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Glucosamine Sulfate:

A Review of Efficacy for the Pharmacy Professional

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Well-documented efficacy and fewer side effects than anti-inflammatory drugs make glucosamine sulfate a leading therapeutic option for treating and preventing osteoarthritis.

Booming interest in the field of complementary and alternative medicine, with increased patient visits to these providers, requires that pharmacy professionals develop an understanding of these therapies, which nearly half of all customers are using.[1]

Furthermore, without mandatory licensing of complementary and alternative providers (many states still allow unrestricted use of the title *Naturopathic Doctor* [ND], for example), it is important that pharmacists educate consumers not only on well-documented therapies but also on finding well-educated com-plementary- and alternative-medicine professionals. Advice-giving laypersons, mail-order complementary- and alternative-medicine diploma holders and healthfood-store clerks have little, if any, formal clinical experience and have not taken boards in complementary and alternative medicine, and – because they lack formal education in botanical medicine, therapeutic nutrition and the interactions of these therapies with pharmaceuticals – may make harmful recommendations.

This situation affords the pharmacy professional a few options: (1) Enroll in one of two accredited naturopathic medical schools for a minimum four- to five-year, full-time postgraduate program of study for a degree in naturopathic medicine (Council on Naturopathic Medical Education, oral communication, September 1998);[2] (2) enroll in one of over 50 accredited schools of acupuncture and a minimum three-year course for a degree in acupuncture or Chinese herbal medicine; (3) self educate with reputable resources, becoming familiar with complementary- and alternative-medicine therapies that may be of benefit; or (4) find and develop a cross-referral relationship with a credentialed ND or licensed acupuncturist. The latter two options, more practical for most pharmacists in practice, are what I will attempt to begin to facilitate by, first, reviewing the evidence on clinical applications of glucosamine sulfate (one of the most popular nutritional supplements); and, second, providing referral resources for well-trained complementary- and alternative-medicine providers.

Structure and Biochemistry

Although most health professionals are introduced to glucosamine's effects through anecdotal reports or research analysis, review of glucosamine's biochemistry alone affords understanding of its in vivo efficacy for cartilaginous health.

Glucosamine (or 2-deoxy-2-amino-a-D-glucopyranose) is one of the two most common 2-amino-aldohexoses, the other being galactosamine. These amino sugars serve as components of polysaccharides, glycosaminoglycans and glycosphingolipids, which in turn provide structure to all cells in the living organism.[3] Aside from providing a matrix for all cells, glycosaminoglycans (including hyaluronate, keratan sulfate, heparan sulfate and heparin) are the fundamental subunits of cartilage, synovial fluid, intervertebral disks, lung tissue, vessel walls and intestinal mucosa.[3] Glucosamine, therefore, by serving as an essential constituent of these glycosaminoglycans, is an even more basic subunit of cartilage and the other structures. With an appreciation of this biochemistry, it would be unexpected for glucosamine supplementation not to promote cartilaginous health.

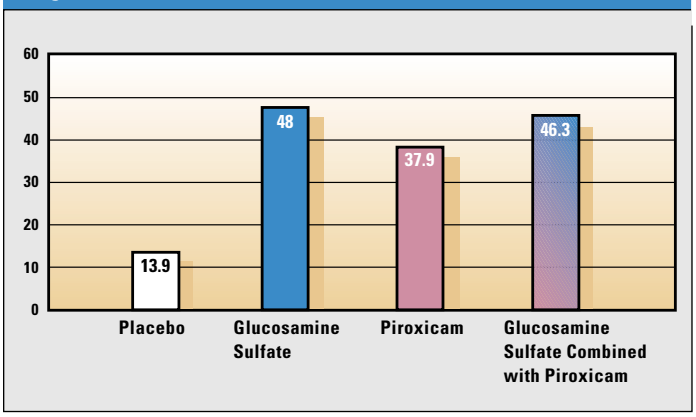
Sulfate also seems important in this equation for several reasons. First, with the exception of hyaluronate, all glycosaminoglycans contain sulfate groups in ester linkages with the hydroxyl groups of the amino sugar residues, meaning sulfate is an integral component of the subunits of the cartilaginous matrix. Second, the presence of sulfate groups provides the glycosaminoglycans with a high negative-charge density that makes them hydrophilic. This in turn increases the osmotic pressure within the matrix, contributing to important characteristics including turgor, tensile strength, resistance to compression and maintenance of volume.[3] Third, studies have not only demonstrated that sulfate depletion inhibits normal glycosaminoglycan synthesis, but also that supplemental sulfur can benefit patients with chronic arthritis.[4-6] Considering this biochemical and investigatory evidence, using the combination of glucosamine and sulfate seems appropriate, as both are precursors for glycosaminoglycans and joint cartilage.

