

Glucosamine – what are the adverse effects?

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Background

Glucosamine is a naturally occurring substance that is a basic building block of several important constituents of articular (joint) cartilage. It is important for maintaining elasticity, strength and resilience of cartilage in joints, which helps to reduce joint damage (1). Administration of glucosamine is believed to stimulate production of cartilage components and allow rebuilding of damaged cartilage (1).

Glucosamine is commonly used for relieving pain and symptoms associated with osteoarthritis and other joint disorders. It is available in the form of tablets and capsules as glucosamine sulfate, glucosamine hydrochloride and N-acetyl-D-glucosamine (NAG); it is sometimes used in combination with chondroitin sulfate (1). Glucosamine supplements are either produced synthetically or derived from the shells of shellfish (2). Products vary in their content and strength of active ingredients.

Glucosamine appears to be well tolerated, at least in the short-term; glucosamine sulfate has been used safely in multiple clinical trials lasting up to three years duration, glucosamine hydrochloride has been used safely in studies lasting up to two years (3,4). The incidence of adverse effects in clinical studies has generally been comparable to that with placebo (5).

This Medicines Q&A describes the adverse effects associated with the use of glucosamine.

Answer

When taken orally, the most common adverse effects of glucosamine include nausea, vomiting, heartburn, diarrhoea, constipation and epigastric pain/tenderness; symptoms may be reduced if glucosamine is taken with or after food (6,7). Other adverse effects include headache, drowsiness and insomnia, and skin reactions such as erythema and pruritus (6). Peripheral oedema and tachycardia have been reported in a few patients in larger clinical trials investigating oral or intramuscular glucosamine, but a causal relationship has not been established (6).

Allergy

It has been suggested that non-synthetic glucosamine products may cause allergic reactions in people sensitive to shellfish (3,4). Shellfish allergy is caused by IgE antibodies to antigens in the flesh of shellfish (tropomyosin), and not to the shell. Therefore in theory, it should be safe for patients with shellfish allergy to take glucosamine supplements (8,9). This assertion is supported by a small study in 15 subjects with a history of systemic reaction and a positive skin test to shellfish; all 15 had an uneventful oral challenge with 1,500mg of shrimp-derived glucosamine (10). As of 2005, the Australian Adverse Drug Reactions Advisory Committee had received 51 reports of allergic skin reactions to glucosamine, including angioedema, and note that in some cases, patients tolerated a different glucosamine product without adverse effect (11). The report implies that these patients may have had a shellfish allergy. Additionally, a study analysing reports of adverse effects to glucosamine/chondroitin sent to the Australian Therapeutic Goods Administration (TGA) between 2000 and 2011 found 71.9% of cases were hypersensitivity reactions and 1% anaphylaxis; it was not clear if affected patients had a history of shellfish allergy or atopy (9).

The Anaphylaxis Campaign advises people with a history of shellfish allergy who wish to take glucosamine to be cautious, and ask for shellfish-free preparations (12); similarly, the Summary of Product Characteristics (SPC) for the licensed brands of glucosamine (Alateris, Dolenio, Glusartel and YOINTY) all contraindicate use of glucosamine in patients allergic to shellfish (13-16).

The possibility of an allergic response to glucosamine in patients with asthma has been raised by a case report (17); exacerbation of the condition occurred in a woman with a 10-year history of asthma, after she started taking a preparation containing glucosamine 500mg plus chondroitin 400mg three times daily for arthritis. The exacerbation included periodic attacks of wheezing, shortness of breath

and decreases in peak expiratory flow rate and pulse oxygenation. Symptoms did not respond to oral steroids or increased doses of short-acting beta-2 agonist, but within 24 hours of stopping glucosamine plus chondroitin, asthma symptoms resolved completely. The authors of the aforementioned Australian study (9) postulated that the presence of sulphites in glucosamine supplements may be responsible for an inflammatory reaction in patients with asthma, and noted that dyspnoea was reported as an adverse effect to the TGA nine times in the eleven year analysis period, and asthma reported three times.

Despite this, a lack of collaborating evidence from clinical trials or further case reports suggests there is no need to contraindicate use in patients with asthma, but caution is warranted. Summaries of product characteristics (SPCs) for glucosamine advise that patients starting glucosamine should be aware of potential worsening symptoms of asthma (13-16).

