Glucosamine

Evidence Summary
Besides benefits in osteoarthritis, glucosamine use is associated with reduced all-cause, cardiovascular, respiratory, and cancer mortality, and potential benefits in some cognitive functions.

**Neuroprotective Benefit:** Clinical evidence for glucosamine on cognitive function is limited to a single observational study. Preclinical studies have reported that glucosamine decreases inflammation and oxidative stress, while increasing BDNF.

**Aging and related health concerns:** Besides benefits in osteoarthritis, regular use of glucosamine is associated with reduced all-cause, cardiovascular, respiratory, and cancer mortality. A genetic study also supports higher glucosamine levels with longevity.

**Safety:** Glucosamine supplements are widely used by people with osteoarthritis and are generally safe, though some drug interactions are known. Glucosamine may increase intraocular pressure.
**What is it?** Glucosamine (2-amino-2-deoxy-β-d-glucopyranose) is an aminosugar naturally occurring in the human body and found in high concentrations in joints and cartilage. Glucosamine is a precursor for glycosaminoglycans, and glycosaminoglycans are a major component of joint cartilage (DrugBank.com). Glucosamine supplements may promote collagen synthesis, reduce collagen degradation, and stimulate cartilage synthesis, thereby improving symptoms of arthritis. Glucosamine supplements are derived from shellfish and are primarily used as a joint health supplement that can provide minor pain relief. Glucosamine sulfate may slightly delay the progression of knee osteoarthritis. Glucosamine has also drawn some attention as a potential anti-aging agent [1].

**Neuroprotective Benefit:** Clinical evidence for glucosamine on cognitive function is limited to a single observational study. Preclinical studies have reported that glucosamine decreases inflammation and oxidative stress, while increasing BDNF.

**Types of evidence:**
- 1 cross-sectional cohort study that examined the association between commonly prescribed drugs and cognitive functions
- 3 rodent studies on cognitive function, 1 of which also examined blood-brain-barrier penetrance
- Numerous other laboratory studies
Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?
A population-based cross-sectional cohort study that included 482,766 UK Biobank participants reported that regular use of glucosamine was associated with a positive effect on reasoning and reaction time, but not on memory [2]. While encouraging, there are some limitations to this study. The data come from a cross-sectional cohort and with self-reported medication use. Also, no information on duration or dosage was collected.

Human research to suggest benefits to patients with dementia: None available.

Mechanisms of action for neuroprotection identified from laboratory and clinical research
Glucosamine readily penetrates the blood-brain-barrier based on a study in rats [3]. This study also showed that intravenous administration of glucosamine had a positive effect on a discrimination task. In a different study, glucosamine treatment (1 or 2 g/kg/day) for 5 days improved spatial memory in rats experiencing scopolamine-induced memory deficits [4], though the glucosamine effect was not robust. In a study in mice, glucosamine treatment (3, 10, and 30 mg/day, i.p.) for 2 weeks improved cognitive function as measured by the novel object recognition test in a dose-dependent manner [5]. Glucosamine treatment also increased the expression of the neurotrophic factor BDNF and components of the cAMP/PKA/CREB pathway in the hippocampus.

There are several potential mechanisms of glucosamine’s neuroprotective effects. Cell culture studies suggest that glucosamine inhibits inflammation by downregulating IL-1 [6], MMP expression [7], COX2 activity, and prostaglandin E(2) production [8]. In mice and nematodes, glucosamine exerts a “mitohormetic” effect by impairing glycolysis, activating the fuel-sensing enzyme AMPK, and promoting mitochondrial biogenesis (details of this study are described below)[9].

APOE4 interactions: Unknown.
Aging and related health concerns: Besides benefits in osteoarthritis, regular use of glucosamine is associated with reduced all-cause, cardiovascular, respiratory, and cancer mortality. A genetic study also supports higher glucosamine levels with longevity.

