



Osteoarthritis Supplements: Glucosamine, Chondroitin Sulfate, and Methylsulfonylmethane (MSM)

Glucosamine sulfate, chondroitin sulfate, and methylsulfonylmethane (MSM) are alternative therapies used in the treatment of osteoarthritis. In this protocol, the proper uses of these substances are discussed, their doses, adverse effects, contraindications, and interactions with other medications. Research investigating the properties and effectiveness of glucosamine sulfate and chondroitin sulfate is substantial compared to other alternative therapies, but is not as extensive as for most prescription medications. MSM research is even more limited. Therefore, some conclusions regarding any of these supplements must be considered preliminary.

Bottom Line

Glucosamine sulfate (GS) has generally been shown to be moderately effective for reducing symptoms and slowing the progression of osteoarthritis, primarily of the knee, and may help postpone joint replacement surgery. GS produced by Rotta Pharmaceutical Company (Dona[®]) may be superior to other similar products. Glucosamine hydrochloride appears not to be effective.

Chondroitin sulfate (CS) has been shown effective for reducing symptoms and slowing progression of osteoarthritis. Comparisons to the evidence for glucosamine have resulted in disparate opinions of whether one is superior or has more consistent or high quality evidence to the other. Formal comparison trials between glucosamine sulfate and CS are needed, but have yet to be done.

Use of these supplements may be able to reduce a patient's dependence on NSAIDs (Morelli 2003, Towheed 2005).

Either GS or CS would be a rational choice for first line dietary supplement therapy for patients with OA of the knees, and perhaps other hyaline cartilage joints. GS/CS combinations are another option, but the much more prevalent GHCl/CS combinations seem to be no better choices than CS alone. There is no research yet that GS, CS or their combination might be helpful for preventing osteoarthritis, or for treating other joint conditions such as traumatic sprains.

In summary, three small trials of variable quality found some benefits of MSM for treating osteoarthritis, but the evidence is weak compared to research supporting GS and CS.

Morelli V, Naquin C, Weaver, V Alternative therapies for traditonal disease states: osteoarthritis. Am Fam Physician 2003; 67(2):339-44.

Towheed T, Maxwel L, Anastassiades T, et al. Glucosamine therapy for treating osteoarthritis. Cochrane Database of Systematic Reviews 2005.

Supplement	Dose	Side effects/Precautions
Glucosamine sulfate	1500 mg/day, all at once or in 2-3 divided doses	<ul style="list-style-type: none"> ▫ Possible allergic reaction in cases of shellfish allergy (not with synthetic glucosamine sulfate products) ▫ Possible mild gastrointestinal upset ▫ Monitor diabetics for impairment of blood glucose control
Chondroitin sulfate	800-1200 mg/day, all at once or in 2-3 divided doses	None for indicated doses
Methylsulfonylmethane	1500-6000 mg/day	None for indicated doses

BACKGROUND

Osteoarthritis is a common degenerative joint disease, affecting about 12% of the general population, with a higher incidence among women and the elderly.¹ Standard conservative management of this condition includes education and self-care, weight control, exercise therapy, physical and occupational therapies, and pain control medication.^{2 3 4 5} Chiropractors also usually include joint manipulation in their therapeutic approach to osteoarthritis and many also give nutritional advice and recommend nutritional supplements.

While non-steroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed for osteoarthritis pain, these drugs are known to have adverse effects on articular^{6 7 8 9 10} and non-articular^{11 12} tissues (See CSPE protocol, [NSAIDs](#)). The search for safer alternatives to standard pain control medication has led to interest in the therapeutic effects of certain substances that are precursor molecules in the formation of proteoglycans by chondrocytes. Most research has investigated the usefulness of two proteoglycan precursors: glucosamine or chondroitin sulfate. Limited research has investigated methylsulfonylmethane, a substance that may facilitate proteoglycan synthesis.

Glucosamine

Sources and preparations. Glucosamine is either derived from chitin (an abundant component of the exoskeleton of shrimp, crab, and lobster) or synthesized from simple precursors.¹³

Glucosamine sulfate (GS) is the form used in most human clinical research; other forms include glucosamine HCl and N-acetyl glucosamine. GS is typically stabilized with

either sodium chloride or potassium chloride. Single ingredient glucosamine supplements typically contain 500-1000 mg per tablet/capsule.

