

GLUCOSAMINE:

Review of its effectiveness in treating
knee osteoarthritis.

by
WCB Evidence Based Practice Group
Dr. Craig W. Martin, Senior Medical Advisor

January 2004



Compensation and Rehabilitation Services Division

TABLE OF CONTENTS

	Page
Table of contents	i
Background.....	1
Osteoarthritis.....	1
Glucosamine	3
Glucosamine and OA: biological plausibility.....	3
Objectives of this review	5
Materials and methods.....	5
Results.....	6
Systematic reviews	6
Contraindications and side effects	10
Additional clinical trials	11
Summary/Conclusions	13
References	14
Other reading of interest	17
Appendix 1. Workers' Compensation Board of BC - Evidence-based Practice group. Quality of published evidence	21

Glucosamine: review on its effectiveness in treating knee osteoarthritis.

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, hence the Evidence Based Practice Group has been asked to undertake a systematic review on the subject of glucosamine, a dietary supplement (North American definition), and its effectiveness in treating osteoarthritis.

Throughout this paper, the reader will note that we repeatedly make reference to 'level of evidence' when assessing the literature. The definition of each of these levels is presented in Appendix 1.

Osteoarthritis (Evidence level 3 or 4)

Worldwide, arthritis is the most common cause of long-term disability⁽¹⁾. In Canada, it is estimated that arthritis causes 25 per cent of all long-term disability cases. It is estimated that arthritis and related disorders cost the Canadian economy nearly \$18 billion yearly⁽¹⁾. Osteoarthritis (OA), also known as degenerative joint disease, degenerative arthritis, and osteoarthrosis, is the most common form of arthritis⁽²⁾. OA affects people of all ethnic groups in all geographic locations^(3,4). It is more common in women. Nearly three million Canadians - approximately 1 in 10 - have osteoarthritis. OA is the most frequent joint disorder in seniors. It is estimated that 85% of Canadians are afflicted with osteoarthritis by age 70. The prevalence of osteoarthritis is two and a half times greater than heart disease and more than six times greater than cancer. It is estimated that by the year 2031, the number of people with arthritis (osteoarthritis and rheumatoid arthritis) in Canada will increase by 124%⁽⁵⁾. In the US, it is estimated that more than 1/3 of people older than 45 years report joint symptoms that vary from a sensation of occasional joint stiffness and intermittent aching associated with activity to permanent loss of motion and constant pain^(6,7).

The joint degeneration that causes the clinical syndrome of osteoarthritis occurs most frequently in the hand, foot, knee, hip and spine. However, it can develop in any synovial joint. In all synovial joints, the prevalence of degenerative changes increases with age. 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). The age of onset of secondary OA depends on the underlying cause. However, primary OA is strongly associated with age. The prevalence of primary OA increases sharply from less than 5% among those aged between 15 - 44 years and then rises rapidly up to 90% in some populations older than 65 years^(6,7).

The concept that OA is the result of normal wear and tear has evolved over time. Studies have shown that the changes observed in articular cartilage from older individuals differ from those observed in articular cartilage from individuals with OA. It has been shown that the clinical syndrome of joint pain and loss of joint function in OA is generally caused by progressive loss of articular cartilage, which is then accompanied by attempted repair of articular cartilage, remodelling and sclerosis of subchondral bone. In many instances, it is accompanied by the formation of subchondral bone cysts and osteophytes. Normal life-long joint use has not been shown to cause all of these degenerative changes. Thus, OA is not simply a result of mechanical 'wear and tear' of a synovial joint over time⁽⁸⁻¹¹⁾.

It is generally accepted that OA is a progressive disease. However, this is not always true. A summary of, on the average, 13 year follow-up studies among 426 patients with OA of the hip and knee suggested that only 39% patients had radiological signs of joint degeneration across time. These studies also showed that there was no strong correlation between radiological changes and the clinical course of the disease⁽¹²⁾. The clinical course of OA can remain stationary, slowly progress for many years, improve temporarily or in some instances progress rapidly such that the patient becomes significantly functionally impaired within a few years. Most OA patients will have intervals of symptomatic improvement. To date, much is still unknown regarding the natural history of OA. However, it has been shown that joint torsion and impact loading, crystal deposition and neuromuscular dysfunction are associated with more rapid progression of joint degeneration and subsequent development of clinically significant OA^(7,12).

The principal clinical features usually reported by patients with OA include joint pain and decreased joint function. Typically, pain is worse with weight bearing or joint 'loading' activities and improves with rest. Despite its importance, much remains unknown regarding the nature, cause and the natural history of OA pain. 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 intraosseous pressure, microfractures, ligament damage, capsular tension, meniscal injury and surrounding synovitis⁽¹³⁾. Inflammation may be present in OA and may cause pain by direct stimulation of peripheral afferent nociceptive fibers (PAN) or by sensitizing PAN fibres to mechanical or other noxious stimuli. Systemic markers of inflammation, such as C-reactive protein, are raised in many patients with OA and may predict future progression of the disease although this continues to be debated in the literature. There is also a central component of pain, and emotional influences, such as anxiety and depression may well be significant contributors to its clinical course. 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^(7,12-15).