Pharmacology

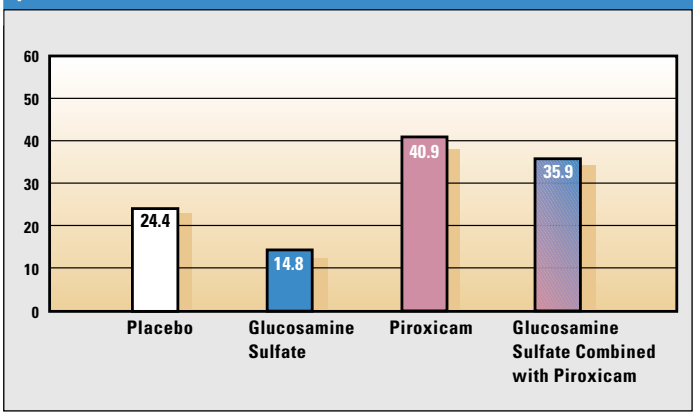
Glucosamine sulfate has several actions. It serves as a precursor for, and inhibits the degradation of, proteoglycans (the ground substance of articular cartilage); it rebuilds experimentally induced cartilaginous damage; and it has chondroprotective and antiarthritic effects.[7-10] Furthermore, glucosamine sulfate's stimulation of proteoglycan synthesis is dose dependent.[11] Glucosamine sulfate has very mild anti-inflammatory and antireactive effects on edema-provoking agents including carrageenan, dextran, acetic acid and formalin. Glucosamine sulfate also inhibits in vitro superoxide generation and lysosomal enzymes of the liver.[10,12]

Absorption of oral glucosamine sulfate is highly efficient (with studies showing a 90% to 98% absorption), although parenteral use of glucosamine sulfate does achieve a fivefold higher plasma concentration.[13,14] In animal and human studies, radiolabeled intravenously (IV) or intramuscularly (IM) administered glucosamine sulfate showed a demonstrated serum clearance half-life (initial) of 13 minutes. Incorporation of glucosamine sulfate into a and ß globulins of the plasma begins at 20 minutes after administration, reaches a peak at eight to ten hours, and then declines, with a half-life of 2.9 days. Interestingly, articular cartilage and a few other tissues display active uptake for glucosamine sulfate; while passive diffusion is typical of most tissues.[14-16] Glucosamine sulfate has been shown to cross the blood-synovial barrier; and, despite resulting in lower serum concentrations than with parenteral use, orally administered glucosamine sulfate has near-identical pharmacokinetics after the first-pass effect of

Percent reduction of Lequesne's Index of Severity in 90-day study comparing glucosamine sulfate and other drugs used to treat osteoarthritis.



Comparison of percentages of adverse effects in two studies comparing glucosamine sulfate and piroxicam.



the liver.[11, 14, 15] Clearance of the radioactivity from radiolabeled glucosamine sulfate was primarily via the lungs (~50%) as carbon dioxide, the kidney (~35%) as glucosamine and the feces (~2%).[15, 16]

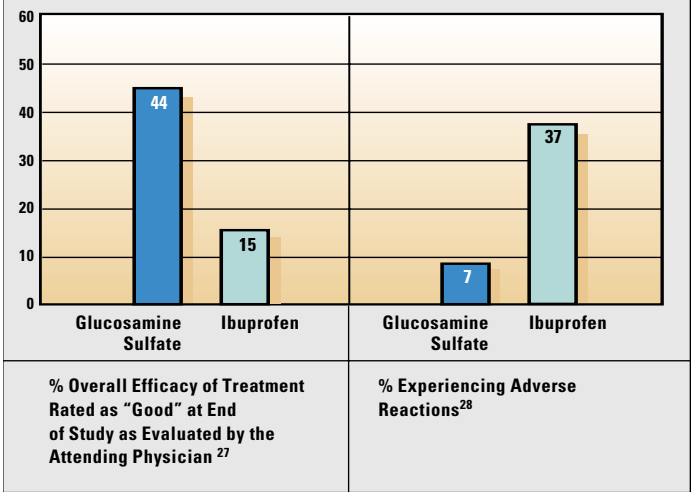
Oral Use for Osteoarthritis and Degenerative Joint Disease

