

Glucosamine and Chondroitin for Treatment of Osteoarthritis

A Systematic Quality Assessment and Meta-analysis

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OSTEoarthritis (OA) IS A major public health problem for which there are few effective medical remedies.¹ Nonsteroidal anti-inflammatory agents are the most commonly prescribed agents for this disorder but are a frequent cause of serious adverse effects.^{2,3} Glucosamine and chondroitin are compounds extracted from animal products that have been used in various forms for OA in Europe for more than a decade and have recently acquired substantial popularity because of several lay publications.⁴ Because of their safety, these remedies would have great utility in the treatment of OA even if they were only modestly effective. They are absorbed from the gastrointestinal tract^{5,6} and appear to be capable of increasing proteoglycan synthesis in articular cartilage.^{7,8} Furthermore, these agents have been tested in a number of clinical trials that are widely interpreted as demonstrating efficacy for osteoarthritis.⁹⁻²¹ The medical community in the United Kingdom and the United States, on the other hand, appears to have paid little attention to the potential benefits of these compounds.²² This skepticism appears to be

Context Glucosamine and chondroitin preparations are widely touted in the lay press as remedies for osteoarthritis (OA), but uncertainty about their efficacy exists among the medical community.

Objective To evaluate benefit of glucosamine and chondroitin preparations for OA symptoms using meta-analysis combined with systematic quality assessment of clinical trials of these preparations in knee and/or hip OA.

Data Sources We searched for human clinical trials in MEDLINE (1966 to June 1999) and the Cochrane Controlled Trials Register using the terms *osteoarthritis*, *osteoarthrosis*, *degenerative arthritis*, *glucosamine*, *chondroitin*, and *glycosaminoglycans*. We also manually searched review articles, manuscripts, and supplements from rheumatology and OA journals and sought unpublished data by contacting content experts, study authors, and manufacturers of glucosamine or chondroitin.

Study Selection Studies were included if they were published or unpublished double-blind, randomized, placebo-controlled trials of 4 or more weeks' duration that tested glucosamine or chondroitin for knee or hip OA and reported extractable data on the effect of treatment on symptoms. Fifteen of 37 studies were included in the analysis.

Data Extraction Reviewers performed data extraction and scored each trial using a quality assessment instrument. We computed an effect size from the intergroup difference in mean outcome values at trial end, divided by the SD of the outcome value in the placebo group (0.2, small effect; 0.5, moderate; 0.8, large), and applied a correction factor to reduce bias. We tested for trial heterogeneity and publication bias and stratified for trial quality and size. We pooled effect sizes using a random effects model.

Data Synthesis Quality scores ranged from 12.3% to 55.4% of the maximum, with a mean (SD) of 35.5% (12%). Only 1 study described adequate allocation concealment and 2 reported an intent-to-treat analysis. Most were supported or performed by a manufacturer. Funnel plots showed significant asymmetry ($P \leq .01$) compatible with publication bias. Tests for heterogeneity were nonsignificant after removing 1 outlier trial. The aggregated effect sizes were 0.44 (95% confidence interval [CI], 0.24-0.64) for glucosamine and 0.78 (95% CI, 0.60-0.95) for chondroitin, but they were diminished when only high-quality or large trials were considered. The effect sizes were relatively consistent for pain and functional outcomes.

Conclusions Trials of glucosamine and chondroitin preparations for OA symptoms demonstrate moderate to large effects, but quality issues and likely publication bias suggest that these effects are exaggerated. Nevertheless, some degree of efficacy appears probable for these preparations.

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Table 1. Hierarchy of Outcome Measures Used in the Meta-analysis*

Global pain score for index joint (visual analog or Likert scale)
Pain on walking for index joint (visual analog or Likert scale)
Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index Pain Subscale (visual analog or Likert version)
Lequesne index†
Pain in index joint during activities other than walking (visual analog or Likert scale)

*To be eligible for our analysis, studies had to report results for at least 1 of these outcomes.

†The Lequesne index is a questionnaire-based disability score.³⁶

based largely on concerns about the quality of these trials, although this matter has not been evaluated formally.²³

Such concerns may be well founded. Considerable progress has been made recently in elucidating the specific aspects of methods used in these trials that affect the validity of their conclusions.^{24,25} These studies have shown that trials with methodological flaws, especially inadequate allocation concealment and absence of intent-to-treat approaches,²⁵ are associated with exaggerated estimates of benefit.^{26,27}

Therefore, we appraised the evidence provided by clinical trials of glucosamine and chondroitin preparations in OA by combining a systematic quality assessment with a meta-analysis.