Types of evidence:
- 13 meta-analyses or systematic reviews on osteoarthritis
- 1 systematic review on spinal degenerative joint/disc disease
- 1 randomized controlled trial on the effect of glucosamine on intraocular pressure
- 1 clinical trial on the effect of glucosamine on flow-mediated vasodilation
- 3 large observational studies on mortality
- 1 Mendelian randomization study
- 9 observational studies on risk of various cancers
- 1 observational study on risk of age-related macular degeneration
- Numerous laboratory studies

Lifespan: ASSOCIATED WITH BENEFIT BASED ON OBSERVATIONAL STUDIES AND GENETICS
In a prospective cohort study of 77,510 people (Washington residents), current use of glucosamine supplements (with or without chondroitin) was associated with a statistically significant 18% reduced risk of total mortality compared with never users (HR 0.82; 95% CI, 0.75-0.90)[10]. An older study from the same cohort also reported that when people took glucosamine for more than 4 days/week or over 3 years, their HR was 0.83 compared to nonusers [11]. There are some confounding factors to these studies. For example, current use of glucosamine was higher among older individuals, women, whites, and those with greater education. Glucosamine use was less common with increased smoking and fat intake, and more common with greater BMI, physical activity, and vegetable intake. In terms of formulation, the risk reduction was somewhat less for current users of chondroitin (included in about two-thirds of glucosamine supplements), somewhat greater for current users of glucosamine alone, with no benefit for supplements containing methylsulfonylmethane (MSM).

In a large prospective cohort study of 495,077 participants from the UK Biobank who were followed for a median of 8.9 years, regular use of glucosamine supplement was associated with a lower all-cause mortality (HR=0.85; 95% CI, 0.82 to 0.89), after adjusting for multiple variables [12]. The association between glucosamine use and lower all-cause mortality was stronger among current than non-current smokers (p for interaction=0.00080). The association between glucosamine use and lower mortality was not significantly changed when they excluded participants who used any other supplements, or when the analyses were restricted to non-users of chondroitin. Compared with non-users, regular glucosamine
users were older, more likely to be women, current non-smokers, more physically active and with higher comorbidities, including cancer, hypertension and arthritis, but had a lower prevalence of cardiovascular disease and diabetes. Glucosamine users also tended to take more chondroitin, non-aspirin NSAIDs, vitamins, minerals, and other dietary supplements than non-users. The authors noted a few limitations of this study, including the lack of information on dosage and duration of glucosamine, and the possibility that regular glucosamine use may be a marker for a healthy lifestyle, though the study adjusted for potential confounding lifestyle-related factors.

In a smaller observational study of 16,689 participants from the US NHANES Cohort who were followed up for a median of 107 months, people who had been taking glucosamine/chondroitin for a year or longer had lower all-cause mortality (HR=0.61; 95% CI, 0.49 to 0.77), after controlling for age [13]. This association was maintained after adjustment for age, sex, race, education, smoking status, and physical activity (HR=0.73; 95% CI, 0.57 to 0.93). The authors note limitations of this study, including the fact that the amount and consistency of supplement intake was not tracked during the follow-up period, and that other supplements (and medications) may have accounted for some of these findings.

In a Mendelian randomization study of 461,384 individuals, 5 genetic variants associated with glucosamine status were analyzed with parental age at death [14]. The study found a positive effect of genetically predicted higher glucosamine status on life expectancy using combined parental age at death, such that a 1-standard-deviation increase in genetically predicted glucosamine was associated with higher odds of combined parental age at death (OR=2.64; 95% CI, 1.26 to 5.54; p=0.01), and maternal age at death (OR= 1.73; 95 CI, 1.04 to 2.89; p=0.03), but not paternal age at death (OR=1.32; 95% CI, 0.81 to 2.15; p=0.27). This study suggests that having higher levels of glucosamine throughout the life course may be associated with increased life expectancy. The 5 SNPs that had genome-wide significant associations (p< 5×10^{-8}) were: rs11915360 - HSPE1P19, rs1466978 - DCAF4L1, rs2565185 - MRPL35P2, rs34084719 - COG5, and rs735465 - FAM222A. This is a different type of evidence compared to observational studies of glucosamine supplement intake, as Mendelian randomization generates an estimate of an effect purely based on genetics, and not personal choices or environmental factors. In this study, glucosamine supplement users were more likely to be older women, current non-smokers, and physically active, with higher prevalence of hypertension and arthritis, but lower prevalence of cardiovascular disease and diabetes.