Multiple double-blind studies have demonstrated efficacy of oral glucosamine sulfate in the treatment of degenerative joint disease, which affects over 40 million Americans, an estimated 90% of persons over age 60, and is the leading cause of disability in persons over age 65.[17] One such study includes Drovanti's comparison of glucosamine sulfate to placebo in 80 inpatients with established osteoarthrosis. With a dosage of 500 mg three times a day for 30 days, patients in the active treatment group showed a 32% greater improvement in articular pain, joint tenderness, swelling and restrictions in active and passive range of motion. Likewise, patients in the glucosamine sulfate group improved significantly faster and had articular cartilage more healthy in appearance (via electron microscopy) than those taking placebo.[18]

A study with glucosamine sulfate by Noack and colleagues on 252 outpatients with osteoarthritis of the knee, however, found more conservative benefits. Lesquesne's severity index of at least four, symptom duration of at least six months and radiological disease stage between I and III were required for admission to the study. Patients were treated with either glucosamine sulfate 500 mg three times a day, or placebo, for four weeks; and response was defined as a three-point reduction in Lequesne's severity index and a positive assessment by the investigator. Results produced a 55% response in the glucosamine sulfate group vs. 38% in the placebo group, demonstrating a conservative 17% greater margin of efficacy for glucosamine sulfate, with no differences in tolerability between the two substances.[19]

Several other studies, however, have also shown glucosamine sulfate to have a significantly greater efficacy in reducing pain, joint tenderness, swelling, and restricted movement compared to placebo, with measured improvements in physical-exam scores of 43.3% in as little as 16 weeks in patients with osteoarthritis.[20,21] Glucosamine sulfate also has demonstrated chondroprotective effects as measured by urinary pyridinoline.[22]

Results of two studies comparing glucosamine sulfate and ibuprofen.



% Overall Efficacy of Treatment Rated as "Good" at End of Study as Evaluated by the Attending Physician [27]

% Experiencing Adverse Reactions[28]

More convincing, perhaps, are studies that compare glucosamine sulfate to other drugs used to control osteoarthritic pain. In one such study, where glucosamine sulfate 1500 mg/day was compared with piroxicam 20 mg/day, glucosamine sulfate + piroxicam and placebo, glucosamine sulfate was determined to be more effective. Random assignment of 329 patients to the four groups, with treatment lasting 90 days and evaluation at 90 days and 60 days after treatment cessation, was carried out using Lequesne's index of severity as the primary outcome measure. Data at end of treatment showed Lequesne's index of severity reductions of 48% (glucosamine sulfate), 37.9% (piroxicam), 46.3% (glucosamine sulfate + piroxicam) and 13.9% (placebo). Likewise, reduction of Lequesne's index of severity scores from baseline 60 days after treatment cessation were 46.3% (glucosamine sulfate), 21.1% (piroxicam), 44.6% (glucosamine sulfate + piroxicam) and 9.9% (placebo), showing not only glucosamine sulfate's superiority, but also its retained therapeutic effect after discontinuation of treatment.[23]

Likewise, at least two studies (one multicenter, both randomized and placebo controlled) comparing the occurrence of adverse events with glucosamine sulfate and piroxicam also showed glucosamine sulfate to be superior.[24,25] Occurrence of side effects was 40.9% (piroxicam), 35.9% (glucosamine + piroxicam), 14.8% (glucosamine sulfate) and 24.4% (placebo).[24]

Studies comparing glucosamine sulfate to ibuprofen are also impressive. In one, by Miller-Fassbender and others, 200 patients with osteoarthritis of the knee, with an average Lequesne severity index of 16 for at least three months, were enrolled. Patients were randomly assigned to receive either 500 mg glucosamine sulfate three times a day or 400 mg ibuprofen three times a day for four weeks, with evaluation of efficacy after each week of treatment. Although after the first week there was a higher number of responders in the ibuprofen vs. the glucosamine-sulfate group (48% to 28%), by week two there was no statistically significant difference in the number of responders in each group (about 50% responders). This congruence in the response rate between the two groups continued for the remaining weeks of the study, with an average drop in Lequesne severity index of greater than six points by the study's end. Comparison of adverse effects between the two groups, however, showed considerable variance. Glucosamine sulfate had a 6% and 1% occurrence of adverse events and related dropouts compared to ibuprofen's 35% and 7%, respectively.[25]

