National Council for
NCOR
Osteopathic Research

Glucosamine – a snapshot summary report (Nov 2012)

- **Key messages**
- Glucosamine and chondroitin are classified as supplements and are not currently licensed under the Medicines Act. This has implications for ensuring content and quality.
- A large number of studies have been carried out which are of varying quality.
- The conclusions are conflicting largely because patients with vastly different symptoms have been considered en masse.
- Glucosamine may reduce pain, improve physical function and will probably have no side effects when taken by people with osteoarthritis.
- The Rotta brand of glucosamine has consistently been shown to reduce pain more than placebos.
- Glucosamine has been theorised to work in a number of ways and there is some evidence to show that it has anabolic and anticatabolic effects; there is a stronger evidence base for the latter. There is also some evidence to support that it is the sulphate of glucosamine sulphate that is responsible for the therapeutic effect.

Definitions

Glucosamine is a naturally occurring amino-monosaccharide found in high concentrations as a normal constituent in cartilage matrix and synovial fluid; most supplements are manufactured synthetically or are derived from shellfish shells. It can commonly be found in two forms: glucosamine sulphate and glucosamine hydrochloride.

Chondroitin (sometimes combined with glucosamine in supplements) is a large gel-forming molecule. It forms part of cartilage and its properties include resisting compression[1].

Context

Glucosamine is a popular supplement which is widely taken, particularly for osteoarthritis (OA). This raises the questions 'what is the evidence to support its use?'

Osteoarthritis is the most common joint disease among the population. Osteoarthritis of the knee joint is more common than in the hip, but when considered together, they are found to occur in 10-20% of the population aged 65 and over. Approximately 196400 people in the United Kingdom seek help from their GP for this condition[2].

Current treatment strategies include prescribed medication (non-steroidal anti-inflammatories), exercise, osteopathic, chiropractic or physiotherapy treatment, acupuncture, walking aides, injections and, ultimately, joint replacement surgery. Analgesia and non-steroidal anti-inflammatories (NSAIDs) have suboptimal effectiveness[3,4], and recent reports of increased cardiovascular risk make NSAIDs a less attractive option for many patients[5,6,7]. Glucosamine is being increasingly used, either singly or in combination with chondroitin[8]. A variant, D-glucosamine is being used as the basis for supramolecular hydrogels to promote a variety of actions including wound healing[9]. While glucosamine sulphate is more commonly used in the human population, glucosamine chloride is being used in the animal population, particularly in veteran, athletic or arthritic horses to provide symptomatic relief[10].

Mechanism of action

Black et al, 2009 highlight that first and foremost, it needs to be established that glucosamine and chondroitin, being large macromolecules, are actually orally bio-available[1]. This has been shown to be the case in a significant body of evidence.

The mechanism of action of glucosamine in OA is unknown but it is hypothesised that the supply of glucosamine is a rate-limiting step in the formation of lubricating hyaluronic acid in connective tissue[11]. Glucosamine sulphate has been shown to interfere with the intracellular cytokine (interleukin 1)-signalling cascade that modulates several of the joint deteriorating events in OA[12,13]: a further study showed it can increase ALP activity, collagen synthesis, osteocalcin secretion, and mineralisation in osteoblastic cells in vitro. In the same study, glucosamine sulphate exhibited also an anti-inflammatory effect on the production of TNF-alpha (tumour necrosis factor), IL-1beta (Interleukin) and PGE(2) (prostaglandin) in macrophage RAW264.7 cells[14].

The rationale for using glucosamine sulphate to aid osteoarthritis is based largely on in-vitro and animal models of osteoarthritis. Glucosamine sulphate has been shown to normalise cartilage metabolism, rebuild experimentally damaged cartilage, and

demonstrate mild anti-inflammatory properties[15,16,17,18,19,20]. The Arthritis Research Campaign discusses glucosamine and states that where patients wish to try it, it would be perfectly reasonable to try 1500mg of glucosamine and 1200mg of chondroitin per day for three months (administered orally in the form of coated tablets, capsules or powder) to try and assess an improvement[21].

Black et al, 2009 describe various possible mechanisms for glucosamine and chondroitin, including the theory that it is in fact the sulphate component of oral preparations that has the therapeutic effect and that there is evidence to support this hypothesis[1]. They explain that cartilage contains tissue-specific glycosaminoglycans, the synthesis of which needs a source of inorganic sulphate. It is thought that part of the disease process of OA could be due to a sulphate deficiency and human cartilage is particularly sensitive to this. In addition to the sulphate theory, there is evidence to show that glucosamine has both anabolic and anticatabolic effects (some of which are described above) with the latter currently having a stronger evidence base[1].

What is the evidence for glucosamine?