Absorption and metabolism. Glucosamine is readily absorbed from the intestine, but undergoes significant catabolism in the liver, resulting in about 26% bioavailability of an oral dose.¹⁴ Oral supplements of GS and glucosamine hydrochloride appear to produce higher blood levels than does oral N-acetyl-glucosamine.¹⁵

In vitro studies have suggested that glucosamine stimulates proteoglycan synthesis,^{16 17} and animal studies document limited anti-inflammatory effects but no analgesic effects.¹⁸

Clinical effectiveness. Virtually all clinical research on glucosamine has addressed its effectiveness in degenerative joint conditions, primarily osteoarthritis of the knee. No investigations have been done of potential applications such as prevention of joint disease or treatment of musculoskeletal trauma. Most research has evaluated GS stabilized with NaCl rather than other glucosamine preparations.

Numerous controlled studies have reported that oral GS improves knee osteoarthritis symptoms significantly better than placebo^{19 20 21 22 23} or comparably to the effects of moderate doses of NSAIDs.^{24 25 26 27 28} Some recent randomized controlled trials (RCTs) have reported no significant improvement from GS supplementation in osteoarthritis patients.^{29 30 31 32 33} Methodologies in some of these trials differed from those in previous trials. Subjects in one tended to be older, heavier, and had more long-standing and severe disease. Another trial focused solely on hip osteoarthritis, which may

not respond as well to GS. Two trials allowed the continued use of traditional pain medications, which might have blunted or masked a beneficial affect of GS. All of these trials used GS products other than the European prescription formula patented by Rotta Pharmaceutical Company, which is the only product available stabilized with sodium chloride rather than another salt. While it is difficult to conceive of a reason why sodium chloride might be an important ingredient, studies of the Rotta preparation have yielded very consistent positive results. The Rotta preparation is available in North America under the brand name Dona[®].³⁴

The usefulness of GS for low back pain associated with osteoarthritis is controversial. A double blind RCT conducted for six months found 1500 mg/day GS to be no more beneficial than placebo for patients with MRI- confirmed degenerative lumbar osteoarthritis.³⁵ However, the majority of subjects used concomitant therapies, including medication, physical therapies, and chiropractic, and both placebo and GS groups achieved 46-48% reductions in pain-related disability, improvements that persisted for six months after the intervention. Earlier double blind trials have shown improvement in some pain and function measures in patients with spinal osteoarthritis treated with 1500 mg/day GS.^{36 37} Future research may clarify the role of GS in the management of spinal osteoarthritis.

Some studies have evaluated glucosamine HCl (GHCl) instead of GS, with generally poor results. One RCT found no significant benefit of 1500 mg/day GHCl for eight weeks in patients with osteoarthritis of the knee who were taking up to 4000 mg/day of acetaminophen.³⁸ GHCl was one of four treatments that failed to show effectiveness superior to placebo against OA in the recent large trial sponsored by the National Institutes of Health.³⁹ Two small studies reported more encouraging results. An Australian trial found 2000 mg/day of GHCl improved subjective but not objective measures of pain and function in middle-aged adults with undiagnosed knee pain.⁴⁰ A short-term Chinese trial lacking a placebo control reported that GHCl was as effective as GS.⁴¹ All in all, the evidence supporting GHCl as a suitable alternative to GS seems considerably weak. Some authors have postulated that sulfate may play an active part of the therapeutic effectiveness of

GS.⁴² N-acetyl glucosamine (NAG) has not been studied in patients with osteoarthritis except in one trial of ten patients that did not include a control group.⁴³

A meta-analysis in 2000⁴⁴ identified five RCTs of acceptable design quality that tested oral GS therapy for osteoarthritis. All of these studies reported significant positive benefits of GS compared to placebo, and this analysis characterized the effect size for GS efficacy versus placebo as “moderate.” According to Natural Standard, an evidence-based database, the Number Needed to Treat (NNT) calculated from this meta-analysis was 3.⁴⁵ NNT calculated by Natural Standard from individual studies of glucosamine sulfate for osteoarthritis range from 2 to 11. A 2003 meta-analysis of seven glucosamine sulfate studies reported effect sizes of 0.30-0.49 (considered low to moderate), and a NNT of 4.9.⁴⁶