METHODS

Identification of Clinical Trials

We searched for clinical trials of glucosamine or chondroitin compounds using electronic searches of MEDLINE (from 1966 to June 1999) and the Cochrane Controlled Trials Register.²⁸ *Osteoarthritis, osteoarthrosis, degenerative arthritis, glucosamine, chondroitin, and glycosaminoglycans* were entered as Medical Subject Heading terms and as textwords. The terms were then connected through Boolean operators and the result was limited to studies reporting only on human subjects and clinical trials. We had no limitations on whether clinical trial was controlled or randomized, on language, or age group. Manuscript or abstract publications were also sought by screening citation lists in review articles and published manu-

scripts. Abstracts presented at national and regional meetings of the American College of Rheumatology, the British Society for Rheumatology, and the Osteoarthritis Research Society were manually searched in supplement issues of *Arthritis and Rheumatism*, the *British Journal of Rheumatology*, and *Osteoarthritis and Cartilage* published between 1978 and 1998. Where abstract data were incomplete, we contacted the primary author to request further information. Finally, we attempted to identify unpublished data by contacting content experts, study authors, and manufacturers of glucosamine or chondroitin.

Inclusion Criteria

Because of evidence that these compounds may take several weeks to exert any therapeutic effect, we included only controlled trials that were at least 4 weeks in duration and trials that tested oral or parenteral glucosamine sulfate, glucosamine hydrochloride, or chondroitin sulfate against placebo among individuals with knee or hip OA. Only trials clearly stated to be double-blind and that had randomized treatment assignments were included in our meta-analysis. We also required that each trial include at least 1 of the outcome measures currently recommended for OA clinical trials (TABLE 1).²⁹

Trial Efficacy Measures

We adopted 2 approaches in defining the outcome of each trial. In the primary analysis, we tested the outcome that the authors stated to be the main measure used in their trial. For the secondary analyses, however, we compiled a list of 5 outcome measures recently recommended for OA clinical trials²⁹ and extracted the reported outcome that was highest on this list. We took this approach to examine the possibility of bias resulting from post hoc selection of "primary outcomes" among these trials.

Data Extraction

The data extraction was performed by 2 reviewers (M.P.L. and J.P.G.) using a standardized form. Where neces-

sary, means and measures of dispersion were approximated from figures in the manuscripts. For 4 trials^{9,30-32} that presented mean values without measures of variability, we imputed SDs by multiplying the means for the trial arm by the median coefficient of variability (a measure of variability that is not sensitive to trial duration) from other trial arms included in the meta-analysis that used the same outcome.

Quality Assessment Instrument

We evaluated each reported clinical trial by applying a quality assessment instrument that has been developed and tested in studies by Chalmers et al²⁵ and Rochon et al.³³ This instrument assigns a score for reported compliance with each of 14 aspects of clinical trial conduct (control appearance, allocation concealment, patient blinding, observer blinding to treatment, observer blinding to results, prior estimate of numbers, compliance testing, inclusion of pretreatment variables in analysis, presentation of statistical end points, statistical evaluation of type II error, presentation of confidence limits around between-group differences in statistical end points, quality of statistical analyses, withdrawals, side-effects discussion). The potential scores derived from this system range from 0 to 68 for negative and from 0 to 65 for positive studies and are expressed as a percentage of the maximum possible score for each trial.

The instrument has been shown to be consistent between reviewers, and has been used to evaluate large numbers of trials.³³ These have demonstrated mean (SD) quality scores of 38.5% (13.1%) for journal articles and 33.6% (12.8%) for those published in supplements.³³ In addition to quality scoring, we recorded separately whether an intent-to-treat approach had been undertaken in the study analysis.

Finally, we attempted to determine the presence of industrial sponsorship for each trial. When an article or an abstract included no disclosure for sponsorship, we contacted authors di-

rectly. We asked about source of funding, author affiliation, and level of sponsor involvement in the study.

Quality Scoring

Following a training session, 2 rheumatologists (T.E.M. and D.T.F.) independently reviewed the articles and performed the quality scoring. To optimize consistency, disagreements in quality scores were adjudicated by a process in which the 2 reviewers discussed all discordant items. Reviewers were subsequently allowed to adjust their score assignments, although strict concordance was not considered mandatory. The mean of the postadjudication scores of the 2 reviewers was used in the analyses. One of the articles, published in German,³¹ was scored for quality with the help of a biostatistician fluent in German.

Statistical Approach Efficacy Analyses. We performed separate meta-analyses for trials of glucosamine compounds and trials of chondroitin. Intent-to-treat results were used whenever possible.

