

Dietary Supplements for Osteoarthritis

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A large number of dietary supplements are promoted to patients with osteoarthritis and as many as one third of those patients have used a supplement to treat their condition. Glucosamine-containing supplements are among the most commonly used products for osteoarthritis. Although the evidence is not entirely consistent, most research suggests that glucosamine sulfate can improve symptoms of pain related to osteoarthritis, as well as slow disease progression in patients with osteoarthritis of the knee. Chondroitin sulfate also appears to reduce osteoarthritis symptoms and is often combined with glucosamine, but there is no reliable evidence that the combination is more effective than either agent alone. S-adenosylmethionine may reduce pain but high costs and product quality issues limit its use. Several other supplements are promoted for treating osteoarthritis, such as methylsulfonylmethane, *Harpagophytum procumbens* (devil's claw), *Curcuma longa* (turmeric), and *Zingiber officinale* (ginger), but there is insufficient reliable evidence regarding long-term safety or effectiveness. (*Am Fam Physician*. 2008;77(2):177-184. Copyright © 2008 American Academy of Family Physicians.)

Dietary supplements, commonly referred to as natural medicines, herbal medicines, or alternative medicines, account for nearly \$20 billion in U.S. sales annually.¹ These products have a unique regulatory status that allows them to be marketed with little or no credible scientific research. Since 2000, more than 800 brand name dietary supplement formulations targeting patients with osteoarthritis have been introduced.² Although a handful of these have some evidence of long-term safety and effectiveness, most do not. Approximately 30 percent of patients with osteoarthritis have used a supplement to treat their condition.³

This article is a review of dietary supplements commonly used by patients with osteoarthritis (*Table 1*). Searches were done using evidence-based databases (*Natural Medicines Comprehensive Database* and *The Cochrane Library*) and bibliographic databases (PubMed, International Pharmaceutical Abstracts, the International Bibliographic Information on Dietary Supplements).

Glucosamine

Glucosamine is the supplement most commonly used by patients with osteoarthritis. It is an endogenous amino sugar that is required for synthesis of glycoproteins and

glycosaminoglycans, which are found in synovial fluid, ligaments, and other joint structures. Exogenous glucosamine is derived from marine exoskeletons or produced synthetically. Exogenous glucosamine may have anti-inflammatory effects and is thought to stimulate metabolism of chondrocytes.⁴

Glucosamine is available in multiple forms. The most common are glucosamine hydrochloride and glucosamine sulfate. Some products contain a blend of these, and many combine one of the forms with a variety of other ingredients.

EFFECTIVENESS

Unlike many supplements that reach the market completely untested in clinical trials, glucosamine has been the subject of considerable research. More than 20 randomized controlled trials involving over 2,500 patients have evaluated the use of glucosamine for osteoarthritis.⁵⁻⁷ Most of the research has focused on glucosamine sulfate and its role in treating osteoarthritis of the knee and hip, the two most studied and most commonly afflicted joints.

Despite extensive research, study findings have been inconsistent, possibly because of the different products and methodologies used in trials and/or issues of publication or industry bias. In 2005, a high-quality

SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>	<i>Comments</i>
Glucosamine sulfate may be used for reducing symptoms and possibly slowing disease progression in patients with osteoarthritis of the knee.	B	5-7, 11, 12	Evidence mostly positive, but with some inconsistencies
Chondroitin may provide modest benefit in some patients with osteoarthritis, but it does not appear to offer any advantage over glucosamine sulfate.	B	7, 16-19	Inconsistent evidence; analysis of all studies shows benefit, but analysis of higher-quality studies shows no benefit
S-adenosylmethionine may reduce osteoarthritis pain, but it is a less appropriate treatment option for most patients.	B	23-29	Evidence consistently shows reduced pain, but there are concerns about product quality and high cost

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 page 131 or <http://www.aafp.org/afpsort.xml>.

Table 1. Selected Supplements for Osteoarthritis

<i>Supplement</i>	<i>Typical dosage</i>	<i>Comments</i>	<i>Monthly cost*</i>
Glucosamine	1,500 mg once daily or 500 mg three times daily	Glucosamine sulfate preferred over glucosamine hydrochloride	\$9 to 35 (combination drugs appear to be in the same price range)
Chondroitin	200 to 400 mg two or three times daily	Combination chondroitin/glucosamine no better than glucosamine sulfate alone	\$10 to 25
S-adenosylmethionine	200 mg three times daily	Butanedisulfonate salt form preferred for best stability and bioavailability	\$60 to 120
Methylsulfonylmethane	500 mg three times daily to 3 g two times daily	Not recommended because of insufficient evidence	\$5 to 35
<i>Harpagophytum procumbens</i> (devil's claw)	2.4 to 2.6 g daily standardized extract	Not recommended because of insufficient long-term safety data	\$15 to 40
<i>Curcuma longa</i> (turmeric)	No typical dosage for osteoarthritis	Not recommended because of insufficient evidence	\$8 to 23 (for one tablet daily)
<i>Zingiber officinale</i> (ginger)	510 mg daily standardized extract	Not recommended because of insufficient evidence	\$2 to 3

