



Glucosamine.

Review on its effectiveness in treating knee osteoarthritis.

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Conclusions.

- There is some level 1 evidence on the short and long term effectiveness of glucosamine in alleviating OA symptoms, as measured by pain index, Lequesne index or WOMAC, particularly of the hip or knee joint.
- There is also some level 1 evidence on the possible role of glucosamine as a structure-modifying drug for OA as measured by x-ray imaging of the joint space.
- The majority of research were undertaken on patients with either knee or hip OA. This limits the generalizability of the outcome toward OA of other joints such as those in the hand/wrist, shoulder and ankle.
- The majority of clinical studies were done with glucosamine sulphate and little evidence is available on the efficacy of other forms of glucosamine (e.g. hydrochloride, combination with herbs, vitamin A, vitamin E, or minerals including Mg, K, Cu, Zn or Se).
- The majority of the primary research is funded by manufacturers of the compound.
- The longest reported clinical trial on glucosamine and OA is for 3 years. As such, the information on the long-term toxicity/side effects of glucosamine administration is still lacking.
- Information on possible drug interaction(s) is still lacking.
- There is no evidence that combination of glucosamine & chondroitin is more effective than either supplement alone.
- Currently, the National Center for Complementary and Alternative Medicine (part of the US National Institute of Health) is conducting a large, well designed Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT). This study compares the efficacy of glucosamine, chondroitin, glucosamine and chondroitin, celecoxib & placebo in OA patients (expected publication in 2004).

Recommendations.

- Pharmaceutical grade glucosamine sulphate is reasonably used in WCB of BC accepted knee and probably hip joint OA injuries/diseases.
- Until Health Canada provides glucosamine manufacturers/distributors with their product approval, the WCB of BC should not be approving nor paying for its use.

References.

- Copy of References available on this board.
- The complete systematic review can be downloaded from: http://www.worksabc.com/for_health_care_providers/Assets/PDF/glucosamine.pdf
- This systematic review will be updated in summer 2005

10. (continued).
The studies were excluded if the participants were diagnosed with secondary OA, if there was insufficient description of diagnostic criteria and if it was a pharmacological instead of clinical studies. The search was done on Medline (1966 - September 2003) and Embase (1988 - September 2003) databases. 14 RCTs were included in this review. The authors concluded that glucosamine and chondroitin reduced pain and improved function in patients with mild to moderate OA who were treated for at least 3 months. Side effects were comparable with placebo treatment, both in type and frequency, after 3 years follow-up.

11. ...Glucosamine sulphate for pain relief and disease modification in osteoarthritis. New and Emerging Technology Briefing. National Horizon Scanning Centre. July 2003. University of Birmingham, UK. Downloaded from <http://www.publichealth.bham.ac.uk/horizon/2003reports11/glucosamine%20sulphate.pdf>

This review was conducted by the UK National Health Services National Horizon Scanning Centre in anticipation of the marketing application of medicinal quality Glucosamine Sulphate (NSC 758) from Rotta Research Laboratories. This review was conducted based on published systematic reviews by Towheed et al, McAlindon et al, Richey et al and randomized controlled trials by Reginster et al, Pavelka et al, Hughes and Carr and Rindone et al. The NHSC cautiously concluded that glucosamine sulphate may play a part in the long term therapy of OA and even potentially delay the natural progression of the disease. The annual cost of glucosamine was estimated to be comparable with COX-2 selective inhibitors. However, if glucosamine sulphate could alleviate symptoms and slow disease progression, the cost may be offset by reductions in the use of analgesics and NSAIDs.

Contraindications and side effects.