Glucosamine (Evidence level 3 or 4 studies)

Glucosamine has been evaluated as a therapeutic agent for OA in Germany since 1969⁽¹⁶⁾. The compound glucosamine sulphate can be derived from chitin. Chitin is the second most abundant polymer on earth and is available from, for example, crab, lobster, shrimp or oyster shells. It can also be produced by synthetic means. In Europe (except the UK), glucosamine is available as a prescription medication. In the UK and North America, glucosamine is available as a dietary supplement (a.k.a. as nutraceutical i.e. dietary supplements that have proven pharmaceutical properties and efficacy)^(17,18).

Glucosamine is found in almost all human tissues but is highest in concentration in the liver, kidney and cartilage. It is the most fundamental building block required for the biosynthesis of various compounds including glycolipids, glycoproteins, glycosaminoglycans, hyaluronate and proteoglycans, which are all compounds intimately involved with joint structure and function. Glucosamine is also an essential component of cell membranes and cell surface proteins as well as interstitial structural molecules that hold cells together. Directly or indirectly, glucosamine plays a role in the formation of articular surfaces, tendons, ligaments, synovial fluids, skin, bone, nails, heart valves, blood vessels and mucous secretion within the digestive, respiratory and urinary systems⁽¹⁹⁾.

Clinically, glucosamine can be administered via intravenous, intramuscular, intra-articular [these 3 methods are practised in Europe (with the exception of UK)] and oral routes. Approximately 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, 500mg taken three times daily, with or without rescue pain medication as required by the patient⁽²⁰⁾.

The classification of glucosamine 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 glucosamine from different manufacturers and even different batches from the same manufacturer. Investigators from the US National Institute of Health overseeing the largest clinical trial on glucosamine and chondroitin for treatment of OA could not find a satisfactory source that contained consistent amounts from batch to batch and had to manufacture the compounds themselves^(21,22).

Glucosamine and OA: biological plausibility (Evidence level 4) studies

OA results in the progressive catabolism of cartilage proteoglycans due to an imbalance between its synthesis and degradation. This relative decrease in the cartilage proteoglycans alters the affinity of the cartilage matrix for water and the ability of water (H₂O) to easily flow in or out of the joint surface. It has been shown that such structural changes in the composition of these molecules have a negative impact on the biomechanical properties of normal adult articular cartilage and synovial fluid. The changes in the molecular structure make

articular cartilages vulnerable to the effects of compressive, tensile and shear forces that occur during normal joint motion^(22,23).

Proteoglycans, large macromolecules consisting of multiple chains of glycosaminoglycans and oligosaccharides attached to a central protein core, provide a framework for collagen and also helps bind water and cations, forming a viscous, elastic layer that lubricates and protects cartilage. The glycosaminoglycans most common in human connective tissue include keratin sulphate, dermatan sulphate, heparin sulphate, chondroitin sulphate and hyaluronic acid. They consist of amino sugars which are repeating disaccharide units composed of a hexuronic acid (D-glucuronic acid, iduronic acid or L-galactose) and a hexosamine (D-glucosamine or D-galactosamine)^(13,23,,24)

Theoretically, exogenous administration of glycosaminoglycans (e.g. glucosamine sulphate or chondroitin sulphate) to chondrocytes will ameliorate the imbalance between synthesis and degradation of cartilage occurring in the OA patient. It is also theoretically plausible to prevent further damage to the articular cartilage of osteoarthritic joints. Glucosamine (2-amino-2-deoxy-alpha-D-glucose) is an aminosacharide that takes part in the synthesis of glycosaminoglycans and proteoglycans by chondrocytes. Glucosamine serves as a substrate for the biosynthesis of chondroitin sulphate, hyaluronic acid and other macromolecules located in the cartilage matrix⁽²³⁾.

Laboratory studies have suggested that glucosamine can be absorbed through the gastrointestinal tract. Radioisotope studies of glucosamine have shown rapid distribution throughout the body with selective uptake by articular cartilage. In vitro studies have indicated that glucosamine can stimulate glycosaminoglycan and proteoglycan synthesis within the joint tissue. In animal studies, high doses of glucosamine have been shown to have mild anti-inflammatory effects. The mechanism of anti-inflammatory effects of glucosamine is apparently not done via the cyclooxygenase and modification of prostaglandin pathway, such as in non-steroidal anti-inflammatory drugs, but it is probably based on its ability to synthesize proteoglycans needed to stabilize cell membranes and increase the intracellular ground substance. Glucosamine does not have the ability to directly act as an analgesic agent. Instead, glucosamine appears to directly reduce the progression of joint matrix destruction and probably promote regeneration of this substance by stimulating production of osteoglycans. Despite explanations provided by these studies, the physiological explanation on how glucosamine influences cartilage destruction still needs further elucidation^(19,37).

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 searches, up to August 15, 2003, were undertaken on medical literature databases including PubMed, Cochrane Library (including Cochrane Clinical Trial Registry), ACP Journal Club, Clinical Evidence, Bandolier, the US Agency for Healthcare Research and Quality, the US Institute for Clinical System Improvement and the NHS Centre for Reviews and Dissemination at the University of York.; websites of members of the International Network of Agencies for Health Technologies Assessment (including Canada, the US, Great Britain, New Zealand, Australia, Sweden and Denmark), British Society for Rheumatology, Canadian and the US Arthritis Societies.