We calculated an effect size for each trial from the difference in mean outcome value between the treatment and placebo arms at the end of the trial, divided by the SD of the outcome value in the control group at trial end. Our use of the SD of the control group at the end of the trial was based on our concern that treatment might artificially change variation in the treated group.³⁴ If trial end values were not presented in the report, change from baseline was used as a proxy measurement. To reduce bias, we multiplied all effect sizes by a correction factor that depended on the sample size as defined by Hedges and Olkin.³⁵ Effect sizes provide unitless measures of treatment efficacy that are centered at zero if the treatment effect is similar to placebo. A scale for effect sizes has been suggested by Cohen,³⁶ with 0.8 reflecting a large effect, 0.5 a moderate effect, and 0.2 a small effect. We pooled effect sizes in our analyses using a random effects model, since this tends to produce more conservative estimates than the fixed effects model.³⁷

Sensitivity Analyses. To assess the effect of choice of primary outcome on the results, we derived a pooled estimate based on the secondary outcome measure selected from our predefined hierarchy. When 1-month results were presented for a trial, we tested the treatment effect at this time point in a separate meta-analysis. Also, to investigate the influence of trial quality on the study outcome, we dichotomized each group about the median quality score and the median trial size and repeated the meta-analyses among these subsets. We repeated the analyses after excluding the 4 trials for which data imputations had been made. Finally, to investigate possible biases associated with combining heterogeneous outcome measures, we performed subset analyses in which the models were confined to only trials with pain outcomes or with algofunctional outcomes (ie, Lequesne index, a questionnaire-based disability score).³⁸

Evaluation for Bias. We tested for the possibility of bias among our sample of clinical trials using 2 approaches. In the first, we generated funnel plots, which graph the effect size for a trial on the horizontal axis and the number of subjects in that trial on the vertical axis. Asymmetry in the funnel plot suggests bias. In a second analysis, we regressed effect size on the inverse of the study variance, using a method described by Egger et al,³⁹ which considers bias to be present if the intercept for the regression is different from null at $P < .138$.

RESULTS

Trials

We identified 17 placebo-controlled clinical trials that fulfilled our inclusion criteria.* We excluded 2 studies that did not report sufficient numerical results to permit data extraction.^{44,46} Therefore, our meta-analysis is based on 15 trials. The characteristics of the included studies are presented in TABLE 2. Four glucosamine^{18,30,42,43} and 4 chondroitin trials^{10,15,31,45} also reported outcome observations at the 4-week time

point. Three trials reported mean values for outcome variables but did not list the variability associated with the means.^{9,30,31} For 4 trials^{9,30,32} variability was imputed from other studies in the meta-analysis.

Meta-analysis

We found moderate treatment effect sizes for glucosamine (0.44; 95% confidence interval [CI], 0.24-0.64) and large effects for chondroitin (0.96; 95% CI, 0.63-1.3); FIGURE 1). The test for heterogeneity was significant ($P < .001$) among the chondroitin trial sample, however. One chondroitin trial⁴⁷ had a substantially larger effect (effect size, 4.6) than any other trial. When this trial was removed from the chondroitin analysis, the test for heterogeneity became nonsignificant ($P = .5$) and the effect diminished to 0.78 (95% CI, 0.60-0.95). These results were not substantially altered when we repeated the analyses using the outcome measures imposed from our predefined hierarchy (glucosamine, 0.49 [95% CI, 0.24-.074]; chondroitin, 0.88 [95% CI, 0.67-1.1]). Smaller effect sizes were observed for the 1-month outcome among the 9 trials that reported observations at this time point (glucosamine, 0.26 [95% CI, 0.10-0.42]; chondroitin, 0.40 [95% CI, 0.17-0.62]). Effects sizes were similar without correction for bias (glucosamine, 0.46; chondroitin, 1.0), and after excluding the 4 studies for which imputations had been made (glucosamine, 0.35; chondroitin, 0.87). Similar results were also observed on confining the models to trials with pain outcomes (3 glucosamine trials: effect size, 0.51 [95% CI, 0.05-0.96]; 8 chondroitin trials: effect size, 0.86 [95% CI, 0.64-1.09]) and trials reporting Lequesne index (3 glucosamine trials: effect size, 0.41 [95% CI 0.14-0.69]; 2 chondroitin trials: effect size, 0.63 [95% CI, 0.32-0.94]).

Quality Scores

The level of agreement between the 2 reviewers was good with intraclass correlation coefficients of 0.75 prior to and 0.92 after adjudication ($P < .01$). Quality scores ranged from 12.3% to 55.4%

*References 9, 10, 15, 16, 18, 20, 30, 31, 32, 41-47, 49.

with a mean (SD) of 35.5% (12%). Only 1 provided sufficient information to determine that allocation concealment had been adequate.⁴³ Furthermore, only 2 articles reported an intent-to-treat analysis,^{32,43} and only 1 of these gave

sufficient statistical information for this to be incorporated in our meta-analysis. Indeed, 7 studies did not present dropout rates, and the remainder reported a mean (SD) rate of 1.2% (4.2%) per month.