- All very high doses (5000mg/kg oral, 3000 mg/kg IM and 1500 mg/kg IV) of glucosamine administration, there is no mortality observed in mice or rats. As such, there is no LD50 for glucosamine.
- Evidence from case series, short term clinical trials and 3 year follow-up clinical trials show that side effects caused by administration of glucosamine (mostly oral administration) are generally mild, always lower than the standard first choice treatment for OA (NSAIDs) and sometimes even less than placebo.
- The side effects of glucosamine include epigastric pain/tenderness, heartburn, diarrhoea, nausea, dyspepsia, vomiting, drowsiness, constipation, gastric reflux, tachycardia, allergic epiglottis, headaches, vertigo, anorexia, abdominal pain, somnolence, insomnia, neuritis, depressive mood, edema, tachycardia, increased or decreased blood pressure, cardiac failure (4% in glucosamine vs. 7% in placebo).
- Glucosamine also has an important role in glucose metabolism by increasing insulin resistance. Currently, there is no contraindication to administering glucosamine in diabetic patients. However, appropriate rigorous follow-up of such diabetic patients would be warranted.
- Some experts have suggested that glucosamine **not be prescribed** for patients with rheumatoid arthritis, crystalline arthropathies such as gout nor in pregnant women or children.
- Patients allergic to shellfish should not use glucosamine.

Important clinical trials.

1. **Reginster JY, Deroisy R, Rovati LC et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomized, placebo controlled clinical trial. Lancet. January 27 2001;357:251-256.** This is the first clinical trial that shows the potential structure modifying effect of glucosamine in treating knee OA.
2. **Pavelka K, Gatterova J, Olejárová M et al. Glucosamine sulfate use and delay of progression of knee osteoarthritis. Archive of Internal Medicine, October 14 2002;162:2113-2123.** Also shows the potential structure modifying effect of glucosamine in treating knee OA.
3. **Cohen M, Wolfe R, Mai T and Lewis D. A randomized, double blind, placebo controlled trial of a topical cream containing glucosamine sulfate, chondroitin sulfate, and camphor for osteoarthritis of the knee. Journal of Rheumatology. 2003;30:523-528.** A good RCT. Shows that topical glucosamine, chondroitin and camphor has a greater mean reduction in pain compared to placebo after 8 weeks among knee OA patients.

5. (continued)
This is a high quality systematic review. The primary studies were included if they were double blind RCTs with a minimum of 4 weeks duration whether published or unpublished. There were 17 trials that fulfilled the inclusion criteria. However, only 15 trials were included in the meta analysis since information available on 2 trials did not allow for data extraction. Based on the meta analysis, the authors concluded that glucosamine or chondroitin may have a small to moderate short term effect for the symptomatic management of OA (pain and Lequesne index). However, the predicted effect might have been exaggerated due to methodological flaws in the primary studies. The authors showed the possibility of publication bias.

6. Hauselmann H J. Nutraceuticals for Osteoarthritis. Best Practice and Research Clinical Rheumatology. 2001;15(4):595-607.

This is a systematic review on nutraceuticals for OA (such as glucosamine and or chondroitin, avocado/soy bean, diet, fish oil). Based on recent high quality RCTs, meta analysis showed a small to moderate effect size of glucosamine in reducing pain and increasing function in OA patients and McAlindon et al. Universities Osteoarthritis Index (WOMAC) in knee OA patients. He suggested that the pain reduction due to the administration of glucosamine is comparable to pain reduction achieved by NSAIDs and results in fewer side effects. The author further suggested that the conclusion derived from this review on knee OA may not be generalizable to other joint OA's.

7. Glucosamine & Arthritis Update. Bandolier. Evidence based thinking about healthcare. Mar 2001;85(2).

This is an update of previous review. Bandolier concluded that the evidence on the effectiveness of glucosamine in OA treatment continues to build. However, it was pointed out that glucosamine takes about 1 month to exert its full effect and there was no definitive way to find out which glucosamine preparation provides the best stable and consistent formulation.

8. Ruane R and Griffiths P. Glucosamine therapy compared to ibuprofen for joint pain. British Journal of Community Nursing. 2002;7(3):148-152. In this review, trials with treatment duration of < 4 weeks were excluded. The actual interventions that were compared in the review were 1500 mg/day glucosamine sulphate and 1200 mg/day ibuprofen, each taken in 3 divided doses. There were 2 trials included in this review. The authors concluded that there was no significant difference between ibuprofen and glucosamine with respect to pain reduction in patients with OA. This conclusion needs to be interpreted cautiously due to the low methodological quality of this review.

