Glucosamine

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Glucosamine (C₆H₁₃NO₅) is an amino sugar and a prominent precursor in the biochemical synthesis of glycosylated proteins and lipids. Glucosamine is part of the structure of the polysaccharides chitosan and chitin, which compose the exoskeletons of crustaceans and other arthropods, as well as the cell walls of fungi and many higher organisms. Glucosamine is one of the most abundant monosaccharides.[1] It is produced commercially by the hydrolysis of crustacean exoskeletons or, less commonly, by fermentation of a grain such as corn or wheat.[2]

Glucosamine appears to be safe for use as a dietary supplement; effectiveness has not been established for any condition. In the US it is one of the most common non-vitamin, non-mineral, dietary supplements used by adults.[3]

<table>
<thead>
<tr>
<th>IUPAC name</th>
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<tbody>
<tr>
<td>(3R,4R,5S)-3-Amino-6-(hydroxymethyl)oxane-2,4,5-triol</td>
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<table>
<thead>
<tr>
<th>Other names</th>
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<tr>
<td>2-Amino-2-deoxy-glucose</td>
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<tr>
<td>Chitosamine</td>
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Identifiers

- CAS number: 3416-24-8
- PubChem: 439213
- ChemSpider: 388352
- UNII: N08U5BOQ1K
- EC number: 222-311-2
- DrugBank: DB01296
- KEGG: D04334
- MeSH: Glucosamine
- ChEBI: CHEBI:5417
- ChEMBL: CHEMBL181132
- ATC code: M01AX05 (http://www.whocc.no/ate_ddi_index/?code=M01AX05)
- Beilstein Reference: 1723616
- Gmelin Reference: 720725
- Jmol-3D images: Image 1 (http://chemapps.stolaf.edu/jmol/jmol.php?model=N%5BC%40H%5D1C%2B0%29OC%2B0%29%5BC%40%5D%2B0%29%5BC%40%5D1O)

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Properties
Molecular formula: $\text{C}_6\text{H}_{13}\text{NO}_5$

- **Molar mass**: 179.17 g mol$^{-1}$
- **Density**: 1.563 g/mL
- **Melting point**: 150 °C (302 °F; 423 K)
- **log P**: -2.175
- **Acidity ($pK_a$)**: 12.273
- **Basicity ($pK_b$)**: 1.724

Except where noted otherwise, data are given for materials in their standard state (at 25 °C (77 °F), 100 kPa)

### Medical uses

Oral glucosamine is a dietary supplement and is not a pharmaceutical drug. It is illegal in the US to market any dietary supplement as a treatment for any disease or condition.[4] Glucosamine is marketed to support the structure and function of joints and the marketing is targeted to people suffering from osteoarthritis. Commonly sold forms of glucosamine are glucosamine sulfate, glucosamine hydrochloride, and $N$-acetylglucosamine. Glucosamine is often sold in combination with other supplements such as chondroitin sulfate and methylsulfonylmethane. Of the three commonly available forms of glucosamine, only glucosamine sulfate is given a "likely effective" rating for treating osteoarthritis.[5]

Glucosamine, along with commonly used chondroitin, should not be used to treat patients who have symptomatic osteoarthritis of the knee as evidence shows that these treatments fail to provide relief for that condition.[6]

As is common with heavily promoted dietary supplements, the claimed benefits of glucosamine are based principally on laboratory studies. Clinical studies are divided, with some reporting relief from arthritic pain and stiffness, but larger well-constructed studies reporting no benefit above placebo.[7]

There is no evidence to date that consumption of glucosamine by sport participants will prevent or limit joint damage after injury.[8]

### Adverse effects

One clinical study over three years showed that glucosamine in doses of 1500 mg per day is safe to use.[9] However, a recent Université Laval study shows that people taking glucosamine tend to go beyond recommended guidelines, as they do not feel any positive effects from the dietary supplement. Beyond recommended dosages, researchers found in preliminary studies that glucosamine may damage pancreatic cells, possibly increasing the risk of developing diabetes.[10]

Adverse effects, which are usually mild and infrequent, include stomach upset, constipation, diarrhea, headache and rash.[11] Nevertheless, there have been rare case reports of patients who have chronic liver disease and a worsening of their condition with glucosamine supplementation.[12] Interestingly, the mechanism of action is unknown. However, it is suspected that a possible hypersensitivity to the glucosamine might have occurred. In
regards to adverse effects in pregnancy, only one study has investigated glucosamine in that population and
found it to be safe.[13] As a precaution because of the lack of clinical studies, more information is needed before
recommending glucosamine in pregnancy.