Another comparison study between glucosamine sulfate and ibuprofen showed glucosamine sulfate to be superior. Lopes, using the same dosage pattern as in Miller-Fassbender's study, investigated the effects of glucosamine sulfate and ibuprofen for eight weeks in 40 outpatients with unilateral osteoarthritis of the knee. Again, although treatment with glucosamine sulfate produced a slower rate of pain reduction, its cumulative pain-reducing effects surpassed that of ibuprofen by week eight.[26]

Yet other double-blind, randomized trials comparing glucosamine sulfate and ibuprofen found glucosamine sulfate to be either as effective as, or more effective than, ibuprofen, while being considerably better tolerated.[27,28] For example, Qui and co-workers found glucosamine sulfate to be more effective than ibuprofen in parameters measuring pain at rest; pain during movement; and pain with pressure, swelling and therapeutic utility; while Rovati found adverse reactions rates of 37% with ibuprofen compared to only 7% with glucosamine sulfate.[27,28]

Parenteral Use for Osteoarthritis/Degenerative Joint Disease

Studies using parenteral administration of glucosamine sulfate are particularly intriguing. In a study of 40 patients by Vajaradul, weekly intra-articular injections of glucosamine were compared to 0.9% sodium chloride (of like dosage frequency) for five weeks. Glucosamine was found to reduce pain, produce more pain-free patients and increase the angle of joint flexion at levels significantly better than the sodium chloride. Glucosamine did not increase knee swelling, as did sodium chloride; and the effects of glucosamine persisted for at least one month after cessation of treatment.[29]

Another study by Reichelt and colleagues found efficacy with six weeks of 400-mg biweekly IM injections of glucosamine sulfate in improving Lequesne severity index scores in 155 outpatients with osteoarthritis. In this study, glucosamine sulfate afforded a response rate of 55% compared with placebo's 33%. Furthermore, glucosamine sulfate was shown to reduce Lequesne severity index scores at a level significantly greater than placebo, while having even fewer adverse events.[30]

Combination Parenteral/Oral Use for Osteoarthritis/Degenerative Disc Disease

A few studies using IM or IV glucosamine sulfate or a piperazine/chlorbutanol combination followed by oral glucosamine sulfate or placebo were performed to assess efficacy and tolerability in treatment of osteoarthritis. Patients received either glucosamine sulfate 400 mg or piperazine/chlorobutanol IM or IV daily for seven days, followed by 1500 mg oral glucosamine sulfate or placebo for 14 days. During parenteral treatments, pain at rest, pain during active and passive movement, restricted function and time to walk 20 meters improved to a faster and greater extent in the glucosamine-sulfate group. Likewise, during oral maintenance, the glucosamine-sulfate group continued to improve; while the placebo patients reverted to symptom scores near pretreatment levels. Finally, 27% of the glucosamine-sulfate group achieved symptom-free status vs. none in the control group.[8,31]

Likewise, Mund-Hoym, who also used combination IM and oral administration of glucosamine sulfate, found it as effective, faster to achieve a clinical result and without side effects in comparison to phenylbutazone.[32]

Chondropathia Patella

One study of 68 young athletes with chondropathy (Bentley first to third degree) received glucosamine sulfate 500 mg three times a day for 40 days, then 250 mg three times a day for 90 to 100 days. Seventy-six percent had complete involution of symptoms including pain at rest; while walking, standing, and sitting; and during movement; as well as rubbing noise, pain at displacement and pain with pressure.[33] Perhaps, as this study suggests, glucosamine sulfate may provide benefits in athletes

to promote joint healing postinjury, in addition to its well-documented effects in degenerative joint disease.

