

# GLUCOSAMINE SULFATE AND ARTHRITIS: THE SCIENTIFIC EVIDENCE

Written by Dr. James Meschino, D.C., M.S., -- Research and Clinical Director, RenaiSanté Institute of Integrative Medicine

## Introduction

Osteoarthritis has been reported to affect 40 million Americans, with 80% of individuals over the age of fifty affected to some degree.<sup>(1)</sup> Essentially, osteoarthritis is considered to be an age-related affliction. As a contributing factor to the development of osteoarthritis, is the apparent age-related decline in glucosamine sulfate synthesis by the body, which appears to become pronounced by 45 to 50 years of age.<sup>(2)</sup> Glucosamine sulfate is normally synthesized by chondrocytes and serves as the precursor to the production of N-acetyl-glucosamine sulfate and N-acetyl-galactosamine sulfate, which are essential components of the ground substance material (glycosaminoglycans, proteoglycans or mucopolysaccharides), with the latter required for joint cartilage synthesis.<sup>(3)</sup> Thus, any reduction in glucosamine sulfate synthesis results in a decline in joint cartilage (articular cartilage) ground substance production with subsequent joint space narrowing and arthritic degeneration.<sup>(2)</sup>

In the body, glucosamine is synthesized by the conversion of fructose-6 phosphate to glucosamine-6 phosphate by the enzyme, fructose-6 phosphate amide transferase, in the hexosamine biosynthetic pathway.<sup>(3)</sup> In the aging process, it appears that the fructose-6 phosphate amide transferase enzyme concentrations decline or this enzyme becomes less active, resulting in the noted reduction in glucosamine synthesis seen with aging.<sup>(2)</sup> Since the early 1980's, researchers have conducted a large number of clinical and experimental investigations to determine if oral glucosamine sulfate supplementation can compensate for the age-related decline in glucosamine synthesis and thereby, block the progression of osteoarthritis and/or reverse or repair any existing joint cartilage damage.<sup>(4,5)</sup> In the past twenty years glucosamine sulfate has been the subject of more than 300 scientific investigations and over 20 double-blind clinical studies.<sup>(2)</sup> In a recent review, which appeared in the journal, *Rheumatology Disease Clinics Of North America*, (25; 2 379-395,1999), researchers indicated that glucosamine supplementation has been shown to be highly effective in the treatment of osteoarthritis in all 13 double-blind clinical trials reviewed by these investigators.<sup>(6)</sup>

## Absorption and Metabolism of Oral Glucosamine Sulfate

Glucosamine is a small and simple molecule that is readily absorbed from the gastrointestinal tract. In fact, studies demonstrate that 90-98% of glucosamine sulfate is absorbed intact from the intestinal tract. By contrast, less than 13% of chondroitin sulfate is absorbed from the intestinal tract, making it significantly less effective than glucosamine sulfate as an intervention in the prevention and management of osteoarthritis.<sup>(7,8,9,10,11)</sup> Once absorbed from the gut, glucosamine circulates through the bloodstream, where it can be taken up by cartilage cells (chondrocytes) and used to synthesize N-acetyl- galactosamine sulfate in the production of cartilage ground substance (glycosaminoglycans).<sup>(3, 12)</sup> The ground substance in joint cartilage fills in the gaps between the collagen fibers, which run parallel to each other within the cartilage. As an analogy, the collagen fibers are like the bricks of the cartilage structure and the glycosaminoglycans are like the mortar between the bricks. Not only does glucosamine sulfate supplementation stimulate the synthesis of glycosaminoglycans, but it also stimulates the synthesis of collagen by chondrocytes.<sup>(13)</sup> As well, glucosamine sulfate is required for the synthesis of hyaluronic acid by the synovial membrane of the joint. Hyaluronic acid increases the viscosity of the synovial fluid and thus, serves to reduce the wear and tear stress on the articular cartilage and related joint structures. Thus, glucosamine may be helpful in preventing, reversing or stabilizing the osteoarthritic process by stimulating the synthesis of glycosaminoglycans, collagen and hyaluronic acid.<sup>(13,14)</sup>

