Name

Glucosamine Sulfate or Glucosamine Hydrochloride

Scientific and Common Names[1]

The scientific name for glucosamine sulfate is 2-amino-2-deoxy-beta-D-glucopyranose. Common names include Amino Monosaccharide, Chitosamine, D-Glucosamine, G6S, Glucosamine, Glucosamine Sulphate, Glucose-6-phosphate, Glucose-6-phosphate, Glucose-6-sulphate, GS, Mono-Sulfated Saccharide, Sulfated Monosaccharide, and Sulfated Saccharide.

Description of Active Ingredient[1]

Glucosamine is a glycoprotein derived from marine exoskeletons or produced synthetically as the sulfated or the hydrochloride salt. It is an endogenous substance required for the synthesis of glycoproteins, glycolipids, and glycoaminoglycans that are found in tendons, ligaments, cartilage, and synovial fluid and are required to maintain healthy articular cartilage.

Mechanism of Action[2]

Glucosamine is an endogenous aminomonosaccharide synthesized from glucose and utilized for biosynthesis of glycoproteins. The sulfate salt of glucosamine forms half of the disaccharide subunit of keratan sulfate, which is decreased in osteoarthritis, and of hyaluronic acid, which is found in both articular cartilage and synovial fluid. It is hypothesized that altered glucosamine metabolism contributes to development of osteoarthritis, therefore, glucosamine has been investigated clinically in this disorder as the sulfate salt. Exogenous administration of glucosamine in animals collects in articular cartilage and has been reported to retard cartilage degradation and rebuild experimentally damaged cartilage tissue. Glucosamine enhances cartilage proteoglycan synthesis, thereby inhibiting deterioration of cartilage brought about by osteoarthritis and helping to maintain an equilibrium between cartilage catabolic and anabolic processes.

Current Indications and Efficacy[3-7]

Although glucosamine is not approved by the FDA for the prevention or treatment of osteoarthritis (OA), recent studies have examined glucosamine's effectiveness at reducing joint space narrowing and preserving joint function in patients with diagnosed OA. The details of two well-designed, randomized placebo controlled clinical trials follow on the next page.

Palvekla et al. randomized two hundred two men and women between the ages of 40 and 75 years with previously diagnosed knee osteoarthritis, as defined by the American College of Rheumatology criteria, to receive oral glucosamine sulfate, 1500 mg once a day, or placebo. Changes in radiographic minimum joint space width were measured in the medial compartment of the tibiofemoral joint, and symptoms were assessed using the algo-functional indexes of Lequesne and WOMAC (Western Ontario

and McMaster Universities). The trial was conducted according to a randomized, placebo-controlled design in a single center at the Prague Institute of Rheumatology between June 29, 1995 and January 20, 1999. The protocol was approved by the institutional review board of the center, and patients provided written informed consent. Patients were screened at a baseline visit that included a physical examination, a knee radiograph according to a standardized method, a symptom questionnaire, and routine safety laboratory tests. After enrollment, patients were randomized to the study medication and were followed up until completion of a 3-year treatment course. Clinic visits were performed quarterly and included symptom assessment, and standardized knee radiographs and routine safety laboratory tests were performed at the end of each year.

Palvekla et al. found progressive joint space narrowing with placebo use was -0.19 mm (95% confidence interval, -0.29 to -0.09 mm) after 3 years in patients with mild to moderate osteoarthritis at the time of enrollment as defined by the American College of Rheumatology criteria. Conversely, there was no average change with glucosamine sulfate taken at the dose of 1500 mg once daily in patients also with mild to moderate osteoarthritis at the time of enrollment as defined by the American College of Rheumatology criteria (0.04 mm; 95% confidence interval, -0.06 to 0.14 mm), with a significant difference between groups ($P = 0.001$). Fewer patients treated with glucosamine sulfate experienced predefined severe narrowings (>0.5 mm): 5% vs 14% ($P = .05$). Symptoms improved modestly with placebo use but as much as 20% to 25% with glucosamine sulfate use, with significant final differences on the Lequesne index and the WOMAC total index and pain, function, and stiffness subscales. Safety was good and without differences between groups.

