notwithstanding, we experienced difficulties with only one article.[14] Since the sample sizes for the assessment of the JSN were not clearly mentioned, we finally decided not to include this outcome in our analysis.

It seemed to be counterintuitive to have patients with a long-term disorder deriving benefit from short-term interventions. However, no linear adjustment of effect size on dosage and study duration was performed, since the LI and VAS pain variations at different time points in the global evaluation suggested that a nonlinear model would be more appropriate. This is confirmed by the fact that each study produced that output.[12,13,15-19,21,27] Furthermore, some trials of the same duration but with different chondroitin dosages lead to conflicting results. For instance, a study[18] that used 1200 mg/d of chondroitin sulfate for 180 days provided a lower effect size than another one[13] with the same duration but a lower dosage (800 mg/d). This is likely to

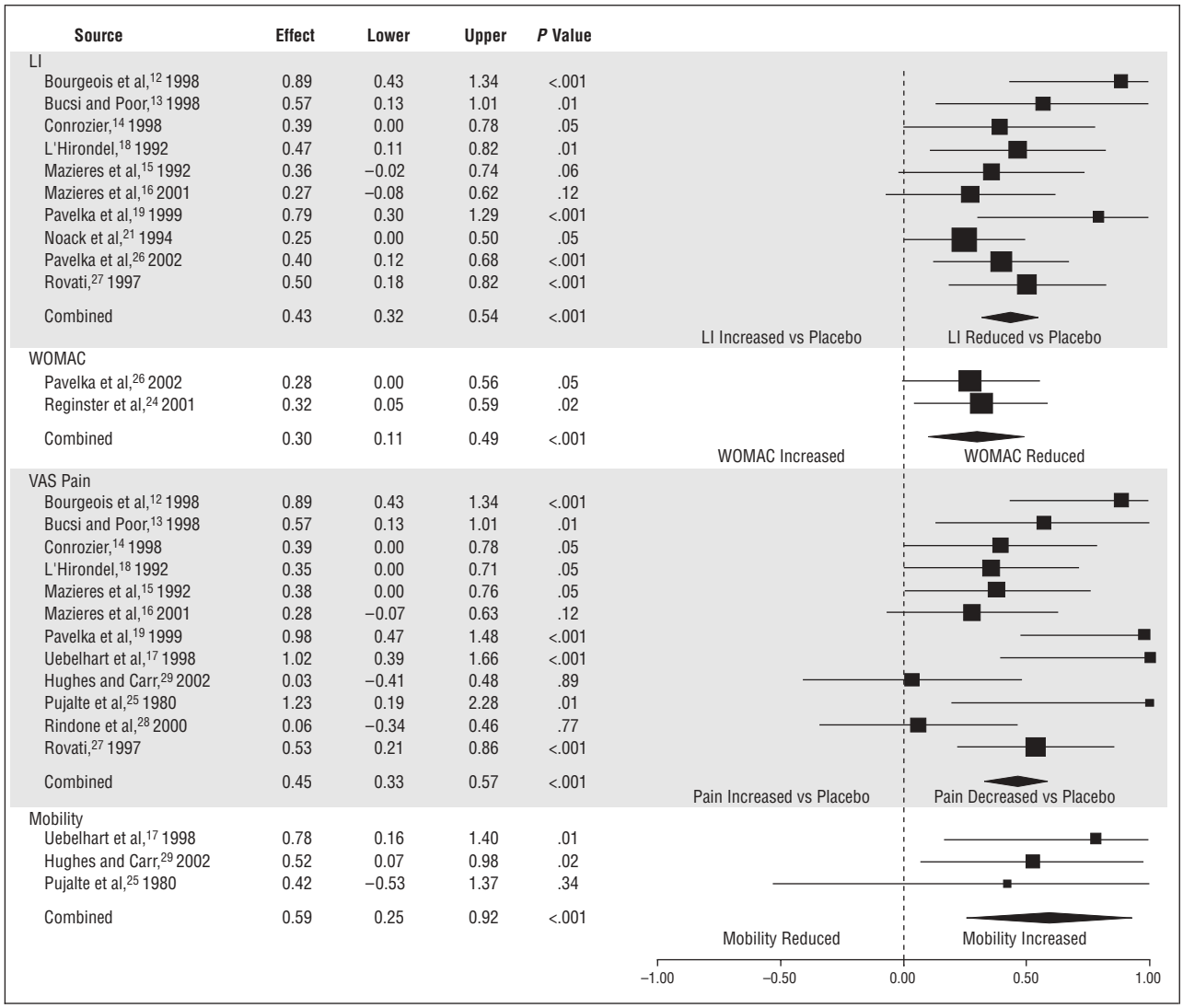

Figure 2. Effect sizes of symptomatic outcomes. LI indicates Lequesne Index; WOMAC, Western Ontario MacMaster University Osteoarthritis Index; and VAS, visual analog scale.

