

Glucosamine – what are its drug interactions?

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals
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Background

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

Glucosamine is commonly used for the relief of pain and symptoms associated with osteoarthritis and other joint disorders. It is available in the form of tablets, capsules and powders as glucosamine sulfate, glucosamine hydrochloride and *N*-acetyl-D-glucosamine (NAG) (1). 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.

Answer

Some drugs have been reported to interact with glucosamine. There are also a number of putative interactions based on theoretical risk, for which the clinical relevance is uncertain.

Oral coumarin anticoagulants

There do not appear to have been any controlled studies of the effects of glucosamine supplements on the pharmacodynamics or pharmacokinetics of oral anticoagulants (3).

However, seven reports suggesting an interaction between warfarin and glucosamine were highlighted by the UK Medicines and Healthcare products Regulatory Agency (MHRA) in 2006. In the cases reported, patients on warfarin with previously stable international normalised ratio (INR) noted an increase in their INR after they started taking glucosamine supplements (4).

A conference abstract published in 2006 noted that the World Health Organisation Adverse Drug Reaction (WHO-ADR) database contained 19 cases of possible interaction between warfarin and glucosamine; of these cases, plus an additional Swedish case, 19 involved an increase in INR and one involved reduced INR (5). Most patients had been on long-term warfarin treatment and had a stable INR when glucosamine was started. Potentiation of warfarin effect was noted within three weeks in the majority of cases and within nine months in others. In 16 cases, INR decreased on glucosamine withdrawal. In an unspecified number of cases, hospitalisation was required or prolonged, and/or vitamin K was given as an antidote. The authors suggested that as glucosamine is a chemical component of heparin, a pharmacodynamic interaction with warfarin may be responsible. None of the cases reported use of chondroitin.

Similarly, an article published in 2008 noted that four cases involving potential interactions between warfarin and glucosamine, and 15 cases between warfarin and glucosamine plus chondroitin, had been reported to the Food and Drug Administration (FDA) MedWatch Adverse Events Reporting System (AERS) database (6). INR data were not consistently reported; however, INR increased in at least 9 of the cases and 12 cases reported active bleeding, or signs of bleeding (e.g. bruising, haematuria). No deaths were reported, but some cases were considered serious and resulted in hospitalisation.

There are two detailed case reports of possible augmentation of warfarin by glucosamine/ chondroitin in the literature. In one case, a 69-year-old man's INR increased from 2.58 to 4.52 four weeks after starting treatment with 3,000mg glucosamine plus 2,400mg chondroitin daily (twice the recommended daily dose). He continued taking the glucosamine/chondroitin combination and his INR stabilised after

his warfarin dose was reduced (7). The report notes that chondroitin may have anticoagulant activity as it is a minor component of danaparoid, a natural anticoagulant, and has been shown to prolong prothrombin time *in vitro*.

The second report describes a 71 year old man who had been taking warfarin 7.5mg and glucosamine 1,000mg with chondroitin 800mg daily for five years; his INR was maintained between 2.5 and 3.2. The patient increased his daily dose of glucosamine/ chondroitin to 3,000mg/ 2,400mg daily; three weeks later his INR value increased to 3.9. The dose of glucosamine with chondroitin was subsequently reduced to 750mg/ 600mg daily; after 16 days his INR was 4.7. Glucosamine/ chondroitin was stopped and warfarin dose reduced to 7.5mg and 3.75mg on alternate days. Sixteen days later, his INR was 2.6 (6).

In contrast to reports of augmentation, one case in the WHO-ADR database reported a decreased INR in a patient on warfarin who had been taking glucosamine for 1.5 months; glucosamine was not discontinued (5). There is also a report of a 71 year old man taking acenocoumarol 15mg weekly; his INR decreased to 1.6 after taking glucosamine 1,500mg daily for 10 days. Glucosamine was stopped and INR increased to 2.1. Glucosamine was then restarted and acenocoumarol dose increased to 17mg weekly, but the INR only reached 1.9; glucosamine was eventually stopped (3). Outcome was not reported.

The Medicines and Healthcare products Regulatory Agency (MHRA) recommends that patients on warfarin should not take glucosamine on the basis of reports received (4). Other sources suggest that more frequent dose adjustment of warfarin/acenocoumarol and monitoring of INR may be necessary when glucosamine is used concomitantly (3,5-11).

The Welsh Medicines Information Centre, which provides specialist advice on complementary medicines, also recommends using glucosamine with caution in those taking antiplatelet agents (e.g. aspirin) due to a theoretical risk that glucosamine may also potentiate their effects (12).

