Glucosamine: an ingredient with skin and other benefits

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Summary

Both glucosamine and its derivative N-acetyl glucosamine are amino-monosaccharides that serve key biochemical functions on their own and as substrate precursors for the biosynthesis of polymers such as glycosaminoglycans (e.g., hyaluronic acid) and for the production of proteoglycans. Glucosamine has an excellent safety profile and has been shown to provide benefits in several clinical disorders. Glucosamine compounds have been reported to have several beneficial effects on the skin or skin cells. Because of its stimulation of hyaluronic acid synthesis, glucosamine has been shown to accelerate wound healing, improve skin hydration, and decrease wrinkles. In addition, as an inhibitor of tyrosinase activation, it inhibits melanin production and is useful in treatment of disorders of hyperpigmentation. Mechanistically, glucosamine also has both anti-inflammatory and chondroprotective effects. Clinical trials have shown benefit in using oral glucosamine supplementation to improve symptoms and slow the progression of osteoarthritis in humans. Glucosamine has also been used to prevent and treat osteoarthritis in animals. Based on other observations, glucosamine has been suggested for additional clinical uses, including treatment of inflammatory bowel disease, migraine headaches, and viral infections. The current clinical uses for topical and oral glucosamine compounds and the mechanistic rationale for these uses are reviewed here.

Keywords: glucosamine, N-acetyl glucosamine, skin, hyperpigmentation, hyaluronic acid, osteoarthritis

Introduction

Glucosamine is an amino-monosaccharide that is present in all human tissues. It is produced in the body by the addition of an amino group to glucose; that molecule is then acetylated to N-acetyl glucosamine (Fig. 1). Glucosamine and N-acetyl glucosamine have key biochemical functions within the body that may reflect their mechanism of benefit in various disease processes in humans. For example, N-acetyl glucosamine is attached to glycoproteins located on the extracellular side of the cell membrane and plays an important role in intercellular recognition.[1] Glucosamine is also a substrate for the biosynthesis of polymers such as glycosaminoglycans, e.g., hyaluronic acid which is composed of repeating units of the dimer N-acetyl glucosamine (glucuronic acid) (Fig. 2) and heparan sulfate, and subsequently for the production of proteoglycans.

While the bulk of the published literature on these sugar amines focuses on their oral use in treatment and prevention of arthritis and its symptoms, there are several studies regarding its topical and oral beneficial effects for skin hydration and wrinkle reduction, and in treating disorders of excess pigmentation in the skin. These uses for glucosamine compounds as well as some potential new uses will be discussed.

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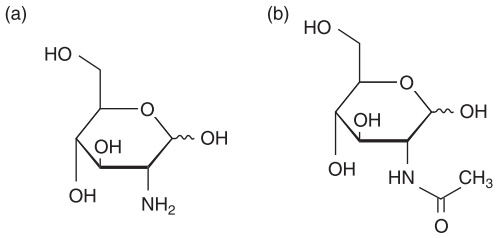

Figure 1 Glucosamine (a) and N-acetyl glucosamine (b).

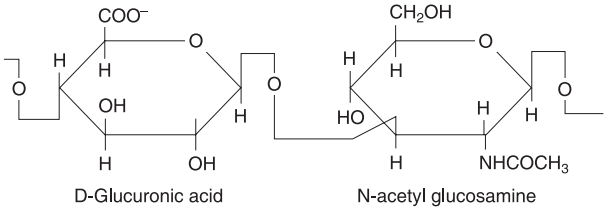

Figure 2 Repeating disaccharide unit of hyaluronic acid.

Skin

Hyaluronic acid is a major component of connective tissue, with the largest amount residing in skin tissue. Keratinocytes, like chondrocytes, actively synthesize and catabolize hyaluronic acid. Hyaluronic acid in the skin has also been described as an effective scavenger of free radicals and, therefore, may serve a protective role in the epidermis by scavenging reactive oxygen species generated, for example, by ultraviolet radiation exposure.[2]

Hyaluronic acid is also widely recognized to play a key role in wound healing. Early in the wound-healing process, there is an abundance of hyaluronic acid in the extracellular matrix. Hyaluronic acid has both a structural role, contributing to the formation of a scaffolding along which fibroblasts can migrate, as well as a regulatory role, promoting cell proliferation, cell migration, and angiogenesis.[2] In fact, it is the early appearance and prolonged maintenance of an environment rich in hyaluronic acid that allows fetal wounds to heal rapidly and without scar formation.[3] Studies of topical hyaluronic acid have shown benefit in accelerating wound healing in acute radioepithelitis, venous leg ulcers, and acute burns.[2,4]