A preclinical study has also shown that glucosamine extends lifespan in both aged mice and *C. elegans* [9]. In aged mice receiving D-glucosamine (10 g/kg diet) from 100 weeks old, maximum lifespan was extended by about 8 weeks (or ~6%) with glucosamine, but the effects were more pronounced in
females than males. Glucosamine increases mitochondrial reactive oxygen species and impairs glucose metabolism (by inhibiting hexokinase), which in turn activates the fuel-sensing enzyme AMPK (AAK-2 in *C. elegans*). AMPK then promotes mitochondrial biogenesis. In mice, glucosamine also lowers blood glucose levels, enhances expression of amino acid transporters, and increases protein metabolism. Therefore, it is thought that glucosamine extends lifespan by mimicking a low-carbohydrate diet.

**Osteoarthritis: BENEFIT**

There have been numerous meta-analyses that examined the effects of glucosamine in people with osteoarthritis [15; 16; 17; 18; 19; 20]. A 2015 meta-analysis of 54 randomized controlled trials (total of 16,427 patients) reported that glucosamine plus chondroitin or glucosamine alone were more effective than placebo in pain relief and functional improvement, and both treatments achieved a statistically significant reduction in joint space narrowing [20]. An older Cochrane meta-analysis of 20 randomized controlled trials reported that glucosamine was associated with a 28% improvement in pain and a 21% improvement in function [16]. A 2022 meta-analysis of 6 randomized controlled trials reported that glucosamine combined with chondroitin is more effective than glucosamine or chondroitin alone in the treatment of knee osteoarthritis (measured by joint pain, tenderness, swelling, and dysfunction score), though this conclusion needs to be supported by a large, high-quality, double-blind randomized controlled trial [21]. A 2018 meta-analysis of 30 randomized controlled trials (14 of glucosamine, 23 of chondroitin, and 3 of the combination) reported that glucosamine treatment improved stiffness (but not pain or function), while chondroitin treatment alleviated pain and improved function; the combination therapy did not have enough data to show superiority over placebo [22]. In a 2018 meta-analysis of 18 randomized controlled trials, treatment with glucosamine or glucosamine-containing supplement for 6 weeks to 2 years did not affect knee function as measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), but did improve knee function measured with the Japanese Knee Osteoarthritis Measure (JKOM), commonly used in Japan [23]. This meta-analysis also showed a significant reduction in pain score (VAS pain score) with glucosamine/glucosamine-containing supplement with an effect size of -0.19 (95% CI, -0.36 to -0.03). Because 6 out of 19 trials tested glucosamine and chondroitin sulfate together, the effects of glucosamine alone could not be assessed fully. Another meta-analysis of 19 randomized controlled trials suggested that while glucosamine may improve function in people with knee osteoarthritis after 6 months, there appears to be no further pain reduction with longer therapy [19].

In a meta-analysis and comparative effectiveness study of 61 randomized controlled trials in patients with knee and/or hip osteoarthritis, oral glucosamine, chondroitin, the combination of glucosamine and chondroitin, acetaminophen, and celecoxib were compared for outcomes of efficacy, pain, function, and
stiffness [24]. For pain, celecoxib showed the best efficacy, followed by the combination of glucosamine and chondroitin. For physical function, all interventions were significantly superior to oral placebo except for acetaminophen; celecoxib showed the greatest difference compared to placebo, followed by the combination of glucosamine and chondroitin. For stiffness, glucosamine and celecoxib were significantly better than placebo, while other treatments did not show statistically significant effects.

Some meta-analyses have noted that the effect sizes ranged widely and depended on the formulation [17]. For example, effect sizes ranged from 0.05 to 0.16 in trials without industry involvement, but the range was 0.47-0.55 in trials with industry involvement (e.g., clinical trials run by supplement manufacturers). Also, the effect size was 0.44 for trials using glucosamine sulfate, but 0.55 for trials using Rottapharm products. Glucosamine hydrochloride had an effect size of 0.06 and therefore considered to be ineffective.