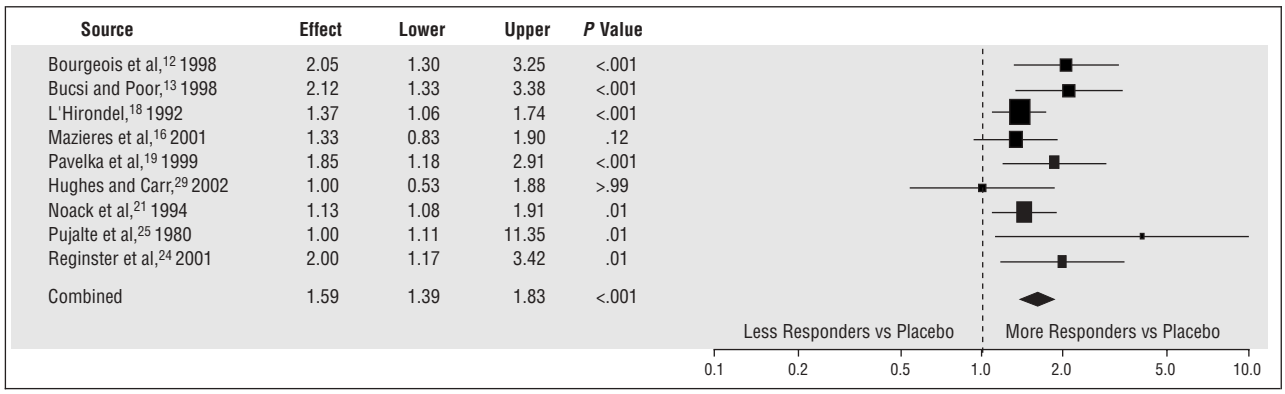

Figure 3. Relative risks of being a responder.

be attributable to a relative small study effect. Nevertheless, the correlation between sample sizes and effect sizes is not statistically different to 0 for both compounds and all analyzed variables except the WOMAC score, even if a trend exists ($r=0.44$, $P=.11$). A meta-analysis on individual outcomes would allow for a multivariate meta-regression (using, for example, a Cox model) of efficacy on time, controlling for dose, compound, and patient characteristics. Unfortunately, such an enterprise requires original databases, which were impossible to obtain.

One of the main criticisms expressed against reviews is the existence of a publication bias generated by the pref-

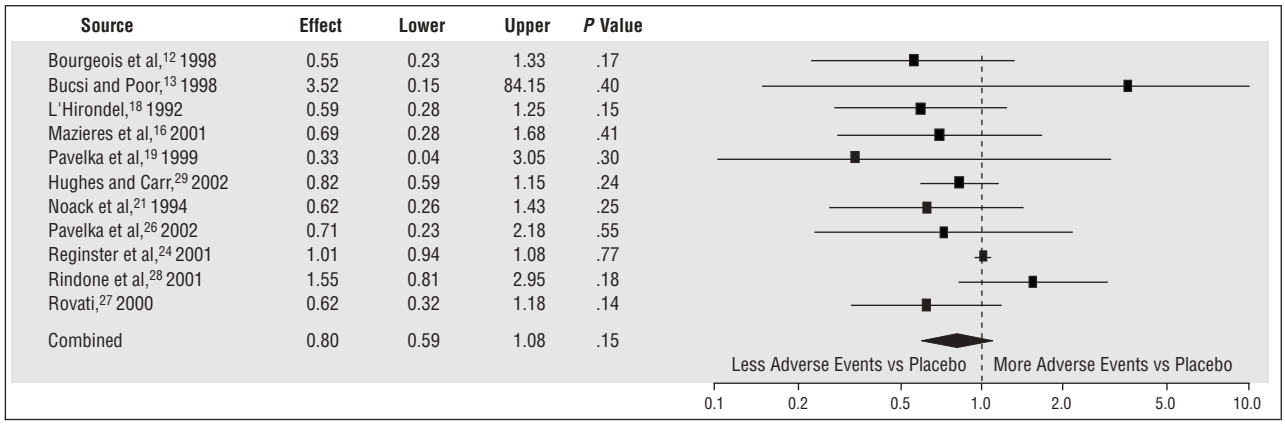

Figure 4. Relative risks of experiencing adverse events.

