Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis: a comprehensive meta-analysis
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CRD summary
This review assessed the effects of glucosamine and chondroitin in knee or hip osteoarthritis. The authors concluded that glucosamine has a beneficial effect on joints and that both drugs improve arthritis symptoms significantly and to a similar degree. Some aspects of the review methods weaken the soundness of this conclusion.

Authors' objectives
To assess the structural and symptomatic efficacy and safety of oral glucosamine sulfate and chondroitin sulfate in knee osteoarthritis.

Searching
The sources searched included MEDLINE, PREMEDLINE, BIOSIS Previews, HealthSTAR, EMBASE, the Cochrane Controlled Trials Register, Current Contents, EBM Reviews and the Internet. The searches covered the period January 1980 to March 2002, and the search terms were referred to in the paper. Handsearches of reference lists and conference abstracts were undertaken, and experts and manufacturers were contacted. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Double-blind, placebo-controlled, parallel-group, prospective randomised controlled trials (RCTs) were included in the review.

Specific interventions included in the review
Studies that compared oral glucosamine or chondroitin and lasted at least 4 weeks were eligible for inclusion. Within the selected studies, glucosamine treatment was given from 4 weeks to 3 years at a dose of 750 or 1,500 mg/day. Chondroitin treatment was evaluated at doses from 200 to 2,000 mg/day for a period of 90 days to 1 year. All of the included studies allowed the use of rescue medications.

Participants included in the review
Studies of patients with knee or hip osteoarthritis were eligible for inclusion.

Outcomes assessed in the review
Studies were included in the review if they reported one of the following outcomes: joint space narrowing (JSN), Lesquesne Index (LI), Western Ontario MacMaster University Osteoarthritis Index (WOMAC), visual analogue scale (VAS) for pain or for mobility assessment, responders to treatment and safety. The primary review outcome was JSN.

How were decisions on the relevance of primary studies made?
Two reviewers, blinded to study authorship, independently assessed studies for inclusion. Any disagreements were resolved by consulting a third reviewer.

Assessment of study quality
The studies were scored on the basis of randomisation, use of blinding and the description of withdrawals and drop-outs, as described by Jadad. The review also assessed use of intention-to-treat analysis. Two reviewers, blinded to study authorship, independently assessed study validity. Any disagreements were resolved by consulting a third reviewer.
Data extraction
Two reviewers, blinded to study authorship, independently extracted the data from the included studies. Any disagreements were resolved by consulting a third reviewer. Data were extracted on participant numbers and inclusion criteria, treatment details, outcomes and drop-outs. Authors of abstracts were contacted for additional information. For each study, mean differences with standard deviations (SDs) between treatments were extracted or calculated. The reviewers classified patients with very good or good results as responders.

Methods of synthesis
How were the studies combined?
Where there were no statistically significant differences in the results for chondroitin and glucosamine, data from these two drugs were combined. Pooled effect sizes (ESs) with 95% confidence interval (CIs) were calculated for dichotomous and continuous outcomes using a meta-analysis. Publication bias was investigated using linear regression and funnel plots.

How were differences between studies investigated?
The Cochran Q test was used to investigate statistical heterogeneity.

Results of the review
Fifteen RCTs (n=1,775) were included: seven evaluated glucosamine sulphate and eight evaluated chondroitin sulphate.

The quality scores ranged from 60 to 100%, with a mean of 78.4% (SD=17.2%). The mean quality of glucosamine RCTs (90%) was significantly higher than that of chondroitin RCTs (68.4%) (Mann-Whitney U-test, adjusted z=2.27, P=0.02). None of the pooled analyses were reported to have statistical heterogeneity.

Glucosamine statistically significantly decreased JSN (2 RCTs; ES 0.41, 95% CI: 0.21, 0.60, P<0.001)).

LI (10 RCTs): active treatment (with either glucosamine or chondroitin) was found to significantly reduce the LI in comparison with placebo (ES 0.43, 95% CI: 0.32, 0.54, P<0.001). There was no significant difference between glucosamine and chondroitin RCTs (heterogeneity, P=0.68).

WOMAC (2 RCTs): 1,500 mg/day glucosamine for 3 years significantly reduced the WOMAC (ES 0.30, 95% CI: 0.11, 0.49, P<0.001).

Pain (12 RCTs): active treatment (with either glucosamine or chondroitin) was found to significantly reduce pain measured by VAS in comparison with placebo (ES 0.45, 95% CI: 0.33, 0.57, P<0.001).

Mobility (3 RCTs): active treatment (with either glucosamine or chondroitin) was found to significantly increase mobility (ES 0.59, 95% CI: 0.25, 0.92, P<0.001).

Responders (9 RCTs): there were significantly more responders in the active treatment groups (either glucosamine or chondroitin) than in the placebo group (ES 1.59, 95% CI: 1.39, 1.83, P<0.001).

Safety (11 RCTs): there was no significant difference in the overall number of adverse events reported for active treatment compared with placebo (ES 0.80, 95% CI: 0.59, 1.08, P=0.15).

Funnel plot asymmetry was observed (in addition, P=0.08), suggesting publication bias in favour of the intervention.

Authors' conclusions
The data demonstrated the efficacy of glucosamine on JSN and WOMAC, and comparable efficacies of chondroitin and glucosamine on LI, VAS pain and VAS mobility. Both compounds were well tolerated.

CRD commentary
This review was based on a generally well-defined question, supported by appropriate inclusion criteria. It identified studies from a fairly extensive search of electronic and other sources. Attempts were made to minimise language and publication bias, and publication was assessed using appropriate methods. Relevant details of the included studies were extracted, including aspects of study validity, and efforts were made throughout the review process to minimise bias and error through the use of multiple reviewers.

While the authors did not report significant statistical heterogeneity for any of their pooled comparisons, some of these comparisons included studies that differed in the type of treatment given as well as other clinically important characteristics. The lack of statistical heterogeneity for a meta-analysis incorporating a mixture of glucosamine and chondroitin trials does not necessarily indicate that the two treatments have similar efficacy. If a direct comparison of the two treatments is not available, then extra efforts should be made to take issues such as study baseline comparability into account before indirect comparisons of this kind can be attempted. In addition, there was no discussion of the reasons for high drop-out rates in the 2 studies with the longest follow-up of glucosamine treatment (34% and 42% at 3 years). Consequently, the authors' conclusions regarding the effectiveness of the two treatments should be interpreted with care.

**Implications of the review for practice and research**

*Practice:* The authors did not state any implications for practice.

*Research:* The authors stated that further long-term studies are needed to confirm and evaluate the structural efficacy of chondroitin. They added that further studies of glucosamine, examining the relationship between structural and symptomatic changes, controlling for baseline characteristics including osteoarthritis stage, and on its possible use in prevention, are required to determine the role of this compound as a disease-modifying agent in osteoarthritis.

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