Sponsorship

None of the studies reported independent funding from any governmental or non-for-profit organization. Six articles presented sufficient information to ascertain manufacturer support. Con-

Table 2. Characteristics of Eligible Clinical Trials of Glucosamine and Chondroitin Preparations*

Source, y	No. of Subjects	Type of Study	Mode of Administration	Joint Studied	Outcome Ex-tracted*	Study Support	Quality Score, %	Allocation Concealment	Intent to Treat	Effect Size†
Glucosamine Trials										
Reichelt et al, ¹⁸ 1994	155	Article	Oral	Knee	Lequesne	Author affiliation with manufacturer	44.6	Inadequate	No	0.37
Rovati, ³⁰ 1997	329	Abstract	Oral	Knee	Lequesne	Author affiliation with manufacturer	12.3	Inadequate	No	0.69
Vajjaradul, ⁴² 1981	54	Article	Intra-arterial	Knee	Pain	Independent	37.7	Inadequate	No	0.54
Pujalte et al, ¹⁶ 1980	20	Article	Oral	Knee	Pain	Author affiliation with manufacturer	38.5	Intermediate	No	1.28
Houpt et al, ⁴¹ 1998	101	Abstract	Oral	Knee	WOMAC	Drug provided by manufacturer	40	Inadequate	No	0.34
Noack et al, ⁴³ 1994	252	Article	Oral	Knee	Lequesne	Author affiliation with manufacturer	51.9	Adequate	Yes‡	0.23
Chondroitin Trials										
Bourgeois et al, ⁹ 1998	127	Supplement	Oral	Knee	Lequesne	Financially supported by manufacturer	13.8	Inadequate	No	0.64
Bucsi and Poor, ¹⁰ 1998	80	Supplement	Oral	Knee	Pain	Financially supported by manufacturer Manufacturer conducted data collection, randomization, or statistical analysis	36.9	Inadequate	No	0.87
Uebelhart et al, ²⁰ 1998	46	Supplement	Oral	Knee	Pain	Financially supported by manufacturer Manufacturer conducted data collection, randomization, or statistical analysis	36.9	Inadequate	No	1.04
Pavelka et al, ⁴⁹ 1998	140	Supplement	Oral	Knee	Pain	Financially supported by manufacturer	28.5	Inadequate	No	1.16
L'Hirondel, ³¹ 1992	125	Article	Oral	Knee	Pain	Financially supported by manufacturer	38.5	Inadequate	No	0.98
Kerzberg et al, ⁴⁵ 1987	17	Article	Intramuscular	Knee	Mobility	Author affiliation with manufacturer Manufacturer conducted data collection, randomization, or statistical analysis	31.9	Inadequate	No	1.47
Mazieres et al, ¹⁵ 1992	120	Article	Oral	Knee and hip	NSAID use	Author affiliation with manufacturer	55.4	Intermediate	No	0.53
Rovetta et al, ⁴⁷ 1991	40	Article	Intramuscular	Knee	Pain	Manufacturer conducted data collection, randomization, or statistical analysis	31.9	Inadequate	No	4.56§
Conrozier, ³² 1998	104	Article	Oral	Knee	Lequesne	Unknown	34.6	Inadequate	Yes	0.61

*Lequesne indicates Lequesne Algofunctional Index; Pain, global pain score (Likert or visual analog); WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; Mobility, mobility score; and NSAID, nonsteroidal anti-inflammatory drug.

†Effect size is based on the scale proposed by Cohen³⁶ in which 0.8 reflects a large effect, 0.5 a moderate effect, and 0.2 a small effect.

‡This study reported an intent-to-treat analysis for dichotomous response or nonresponse outcome variable only. It did not provide the means and SDs necessary to compute an effect size in an intent-to-treat fashion.

§This study was a significant outlier and was dropped from the final analysis.

tact with authors from the remaining studies confirmed some level of manufacturer sponsorship for all except 2 studies. Six studies received direct financial support from a manufacturer. Seven articles included an investigator from the company as an author. In at least 4 studies, the manufacturer conducted key aspects of the trial such as randomization, data collection, or statistical analysis. These results are summarized in Table 2.

Evaluation for Publication Bias

The funnel plots for the trials included in our analyses are depicted in FIGURE 2. Both plots showed significant asymmetry, reflecting a relative absence of trials with both small numbers and small or null treatment effects. Analyses in which we tested quantitatively for publication bias by regressing effect size with inverse of study variance showed strong evidence for bias (glucosamine, intercept estimate, 1.3, $P = .01$; chondroitin, 3.8, $P = .002$).

Influence of Trial Quality Scores

Pooled effect sizes were substantially higher among lower-quality compared with higher-quality trials. For glucosamine, the pooled effect for trials with a quality score below the median was 0.7 (95% CI, 0.4-1.0) vs 0.3 (95% CI, 0.1-0.5) for trials with a quality score above the median. For chondroitin, the pooled effect for trial with a quality score below the median was 1.7 (95% CI, 0.7-2.7) vs 0.8 (95% CI, 0.6-1.0).