Hyaluronic acid also holds water and maintains the extracellular space and is therefore important in skin hydration and elasticity.[5] A decline in skin epidermal hyaluronic acid content occurs during aging, contributing to decreased turgidity and increased wrinkle formation.[6] Hyaluronic acid has been used successfully as an injectable filler agent for improving wrinkles. More recently, it has also been injected into the superficial dermis and epidermis to hydrate and "rejuvenate" the skin.[7]

Because of its precursor role in hyaluronic acid synthesis, glucosamine could also be expected to accelerate wound healing, improve skin hydration, and possibly be used as an antiwrinkle treatment.[2,5] During *in vitro* aging of human fibroblasts, there is an age-related relatively stronger decline of ^{14}C-glucosamine incorporation into cellular and extracellular hyaluronic acid in comparison with other glycosaminoglycan types.[8] In addition, supplementation of a culture medium with N-acetyl glucosamine causes a dose-dependent increase in hyaluronic acid synthesis by human keratinocytes.[5] More recent *in vitro* studies[9] using human skin equivalent cultures have shown increased production of hyaluronic acid from topical treatment with N-acetyl glucosamine, alone and in combination with niacinamide (as precursor to NAD(P), an essential cofactor for hyaluronic acid synthesis).

Clinically, N-acetyl glucosamine has been documented to improve skin condition. In a randomized double-blind study, human female volunteers with xerosis and rough skin were given a daily 1000-mg dose of N-acetyl glucosamine or placebo orally for 60 days. After treatment, there was a significant increase in skin moisture content, and a decrease in the oil and fat content. There was also a decrease in epidermolysis of the corneum. These results led the authors to conclude that oral N-acetyl glucosamine supplementation may be of benefit in enhancing skin hydration.[10] An additional randomized double-blind study in human female volunteers with topical 2% N-acetyl glucosamine revealed improvement in facial wrinkles, particularly in the eye area.[9]

In addition to its roles in wound healing, moisturization, and wrinkle reduction, there is also evidence that glucosamines may be of benefit in disorders of excess pigmentation such as age spots, which are localized accumulations of epidermal melanin. A key enzyme in melanin biosynthesis is tyrosinase. It is initially produced in the cell as an inactive pro-enzyme, which is then glycosylated to the active enzyme. While glucosamine is not a direct inhibitor of tyrosinase, it does inhibit the glycosylation of tyrosinase,[11] thus preventing its activation. This results in marked loss of pigmentation in cell culture model systems. In three recently described randomized double-blind clinical studies in human female volunteers,[12,13] topical 2% N-acetyl glucosamine, alone and in combination with niacinamide, reduced facial hyperpigmentation. Example facial images from one of those studies shown are in Figure 3.

In addition to the mechanisms discussed above, the reported anti-inflammatory effects of glucosamines may be involved in the observed skin benefits. *In vitro*, glucosamine has been documented to suppress several neutrophil functions. It inhibits superoxide generation,