Atheroscleros is (Theoretical Use)

Several investigators have postulated that glucosamine sulfate, which serves as a subunit in the development of glycosaminoglycans like heparan sulfate, may have antiatherogenic effects. A proposed mechanism includes promotion of endothelial heparan sulfate production, which in turn may prevent migration, multiplication and phenotypic transition of smooth muscle cells; and/or maintenance of an anticoagulant luminal surface by bonding with and activating antithrombin III.[34] Preliminary studies seem to support the hypothesis of the antiproliferative effects of glucosamine on smooth muscle cells, but sufficient evidence is unavailable to determine if glucosamine sulfate has any antiatherogenic effects.[35, 36]

Dosage and Toxicity

Virtually all supporting evidence behind the use of glucosamine sulfate has been on an adult oral dosage of 500 mg three times a day (1500 mg/day) or 400 mg parenteral use (varying from daily dosage for seven days to biweekly dosage lasting six weeks).[8,17-32] Despite parenteral use achieving fivefold higher serum concentrations, oral glucosamine sulfate (typically derived from chitin) does show a high efficiency of absorption and yields similar symptom improvements in objective parameters of evaluation.[13,14] Recommended oral daily dosage for obese individuals is 20 mg/kg body mass[13,37] in divided doses, and evaluation of efficacy (for all adults) should ideally begin after at least six weeks of administration. Since effects of glucosamine sulfate are not permanent despite being typically maintained for three to six weeks after treatment cessation, long-term use is generally required to maintain therapeutic effect.

No toxicity has been reported with glucosamine sulfate use. No LD50 is established; and glucosamine sulfate has been safely administered to patients with circulatory, liver and lung disorders, diabetes, and depression without observed interference in the condition's course.[37]

Side Effects and Potential Interactions

Glucosamine sulfate is extremely well tolerated, with no reports of allergic reactions.[13,22-29] In fact, several studies demonstrated glucosamine sulfate to have the same or an even lower incidence of side effects compared to placebo.[8, 19-21, 30-32] Side effects, although infrequent, can include epigastric pain, heartburn, diarrhea and nausea.[37] Since glucosamine is predominantly eliminated via the genitourinary system, use of agents that promote diuresis can increase clearance; reduce bioavailability; and, therefore, necessitate increasing the dose of glucosamine sulfate.[13,37] Individuals with peptic ulcers seem to have an increased incidence of side effects and, therefore, may need to take glucosamine sulfate with meals.[13,38]

With a growing public demand for alternative, complementary, natural or integrated approaches in treating disease, it is increasingly important for pharmacy professionals to not only self educate on complementary and alternative medicine using reputable resources, but also to develop referral relationships with well-trained complementary and alternative-medicine providers. Glucosamine sulfate, a popular and effective

"natural" medicine, is well documented for osteoarthritis; not only through our understanding of the biochemical pathways in glycosaminoglycan production leading to cartilage formation, but also through numerous double-blind clinical trials as well. Comparative studies of glucosamine sulfate with nonsteroidal anti-inflammatory drugs have shown glucosamine sulfate to be either similarly or more effective in subjective and objective parameters of measure. Glucosamine sulfate is, however, superior to nonsteroidal anti-inflammatory drugs in that it is better tolerated and does not share nonsteroidal anti-inflammatory drugs' side effects and toxicity.

In addition, unlike nonsteroidal anti-inflammatory drugs (which inhibit cartilage formation), glucosamine analogously promotes cartilage repair.[39, 40] Parenteral use of glucosamine sulfate is well studied; affords considerably higher serum con-centrations; and, if available, seems appropriate in preceding oral glucosamine-sulfate therapy. While preliminary and hypothesized use of glucosamine sulfate to promote recovery after joint injury and as an antiatherogenic agent is fascinating and deserves more investigation, the use of glucosamine sulfate in osteoarthritis is well established. Although other effective natural approaches, including hypoallergenic diets; manipulation or plant medicines like zingiber, boswellia, curcuma and capsaicin; or even conventional pain-controlling measures, can be employed, such methods do not share glucosamine's unique position as an effective treatment for joint degeneration.[41-44] Glucosamine's notable effects – including reduction of pain; improvement of mobility; improvement of range of motion; and, perhaps most importantly, promotion of cartilage regeneration (all with a high index of tolerability) – make it a leading choice in the treatment and prevention of osteoarthritis.

