



National Prescribing Service Limited

Glucosamine and chondroitin in osteoarthritis

Glucosamine

Summary

Most trials show efficacy of glucosamine in osteoarthritis of the knee compared to placebo. However, they are of varying quality and the long-term effectiveness and toxicity of glucosamine is not established. Favourable trials have used the sulfate salt. It is unclear whether results are reproducible with other salts.

What is the evidence for using glucosamine?

There are no trials that compare the efficacy of glucosamine with paracetamol.

Two systematic reviews and one small trial have compared glucosamine with placebo or an NSAID in osteoarthritis of the knee or hip.¹⁻³ Results were generally in favour of glucosamine. However, conclusions are limited by the short duration of trials (mean 6.25 weeks), poor design and likely publication bias.^{2,4}

Two double-blind, placebo controlled trials of 3-years duration compared glucosamine sulfate (1500 mg/day) with placebo in 414 patients with osteoarthritis of the knee.^{5,6} Symptom changes were assessed using the WOMAC* osteoarthritis index, a validated, disease-specific score of severity of joint pain, stiffness and limitation of physical function.⁵ Both trials reported that glucosamine sulfate significantly improved symptoms.^{5,6} The use of rescue medications and rates of withdrawal due to adverse effects were similar between groups.

Conflicting results were reported in a smaller study of 2-months duration involving 98 patients with osteoarthritis of the knee.⁷ The study reported no difference in pain intensity between glucosamine (salt not known) and placebo.⁷ Similar results were reported in a 6-month trial involving 80 patients with osteoarthritis of the knee who received glucosamine sulfate (1500 mg/day) or placebo.⁸ No significant differences were seen in the WOMAC osteoarthritis index or other outcome variables. This trial included patients with more severe structural osteoarthritis than the two trials of 3-years duration.^{5,6}

Effects on joint-space narrowing

It has been proposed that glucosamine may influence disease progression in osteoarthritis.⁹ A recent systematic review reported the potential minimal joint-space narrowing difference would be 0.27 mm (95% CI, 0.13–0.41 mm) after 3 years of glucosamine sulfate (1500 mg/day) compared with placebo.⁹ However, in patients with non-flaring osteoarthritis of the knee, joint-space narrowing has been reported as unrelated to the radiographic severity of osteoarthritis or to the magnitude of changes in pain scores.⁹ Joint-space narrowing is therefore a surrogate marker of cartilage loss and it is not known if such differences will be of clinical importance.⁵

What dose of glucosamine has been commonly used in trials?

Adults: 1500 mg daily (as sulfate salt).¹⁰

What adverse effects should be considered?

Avoid in patients with seafood or shellfish allergy.⁴

May cause gastrointestinal disturbances (dyspepsia, nausea and diarrhoea); minimise by administering with food.¹¹

May affect insulin resistance; closely monitor blood glucose levels in patients with diabetes.¹²

* WOMAC = Western Ontario and McMaster Universities

Chondroitin

Summary

The evidence is conflicting regarding the efficacy of chondroitin in the management of osteoarthritis of the knee. In trials, withdrawal of existing therapy (paracetamol or NSAIDs) was not possible.

The efficacy and safety of chondroitin is yet to be established due to small patient numbers and trials of short duration.

What is the evidence for using chondroitin?

Chondroitin is a relatively large molecule with poor absorption from the gastrointestinal tract, oral bioavailability is estimated to be 10% of the orally administered dose.¹⁰

There are no trials that compare the efficacy of chondroitin with paracetamol.

A randomised, double-blind trial compared chondroitin sulfate (1200 mg/day) with diclofenac sodium (150 mg/day) for osteoarthritis of the knee.¹³ Using the Lequesne index (a validated score of pain, function and stiffness of the knee and hip) diclofenac was significantly better than chondroitin after 1 month.

Two systematic reviews concluded chondroitin offered benefit in symptom control compared to placebo.^{2,14} However, complete withdrawal of other analgesics, such as paracetamol or NSAIDs, was not possible.^{2,14} In addition, poor trial design and likely publication bias limit conclusions that can be drawn.²

One double-blind, placebo-controlled trial of 130 patients with osteoarthritis of the knee found no significant difference between chondroitin sulfate (1000 mg/day) and placebo over 6 months using the Lequesne index.¹⁵

What dose of chondroitin has been commonly used in trials?

Adult: 800–1200 mg daily in divided doses.

What adverse effects should be considered?

May cause gastrointestinal disturbances such as dyspepsia and nausea.¹⁶

Combined glucosamine and chondroitin

Summary

The evidence is conflicting regarding the efficacy of glucosamine combined with chondroitin in the management of osteoarthritis of the knee.

The variety of combinations used, small patient numbers and trials of short duration mean that the long-term effectiveness and toxicity of such preparations is yet to be established.

What is the evidence for combining glucosamine and chondroitin?

There are no trials that compare the efficacy of a combination of glucosamine and chondroitin with paracetamol.

