Do glucosamine and chondroitin treat the symptoms of osteoarthritis?

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Research question
Are glucosamine and chondroitin preparations beneficial for symptomatic treatment of osteoarthritis (OA)?

Type of article and design
Overview of a systematic quality assessment and meta-analysis.

Relevance to family physicians
Osteoarthritis is the most common joint disease; is a leading cause of disability, impaired quality of life, and health care use; and is recognized as a serious public health problem with enormous economic impact.1-3

Most practitioners prescribe acetaminophen as first-line therapy, often using nonsteroidal anti-inflammatory drugs (NSAIDs) or cyclooxygenase-2 (COX-2) inhibitors as second-line therapy. The recent popularity of COX-2 inhibitors reflects the need for more safe and effective alternatives.

Glucosamine is a hexosamine sugar and a primary constituent in biosynthesis of glycosaminoglycans and proteoglycans, which are fundamental components of articular cartilage. Chondroitin is a glycosaminoglycan found in the proteoglycans of articular cartilage. Both substances are derived from animal sources, and their mechanism of action in treatment of OA is not completely understood. Both appear to have anti-inflammatory effects4,5 and to affect cartilage metabolism favourably, likely by stimulating proteoglycan synthesis in the chondrocytes of articular cartilage.6,7 Recent radiologic evidence shows both could slow the progression of OA.8-10

In Europe, physicians have been using glucosamine and chondroitin to treat OA for more than a decade, but skepticism about their efficacy prevails elsewhere largely due to concerns about the quality of existing clinical evidence. Most of us have patients taking one or both of these products. We wondered whether the drugs worked and whether there were disadvantages to them.

Overview of study and outcomes
The authors performed a systematic quality assessment and meta-analysis of clinical trials evaluating the efficacy of glucosamine and chondroitin preparations for treatment of the symptoms of knee and hip OA. MEDLINE (from January 1966 to June 1999) and the Cochrane Controlled Trials Register were searched using the MeSH terms and textwords osteoarthritis, osteoarthrosis, degenerative arthritis, glucosamine, chondroitin, and glycosaminoglycans. Results were limited to clinical trials of human subjects. A manual search of review articles, manuscripts, and supplemental issues of rheumatology and OA journals was carried out to discover abstract publications and abstracts presented at national and regional meetings of rheumatology and OA societies. If abstract data were incomplete, the primary author was contacted for further information.

Last, efforts were made to identify unpublished material by contacting experts, study authors, and manufacturers of glucosamine and chondroitin products.

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trials of glucosamine and chondroitin. The results of each study were summarized as an effect size. Then, effect sizes for combined glucosamine and chondroitin trials were pooled using a random effects model. Testing for trial heterogeneity was also undertaken to determine whether the findings of the primary studies were combined appropriately.

Methodologic quality was evaluated with a quality assessment instrument\(^\text{12-13}\) that provided a score for compliance with 14 different aspects of clinical trial conduct. Two rheumatologists independently scored the quality assessment. Inter-rater agreement was evaluated to ensure that assessment of the primary studies was reproducible and free from bias. Sensitivity analyses assessed the influence of trial size and trial quality score on study outcome.

Testing for publication bias was performed (ie, the greater likelihood that research with statistically significant positive results will be published than that research with negative results will). Attempts were also made to ascertain sources of funding, author affiliation, and existence of manufacturer sponsorship for each trial included.

**Results**

The pooled effect size for glucosamine was 0.44 (95% confidence interval [CI] 0.24 to 0.64), indicating a moderate treatment effect. After removal of one outlier trial, the pooled effect size for chondroitin was 0.78 (95% CI 0.60 to 0.95), demonstrating a large treatment effect. Smaller effect sizes were found among the nine trials reporting data at the 1-month interval (glucosamine 0.26 [95% CI 0.10-0.42]; chondroitin 0.40 [95% CI 0.17-0.62]). This further supports previous evidence suggesting that 4 or more weeks’ treatment with these compounds might be required before a clinically significant therapeutic effect is achieved.