The Cochrane Collaboration has published systematic reviews of glucosamine for osteoarthritis therapy in 2001⁴⁷ and in 2005 (updated online in 2008).⁴⁸ One shortcoming of these meta-analyses was that data from studies using GHCl were combined with those from GS studies, as were studies using parenteral administration of glucosamine. The most recent update included 25 studies and concluded that glucosamine was superior to placebo for reducing pain (by 22%) and for improving function according to one instrument (by 11%), but not when another instrument was used to assess function. These magnitudes of benefits are lower than reported in other reviews, possibly due to dilution from including GHCl studies, which represented over one-third of patients included in the analysis. The Cochrane reviewers further determined that pooled results from studies using the Rotta preparation reported more consistent and significant results than pooled results of studies using non-Rotta preparations (which include both GS and GHCl formulations).

Some GS trials have lasted long enough to assess subjects for long-term objective measures of osteoarthritis progress. The first was a three-year study using a single daily dose of 1500 mg GS.⁴⁹ GS treatment resulted in 24% reduction of symptoms after three years (while symptoms worsened by 10% with placebo), and radiographic knee changes indicating deterioration were seen only in the placebo group. No significant side

effects, including blood sugar changes (see below), were reported in the GS group. A second three-year trial confirmed these findings.⁵⁰ In 2005, a systematic review of trials lasting at least one year reported that the risk of disease progression was reduced 54% by GS compared to placebo, with concomitant improvements in pain reduction and physical function of 41% and 46% respectively.⁵¹ Subsequent systematic reviews reached similar conclusions.⁵²

Recently, data on subjects who had participated in the two three-year trials described above were pooled after an additional five years to determine whether glucosamine sulfate altered the need for total joint replacement surgery.⁵³ Although 16% of subjects were lost to follow-up, analysis of available data showed that total knee replacement had occurred in over twice as many patients from the placebo group (P = 0.024), despite initially having similar disease severity, joint space width, age, and body mass index at baseline compared to the group receiving glucosamine sulfate. The authors calculated a NNT of 12 to avoid one knee replacement.

Glucosamine Summary

In summary, glucosamine sulfate has generally been shown to be moderately effective for reducing symptoms and slowing the progression of osteoarthritis, primarily of the knee, and may help postpone joint replacement surgery. One review, along with the Natural Standard data base and Natural Medicines Comprehensive Database, have given GS an evidence rating of A for treating osteoarthritis of the knee.^{54 55} (See the Appendix for their rating systems). GS produced by Rotta Pharmaceutical Company may be superior to other similar products.

Glucosamine hydrochloride appears not to be effective. In the case, of degenerative lumbar osteoarthritis, no benefits above placebo have been reported.³⁵

Dosage considerations. Virtually every clinical trial investigating oral glucosamine has used a regimen of 1500 mg either once daily or in divided doses. Some reviewers have suggested that once daily dosing may result in higher plasma levels and greater effectiveness.⁵⁶ Whether lower amounts than 1500 mg daily might be effective or whether larger amounts might produce better results is unknown.

Adverse effects, contraindications and interactions. Adverse effects reported in clinical trials of glucosamine have been limited to mild reversible gastrointestinal symptoms, such as nausea or constipation, but often no more than in the placebo groups. One study reported that patients with peptic ulcers and those taking diuretics were more likely to experience side effects.⁵⁷ Animal research has suggested that intravenous glucosamine can impair insulin secretion⁵⁸ and/or increase insulin resistance.⁵⁹ However, several human studies employing a total of over 3000 subjects have found no adverse effects on glucose metabolism, even among diabetics,^{61 62} and one evidence-based review gave a Strength of Recommendation (SOR) grade of A for glucosamine safety among patients with well-controlled diabetes.⁶³ Nonetheless, it may be prudent to ensure regular monitoring of glucose control in diabetics who begin a regimen of glucosamine supplementation.

While patients with shellfish allergy might be considered susceptible to reactions from chitin-derived glucosamine, only one case of confirmed allergic reaction to glucosamine has been reported.⁶⁴ Patients with known shellfish allergies should be told about the possibility of antigen contamination of some glucosamine products. If desired, suppliers may be contacted to locate a source of synthetic glucosamine, or chondroitin sulfate may be offered as a substitute. Patients who have been told they are allergic to sulfa drugs may believe this means they should avoid dietary supplements containing sulfate. They should be reassured that the sulfur in sulfa drugs is not the cause of allergic reactions to that drug, and that sulfate is a normal component of many body tissues.