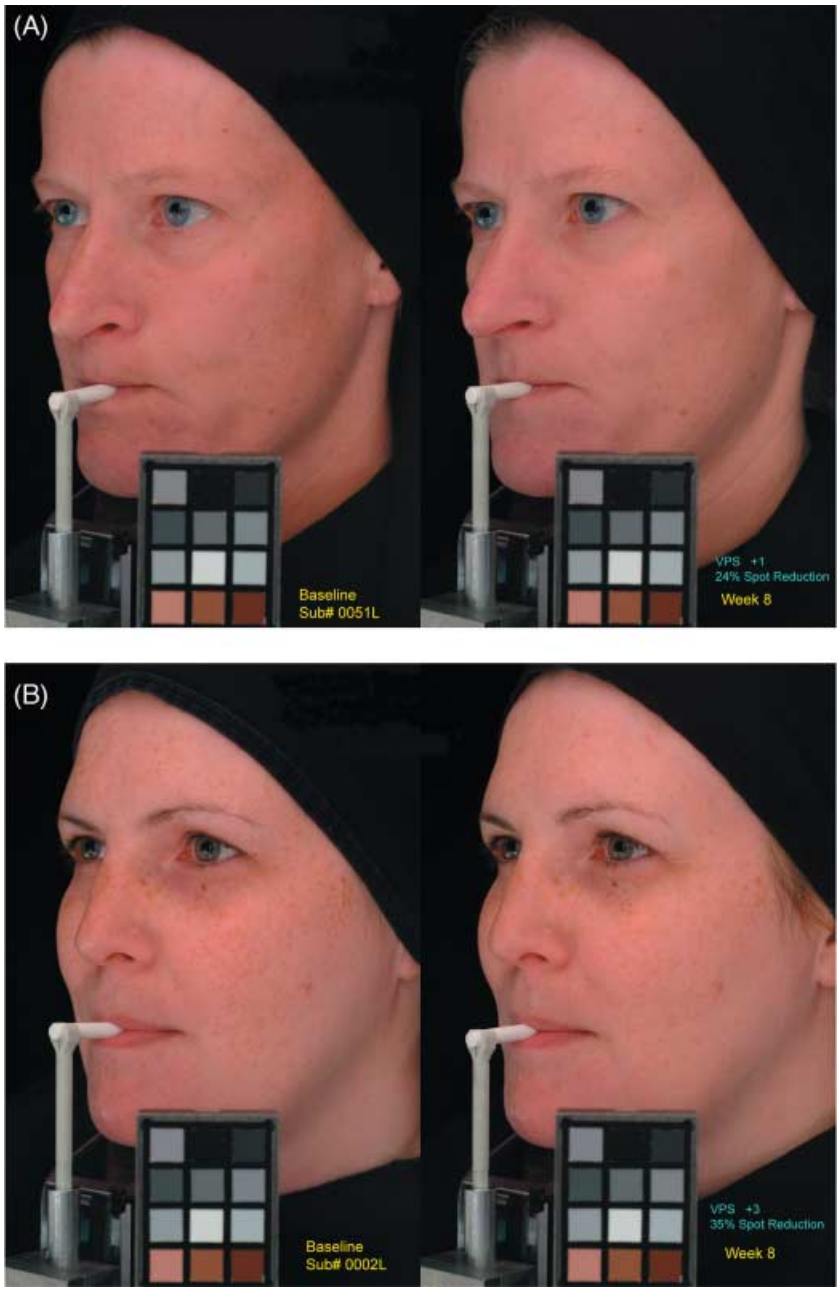

Figure 3 Example images from 8-week clinical testing of topical formulation containing 2% N-acetyl glucosamine in treatment of hyperpigmented spots. In both A and B, the before-treatment image is on the left, and the after-treatment image is on the right. (The complete methodology and set of data from this clinical testing have been submitted separately for publication.)

phagocytosis, granule enzyme lysozyme release, and neutrophil chemotaxis.[14] It also suppresses interleukin-1-induced nitric oxide (NO) production in human articular chondrocytes.[15] In a rat model of inflammation, glucosamine was shown to decrease NO production by inhibiting inducible NO synthase (iNOS) protein expression.[16]

In another rat model, glucosamine exhibited anti-inflammatory activity against several nonspecific agents (including formalin and acetic acid).[17] However, it did not show anti-inflammatory activity against other specific mediators of inflammation (serotonin, bradykinin, and histamine). It had no effect on cyclooxygenase activity, its effects were prostaglandin independent, and no analgesic activity was demonstrated. But glucosamine did reduce the generation of superoxide radicals by macrophages. Glucosamine was also compared to indomethacin and aspirin, with the finding that it had a relatively low potency. However, because the toxicity of glucosamine is so much lower (discussed in more detail below), the therapeutic margin actually favors glucosamine.[17]

Arthritis

The most well-documented clinical use for oral glucosamine supplementation is in the treatment of osteoarthritis. Osteoarthritis is the most common form of arthritis, and is characterized by erosion of articular cartilage in synovial joints, which leads to joint pain and stiffness. There are two classes of drugs aimed at treating osteoarthritis.[18] Symptom-modifying agents are geared toward relieving pain and thereby improving physical function. Traditionally, the pharmacologic agents used in this approach have been analgesics or nonsteroidal anti-inflammatory drugs.[19] The second class is structure-modifying agents, which are geared toward decreasing joint structural changes and thereby lessening disease progression. Several agents, including glucosamine, are currently being investigated in this category.

