Role of glucosamine in osteoarthritis

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\textbf{KEYWORDS}
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\textbf{Summary}
Long-term follow-up studies on the effects of glucosamine preparations are still awaited. At present, only short-term results are available. They are known to relieve pain and decrease the rate of joint space narrowing clinically in osteoarthritis of knee, whilst the side effects are less when compared to the anti-inflammatory drugs and even placebos. It is probably safe – but there is no good evidence that it works. It would be ideal to have a medication that is a normal constituent of the human cartilage, which modifies the natural history of the disease. It is possible that long-term clinical studies with glucosamine may result in modifications to the indications for joint surgery or the time patients can live with osteoarthritis before developing substantial disability.

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\textbf{Introduction}
Glucosamine sulphate is a normal constituent of the extracellular matrix of mammalian articular cartilage and synovial fluid, which is required for synthesis of glycosaminoglycans (GAGs).\textsuperscript{1} It also helps in synthesising mucin or mucous secretions, which act as lubricant or protective agents in human joints.

In 1956, Lennart Roden from Stockholm first showed glucosamine HCL-stimulated production of chondroitin sulphate in cartilage matrix by at least three times its control value. It was not until the 1980s that clinical trials of glucosamine as a therapeutic drug for osteoarthritis (OA) of knee began.

Now, it is readily available for purchase from health/food shops and pharmacies in the UK, USA and throughout Europe, for the relief of musculoskeletal symptoms.\textsuperscript{2,3} The range of products that includes chondroitin sulphate, vitamins C, D and E, minerals and herbs, as well the oligo-elements (such as zinc, selenium, manganese and copper) are together called nutripharmaceuticals.\textsuperscript{4} Glucosamine has gained popularity in the last two decades for the treatment of OA.\textsuperscript{5}

\textbf{Glucosamine and its properties}
Glucosamine is an amino monosaccharide found in chitin, glycoproteins and in GAGs (formerly known as mucopolysaccharides), such as hyaluronic acid and heparan sulphate.
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It is the basic building block of the amino sugars and hence is an important constituent of the cell wall and interstitial proteins.

The chemical structure of glucosamine is shown in Fig. 1.

Glucosamine (2-amino-2-deoxy-D-glucose) is one of the two hexosamine sugars (six carbon amino sugars) common in human cells. Structurally, glucosamine is modified glucose, with an \( \text{NH}_2 \) group replacing the \( \text{-OH} \) group found on carbon two (C-2). G6-P is an amino monosaccharide (amino sugar) produced in the body by the combination of glutamine with fructose, through the enzymatic action of glucosamine synthetase.

Glucosamine is available commercially as a nutritional supplement in three forms: glucosamine HCl, glucosamine sulphate and N-acetyl-glucosamine. All three forms are water soluble, the salt acting as a delivery vehicle. At neutral and physiological pH, the amino group in glucosamine is protonated, resulting in a positive charge. Salt forms of glucosamine contain negative anions to neutralize the charge.

In the case of glucosamine hydrochloride, the anion is chloride, and in glucosamine sulphate the anion is sulphate. N-acetylg glucosamine is a delivery form of glucosamine in which the amino group is acetylated, thus neutralizing its charge. To date, most of the clinical studies examining the effect of glucosamine on OA have been performed with either the sulphate or the chloride salts of glucosamine.

The glucosamine used in supplements is typically derived from marine exoskeletons. Synthetic glucosamine is also available.

Pharmacokinetics

About 90% of glucosamine administered orally as a glucosamine salt gets absorbed from the small intestine and from there it is transported, via the portal circulation, to the liver. It appears that a significant fraction of the ingested glucosamine is catabolized by first-pass metabolism in the liver.

Healthy men have serum glucosamine concentrations of 0.04 mmol/L when they are not consuming supplemental glucosamine. Ingestion of recommended oral doses of glucosamine in humans achieves serum levels of approximately 0.06 mmol/L. It is not presently known how much of an ingested dose is taken up in the joints in humans.

Most relevant clinical trials have used patented crystalline glucosamine sulphate in 1500 mg, once a day, soluble powder form. This is a prescription drug in most European and non-European countries. However, the Dietary Supplement Health and Education Act of 1994 favoured the appearance of several undocumented glucosamine salts (e.g. hydrochloride), derivatives (e.g., N-acetyl-glucosamine) on the dietary supplement market in the USA and other countries, and various other dosage forms and regimens.

Persiani et al. studied the pharmacokinetics of glucosamine and found that it is bioavailable after oral administration of crystalline glucosamine sulphate. This persists in circulation, and its pharmacokinetics support once-daily dosage.

Steady-state peak concentrations after a therapeutic oral dose of 1500 mg show bioavailability at concentrations that are in line with those found to be effective in selected in vitro models, which may explain the favourable clinical results in OA.

Mechanism of action of glucosamine in human tissues

Glucosamine is preferentially incorporated by chondrocytes into the components of the GAG chains in intact cartilage and stimulates the synthesis of physiological proteoglycans. It also decreases the activity of catabolic enzymes, including matrix metalloproteases (MMP).

In certain tissues, glucosamine has a higher affinity for glucose transporters than glucose itself and is incorporated into glycoproteins faster than glucose. It also inhibits the degradation of equine articular cartilage induced by interleukin 1 and lipopolysaccharides. This supports the suggestion that exogenous glucosamine acts mainly as a substrate for biosynthesis of mucopolysaccharides and biopolymers of joints and bones and, thus, contributes to restoration of damaged cartilage.

