Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Glucosamine

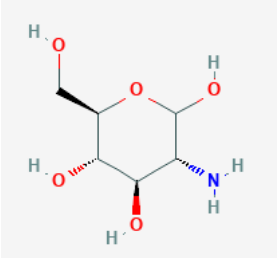
Evidence Summary

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.

Availability: OTC	**Dose**: The Dona crystalline glucosamine sulfate by Rottapharm reaches high circulating levels with a once daily dose of 1,500 mg. Other glucosamine supplements are often used 3 times daily at doses between 300-500 mg.	**Chemical formula:** $C_6H_{13}NO_5$ **MW**: 179.17  Source: PubChem
Half-life: ~15 hours	**BBB**: penetrant	
Clinical trials: Some meta-analyses of randomized controlled trials included tens of thousands of osteoarthritis patients.	**Observational studies**: The UK Biobank study on mortality included ~500,000 people, of whom ~20% used glucosamine.	

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 ($p< 5\times10^{-8}$) 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 join 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), muco-polysaccharide (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, NFκB, 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 change 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:

1. Giuliano V (2014) Glucosamine for longevity. *Anti-Aging Firewalls*.http://www.anti-agingfirewalls.com/2014/06/09/glucosamine-for-longevity/

2. Nevado-Holgado AJ, Kim CH, Winchester L *et al.* (2016) Commonly prescribed drugs associate with cognitive function: a cross-sectional study in UK Biobank. *BMJ Open* 6, e012177.https://www.ncbi.nlm.nih.gov/pubmed/27903560

3. Popov N (1985) Effects of D-galactosamine and D-glucosamine on retention performance of a brightness discrimination task in rats. *Biomed Biochim Acta* 44, 611-622.https://www.ncbi.nlm.nih.gov/pubmed/4026816

4. Jamialahmadi K, Sadeghnia HR, Mohammadi G *et al.* (2013) Glucosamine alleviates scopolamine induced spatial learning and memory deficits in rats. *Pathophysiology* 20, 263-267.https://www.ncbi.nlm.nih.gov/pubmed/23735432

5. Chou LY, Chao YM, Peng YC *et al.* (2020) Glucosamine Enhancement of BDNF Expression and Animal Cognitive Function. *Molecules* 25.http://www.ncbi.nlm.nih.gov/pubmed/32806562

6. Herrero-Beaumont G, Rovati LC, Castaneda S *et al.* (2007) The reverse glucosamine sulfate pathway: application in knee osteoarthritis. *Expert Opin Pharmacother* 8, 215-225.https://www.ncbi.nlm.nih.gov/pubmed/17257091

7. Rajapakse N, Mendis E, Kim MM *et al.* (2007) Sulfated glucosamine inhibits MMP-2 and MMP-9 expressions in human fibrosarcoma cells. *Bioorg Med Chem* 15, 4891-4896.https://www.ncbi.nlm.nih.gov/pubmed/17498959

8. Jang BC, Sung SH, Park JG *et al.* (2007) Glucosamine hydrochloride specifically inhibits COX-2 by preventing COX-2 N-glycosylation and by increasing COX-2 protein turnover in a proteasome-dependent manner. *J Biol Chem* 282, 27622-27632.https://www.ncbi.nlm.nih.gov/pubmed/17635918

9. Weimer S, Priebs J, Kuhlow D *et al.* (2014) D-Glucosamine supplementation extends life span of nematodes and of ageing mice. *Nat Commun* 5, 3563.https://www.ncbi.nlm.nih.gov/pubmed/24714520

10. Bell GA, Kantor ED, Lampe JW *et al.* (2012) Use of glucosamine and chondroitin in relation to mortality. *Eur J Epidemiol* 27, 593-603.https://www.ncbi.nlm.nih.gov/pubmed/22828954