Tests for heterogeneity were not significant (after removal of the outlier trial), indicating that the trials included in the analysis could be so varied that we should be cautious in interpreting the results of the pooled effects.

Quality scores had a mean of 35.5% similar to mean quality scores found by others\(^\text{13}\) in evaluating this instrument using large numbers of trials. Inter-rater agreement was found to be good between the two reviewers (\( P < .01\)). Only one of 15 studies gave adequate information to establish that allocation concealment was sufficient; two reported an intent-to-treat analysis; and seven did not cite drop-out rates. Therefore, it is possible that most trials were not perfectly “blinded” and not everyone who entered the trials was accounted for at the end. These are serious methodologic flaws that can result in exaggeration of treatment benefits and thus affect the validity of a study’s conclusions.

Sensitivity analyses revealed pooled effect sizes to be considerably larger among smaller trials and those with lower quality scores. This basically indicates that the better quality the trial is, the smaller the treatment effect, and vice versa.

At least 13 of the 15 studies had some level of manufacturer association—sponsorship, financial support, author affiliation, or performance of large components of the trial. Qualitative testing for publication bias using funnel plots demonstrated significant asymmetry (\( P \leq .01\)) indicating probable publication bias. Quantitative testing by regressing effect size with inverse of study variance also showed strong evidence of publication bias. These findings put the review at risk of overestimating treatment efficacy because it appears that only trials with positive results have been published.

**Analysis of methodology**

The review was methodologically sound, satisfying quality criteria for overviews described by Oxman et al.\(^\text{14}\) It clearly stated and addressed a focused clinical question. Explicit and appropriate criteria were used to determine which studies were to be included in the analysis; it is unlikely that important relevant studies were missed. The validity of each trial included in the review was assessed and the methods clearly reported. Assessments of studies were reproducible with a good level of inter-rater agreement.

The main limitations of the review are its lack of homogeneity among trials and its failure to provide data that would allow readers to decide whether results are generalizable to their individual patients with OA. Important demographic data displaying the differences between study populations (eg, mean age, sex distribution, severity of OA, and concurrent use of analgesics or NSAIDs) and side effect data were not presented.

**Application to clinical practice**

Results from this meta-analysis established that preparations of glucosamine and chondroitin produce moderate to large treatment effects on symptoms of knee or hip OA. Results of the quality assessment strongly suggest, however, that these beneficial therapeutic effects are likely exaggerated because of serious methodologic flaws and biases in the available literature. This might be attributable to the high level of manufacturer affiliation and support involved in these studies, which indicates the need for independently produced clinical trials.

Probably the greatest limitation of this overview is that it does not help physicians decide how to care for their
patients with OA. Many questions remain unanswered. Are these results generalizable to patients with OA of the hand, shoulder, ankle, etc? Which patient population will benefit most from treatment with these compounds (eg, mild or severe OA, primary or secondary OA)?

What is the long-term efficacy and, perhaps more importantly, what are the long-term risks, possible toxic side effects, and drug interactions associated with these preparations? As general practitioners who do not “prescribe” these medications, perhaps our first concern should be drug interactions and safety. The authors of this overview did not comment on toxicity at all, other than referring to the products as “safe.” This opinion, however, is based on results from trials of relatively short duration. To date, no real long-term data support these conclusions. As well, preparations made by different manufacturers might contain different concentrations of these compounds, and could have different efficacy and side effect profiles.

What is the optimal dosage? Currently, the trend is 500 mg of glucosamine and 400 mg of chondroitin three times daily. Glucosamine and chondroitin sell on the shelf at local pharmacies for anywhere between $10 and $25 for 90 tablets (ie, a 1-month supply). As confirmed in this review, it could take more than 1 month before the full therapeutic effect is achieved. Also, is one compound more efficacious than the other? Do they act independently or synergistically? Is there a role for use in conjunction with NSAIDs or acetaminophen, and if so, is it safe? We cannot yet provide our patients with the data to make truly informed treatment decisions. Additional large, well-designed, independent randomized controlled trials evaluating glucosamine and chondroitin therapy are needed. One such study has recently been sponsored by the National Institutes of Health in the United States.

References