Essentially all of the research on glucosamine has employed the use of glucosamine sulfate. Only glucosamine sulfate is approved as a treatment for osteoarthritis in more than 70 countries around the world and has been used by millions of people for this purpose for more than 20 years.<sup>(2)</sup> Glucosamine sulfate also delivers the mineral sulfur (hence the name glucosamine *sulfate*) to the joint cartilage. It has been recognized for many years that sulfur is a vital nutrient for the maintenance of joint cartilage. Sulfur is required to stabilize the connective tissue matrix of cartilage, tendons, and ligaments. Sulfur hot springs and the recent popularity and use of MSM (methyl sulfonyl methane) by arthritis patients have provided strong anecdotal evidence that increasing the delivery of sulfur to the joints can help to alleviate arthritic symptoms to an appreciable degree. Experimental evidence indicates that sulfur has an anti-inflammatory effect and directly helps to maintain the structure and the integrity of joint cartilage. The veterinary use of DMSO (dimethylsulfoxide), a rich source of sulfur, has demonstrated effective anti-inflammatory effects in animals when applied topically. Preliminary trials with oral MSM in humans have revealed significant improvement in the symptoms of osteoarthritis.<sup>(15,16,17,18,19)</sup> As such, the use of glucosamine *sulfate* provides the joint structures with the mineral sulfur as well as glucosamine and thus, this form of glucosamine offers a double benefit in the management of osteoarthritis cases.

Other forms of glucosamine are present in the commercial market place such as N-acetyl-glucosamine and glucosamine hydrochloride. There is presently insufficient evidence to support their use and neither one of these forms provides the addition of the mineral sulfur, which has shown to be of value in osteoarthritis cases.<sup>(2)</sup>

### **Clinical Studies With Glucosamine Sulfate**

Glucosamine sulfate has been the subject of more than 300 scientific investigations and over 20 double – blind clinical studies.<sup>(2)</sup> In a recent meta-analysis of glucosamine clinical trials in the treatment of osteoarthritis, McAlindon and colleagues indicated that all 13 studies that met the inclusion criteria (double –blind, placebo-controlled trials of greater than 4 weeks' duration; using global pain score or the Lequesne index joint as the primary outcome measure and considered the trial positive if improvement in the treatment group was equal to or greater than 25% compared with the placebo group), were classified as positive, demonstrating that glucosamine supplementation is highly effective in the treatment of osteoarthritis. This meta-analysis revealed that glucosamine supplementation reduced the symptoms and signs of osteoarthritis by 40.2% on average, compared with the placebo.<sup>(6)</sup>

Glucosamine sulfate supplementation has also been investigated in head-to-head studies against non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of osteoarthritis. In a number of these trials glucosamine supplementation was shown to produce better results than ibuprofen and other NSAIDs in relieving the pain and inflammation of osteoarthritis. Unlike many NSAIDs, glucosamine has not been shown to produce any of the adverse side effects that are frequently encountered with the use of NSAIDs (gastritis, peptic ulcer, GI bleeding and erosion of the intestinal lining, liver and kidney toxicity, tinnitus).<sup>(20,21,22,23,24)</sup>

In a recent therapeutic investigation involving 178 Chinese patients suffering from osteoarthritis of the knee, the group given a daily dose of 1500mg of glucosamine sulfate demonstrated better results than did the group given ibuprofen at 1200mg per day (NSAID) with respect to reduction in symptoms of osteoarthritis. In this study, glucosamine sulfate was shown to be better tolerated than ibuprofen. Sixteen percent of the ibuprofen group dropped out due to adverse side effects from the drug. A six percent drop out rate occurred in the glucosamine group. The authors of the study conclude that glucosamine sulfate is a selective intervention for osteoarthritis, as effective on the symptoms of the disease as NSAIDs but significantly better tolerated. As such, glucosamine sulfate seems particularly indicated in the long-term treatment needed in osteoarthritis.<sup>(25)</sup>