Articular cartilage is a connective tissue made up of cells called chondrocytes that are sparsely placed in an extracellular matrix. The chondrocytes produce collagen and large proteoglycans (aggrecans), which together with water, comprise the extracellular matrix. This combination provides tensile strength and compressive strength, and allows the cartilage to distribute weight and decrease friction. The functional integrity of articular cartilage is determined by a balance between chondrocyte biosynthesis of extracellular matrix and its degradation. Over time, repetitive stress and wear on the articular cartilage can lead to mechanical breakdown, or the beginning of osteoarthritis. This mechanical breakdown of cartilage disrupts the normal homeostasis of the extracellular matrix, resulting in an imbalance in matrix turnover, with degradation exceeding synthesis.[20] A decrease in the biosynthesis of extracellular matrix molecules, such as collagen type II and aggrecan, and an increase in matrix degradative enzymes occur.[21]

The disease-modifying role of glucosamine in osteoarthritis is most likely related to both anti-inflammatory and chondroprotective effects. Glucosamine has been shown to stimulate human articular chondrocytes to synthesize increased amounts of proteoglycans in a dose-dependent manner.[22] It has also been documented to stimulate the biosynthesis of aggrecan in human articular chondrocytes.[21] The degradation of the extracellular matrix is mediated by proteolytic enzymes such as aggrecanases and matrix metalloproteinases (MMP); human articular chondrocytes treated with glucosamine have inhibited production and enzymatic activity of MMP-3.[21]

The level of interleukin-1 (which inhibits proteoglycan synthesis and stimulates proteoglycan degradation by cartilage in organ culture) is elevated in osteoarthritis cartilage.[23] Glucosamine has been shown to decrease the down regulation of proteoglycan synthesis caused by interleukin-1 in equine articular cartilage.[20] Inflammatory molecules such as NO and phospholipase A2 are also present at increased levels in osteoarthritis cartilage. Glucosamine decreases the interleukin-1-mediated production of NO as well as decreases cellular phospholipase A2 activity in human articular chondrocytes.[15,24] Examination of osteoarthritis cartilage reveals decreased adhesion of chondrocytes to the extracellular matrix protein fibronectin (which is involved in tissue repair); however, adhesion significantly increases after treatment with glucosamine.[25]

Finally, hyaluronic acid is produced by the synovium and is primarily responsible for its high viscosity and its protective lubricating and shock-absorbing properties. In addition, hyaluronic acid appears to protect cartilage from chemical mediators of proteolysis such as interleukin-1.[26] There is a reduced concentration of hyaluronic acid in the synovial fluid in osteoarthritis, and intra-articular hyaluronic acid injection has been shown to provide significant pain relief in patients with osteoarthritis of the knee.[27] There is evidence that glucosamine administration may enhance the synovial production of hyaluronic acid, which may lead to symptom improvement as well.[26]

There has been some evaluation of the anti-arthritic properties of glucosamine in animal models. Glucosamine was found to be effective in reducing inflammation and the incidence of arthritis in a rat model of adjuvant arthritis.[28] In another rat model of adjuvant arthritis, glucosamine significantly suppressed the progression of the arthritis (synovial hyperplasia, cartilage destruction, and inflammatory cell infiltration were all decreased), as well as reduced the production of NO and prostaglandin E2 in plasma.[29] Glucosamine was also found to significantly reduce the level of chondropathy in rabbits after transection of their anterior cruciate ligament.[30]

There have been multiple human clinical trials evaluating glucosamine for osteoarthritis symptom relief in humans. Early studies documented short-term benefit with relief of joint pain and improved mobility.[31] However, these trials were limited by short duration and small sample sizes.[31,32]

There have been two long-term (> 1 year), double-blind, randomized, controlled clinical trials comparing glucosamine with placebo in the treatment of osteoarthritis.[33,34] Each trial included over 200 patients with knee osteoarthritis and randomly assigned them 1500 mg glucosamine sulfate or placebo once daily for 3 years. Both trials found that while the placebo group had progressive joint-space narrowing, the glucosamine group had no significant joint-space loss. The glucosamine group also did significantly better in symptom severity in

both trials. There were no significant adverse events. These two studies document that glucosamine can retard the progression of knee osteoarthritis, and substantiate the theory that it does have structure-modifying effects.