There have been no published reports of interactions between glucosamine and the non-vitamin K oral anticoagulants (NOACs), apixaban, dabigatran, edoxaban and rivaroxaban; however, until more is known, glucosamine should be used cautiously in patients also taking NOACs. See also the UKMi Medicines Q&A [“Is it safe to take herbal medicines with non-vitamin K antagonist oral anticoagulants \(NOACs\)?”](#)

Paracetamol

Anecdotal reports suggest that adding glucosamine to a paracetamol regimen may decrease pain control in patients with osteoarthritis. It has been suggested that increased serum sulfate concentrations arising from glucosamine sulfate might lead to increased metabolism of paracetamol by sulfate conjugation; however, there are no studies assessing this. Increased metabolism of paracetamol would therefore only be expected to occur with glucosamine sulfate salts and not the hydrochloride salt (13,14). Combined use of glucosamine and paracetamol to alleviate symptoms of osteoarthritis is common, and the limited evidence here does not provide any reason to suggest any changes to this practice (13).

Cytotoxic drugs

Theoretically, glucosamine may induce resistance to some chemotherapy agents. *In vitro* studies have reported glucosamine-induced resistance to topoisomerase II inhibitors doxorubicin and etoposide in cancer cells. The clinical effect of oral glucosamine given with these agents is unknown (14,15); however, because of the potential clinical significance of this interaction, glucosamine should not be used concomitantly (15).

Oral medication for diabetes

Research from *in vitro* and animal studies suggests that high-dose intravenous (but not oral) glucosamine may interfere with blood glucose control; few studies have directly examined the effect of glucosamine on glucose control in humans (16,17). A review of the literature found two randomised placebo-controlled studies that assessed the effect of glucosamine in patients with diabetes mellitus, one of which was a cross-over study (17). Scroggie et al. studied patients with type 2 diabetes who were not receiving insulin; participants were randomised to receive glucosamine 1,500mg plus

chondroitin 1,200mg daily (n=26), or placebo (n=12) for 90 days. Haemoglobin A1c (HbA_{1c}) values increased slightly (0.05%) in the active treatment group and decreased slightly in the placebo group (0.16%). These changes did not reach statistical significance (18). The patients in this study had well-controlled type 2 diabetes (baseline HbA_{1c} <6.5%) and were taking a median of one oral hypoglycaemic agent. It is unclear whether these results would apply to patients with less well-controlled disease, or to those with type 1 diabetes. Albert et al. investigated the effects of glucosamine on several diabetes-related end points in subjects with either type 1 (n=2) or type 2 diabetes (n=10) using a double-blind, placebo-controlled cross-over study design (19). 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 either glucosamine 1,500mg or placebo for two weeks, followed by a four-week washout period. Fasting plasma glucose and HbA_{1c} were measured serially; results demonstrated no significant changes in glycaemic control relative to baseline. Some of the study limitations include the small sample size and short duration of use (17).

Although the effect of glucosamine in patients with diabetes is not well studied, it has been suggested that patients with diabetes should monitor their blood glucose levels more closely and, where relevant, insulin requirements, if glucosamine is initiated, the dose is increased or the product being taken is changed (8-12,16).

Summary

- There are a number of reports describing enhanced anticoagulant effects when glucosamine has been taken with warfarin. The mechanism of the interaction is unclear. The MHRA recommend that patients on warfarin should not take glucosamine. It has also been suggested that glucosamine should be used with caution in patients taking antiplatelet agents.
- No reports of interaction between glucosamine and the NOACs were located; until more is known, caution is warranted.
- There is a theoretical risk that glucosamine may interact with doxorubicin and etoposide; because of the potential clinical significance of this interaction, glucosamine should not be used concomitantly.
- 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 limited. It would be prudent for patients with diabetes to monitor their blood glucose levels more closely if they start to take glucosamine, increase the dose or change the product being taken.
- More research is required to identify which drugs interact with glucosamine supplements and to determine the significance of such interactions.

Limitations

There are few published data. Patients/clinicians should be aware of the potential for altered/unusual response to medicinal products used concurrently with glucosamine, and consider reporting potential reactions to the Yellow Card scheme at <https://yellowcard.mhra.gov.uk/>.

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Quality Assurance

Prepared by

Eimear Maguire, North West Medicines Information Centre (NWMIC).

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Checked by

Leanne Bloxam, NWMIC and Joanne McEntee, NWMIC.

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Search strategy

1. Embase [expGLUCOSAMINE/ AND expDRUG INTERACTION/]; [expGLUCOSAMINE/ AND expANTICOAGULANT AGENT/]; [expGLUCOSAMINE/ AND APIXABAN/]; [expGLUCOSAMINE/ AND RIVAROXABAN/]; exp[GLUCOSAMINE/ AND DABIGATRAN/]; [expGLUCOSAMINE/ AND EDOXABAN]
2. Medline [expGLUCOSAMINE/ AND expDRUG INTERACTIONS/]; [expGLUCOSAMINE/ AND expANTICOAGULANTS/]; [expGLUCOSAMINE/ AND (apixaban)]; [expGLUCOSAMINE/ AND (rivaroxaban)]; [expGLUCOSAMINE/ AND (dabigatran)]; [expGLUCOSAMINE/ AND (edoxaban)].
3. In-house database/ resources (including Natural Medicines Database, Stockley's Herbal Medicines Interactions, Stockley's Drug Interactions and Drugdex).