11. Pocobelli G, Kristal AR, Patterson RE *et al.* (2010) Total mortality risk in relation to use of less-common dietary supplements. *Am J Clin Nutr* 91, 1791-1800.https://www.ncbi.nlm.nih.gov/pubmed/20410091

12. Li ZH, Gao X, Chung VC *et al.* (2020) Associations of regular glucosamine use with all-cause and cause-specific mortality: a large prospective cohort study. *Ann Rheum Dis* 79, 829-836.http://www.ncbi.nlm.nih.gov/pubmed/32253185

13. King DE, Xiang J (2020) Glucosamine/Chondroitin and Mortality in a US NHANES Cohort. *Journal of the American Board of Family Medicine : JABFM* 33, 842-847.http://www.ncbi.nlm.nih.gov/pubmed/33219063

14. Yoon SY, Narayan VP (2022) Genetically predicted glucosamine and longevity: A Mendelian randomization study. *Clinical nutrition ESPEN* 49, 556-559.http://www.ncbi.nlm.nih.gov/pubmed/35623867

15. McAlindon TE, LaValley MP, Gulin JP *et al.* (2000) Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. *JAMA* 283, 1469-1475.https://www.ncbi.nlm.nih.gov/pubmed/10732937

16. Towheed TE, Maxwell L, Anastassiades TP *et al.* (2005) Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev*, CD002946.https://www.ncbi.nlm.nih.gov/pubmed/15846645

17. Vlad SC, LaValley MP, McAlindon TE *et al.* (2007) Glucosamine for pain in osteoarthritis: why do trial results differ? *Arthritis Rheum* 56, 2267-2277.https://www.ncbi.nlm.nih.gov/pubmed/17599746

18. Wandel S, Juni P, Tendal B *et al.* (2010) Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. *BMJ* 341, c4675.https://www.ncbi.nlm.nih.gov/pubmed/20847017

19. Wu D, Huang Y, Gu Y *et al.* (2013) Efficacies of different preparations of glucosamine for the treatment of osteoarthritis: a meta-analysis of randomised, double-blind, placebo-controlled trials. *Int J Clin Pract* 67, 585-594.https://www.ncbi.nlm.nih.gov/pubmed/23679910

20. Zeng C, Wei J, Li H *et al.* (2015) Effectiveness and safety of Glucosamine, chondroitin, the two in combination, or celecoxib in the treatment of osteoarthritis of the knee. *Sci Rep* 5, 16827.https://www.ncbi.nlm.nih.gov/pubmed/26576862

21. Wang Z, Wang R, Yao H *et al.* (2022) Clinical Efficacy and Safety of Chondroitin Combined with Glucosamine in the Treatment of Knee Osteoarthritis: A Systematic Review and Meta-Analysis. *Computational and mathematical methods in medicine* 2022, 5285244.http://www.ncbi.nlm.nih.gov/pubmed/35924114

22. Zhu X, Sang L, Wu D *et al.* (2018) Effectiveness and safety of glucosamine and chondroitin for the treatment of osteoarthritis: a meta-analysis of randomized controlled trials. *Journal of orthopaedic surgery and research* 13, 170.http://www.ncbi.nlm.nih.gov/pubmed/29980200

23. Ogata T, Ideno Y, Akai M *et al.* (2018) Effects of glucosamine in patients with osteoarthritis of the knee: a systematic review and meta-analysis. *Clinical rheumatology* 37, 2479-2487.http://www.ncbi.nlm.nih.gov/pubmed/29713967

24. Zhu X, Wu D, Sang L *et al.* (2018) Comparative effectiveness of glucosamine, chondroitin, acetaminophen or celecoxib for the treatment of knee and/or hip osteoarthritis: a network meta-analysis. *Clinical and experimental rheumatology* 36, 595-602.http://www.ncbi.nlm.nih.gov/pubmed/29465368