Quality issues. In the past, some commercial over-the-counter GS products have been found to vary in content compared to label claims,^{65 66 67} but a more recent survey of 38 retail products found no problems with glucosamine content.⁶⁹ However, the same survey found four products that exceeded California limits on lead content in supplements, and one tablet product that failed to break apart properly. Supplements distributed directly to health professionals are not included in most of these surveys, so professional suppliers should be asked to provide independent proof of labeled content and purity.

Chondroitin Sulfate

Sources and preparations. Chondroitin sulfate is typically derived from bovine tracheal cartilage or shark cartilage. Bovine tracheal cartilage is the form used in most human clinical research. Single ingredient chondroitin sulfate supplements typically contain 100-500 mg per tablet/capsule. More typically, chondroitin sulfate is combined with glucosamine and/or MSM.

Absorption and metabolism. The bioavailability of oral chondroitin sulfate in humans has been reported to be about 12%,⁷⁰ although CS appears to be better absorbed if the powder is consumed after dissolving it in water. Some animal research⁷¹ and one human study⁷² has failed to document significant absorption of intact CS, suggesting that the numerous documented positive clinical results for CS may depend upon the activity of absorbed digestive breakdown products of supplemental CS.

In vitro studies have demonstrated that CS stimulates proteoglycan production in human articular chondrocytes⁷³ as well as animal tissues.⁷⁴

Clinical effectiveness. Most clinical research on CS has addressed its effectiveness in degenerative joint conditions, primarily osteoarthritis of the knee and/or hip. No investigations have been done of other potential applications (prevention of joint disease, treatment of musculoskeletal trauma) of oral CS.

Numerous RCTs have reported that oral CS is significantly better than placebo for alleviating symptoms and clinical signs of osteoarthritis.^{75 76 77 78 79 80 81 82 83 84} One RCT showed CS was comparable in effectiveness to moderate doses of non-steroidal anti-inflammatory drugs.⁸⁵ Several CS trials permitted concomitant use of analgesic drugs. These trials not only found CS effective even when added to analgesic therapy, but many reported significant reductions in analgesic use by subjects taking CS. A 2004 trial demonstrated that CS could be effective even when taken intermittently, three months on and three off.⁸⁶ Finally, several CS trials found objective evidence of disease stabilization based upon either x-ray evidence of erosive changes, joint space width,^{87 88 89} or echographic

measurement of cartilage thickness. Negative trials of CS alone are limited to another arm of the NIH-sponsored study discussed elsewhere in this document that suffered from an exceptionally large placebo effect and a French trial with a large dropout rate in which trends for CS effectiveness over placebo did not reach statistical significance.⁹⁰ In a meta-analysis of seven trials published in 2000, the proportion of subjects who responded to CS was calculated to be 55-65% and average symptom reduction ranged from 49-58% in CS studies.⁹¹ Another meta-analysis of six GS and nine CS studies calculated a “large” effect size for CS versus placebo while the effect size for GS was characterized as “moderate.” A third meta-analysis in 2003 that included newer trials found both GS and CS equally effective for symptomatic relief, and reported effect sizes of 0.30-0.49 (considered small to moderate), and a NNT of 4.9. The most recent meta-analysis of CS trials judged most trials not to be of sufficient quality and combined the results of only three trials, concluding that CS was of minimal or nonexistent benefit.⁹² These disparate conclusions were reviewed in 2008, the authors concluding that CS “has a slight to moderate efficacy in the symptomatic treatment of OA, with an excellent safety profile.”⁹³

The overall evidence for the impact of CS on progression of osteoarthritis has also received attention in systematic reviews. A meta-analysis in 2003 found no studies of sufficient quality to include, but two meta-analyses were published in 2008 and 2009, both of which accepted four trials for analysis, and concluded that CS had a small protective effect (effect size = 0.26) against progression of joint space narrowing in the knee.^{94 95}

Chondroitin Sulfate Summary

In summary, chondroitin sulfate (CS) has been shown effective for reducing symptoms and slowing progression of osteoarthritis. Comparisons to the evidence for glucosamine have resulted in disparate opinions of whether one is superior or has more consistent or high quality evidence to the other. Formal comparison trials between glucosamine sulfate and CS are needed, but have yet to be done. The Natural Medicines Comprehensive Database and Natural Standards database have given CS an

evidence rating of either A or B for treating osteoarthritis.⁹⁶

Dosage considerations. While most RCTs used 1200 mg/day of CS, usually in three divided doses, positive results have been reported in studies using only 800 mg/day, divided most often into two doses. There is no evidence for the effectiveness of CS in daily doses below 800 mg. In all but one trial, bovine tracheal cartilage was the source material used for CS therapy.