Searches were undertaken by employing a combination of medical subject heading and textwords of; glucosamine, glycosaminoglycans, glucosamine and chondroitin, osteoarthritis, arthritis, degenerative joint disease, osteoarthrosis and review or systematic review or meta analysis. *Inclusion criteria:* publications were selected if they were systematic reviews and/or meta-analyses. The primary studies were restricted to humans with no restriction to age, sex or ethnicity of the participants. There was no restriction placed on the year of publication. However, these systematic reviews or meta-analyses were required to have glucosamine as the primary treatment modality in the study. Publications were restricted to those available in English. *Exclusion criteria:* publications were excluded if the methodology used to evaluate the quality of the primary studies was not apparent.

A second search was undertaken by substituting keywords review or systematic review or meta analysis with controlled trials or randomized controlled trials limited to the publication years of the latest available systematic review. The purpose of the second search was to identify newly published controlled or randomized controlled trials on the subject that have not been included in the latest published systematic review(s).

Results

Systematic reviews (Evidence level 1)

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⁽²⁴⁻³²⁾.

1. A systematic review on pharmacological therapy in OA of the knee was conducted by Towheed and Hochberg in 1997⁽²⁴⁾. The emphasis of that review was on nonsteroidal anti-inflammatory agents (NSAIDs). However, the review included 266 patients in 6 glycosaminoglycan trials (1 trial in 1982, 2 trials in 1987, 2 trials in 1989 and 1 trial in 1993). With regard to glycosaminoglycans, 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 limitations by virtue of its methodology including English language only inclusion, limited literature searches and published primary research on knee OA only ('mixed' trial of knee and hip OA, for example, was excluded).
2. Bandolier did a review on glucosamine and arthritis in 1997⁽²⁵⁾. There were 8 randomized double blind controlled trials identified on patients with various anatomical locations of OA. Four trials listed intra-muscular administration of glucosamine and another 4 used oral administration of the agent. Five trials were placebo-controlled trials and three trials were active-controlled trials. All trials showed superiority of glucosamine against placebo with overall Number Needed to Treat (NNT) of 5 (i.e. one of every five patients with OA being treated with glucosamine would have short term benefit in reduced pain who would not have had it if they had been given placebo). The active-controlled trials showed that there was no difference in terms of pain between OA patients treated with glucosamine or NSAIDs. Overall, 2.31% 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, Tsourounis and McCart published a systematic review on the subject in 1998⁽²⁶⁾. The authors included published randomized controlled trials (RCT) 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 with a total of 275 patients. 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. However, the authors also pointed out the flaws in the design and data analysis of these trials including its blinding method, inclusion/exclusion

criteria, concomitant medication use and the failure to conduct intention to treat analysis. Adverse effects observed in these trials include constipation, nausea, heartburn, edema, painful/heavy legs, palpitation/exhaustion and skin reaction. The incidence of adverse effects ranged from 0.08% for tachycardia to 3.48% for epigastric pain

4. Towheed, Anastassiades, Shea et al (2003)⁽²⁷⁾ published a systematic review on the subject in the Cochrane Library. The authors did a thorough search of RCT on the effectiveness in treating OA and toxicity of glucosamine. The literature search, which included manual searching and personal communications, was done up to November 1999. This appears to be the first published systematic review on glucosamine use in OA that had been undertaken by employing the rigorous methodology required when conducting such reviews. The majority of the primary studies reported outcome measures on pain, range of motion and functional status. 16 RCTs (12 on knee OA, one on spine OA, one on multiple sites and two 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%. Of the 992 subjects on glucosamine, only 61 reported adverse reactions. With regard to the quality of the primary studies, the authors concluded that median design score was 2/8, median data analysis score was 7/8 and total median quality score was 9/16. The authors also pointed out what they considered to be serious flaws in the primary studies, including the lack of standardization in the diagnostic criteria of OA, short duration of follow-up, blinding and randomization methods, lack of sample size calculation and intention to treat analysis as well as lack of pre-randomization inclusion and exclusion criteria. Further, the authors noticed that 13 out of 16 primary studies were somewhat associated with Rotha 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 Rotha Pharmaceutical would be as effective in treating OA. In this systematic review, the authors did not assess the possibility and the impact of publication bias, for example, by employing a simple funnel plot analysis.
5. McAlindon, LaValley, Gulin and Felson published a systematic review and meta analysis on glucosamine and chondroitin for treatment of OA in 2000⁽²⁸⁾. The authors searched Medline (1996 to June 1999) and the Cochrane trial registry for trials on glucosamine and or chondroitin for treating knee or hip

OA. The primary studies were included if they were randomized, double blind controlled trials with a minimum of 4 weeks duration whether published or unpublished. The authors provided a clear review methodology including inclusion and exclusion criteria. 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 e.g. inadequate blinding, not analyzed by intention to treat, publication bias, factory sponsored trials (14 of 15 trials) and the inverse relationship between trial effect size and the trial size and quality (lower quality and or smaller trials showed a larger effect). The authors undertook a funnel plot analysis in order to assess the possibility of publication bias. An asymmetric funnel plot confirmed the possibility of publication bias. In light of the relatively poor quality of the primary studies, high probability of publication bias and short term duration of follow-up, the conclusion that glucosamine or chondroitin use demonstrated a small to moderate effect in relieving symptoms of OA needs to be interpreted with caution. The authors did not summarize the safety profile of the compounds.