9. Richey F, Bruyere O, Etgen O et al. Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis. A comprehensive meta analysis. Archive of Internal Medicine. July 14 2003;163:1514-1522.

The authors did an exhaustive search on published and unpublished RCTs of at least 4 weeks duration on glucosamine or chondroitin in treating knee or hip OA between January 1980 to March 2002. The authors approved of a clear description on the objectives and methodology being followed in this review. 15 studies fulfilled the selection criteria. 7 of these trials (1203 participants) were on glucosamine alone. The authors concluded that there was a small effect size of glucosamine in reducing joint space narrowing among knee OA patients (radiological measure). There was also a small to moderate effect size of glucosamine, as measured by Lequesne Index, overall WOMAC score, visual analog pain scale and mobility, in treating hip or knee OA patients. The authors concluded that the minimal time reported for the onset of glucosamine beneficial effect was 2 weeks. The number needed to treat for glucosamine was assessed at 4.9. With regard to side effects, the authors concluded that the observed, serious side effects were low and statistically identical between treated and placebo groups.

10. Christensen BS, Haga HJ, Nordrhaug I. Norwegian Health Technology Assessment. Glucosamine and Chondroitin for Osteoarthritis. Early Warning no. 2. September 2003. Downloaded http://www.sinet.no/snm/Publications/Etvasndrag_FramesetPublications.htm

This review was conducted by the Norwegian Health Technology Assessment team. The authors included all randomized controlled trials of patients diagnosed with primary knee OA who were treated with glucosamine and or chondroitin sulphate.

Results.

Systematic reviews (Evidence level 1):
• 9 published systematic reviews with the earliest review published in 1997 and the latest was in 2003.

1. Towheed TE, Hochberg MC. A systematic review of randomized controlled trials of pharmacological therapy in osteoarthritis of the knee with an emphasis on trial methodology. Seminars In Arthritis and Rheumatism. April 1997;26(5):755-770. This was systematic review on pharmacological therapy in OA of the knee. The emphasis of this review was on nonsteroidal anti-inflammatory agent. With regard to glucosamine the published glucosamine studies, the authors concluded that there was no evidence on the effectiveness of glycosaminoglycans in treating OA. However, this review did not employ a standardized review methodology and had a number of methodological limitations.

2. ... Glucosamine and Arthritis. Bandolier. Evidence based thinking about healthcare. Dec 1997;46(2). There were 8 double blind, randomized controlled trials (RCT) identified on patients with various anatomical locations of OA. Four trials listed IM administration and another 4 used oral administration of glucosamine. 5 were placebo-controlled trials and 3 were active-controlled trials. All trials showed superiority of glucosamine against placebo with overall Number Needed to Treat of 5. Overall, 231% of patients stopped taking glucosamine due to adverse effects. The majority of side effects noted were epigastric pain, heartburn, diarrhea and nausea. However, the trials being reviewed in this study were of short duration. The longest follow-up was only 8 weeks.

3. Barclay TS, Tsourounis C and McCart GM. Glucosamine. Annals of Pharmacotherapy. May 1998;32:574-579.

The authors included published RCTs from 1965 to 1997 with 30 or more participants being given oral glucosamine. There were 3 RCTs (2 placebo-controlled and 1 ibuprofen controlled) included in the review. All these trials were of short duration with the longest being 8 weeks. The authors concluded that glucosamine administration provided better improvement in OA symptoms, as measured by Lequesne index or pain score, compared to placebo or the same with improvement observed among OA patients treated with ibuprofen. The authors also pointed out the flaws in the design and data analysis of these trials. Adverse effects observed in these trials include constipation, nausea, heartburn, edema, painful/heavy legs, palpitation/tremor and skin reaction. The incidence of adverse effects ranged from 0.08% for tetracycline to 3.48% for epigastric pain.