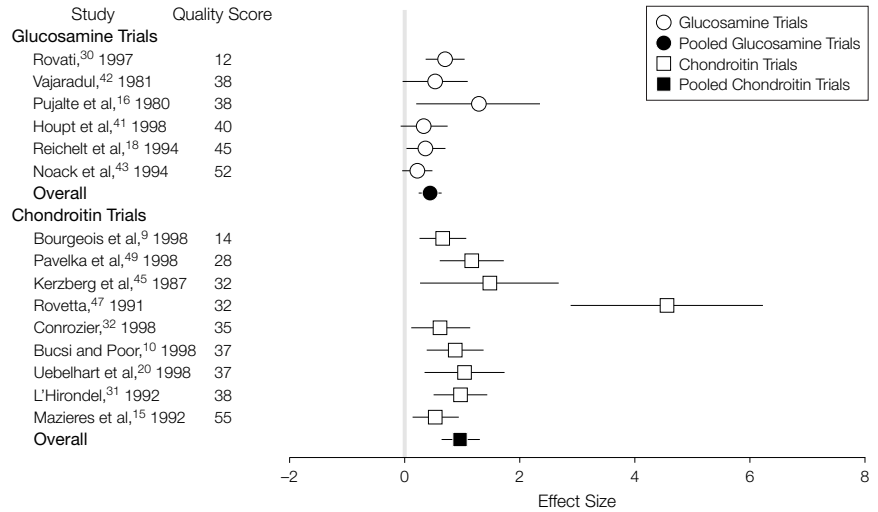
Influence of Trial Size

For glucosamine, the pooled effect for small trials was 0.5 (95% CI, 0.1-0.9) compared with 0.4 (95% CI, 0.1-0.7) for large trials. In contrast, for chondroitin, the pooled effect for small trials was much greater (1.7 [95% CI, 0.5-2.8]) than large trials (0.8 [95% CI, 0.6-1.0]) for large trials.

COMMENT

Trials of glucosamine and chondroitin preparations for OA collectively demonstrate moderate to large treatment effects on symptoms, but our assess-

Figure 1. Forest Plot of Effect Sizes for Trials and Pooled Effects

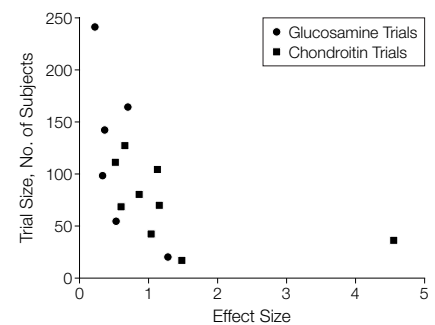


95% confidence intervals are shown using lines extending from the symbols. Effect size is based on the scale proposed by Cohen³⁶ in which 0.8 reflects a large effect, 0.5 a moderate effect, and 0.2 a small effect.

ments of methodological aspects of these studies suggest that the actual efficacy of these products is likely to be substantially more modest. Furthermore, the efficacy was smaller when measured after only 4 weeks of treatment, suggesting that induction of full therapeutic benefit may take longer than 1 month. Nevertheless, even modest efficacy could have clinical utility, given the safety of these preparations.

We evaluated the quality of each clinical trial by applying a validated assessment instrument, which has been developed and described in detail in Chalmers et al²⁵ and Rochon et al.³³ This instrument scores aspects of how a trial is reported to have been conducted, including allocation concealment. Allocation concealment is separately assessed from blinding as it relates to preventing selection bias and protecting assignment sequence before and until treatment allocation, while blinding is concerned with preventing ascertainment bias and protecting assignment sequence after allocation.⁵⁰ Using this instrument, a full score of 10 points is assigned if a report outlines its procedural methods that would ensure allocation concealment (eg, in the study by Noack et al,⁴³ indistinguishable treatments randomly precoded by a central

Figure 2. Funnel Plot of Glucosamine and Chondroitin Trials



Effect size is based on the scale proposed by Cohen³⁶ in which 0.8 reflects a large effect, 0.5 a moderate effect, and 0.2 a small effect.

pharmacy). Partial credit of 5 points is given when a method is used that generates a small chance of the next treatment assignment being predicted (eg, in the study by Pujalte et al,¹⁶ indistinguishable treatments “blindly assigned” from a “previously randomized list”). No credit is given when quasi-randomization procedures are used (eg, chart numbers), or when the method cannot be discerned from the report, as in the majority of these trials.

In theory, a poorly described study could receive a low score even if well conceived. It should be noted, how-

ever, that it is poor quality reports that have been associated with inflated estimates of benefit.^{27,51} These and other investigations in this field⁵² strongly suggest that inadequate reports generally reflect inadequate methods. Nevertheless, it is possible that some well-performed trials have been given low scores because of inadequate descriptions of their methods.

There is also some potential for variability of quality scoring between observers in the application of this instrument to individual studies. While the interobserver reproducibility was found to be good, we chose to further increase reliability by taking the mean of their final scores following a session to adjudicate differences.

