

Review article: Glucosamine

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ABSTRACT

It has been claimed that glucosamine is able to alleviate pain, slow down losses of, and even restore articular cartilage in patients with damaged or osteoarthritic joints. It is classified as a food additive or nutraceutical; therefore manufacturers do not need to comply with the same regulations that apply for quality assurance within the pharmaceutical industry. Osteoarthritis can be managed by pharmacological and non-pharmacological methods. It is controversial whether glucosamine sulphate is the first structure-modifying drug commercially available. Little evidence suggests that glucosamine is superior to a placebo treatment in restoring articular cartilage.

Key words: *biochemistry; cartilage, articular; glucosamine; pharmacology*

INTRODUCTION

Glucosamine is claimed to alleviate pain, slow down

losses of, and even restore articular cartilage in patients with damaged or osteoarthritic joints.¹⁻³ It is a naturally occurring compound in mammalian articular cartilage. However, whether oral administration can repair hyaline cartilage defects is controversial.

Glucosamine is classified as a food additive or nutraceutical and thereby not regulated by the US Food and Drug Administration. Manufacturers do not need to comply with the same regulations that apply for quality assurance within the pharmaceutical industry. Commercially available glucosamine is mainly derived from chitin in crustacean shells.^{4,5} Caution for hypersensitivity is needed in patients with shellfish allergy. In Australia, glucosamine is not listed on the Schedule of Pharmaceutical Benefits, and thereby there is no government rebate for patients. An Australian federal government taskforce is assessing the evidence relating to the clinical use of glucosamine.⁶

In the USA in 2004, osteoarthritis was the commonest form of arthropathy in older age-groups and estimated to affect 10 to 20 million people (i.e. 4.2 to 8.4% of the US population). The cost of treating patients with OA in the USA amounted to about \$86 billion per annum.⁷ Sales of glucosamine and

chondroitin amount to approximately \$730 million.⁷ Extrapolating from this US data, Australia, with a population of about 20 million, might spend around A\$72 million per year on glucosamine products. A bottle of 120 tablets of glucosamine for 30 to 40 days costs approximately A\$50 (A\$1.25 per day).

Osteoarthritis can be managed by pharmacological and non-pharmacological methods.^{8,9} Agents that improve pain and joint function (paracetamol and non-steroidal anti-inflammatory drugs [NSAID]) are symptom modifying, whereas those that alter the progression of cartilage loss are structure modifying. It is controversial whether glucosamine sulphate is the first commercially available structure-modifying drug, as suggested by 2 randomised controlled trials.^{2,10}

Based on our literature review, there is little or no evidence to suggest that glucosamine is superior to placebo for restoring articular cartilage, reversing degenerative chondral changes, or slowing down any chondral deterioration.

BASIC SCIENCE

Histology

Cartilage is a semi-rigid form of supporting tissue, which mainly stems from the nature and predominance of ground substance in the extracellular matrix. Proteoglycans, dispersed in proteoglycan aggregates, make up the ground substance and account for the ability of the solid chondral tissue to undergo elastic deformation. Sulphated glycosaminoglycans (GAG, chondroitin sulphate, and keratan sulphate) predominate in the proteoglycan aggregates with molecules of the non-sulphated GAG, hyaluronic acid, forming the central backbone of the complex.¹¹ Varying proportions of collagen and elastic fibres are embedded in the ground substance, giving rise to 3 main types of cartilage: hyaline cartilage, fibrocartilage, and elastic cartilage.¹¹

Cartilage formation commences with the differentiation of stellate-shaped, primitive mesenchymal cells to form rounded cartilage precursor cells called chondroblasts. Subsequent mitotic divisions give rise to aggregations of closely packed chondroblasts, which grow and begin synthesis of ground substance and fibrous extracellular material. Secretion of extracellular material traps each chondroblast within the cartilaginous matrix thereby separating the chondroblasts from one another. Each chondroblast then undergoes one or 2 further mitotic

divisions to form a cluster of mature cells separated by a small amount of extracellular material. Mature cartilage cells, known as chondrocytes, maintain the integrity of the cartilage matrix. This differentiation and maturation sequence is most advanced in the centre of a mass of growing cartilage. Towards the periphery of the cartilage, chondroblasts at progressively earlier stages of differentiation merge with the surrounding loose-supporting tissue. On completion of growth, the cartilage mass consists of chondrocytes embedded in a large amount of extracellular matrix. At the periphery of mature cartilage is a zone of condensed supporting tissue called perichondrium-containing chondroblasts with cartilage-forming potential. Growth of cartilage occurs by interstitial growth from within and appositional growth at the periphery.¹¹

There are no nerves in articular cartilage.¹² Most cartilage is devoid of blood vessels and consequently the exchange of metabolites between chondrocytes and surrounding tissue depends on diffusion. This limits the thickness to which cartilage may develop while maintaining viability of the innermost cells. In sites where cartilage is particularly thick (e.g. costal cartilage), cartilage canals convey small vessels into the centre of the cartilage mass.¹¹ Pharmaceutical molecules can only reach the cartilage by intra-osseous blood flow, which terminates at the osteochondral junction, by intra-capsular vessels, or by diffusion through synovial fluid. This is particularly relevant for any drugs if they are to have any effect on articular cartilage.