25. Issa AY, HA AL, Awad WB *et al.* (2021) The impact of pharmaceutical care on the efficacy and safety of transdermal glucosamine sulfate and capsaicin for joint pain. *International journal of clinical pharmacy* 43, 101-106.http://www.ncbi.nlm.nih.gov/pubmed/32776178

26. Stuber K, Sajko S, Kristmanson K (2011) Efficacy of glucosamine, chondroitin, and methylsulfonylmethane for spinal degenerative joint disease and degenerative disc disease: a systematic review. *J Can Chiropr Assoc* 55, 47-55.https://www.ncbi.nlm.nih.gov/pubmed/21403782

27. Olaseinde OF, Owoyele BV (2022) Chondroitin and glucosamine sulphate reduced proinflammatory molecules in the DRG and improved axonal function of injured sciatic nerve of rats. *Sci Rep* 12, 3196.http://www.ncbi.nlm.nih.gov/pubmed/35210446

28. Lin PC, Jones SO, McGlasson DL (2010) Effects of glucosamine and Celadrin on platelet function. *Clin Lab Sci* 23, 32-36.https://www.ncbi.nlm.nih.gov/pubmed/20218092

29. Katoh A, Kai H, Harada H *et al.* (2017) Oral Administration of Glucosamine Improves Vascular Endothelial Function by Modulating Intracellular Redox State. *International heart journal* 58, 926-932.http://www.ncbi.nlm.nih.gov/pubmed/29151484

30. Kantor ED, Zhang X, Wu K *et al.* (2016) Use of glucosamine and chondroitin supplements in relation to risk of colorectal cancer: Results from the Nurses' Health Study and Health Professionals follow-up study. *Int J Cancer* 139, 1949-1957.https://www.ncbi.nlm.nih.gov/pubmed/27357024

31. Brasky TM, Lampe JW, Slatore CG *et al.* (2011) Use of glucosamine and chondroitin and lung cancer risk in the VITamins And Lifestyle (VITAL) cohort. *Cancer Causes Control* 22, 1333-1342.https://www.ncbi.nlm.nih.gov/pubmed/21706174

32. Satia JA, Littman A, Slatore CG *et al.* (2009) Associations of herbal and specialty supplements with lung and colorectal cancer risk in the VITamins and Lifestyle study. *Cancer Epidemiol Biomarkers Prev* 18, 1419-1428.https://www.ncbi.nlm.nih.gov/pubmed/19423520

33. Brasky TM, Kristal AR, Navarro SL *et al.* (2011) Specialty supplements and prostate cancer risk in the VITamins and Lifestyle (VITAL) cohort. *Nutr Cancer* 63, 573-582.https://www.ncbi.nlm.nih.gov/pubmed/21598177

34. Li G, Zhang X, Liu Y *et al.* (2022) Relationship between glucosamine use and the risk of lung cancer: data from a nationwide prospective cohort study. *The European respiratory journal* 59.http://www.ncbi.nlm.nih.gov/pubmed/34326189

35. Feng KM, Chien WC, Chen JT *et al.* (2021) The impact of glucosamine on age-related macular degeneration in patients: A nationwide, population-based cohort study. *PLoS One* 16, e0251925.http://www.ncbi.nlm.nih.gov/pubmed/34010361

36. Esfandiari H, Pakravan M, Zakeri Z *et al.* (2017) Effect of glucosamine on intraocular pressure: a randomized clinical trial. *Eye* 31, 389-394.http://www.ncbi.nlm.nih.gov/pubmed/27768119

37. Navarro SL, White E, Kantor ED *et al.* (2015) Randomized trial of glucosamine and chondroitin supplementation on inflammation and oxidative stress biomarkers and plasma proteomics profiles in healthy humans. *PLoS One* 10, e0117534.https://www.ncbi.nlm.nih.gov/pubmed/25719429