6. In 2001 Hausellman published a systematic review on nutraceuticals for OA (such as glucosamine and or chondroitin, avocado/soy bean, diet, fish oil) ⁽²⁹⁾. The inclusion criteria included published peer-reviewed primary research on knee OA treated with glucosamine and or chondroitin as the only orally given 'drug'. He found 5 studies of 331 patients that fulfilled the inclusion criteria for glucosamine alone. He concluded that there was a moderate to large effect size of glucosamine in treating knee OA. However, the effect size diminished when the meta analysis was limited to the more recent high quality trials. Meta analysis limited to these high quality trials showed a small to moderate effect size of glucosamine in reducing pain and increasing function [Western Ontario and McMaster 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. The highlight of this review was the inclusion of a 3 year follow-up, high quality clinical trial that was published in 2001 by Reginster et al. This particular trial will be discussed separately in the section on additional clinical trials.
7. In March 2001, Bandolier up-dated their previous review on glucosamine ⁽³⁰⁾. In this review, Bandolier included the systematic review by Towheed et al ⁽²⁷⁾ and McAlindon et al ⁽²⁸⁾. Bandolier concluded that based on these 2 reviews short-term primary studies, the evidence on the effectiveness of glucosamine

on short-term primary studies, 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 and Griffiths (2002) published a systematic review comparing oral glucosamine with ibuprofen for joint pain⁽³¹⁾. 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. The authors did not provide information on how the trials were selected or reviewed and they did not comment on how the validity of the primary research was assessed. Unpublished trials were not included in this review. There were 2 trials (218 patients) 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 et al published a meta analysis on oral glucosamine or chondroitin in knee OA (2003)⁽³²⁾. The authors did an exhaustive search on published and unpublished randomized placebo controlled trials of at least 4 weeks duration on glucosamine or chondroitin in treating knee or hip OA between January 1980 to March 2002. Richey et al provided a clear description on the objectives and methodology being followed in this review. Fifteen studies fulfilled the selection criteria. Seven 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. The Norwegian Health Technology Assessment team conducted a systematic review on the clinical effectiveness of glucosamine and chondroitin sulphate in the treatment of osteoarthritis. The authors included all randomized controlled trials of patients diagnosed with primary knee OA who were treated with glucosamine and or chondroitin sulphate. 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 authors also attempted to conduct an economic evaluation as part of the review. The search was done on Medline (1966 -

September 2003) and Embase (1988 – September 2003) databases. Fourteen RCTs with a total of 2100 patients were included in this review. The authors concluded that glucosamine and chondroitin relieved 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. The authors were not able to find any published cost-effectiveness study on the subject. However, based on the retail price of Artrox® (medicinal grade glucosamine preparation from Pfizer), the authors estimated the cost around 7.00 Nkr (Norwegian kroner) for 1000 mg of Artrox® glucosamine. In contrast, dietary supplement grade of glucosamine varied from 0.6 - 1.25 Nkr/1000 mg of glucosamine.

11. The UK National Health Services National Horizon Scanning Centre (NHSC) undertook a review on glucosamine sulphate for treating osteoarthritis in anticipation of the marketing application of medicinal quality Glucosamine Sulphate (NSC 758) from Rotta Research Laboratorium. The available brief manuscript did not specify the methodology employed in this review. However, the review was conducted based on published systematic reviews by Towheed et al⁽²⁾, McAlindon et al⁽²⁸⁾, Richy et al⁽³²⁾ and randomized controlled trials by Reginster et al⁽³³⁾, Pavelka et al⁽³⁴⁾, Hughes and Carr⁽³⁷⁾. Other readings of interest) and Rindone et al⁽³⁵⁾. Other readings of interest). An abstract based cost-benefit analysis of glucosamine sulphate compared with piroxicam demonstrated that glucosamine sulphate was more expensive (€ 81 vs. € 33), and that glucosamine sulphate resulted in a potential net saving of almost € 11 per patient in 90 days, and € 110 per patient in 150 days. The authors attributed this to glucosamine's higher efficacy. However, it was not clear whether that was a direct or indirect evaluation. The NHSC cautiously concluded that glucosamine sulphate may play a part in the long term therapy of OA and even potentially delaying 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. At the time of publication, it was estimated that the Rotta's glucosamine sulphate would cost about £ 1 per day per patient.

Contraindications and side effects

At 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^(19,22). Evidence from case series (Evidence level 3,4), short term clinical trials (evidence level 1,2) and 3 year follow-up clinical trials (evidence level 1)^(33,34) 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, diarrhea, nausea, dyspepsia, vomiting, drowsiness, constipation, gastric heaviness, itchiness/allergic episode, 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. Animal studies have shown that glucosamine increased glucose insulin resistance in normal and experimentally diabetic animals. Patients with OA tend to be elderly and obese, as such they tend to be prone to type 2 diabetes. A subtle worsening of insulin resistance in this type of patients may well then result in subsequent longer-term sequelae. However, 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 (Evidence level 4)^(23,38,39).