Glucosamine and chondroitin are classified as supplements and are not currently licensed under the Medicines Act[22]. In some countries glucosamine and chondroitin are classified as food supplements, while in certain European countries glucosamine is available on prescription as a sulphate salt from Rotta Research Laboratorium[23].

A large number of research studies have been carried out which are of varying quality; the findings are conflicting in their final conclusions, largely because patients with extreme variations in their symptoms have been considered en masse. An increasing number of clinical studies have been undertaken, but often of varying quality and varying results. A small number of systematic reviews and a meta-analysis have been undertaken examining different clinical areas[24,25]. The reviews came to different conclusions: Poolsup et al, 2005 concluded that glucosamine sulphate may be effective (and safe) in delaying the progression and improving the symptoms of OA of the knee joint; a met-analysis by Richy et al, 2003looking also at OA of the knee concluded that highly significant efficacy of glucosamine was demonstrated on all outcomes including joint space narrowing and Western Ontario and McMaster Universities Osteoarthritis Index WOMAC scores[24,25,]. Chondroitin was found to be effective on a Visual Analogue Scale (VAS) for pain, mobility and responding status. The Cochrane Collaboration looked at glucosamine therapy for non-specific OA[26]. Analysis was restricted to eight studies but failed to show a benefit for pain and WOMAC function. Ten studies were reviewed which had used glucosamine from the Rotta Laboratorium; glucosamine was found to be superior to placebo in pain and function. In four randomised controlled trials (RCTs) comparing Rotta glucosamine and Non-Steroidal Anti-Inflammatories (NSAIDs), glucosamine was found to be superior in two and equivalent in two. Two RCTs looking at Rotta's glucosamine demonstrated a slowing of radiological progression of OA of the knee joint over a three year period.

One of the largest studies was carried out in the United States[27]. This GAIT study enrolled 1583 patients; patients were assessed on entering the study using WOMAC and classified as either experiencing mild, or moderate to severe pain. The mild pain subgroup accounted for 78% of the study sample; 22% were classified as moderate to severe pain. Patients were randomly assigned to receive one of five treatments daily for 24 weeks:

1. glucosamine alone (1500mg)
2. chondroitin sulphate alone (1200mg)
3. glucosamine and chondroitin sulphate combined (1500mg and 1200mg respectively)
4. a placebo
5. celecoxib (200mg)

The study showed that glucosamine resulted in improvement in symptoms for patients with moderate to severe OA, but did not produce symptomatic improvement in the mild pain group. The relatively small sample size in the moderate severe pain group means that the study findings should be considered as preliminary; further work should be undertaken to confirm these findings.

In 2009, The Cochrane Collaboration updated their review and included an additional 10 trials resulting in a combined number of 3803 additional participants[28]. They found using this new data that the combined effectiveness of glucosamine from the trials was reduced, which leads to the question: why has this changed? They summarised that if they had included some of the lower quality and older trials in the review then glucosamine would have been shown to be more effective.

The Cochrane Collaboration still, however, concludes that the Rotta preparation of glucosamine appears to be the most effective[28].

Predicting a response to glucosamine

An exploratory study was carried out to examine whether patient characteristics and/or radiographic evidence of disease could predict a symptomatic response to glucosamine in patients with OA in the knee joints. Patients were evaluated who had evidence of pain, osteophytes at the medial and lateral tibiofemoral joint (TFJ), and patellofemoral joint). Pain and physical function were assessed using visual analogue scales (VAS) and participant-perceived global change scores (GCS); age and body mass index (BMI) were also recorded. The researchers involved reported that patients reported that decreased function self-efficacy, presence of PFJ osteophytes, and absence of medial TFJ osteophytes predicted functional improvement on VAS. BMI, pain self-efficacy and function self-efficacy predicted pain improvement by GCS[25].

Cost effectiveness

Mantovani et al, 2001 conducted a study to compare the cost of glucosamine sulphate with piroxicam. Although glucosamine was shown to be more expensive (€81 vs. €33), it resulted in a potential net saving of approximately €11 per patient in 90 days, and €110 per patient in 150 days which was attributed to its higher efficacy[30]. It is not known whether this was a direct or indirect valuation.

Black et al, 2009 state in their review that the cost-effectiveness of glucosamine has not been conclusively demonstrated[1].

Adverse reactions

Glucosamine is generally well tolerated but, as with all interventions, it is associated with side effects. A small variety of cautions and adverse reactions have been reported which include:

Mild and reversible effects	**Avoidance recommended due to unknown effect or drug interaction**
Upset stomach Headache Itch Rash Flushing Drowsiness Insomnia	Patients taking warfarin[31]. Pregnant patients, although no known side effects have been documented[32] Seafood allergies*[33]

* Studies have been undertaken to examine products from specific manufacturers. One study examined patients with positive responses to tests for shrimp reactivity and an ImmunoCAP class level of two or greater; immediate reactions, including peak flow changes and blood pressure, and reactions 24 hours later were examined. None of the subjects in the study were affected by the glucosamine. However, it must be stressed that since glucosamine is not a medically licensed product, content and quality control of the product remain a source of concern[33].