In a cross-sectional study of 79 patients with osteoarthritis, rheumatoid arthritis, or chronic joint pain, treatment with transdermal glucosamine sulfate and capsaicin (TGC-Plus cream; twice daily; 10% w/w glucosamine sulfate, 0.025% w/w capsaicin) for 12 weeks significantly reduced numerical pain score (7 ± 1.40 vs. 3.53 ± 2.13; p<0.05) and the limitation of joint movement (6.18 ± 2.14 vs. 3.47 ± 2.23; p<0.05) [25]. The need for analgesics (1.99 ± 2.77 vs. 0.71 ± 1.90; p<0.05) and the number of doctor’s visits (1.11 ± 1.28 vs. 0.06 ± 0.293, p < 0.05) were also significantly reduced with the treatment. Most patients reported a noticeable reduction in joint pain after 5 days, with maximum analgesic effect reached after 12 days of treatment. The average duration of analgesic effect was 12 hours after application of the cream. In this study, all recruited patients had previously taken glucosamine sulfate supplements for at least 3 weeks, but without achieving satisfactory pain relief. The intervention was supervised by pharmacists, but the main weakness of the study is that it did not have a placebo group.

**Spinal degenerative joint/disc disease**: INCONCLUSIVE

A systematic review based on 2 randomized controlled trials reported that there is little literature to support the use of glucosamine for spinal degeneration [26]. One study of good quality reported negative results. The other study of lower quality reported that the use of a combination treatment that included glucosamine (1800 mg/d), calcium (900 mg/day), skin collagen (10,500 mg/day), mucopolysaccharide (600 mg/day), and vitamin C (600 mg/day) significantly improved pain and lumbar bone mineral density, though this effect was not statistically significant compared with the placebo group.

**Peripheral neuropathy**: POTENTIAL BENEFIT BASED ON PRECLINICAL STUDIES
In a rat model of sciatic nerve injury (induced by chronic constriction injury), a combination of glucosamine sulfate (240 mg/kg, orally) and chondroitin sulphate (900 mg/kg, orally) for 21 days reduced hyperalgesia, allodynia, sciatic nerve functional aberration, and pro-inflammatory biomarkers (IL-1β, NFkB, NGF, TNF-α, IL-6, PGE2) [27]. Glucosamine alone and chondroitin sulfatE alone also reduced these pro-inflammatory biomarkers to the same degree as the combination therapy.

**Cardiovascular disease: ASSOCIATED WITH LOWER RISK**

In a prospective cohort study of 77,510 people, current use of glucosamine was associated with a non-significant 12% reduced risk of death from cardiovascular disease. The interaction by gender was statistically significant for cardiovascular disease death, with a significantly lower risk of cardiovascular death associated with current glucosamine use among women (HR 0.71; 95% CI, 0.53–0.96) and no association among men (HR 1.03; 95% CI, 0.82–1.29). One small human trial found that glucosamine inhibited platelet aggregation in some subjects, similar to the effects of aspirin [28].

In the UK Biobank study of 495,077 participants who were followed up for a median of 8.9 years, regular use of glucosamine supplement was associated with lower cardiovascular mortality (HR=0.82; 95% CI, 0.74 to 0.90), after adjusting for multiple variables [12].

In a smaller observational study of 16,689 participants from the US NHANES Cohort who were followed up for a median of 107 months, people who had been taking glucosamine/chondroitin for a year or longer were less likely to have cardiovascular mortality (HR=0.51; 95% CI, 0.28 to 0.92) [13]. After controlling for age, glucosamine/chondroitin use for over a year was associated with a 65% reduction in cardiovascular mortality (HR = 0.35; 95% CI, 0.20-0.61). These associations were maintained after adjustment for age, sex, race, education, smoking status, and physical activity (HR=0.42; 95% CI, 0.23 to 0.75). However, the use of NSAIDs does not appear to be accounted for. The authors note limitations of this study, including the fact that the amount and consistency of supplement intake was not tracked during the follow-up period, and that other supplements (and medications such as NSAIDs) may have accounted for some of these findings, which could not be controlled for.

