Do glucosamine and chondroitin treat the symptoms of osteoarthritis?

Darren D. Edelist, MD Michael F. Evans, MD, CCFP

McAlindon TE, LaValley MP, Gulin JP, Felson DT. Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. *JAMA* **2000;283:1469-75.**

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 cycloxygenase-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 effects[4,5] 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.

Critical Appraisal reviews important articles in the literature relevant to family physicians. Reviews are by family physicians, not experts on the topics. They assess not only the strength of the studies but the "bottom line" clinical importance for family practice. We invite you to comment on the reviews, suggest articles for review, or become a reviewer. Contact Coordinator Michael Evans by e-mail michael.evans@utoronto.ca or by fax (416) 603-5821.

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.

Published and unpublished, double-blind, randomized placebo-controlled trials that tested the effect of glucosamine or chondroitin on symptoms of knee or hip OA were included. Only trials of at least 4 weeks' duration were selected because prior evidence suggests it could take several weeks of treatment before any therapeutic effect is achieved. Also, only trials reporting extractable data, using at least one of the outcome measures currently recommended for OA clinical trials were included.[11] For the final analysis, 15 of 37 studies were included.

Two reviewers extracted the data from each trial using a standardized form. Separate meta-analyses were performed for

Drs Edelist *and* **Evans** *practise family medicine at the Toronto Western Hospital University Health Network in Toronto, Ont.*

← FOR PRESCRIBING INFORMATION SEE PAGE 404

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[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[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.[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.

Bottom line

- Both glucosamine and chondroitin could be effective therapies for symptoms of OA, but the degree of benefit demonstrated by the available literature is probably overestimated due to methodologic flaws and biases in the studies.
- Full therapeutic benefit might take more than 4 weeks.
- Suggested dosage is 500 mg of glucosamine and 400 mg of chondroitin, both three times daily.
- Each can cost up to $25 each month.
- Generally thought to have benign limited side effect profiles, but no long-term data validate this.
- As with all "neutraceuticals" sold off-the-shelf in pharmacies, no standardization of product content and purity exists. Therefore, anything purchased off-the-shelf might not be equivalent to what was used in the trials.

Points saillants

- Autant la glucosamine que la chondroitine pourraient se révéler des thérapies efficaces pour soulager les symptômes de l'arthrite, mais le degré de bienfait démontré dans les ouvrages scientifiques publiés est probablement surestimé en raison de lacunes méthodologiques et de partialité dans les études.
- Les bienfaits thérapeutiques complets pourraient prendre jusqu'à quatre semaines avant d'apparaître.
- La posologie suggérée est de 500 mg de glucosamine et de 400 mg de chondroitine respectivement, trois fois par jour.
- La thérapie peut coûter jusqu'à 25$ par mois.
- On croit généralement qu'elles comportent des effets secondaires bénins limités, mais aucune donnée à long terme ne le prouve.
- Comme c'est le cas de tous les produits «neutraceutiques» vendus sans ordonnance dans les pharmacies, il y a absence de normalisation en matière de contenu ou de pureté du produit. Par conséquent, tout produit procuré sans ordonnance pourrait ne pas être équivalent à ceux utilisés dans les essais.

References

1. Felson DT. Osteoarthritis. *Rheum Dis Clin North Am* 1990;16:499-512.
2. Guccione AA, Felson DT, Anderson JJ, Anthony JM, Zhang Y, Wilson PW. The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. *Am J Public Health* 1994;84:351-8.
3. Kramer JS, Yelin EH, Epstein WV. Social and economic impacts of four musculoskeletal conditions: a study using national community-based data. *J Rheumatol* 1983;26:901-7.
4. Setnikar I, Cereda R, Pacini MA, Revel L. Antireactive properties of glucosamine sulfate. *Arzneimittelforschung* 1991;41:157-61.
5. Ronca F, Palmieri L, Panicucci P, Ronca G. Anti-inflammatory activity of chondroitin sulfate. *Osteoarth Cartilage* 1998;6(Suppl A):14-21.
6. Bassleer CT, Combal JP, Bougaret S, Malaise M. Effects of chondroitin sulfate and interleukin-1 beta on human articular chondrocytes cultivated in clusters. *Osteoarth Cartilage* 1998;6:196-204.
7. Bassleer CT, Rovati L, Franchimont P. Stimulation of proteoglycan production by glucosamine sulfate in chondrocytes isolated from human osteoarthritic articular cartilage in vitro. *Osteoarth Cartilage* 1998;6:427-34.
8. Reginster JY, Deroisy R, Paul I. Glucosamine sulfate significantly reduces progression of knee osteoarthritis over 3 years. *Arthritis Rheum* 1999;42(Suppl 9):S400.
9. Verbruggen G, Goemaere S, Veys EM. Chondroitin sulfate: S/DMOAD (structure/disease modifying anti-arthritis drug) in the treatment of finger joint OA. *Osteoarth Cartilage* 1998;6(Suppl A):37-8.
10. Uebelhart D, Thonar EJ, Delmas PD, Chantraine A, Vignon E. Effects of oral chondroitin on the progression of knee osteoarthritis: a pilot study. *Osteoarth Cartilage* 1998;6(Suppl A):6-13.
11. 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. *Osteoarth Cartilage* 1996;4:217-43.
12. Chalmers TC, Smith H Jr, Blackburn B, Silverman B, Schroeder B, Reitman D. A method for assessing the quality of a randomized control trial. *Control Clin Trials* 1981;2:31-49.
13. 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;272:108-13.
14. Oxman AD, Cook DJ, Guyatt GH. Users' guides to the medical literature. VI: How to use an overview. *JAMA* 1994;272:1367-72.