Diabetic patients – intravenous administration causes insulin resistance and endothelial dysfunction[34]. Studies have been carried out to investigate changes in insulin resistance, endothelial dysfunction, triglycerides, total cholesterol, low density lipoprotein (LDL) and high density lipoprotein HDL) levels. Glucosamine was not found to significantly affect blood levels of cholesterol or triglycerides[35]. Insulin resistance and epithelial dysfunction were not found to be induced or worsened when both obese and lean patients took oral glucosamine for 6 weeks[34,36]. Questions still remain concerning the

effect of glucosamine in undiagnosed or untreated glucose intolerant or diabetic patients[37]; further work is required in this area.

Future research

The updated Cochrane review[28] identified a number of areas that require clarification:

- Are the varying glucosamine preparations produced by different manufacturers equally safe and effective in the treatment of OA?
- Is glucosamine sulphate as effective as glucosamine hydrochloride?
- Can further benefit be obtained by adding other products e.g. chondroitin sulphate?
- Is glucosamine helpful for all joints and at different stages of severity?
- Is the dose and route of administration important in maximising efficacy and minimising toxicity?
- What are the patient specific factors that predict favourable effects on the radiological progression of OA?

Although there is some evidence to show that glucosamine may be helpful in the treatment of OA, Black et al, 2009 highlight that there was no UK trial data in their systematic review, so in the absence of good trial data from the UK we should be careful generalising the available data from elsewhere to the UK healthcare setting[1].

Author: Carol Fawkes, NCOR Research Development Officer

Updated by: Elena Ward, NCOR Research Assistant

References

1. Black C, Clar C, Henderson R, MacEachern C, McNamee P, Quayyum Z, Royle P, Thomas S. The clinical effectiveness of glucosamine and chondroitin supplements in slowing or arresting progression of osteoarthritis of the knee: a systematic review and economic evaluation. *Health Technology Assessment.* 2009;13(52)

2. http://www.arthritisresearchuk.org/arthritis-information/data-and-statistics/osteoarthritis.aspx Accessed 28th November, 2012.

3. Williams HJ, Ward JR, Egger MJ et al. Comparison of naproxen and acetaminophen in a two year study of treatment of osteoarthritis of the knee. *Arthritis and Rheumatism*. 1993;36:1196-206.

4. Bradley JD, Brandt KD, Katz BP et al. Comparison of an ant-inflammatory dose of ibuprofen, and acetaminophen in the treatment of patients with osteoarthritis of the knee. *New England Journal of Medicine*. 1991;325:87-91.

5. Ray WA, Griffin MR, Stein CM. Cardiovascular toxicity of valdecoxib. *New England Journal of Medicine*. 2004;351:2767.

6. Bresalier RS, Sandler RS, Quan H et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *New England Journal of Medicine*. 2005;352:1092-102.

7. Nussmeier NA, Whelton AA, Brown MT et al. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. *New England Journal of Medicine*. 2005;352:1081-91.

8. Singh JA, Wilt TJ, McDonald R. Chondroitin for osteoarthritis (Protocol). *The Cochrane Library*. 2007; Issue 2.

9. Yang Z, Liang G, Ma M et al. D-glucosamine-based supramolecular hydrogels to improve wound healing. *Chemistry Communications (Camb*). 2007;8:843-5.

10. Forsyth RK, Brigden CV, Northrop AJ. Double blind investigation of the effects of oral supplementation of combined glucosamine hydrochloride (GHCL) and chondroitin sulphate (CS) on stride characteristics in veteran horses. *Equine Veterinary Journal Supplement*. 2006;36:622-5.

9. Basleer C, Henrotin Y, Franchimont P. In-vitro evaluation of drugs proposed as chondroprotective agents. *International Journal of Tissue Reactions*. 1992:14:231-241.

11. McCarty MF. Enhanced synovial production of hyaluronic acid may explain rapid clinical response to high dose glucosamine in osteoarthritis. *Medical Hypotheses*. 1998;50:507-510.

12. Largo R, Alvarez-Soria MA, Díez-Ortego BS et al. Glucosamine inhibits IL-1β-induced NF?B activation in human osteoarthritic chondrocytes. *Osteoarthritis and Cartilage*. 2003;11:290-298.

13. Chen JT, Chen CH, Horng CT et al. Glucosamine sulphate inhibits proinflammatory cytokine-induced icam-1 production in human conjunctival cells in vitro. *Journal of Ocular Pharmacology and Therapeutics.* 2006;22(6):402-16.