As in trials of other pharmacologic agents for arthritis disorders,⁵³ these studies exhibited numerous methodological problems and biases. Particular methodological flaws that have been associated with inflation of treatment effects and that were frequent in these trials included inadequate allocation concealment^{26,27} and absence of intent-to-treat approaches.²⁵ Further empirical evidence for inflated estimates of benefit is suggested by our observation of smaller effect sizes among the higher-quality and the larger studies.

The second major concern is that we found statistical evidence of bias reflecting an absence of trials with both small numbers of participants and small (or null) treatment effects. Such bias may arise from various sources including selective publication of positive trials, post hoc selection of study outcome measures, and premature trial termination once a positive outcome is achieved.³⁹ The imposition of an outcome measure chosen independently of the investigators made little difference to the overall results, suggesting that publication bias may be a more likely explanation for this asymmetry. This possibility is strengthened by the finding that most, if not all, of the trials received some level of sponsorship from a manufacturer of the study compound. On the other hand, we contacted authors of published articles, and content experts, in attempts

to determine the existence of any unpublished trials of these compounds, and found none.

We included trials reported in supplements and as abstracts in this analysis. Although absence of peer review has been associated with lower quality scores,³³ we chose to include these trials for 2 reasons: First, we had envisaged that negative studies would more likely be represented among this group; second, we intended to include trials in our review that were cited in lay publications and that likely contributed to the current vogue for these preparations.

A possible limitation to our analysis and to any meta-analysis is that the trials may be so varied (heterogeneous) that producing a pooled effect is meaningless. Although we did not pool glucosamine and chondroitin trials, 2 possible sources of heterogeneity still exist in our analysis. The first is that we combined studies that were heterogeneous in the routes of administration, and preparations were tested within the 2 compound types. It might be argued that difference in administration and preparation of trial compounds could result in biological differences in the mode of action of these nutritional compounds. However, from an empirical perspective, this consideration has little impact on our analyses because all our sample trials showed positive effects, and statistical assessments consistently found little or no evidence of heterogeneity.

A second potential source of heterogeneity is that we pooled trials that measured the outcome in different ways (eg, pain or function) and used different instruments (eg, visual analog scales, Lequesne index³⁸ Western Ontario and McMaster Universities Osteoarthritis Index). To address this, we used an effect size that was derived from the standardized mean difference, which should enhance comparability between different outcome types. To explore further the possibility of heterogeneity due to different outcome measures, we performed analyses confined to trials with pain-based outcomes and to those that used the Lequesne index. The effect sizes

remained relatively consistent in these analyses, suggesting that heterogeneity due to different outcome measures did not adversely affect our analyses.

We also made imputations for the measures of variability from 4 trials that did not report these data.^{30-32,54} We did this because we wished to include as many trials as possible, yet we were aware that some articles would not include enough detail to allow calculation of effect size. Because trials could be of different durations, we used the coefficient of variability, a measure that is not sensitive to trial duration, to calculate the SD and effect size. This approach has been used in previous meta-analyses.⁵⁴ Because of potential concerns, however, we repeated the main analyses after excluding studies for which imputations had been made. This made little difference in the results of the meta-analyses.

In summary, we have found that trials of glucosamine and chondroitin preparations for OA symptoms demonstrate moderate to large effects but exhibit methodological problems that have been associated with exaggerated estimates of benefit.³⁹ Overall, it seems probable that these compounds do have some efficacy in treating OA symptoms and that they are safe. Because of this, they may have considerable utility in OA treatment. We recommend further high-quality, independent studies to determine the actual efficacy and utility of these preparations.

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REFERENCES

1. Felson DT, Zhang Y. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. *Arthritis Rheum.* 1998;41:1343-1355.
2. Smalley WE, Ray WA, Daugherty JR, Griffin MR. Nonsteroidal anti-inflammatory drugs and the incidence of hospitalizations for peptic ulcer disease in elderly persons. *Am J Epidemiol.* 1995;141:539-545.
3. Tamblyn R, Berkson L, Dauphinee WD, et al. Unnecessary prescribing of NSAIDs and the manage-