Since glucosamine is usually derived from the shells of shellfish while the allergen is within the flesh of the
animals, it is probably safe even for those with shellfish allergy.[14] However, many manufacturers of

Another concern has been that the extra glucosamine could contribute to diabetes by interfering with the normal
regulation of the hexosamine biosynthesis pathway,[17] but several investigations have found no evidence that
this occurs.[18][19][20] A manufacturer-supported review conducted by Anderson et al. in 2005 summarizes the
effects of glucosamine on glucose metabolism in in vitro studies, the effects of oral administration of large
doses of glucosamine in animals, and the effects of glucosamine supplementation with normal recommended
dosages in humans, concluding that glucosamine does not cause glucose intolerance and has no documented
effects on glucose metabolism.[21] Other studies conducted in lean or obese subjects concluded that oral

Biochemistry

Glucosamine is naturally present in the shells of shellfish, animal bones, bone marrow, and fungi.[27]
D-Glucosamine is made naturally in the form of glucosamine-6-phosphate, and is the biochemical precursor of
all nitrogen-containing sugars.[28] Specifically, glucosamine-6-phosphate is synthesized from fructose
6-phosphate and glutamine by glucosamine-6-phosphate deaminase[29] as the first step of the hexosamine
biosynthesis pathway.[30] The end-product of this pathway is Uridine diphosphate N-acetylglucosamine
(UDP-GlcNAc), which is then used for making glycosaminoglycans, proteoglycans, and glycolipids.

As the formation of glucosamine-6-phosphate is the first step for the synthesis of these products, glucosamine
may be important in regulating their production; however, the way that the hexosamine biosynthesis pathway is
actually regulated, and whether this could be involved in contributing to human disease remains unclear.[17]

History

Glucosamine was first prepared in 1876 by Georg Ledderhose by the hydrolysis of chitin with concentrated
hydrochloric acid.[31][32][33] The stereochemistry was not fully determined until the 1939 work of Walter
Haworth.[1][34]
Legal status

United States

In the United States, glucosamine is not approved by the Food and Drug Administration for medical use in humans.[35] Since glucosamine is classified as a dietary supplement in the US, safety and formulation are solely the responsibility of the manufacturer; evidence of safety and efficacy is not required as long as it is not advertised as a treatment for a medical condition.[36] The U.S. National Institutes of Health is currently conducting a study of supplemental glucosamine in obese patients, since this population may be particularly sensitive to any effects of glucosamine on insulin resistance.[37]

Europe

In most of Europe, glucosamine is approved as a medical drug and is sold in the form of glucosamine sulfate.[38] In this case, evidence of safety and efficacy is required for the medical use of glucosamine and several guidelines have recommended its use as an effective and safe therapy for osteoarthritis. The Task Force of the European League Against Rheumatism (EULAR) committee has granted glucosamine sulfate a level of toxicity of 5 in a 0-100 scale,[38] and recent OARSI (OsteoArthritis Research Society International) guidelines for hip and knee osteoarthritis indicate an acceptable safety profile.[39]

Class action lawsuits

In 2013, without admitting fault, manufacturer Rexall Sundown, Inc., and NBTY, Inc., agreed to pay up to $2 million to settle consumer claims related to the wording of certain claims on the packaging of glucosamine bottles sold at Costco under the Kirkland label.[40]

In August 2012, a class action lawsuit was filed in New York claiming that 21st Century Healthcare, Inc. falsely advertises that its “Glucosamine 750 Chondroitin 600 Triple Strength” dietary supplements will restore lost cartilage.[41] In April 2013, a San Diego man launched a proposed class action lawsuit in California Federal Court accusing Nutramax Laboratories, Walmart and Rite Aid of falsely advertising the effectiveness of glucosamine.[42] The two class actions are still pending.

Research

Clinical trials on glucosamine and chondroitin

Since glucosamine is a precursor for glycosaminoglycans, and glycosaminoglycans are a major component of cartilage, some have hoped that supplemental glucosamine could beneficially influence cartilage structure, and alleviate arthritis. Its use as a therapy for osteoarthritis appears safe, but there is no unequivocal evidence for its effectiveness. There have been multiple clinical trials testing glucosamine as a potential medical therapy for osteoarthritis, but the results have not supported its use.