38. Largo R, Alvarez-Soria MA, Diez-Ortego I *et al.* (2003) Glucosamine inhibits IL-1beta-induced NFkappaB activation in human osteoarthritic chondrocytes. *Osteoarthritis Cartilage* 11, 290-298.https://www.ncbi.nlm.nih.gov/pubmed/12681956

39. Muniyappa R, Karne RJ, Hall G *et al.* (2006) Oral glucosamine for 6 weeks at standard doses does not cause or worsen insulin resistance or endothelial dysfunction in lean or obese subjects. *Diabetes* 55, 3142-3150.https://www.ncbi.nlm.nih.gov/pubmed/17065354

40. Tannis AJ, Barban J, Conquer JA (2004) Effect of glucosamine supplementation on fasting and non-fasting plasma glucose and serum insulin concentrations in healthy individuals. *Osteoarthritis Cartilage* 12, 506-511.https://www.ncbi.nlm.nih.gov/pubmed/15135147

41. Scroggie DA, Albright A, Harris MD (2003) The effect of glucosamine-chondroitin supplementation on glycosylated hemoglobin levels in patients with type 2 diabetes mellitus: a placebo-controlled, double-blinded, randomized clinical trial. *Arch Intern Med* 163, 1587-1590.https://www.ncbi.nlm.nih.gov/pubmed/12860582

42. Pham T, Cornea A, Blick KE *et al.* (2007) Oral glucosamine in doses used to treat osteoarthritis worsens insulin resistance. *Am J Med Sci* 333, 333-339.https://www.ncbi.nlm.nih.gov/pubmed/17570985

43. Biggee BA, Blinn CM, Nuite M *et al.* (2007) Effects of oral glucosamine sulphate on serum glucose and insulin during an oral glucose tolerance test of subjects with osteoarthritis. *Ann Rheum Dis* 66, 260-262.https://www.ncbi.nlm.nih.gov/pubmed/16818461

44. Moon JM, Finnegan P, Stecker RA *et al.* (2021) Impact of Glucosamine Supplementation on Gut Health. *Nutrients* 13.http://www.ncbi.nlm.nih.gov/pubmed/34202877

45. Tapadinhas MJ, Rivera IC, Bignamini AA (1982) Oral glucosamine sulphate in the management of arthrosis: report on a multi-centre open investigation in Portugal. *Pharmatherapeutica* 3, 157-168.https://www.ncbi.nlm.nih.gov/pubmed/7134225

46. Asthana C, Peterson GM, Shastri MD *et al.* (2020) Variation in Plasma Levels of Glucosamine With Chronic Dosing: A Possible Reason for Inconsistent Clinical Outcomes in Osteoarthritis. *Clinical therapeutics* 42, e140-e149.http://www.ncbi.nlm.nih.gov/pubmed/32713600

47. Asthana C, Peterson GM, Shastri MD *et al.* (2021) Variation in the pharmacokinetics of glucosamine in healthy individuals. *Rheumatology* 60, 1205-1209.http://www.ncbi.nlm.nih.gov/pubmed/32901283

48. Glucosamine drug interactions. *Drugscom*.https://www.drugs.com/drug-interactions/glucosamine.html

49. (2017) Glucosamine sulfate. *WebMD*.http://www.webmd.com/vitamins-and-supplements/glucosamine-sulfate-uses-and-risks#2

50. De Wan M, Volpi G (1998) Method of preparing mixed glucosamine salts. *USPTO*.http://patft.uspto.gov/netacgi/nph-Parser?Sect2=PTO1&Sect2=HITOFF&p=1&u=/netahtml/PTO/search-bool.html&r=1&f=G&l=50&d=PALL&RefSrch=yes&Query=PN/5847107

51. Persiani S, Roda E, Rovati LC *et al.* (2005) Glucosamine oral bioavailability and plasma pharmacokinetics after increasing doses of crystalline glucosamine sulfate in man. *Osteoarthritis Cartilage* 13, 1041-1049.https://www.ncbi.nlm.nih.gov/pubmed/16168682

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