4. Towheed TE, Anastasiades TP, Shea B et al. Glucosamine therapy for treating osteoarthritis (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software.

This is a standard high quality Cochrane review. 16 RCTs (12 on knee OA, one on spine OA, one on multiple sites and one did not specify the site) were identified. 13 RCTs were placebo-controlled and 4 RCTs were active-NSAIDs-controlled. The method of glucosamine administration varied across the studies. In the 13 placebo-controlled RCTs, glucosamine was found to be superior in all but one. In the 4 active-NSAIDs-controlled RCTs, glucosamine was found to be equivalent in two trials and superior in the other two trials. The authors noted that glucosamine had an excellent safety profile in the 16 RCTs. The ratio of withdrawal due to glucosamine toxicity was estimated at 1.4%. With regard to the quality of the primary studies, the authors concluded the median quality score was 9/16. The authors noticed that 13 out of 16 primary studies were somewhat associated with Rotta Pharmaceutical (one of the manufacturers of glucosamine in Italy). The authors concluded that there was good evidence that glucosamine was both effective and safe in treating OA. However, the long term effectiveness and toxicity of glucosamine therapy in OA remained unclear. The authors concluded that at that stage it was not known whether glucosamine prepared by manufacturers other than Rotta Pharmaceutical would be as effective in treating OA.

5. McAlindon TE, LaValley MP, Gulin JP, Falson DT. Glucosamine and chondroitin for treatment of osteoarthritis. A systematic quality assessment and meta analysis. JAMA. March 15 2000;283(11):1469-1475.

Abstract:

Background: Injured workers at the WCBBC have been submitting receipts for reimbursement after purchasing glucosamine sulfate as a potential treatment for their work-related joint problem. At present, reimbursement has been handled inconsistently.

Objectives: To conduct a systematic review on the effectiveness of glucosamine in treating osteoarthritis

Methods: Literature searches, up to August 15, 2003, were undertaken on various medical literature databases, health technology assessments and arthritis societies' websites. Searches were undertaken by employing a combination of medical subject heading and textwords of glucosamine, glycosaminoglycans, glucosamine and chondroitin, osteoarthritis, arthritis, degenerative joint disease, osteoarthritis and review or systematic review or meta-analysis or controlled trials or randomized controlled trials. Various inclusion and exclusion criteria were applied.

Results: There were 9 published systematic reviews that could be identified and retrieved. The earliest review was published in 1997 and the latest was in 2003. In addition, there were 5 published randomized controlled trials that were appraised separately. The results of these systematic reviews and clinical trials will be presented. Available data on contra indications and side effects will also be presented.

Conclusions:

- There is some level 1 evidence (Canadian Task Force on the Periodic Health Examination) on the short and long term effectiveness of glucosamine in alleviating OA symptoms, as measured by pain index, Lequesne index or WOMAC, particularly of the hip or knee joint.
- There is some level 1 evidence on the possible role of glucosamine as a structure-modifying drug for OA as measured by x-ray imaging of the joint space.
- The majority of research regarding glucosamine and OA were undertaken on patients with either knee or hip OA.
- The majority of the primary research on glucosamine is funded by manufacturers of the compound.
- The longest reported clinical trial on glucosamine and OA is for 3 years.

Background.

Over the last few years, injured workers have been submitting receipts for reimbursement after purchasing glucosamine sulfate as a potential treatment for their work-related joint problem - usually trauma induced osteoarthritis.