In North America, the medical profession has taken a skeptical view of the original research on glucosamine that has largely been performed in Europe and Asia. Acknowledging that oral glucosamine has

been shown to be highly bioavailable (26% bioavailability after first pass through the liver to enter the bloodstream) and demonstrates impressive results in clinical trials with osteoarthritis patients, some researchers have criticized the research methodology of some of these trials, suggesting that North American trials are required before glucosamine can be recommended as a treatment for arthritis.<sup>(26)</sup> In 1999 and 2001, this request was answered when Reginster et al published their findings in the journals, *Arthritis and Rheumatology* (1999;42, suppl) and *Lancet* (2001;357) . The three-year randomized study by Dr. Reginster was a large randomized controlled analysis that was placebo-controlled, double-blind, and prospective in nature. It involved 212 patients with knee osteoarthritis. Weight-bearing and antero-posterior radiographs of each knee were done at 1 and 3 years. Joint space width was also measured. Symptom and functional status were scored every 4 months using the Western Ontario and McMaster University Osteoarthritis index (WOMAC). The two groups had comparable baseline status, but after 3 years there was no further joint space narrowing in the glucosamine group. The placebo group had further joint space narrowing and objective evidence of disease progression. As well, subject symptoms worsened in the placebo group, but the group taking glucosamine realized a marked reduction in symptoms of osteoarthritis over the three-year period. The authors concluded that glucosamine sulfate supplementation significantly reduced progression of knee osteoarthritis. Patients in the glucosamine group did not experience any untoward side effects.<sup>(27, 28)</sup> In the *Lancet* editorial, medical practitioners were encouraged to begin embracing certain aspects of the alternative movement, including the use of glucosamine as an effective lifelong intervention for osteoarthritis. As stated in the article, *“It is time for (medical doctors) to accommodate the possibility that many nutritional products may have valuable therapeutic effects and to regain the credibility of the public at large”*.<sup>(41)</sup>

### **Other Clinical Uses Of Glucosamine**

The clinical use of glucosamine supplementation may extend beyond the treatment of osteoarthritis. Glucosamine sulfate is also required for the synthesis of other glycosaminoglycans that are integral components of the basement membrane below the skin and intestinal tract lining and blood vessels. As reviewed by McCarty, glucosamine supplementation can be used to enhance wound healing (e.g., post-surgical), through its effects on stimulating the synthesis of hyaluronic acid. Experimental studies and human anecdotal evidence supports this application at the present time.<sup>(29)</sup> Glucosamine sulfate has also been used in a clinical trial involving 50 patients with temporomandibular disorders, stemming from internal derangement and a diagnosis of osteoarthritis. These patients experienced decreased joint noises, pain and swelling, after the administration of therapeutic doses of glucosamine and chondroitin sulfate.<sup>(30)</sup> However it should be noted that experts in this area conclude that adding chondroitin to glucosamine administration has not been shown to further improve the benefits available from glucosamine alone. Thus, at this time, the addition of chondroitin sulfate is seen to impose additional cost with no added benefit.<sup>(13)</sup>

There is also evidence to suggest that glucosamine sulfate supplementation may be beneficial as part of a nutritional regime to aid in the management of inflammatory bowel diseases. Experimental studies and human anecdotal evidence suggests that this may be the case. It is proposed that glucosamine supplementation can strengthen the basement membrane of gut blood vessels helping to prevent leakage of blood into the intestinal lumen, which may otherwise trigger an inflammatory immune reaction. Further, glucosamine has been shown to have a healing effect on the mucosal lining of the G-I tract itself. Anecdotal evidence supports the trial of glucosamine in both Crohn’s disease and ulcerative colitis.<sup>(31,38)</sup>

As a final consideration, the decline in glucosamine sulfate synthesis with age may imply that a prudent anti-aging strategy is to use a low to moderate dose of glucosamine sulfate (500mg per day) as an anti-aging strategy beginning at 45-50 years of age. This intervention may help to prevent or minimize the development of osteoarthritis changes to our joints, helping to preserve quality of life to a significant degree. This practice may also serve to reduce the chances of capillary fragility that is associated with risk of stroke and vein disorders