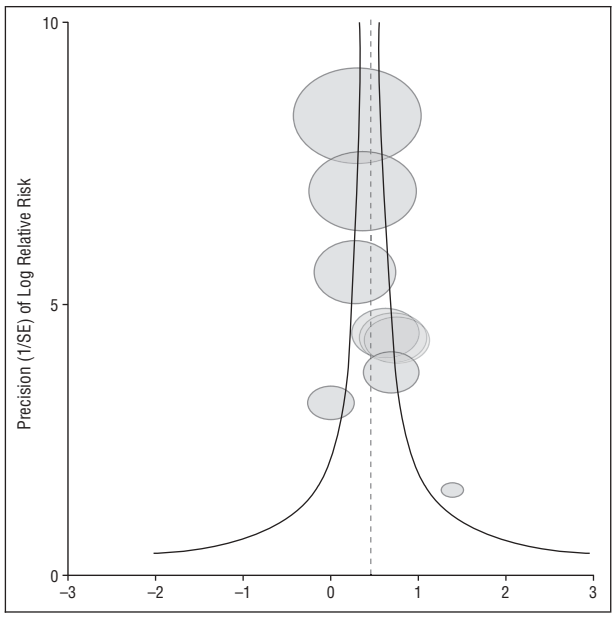

Figure 5. Funnel plot graph for responders.

erential diffusion of trials that report results in favor of the investigated drug. The global estimator of a meta-analysis is likely to be overestimated in this case. We drew a funnel plot graph (**Figure 5**) that reports the sample size of a randomized controlled trial according to its effect size. In the absence of a publication bias, the obtained distribution displays a symmetrical inverted funnel. The method applied to our results showed a light asymmetry on the right side of the graph (ie, there seems to be more small sample studies associated with high effect sizes than small sample studies showing small effects). The Fisher symmetry coefficient was 0.6, confirming this preliminary visual inspection. The null hypothesis requires that trials considered individually provide randomly distributed estimators around the real efficacy of the molecules; thus, the asymmetry was statistically significant at $P = .08$. We wish to point out that publication bias is not the only source of funnel plot asymmetry[59] and that this test has limited power unless substantial bias is present.[60] True heterogeneity in response to treatment, inadequate analyses, chance, different methodologic qualities, and lack of data can also make a funnel plot drawing asymmetrical.[58]

To evaluate the potential effect of a publication bias, we performed robustness analyses on our results. We first simulated the variance of a nonsignificant study requested to induce a nonsignificant global estimator. For instance, considering VAS pain, the variance of the study by Rindone et al,[28] which is inversely related to its relative weight in the meta-analysis, should be 100 times lower than the observed one, which is unrealistic. We also simulated the hypothetical unpublished negative trials requested to obtain nonsignificant global estimators. Three unpublished negative studies opposite to the one by Rovati[27] or 12 studies mirroring the study by Rindone et al[28] would be necessary to reach this goal. Furthermore, all unselected studies provided significant efficacy for both glucosamine and chondroitin. Even if a publication bias is statistically present, considering the conservative approach, the robustness of our results, and the data from unselected studies, it can be concluded that our global estimators show substantial beneficial effects on symptoms of glucosamine and chondroitin therapy compared with placebo.

The structural efficacy of glucosamine is highly significant and ranges from low to medium. Large studies that provide sufficient data are currently lacking to assess the effects of chondroitin on JSN. Currently no detailed, long-term, prospective, placebo-controlled data are available for JSN with chondroitin; therefore, we had to restrict our analyses of the structural benefits of matrix precursors to glucosamine. A mean of the joint space differences weighted by the inverse of the variances of the effect sizes may express the global results in original units under the condition that variances are not strongly unequal. When applied to the evaluation of the structural efficacy of glucosamine, the estimated mean difference in JSN between glucosamine and placebo groups in our study was at least 0.27 mm (95% CI, 0.13-0.41 mm) throughout 3 years. In both studies[24,26] that evaluated the structural properties of glucosamine, radiographic films were taken with a weightbearing anteroposterior incidence, with the knees fully extended. It was recently reported that in patients with highly symptomatic osteoarthritis, changes in patient positioning due to symptom changes during the study (eg, better knee extension and consequently lower apparent JSN due to symptom improvement) could affect the evaluation of structural outcomes of the study. However, in both glucosamine studies,[24,26] it is rather unlikely that the symp-