*—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.

systematic review of glucosamine trials for osteoarthritis identified some interesting patterns in the research.⁶ The pooled data from all glucosamine trials, regardless of product type, trial quality, or assessment instrument, show that glucosamine significantly reduces pain. A previous meta-analysis found similar results.⁷

A subgroup analysis of studies shows different outcomes depending on whether the study used the Lequesne index or the Western Ontario and McMaster Universities (WOMAC) osteoarthritis index to assess outcomes. Both are validated scales for the

assessment of patients with osteoarthritis of the knee or hip. The Lequesne index assesses pain and discomfort, maximal walking distance, and activities of daily living. The WOMAC index assesses pain, stiffness, and physical disability. One pooled analysis found that studies using the Lequesne index showed benefit, whereas those using the WOMAC index did not.⁶ However, a different analysis did show improvement in outcomes when using the WOMAC index as an assessment tool.⁷

The type of glucosamine product used appears to have a significant impact on

outcomes. Many studies used a specific commercial glucosamine sulfate product called Dona. Pooled findings from these studies, regardless of the assessment scale used, suggest that this formulation significantly reduces osteoarthritis pain. Findings from studies using different formulations suggest no significant improvement.⁶

Consistent with this analysis are results of the highly-publicized Glucosamine/chondroitin Arthritis Intervention Trial, which did not use a glucosamine sulfate formulation, but rather a glucosamine hydrochloride product.⁸ The investigators found that when used alone or in combination with chondroitin, glucosamine hydrochloride does not reduce symptoms of knee osteoarthritis; however, subgroup analysis suggests that the combination does reduce pain in patients with severe symptoms. Of note, the placebo response rate in this trial was high; approximately 60 percent of patients in the placebo group had a 20 percent decrease in the WOMAC index. It would be difficult for a treatment to surpass this effect, which may also explain the negative findings of this trial.⁹

Glucosamine sulfate has been compared with acetaminophen and the nonsteroidal anti-inflammatory drugs (NSAIDs), ibuprofen (Motrin) and piroxicam (Feldene), in the treatment of osteoarthritis. These trials show that glucosamine sulfate is effective for reducing pain and improving function.^{6,10} The effect of glucosamine sulfate on joint-space narrowing has been evaluated in two studies; the results of both studies suggest that glucosamine sulfate significantly reduces knee-joint-space narrowing over three years of treatment.^{11,12} Similar long-term research using other formulations has not been conducted.

SAFETY

Glucosamine has been safely used in long-term clinical trials. Side effects from glucosamine occurred at a rate similar to that of placebo and less than that of NSAIDs.⁶

There have been concerns that glucosamine worsens glycemic control in patients with diabetes. This is based on anecdotal

evidence and animal research suggesting increased insulin resistance. However, clinical research shows that glucosamine does not increase blood glucose or A1C levels in patients with type 2 diabetes.^{13,14} Because glucosamine is derived from the exoskeleton of shellfish, there is also concern that glucosamine may cause reactions in persons who are allergic to shellfish. However, shellfish allergies are caused by antigens in the meat of the shellfish (not the shell) and there have been no reports of reactions in persons with shellfish allergies who take glucosamine.¹⁵

Glucosamine sulfate is effective for reducing osteoarthritis pain and improving function, and might have disease-modifying effects.

CLINICAL RECOMMENDATIONS

Overall, the evidence supports the use of glucosamine sulfate for modestly reducing osteoarthritis symptoms and possibly slowing disease progression. However, there is not enough evidence to recommend the use of other glucosamine formulations. Patients should be advised that they may need additional pain relief from analgesics on an as-needed basis.

Chondroitin

Chondroitin, an endogenous glycosaminoglycan, is a building block for the formation of the joint matrix structure.⁴ Chondroitin is almost always combined with other ingredients in commercial products; however, most research on chondroitin has focused on single-ingredient chondroitin sulfate preparations.

EFFECTIVENESS

Less research is available on chondroitin than on glucosamine sulfate. Also, the research findings have been inconsistent. Most early clinical trials conducted from the 1980s to 2001 show that a combination of chondroitin and conventional analgesics more effectively reduces pain compared with analgesics alone.^{7,16} Preliminary evidence also shows that long-term use of chondroitin may slow joint-space narrowing, suggesting that the supplement could also slow disease

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progression.¹⁷⁻¹⁹ Two clinical trials evaluating a specific combination product containing chondroitin, glucosamine hydrochloride, and manganese (Cosamin-DS) show that this combination reduces knee pain in patients with osteoarthritis.^{20,21} Of note, these studies used glucosamine hydrochloride and did not include a comparison with glucosamine sulfate alone.