At present, reimbursement has been handled inconsistently

Epidemiology of osteoarthritis (OA):

- Worldwide, arthritis is the most common cause of long-term disability.
- In Canada, it is estimated that arthritis causes as 25 per cent of all long-term disability cases, a 1 in 10 Canadians have OA.
- OA affects people of all ethnic groups in all geographic locations and is more common in women.
- OA occurs most frequently in the hand, foot, knee, hip and spine.
- The cause of OA is mainly unknown (primary or idiopathic osteoarthritis). Less frequently, OA develops as a result of joint injury, infection, hereditary developmental, metabolic or neurologic disorders (secondary OA).
- Studies show that OA is not simply a result of mechanical "wear and tear" of a synovial joint over time.
- OA is not always a progressive disease. To date, much is still unknown regarding the natural history of OA.
- The principal clinical features usually reported by patients with OA include joint pain and decreased joint function.
- Cartilage, the principal structure involved in OA, possesses few, if any, pain sensitive fibers. Potential sources of pain in OA include osteophyte growth with stretching of the periosteum, raised intracapsular pressure, microfractures, ligament damage, capsular tension, meniscal injury and surrounding synovitis.
- As such, it is generally accepted that pain, at least in knee OA, is likely to be heterogeneous in origin. Different causes of pain may dominate different patients or the same patient at different phases of the disease.

Glucosamine:

- G has been evaluated as a treatment for OA in Germany since 1969.
- G can be derived from chitin, which is available from, e.g. crabs, lobster, shrimp or oyster shells. It can also be produced by synthetic means.
- In Europe (except the UK), G is available as a prescription medication. In the UK and North America, G is available as a dietary supplement (k.a. as nutraceutical).
- G is found in almost all animal tissues but is highest in concentration in the liver, kidney and cartilage.
- G is required for the biosynthesis of various compounds including glycolipids, glycoproteins, glycosaminoglycans, hyaluronate and proteoglycans (involved with joint structure and function).
- Clinically, G can be administered via IV, IM, intra-articular and oral routes.
- 70% of the oral glucosamine sulphate is absorbed through the intestine and excreted through the renal system.
- The majority of clinical trials on oral glucosamine have used a standard dosage of glucosamine. Strong taken three times daily, with or without rescue pain medication as required by the patient.
- The classification of G as a dietary supplement instead of a drug implies that the manufacturers do not need to comply with Good Practice in Manufacturing as outlined for pharmaceutical industries.
- Studies have shown that there is a variation in both purity and content of G from different manufacturers and even different batches from the same manufacturer.

Glucosamine and OA: biological plausibility:

- In vitro studies have indicated that G can stimulate glycosaminoglycan and proteoglycan synthesis within the joint tissue.
- G appears to directly reduce the progression of joint matrix destruction and probably promote regeneration of this substance by stimulating production of osteocytogenesis.

Objectives of this review.

- To conduct a systematic review on the available systematic reviews on the effectiveness of glucosamine in treating osteoarthritis
- To up-date the available published systematic reviews with the latest clinical trials on the subject
- To make policy recommendations to the WCB of BC based on the available evidence

Materials and methods.

- Literature searched up to August 15, 2003
- Done on PubMed, Cochrane Library, ACP Journal Club, Clinical Evidence, Bandolier, the US AHRQ, the US ICSI and the NHS CRD websites of members of the INAHTA (incl. Canada, the US, Great Britain, New Zealand, Australia, Sweden and Denmark), British Society for Rheumatology, Canadian and the US Arthritis Societies.

• **Keywords:** (glucosamine OR glycosaminoglycans OR (glucosamine AND chondroitin) AND (osteoarthritis OR arthritis OR degenerative joint disease OR osteoarthritis) AND (review OR systematic review OR meta analysis).

Inclusion criteria:

- systematic reviews and/or meta-analyses
 - humans (no restriction to age, sex or ethnicity of the participants)
 - no restriction placed on the year of publication
 - systematic reviews or meta-analyses were required to have glucosamine as the primary treatment modality in the study
 - Publications available in English
- **Exclusion criteria:**
- if the methodology used to evaluate the quality of the primary studies was not apparent.

Second search:

- Purpose: to identify newly published controlled or randomized controlled trials that have not been included in the latest published systematic review(s)
- Undertaken by substituting keywords review or systematic review or meta analysis with (controlled trials or randomized controlled trials)
- Search was limited to the publication years of the latest available systematic review