Blood glucose levels

Concern has been raised that glucosamine might interfere with blood glucose control. Two published literature reviews report that although alterations in glucose metabolism have been noted in animals given high-doses of intravenous glucosamine, similar effects have not been consistently documented in humans following usual oral doses (18,19). The reviews included a number of studies evaluating long-term use of oral glucosamine for osteoarthritis. In two studies of similar design, non-obese patients with knee osteoarthritis but without diabetes or other clinically significant metabolic abnormalities were randomised to either glucosamine 1,500mg daily or placebo, for three years (20,21). In the first trial (n=212) annual fasting plasma glucose concentrations decreased slightly in glucosamine-treated patients (20). In the second study (n=202), although no specific data on glucose parameters were given, no differences in routine laboratory tests were reported between treatment and placebo groups (21). Smaller, shorter-term studies in subjects without diabetes, have also reported that glucosamine does not affect glucose tolerance or insulin resistance (18,22).

Two placebo-controlled double-blind trials have assessed the effects of glucosamine on glucose control in patients with type 2 diabetes (23,24). In the first study, patients whose conditions were controlled by either strict diet or oral hypoglycaemic medicines were randomised to oral glucosamine 1,500mg plus chondroitin 1,200mg daily (n=22), or placebo (n=12) for 90 days (23). HbA_{1c} values increased slightly (0.05%) in the treatment group and decreased slightly in the placebo group (0.16%). These changes did not reach statistical significance. Patients in this study had well-controlled type 2 diabetes and it is unclear whether these results would apply to patients with less well-controlled disease, or to those with type 1 diabetes.

The second study was a cross-over study involving patients with type 1 (n=2) or type 2 (n=10) diabetes (24). All subjects had stable HbA_{1c} and were not allowed any new classes of hypoglycaemic agents in the preceding two months. Participants were randomised to receive glucosamine 1,500mg daily or placebo for two weeks, followed by a four-week washout period before a two-week cross-over to the alternate therapy. Results demonstrated no significant changes in glycaemic control relative to baseline. Some of the study limitations include small sample size and short duration of use.

Although it is not anticipated that glucosamine would usually have an adverse effect on glucose control, data are limited and the effects of glucosamine in patients with diabetes are not well studied. Until further information becomes available, patients with diabetes should monitor their blood glucose levels more closely when glucosamine is initiated, the dose is modified or the product being taken is changed (13-16,18).

Liver toxicity

There are a few published case reports of hepatotoxicity possibly associated with glucosamine (alone or in combination with chondroitin). Elevated liver enzymes occurred in all cases (25-29). Several patients were asymptomatic, and their liver enzymes returned to normal following withdrawal of glucosamine (25,26). One patient died from fulminant liver failure (26), two developed chronic hepatitis (25,26) and two entered remission from hepatitis after treatment and glucosamine cessation (27,28); one outcome was not reported, however the patient's liver enzymes returned to normal four weeks after stopping glucosamine (29). The precise mechanism of injury is unknown, but potentially involves hypersensitivity reactions or production of toxic metabolites when glucosamine undergoes hepatic metabolism (25,26). Mild forms of hepatotoxicity may remain undiagnosed in the absence of clinical symptoms or analysis of liver enzymes. In patients found to have altered liver enzymes,

consider stopping glucosamine due to the possibility of developing more severe liver injury with continued use (26).

Kidney toxicity

Acute interstitial nephritis has been reported as a possible adverse effect. Two to three months after starting glucosamine (dose unknown), a 75 year old man was diagnosed with tubulointerstitial nephritis after being hospitalised with difficulty passing urine, urgency and nocturia (30). There were no other obvious precipitating causes. His condition significantly improved after a short course of oral steroids and temporary haemodialysis.