Many of the early trials were of moderate or poor quality. The results of more recent research (published since 2005) have been negative. One analysis shows that when the results of all chondroitin studies are pooled, this supplement appears to improve symptoms of pain; however, when only higher-quality studies are pooled, chondroitin does not appear to be beneficial.²²

SAFETY

Chondroitin has been safely used and well tolerated in clinical trials. However, chondroitin is often derived from animal sources, such as bovine cartilage, which has raised questions about the possibility of contamination from animal diseases (e.g., bovine spongiform encephalopathy). Although cartilage tissue is not associated with bovine spongiform encephalopathy, there are concerns that the lack of stringent manufacturing practices in the industry could potentially result in cross-contamination with high-risk tissue types. These concerns are purely theoretical. No reports of disease transmission exist and such risks are probably low.

CLINICAL RECOMMENDATIONS

The evidence for chondroitin is inconsistent. Chondroitin does not offer an advantage over glucosamine sulfate, and there is no evidence that combining chondroitin with any formulation of glucosamine is more effective than glucosamine sulfate alone. Chondroitin also has the disadvantage of being harvested from animal sources. Although chondroitin may provide modest benefit for some patients, glucosamine sulfate is more appropriate for patients interested in trying a dietary supplement for osteoarthritis.

SAMe

S-adenosylmethionine (SAMe) is produced in the liver from methionine. SAMe appears to increase chondrocytes and cartilage thickness and may also decrease cytokine-induced chondrocyte damage.⁴ SAMe has been used to treat osteoarthritis, as well as other conditions such as depression and liver disease.

EFFECTIVENESS

Research on the use of SAMe for osteoarthritis has been consistently positive. A review and meta-analysis conducted by the Agency for Healthcare Research and Quality, as well as several randomized clinical trials, have shown that SAMe is more effective than placebo and comparable to NSAIDs in reducing osteoarthritis pain.²³⁻²⁹ In a recent trial, SAMe (1,200 mg per day) was compared with the cyclooxygenase (COX)-2 inhibitor celecoxib (Celebrex; 200 mg per day). Celecoxib was much more effective than SAMe in reducing pain during the first month of treatment; however, after two months of use, no difference in pain relief was noted between the two agents.²⁹ Although SAMe does provide pain relief, it can take several weeks of treatment before symptoms substantially improve.

SAFETY

SAMe appears to be safe and is possibly better-tolerated than NSAIDs.²³⁻²⁹ In addition to its effects on cartilage, SAMe also affects several neurotransmitters. SAMe increases serotonin turnover and may increase norepinephrine and dopamine levels; therefore, it has the potential to cause central nervous system side effects such as anxiety, headache, insomnia, and nervousness. It also has the potential to interact with other serotonergic drugs, such as antidepressants, tramadol (Ultram), and meperidine (Demerol), possibly resulting in serotonin syndrome (*Table 2*).⁴ There also have been reports of hypomania and mania in patients with depression who took SAMe.⁴

CLINICAL RECOMMENDATIONS

SAMe is an effective treatment for osteoarthritis, but it can be expensive. A one-month supply typically costs between

\$60 and \$120, which is comparable to the cost of celecoxib and higher than that of other NSAIDs or acetaminophen. Because SAME is an unstable compound, product quality is another concern; products on store shelves may contain little or none of the active ingredient. Although it is helpful to choose a SAME product that has been reviewed for quality and contents by a reputable independent company, it is still unclear how long this product remains stable on the shelf. Until these concerns have been resolved, SAME may not be a reliable alternative treatment option. If patients are interested in using SAME, the butanedisulfonate salt formulation should be recommended because it is more stable and has a higher bioavailability.⁴

MSM

Methylsulfonylmethane (MSM) is usually found in combination supplements containing glucosamine and/or chondroitin. It

occurs naturally in small amounts in some green plants, fruits and vegetables, and human adrenal glands. MSM is promoted as having anti-inflammatory and analgesic effects. Preliminary animal research suggests that it may decrease degenerative processes in joints.⁴

EFFECTIVENESS

Two preliminary clinical trials have evaluated MSM alone and in combination with glucosamine in the treatment of patients with osteoarthritis. Results show that MSM modestly reduces pain and swelling, but it does not reduce joint stiffness.^{30,31}

SAFETY

MSM has been well tolerated in clinical trials and does not appear to cause side effects more often than placebo. Clinical trials have lasted 12 weeks or less; therefore, more data are needed to assess long-term safety.