- ment of NSAID-related gastropathy in medical practice. *Ann Intern Med.* 1997;127:429-438.
4. Theodosakis J, Adderly B, Fox B. *The Arthritis Cure.* New York, NY: St Martin's Press; 1997.
 5. Ronca F, Palmieri L, Panucci P, Ronca G. Anti-inflammatory activity of chondroitin sulfate. *Osteoarthritis Cartilage.* 1998;6(suppl A):14-21.
 6. Setnikar I, Giacchetti C, Zanolo G. Pharmacokinetics of glucosamine in the dog and in man. *Arzneimittelforschung.* 1986;36:729-735.
 7. Uebelhart D, Thonar EJ, Zhang J, Williams JM. Protective effect of exogenous chondroitin 4,6-sulfate in the acute degradation of articular cartilage in the rabbit. *Osteoarthritis Cartilage.* 1998;6(suppl A):6-13.
 8. Bassler C, Rovati L, Franchimont P. Stimulation of proteoglycan production by glucosamine sulfate in chondrocytes isolated from human osteoarthritic articular cartilage in vitro. *Osteoarthritis Cartilage.* 1998;6:427-434.
 9. Bourgeois P, Chales G, Dehais J, Delcambre B, Kuntz JL, Rozenberg S. Efficacy and tolerability of chondroitin sulfate 1200 mg/day vs chondroitin sulfate 3 × 400 mg/day vs placebo. *Osteoarthritis Cartilage.* 1998;6(suppl A):25-30.
 10. Bucsi L, Poor G. Efficacy and tolerability of oral chondroitin sulfate as a symptomatic slow-acting drug for osteoarthritis (SYSADOA) in the treatment of knee osteoarthritis. *Osteoarthritis Cartilage.* 1998;6(suppl A):31-36.
 11. Crolle G, D'Este E. Glucosamine sulphate for the management of arthrosis: a controlled clinical investigation. *Curr Med Res Opin.* 1980;7:104-109.
 12. D'Ambrosio E, Casa B, Bompani R, Scali G, Scali M. Glucosamine sulphate: a controlled clinical investigation in arthrosis. *Pharmatherapeutica.* 1981;2:504-508.
 13. Giordano N, Nardi P, Senesi M, et al. Efficacia e tollerabilità della glucosamina solfato nel trattamento della gonartrosi [The efficacy and safety of glucosamine sulfate in the treatment of gonarthrosis]. *Clin Ter.* 1996;147:99-105.
 14. Lopes Vaz A. Double-blind clinical evaluation of the relative efficacy of ibuprofen and glucosamine sulphate in the management of osteoarthritis of the knee in out-patients. *Curr Med Res Opin.* 1982;8:145-149.
 15. Mazieres B, Loyau G, Menkes CJ, et al. Chondroitin sulfate in the treatment of gonarthrosis and coxarthrosis. 5-months result of a multicenter double-blind controlled prospective study using placebo. *Rev Rhum Mal Osteoartic.* 1992;59:466-472.
 16. Pujalte JM, Llavore EP, Ylescupidéz FR. Double-blind clinical evaluation of oral glucosamine sulphate in the basic treatment of osteoarthritis. *Curr Med Res Opin.* 1980;7:110-114.
 17. Qiu GX, Gao SN, Giacovelli G, Rovati L, Setnikar I. Efficacy and safety of glucosamine sulfate versus ibuprofen in patients with knee osteoarthritis. *Arzneimittelforschung.* 1998;48:469-474.
 18. Reichelt A, Forster KK, Fischer M, Rovati LC, Setnikar I. Efficacy and safety of intramuscular glucosamine sulfate in osteoarthritis of the knee: a randomized, placebo-controlled, double-blind study. *Arzneimittelforschung.* 1994;44:75-80.
 19. Setnikar I. Antireactive properties of "chondroprotective" drugs. *Int J Tissue React.* 1992;14:253-261.
 20. Uebelhart D, Thonar EJ, Delmas PD, Chantraine A, Vignon E. Effects of oral chondroitin sulfate on the progression of knee osteoarthritis: a pilot study. *Osteoarthritis Cartilage.* 1998;6(suppl A):39-46.
 21. Verbruggen G, Goemaere S, Veys EM. Chondroitin sulfate: S/DMOAD (structure/disease modifying anti-osteoarthritis drug) in the treatment of finger joint OA. *Osteoarthritis Cartilage.* 1998;6(suppl A):37-38.
 22. McCarty MF. The neglect of glucosamine as a treatment for osteoarthritis: a personal perspective. *Med Hypotheses.* 1994;42:323-327.
 23. Constantz RB. Hyaluronan, glucosamine and chondroitin sulfate: roles for therapy in arthritis? In: Kelley WN, Harris ED, Ruddy S, Sledge CB, eds. *Textbook of Rheumatology.* Philadelphia, Pa: WB Saunders Co; 1998.
 24. Moher D, Jadad AR, Nichol G, Penman M, Tugwell P, Walsh S. Assessing the quality of randomized controlled trials: an annotated bibliography of scales and checklists. *Control Clin Trials.* 1995;16:62-73.
 25. Chalmers TC, Smith H Jr, Blackburn B, et al. A method for assessing the quality of a randomized control trial. *Control Clin Trials.* 1981;2:31-49.
 26. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA.* 1995;273:408-412.
 27. Moher D, Pham B, Jones A, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet.* 1998;352:609-613.