Biochemistry

Sugars containing an amino group are called amino sugars. They include D-glucosamine, D-galactosamine, and D-mannosamine, all of which have been identified in nature. Glucosamine is a constituent of hyaluronic acid.¹³ Sugars can be hexoses or pentoses, depending on the number of carbon atoms in their ring structure. Glucose is a hexose. Glucosamine is one of several naturally occurring 6-carbon amino sugars found in the body. Amino sugars are essential building blocks for mucopolysaccharides, mucoproteins, and mucolipids. Examples include: chondroitin, heparin, and hyaluronic acid.¹³ Glucosamine sulphate is one of the pharmacological derivatives of glucosamine (a naturally occurring amino-monosaccharide). It is a constituent of the GAG chains in aggrecan and other proteoglycans found in the synovial fluid and cartilage of hyaline joints. In articular cartilage, glucosamine exists as one of the monosaccharides that make up a disaccharide proteoglycan. Aggrecan

and other proteoglycans trap water into the matrix of cartilage, providing it with the deformable resilience that is necessary for its function.⁸

Pharmacology

Glucosamine is typically administered orally, however parenteral administration has also been studied. The oral bioavailability of glucosamine is about 26%.¹⁴ Although it has a very short serum half-life, animal studies indicate that it diffuses rapidly into tissues and has a beta half-life of about 28 hours.¹⁵

Glucosamine sulphate is well absorbed orally but undergoes substantial first-pass metabolism.¹⁶ The half-life of glucosamine sulphate has also been calculated as 58 hours.^{2,3,8} It is believed to be distributed to liver, kidney and other tissues including articular cartilage.⁸ However, it is unclear whether orally imbibed glucosamine can reach articular cartilage.¹⁷ Radiolabelled glucosamine given orally to 6 volunteers was 90% absorbed.¹⁸ Moreover, necropsy of dogs given oral radiolabelled glucosamine showed that it had a tropism for articular cartilage.¹⁹

Although most studies typically use a three times daily dosing schedule, we have not been able to find any scientific evidence to support such usage.

The mechanism of action of glucosamine is unknown.³ Pharmacokinetic studies have suggested that it is a substrate for the synthesis of mucopolysaccharides rather than a source of caloric energy.⁸ In early osteoarthritis there is an increase in the production of structural molecules such as aggrecan and collagen, but this is matched by increased catabolism by proteases under the influence of cytokines.⁸ *In vitro*, addition of glucosamine to chondrocyte cultures increases aggrecan synthesis.²⁰ It is possible that glucosamine causes an anti-inflammatory effect, and this may explain its claimed pain-relieving ability in arthropathies.²¹ *In vitro* studies indicate that glucosamine stimulates proteoglycan synthesis and possesses mild anti-inflammatory properties.^{20,22} It is also safer than other anti-inflammatory drugs.^{2,3,8,16,23-25}

In a randomised controlled trial comparing glucosamine to placebo in diabetic elderly patients, there was no difference in terms of their diabetic control or long-term sugar levels as determined by serum HbA1c levels. This suggests that glucosamine is safe for type-II diabetic patients.²⁴

The optimal dose is unknown. Mostly the oral dosage is 1.5 g daily.²⁵ There is a latency of 4 to 8 weeks before the therapeutic effects are believed to emerge.⁸ It is not known whether a monosaccharide, such as glucosamine, can be assembled into a polysaccharide

structure after it survives the intra-articular synovial fluid environment, and whether there is an enzyme to accomplish this task.

Glucosamine for osteoarthritis of the knee

In a multi-centre, double blind, controlled trial, the efficacy of intramuscular glucosamine was compared to intramuscular placebo in 155 patients.¹⁶ Either drug was administered twice weekly in patients with osteoarthritis. Their subjective symptomatic progress was determined at 2 weekly intervals. Intramuscular glucosamine was found to be somewhat more effective than placebo for the short-term relief of subjective symptoms from knee arthritis. Interestingly, the placebo group also showed some symptomatic relief, although not as much as the glucosamine group.