Table 2. Potential Interactions Between Supplements and Conventional Drugs

<i>Supplement</i>	<i>Potential interaction</i>	<i>Level of evidence</i>
Glucosamine	Antimitotic chemotherapy	In vitro
Chondroitin	Warfarin (Coumadin)*	Case report
S-adenosylmethionine	Serotonergic drugs (e.g., antidepressants, dextromethorphan [Delsym], meperidine [Demerol], tramadol [Ultram])	Case reports
	Levodopa (Larodopa; brand not available in the United States)†	Theoretical
	Monoamine oxidase inhibitors	Theoretical
Methylsulfonylmethane	None (known or suspected)	—
<i>Harpagophytum procumbens</i> (devil's claw)	Antihypertensive drugs	Theoretical
	Cytochrome P450 substrates	In vitro
	Hypoglycemic drugs	Theoretical
	Warfarin	Case report
<i>Curcuma longa</i> (turmeric)	Antiplatelet/anticoagulant drugs	Theoretical
<i>Zingiber officinale</i> (ginger)	Antiplatelet/anticoagulant drugs	Theoretical
	Calcium channel blockers	Theoretical
	Hypoglycemic drugs	Theoretical
	Warfarin	Case report

*—Case involved very high dosages of chondroitin/glucosamine combination product. There is no evidence that typical dosages of chondroitin cause this potential interaction.

†—Levodopa is only available in the United States as a combination drug product (e.g., carbidopa/levodopa [Sinemet]).

Information from reference 4.

CLINICAL RECOMMENDATION

MSM was popular for treating osteoarthritis, even before any clinical trials were published. Based on limited research, MSM modestly reduces some osteoarthritis symptoms but, because these trials have been short term and there is no reliable evidence of long-term safety, MSM should not be recommended to treat osteoarthritis.

Other Products

DEVIL'S CLAW

Harpagophytum procumbens (devil's claw) is an African plant that gets its name from the "claws" found on the fruit. The tuber is what is used for medicinal purposes. The pharmacologic activity of devil's claw is attributed to iridoid glycosides, particularly harpagoside. Some products are standardized to contain a specific amount of these components.⁴

Devil's claw is thought to have anti-inflammatory effects, possibly because of inhibition of COX and lipoxygenase; however, it appears to inhibit COX-2, but not COX-1.⁴ Three moderate- to high-quality clinical trials have evaluated devil's claw extracts standardized to contain 2.0% to 2.5% harpagoside. These extracts taken alone or in combination with an NSAID decrease symptoms of osteoarthritis pain and are well tolerated.³²⁻³⁵ Devil's claw can cause side effects including diarrhea, abdominal pain, and skin reactions. In one trial, purpura was reported in a patient on warfarin (Coumadin).⁴ Although devil's claw seems promising, more evidence on effectiveness and long-term safety is needed before it can be recommended.

TURMERIC

Curcuma longa (turmeric) is a spice commonly used in curry powders. The pharmacologically active constituent is curcumin, a pigment that gives the yellow color to some mustards, broth, and other foods. Curcumin appears to have anti-inflammatory effects because of inhibition of COX-2, prostaglandins, and leukotrienes.⁴ Clinical trials have not evaluated the effectiveness of turmeric for osteoarthritis; however, some preliminary clinical research suggests that

it may improve symptoms of rheumatoid arthritis.³⁶ Turmeric is safe when consumed as a spice in foods, and it also appears to be safe and well tolerated when used in the short term for medicinal purposes.⁴ However, until there is reliable clinical evidence, turmeric is not recommended for osteoarthritis.

GINGER

Zingiber officinale (ginger) is best known as a soothing remedy for motion or morning sickness. It is also used for rheumatic conditions such as osteoarthritis and rheumatoid arthritis. Ginger may have anti-inflammatory effects by inhibiting COX and lipoxygenase. It may also affect tumor necrosis factor and decrease synthesis of inflammatory prostaglandins.⁴ Two manufacturer-sponsored trials have evaluated specific ginger extracts called Eurovita Extract 33 and Eurovita Extract 77. Taking these extracts for three to six weeks appears to provide no relief to modest improvement in osteoarthritis pain after standing or walking.^{37,38} Ginger is safe and has been well tolerated in clinical trials; however, there is not enough evidence to support recommending ginger for the treatment of osteoarthritis.

This is one in a series of "Clinical Pharmacology" articles coordinated by Allen F. Shaughnessy, PharmD, Tufts University Family Medicine Residency at Cambridge Health Alliance, Malden, Mass.

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Author disclosure: Nothing to disclose.

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