A 4-month, randomised, controlled trial of 34 patients with osteoarthritis of the knee or lower back compared glucosamine hydrochloride (1500 mg/day), chondroitin sulfate (1200 mg/day) and manganese ascorbate (228 mg/day) with placebo.¹⁷ A significant improvement in pain severity was reported using a visual analogue scale only in those with osteoarthritis of the knee. No significant differences were found using the Lequesne index.

A second trial compared glucosamine hydrochloride (2000 mg/day), chondroitin sulfate (1600 mg/day) and manganese ascorbate (304 mg/day) with placebo for 6 months in 93 patients with osteoarthritis of the knee.¹⁸ No significant differences in symptom changes were seen with the WOMAC osteoarthritis index. Subgroup analysis of 72 patients with mild to moderate disease showed a significant improvement using the Lequesne index for the active preparation. No difference between active or placebo was reported for 21 patients with severe osteoarthritis.

A double-blind, placebo-controlled trial (n=63) compared the use of a topical cream applied when required containing glucosamine sulfate, chondroitin sulfate, shark cartilage, camphor and peppermint oil vs placebo over 8 weeks.¹⁹ A significant improvement in pain severity was reported using a visual analogue scale. However, no significant difference was found using the WOMAC osteoarthritis index.

What adverse effects need to be considered?

Combination products of glucosamine and chondroitin often contain manganese ascorbate. The highest average daily manganese intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population is 11 mg/day.²⁰ As intake increases above this level, the potential risk of adverse effects may increase. Both oral combination products studied exceed this level.

Note: 76 mg manganese ascorbate provides 5 mg elemental manganese.

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decision based on this information should be made in the context of the individual clinical circumstances of each patient.

References

1. Towheed TE, Anastassiades TP, Shea B, et al. Glucosamine therapy for treating osteoarthritis (Cochrane Review). In: The Cochrane Library, Issue 2, 2003. Oxford: Update Software.
2. McAlindon TE, LaValley MP, Gulin JP, Felson DT. Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. *JAMA* 2000;283:1469–75.
3. Thie NMR, Prasad NG, Major PW. Evaluation of glucosamine sulfate compared to ibuprofen for the treatment of temporomandibular joint osteoarthritis: a randomized double blind controlled 3 month clinical trial. *J Rheumat* 2001;28:1347–55.
4. Anonymous. Is glucosamine worth taking for osteoarthritis? *Drug Ther Bull* 2002;40:81–3.
5. Reginster JY, Deroisy R, Rovati LC, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. *Lancet* 2001;357:251–6.
6. Pavelka K, Gatterova J, Olejarova M, et al. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. *Arch Int Med* 2002;162:2113–23.
7. Rindone JP, Hiller D, Collacott E, et al. Randomized, controlled trial of glucosamine for treating osteoarthritis of the knee. *West J Med* 2000;172:91–4.
8. Hughes R, Carr A. A randomized, double-blind, placebo-controlled trial of glucosamine sulphate as an analgesic in osteoarthritis of the knee. *Rheumatol* 2002;41:279–84.
9. Richy F, Bruyere O, Ethgen O, et al. Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis: a comprehensive meta-analysis. *Arch Int Med* 2003;163:1514–22.
10. Simon L, Lipman A, Jacox A, et al. Guideline for the management of arthritis pain in osteoarthritis, rheumatoid arthritis, and juvenile chronic arthritis. APS Clinical Practice Guidelines Series, No 2. Glenview: American Pain Society, 2002.
11. Sutton L, Rapport L, Lockwood B. Glucosamine: con or cure? *Nutrition* 2002;18:534–6.
12. Anonymous. Glucosamine chondroitin adverse reaction. *Hosp Pharmacy* 2002;37:256.
13. Morreale P, Manopulo R, Galati M, et al. Comparison of the antiinflammatory efficacy of chondroitin sulfate and diclofenac sodium in patients with knee osteoarthritis. *J Rheumat* 1996;23:1385–91.
14. Leeb BF, Schweitzer H, Montag K, Smolen JS. A metaanalysis of chondroitin sulfate in the treatment of osteoarthritis. *J Rheumat* 2000;27:205–11.
15. Mazieres B, Combe B, Phan VA, et al. Chondroitin sulfate in osteoarthritis of the knee: a prospective, double blind, placebo controlled multicenter clinical study. *J Rheumatol* 2003;28:173–81.
16. Kelly GS. The role of glucosamine sulfate and chondroitin sulfates in the treatment of degenerative joint disease. *Alt Med Rev* 1998;3:27–39.
17. Leffler CT, Philippi AF, Leffler SG, et al. Glucosamine, chondroitin, and manganese ascorbate for degenerative joint disease of the knee or low back: a randomized, double-blind, placebo-controlled pilot study. *Military Medicine* 1999;164:85–91.
18. Das AJ, Hammad TA. Efficacy of a combination of FCHG49 glucosamine hydrochloride, TRH122 low molecular weight sodium chondroitin sulfate and manganese ascorbate in the management of knee osteoarthritis. *Osteoarthritis Cartilage* 2000;8:343–50.
19. Cohen M, Wolfe R, Mai T, 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. *J Rheumat* 2003;30:523–8.
20. Institute of Medicine. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium and zinc. www.nap.edu/books/0309072794/html/ (Accessed 29 September 2003).

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