Acute tubular necrosis has been detailed in a case report (31). A 67 year old man with type 2 diabetes and hypertension took a capsule containing 1,200mg of glucosamine, 0.3 mg of manganese gluconate and 0.021µmol/L of ascorbic acid daily for three years. His renal function then started to deteriorate over a three month period; following extensive testing, acute tubular necrosis was noted on biopsy and the supplement was stopped. In the following three weeks, his serum creatinine decreased from 138 to 109µmol/L and eGFR rose from 47.5 to 60mL/min. After a glucosamine re-challenge (it was not stated if this was the original supplement, or glucosamine only), his serum creatinine increased to 121µmol/L and eGFR reduced to 53mL/min. Glucosamine was subsequently completely stopped; his serum creatinine decreased to 110µmol/L and eGFR increased to 60mL/min, with these parameters remaining stable at one year follow up.

There have also been anecdotal reports of non-specific renal impairment (32,33), but this has not been observed in longer-term studies (three years) (20,21). Pragmatically, glucosamine should be used with caution in patients with impaired renal function or those taking nephrotoxic medication.

Other adverse effects

Hypercholesterolaemia has been reported in three women aged 60 to 66 years taking glucosamine (doses unknown) for between six and 12 months (34). Increases in total cholesterol ranged from 0.9 to 2.4mmol/L. In one case, total cholesterol returned to levels similar to that of pre-treatment values when glucosamine was discontinued; outcomes in the other patients are unknown. Changes in lipid levels have not been reported in clinical trials lasting three years (20,21). SPCs for glucosamine advise monitoring blood lipid levels in patients taking glucosamine who have known risk factors for cardiovascular disease, but note that causality has not been established (13,15).

Increased intraocular pressure (IOP) has also been reported in a double-blind randomised placebo-controlled trial investigating the effect of glucosamine sulfate on IOP in 88 patients with osteoarthritis (35). Patients underwent a comprehensive ophthalmologic exam (including IOP) at baseline, one month and three months. A clinically significant increase in IOP (defined as ≥ 2 mmHg) was experienced by 34.1% of patients taking glucosamine and 12.5% taking placebo at final follow-up ($p=0.023$). The authors concluded that a statistically significant increase in IOP can be caused by glucosamine, and that the effect was more pronounced in elderly patients. However, the clinical implication of their findings needs to be investigated further.

Summary

- Glucosamine supplements are widely used for relieving pain and symptoms associated with osteoarthritis. They appear to be well tolerated, with a reported frequency of adverse effects similar to that with placebo.
- Mild gastrointestinal disturbance is the most common adverse effect. Other adverse effects include headache, drowsiness, insomnia and skin reactions.
- Glucosamine supplements are either produced synthetically or derived from the shells of shellfish, and should not precipitate allergic reactions in patients sensitive to shellfish. However, some sources contraindicate or recommend cautious use of these products in patients allergic to shellfish.
- Glucosamine does not appear to adversely affect plasma blood glucose in patients without diabetes. However, data relating to its effects in patients with diabetes are lacking. It would be prudent for patients with diabetes to monitor their blood glucose levels more closely if they start to take glucosamine, increase their dose or change the product taken.
- There are a few case reports of hepatotoxicity related to glucosamine, but the mechanism for this has not been established. If a patient develops increased liver enzymes, consider

stopping glucosamine because of the risk of developing more severe liver injury with continued use.

- Glucosamine should be used with caution in patients with renal impairment or those taking nephrotoxic medications.

Limitations

Data on glucosamine are lacking; patients/clinicians should consider reporting adverse reactions suspected to be related to glucosamine use to the Yellow Card scheme at

<https://yellowcard.mhra.gov.uk/>

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Search strategy

1. Embase exp GLUCOSAMINE/ AND exp "SIDE EFFECT" [FROM 2018]; exp GLUCOSAMINE/ae [FROM 2018]
2. Medline exp GLUCOSAMINE/ AND exp "DRUG-RELATED SIDE EFFECTS AND ADVERSE REACTIONS"/[FROM 2018]; exp GLUCOSAMINE/ae [FROM 2018]

3. In-house databases/ resources.
4. Memorial Sloan Kettering Cancer Centre – About Herbs (www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/herbs/search - glucosamine).
5. Anaphylaxis Campaign (www.anaphylaxis.org.uk - shellfish).
6. Clinical expert - Gail Woodland. Senior Medicines Information Pharmacist. Welsh Medicines Information Centre. Contacted 23 Feb 2007 and 25 July 2015.