Additional clinical trials

1. A randomized double blind placebo controlled trial of 212 patients by Reginster et al (2001) is the first long term trial on glucosamine sulfate use in treating knee OA⁽³³⁾. The authors randomly assigned 106 patients, each to receive either placebo or glucosamine for 3 years. This is a high quality randomized controlled trial which has been included in some of the more current systematic reviews as noted above. This is the first clinical trial that shows the potential structure modifying effect of glucosamine in treating knee OA. In the three years follow-up the authors found that among placebo treated patients there were progressive joint space loss (mean joint space loss of - 0.31 mm) while no significant joint space loss was observed among patients treated with glucosamine (mean joint space loss - 0.06 mm).
2. Another more recent randomized double blind controlled trial by Pavelka et al (2002)⁽³⁴⁾ also shows the potential structure modifying effect of glucosamine in treating knee OA. Pavelka et al found that at the end of 3 year follow-up, there was a mean joint space narrowing of - 0.19 mm among placebo treated patients and a mean improvement of joint space of 0.04 mm among glucosamine treated patients. However, the quality of this study is lower than the previous study undertaken by Reginster et al⁽³³⁾.
3. A good randomized double blind controlled trial by Cohen et al⁽³⁵⁾ (2003) shows that topical glucosamine, chondroitin and camphor has a greater mean reduction in pain compared to placebo after 8 weeks among knee OA patients. At the end of eight week follow-up, Cohen et al found that patients treated with the active substance had a significantly higher reduction in pain

score (mean reduction (SD) 34 ± 26 mm) compared to the placebo treated group (mean reduction (SD) 16 ± 27 mm).

4. Braham et al published a double blind 'randomized' controlled trial on glucosamine in patients with regular knee pain (not necessarily due to OA) (2003)⁽³⁶⁾. There are several methodological flaws in this study including patient selection process, inclusion/exclusion criteria and the use of pseudo-randomization instead of true randomization. However, this is a unique study with regard to the assessment of knee pain in general. The authors found that patients treated with glucosamine had a better quality of life score (as measured by Knee Injury and Osteoarthritis Outcome Score) at week eight and twelve, and lower knee pain (as measured by Knee Pain Scale) at week eight.
5. A recent small (n = 18) randomized placebo controlled trial in Canada on glucosamine in treating OA of the knee was conducted by Kumbhare et al⁽⁴⁰⁾. The study showed that both the glucosamine and placebo group showed improvement in pain scores and range of motion, suggesting a placebo effect. However, there was a 42% drop out of participants in this study. This study has not been published in any peer reviewed journal nor has it been included in any of the systematic reviews reviewed above.
6. The meta analysis by Richy et al⁽⁹⁾, systematic review published by the Norwegian Health Technology Assessment⁽⁴⁰⁾ and the National Health Services National Horizon Scanning⁽⁴¹⁾ have already incorporated the latest published clinical trials.

Summary/Conclusions

- There is some level 1 evidence (Appendix 1) 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 regarding glucosamine and OA were undertaken on patients with either knee or hip OA. This limitation raises questions regarding 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, chlorhydrate salt, hydroiodide, combination with herbs, vitamin A, vitamin E, or minerals including Mg, K, Cu, Zn or Se).
- 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. Given the nature of OA as a chronic disease process, the information on the long-term toxicity/side effects of glucosamine administration is still lacking.
- Information on possible drug interaction(s) is still lacking.
- The use of combination glucosamine and chondroitin for treatment of OA has become extremely popular. However, there is no evidence that this combination 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 (as of September 16, 2003 is still recruiting participants) Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT). This study is designed to compare the efficacy of glucosamine, chondroitin, glucosamine and chondroitin, celecoxib (COX-2 inhibitor) and placebo on patients with OA. The results of this major clinical trial are expected to be published in 2004 and will provide more definitive evidence on the efficacy of glucosamine in particular. The Evidence Based Practice Group will update this review accordingly⁽²¹⁾.

References

1. Arthritis Society Canada website accessed on September 15, 2003. <http://www.arthritis.ca/local%20programs/alberta/about%20us/arthritis%20in%20ab/default.asp?s=1>
2. Towheed TE, Anastassiades TP, Shea B et al (2001). Glucosamine therapy for treating osteoarthritis (Cochrane Review). In: Cochrane Library Issue 3. Oxford Update Software.
3. Buckwalter JA, Stanish WD, Rosier RN et al. The increasing need for nonoperative treatment of patients with osteoarthritis. *Clinical Orthopaedics and Related Research*. 2001;385:36-45.
4. Manek NJ. Medical management of osteoarthritis. *Mayo Clinic Proceedings*. 2001;76:533-539.
5. Arthritis Society Canada website accessed on September 15, 2003. <http://www.arthritis.ca/resources%20for%20advocates/arthritis%20advocacy%20priorities/orthopaedic%20care/problem/default.asp?s=1>.
6. Felson DT et al. NIH Conference. Osteoarthritis: New Insights. Part 2. Treatment approaches. *Annals of Internal Medicine*. 2000;133(9):726-737.
7. Felson DT et al. NIH Conference. Osteoarthritis: New Insights. Part 1. The disease and its risk factors. *Annals of Internal Medicine*. 2000;133(8):635-646.
8. Sutton L, Rapport L, Lockwood B. Glucosamine: Con or Cure?. *Nutrition*. 2002;18:534-536.
9. Schenck Jr. RC. New approach to the treatment of osteoarthritis: oral glucosamine and chondroitin sulfate. *AAOS Instructional Course Lectures*. 2000;49:491-494.
10. McAllindon T. Glucosamine for osteoarthritis: dawn of a new era? *Lancet*. January 27 2001;357:247.
11. Creamer P. Osteoarthritis pain and its treatment. *Current Opinion in Rheumatology*. 2000;12:450-455.
12. Buckwalter JA (moderator). Year 2000 American Academy of Orthopedic Surgeons Symposium. Non operative treatment of knee osteoarthritis. Accessed through <http://www.aaos.org/wordhtml/anmt2000/sympos/symp-b.pdf> in August 1, 2003.
13. Brief AA, Maurer SG, DiCesare PE. Use of glucosamine and chondroitin sulfate in the management of osteoarthritis. *Journal of the American Academy of Orthopedic Surgeons*. 2001;9:71-78.
14. Bruyere O, Honore A, Ethgen O et al. Correlation between radiographic severity of knee osteoarthritis and future disease progression. Results from a 3-year prospective placebo-controlled study evaluating the effect of glucosamine sulfate. *Osteoarthritis and Cartilage*. 2003;11:1-5.
15. Bruyere O, Honore A, Rovati LC et al. Radiologic feature poorly predict clinical outcomes in knee osteoarthritis. *Scandinavian Journal of Rheumatology*. 2002;31:13-16.
16. McAllindon T. Glucosamine and chondroitin for osteoarthritis? *Bulletin on the rheumatic diseases*. 2001;50(7):1-4.