In a controlled clinical study in healthy volunteers, oral glucosamine (3,000 mg/day) for 4 weeks increased flow-mediated vasodilation of the brachial artery (from 7.0 ± 2.3 to 8.7 ± 2.3%; p=0.022)[29]. Glucosamine administration also significantly increased intraerythrocyte total glutathione levels (from 212.9 ± 46.2 to 240.6 ± 49.4 μmol/L; p=0.006), intraerythrocyte GSH levels (from 124.7 ± 42.6 to 155.2 ± 47.7 μmol/L; p= 0.004), and intraerythrocyte GSH/GSSG ratios (from 3.18 ± 1.64 to 3.88 ± 1.61; p=0.04). No glutathione parameters were altered in the control group. These results suggest that glucosamine
treatment might improve vascular endothelial function by modulating the intracellular redox state. The authors noted the possibility that glucosamine might have anti-atherosclerotic properties through the improvement of endothelial function induced by antioxidant effects.

**Respiratory disease:** ASSOCIATED WITH LOWER RISK
In a prospective cohort study of 77,510 people, current use of glucosamine was associated with a large reduction in mortality from respiratory diseases (HR=0.59; 95% CI, 0.41 to 0.83)[10].

In the UK Biobank study of 495,077 participants who were followed up for a median of 8.9 years, regular use of glucosamine supplement was associated with reduced respiratory disease mortality (HR=0.73; 95% CI, 0.66 to 0.81), after adjusting for multiple variables [12].

**Cancers:** ASSOCIATED WITH LOWER RISK FOR SOME TYPES
Many large epidemiological studies have assessed the relationships between glucosamine use and cancer risk. A prospective cohort study of 77,150 people reported that current use of glucosamine supplements (with or without chondroitin) was associated with a significant decreased risk of death from cancer (HR 0.87; 95% CI, 0.76-0.98)[10]. Among the 5 types of cancers with the most deaths, there was a non-significant reduction in death associated with current glucosamine use for lung cancer and haematopoietic cancers, but no effects were seen for colorectal, breast or pancreatic cancer. However, a larger study of 2 prospective cohorts (96,400 people total) reported that the use of glucosamine + chondroitin was associated with a significant reduction in risk for colorectal cancer (RR, 0.77; 95% CI, 0.58-1.00), though this effect was not observed in people who used glucosamine alone [30]. Other large studies with over 76,000 people have reported that high 10-year use of glucosamine (HR, 0.77; 95% CI, 0.56-1.07), but not chondroitin, was associated with a significant reduction in lung cancer risk [31; 32]. The association with glucosamine was limited to adenocarcinoma (HR, 0.49; 95% CI: 0.27-0.90) [31]. There were no associations for use of glucosamine on prostate cancer risk [33].

In the UK Biobank study of 495,077 participants who were followed up for a median of 8.9 years, regular use of glucosamine supplement was associated with a lower cancer mortality (HR=0.94; 95% CI, 0.88 to 0.99), after adjusting for multiple variables [12]. In a different study of the UK Biobank including 439,393 participants with a median follow-up of 11 years, regular use of glucosamine was significantly associated with a decreased risk of lung cancer (HR=0.84; 95% CI, 0.75 to 0.92; p<0.001) and lung cancer mortality (HR=0.88; 95% CI, 0.81 to 0.96; p=0.002) in fully adjusted models [34]. A stronger association between regular glucosamine use and lower lung cancer risk was observed in participants with a family history of lung cancer when compared with those without a family history.
**Age-related macular degeneration:** ASSOCIATED WITH LOWER RISK

Age-related macular degeneration is the leading cause of visual impairment in the developed world. It is classified into two types, dry (non-neovascular) and wet (neovascular), and the dry type is predominant, accounting for 85–90% of all patients. In a population-based cohort study in Taiwan, the incidence rate of age-related macular degeneration was lower with glucosamine use (3.65%) than without glucosamine use (5.26%; p=0.014) [35]. Glucosamine use was associated with a lower risk of developing age-related macular degeneration in patients with hyperlipidemia, coronary artery disease, chronic obstructive pulmonary disease, stroke, other neurological disorders, or degenerative arthritis. The incidence of wet type age-related macular degeneration was not significantly different between glucosamine users and non-users, but the incidence of dry type age-related macular degeneration was lower in patients who used glucosamine (2.9% vs 4.84%; p=0.003).