Adverse effects, contraindications and interactions. Nausea has been reported from CS intakes over 10 grams per day, but more typical amounts used in clinical research have not been reported to cause adverse effects. No allergic reactions to chondroitin sulfate have been reported.

Quality issues. There has been concern over the quality of CS supplements similar to that of glucosamine.^{65 66 67} Unlike glucosamine, however, recent surveys have continued to find products mislabeled for CS content. Again, professional suppliers should be asked to provide proof of labeled content. ConsumerLab, approved the following CS products, some of which also contain GS:

- LifeExtension Chondroitin Sulfate Concentrate 400 mg
- NOW® Chondroitin Sulfate 600 mg
- 21st Century Triple Strength Glucosamine 750 mg Chondroitin 600 mg
- Finest Natural Glucosamine Chondroitin (Walgreens brand)
- SISU Glucosamine and Chondroitin Sulfate
- Solgar Extra Strength Glucosamine Chondroitin Complex
- NSI Glucosamine, Chondroitin and MSM
- Swanson Health Products Glucosamine, Chondroitin & MSM
- The Vitamin Shoppe Joint Solutions Triple Strength Glucosamine and Chondroitin with MSM

Glucosamine/ Chondroitin Sulfate Combinations

Products containing both glucosamine (usually in the GHCl form) and CS are quite popular, owing to recommendations made in a bestselling arthritis book in 1997.⁹⁷ However, such combinations have never been compared to using one or the other by itself until quite recently.

Several trials have compared such combinations favorably to placebo,^{98 99 100 101} but since either GS or CS alone can produce similar results, these studies prove nothing about the superiority of combinations over single ingredient products. The long-awaited NIH-sponsored clinical trial compared four regimens to placebo: glucosamine HCl, chondroitin sulfate, a GHCl/CS combination, and the Cox-2 inhibiting drug celecoxib. Remarkably, placebo produced a significant response in over 60% of subjects. All of the therapies produced higher response rates, but the effects of the GHCl, CS, and GHCl/CS combination were quite similar and only celecoxib achieved a statistically significant benefit over the large placebo effect. In a subgroup that began the study in more severe pain, the GHCl/CS combination did achieve a significantly higher response rate than placebo. A more recent study comparing a GHCl/CS combination to placebo found no overall benefit, but reported that, compared to less compliant subjects, more compliant subjects in the treatment group, but not the placebo group, achieved significant reduced pain and higher mobility. A single RCT tested a topical cream containing glucosamine sulfate and chondroitin sulfate, and reported significant pain relief compared to placebo; however, the cream also contained camphor, a topical agent with known analgesic effects.¹⁰² No trial has evaluated an oral combination of GS and CS.

Further Considerations

Therapeutic options. Both glucosamine sulfate and bovine trachea-derived chondroitin sulfate have repeatedly demonstrated effectiveness in relieving symptoms of OA, primarily of the knees.

Evidence for the effectiveness of these supplements in spinal degenerative joint disease is limited to a single positive controlled trial of GS versus placebo reported in abstract form which, unfortunately, omits details that would help evaluate the quality of the study.¹⁰³ The researchers reported significant improvement in range of motion and pain ratings, but not in other outcome measures.

Either GS or CS would be a rational choice for first line dietary supplement therapy for patients with OA of the knees, and perhaps other hyaline cartilage joints. GS/CS combinations are another

option, but the much more prevalent GHCl/CS combinations seem to be no better choices than CS alone.

It is tempting to speculate that GS, CS or their combination might be helpful for preventing osteoarthritis, or for treating other joint conditions such as traumatic sprains. However, there is no research yet that has investigated these possibilities.

Relative cost and labeling issues. GS products are less expensive than CS products on the basis of monthly costs for dosages of documented effectiveness. (Table 1) Furthermore, the labeling of GS content in milligrams per tablet/capsule is universally straightforward in GS products, while CS-containing products are sometimes unclear as to the actual content of chondroitin sulfates.