16. Kim MM, Mendis E, Rajapakse N Kim, SK. Glucosamine sulphate promotes osteoblastic differentiation of MG-63 cells via anti-inflammatory effect. *Bioorganic and Medicinal Chemistry Letters*. 2007;17(7):1938-42.

17. Basleer C, Henrotin Y, Franchimont P. In-vitro evaluation of drugs proposed chondroprotective agents. *International Journal of Tissue Reactions*. 1992;14:231-241.

18. McCarty M. The neglect of glucosamine as a treatment for osteoarthritis. A personal perspective. *Medical Hypotheses*. 1994;42:323-327.

19. Rotate LC. The clinical profile of glucosamine sulphate as a selective symptom modifying drug in osteoarthritis: current data and perspectives. *Osteoarthritis Cartilage.* 1997;5:72.

20. Setnikar I, Pacini M, Revel L. Antiarthritic effects of glucosamine sulphate studied in animal models. *Arzneimittelforschung.* 1991;41:542-545.

21. Vidal Y, Plana R, Bizzarri D et al. Articular cartilage pharmacology. In vitro studies on glucosamine and non-steroidal anti-inflammatory drugs. *Pharmaceutical Research Communications*. 1978;10:557.

22. http://www.opsi.gov.uk/about/ Accessed 12th June, 2007.

23. Rotta Research Laboratories. http://www.rotta.com. (Accessed 28-11-2012)

24. Poolsup N, Suthisisang C, Channark P, Kittikulsuth W. Glucosamine long term treatment and the progression of knee osteoarthritis: systematic review of randomised controlled trials. *Annals of Pharmacotherapy*. 2005;39(6):1080-7.

25. Richy F, Bruyere O, Ethgen O et al. Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis: a comprehensive meta-analysis. *Archives of Internal Medicine*. 2003;163(13):1514-22.

26. Towheed TE, Maxwell L, Anastassiades TP et al. Glucosamine therapy for treating osteoarthritis (Review). *The Cochrane Library*. 2007;2.

27. Clegg DO, Reda DJ, Harris CL et al. Glucosamine, chondroitin sulphate, and the two in combination for painful knee osteoarthritis. *The New England Journal of Medicine.* 2006;354(8):795-808.

28. Towheed T, Maxwell L, Anastassiades TP, Shea B, Houpt JB, Welch V, Hochberg MC, Wells GA. Glucosamine therapy for treating osteoarthritis (Review). *Cochrane Database of Systematic Reviews* 2009, Issue 4. DOI: 10.1002/14651858.CD002946.pub2

29. Bennett AN, Crossley KM, Brukner PD, Hinman RS. Predictors of symptomatic response to glucosamine in knee osteoarthritis: an exploratory study. *British Journal of Sports Medicine.* 2007;Jan 29 (epub).

30. Mantovani LG, Belisari A, Cristoforetti et al. Cost-benefit analysis of glucosamine sulphate use. *Annals of Rheumatic Disease*. Annual European Congress on Rheumatology, Eular. 2001;60(suppl 1):236(abstract).

31. *Current problems in pharmacovigilance*. 2006;31:8. www.mhra.gov.uk. Accessed 5th June, 2007.

32. Sivojelezova A, Koren G, Einarson A. Glucosamine use in pregnancy: an evaluation of pregnancy outcome. *Journal of Women's Health (Larchmt)*. 2007;16(3):345-8.

33. Villacis J, Rice TR, Bucci LR et al. Do shrimp-allergic individuals tolerate shrimp-derived glucosamine? *Clinical and Experimental Allergy*. 2006;36(11):1457-61.

34. Muniyappa R, Karne RJ, Hall G et al. Oral glucosamine for 6 weeks at standard doses does not cause or worsen insulin resistance or endothelial dysfunction in lean or obese subjects. *Diabetes*. 2006;55(11):3142-50.

35. Østergaard K, Hviid T, Hyllested-Winge JL. The effect of glucosamine sulphate on the blood levels of cholesterol or triglycerides – a clinical study. *Ugerskr Laeger*. 2007;169(5):407-10.

36. Scroggie DA, Albright A and Harris MD. The effects of glucosamine-chondroitin supplementation on glycosylated haemoglobin levels in patients with Type-2 diabetes mellitus: A placebo controlled, double blind, randomised clinical trial. *Archives of Internal Medicine.* 2003;163:1587-1590.

37. Marshall PD, Poddar S, Tweed EM, Brandes L. Clinical enquiries: Do glucosamine and chondroitin worsen blood sugar control in diabetes? *Journal of Family Practice*. 2006;12:1091-3.

Further sources of information

New England Journal of Medicine. http://www.nejm.org. (free online registration and access to articles published six months ago or more).

Medicines and Healthcare Regulatory Agency. http://www.mhra.gov.uk.

The Cochrane Library. http://www.cochranelibrary.com. (free to access database)

Best evidence topics. http://www.bestbets.org/