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Editor's Note: The widespread use of complementary and alternative medicine (CAM) by patients in the United States makes it imperative for physicians to have a better understanding and knowledge about CAM modalities in order to provide best care for their patients.

The University of Washington School of Medicine (UW-SOM), in collaboration with Bastyr University, has been awarded a grant from the National Center for Complementary and Alternative Medicine (NCCAM) directed at developing educational materials and integrating CAM into the UW-SOM curriculum. One aim of the grant was to develop evidence-based monographs for the most important herbs and supplements for physicians to know about.

Made possible by funds from this NCCAM grant (AT00813-01), this insert to *Drug Therapy Topics* reviews one of these supplements.

Glucosamine and Chondroitin

by Barak Gaster, M.D.

Osteoarthritis (OA) is the most common cause of disability in adults.[1] Interest in alternative treatments for OA has grown as more data has emerged about the risks of nonsteroidal anti-inflammatory drugs (NSAIDs).[2] Glucosamine and chondroitin, two therapies promoted for "healthy joints," are now the most commonly used dietary supplements in the United States.[3] In four years, sales have doubled from $288 million in 2000 to $730 million in 2004.

Pharmacology

Articular cartilage is made up mostly of extra-cellular matrix. This matrix contains giant proteoglycan molecules which are made of a hyaluronic acid backbone to which giant glycosaminoglycan chains (GAGs) are attached. Chondroitin is one type of GAG, and glucosamine is a building block for many different GAGs. Both are thus naturally occurring substrates for the production of articular cartilage. Commercial glucosamine is primarily derived from the shells of crabs and other shellfish while commercial chondroitin is produced primarily from the cartilage of cows.

Glucosamine is a small, easily absorbed amino sugar. Though easily absorbed, its bioavailability is still less than 20% due to a high first-pass effect in the liver. Chondroitin is a very large, poorly absorbed molecule. Its oral bioavailability is less than 20%.

Both glucosamine and chondroitin can stimulate proteoglycan production in vitro.[4] Chondroitin also seems to inhibit the inflammatory enzyme leukocyte elastase, an effect which may provide some analgesia and may contribute to the slowing of cartilage degradation.[5]

Clinical studies

Numerous randomized controlled trials (RCTs) of glucosamine have suggested possible efficacy, although the results have been somewhat mixed. A meta-analysis published in 2002 aggregated the results from 15 studies and found highly significant results for glucosamine.[6] A subsequent Cochrane review, updated in 2005, included the results from 5 additional RCTs and found greater trial heterogeneity and more mixed results.[7]

In the largest and longest glucosamine study, 212 patients were followed for 3 years.[8] Patients who received glucosamine had significantly improved symptom and function scores as well as significantly less joint space narrowing on serial knee x-rays. This last finding raises the question of whether glucosamine may be disease modifying for OA, an outcome which has not been demonstrated for NSAIDs.

In February 2006, the first results from the long-awaited GAIT trial were published.[9] This NIH funded, multi-center trial randomized 1583 patients to glucosamine, chondroitin, combination glucosamine and chondroitin, or placebo. The primary outcome (>20% reduction in pain score) was not significantly better in those receiving glucosamine, chondroitin, or their combination. There were, however, dramatically favorable results for the subset of patients with moderate to severe pain at baseline, as well as in all patients when a more robust outcome

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References

1. Guccione AA, et al. The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. Am J Public Health 1994;84:351-8.
2. Howard PA, et al. Nonsteroidal anti-inflammatory drugs and cardiovascular risk. J Am Coll Cardiol 2004;43:519-25.
3. Annual Supplement Industry Overview. Nutr Bus J June 2005:1-11.
4. Bassleer C, et al. In-vitro evaluation of drugs proposed as chondroprotective agents. Int J Tissue React 1992;14:231-41.
5. Bali JP, et al. Biochemical basis of the pharmacologic action of chondroitin sulfates on the osteoarticular system. Semin Arthritis Rheum 2001; 31(1):58-68.