Reginster et al. completed a randomized, double-blind placebo controlled trial in which 212 men and women over the age of 40 years with knee osteoarthritis, as defined by the American College of Rheumatology criteria, were randomly assigned 1500 mg sulfated oral glucosamine or placebo once daily for 3 years. Weight bearing, anteroposterior radiographs of each knee in full extension were taken at enrollment and after 1 and 3 years. Mean joint-space width of the medial compartment of the tibiofemoral joint was assessed by digital image analysis, whereas minimum joint-space width at the narrowest point within the knee joint was measured by visual inspection with a magnifying lens. Symptoms were scored by the Western Ontario and McMaster Universities (WOMAC) osteoarthritis index.

Reginster et al. found in that the 106 patients with mild to moderate osteoarthritis on placebo in their trial had progressive joint-space narrowing, with a mean joint-space loss after 3 years of 0.20-0.31 mm (95% CI). There was no significant joint-space loss in the 106 patients also with mild to moderate disease on glucosamine sulfate at the dose of 1500 mg taken once daily (95% CI). WOMAC scores were used to evaluate symptoms, and patients on placebo were found to have statistically significantly higher scores as compared with those of the intervention group after treatment with glucosamine sulfate ($P = 0.0044$). There were no differences in safety or reasons for early withdrawal between the treatment and placebo groups.

Recent meta-analyses[5,6] conclude that in patients with osteoarthritis, glucosamine is effective in decreasing joint space narrowing and preserving joint function. However, the magnitude of these effects is unclear because of inconsistencies in study design and dependence on industry support for study execution[7]. Unfortunately, both of these

studies excluded individuals with severe osteoarthritis of the knee. Thus, the long-term combined structure modifying and symptom modifying effects of glucosamine sulfate suggest that it could be a disease-modifying agent in mild to moderate osteoarthritis of the knee.

Contraindications and Allergies[1,2]

Due to the lack of reliable data, glucosamine should be avoided in pregnancy and lactation. Some glucosamine products are derived from marine exoskeletons which have the potential to cause reactions in individuals allergic to shellfish. No reactions have been reported, and manufacturers claim that their glucosamine product is purified to such an extent that shellfish allergies are of little concern. However, since preparation methods and quality standards can vary significantly between manufacturers, glucosamine should be avoided in patients who have a documented shellfish allergy.

Dosage Forms, Recommended Doses, and Duration[1,2]

The typical dose for osteoarthritis and temporomandibular joint (TMJ) arthritis is 500 mg taken three times each day with meals. It is recommended that each dose be taken with meals simply to increase compliance as glucosamine's oral absorption and ninety percent bioavailability is not significantly altered when taken with or without food. Intravenous, intramuscular, and intra-articular products are used in other countries but are not available in the United States. Glucosamine has been used safely in multiple clinical trials lasting from four weeks to three years and is generally considered safe for long term use at the dose of 500 mg PO TID. However, the sulfated form is generally preferred over the chloride salt, as the sulfated form most closely resembles endogenously synthesized aminomonosaccharides.

Drug Interactions and Drug Disease Interactions[1,2]

Adverse effects of glucosamine by any route are minimal with gastrointestinal symptoms, drowsiness, headache, and skin rash being reported. Although no known interactions exist between glucosamine and foods or other herbal supplements, there are two well-documented interactions between glucosamine and antidiabetic and cancer chemotherapy drugs. Glucosamine might increase insulin resistance or decrease insulin production resulting in elevated blood glucose levels. This increase in blood glucose may require increases in administered insulin and/or hypoglycemic agents such as sulfonylureas and metformin. Therefore, glucosamine should be used only in diabetic patients who exhibit tight blood glucose control. In addition, glucosamine may theoretically induce resistance to etoposide and doxorubicin by reducing these drugs' inhibition of topoisomerase II, an enzyme required for DNA replication in tumor cells. Thus, glucosamine should be avoided in patients receiving etoposide or doxorubicin therapy.

There is some concern that glucosamine might increase cholesterol and triglyceride levels due to preliminary evidence which suggests that glucosamine may increase insulin levels. Since hyperinsulinemia is often associated with elevated triglycerides and cholesterol, individuals with hyperlipidemia who wish to begin taking glucosamine should be apprised of the risk and have a complete cholesterol screening every six months.

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There is also some concern that glucosamine may increase blood pressure due to preliminary evidence which suggests that glucosamine may increase insulin levels. Since hyperinsulinemia is often associated with elevated blood pressure, patients with hypertension, heart failure, renal insufficiency, peripheral vascular disease, or cardiovascular disease who wish to begin taking glucosamine should first speak with their physician to determine if glucosamine supplementation is indicated.

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