 28. The Cochrane Controlled Trials Registry. Oxford, England: The Cochrane Library; 1998.
 29. Altman R, Brandt KD, Hochberg MC, Moskowitz R. Design and conduct of clinical trials in patients with osteoarthritis: recommendations from a task force of the Osteoarthritis Research Society. *Osteoarthritis Cartilage.* 1996;4:217-243.
 30. Rovati LC. The clinical profile of glucosamine sulfate as a selective symptom modifying drug in osteoarthritis: current data and perspectives. *Osteoarthritis Cartilage.* 1997;5(suppl A):72.
 31. L'Hirondel JL. Klinische doppelblind-studie mit oral verabreichtem chondroitinsulfat gegen placebo bei der tibiofemorale gonarthrose (125 patienten) [Double-blind clinical trial of oral chondroitin sulfate versus placebo for tibiofemoral osteoarthritis (125 patients)]. *Literra Rheumatologica.* 1992;14:77-84.
 32. Conrozier T. Anti-arthrosis treatments: efficacy and tolerance of chondroitin sulfates (CS 4&6). *Presse Med.* 1998;27:1862-1865.
 33. Rochon PA, Gurwitz JH, Cheung CM, Hayes JA, Chalmers TC. Evaluating the quality of articles published in journal supplements compared with the quality of those published in the parent journal. *JAMA.* 1994;272:108-113.
 34. Hedges LV. Distribution theory for Glass's estimator of effect size and related estimators. *J Educ Stat.* 1981;6:107-128.
 35. Hedges LV, Olkin I. *Statistical Methods for Meta-Analysis.* San Diego, Calif: Academic Press Inc; 1985.
 36. Cohen J. *Statistical Power Analysis for the Behavioral Sciences.* 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Assoc; 1988.
 37. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986;7:177-188.
 38. Lequesne MG. The algofunctional indices for hip and knee osteoarthritis. *J Rheumatol.* 1997;24:779-781.
 39. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997;315:629-634.
 40. Rovati LC. Clinical research in osteoarthritis: design and results of short-term and long-term trials with disease-modifying drugs. *Int J Tissue React.* 1992;14:243-251.
 41. Houpt JB, McMillan R, Paget-Dellio D, Russell A, Gahunia HK. Effect of glucosamine hydrochloride (GHCl) in the treatment of pain of osteoarthritis of the knee. *J Rheumatol.* 1998;25(suppl 52):8.
 42. Vajaradul Y. Double-blind clinical evaluation of intra-articular glucosamine in outpatients with gonarthrosis. *Clin Ther.* 1981;3:336-343.
 43. Noack W, Fischer M, Forster KK, Rovati LC, Setnikar I. Glucosamine sulfate in osteoarthritis of the knee. *Osteoarthritis Cartilage.* 1994;2:51-59.
 44. Blotman FL, Loyau G. Clinical trial with chondroitin sulfate in gonarthrosis. *Osteoarthritis Cartilage.* 1993;1:68.
 45. Kerzberg EM, Roldan EJ, Castelli G, Huberman ED. Combination of glycosaminoglycans and acetylsalicylic acid in knee osteoarthritis. *Scand J Rheumatol.* 1987;16:377-380.
 46. Conrozier T, Vignon E. Die Wirkung von Chondroitinsulfat bei der Behandlung der Hüftgelenksarthrose Eine Doppelblindstudie gegen Placebo [The efficacy of chondroitin sulfate for the treatment of osteoarthritis of the hip: a double blind trial versus placebo]. *Literra Rheumatologica.* 1992;14:69-75.
 47. Rovetta G. Galactosaminoglycuronoglycan sulfate (matrix) in therapy of tibiofemoral osteoarthritis of the knee. *Drugs Exp Clin Res.* 1991;17:53-57.
 48. Pavelka K Jr, Sedlackova M, Gatterova J, Becvar R, Pavelka K Sr. Glycosaminoglycan polysulfuric acid (GAGPS) in osteoarthritis of the knee. *Osteoarthritis Cartilage.* 1995;3:15-23.
 49. Pavelka K, Bucsi L, Manopulo R. Double-blind, dose effect study of oral CS 4&6 1200 mg, 800 mg, 200 mg against placebo in the treatment of femorotibial osteoarthritis. *Eular Rheumatol Literra.* 1998;27(suppl 2):63.
 50. Schulz KF. Subverting randomization in controlled trials. *JAMA.* 1995;274:1456-1458.
 51. Schulz KF, Chalmers I, Grimes DA, Altman DG. Assessing the quality of randomization from reports of controlled trials published in obstetrics and gynecology journals. *JAMA.* 1994;272:125-128.
 52. Liberati A, Himmel HN, Chalmers TC. A quality assessment of randomized control trials of primary treatment of breast cancer. *J Clin Oncol.* 1986;4:942-951.
 53. Towheed TE, Hochberg MC. A systematic review of randomized controlled trials of pharmacological therapy in osteoarthritis of the hip. *J Rheumatol.* 1997;24:349-357.
 54. Felson DT, Anderson JJ, Meenan RF. The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis: results of two meta-analysis. *Arthritis Rheum.* 1990;33:1449-1461.