Author Information

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References

1. Eisenberg DM, Davis RB, Etiner SL et al. Trends in alternative medicine use in the United States, 1990-1997: Results of a follow-up national survey. *JAMA* 1998;280:1569-1575.
2. Pournadeali K, Yarnall S. Nonphysician clinicians in the health care workforce. *JAMA* 1999;281:510-511.
3. Bhagavan N. *Medical Biochemistry*. Boston, MA, Jones and Bartlett Publishers, Inc., 1992, pp 142-143, 188-192.
4. Van der Kraan PM, de Vries BU, Vitters EL et al. Inhibition of glycosaminoglycan synthesis in anatomically intact rat patellar cartilage by paracetamol-induced serum sulfate depletion. *Biochem Pharmacol* 1988;37:368-3690.
5. Van der Kraan PM, de Vries BU, Vitters EL et al. High susceptibility of human articular cartilage glycosaminoglycan synthesis to changes in inorganic sulfate availability. *J Orthop Res* 1990;8:565-571.
6. Senturia B. Results of treatment of chronic arthritis and rheumatoid conditions with colloidal sulphur. *J Bone Joint Surg* 1934;16:119-125.
7. D'Ambrosia E, Casa B, Bompani R et al. Glucosamine sulphate: A controlled clinical investigation in arthrosis. *Pharmatherapeutica* 1981;2:504-508.
8. Vidal y Plana RR, Bizzari D, Rovati AL. Articular cartilage pharmacology: I. In vitro studies on glucosamine and non-steroidal anti-inflammatory drugs. *Pharmacol Res Commun* 1978.10:556-569.
9. Eichler J, Noh E. Behandlung der Arthrosis Deformans durch Beeinflussung des Knorpelstoffwechsel. *Orthop Praxis* 1970;9:225.

Complementary- and Alternative-Medicine Referral Information/ Resources

Naturopathic Physicians

- American Association of Naturopathic Physicians
  http://www.naturopathic.org
  (206) 298-0126
- Author's Information
  http://home.earthlink.net/~naturalmed
  (425) 744-1780

Licensed Acupuncturists

- American Association of Oriental Medicine:
  http://www.aaom.org
  (610) 266-1433
- National Certification Commission for Acupuncture and Oriental Medicine
  http://www.nccaom.org

General Alter native Medicine Refer ral

- Healthworld Professional Referral Network
  http://healthreferral.com
- Natural Healers School Information Resource
  http://www.naturalhealers.com