Impact on overall management. Patient response to either GS or CS typically takes up to four weeks, and longer may be required for the full effects to be seen. For this reason, other symptom control measures may be needed during the initial weeks of GS or CS therapy.

Patients should be informed that GS or CS will not act immediately on their symptoms, and must be taken for 6-12 weeks to evaluate whether it is helping. Patients should also know that if GS or CS provides relief, such relief will only last as long as they are willing to continue regular supplementation.

Methylsulfonylmethane (MSM)

Sources and preparations.

Methylsulfonylmethane (MSM) is an organic sulfur compound found throughout nature. Precursors are formed initially by ocean plankton, which are released into atmosphere, interact with ozone and sunlight, and returns to earth as MSM in rainfall. MSM in soil and water is readily taken up by plants and incorporated into their structure, and traces of MSM are detectable in food and in the blood, urine and milk of normal humans.¹⁰⁴

¹⁰⁵ ¹⁰⁶ For use in supplements, MSM is synthetically manufactured.

Biological basis, absorption and metabolism. MSM is proposed for use in osteoarthritis therapy primarily for its sulfur content, in recognition of the high concentrations of sulfur present in

normal human connective tissue.¹⁰⁷ Animal studies have shown that sulfur from MSM has good bioavailability, is incorporated into critical tissue sulfur pools.¹⁰⁸ Sulfur participates in disulfide bridges, which are responsible for the maintenance of the physical configuration of proteins, and is required for the production of sulfated cartilage components that adds more water-holding ability to connective tissue, increasing the cushioning effect in articular tissues.¹⁰⁹ Tissue deficiency of sulfur groups is a characteristic of many arthritides and connective tissue disorders, including osteoarthritis.¹¹⁰ ¹¹¹

¹¹² Additional proposed mechanisms for the clinical utility of MSM are anti-inflammatory and antioxidant effects demonstrated *in vitro*¹¹³ ¹¹⁴ and in one animal study.¹¹⁵

Research on the uses of MSM in preventing and treating disease in humans is still in the preliminary stages. However, its parent compound, dimethylsulfoxide (DMSO), has been investigated for many decades as a topical anti-inflammatory and analgesic agent in the treatment of musculoskeletal disease.¹¹⁶ ¹¹⁷ ¹¹⁸ Topical DMSO has been shown in placebo-controlled studies to relieve the pain of osteoarthritis,¹¹⁹ tendinitis,¹²⁰ ¹²¹ and reflex sympathetic dystrophy.¹²² However, research on the use of topical DMSO for osteoarthritis symptoms has been criticized for poor methodology and inconsistent effectiveness.

Clinical effectiveness. Animal studies have reported reduced inflammation and joint deterioration in arthritic mice given MSM.¹²³ ¹²⁴

¹²⁵ Anecdotal reports exist as well of positive results in humans with degenerative joint disease treated with MSM.¹²⁶ To date only three clinical trials have been reported. A brief report¹²⁷ described a small controlled trial in 1998 comparing the effects of 2250 mg/day of MSM to placebo in a randomized, double blind study of only 16 patients, aged 55-78 years old, with osteoarthritis of the spine, knee, hip, and/or shoulder. Outcome pain measurements were determined by visual analogue scale (VAS) after four and six weeks. MSM treatment resulted in pain reduction by 60% and 82% after four and six weeks respectively, while corresponding reductions in the placebo group were reported to be 20% and 18% respectively. No statistical analysis of these results were included in the report.

A randomized, controlled study¹²⁸ in India recruited 118 subjects with DJD of the knee, but divided these into four groups in order to test three supplement combinations versus placebo. One group of 27 subjects received 1500 mg/day MSM. Out of several outcome measures, only improvement in pain and swelling was reported to be superior to placebo. Interestingly, a group receiving both MSM and 1500 mg/day of glucosamine sulfate achieved better improvements in pain, swelling, and function than groups taking only MSM or glucosamine sulfate, suggesting that this combination may be more helpful.