Osteoarthritis is also the most common joint disease in dogs, and is a principal cause of lameness and decreased performance in horses.[20] While clinical studies involving veterinary patients are extremely limited, the use of glucosamine has become a mainstay of preventative maintenance programs that provide support for aging animals and may aid in extending competitive careers of horses.[35]

Other uses

There is evidence that glucosamine exhibits antiviral activity both *in vitro* and *in vivo*.[36–38] It has been documented to inhibit the multiplication of various enveloped animal viruses by interfering with the synthesis of viral envelope glycoproteins in cell culture.[36] It has also been shown to possess antiviral activity against nonenveloped viruses, but the mechanism of action is less clear.[37]

In inflammatory bowel disease, widespread breakdown of sulfated glycosaminoglycans in the extracellular matrix occurs. This breakdown happens as a result of tumor necrosis factor–induced production of MMPs.[39] Salvatore *et al*. postulated that glucosamine, because of its role as a substrate for fibroblast and epithelial glycosaminoglycan synthesis, may augment tissue repair in inflammatory bowel disease. They performed a small open-label study, administering N-acetyl glucosamine either rectally or orally to pediatric patients with inflammatory bowel disease and found clear preliminary evidence of its clinical efficacy (5/7 rectal improved, 8/12 oral improved). In fact, pre- and posttreatment biopsies showed an enhancement of matrix and epithelial expression of sulfated glycosaminoglycans.

There have been anecdotal reports of improvement in migraine symptoms after treatment with oral glucosamine.[40] There is some evidence that mast cells are central mediators of neurogenic inflammation in migraine headaches. The mechanism for symptom improvement may be related to glucosamine-stimulating heparin synthesis by mast cells; heparin seems to have anti-inflammatory activity, and may be able to inhibit mast cell degranulation.[40] In addition, exogenous glucosamine could enhance heparan sulfate proteoglycan production by vascular endothelial cells, and thereby act to retard atherogenesis.[41]

Safety

Glucosamine is commercially available as an oral nutritional supplement in three forms: glucosamine hydrochloride, glucosamine sulfate, and N-acetyl glucosamine. Most of the glucosamine in these supplements is derived from chitin found in marine exoskeletons. Approximately 90% of oral glucosamine is absorbed.[42] Oral administration of glucosamine at very large doses (5000–15 000 mg/kg body weight) is well tolerated without documented toxicity. The LD_{50} for glucosamine in multiple animal models exceeds 5000 mg/kg.[42] Animal studies also indicate that there is no overall subchronic toxicity, with oral glucosamine being well tolerated by rats, mice, rabbits, dogs, and horses.[42]

There is evidence that overactivity of the hexosamine biosynthetic pathway may underlie hyperglycemia-associated insulin resistance; this pathway can be activated by glucosamine.[43] This has raised some concern about the oral use of glucosamine in regard to potential subsequent insulin resistance. However, when healthy human subjects were administered high doses of intravenous glucosamine, no change in serum glucose level was noted.[43] Anderson critically reviewed the human clinical trials that used oral glucosamine, and found that in total 854 subjects followed for a weighted average of 37 weeks showed no significant changes in blood glucose values. For the entire group of 33 chronic studies of predominantly older subjects, three developed diabetes with placebo treatment and only two developed diabetes with glucosamine treatment.[42]

Glucosamine does not appear to have any other side effects in humans. Anderson's review also looked at the incidence of nonspecific symptoms reported by patients in clinical trials of oral glucosamine. Overall they found that symptoms were 24% less common with glucosamine than placebo, and that this was statistically significant. The safety profile of glucosamine was evaluated in another systematic review of 12 randomized, controlled trials and was deemed excellent, with 7 of 1486 randomized patients being withdrawn for glucosamine-related issues and only 48 having reported any glucosamine-related adverse reactions.[44]

Conclusion

Glucosamine serves several key biochemical functions, both on its own and as a substrate for the production of glycosaminoglycans and proteoglycans. While there is significant *in vitro* evidence to guide our understanding of the disease-modifying mechanisms of glucosamine, it can be difficult to extrapolate these findings to the *in vivo* situation and clinical benefits. Glucosamine does seem to be beneficial in a variety of clinical disorders, especially in osteoarthritis and in providing skin benefits. As research continues, glucosamine may also be found to be of benefit for an array of other clinical uses.

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