tom changes observed in the 2 groups might have affected the results, given the mild-to-moderate disease and symptom conditions at baseline and throughout the study. Furthermore, the general correlation between symptoms and structure changes was poor, as suggested by another study.[63] Patients receiving glucosamine with severe JSN had an improvement in their symptoms, which did not prevent the radiographic structure impairment. In a recent study evaluating the effect of changes in knee pain of varying magnitudes on radiographic joint space width, when using the weight-bearing extended anteroposterior view of the knee, Mazzuca et al[64] concluded that not all levels of changes in knee pain altered the appearance of radiographic joint space width. In patients with nonflaring knees, changes in joint space width were unrelated to the radiographic severity of osteoarthritis or to the magnitude of concomitant changes in WOMAC pain scores.

Our results suggest that the long-term administration of daily oral glucosamine sulfate at the minimal dosage of 1500 mg during a minimal period of 3 year slows the degenerative process of the joint cartilage. Symptomatic activity had already been related in the reviews previously published by Leeb et al,[47] McAlindon et al,[48] and Towheed et al.[49] The corresponding effect sizes observed in our study were lower than theirs, mainly because of the restrictive inclusion criteria and the more conservative combination model. McAlindon et[48] al included heterogeneous studies, allowing for various routes of administration and for different outcomes units. The global estimators used in their meta-analysis were Glass scores. Leeb et al[47] restricted to per protocol analyses and used a modified Glass score, which does not take directly into account the variability of the response to active treatment. Towheed et al[49] focused on effectiveness and safety and included both placebo and comparative controls and single and double-blinded studies.

Our work provides a clear, evidence-based advance regarding the interest in the wide use of glucosamine and chondroitin as disease-modifying compounds in the treatment of knee osteoarthritis through an accurate, conservative analysis of the most reliable experiments performed until now. Regarding the analgesic effects of glucosamine and chondroitin, it is important to note that in all trials, rescue medications (eg, NSAIDs) were allowed. However, the combination of glucosamine or chondroitin and NSAIDs at lower cumulative doses than alone shows better efficacy on pain reduction than placebo and NSAIDs. However, given the cumulative low dose of the rescue medications in most of the trials and the favorable results on all other symptom outcome measures, it might be unlikely that rescue medication use affected the osteoarthritis pain-relieving effect of glucosamine and chondroitin.

The estimated minimal LI and VAS pain differences between the chondroitin or glucosamine group and the placebo group are 2.08 points (95% CI, 1.51-2.65 points) and 1.26 cm (95% CI, 0.94-1.58 cm), respectively, after 90 days of treatment. Responders to treatment were defined on the basis of dichotomization by the authors of the different studies or on the basis of their global assessment. The global relative risk for being a responder to treatment, depending on the allocation to glucosamine or chondroitin or placebo, is 1.6 (95% CI, 1.38-1.82; P for association $<.001$). Such a relative outcome deserves a comparison with an additive measurement. The absolute risk difference of being classified as a responder according to allocated glucosamine or chondroitin or placebo is 20%, and the associated number needed to treat is 4.87. In accordance with our results, it can be definitively stated that the oral administration of glucosamine or chondroitin decreases the symptoms of osteoarthritis. The tolerance of the 2 compounds is excellent, with no study showing a higher adverse events rate in the treated group compared with the placebo group.

CONCLUSIONS

The goals of this study were to clearly assess the potential activity of glucosamine and chondroitin on structure and symptoms in knee osteoarthritis. We performed 7 individual outcome-oriented meta-analyses of randomized clinical trials selected on the basis of their high methodologic quality. Our data demonstrates efficacy for glucosamine on JSN and WOMAC and comparable efficacies of chondroitin and glucosamine on LI, VAS pain, and VAS mobility in light of the most reliable scientific evidence. Both compounds are well tolerated. Nevertheless, further long-term studies are needed to confirm and evaluate the structural efficacy of chondroitin. Now that a structure-modifying effect has been demonstrated for glucosamine, further studies on the relationship between structural and symptomatic changes controlling for baseline characteristics, including osteoarthritis stage, and on the possible use in prevention are required to determine the role of this compound as a disease-modifying agent in osteoarthritis.

Accepted for publication September 19, 2002.

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