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measure, designed to more effectively cull out placebo responders, was used. Another noteworthy finding was the consistently superior response seen in the group receiving the combination of glucosamine and chondroitin, suggesting for the first time a possible synergistic effect from using these 2 agents together. The GAIT trial will continue for 2 more years, providing longer term data and including an analysis of joint space changes seen on serial x-rays.

Adverse effects and drug interactions

Both glucosamine and chondroitin are extremely well-tolerated with no significant adverse effects greater than placebo. Although theoretical concerns have been raised about whether glucosamine might worsen glycemic control in patients with diabetes or might contribute to atherosclerosis in patients with coronary artery disease, there has been no clinical evidence to support either possibility.[10-12]

Because chondroitin is derived from cattle, its potential to transmit bovine spongiform encephalitis (BSE) has been raised. Because BSE prion particles are generally not found in cartilage, however, it is exceedingly unlikely that this could occur, with a vanishingly small risk of less than 1 case per 10 billion servings, similar to eating beef.[13]

Theoretically, patients who have seafood allergies should avoid glucosamine since it is derived from shellfish, although despite millions of users around the world there have been no case reports of such reactions. No significant drug interactions have been reported with either chondroitin or glucosamine.

Formulation and dosage

The most commonly used doses in RCTs have been chondroitin 400mg TID and glucosamine 500mg TID. Products containing the two in combination are generally similar in price to those containing either agent alone.

Patients should be warned that symptom relief may take 4-8 weeks, which is longer than patients may be used to with NSAIDs. More trials have tested the glucosamine sulfate rather than the glucosamine hydrochloride form, although this difference is unlikely to be important since the salts disassociate in the stomach after ingestion.

Although product quality remains poorly regulated by the FDA, ConsumerLab recently tested a large sample of combination glucosamine chondroitin products and found that all 11 products analyzed contained the amounts of each substance that was listed on the labels.[14]

Summary of the Evidence

- Substantial evidence suggests that glucosamine may be effective for OA of the knee although the results have not been consistent. The body of data for chondroitin is smaller but also suggestive.
- Both agents are safe and very well tolerated.
- There is preliminary evidence that the two agents when taken in combination have a synergistic effect.
- Symptom relief may take 4-8 weeks to appear which is much longer than patients may be accustomed to with NSAIDs.

Note:
More than twenty other similar monographs are available at *www.uwcam.org* including: black cohosh, echinacea, feverfew, garlic, ginkgo biloba, kava, milk thistle, phytoestrogens, saw palmetto, and St. John's wort. For more information on the UW-SOM CAM curriculum project, contact Ronald Schneeweiss, MBChB (sron@fammed.washington.edu) or Barak Gaster, MD (barakg@u.washington.edu).

References (continued)

6. Richy F, et al. Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis. A comprehensive meta-analysis. Arch Int Med 2003;163:1514-1522.
7. Towheed TE, et al. Glucosamine therapy for treating osteoarthritis. The Cochrane Database of Systematic Reviews 2005, Issue 2. Art. No.: CD002946.
8. Reginster JY, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled trial. Lancet 2001;357:251-6.
9. Clegg DO, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med 2006 Feb 23;354(8):795-808.
10. Scroggie DA, et al. The effect of glucosamine-chondroitin supplementation on glycosylated hemoglobin levels in patients with type 2 diabetes mellitus: a placebo-controlled, double-blinded, randomized clinical trial. Arch Intern Med 2003 Jul 14;163(13):1587-90.
11. Duan W, et al. Distinct effects of glucose and glucosamine on vascular endothelial and smooth muscle cells: evidence for a protective role for glucosamine in atherosclerosis. Cardiovasc Diabetol 2005 Oct 5;4:16.
12. Tannock LR, et al. Arterial smooth muscle cell proteoglycans synthesized in the presence of glucosamine demonstrate reduced binding to LDL. J Lipid Res 2002 Jan;43(1):149-57.
13. "Bovine Spongiform Encephalopathy." National Center for Infectious Diseases June 27, 2005. Available from www.cdc.gov/ncidod/dvrd/vcjd/risk_travelers.htm
14. Joint Supplements: Glucosamine and Chondroitin Consumer Product Review. www.consumerlab.com. Posted Nov 2, 2003. Accessed June 20, 2006.

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