17. Deal CL, Moskowitz RW. Nutraceuticals as therapeutic agents in osteoarthritis. *Rheumatic Disease Clinics of North America*. May 1999;25(2):379-395.
18. Morelli V, Naquin C, Weaver V. Alternative therapies for traditional disease states: osteoarthritis. *American Family Physician*. Jan 15 2003;67(2):339-344.
19. De los Reyes G, Koda RT, Lien EJ. Glucosamine and chondroitin sulfates in the treatment of osteoarthritis: a survey. *Progress in Drug Research*. 2000;55:82-103.
20. Hungerford DS, Jones LC. Glucosamine and chondroitin sulfate are effective in the management of osteoarthritis. *Journal of Arthroplasty*. 2003;18(3) suppl. 1:5-9.
21. ...Glucosamine/chondroitin Arthritis Intervention Trial (GAIT). *ClinicalTrials.gov*. Accessed through www.clinicaltrials.gov/ct/show/nct00032890?order=2 on August 1, 2003.
22. ... Problems with dietary supplements. *The Medical Letter*. September 30 2002;44(1140):85-86.
23. Kelly GS. The role of glucosamine sulfate and chondroitin sulfates in the treatment of degenerative joint disease. *Alternative Medicine Review*. Febr 1998;3(1):27-39.
24. 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.
25. ... Glucosamine and Arthritis. *Bandolier*. Evidence based thinking about healthcare. Dec 1997;46(2).
26. Barclay TS, Tsourounis C and McCart GM. Glucosamine. *Annals of Pharmacotherapy*. May 1998;32:574-579.
27. Towheed TE, Anastassiades TP, Shea B et al. Glucosamine therapy for treating osteoarthritis (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2003. Oxford: Update Software.
28. McAlindon TE, LaValley MP, Gulin JP, Felson DT. Glucosamine and chondroitin for treatment of osteoarthritis. A systematic quality assessment and meta analysis. *JAMA*. March 15 2000;283(11):1469-1475.
29. Hauselmann HJ. Nutripharmaceuticals for osteoarthritis. *Best Practice and Research Clinical Rheumatology*. 2001;15(4):595-607.
30. ...Glucosamine and Arthritis Update. *Bandolier*. Evidence based thinking about healthcare. Mar 2001;85(2).
31. Ruane R and Griffiths P. Glucosamine therapy compared to ibuprofen for joint pain. *British Journal of Community Nursing*. 2002;7(3):148-152.
32. Richy F, Bruyere O, Ethgen 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.
33. Reginster JY, Derolsy 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.

34. Pavelka K, Gatterova J, Olejarova M et al. Glucosamine sulfate use and delay of progression of knee osteoarthritis. *Archive of Internal Medicine*. October 14 2002;162:2113-2123.
35. 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.
36. Braham R, Dawson B and Goodman C. The effect of glucosamine supplementation on people experiencing regular knee pain. *British Journal of Sports Medicine*. 2003;37:45-49.
37. Adams ME. Hype about glucosamine. *Lancet*. July 31 1999;354:353-354.
38. Rovati LC, Anfield M, Giacobelli G et al. Glucosamine in osteoarthritis. *Lancet*. November 6 1999;354:1640.
39. Russell AI and McCarty MF. Glucosamine in osteoarthritis. *Lancet*. November 6 1999;354:1641.
40. Christensen BS, Haga HJ, Norderhaug I. Norwegian Health Technology Assessment. Glucosamine and Chondroitin for Osteoarthritis. Early Warning no. 2. September 2003. Downloaded from <http://www.sintef.no/smm/Publications/Engsmdrag/FramesetPublications.htm> in January 7, 2004.
41. ...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/2003reports/glucosamine%20sulphate.pdf> in January 7, 2004.

