

Glucosamine

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Glucosamine is one of the most popular dietary supplements sold in the United States. Most clinical trials have focused on its use in osteoarthritis of the knee. The reported adverse effects have been relatively well studied and are generally uncommon and minor. No significant supplement–drug interactions involving glucosamine have been reported. The National Institutes of Health–sponsored Glucosamine/chondroitin Arthritis Intervention Trial, the largest randomized, double-blind, placebo-controlled study involving the supplement, still has not confirmed whether glucosamine is effective in the treatment of osteoarthritis. Despite conflicting results in studies, there is no clear evidence to recommend against its use. If physicians have patients who wish to try glucosamine, it would be reasonable to support a 60-day trial of glucosamine sulfate, especially in those at high risk of secondary effects from other accepted treatments. The decision to continue therapy can then be left to patients on an individual basis, while the physician monitors for possible adverse effects. Glucosamine should be used with caution in patients who have shellfish allergies or asthma, and in those taking diabetes medications or warfarin. (*Am Fam Physician*. 2008;78(4):471-476, 481. Copyright © 2008 American Academy of Family Physicians.)

► Patient information:

A handout on glucosamine, written by the authors of this article, is provided on page 481.

Glucosamine and chondroitin sulfate are among the most popular dietary supplements sold in the United States.¹ The U.S. consumer market for glucosamine and chondroitin was estimated at \$810 million in 2005.² Glucosamine is also one of the most studied supplements, with more than 20 randomized controlled trials involving over 2,500 patients.³ Glucosamine sulfate attracted the attention of the scientific community after two long-term clinical trials showed that it could slow the progression of anatomic joint structure changes in knee osteoarthritis and control the progression of symptoms.^{4,5} Subsequent trials have had conflicting results, including the largest study, the National Institutes of Health–funded Glucosamine/chondroitin Arthritis Intervention Trial (GAIT).⁶ Although most studies are of glucosamine alone, it is often sold in combination with chondroitin. It is not known if this combination is better than glucosamine alone, but animal studies suggest that this may be the case.^{7,8} This article focuses on a literature review of glucosamine and its use in osteoarthritis.

Pharmacology

Glucosamine (2-amino-2-deoxy-β-D-glucopyranose) is an endogenous aminomono-

saccharide synthesized from glucose and utilized for biosynthesis of glycoproteins and glycosaminoglycans.⁹ Glucosamine is present in almost all human tissues, highly concentrated in connective tissues of the human body, and found at highest concentrations in the cartilage. In humans, about 90 percent of glucosamine is absorbed when administered as an oral dose of glucosamine sulfate, and is rapidly incorporated into articular cartilage.¹⁰ Glucosamine can be found in many forms, including sulfate, hydrochloride, *N*-acetylglucosamine, or chlorohydrate salt, and as a dextrorotatory isomer. There is some dispute over which form is most effective. Pooled findings from studies using a specific commercial glucosamine sulfate product called Dona suggest that this formulation reduces osteoarthritis pain, whereas other formulations do not.¹¹ Another study performed in China provides some evidence that glucosamine hydrochloride and glucosamine sulfate are equally effective.¹²

The sulfate salt of glucosamine forms one half of the disaccharide subunit of keratan sulfate, which decreases in patients with osteoarthritis. Hyaluronic acid (found in articular cartilage and synovial fluid) is composed of repeating dimeric units of glucuronic acid and *N*-acetylglucosamine.¹³

SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>
Treatment with glucosamine sulfate is a reasonable option in patients who wish to try it or in those who cannot tolerate traditional therapies for knee pain in osteoarthritis.	A	4, 5, 17, 18, 25
Caution is advised when using glucosamine in patients with an allergy to shellfish, patients with asthma, and those taking diabetes medications or warfarin (Coumadin).	C	34, 35, 37, 38

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see <http://www.aafp.org/afpsort.xml>.

Possible mechanisms of action for the chondroprotective effect of glucosamine include direct stimulation of chondrocytes, incorporation of sulfur into cartilage, and protection against degradative processes within the body through altered gene expression.^{10,14,15} The exact mechanism of action for the possible effect of glucosamine is unknown.