Possibility of bioavailability

Two studies (funded by the Rottapharm Group, Monza, Italy, who supplied the crystalline glucosamine sulfate) published in 2007 measured the concentrations of glucosamine in the synovial fluid and plasma after oral
administration of glucosamine sulfate to both healthy volunteers and patients with osteoarthritis.[43][44]

In the first study, glucosamine sulfate was given to healthy volunteers at a range of doses (750, 1500 and 3000 mg) once daily. In the second study, oral glucosamine sulfate capsules (1500 mg) were given daily for two weeks to 12 patients with osteoarthritis. Glucosamine concentrations in plasma and synovial fluid increased significantly from baseline levels and the levels in the two fluids were highly correlated. The authors interpreted these levels could be biologically advantageous to articular cartilage, however the levels are still 10 - 100 fold lower than required to positively affect the cartilage (chondrocytes) to build new tissue.[45] Glucosamine sulfate uptake in synovial fluid may be as much as 20%, or could be negligible, indicating no biological significance.[46]

Veterinary medicine

Some studies have shown efficacy of glucosamine supplementation for dogs with osteoarthritis pain, particularly in combination with other nutraceuticals like chondroitin[47][48] while others have not.[49] A trial of oral combination capsules (glucosamine/chondroitin/manganese ascorbate) in dogs with osteoarthritis found no benefit on either gait analysis or subjective assessments by the veterinarian or owner.[49]

The use of glucosamine in equine medicine exists, but one meta-analysis judged extant research too flawed to be of value in guiding treatment of horses.[50]

A number of studies have measured the bioavailability of glucosamine after oral administration to horses. When given as a single oral dose (nine grams) with or without chondroitin sulfate (three grams) to ten horses, glucosamine (hydrochloride) was detected in the blood with a maximum level of 10.6 (+/- 6.9) micrograms per millilitre at two hours after dosing.[51] Another study examined both the serum and the joint synovial fluid after nasogastric (oral) or intravenous administration of 20 mg/kg glucosamine hydrochloride to eight adult horses.[52] Although joint fluid concentrations of glucosamine reached 9 - 15 micromolar following intravenous dosing, it was only 0.3 - 0.7 micromolar with nasogastric dosing. The authors calculated that these glucosamine synovial fluid levels achieved by the oral route were 500 fold lower than that required to have a positive effect on the metabolism of cartilage cells. A follow up study by the same research group compared glucosamine sulfate with glucosamine hydrochloride at the same dose (20 mg/kg) in eight horses and found a higher fluid concentration with the sulfate preparation (158 ng/mL compared to 89 ng/mL one hour post oral dose).[53] They concluded that these higher synovial fluid levels obtained with the sulfate derivative were still too low to have a relevant biological effect on articular cartilage.

A three month trial of an oral dosage regime of a commercial preparation of glucosamine sulfate, chondroitin sulfate and methyl sulfonyl methane was performed in veteran horses with no effect on gait stiffness, with exercise alone in the control group being effective.[54] The intravenous use of a combination of N-acetylglucosime, pentosan polysulfate and sodium hyaluronate in horses with surgically-induced osteoarthritis saw improvements in xray changes to the cartilage but not histologically or in biochemical outcomes,[55] suggesting more evidence is needed for this combination and route of administration.

See also

- Chitobiose
- Chitosan
- Chondroitin sulfate
- Methylsulfonylmethane

References

4. ^ Staff, FDA Last Updated April 11, 2013 Q&A on Dietary Supplements (http://www.fda.gov/Food/DietarySupplements/QADietarySupplements/default.htm)


37. ClinicalTrials.gov NCT00065377 Effects of Oral Glucosamine on Insulin and Blood Vessel Activity in Normal and Obese People (http://www.clinicaltrials.gov/show/NCT00065377)


53. Meulyzer, M; Vachon, P; Beaudry, F; Vinardell, T; Richard, H; Beauchamp, G; Laverty, S (2008). "Comparison of


External links

- Glucosamine article, Mayo Clinic (http://www.mayoclinic.com/health/glucosamine/NS_patient-glucosamine)
- General glucosamine and chondroitin sulfate information (http://www.arthritis.org/conditions/alttherapies/Glucosamine.asp) from the Arthritis Foundation.
- "UDP-N-acetylg glucosamine biosynthesis (http://www.chem.qmul.ac.uk/iubmb/enzyme/reaction/polysacc/UDPGlcN.html)," diagram including IUBMB nomenclature and links.
- "Glucosamine and chondroitin for arthritis: Benefit is unlikely (http://www.quackwatch.org/01QuackeryRelatedTopics/DSH/glucosamine.html)," Summary of and commentary on research findings, including GAIT clinical trial.


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