that are also seen with increasing frequency with advancing age. Optimizing the heparan sulfate (a glycosaminoglycan made from glucosamine sulfate) content of ground substance between body cells has also been shown in animal experiments to reduce the ability of cancer cells to metastasize. The metastatic capacity of cancer cells tends to correlate with their ability to produce heparanase enzyme. Heparanase enzyme eats through the heparan sulfate ground substance (mortar) between cells, allowing cancer cells to affect neighboring host cells. As well, many viruses spread from cell to cell by breaking down the heparan sulfate ground substance between cells through the secretion of heparanase enzyme. Once again, glucosamine sulfate is required for the optimum synthesis of heparan sulfate, thickening the mortar between cells and making it more difficult for heparanase enzyme to break it down. With realization that heparan sulfate production may decline as we age due to reduced glucosamine sulfate synthesis, the prophylactic administration of glucosamine may also be of value in these facets of disease prevention.<sup>(32,33,34,35,36,37)</sup>

### **Side Effects, Toxicity and Contra-Indications To The Use Of Glucosamine**

Reported short-term adverse side effects from the use of glucosamine are generally mild and infrequent. These include mild gastrointestinal upset, drowsiness, skin reactions, and headache.<sup>(26)</sup> Glucosamine sulfate has been shown to be non-toxic at prescribed doses.<sup>(14)</sup> Patients allergic or sensitive to sulfa drugs or sulfate-containing food additives can safely take glucosamine sulfate. The word sulfate in this instance indicates the presence of the mineral sulfur, not the sulfa compounds used in sulfa drugs and sulfate-containing food additives. All cells of the body contain the mineral sulfur and thus, it is not possible to be allergic to this mineral. However, glucosamine sulfate is manufactured from the chitin exoskeleton of shellfish, such as lobster crab and shrimp. Therefore, it is conceivable that a person with a severe allergy to shellfish may be sensitive to the use of glucosamine, although the pharmaceutical grade of glucosamine is generally devoid of shellfish contaminants. Nevertheless, caution should be exercised in these cases.<sup>(2,14)</sup> Some preliminary animal experiments and human trials on healthy individuals reveals that glucosamine supplementation may increase insulin resistance in some individuals by down-regulating the synthesis of insulin receptors by the nuclear DNA<sup>(39)</sup>. In large clinical trials this has not surfaced as a concern and no indication of pronounced glucose intolerance has been demonstrated in the many well-documented glucosamine studies, including the study in *Lancet* and the glucosamine meta-analysis appearing in *The Journal of The American Medical Association*.<sup>(22, 40)</sup> It is advisable for diabetic patients and pre-diabetic patients to have their blood glucose monitored during the first few weeks of glucosamine sulfate supplementation however, at this time these conditions are not an absolute contra-indication to the use of glucosamine

### **Dosage**

In regards to the treatment of osteoarthritis, the usual daily dosage of glucosamine sulfate is 1500mg per day, which can be taken all at one time<sup>(28)</sup> or in divided doses of 500mg per dose.<sup>(2,14)</sup> Individuals taking diuretic drugs may require an additional 500mg per day to compensate for the increased excretion rate. Individuals weighing more than 200 pounds may also be advised to up their dosage to 2000mg per day.<sup>(2)</sup>

### **Quality Assurance.**

In many European countries, glucosamine is available only by prescription from a medical practitioner. In North America, glucosamine is classified as a natural health product and is readily available as an over-the-counter product. As such, glucosamine products are held to much lower standards in regards to purity and potency than are prescription medications. A recent independent study revealed that up to one-third of the glucosamine products tested did not contain the amount of glucosamine stated on the label.<sup>(42)</sup> For this reason, it is imperative that health practitioners recommend only those glucosamine products whereby the manufacturer can issue a certificate of analysis and/or a third party true-to-label claim document that verifies the purity and

potency of the product. This should be a standing policy for practitioners in regards to the recommendation of all herbal or accessory nutrient (e.g. glucosamine, CoQ-10, MSM) supplements.