10. Setnikar I. Antireactive properties of "chondroprotective" drug. Int. J Tiss Reac 1992;14:253-261.
11. Arthritis and Articular Cartilage: *Profile of Glucosamine Sulfate*. Monza, Italy, Rotta Research Lavoratorium.
12. Setnikar I, Cereda R, Pacini MA et al;. Antireactive properties of glucosamine sulfate. *Arzneim Forsch* 1991;41:157-161.
13. Murray MT. *Encyclopedia of Nutritional Supplements*. Rocklin, CA, Prima Publishing, 1996, pp 336-341.
14. Setnikar I, Palumbo R, Canali S et al. Pharmacokinetics of glucosamine in man. *Arzneim Forsch* 1993;44:1109-1113.
15. Setnikar I, Giacchetti C, Zanolo G. Pharmacokinetics of glucosamine in the dog and in man. *Arzneim Forsch* 1986;36:729-735.
16. Setnikar I, Giachetti C, Zanolo G. Absorption, distribution, and excretion of radioactivity after a single intravenous or oral administration of [14C] glucosamine to the rat. *Pharmatherapeutica* 1984;3:538-550.
17. Geyman J, Gilliland B. Arthritis. In Dambro M, Griffith JA (eds). *Griffith's Five Minute Clinical Consult* (CD Rom). St Louis, MO, Williams & Willkins, 1997.
18. Drovanti A, Bignamini AA, Rovati AL. Therapeutic activity of oral glucosamine sulfate in osteoarthrosis: A placebo-controlled double-blind investigation. *Clin Ther* 1980;3:260-272.
19. Noack W, Fischer M, Forster K et al. Glucosamine sulfate in osteoarthritis of the knee. *Osteoarthritis and Cartilage* 1994;2:51-59.
20. Pujalte J, Llavore EP, Ylescupidez FR. Double-blind clinical evaluation of oral glucosamine sulphate in the basic treatment of osteoarthrosis. *Curr Med Res Opin* 1980;7:110-114.
21. Leffler C, Philippi A, Leffler S et al. Glucosamine, chondroitin, and manganese ascorbate for degenerative joint disease of the knee or low back: A randomized, double-blind, placebo-controlled pilot study. *Mil Med* 1999;164:85-91.
22. Giordano N, Nardi P, Senesi M et al. The efficacy and safety of glucosamine sulfate in the treatment of gonarthritis. *Clin Ter* 1996; 147:99-105.
23. Forster K, Schmid K, Rovati L et al. Longer-term treatment of mild-to-moderate osteoarthritis of the knee with glucosamine sulfate – A randomized, controlled, double-blind clinical study. *Europ J Clin Pharm* 1996;50:542.
24. Rovati L, Giacovelli G, Annefeld M et al. A large randomized, placebo controlled, double-blind study of glucosamine sulfate vs piroxicam and vs their association, on the kinetics of symptomatic effect in knee osteoarthritis (abstract). *Osteoarthritis and Cartilage* 1994;2(Suppl 1).
25. Miller-Fassbender H, Bach G, Haase W et al. Glucosamine sulfate compared to ibuprofen in osteoarthritis of the knee. *Osteoarthritis and Cartilage* 1994;2:61-69.
26. Lopes Vaz A. Double-blind clinical evaluation of the relative efficacy of ibuprofen and glucosamine sulphate in the management of osteoarthrosis of the knee in out-patients. *Curr Med Res Opin* 1982;8:145-149.
27. Qiu GX, Gao SN, Glacovelli G et al. Efficacy and safety of glucosamine sulfate versus ibuprofen in patients with knee osteoarthritis. *Arzneim Forsch* 1998;48:469-474.
28. Rovati L. Clinical research in osteoarthritis design and results of short-term and long-term trials with disease modifying drugs. *Int J of Tissue Reac* 1992;14:243-251.
29. Vajaradul Y. Double-blind clinical evaluation of intra-articular glucosamine in outpatients with gonarthrosis. *Clin Ther* 1981;3:336-343.
30. Reichelt A, Forster KK, Fischer M et al. Efficacy and safety of intramuscular glucosamine sulfate in osteoarthritis of the knee. *Arzneim Forsch* 1994;44:75-80.
31. Crolle G, D'Este E. Glucosamine sulphate for the management of arthrosis: A controlled clinical investigation. *Curr Med Res Opin* 1980;7:104-109.
32. Mund-Hoym W. Conservative treatment of spinal arthrosis with glucosamine sulfate and phenylbutazone – A controlled study (abstract). *Therapiewoche* 1980;30:5922-5928.
33. Bohmer D et al. Treatment of chondropathia patellae in young athletes with glucosamine sulfate(abstract). In Bachl N, Prokop L, Suchert R (eds): *Current Topics in Sports Medicine. Proc World Congress of Sports Med Vienna,1982*. Urban & Schwarzenberg, 1984.
34. McCarty M. Glucosamine may retard atherogenesis by promoting endothelial production of heparan sulfate proteoglycans. *Med Hypoth* 1997;48:245-251.
35. Norgard-Sumnicht K, Varki A. Endothelial heparan sulfate proteglycans that bind to L-selectin have glucosamine residues with unsubstituted amino groups. *J Biol Chem* 1995;270:12012-12024.
36. Garg H, Joseph PA, Yoshida K et al. Antiproliferative role of 3-O-sulfate glucosamine in heparin on cultured pulmonary artery smooth muscle cells. *Biochem Biophys Res Commun* 1996;224:468-473.
37. Kelly G. The role of glucosamine sulfate and chondroitin sulfates in the treatment of degenerative joint disease. *Alt Med Rev* 1998;3:27-39.
38. Tapadinhas M, Rivera I, Bignamini A. Oral glucosamine sulfate in the management of arthrosis: Report on a multi-centre open investigation in Portugal. *Pharmatherapeutica* 1982;3:157-168.

39. Newman N, Ling SR. Acetabular bone destruction related to non-steroidal anti-inflammatory drugs. *Lancet* 1985; 2(8445):11-14.
40. Brooks P, Potter SS, Buchanan W. NSAID and osteoarthritis—help or hindrance? *J Rheum* 1982;8:145-149.
41. Gottlieb M. Conservative management of spinal osteoarthritis with glucosamine sulfate and chiropractic treatment. *J Manip Physiol Ther* 1997;20:400-414.
42. Gonarthrosis – Current aspects of therapy with glucosamine sulfate (dona200-S). *Fortsch Med Suppl* 1998;183:1-12.
43. Gaby A. The role of hidden food allergy/intolerance in chronic disease. *Alt Med Rev* 1998;3:90-100.
44. Fleming T, Deutsch M, Hamid M et al. *PDR® for Herbal Medicines*. Montvale, NJ, Medical Economics Inc.,1998.

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