**Glaucoma:** MAY INCREASE INTRAOCULAR PRESSURE

In a randomized controlled double-masked study of 88 patients with osteoarthritis, glucosamine sulfate treatment (Avicenna Laboratories, Iran) for 3 months increased intraocular pressure, but did not alter ocular response analyzer parameters [36]. The mean intraocular pressure at baseline, 1 month, and 3 months were 12.4±2.7 mmHg, 12.6±2.4 mmHg, and 13.5±2.3 mmHg, respectively, in the glucosamine group, and 13±2.8 mmHg, 12.9±2.4 mmHg, and 13±2.7 mmHg, respectively, in the placebo group. About 34.1% in the glucosamine group and 12.5% in the placebo group had clinically significant (defined as ≥ 2 mmHg) rise in intraocular pressure at final follow-up (p=0.023). Clinical implications of this finding require further research.

**Inflammation:** DECREASED

In a double-blind randomized controlled cross-over trial of 18 healthy overweight adults, serum CRP concentrations were 23% lower after glucosamine and chondroitin intake compared to placebo [37]. However, other inflammation biomarkers such as IL6, TNF receptors I and II, and prostaglandin E2 metabolite were not affected. In a proteomics analysis, glucosamine and chondroitin significantly reduced the “cytokine activity” pathway. Laboratory studies suggest that glucosamine and chondroitin may affect inflammation by inhibiting NFkB from translocating to the nucleus [38]. Other cell culture studies suggest that glucosamine inhibits inflammation by downregulating IL-1 [6], MMP expression [7], COX2 activity, and prostaglandin E(2) production [8].

**Insulin resistance:** MIXED/POTENTIAL HARM

Because of the high structural similarity between glucose and glucosamine (an -NH2 group instead of an -OH group on one of the 6 carbons), there have been many studies examining whether glucosamine
interacts with glucose metabolism or insulin resistance. A 2005 Cochrane meta-analysis reviewed several such studies [16]. Most studies have shown that glucosamine supplementation do not result in changes in glucose metabolism or insulin resistance in healthy adults [39; 40] or in patients with type 2 diabetes [41]. However, a few small clinical studies have reported that in people with underlying poorer insulin sensitivity [42] or those with untreated glucose intolerance [43], glucosamine may worsen insulin resistance.

**Gut microbiome:** INCONCLUSIVE

In a double-blind randomized controlled crossover trial of 11 healthy adults, glucosamine hydrochloride (3,000 mg GlucosaGreen®, TSI Group Ltd., Missoula, MT, USA) for 3 weeks significantly reduced phylogenetic diversity and proportions of Pseudomonadaceae, Peptococcaceae, and Bacillaceae, while also decreasing individual, total branched-chain, and total amino acid excretion [44]. These changes occurred in the absence of modifications to the fecal metabolome. Clinical implications of these findings are unclear.

**Safety:** Glucosamine supplements are widely used by people with osteoarthritis and are generally safe, though some drug interactions are known. Glucosamine may increase intraocular pressure.

**Types of evidence:**
- 5 meta-analyses of numerous randomized controlled trials
- 3 clinical trials
- 1 cross-sectional study with a transdermal glucosamine formulation
- Several laboratory studies

Much of the data on safety comes from randomized clinical trials in people with osteoarthritis, which have consistently shown that glucosamine use is generally safe. A 2005 Cochrane meta-analysis of 20 randomized controlled trials enrolling a total of 2,570 patients reported that glucosamine was as safe as placebo in terms of the number of subjects reporting adverse reactions (RR=0.97, 95% CI, 0.88, 1.08) [16]. The safety profile for glucosamine was significantly better than that of NSAIDs. An open-label study carried out by 252 physicians throughout Portugal evaluated the tolerability of glucosamine sulfate in 1,208 patients [45]. Patients were treated with glucosamine sulfate for a mean duration of 50 days. Eighty-eight percent of the study population was free of any adverse effects, and of those experiencing adverse effects, the reactions were generally mild and predominantly affected the gastrointestinal tract. All of the reported complaints were reversible after discontinuation of glucosamine sulfate. A 2015
meta-analysis with 54 randomized controlled trials including a total of 16,427 patients also reported no significant differences between glucosamine and placebo in the number of serious adverse events or the number of patients experiencing adverse events [20].

A 2018 meta-analysis of 30 clinical trials in osteoarthritis reported that there was no significant difference in the incidence of adverse events or discontinuations when glucosamine, chondroitin, and the combination were compared with placebo [22]. Adverse events included diarrhea, abdominal pain, nausea, headache, and others, but the incidences were not different compared with placebo.