## References

1. Bland, J.H., and Cooper, S.M. Osteoarthritis: A review of the cell biology involved and evidence for reversibility. Management rationally related to known genesis and pathophysiology. *Sem Arthr Rheum* 14:106-33, 1984.
2. Murray, Michael, T. Glucosamine sulfate: nature's arthritis cure. Excerpt from *The Chiropractic Journal* – March 1998
3. Williams & Wilkins. *Basic Medical Biochemistry: A Clinical Approach*. 1996: 452-453.
4. Glucosamine Sulfate. *Altern Med Rev* 1999 Jun; 4(3): 193-5 (ISSN: 1089-5159)
5. Vidal, Y., and Plana, R.R., et al. Articular cartilage pharmacology. In vitro studies on glucosamine and non-steroidal anti-inflammatory drugs. *Pharmacol Res Comm* 10, 557-569, 1978.
6. Deal, C.L., Moskowitz, R.W. Nutraceuticals as therapeutic agents in osteoarthritis. The role of glucosamine, chondroitin sulfate, and collagen hydrolysate. *Rheum Dis Clin North Am*, 1000 May; 25 (2): 379-95 (ISSN: 0889-857X)
7. Setnikar, I., et al: Pharmacokinetics of glucosamine in the dog and man. *Arzneim Forsch*, 43: (10) 1109-13, 1993.
8. Setnikar, I, et al: Pharmacokinetics of glucosamine in the dog and man. *Arzneim Forsch*, 36 (4) 729-35, 1986.
9. Baici, A., et al. Analysis of glycosaminoglycans in human sera after oral administration of chondroitin sulfate. *Rheumatol Int* 12:81-8, 1992.
10. Conte, A., et al. Biochemical and pharmacokinetic aspects of oral treatment with chondroitin sulfate. *Arzneim Forsch* 45:918-25, 1995.
11. Baici, A. and Wagenhauser, F.J.: Bioavailability of oral chondroitin sulfate. *Rheumatology Int*. 13:41-43, 1993.
12. Peperno, M., Reboul, P., Hellio Le Graverand, M.P., Peschard, J.J., Anefeld, M., Richard, M., Vignon, E. Glucosamine sulfate modulates dysregulated activities of human osteoarthritic chondrocytes in vitro. *Osteoarthritis Cartilage*, 2000 May; 8 (3): 207-12 (ISSN: 1063-4584)
13. Kelly, G.S. The role of glucosamine sulfate and chondroitin sulfates in the treatment of degenerative joint disease. *Altern Med Rev* 1998 Feb.; 3 (1): 27-29 (ISSN: 1089-5159)
14. Gottlieb, Marc S. Conservative Management of Spinal Osteoarthritis with Glucosamine Sulfate and Chiropractic Treatment. *Journal of Manipulative and Physiological Therapeutics*, Volume 20, (6) July/August, 1997.
15. Sullivan, M.S. and Hess, W.C. Cystine content of fingernails in arthritis. *J Bone Joint Surg* 16: 185-8, 1935.
16. Senturia, B.D., "Results of treatment of chronic arthritis and rheumatoid conditions with colloidal sulphur." *J Bone Joint Surg* 16: 119-25, 1934.