Other reading of interest

These include articles on this subject that the Evidence Based Practice Group is aware of and has evaluated and did not use as a reference in this particular document. Italicized sentences indicate the type of article, along with a descriptive comment.

1. Leeb BF, Schweitzer H, Montag K, Smolen JS. A meta-analysis of chondroitin sulfate in the treatment of osteoarthritis. *Journal of Rheumatology*. Jan 2000;27(1):205-211.
2. Mazieres B, Combe B, Van AP et al. Chondroitin sulfate in osteoarthritis of the knee: a prospective double blind placebo controlled multicenter clinical study. *Journal of Rheumatology*. 2001;28:173-181.
3. Ernst E. Complementary and alternative medicine in rheumatology. (*non systematic review*) *Bailliere's Clinical Rheumatology*. 2000;14(4):731-749.
4. Fillmore CM, Bartoli L, Bach R, Park Y. Nutrition and dietary supplements. *Physical Medicine and Rehabilitation Clinics of North America*. August 1999;10(3):673-703.
5. Leslie M. Knee osteoarthritis management therapies (*Non-systematic review*). *Pain Management Nursing*. June 2000;1(2):51-57.
6. Hochberg MC. What difference a year makes: reflections on the ACR recommendations for the medical management of osteoarthritis. *Current Rheumatology Report*. 2001;3:473-478.
7. Rovati LV. Clinical research in osteoarthritis: design and results of short term and long term trials with disease-modifying drugs (*review of 3 trials on Rotta Research Lab glucosamine compound*). *International Journal of Tissue Reaction*. 1992;XIV(5):243-251.
8. Da Camara CC and Dowless GV. Glucosamine sulfate for osteoarthritis. (*Non-systematic Review*) *Annals of Pharmacotherapy*. May 1998;32:580-587.
9. O'Rourke M. Determining the efficacy of glucosamine and chondroitin for osteoarthritis. *The Nurse Practitioner*. June 2001;26(6):44-52.
10. Gottlieb MS. Conservative management of spinal osteoarthritis with glucosamine sulfate and chiropractic treatment. (*non systematic review*) *Journal of Manipulative and Physiological Therapeutics*. July-Aug 1997;20(6):400-414.
11. Schnitzer TJ. Update of ACR Guidelines for Osteoarthritis: Role of the Coxibs. Proceedings from the symposium 'The evolution of anti-inflammatory treatments in arthritis: current and future perspectives. *Journal of Pain and Symptom Management*. April 2002;23(4S):S24-S30.
12. Hochberg MC, Dougados M. Pharmacological therapy of osteoarthritis. (*non systematic review*). *Best Practice and Research. Clinical Rheumatology*. 2001;15(4):583-593.
13. Blake G. Glucosamine for osteoarthritis. (*non systematic review*). *Advance for Nurse Practitioners*. August; 2002:26-27.

14. Spencer-Green G. Drug treatment of arthritis. Update on conventional methods. (*non systematic review*). Postgraduate Medicine. May 15 1993;93(7):129-140.
15. Murad H and Tabibian MP. The effect of an oral supplement containing glucosamine, amino acids, minerals and antioxidants on cutaneous aging: a preliminary study. Journal of Dermatological Treatment. 2001;12:47-51.
16. Freeze HH. Sweet solution: sugars to the rescue. (*hypothesis on how glucosamine may work in treating OA*). Journal of Cell Biology. Aug 19;158(4):615-616.
17. Harris GR, Susman JL. Managing musculoskeletal complaints with rehabilitation therapy: Summary of the Philadelphia Panel evidence-based clinical practice guidelines on musculoskeletal rehabilitation interventions. (*Summarized the available systematic review*). Journal of Family Practice. December 2002;51(12):1042-1046.
18. Priebe D., McDiarmid T., Mackler L. Do glucosamine or chondroitin cause regeneration of cartilage in osteoarthritis. (*Evidence-based question and answer type using available systematic review*). Journal of Family Practice. March 2003;52(3):237-239.
19. Carter IR. Does glucosamine sulfate affect progression of symptoms and joint structure changes in osteoarthritis? (*Evidence-based question and answer type using available systematic review*). Journal of Family Practice. May 2001;50(5):394.
20. Edelist DD and Evans MF. Do glucosamine and chondroitin treat the symptoms of osteoarthritis? (*Evidence-based question and answer type using available systematic review*). Canadian Family Physician. Febr 2001;47:275-277.
21. Hooper M. Is glucosamine an effective treatment for osteoarthritic pain? (*Evidence-based question and answer type using available systematic review*). Cleveland Clinic Journal of Medicine. June 2001;68(6):494-495.
22. Vas AL. Double blind clinical evaluation of the relative efficacy of ibuprofen and glucosamine sulphate in the management of osteoarthritis of the knee in out-patients (*one of the earliest equivalency trial. Poor methodology*). Current Medical Research and Opinion. 1982;8(3):145-149.
23. D'Ambrosio E, Casa B, Bompani R et al. Glucosamine sulphate: a controlled clinical investigation in arthrosis. (*one of the earliest superiority trials. Poor methodology*). Pharmatherapeutica. 1981;2(8):504-508.
24. Reichelt A, Forster KK, Fischer M et al. Efficacy and safety of intramuscular glucosamine sulfate in osteoarthritis of the knee. (*one of the earliest intramuscular trials. Poor methodology*). Arzneimittelforschung. 1994; 44(1): 75-80. (article in English)
25. Crolle G, D'Este E. Glucosamine sulphate for the management of arthrosis: a controlled clinical investigation. (*one of the earliest intramuscular and intraarticular trials. Poor methodology*). Current Medical Research and Opinion. 1980;7(2):104-109.