A third small RCT¹²⁹ conducted at a naturopathic college in Arizona is the highest quality of the three clinical trials of MSM to date.¹³⁰ Fifty subjects with knee osteoarthritis were treated with either 6000 mg/day MSM or placebo for 12 weeks. Pain and function were improved by MSM compared to placebo, but stiffness and overall improvement were not better than placebo. Moreover, the size of the statistically significant benefits was challenged for being modest and not necessarily clinically relevant.

MSM Summary

In summary, three small trials of variable quality found some benefits of MSM for treating osteoarthritis, but the evidence is weak compared to research supporting GS and CS.

Dosage considerations. 1500-6000 mg/day is the range of dosages tested in clinical trials. There is no evidence from the limited research that higher amounts in this range are more effective.

Adverse effects, contraindications and interactions. Animal studies have found MSM to have a very low potential for toxicity^{131 132} In the short-term (12 weeks) clinical trials described above, up to 6000 mg/day was used without serious side effects. Diarrhea, skin rash, headache, or fatigue was reported in similar numbers in either treatment or placebo groups.

Quality issues. Of 20 products containing MSM evaluated by ConsumerLab.com, none were found to have problems with the accuracy of claimed amounts or with contamination.¹³³

Conclusions

The evidence for the effectiveness of glucosamine sulfate (1500 mg/day) and bovine trachea-derived chondroitin sulfate (800-1200 mg/day) is similarly positive, and far stronger than research supporting either glucosamine HCl and shark-derived CS, or MSM. Only GS and bovine CS trials have demonstrated reduced analgesic requirements or long-term protection against OA progression, which suggests that very long-term supplementation may be preferable. OA of the knee has been studied far more than other skeletal sites, and while other hyaline cartilage joints may be good candidates for GS or CS therapy, more research is needed to confirm this. At this time, there is no evidence to support the preferential use of more expensive GS/CS combinations (Table 1). The weak research supporting MSM suggests it should not be considered a suitable substitute for either GS or CS.

TABLE 1. Cost Comparison of 30-Day Supply of High Quality¹ Glucosamine Sulfate (GS), Chondroitin Sulfate (CS), and Combination (GS/CS) Products (based on cost survey in June 2010)

Ingredients	GS, 1500 mg/day	CS, 800 –1200 mg/day	GS/CS, 1500 mg/ 800 –1200 mg/day
GS KCl	\$5-\$21		
GS NaCl (Dona [®]) ²	\$20-\$30		
CS only		\$8-\$24.00	
CS + GS KCl			\$9-\$15
CS + GS KCl + MSM			\$11-\$20

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¹ As verified from independent laboratory analysis or use in clinical trials

² This patented formula used in European clinical trials is stabilized with NaCl; all other GS products are stabilized with KCl

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APPENDIX: Rating Systems

Natural Medicines Comprehensive Database

A = EFFECTIVE

This product has a very high level of reliable clinical evidence supporting its use for a specific indication. Products rated Effective are generally considered appropriate to recommend. To achieve this Effectiveness Rating a product is supported by all of the following:

- Evidence consistent with or equivalent to passing a review by the Food and Drug Administration (FDA), Health Canada, or similarly rigorous approval process.
- Evidence from multiple (2+) randomized clinical trials or meta-analysis including several hundred to several thousand patients (level of evidence = A).
- Studies have a low risk of bias and high level of validity by meeting stringent assessment criteria (quality rating = A).
- Evidence consistently shows POSITIVE outcomes for a given indication without valid evidence to the contrary.

B = LIKELY EFFECTIVE

This product has a very high level of reliable clinical evidence supporting its use for a specific indication. Products rated “Likely Effective” are generally considered appropriate to recommend.

Natural Standard

A = Statistically significant evidence of benefit from >2 properly randomized trials (RCTs), OR evidence from one properly conducted RCT AND one properly conducted meta-analysis, OR evidence from multiple RCTs with a clear majority of the properly conducted trials showing statistically significant evidence of benefit AND with supporting evidence in basic science, animal studies, or theory.

B = Statistically significant evidence of benefit from 1-2 properly randomized trials, OR evidence of benefit from >1 properly conducted meta-analysis OR evidence of benefit from >1 cohort/case-control/non-randomized trials AND with supporting evidence in basic science, animal studies, or theory. This grade applies to situations in which a well designed randomized controlled trial reports negative results but stands in contrast to the positive efficacy results of multiple other less well designed trials or a well designed meta-analysis, while awaiting confirmatory evidence from an additional well designed randomized controlled trial.

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