17. Lawrence, R.M. Methylsulfonylmethane (MSM): A double-blind study of its use in Degenerative Arthritis. *Int J Anti-Aging Med.*, 1998; 1, 1:50
18. Challem, J., Sulfur Power. *Natural Way For Better Health* (magazine). 1999 (02/28): 34-35
19. Methylsulfonylmethane (MSM). *Herbal Advisor*. [www.herbaladvisor.com](http://www.herbaladvisor.com), Samtech Research, 2001
20. Noack, W., et al. Glucosamine sulfate in osteoarthritis of the knee. *Osteoarthritis Cartilage* 2: 51-9, 1994.
21. Vaz, A.L. Double-blind clinical evaluation of the relative efficacy of ibuprofen and glucosamine sulfate in the management of osteoarthrosis of the knee in out-patients. *Curr Med Res Opn* 8. 145-9, 1982.
22. Muller-Fassbender, H. et al. Glucosamine sulfate compared to ibuprofen in osteoarthritis of the knee. *Osteoarthritis Cartilage* 2: 61-9, 1994.
23. Rovati, L.C., et al. A large randomized placebo-controlled, double-blind study of glucosamine sulfate vs. piroxicam and vs. their association on the kinetics of the symptomatic effect in knee osteoarthritis. *Osteoarthritis Cartilage* 2 (suppl 1): 56, 1994.
24. Tapadinhas, M.J., et al. Oral glucosamine sulfate in the management of arthrosis: report on a multi-centre open investigation in Portugal. *Pharmatherapeutica* 3: 157-68, 1982.
25. Qiu, G.X., Gao, S.N., Giacobelli, G., Rovati, L., Setnikar, I. Efficacy and safety of glucosamine sulfate versus ibuprofen in patient with knee osteoarthritis. *Arzneimittelforschung*. 1998 May; 48 (5): 469-74 (ISSN: 0004-4172)
26. Barclay, T.S., Tsourounis, C., McCart, G.M. Glucosamine. *Ann Pharmacother* 1998 May; 32 (5): 574-9 (ISSN: 1060-0280)
27. Reginster, Y.J., Deroisy, R., Paul, I., et al. Glucosamine sulfate significantly reduces progression of knee OA over 3 years: a large randomized, placebo-controlled, double-blind prospective trial. *Arthritis Rheum*. 1999; 42 (suppl).
28. Reginster, J.Y., Deroisy, R., Rovati, L.C., Lee, R.L., Lejeune, E., Bruyere, O., Giacobelli, G., Henrotin, Y., Dacre, J.E., Gossett, C. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomized, placebo-controlled clinical trial. *Lancet* 2001, Jan. 27; 357 (9252): 251-6 (ISSN: 0140-6736)
29. McCarty, M.F. Glucosamine for Wound Healing. *Medical Hypotheses*, 1996. 47; 273-275.
30. Shankland, W.E. The effects of glucosamine and chondroitin sulfate on osteoarthritis of the TMJ: a preliminary report of 50 patients. *Cranio* 1998 Oct.; 16 (4): 230-5 (ISSN: 0886-9634)
31. McCarty, Mark F. Vascular Heparan Sulfates May limit the Ability of Leukocytes to Penetrate the Endothelial Barrier – Implications for Use of Glucosamine in Inflammatory Disorders.
32. Vlodaysky, I., Fuks, Z., Bar-Ner, M., et al. Lymphoma-cell-mediated degradation of sulfated proteoglycans in the subendothelial extracellular matrix: Relationship to tumor cell metastasis. *Cancer Res* 1983; 43: 2704-2711.
33. Nakajima, M., Irimura, T., Di Ferrante, D., et al. Heparan sulfate degradation: Relation to tumor invasion and metastatic properties of mouse B16 melanoma sublines. *Science* 1983; 220: 611-612

34. Ricoveri, W., Cappelletti, R. Heparan sulfate endoglycosidase and metastatic potential in murine fibrosarcoma and melanoma. *Cancer Res* 1986; 45: 3855-3861.
35. Nakajima, M., Irimura, T., Nicolson, G.L. Heparanase and tumor metastasis. *J Cell Biochem* 1988; 36: 157-167.
36. Vlodavsky, I., Eldor, A., Bar-Ner, M., et al. Heparan sulfate degradation in tumor cell invasion and angiogenesis. *Adv Exp Med Biol* 1988; 233: 201-210.
37. Vlodavsky, I., Korner, G., Ishai-Michaeli, R., et al. Extracellular-matrix-resident growth factors and enzymes: Possible involvement in tumor metastasis and angiogenesis. *Cancer Metastasis Rev* 1990; 9: 203-226.
38. Russell, A.L. Glucosamine in osteoarthritis and gastrointestinal disorders: an example of the need for a paradigm shift. *Med Hypotheses* 1998 Oct.; 51 (4): 347-9 (ISSN: 0306-9877)
39. Monauni, T., Zenti, M.G., Cretti, A., et al. Effects of glucosamine infusion on insulin secretion and insulin action in humans. *Diabetes* 2000 Jun.; 49 (6): 926-35 (ISSN: 0012-1797)
40. McAlindon, T.E., La Valley, M.P., Gulin, J.P., Felson, D.T. Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. *JAMA* 2000 Mar. 15; 283 (11): 1469-75 (ISSN: 0098-7484)
41. McAlindon, T., Glucosamine for osteoarthritis: dawn of a new era? *Lancet*, 2001; 357, 9252: 247-248.
42. *Nutrition News Focus*, February 13, 2001.