A clinical study of 91 osteoarthritis patients reported that there was substantial variation in the steady-state minimum plasma concentrations, with a 45% coefficient of variation and up to a 106-fold variation across subjects [46]. These findings suggest that differences in the pharmacokinetic parameters of glucosamine and resulting plasma concentrations could partly be responsible for the observed inconsistencies in clinical outcomes in patients with osteoarthritis. A different clinical crossover trial of 14 healthy participants studied the pharmacokinetic parameters of two different glucosamine supplements (1500 mg/day of Rotta; DONA powder sachets, Mylan Health, Australia; 1500 mg/day of glucosamine sulfate one-a-day tablet; Blackmores, Warriewood, NSW, Australia) [47]. Although no significant differences were observed between the two brands of glucosamine supplements in pharmacokinetic parameters, for both brands, there were large differences in parameters between participants. Coefficients of variation for steady state plasma concentration, maximum plasma concentration, and area under the plasma concentration curve exceeded 20% for both products. Thus there are interindividual differences in the absorption and elimination of glucosamine, which could partly be responsible for variable clinical outcomes.

In a randomized controlled double-masked study of 88 patients with osteoarthritis, glucosamine sulfate treatment (750 mg, 3 times per day; Avicenna Laboratories, Iran) for 3 months increased intraocular pressure, but did not alter ocular response analyzer parameters [36]. The mean intraocular pressure at baseline, 1 month, and 3 months were 12.4±2.7 mmHg, 12.6±2.4 mmHg, and 13.5±2.3 mmHg, respectively, in the glucosamine group, and 13±2.8 mmHg, 12.9±2.4 mmHg, and 13±2.7 mmHg, respectively, in the placebo group. About 34.1% in the glucosamine group and 12.5% in the placebo group had clinically significant (defined as ≥ 2 mmHg) rise in intraocular pressure at final follow-up (p=0.023). It is not clear if glucosamine treatment may increase the risk of glaucoma, or if glucosamine may be harmful in glaucoma patients. Cornea and the trabecular meshwork (tissue in the anterior chamber angle of the eye) are enriched with glycosaminoglycans, and deposition/accumulation of glycosaminoglycans have been seen in some forms of glaucoma.
**Drug interactions:** Glucosamine is known to interact with warfarin, anisindione, or dicumarol, and may raise the risk of bruising and bleeding [48]. Glucosamine may also reduce the effectiveness of acetoaminophen (Tylenol), certain chemotherapy drugs (doxorubicin, etoposide, and teniposide), and diabetes drugs including glimepiride, glyburide, insulin, pioglitazone, and rosiglitazone [49]. Some glucosamine products also contain manganese, so excessive supplementation of such products may lead to manganese overdose.

**Sources and dosing:** Crystalline (salt form) glucosamine sulfate (2:1:2:2 ratio of glucosamine: sulfate: chloride: sodium) patented by Rottapharma of Germany and sold under the brand name Dona [50] appears to be the most efficient form of glucosamine as it reaches high circulating levels with a once daily dose of 1,500 mg [51]. Glucosamine sulfate is a close second, and typical doses are 300-500 mg, 3 times per day (total daily dose of 900-1,500 mg). Glucosamine hydrochloride appears to be ineffective based on clinical studies [17].

Glucosamine supplements are manufactured by processing chitin (long-chain polymer of N-acetylglucosamine) from the shells of shrimp, lobsters, and crabs. Vegans/vegetarians and people with shellfish allergies may use glucosamine supplements derived from fungi (Aspergillus niger) or fermented corn.

**Research underway:** There are numerous ongoing trials registered on ClinicalTrials.gov that are testing glucosamine: 5 for osteoarthritis or joint pain, 3 for different cancers, and several others for other conditions.

**Search terms:**
Pubmed, Google: Glucosamine
- + meta-analysis, + systematic review, + cognitive, + dementia, + Alzheimer, + ApoE4, + neuropathy. + blood-brain-barrier, + lifespan, + mortality, + safety

Clinicaltrials.gov, Examine.com, DrugAge, Anti-Aging Firewalls: Glucosamine
References:


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