26. Delafuente JC. Glucosamine in the treatment of osteoarthritis. (*non systematic review*). Rheumatic Disease Clinics of North America. Febr 2000;26(1):1-11.\
27. Vertullo C. Management of the osteoarthritic knee. New advances in non-operative therapy. (*Non systematic review on non-operative treatment of osteoarthritis including glucosamine and chondroitin*). Australian Family Physician. Sept 2001;30(9):853-857.
28. Chard J and Dieppe P. Glucosamine for osteoarthritis: magic, hype or confusion? It's probably safe-but there's no good evidence that it works. Editorial. (*An editorial article re: glucosamine. Some mistakes in this article that were pointed out in the Letters to the Editor on the 27 Oct 2001 issue of BMJ*). BMJ. 16 June 2001;322:1439-1440.
29. Towheed TE. Published meta-analyses of pharmacological therapies for osteoarthritis. (*Commentaries and summaries of the available two systematic reviews on glucosamine and one on chondroitin*). Osteoarthritis and Cartilage. 2002;10:836-837.
30. March LM and Stenmark J. Non-pharmacological approaches to managing arthritis. (*Summarized evidence on the effectiveness of available osteoarthritis treatment*). Medical Journal of Australia. 19 November 2001;175:S102-S107.
31. Lee J, Thorson D, Jurisson M et al. Health Care Guideline. Diagnosis and Treatment of Adult Degenerative Joint Disease (DJD) of the Knee. (*Provides a general somewhat evidence-based diagnosis and treatment of DJD of the knee*). ICSI. May 2002.
32. Debi R, Robinson D, Agar G, Halperin N. GAG for osteoarthritis of the knee - a prospective study. (*Registered at Cochrane Library, article is in Hebrew. Small study on IV glucosamine and chondroitin compared to placebo. Significant difference in term of knee tenderness and ROM*). Harefuah. Mar 15 2000;138(6):451-453, 518.
33. Walker-Bone K. 'Natural remedies' in the treatment of osteoarthritis. Drugs and Aging. 2003;20(7):517-526. (*provides a brief and concise expert review on various aspect of natural remedies being promoted for treating OA*)
34. Thie NMR, Narasimha GP and Major PW. Evaluation of glucosamine sulfate compared to ibuprofen for the treatment of temporo-mandibular joint osteoarthritis: a randomized double blind controlled 3-month clinical trial. Journal of Rheumatology 2001;28:1347-1355. (*unique trial on OA of TMJ. Glucosamine showed to be as efficacious as ibuprofen in reducing pain. Not good methodologically though*).
35. Rindone JP, Hiller D, Collacot E et al. Randomized, controlled trial of glucosamine for treating osteoarthritis of the knee. Western Medical Journal. 2000;172:91-94. (*unique patient population i.e. from the US Veterans Affair. Glucosamine was not significantly different from placebo in reducing pain or increasing function. However, the study was done for only 60 days, the number of participants were small and without any sample size calculation, the data was not analyzed according to intention to treat principle*)

36. Das A Jr and Hammad TA. Efficacy of a combination of FCHG49™ glucosamine hydrochloride, TRH22™ low molecular weight sodium chondroitin sulfate and manganese ascorbate in the management of knee osteoarthritis. *Osteoarthritis and Cartilage*. 2000;8:343-350. *(First study done in the US to use these combination of drugs. Shows significant effect difference in Lequesne Index)*
37. Hughes R and Carr A. A randomized, double blind, placebo-controlled trial of glucosamine sulfate as an analgesic in osteoarthritis of the knee. *Rheumatology*. 2002;41:279-284. *(one of the current studies that has been included in the latest systematic review. Very good RCT among severe OA patients. Concluded that glucosamine, as a symptom modifier among OA patients, is no more effective than placebo).*

Appendix 1.

Workers' Compensation Board of BC - Evidence-based Practice group.

Quality of published evidence (adapted from 1,2,3,4)

1	Evidence from at least 1 properly randomized controlled trial (RCT) or systematic reviews of RCTs.
2	Evidence from well-designed controlled trials without randomization or systematic reviews of observational studies.
3	Evidence from well-designed cohort or case-control analytic studies, preferably from more than 1 centre or research group.
4	Evidence from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments could also be included here.
5	Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

Reference.

1. Canadian Task Force on the Periodic Health Examination: The periodic health examination. CMAJ. 1979;121:1193-1254.
2. Houston TP, Elster AB, Davis RM et al. The US Preventive Services Task Force Guide to Clinical Preventive Services, Second Edition. AMA Council on Scientific Affairs. American Journal of Preventive Medicine. May 1998;14(4):374-376.
3. Scottish Intercollegiate Guidelines Network (2001). SIGN 50: a guideline developers' handbook. SIGN. Edinburgh.
4. Canadian Task Force on Preventive Health Care. New grades for recommendations from the Canadian Task Force on Preventive Health Care. CMAJ. Aug 5, 2003;169(3):207-208