Uses and Effectiveness

Glucosamine has been studied for many uses, including treatment of temporomandibular joint disorder and rheumatoid arthritis, but most trials have focused on its use in osteoarthritis. Clinical trials have yielded conflicting results. Double-blind studies enrolling more than 400 persons found glucosamine and ibuprofen (Motrin) to be equally effective in reducing symptoms of knee and temporomandibular joint osteoarthritis.¹⁶⁻¹⁸ In four studies involving more than 500 persons, glucosamine failed to provide any meaningful improvement in symptoms.¹⁹⁻²³ A recent study concluded that most of the trials with positive outcomes were funded by manufacturers of glucosamine products, whereas most trials performed by neutral researchers failed to find benefit.²⁴

Two of the largest placebo-controlled trials conducted before 2007 were in Europe and used the glucosamine sulfate formulation.^{4,5} In the 2001 Belgian study, 212 persons with osteoarthritis of the knee were followed for three years, received either placebo or oral glucosamine sulfate in a dosage of 1,500 mg daily, and were evaluated using the Western Ontario

and McMaster Universities (WOMAC) osteoarthritis index.⁴ The WOMAC index is the most commonly employed questionnaire in clinical research to assess degree of pain and stiffness, as well as functional impairment caused by osteoarthritis. The study showed that patients taking glucosamine sulfate had modest pain reduction (average of 11.7 percent relative reduction in the WOMAC index compared with baseline) and reduced joint-space narrowing compared with placebo, as measured by weight-bearing anteroposterior view radiography (0.06 mm versus 0.31 mm). Both differences were statistically significant; however, there was no correlation between improvement in symptoms and radiographic findings.⁴

In a similar 2002 trial conducted in Prague, Czech Republic, 202 patients with osteoarthritis of the knee were given placebo or 1,500 mg of Dona and were followed for three years.⁵ Those receiving Dona showed statistically significant improvement in symptoms of pain and stiffness compared with placebo (26 percent versus 16 percent mean reduction in the WOMAC index) and radiographic evidence of decreased narrowing in the medial joint compartment (mean gain of 0.04 mm versus 0.19 mm of joint-space narrowing).

The most recent meta-analysis of glucosamine was conducted in 2005 and included 20 randomized controlled trials with a total of 2,570 patients.¹¹ The investigators found that current evidence: (1) does not analyze the long-term effectiveness and toxicity

of glucosamine; (2) does not differentiate which joints and which levels of severity of osteoarthritis warrant this therapy; (3) does not differentiate which dosage and route of administration are best; and (4) does not demonstrate whether glucosamine modifies the long-term progression of osteoarthritis. When restricting the analysis to eight studies with the highest-quality design, no overall improvement in pain or function was found.¹¹ The investigators concluded that there was high-quality evidence that glucosamine was not as useful for symptom improvement as had been previously thought.

The authors of the 2006 GAIT also were unable to conclude whether glucosamine is useful in the treatment of osteoarthritis.⁶ GAIT was the first major clinical trial to directly compare glucosamine alone, chondroitin alone, combination glucosamine/chondroitin, a cyclooxygenase inhibitor, and placebo. It included more than 1,500 patients who were followed for six months. The WOMAC index was the primary outcome measure. Although radiographic data have yet to be published, the authors concluded that, compared with placebo, glucosamine alone or in combination with chondroitin did not reduce pain significantly after six months in patients with osteoarthritis of the knee. They did suggest that a combination of the two may be effective in a subgroup of patients with moderate to severe knee pain. An important finding in this study was a placebo effect of around 60 percent, suggesting that the sample size used was possibly inadequate.²⁵ Additional concerns about the study have been raised, including the attrition rate, limitations in data analysis, and the use of glucosamine hydrochloride preparation rather than the glucosamine sulfate preparation.²⁶ A 2008 study of glucosamine sulfate in more than 200 patients with hip osteoarthritis showed no reduction in symptoms or progression of arthritis compared with placebo.²⁷

Glucosamine combined with chondroitin has been used in a topical form in a few small, randomized, double-blind, placebo-controlled trials with favorable results.^{28,29} One study showed statistically significant

improvement in pain reduction after eight weeks with a glucosamine/chondroitin preparation compared with placebo (visual analog scale measurements).²⁹ There have also been some initial studies suggesting that the addition of glucosamine to non-steroidal anti-inflammatory drugs (NSAIDs) could decrease NSAID use in those patients already taking them.³⁰ Because the anti-inflammatory ability of glucosamine is different from that of NSAIDs, it is possible the two might have a synergistic effect in alleviating some types of inflammation.³¹

Finally, a 2007 double-blind, placebo-controlled study of 51 Japanese patients with rheumatoid arthritis showed that glucosamine hydrochloride in a dosage of 1,500 mg daily significantly improved symptoms according to patients' self-evaluation and physician global evaluation.³² It did not, however, alter measures of inflammation as determined through blood tests.