Randomised, controlled, double-blind trials conducted in Belgium and the Czech Republic compared glucosamine sulphate (1.5 g daily) to placebo given to patients with osteoarthritis of the knee for 3 years.^{2,3} Radiography was used to assess joint space narrowing, but was considered an unreliable method.²⁶ Neither study described histological findings. Structural modification was the primary end-point, whereas symptom modification was the secondary end-point. Both trials suggested that glucosamine sulphate had a substantial symptom- and structure-modifying effect in patients with mild-to-moderate osteoarthritis of the knee and a normal body mass index (BMI). Statistically, patients with osteoarthritis of the knee have a higher BMI, but those were excluded.⁸ The hexose sugar structure of glucosamine might exacerbate diabetes. In animal models of diabetes, glucosamine increased insulin resistance through an unknown mechanism.⁸

Some European studies suggest that the Rotta preparation of glucosamine sulphate may slow radiological progression of osteoarthritis of the knee over a 3-year period.⁸ The ability of glucosamine to improve symptoms and delay radiological progression of osteoarthritis affecting other joints needs further review.²⁷

The Cochrane collaboration review of glucosamine sulphate for osteoarthritis of the knee included 20 studies and 2570 patients.²⁷ In 10 randomised controlled trials comparing the Rotta preparation of glucosamine to placebo, glucosamine was reported to be superior for pain (standardised mean difference [SMD], -1.31; 95% confidence interval [CI], -1.99, -0.64) and function using the Lequesne index (SMD, -0.51; 95% CI, -0.96, -0.05). Pooled results for pain (SMD, -0.15; 95% CI, -0.35, 0.05) and function using the WOMAC index (SMD, 0.03; 95% CI, -0.18, 0.25),

in which a non-Rotta preparation of glucosamine was compared to placebo and did not yield a statistically significant difference. In 4 randomised controlled trials comparing the Rotta preparation of glucosamine to an NSAID, glucosamine was superior in 2 and equivalent in 2. The results of long-term, randomised, controlled, double-blind studies of glucosamine in patients with higher BMIs and osteoarthritis of the knee (and other joints) are still pending.

DISCUSSION

There is little evidence that glucosamine can accomplish some of its claimed benefits in patients, particularly in terms of restoring joint cartilage or slowing the progression of arthropathies.²⁸ There is no histological study to support this claim. Only a few randomised double-blind trials of glucosamine treatment have assessed outcomes.

The exact dose and dosing interval seems to have evolved empirically and without scientific scrutiny. Glucosamine is subject to a high degree of first pass metabolism, such that oral bioavailability is poor. The half-life has been reported to vary from 28 to 58 hours.^{2,3,8} The small percentage that survives first pass entry into the circulation is transported by an unknown carrier in the vessels to reach the synovial joint. Any glucosamine molecules that reach the joint need to enter the cartilage. However, there are few or no blood vessels in cartilage. Therefore glucosamine molecules need to either diffuse across synovial fluid or enter via the dense bone-cartilage interface in order to arrive at the hyaline cartilage. Once there, the monosaccharide or sulphated monosaccharide needs to be reassembled into a much larger proteoglycan and GAG macromolecules, but the enzyme that performs this task is unknown. Alternatively, glucosamine

might act as a substrate for an anabolic process in the joint.

It is recommended that glucosamine be taken for 6 to 8 weeks before any symptom relief can be expected, but there is no evidence to support this belief. We consider that it is likely to be no more effective than a placebo.

There are no known binding sites or mechanisms of action for the purported actions of glucosamine. It is unknown whether it inhibits the production of prostaglandins or blocks the cyclo-oxygenase pathway, and how if at all it has any anti-inflammatory effects.

In vitro, glucosamine might act as a substrate that increases the synthesis of proteins, such as aggrecan.^{8,13} Nonetheless, *in vivo*, no biochemical or histological evidence suggests that glucosamine stimulates the production of GAG, which is a complex biochemical event requiring many substrates, cofactors, and enzymes.

The 2 clinical studies from Belgium and from the Czech Republic were sponsored by Rotta pharmaceuticals,⁸ which used standing anteroposterior knee radiographs to assess changes in chondral outcome. This method has inherently poor reproducibility and is subject to errors, including parallax error, even in normal joints the articular surfaces are curved, and minor postural changes will cause apparent changes in chondral height. Any change in patient position in 3 dimensions or in the directions and orientations of the X-ray beam or plate or of the observer will compound and magnify any error.

According to the Cochrane review, there was no significant difference between glucosamine and placebo with respect to effects on pain, function, and range of movement.²⁷ Histological analysis of the alleged benefits of glucosamine is lacking.

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