Articular cartilage in OA of the knee

The degenerative disease OA is a manifestation of an imbalanced synthesis of articular cartilage (AC) matrix and the associated growth factors. Knee cartilage defects, for example, may result in an increased rate of cartilage breakdown, leading to decreased cartilage volume and joint space narrowing. OA represents loss of homeostasis in the normal maintenance of articular cartilage by the degradation and synthesis of the matrix components. The inciting mechanisms are not fully understood, although the aetiology seems multifactorial. The end pathway is an imbalance between proteinases, which break down the matrix constituents, and proteinase inhibitors.

The role of glucosamine in OA of the knee

The long-term combined structure-modifying and symptom-modifying effects of glucosamine sulphate suggest that it could be a disease modifying agent in OA.

Besides synthesis of GAGs, it also exerts an anti-catabolic effect on AC by inhibiting the anti-inflammatory responses. The theory of synthesis of GAGs does not, however, explain the observed glucosamine mediated increase in collagen type II. The literature shows a positive effect of
glucosamine on GAG production in human chondrocytes in cell culture, and the same anabolic effect is found in bovine and rat explants.\textsuperscript{16–18} TGF-\(\beta\) is considered to be a multifaceted cytokine that plays key roles in many downstream effects, such as mesenchymal differentiation, matrix production, stimulation of chondrocytes and controlled differentiation of stem cells.\textsuperscript{24,25} In adults, TGF-\(\beta\)’s are also believed to maintain a critical balance between the various anabolic and catabolic functions of chondrocytes for proper functioning of the cartilage. Varghese et al.\textsuperscript{26} provide evidence that glucosamine mediated increase in the production of specific matrix components involves TGF-\(\beta\)1 up-regulation, possibly through the hexosamine pathway in optimal concentrations of glucosamine. The effect of glucosamine on chondrocytes was found to be dependent upon the culture conditions. Is there an effect on gene expression, in both anabolic and catabolic activities of chondrocytes, in response to glucosamine treatment in the human OA explant model? Another study added a pre-culture experimental agent to human cartilage harvested during knee arthroplasty procedures. To this model, they added different concentration of glucosamine. They found that glucosamine (5 mM) addition to a human OA explant reduced the enzymatic breakdown of the cellular matrix.\textsuperscript{27} The authors of this study also suggested that chondroprotective properties of the glucosamine in vivo may be based on inhibiting further degradation due to catabolic activities, rather than on the ability to rebuild cartilage.\textsuperscript{28}

**Glucosamine in clinical practise**

Three rigorous meta-analyses show that individuals with OA of the knee or spine have significantly less symptoms while taking glucosamine than those taking placebo.\textsuperscript{29–31} McAlindon et al.\textsuperscript{28} conclude that glucosamine is moderately efficacious for the relief of symptoms of OA. Richy et al. conclude that glucosamine has highly significant effects on all aspects of knee OA.\textsuperscript{32} A recent randomized clinical trial included 414 post menopausal women followed for 3 years. The authors documented no decrease in joint space with glucosamine treatment whilst there was a decrease in the placebo group; the differences were significant (\(P<0.001\)).\textsuperscript{20} Reviewing the literature it appears that authors have looked at the knee, focussing on medial compartment arthritis, as a clinical substrate to analyse the effects of glucosamine treatment.\textsuperscript{12,31} Natural joint space narrowing in knee OA is slow (\(<0.1\) mm/yr in average), but can be prevented by glucosamine sulphate, which concurrently induces a significant symptom improvement.\textsuperscript{31} When individual joint-space changes were analysed, twice as many patients receiving placebo had striking joint space narrowing, than those receiving glucosamine sulphate.\textsuperscript{11} Reginster et al.\textsuperscript{12} did a randomised, placebo-controlled clinical trial on 212 patients and found that joint space narrowing was significantly less when compared to the placebo group. They reported 20–25% improvement in symptoms. The joint space narrowing difference between the placebo and the glucosamine group was found to be 0.46 mm after 3 years. Pavelka et al.\textsuperscript{13} did a similar double blind study on 202 patients in Czech Republic. They also found a significant difference between the two groups (\(P = 0.001\)) when they analysed the joint space narrowing at 3 years follow up.

Cochrane reviews have concluded that glucosamine reduces the pain caused by OA but has not shown any effects on stiffness and improvements in function. High-quality preparations of glucosamine probably reduce pain in OA. A review on the efficacy of glucosamine in alleviating pain showed a significantly larger reduction in pain in patients who received glucosamine than in those who received placebo (15 RCTs, standardised mean difference 0.61\%, 95\% CI 0.95–0.28).\textsuperscript{32}

**Side effects**

Oral administration of glucosamine at very large doses (5000–15,000 mg/kg body weight) is well tolerated without documented toxicity.\textsuperscript{11} The most common symptoms reported with placebo and oral glucosamine are: mild gastrointestinal symptoms including constipation, diarrhoea, nausea, dyspepsia, excessive gas, abdominal distension and abdominal cramps. Headache and skin rash or pruritis are also known to occur. Some studies have also shown side effects such as increased musculoskeletal pain, urinary tract infection, vertigo, blood pressure fluctuation and depression.\textsuperscript{12,33}

Although side effects occur with the use of glucosamine, it appears to be a generally safe compound when used in patients with OA. It favourably compares with the adverse effect profiles of other drugs used in the treatment of OA, such as analgesics and NSAIDs.\textsuperscript{12,31}

**Conclusion**

Long-term follow-up studies on the effects of glucosamine preparations are still awaited. At present, only short-term results are available. They are known to relieve pain and decrease the rate of joint space narrowing clinically in osteoarthritis of knee, whilst the side effects are less when compared to the anti-inflammatory drugs and even placebos.

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