Contraindications, Adverse Effects, and Interactions

The reported adverse effects have been generally uncommon and minor. Glucosamine is produced from the shells of lobster, crab, and shrimp. However, the antigen proteins associated with seafood allergies are not found in the shell, and there have been no reports of reactions in persons with shellfish allergies who take glucosamine.³³ There also have been no significant supplement-drug interactions involving glucosamine. In one case report, the addition of glucosamine sulfate to a stable-dose regimen of warfarin (Coumadin) appeared to magnify the anticoagulant effects of warfarin in a 69-year-old man.³⁴ Only one person has been reported to have had an allergic reaction to oral glucosamine.³⁵

In a large open trial (n = 1,208), the most common adverse effects of oral glucosamine sulfate (1.5 g daily) were epigastric pain or tenderness (3.5 percent), heartburn (2.7 percent), diarrhea (2.5 percent), and nausea (1 percent).³⁶ There was a single case report of a glucosamine-chondroitin sulfate compound triggering difficulty walking and climbing steps because of shortness of

Table 1. Key Points About Glucosamine

Effectiveness

Osteoarthritis of the knee: controversial, probably effective
 Pain in rheumatoid arthritis: limited data, possibly effective

Adverse effects

Common: epigastric pain or tenderness, heartburn, diarrhea, nausea
 Severe or rare: potential hypersensitivity (theoretical)

Interactions

Diabetes medications: reduced effectiveness (theoretical)
 Warfarin (Coumadin): increased anticoagulation effect

Contraindications*

Allergy to shellfish
 Asthma
 Use of warfarin or diabetes medications

Dosage

500 mg orally three times daily

Cost†

\$9 to \$35 for one-month supply

Bottom line

Already widely in use
 No clear clinical data for or against use in the indicated conditions, but reasonable to discuss or support a 60-day trial of glucosamine sulfate, especially in patients at high risk of secondary effects from other accepted treatments

*—Use glucosamine with caution in patients with these contraindications.

†—Average retail cost (rounded to the nearest dollar) based on a search of common Internet vitamin stores, including <http://www.vitacost.com> and <http://www.vitaminshoppe.com>. Product quality may vary.

diabetes monitor their blood glucose levels more often when taking glucosamine.³⁹ Scientific evidence for the safe use of glucosamine during pregnancy is not available.

Dosage

Glucosamine is supplied in tablets and capsules. The usual dosing schedule is 500 mg three times daily. In 2001, *Consumer Reports* evaluated 19 products and reported that most brands were reasonably well standardized, delivering at least 90 percent of the amount of glucosamine or chondroitin promised on the label. Only four products failed to meet that standard.⁴⁰ In 2001, one company recalled two products that were found to contain aristolochic acid, a substance that can cause kidney toxicity and cancer.⁴¹ Retail prices for a 30-day supply of glucosamine range from \$9 to \$35 (product quality may vary).³

Bottom Line

The use of glucosamine is widespread in the United States. Physicians should be encouraged to have open discussions with patients, as well as inform them about the controversy regarding the supplement's effectiveness. Because of glucosamine's potential for benefit, there is no reason to recommend against its use, especially in persons at high risk of secondary effects from other accepted treatments.

In trials that have found benefit with glucosamine, most focused on the glucosamine sulfate preparation, and most showed improvements after 30 to 90 days of therapy. Therefore, it would be reasonable to support a 60-day trial of glucosamine sulfate. The decision to continue therapy can then be left to patients on an individual basis, while the physician monitors for possible adverse effects. Caution is advised in patients with shellfish allergies or asthma, and in those taking diabetes medications or warfarin. If a patient chooses to try glucosamine therapy, the physician should recommend glucosamine sulfate (from a reputable source) in a dosage of 500 mg orally three times daily. Key points about glucosamine are summarized in *Table 1*.

breath in a 52-year-old woman with long-standing intermittent asthma.³⁷ Finally, it has been hypothesized that glucosamine is associated with reducing the effectiveness of diabetes medications.³⁸ To date, this has been refuted, and the use of glucosamine in patients with diabetes has not been shown to affect insulin sensitivity or induce insulin resistance. Nonetheless, the Arthritis Foundation recommends that patients with

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