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

Regular glucosamine use is associated with reduced mortality from respiratory diseases and some cancers; it may also improve a few aspects of cognitive function, though the effects are likely small.

Neuroprotective Benefit: The evidence for glucosamine on cognitive function is limited, and while there may be small positive effects, these data are based on people with osteoarthritis.

Aging and related health concerns: Regular use of glucosamine is associated with reduced mortality, particularly from respiratory diseases and cancer.

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

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. Although glucosamine was originally thought to act as a building block for synthesis of collagen (which is composed of N-acetylglucosamine), this theory is not well-supported. Instead, glucosamine appears to promote collagen synthesis, reduce collagen degradation, and stimulate cartilage synthesis. 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: The evidence for glucosamine on cognitive function is limited, and while there may be small positive effects, these data are based on people with osteoarthritis.

Types of evidence:

- 1 cross-sectional cohort study that examined the association between commonly prescribed drugs and cognitive functions
- 2 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.

There are several potential mechanisms of glucosamine's neuroprotective effects. Cell culture studies suggest that glucosamine inhibits inflammation by downregulating IL-1 [5], MMP expression [6], COX2 activity, and prostaglandin E(2) production [7]. 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)[8].

APOE4 interactions: Unknown.

Aging and related health concerns: Regular use of glucosamine is associated with reduced mortality, particularly from respiratory diseases and cancer.

Types of evidence:

- 6 meta-analyses or systematic reviews on osteoarthritis
- 1 systematic review on spinal degenerative joint/disc disease
- 1 large prospective cohort study on mortality
- 5 epidemiological studies on risk of various cancers
- Numerous laboratory studies

Lifespan: BENEFIT. 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)[9]. 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 [10]. 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).

A preclinical study has also shown that glucosamine extends lifespan in both aged mice and *C. elegans* [8]. 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 [11; 12; 13; 14; 15; 16]. The most recent 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 [16]. 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 [12]. Though 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 [15].

Some meta-analyses have noted that the effect sizes ranged widely and depended on the formulation [13]. 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.

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 [17]. 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.

Cardiovascular disease: POTENTIAL BENEFIT. 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 [18].

Respiratory disease: BENEFIT. In the same prospective cohort study described above, current use of glucosamine was associated with a large reduction in mortality from respiratory diseases (HR 0.59; 95 % CI 0.41-0.83)[9].

Cancers: BENEFIT 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)[9]. 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 [19]. 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 [20; 21]. The association with glucosamine was limited to adenocarcinoma (HR, 0.49; 95% CI: 0.27-0.90) [20]. There were no associations for use of glucosamine on prostate cancer risk [22].

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 [23]. 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 [24]. Other cell culture studies suggest that glucosamine inhibits inflammation by downregulating IL-1 [5], MMP expression [6], COX2 activity, and prostaglandin E(2) production [7].

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 [12]. Most studies have shown that glucosamine supplementation do not result in changes in glucose metabolism or insulin resistance in healthy adults [25; 26] or in patients with type 2 diabetes [27]. However, a few small clinical studies have reported that in people with underlying poorer insulin sensitivity [28] or those with untreated glucose intolerance [29], glucosamine may worsen insulin resistance.

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

Types of evidence:

- 2 meta-analyses based on 54 and 20 randomized controlled trials
- 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) [12]. 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 [30]. 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 [16].

Drug interactions: Do not use glucosamine if you take warfarin, anisindione, or dicumarol, as the combination may raise your risk of bruising and bleeding [31]. 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 [32]. 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 [33] has been reported to be an efficient form of glucosamine as it reaches high circulating levels with a once daily dose of 1,500 mg [34]. Glucosamine sulfate is also reported to be effective, 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 [13].

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 8 ongoing trials registered on ClinicalTrials.gov that are testing glucosamine for osteoarthritis and 1 trial is evaluating its effects on tinea pedis (foot infection).

Search terms:

Pubmed, Google: Glucosamine

- + meta-analysis, + systematic review, + cognitive, + dementia, + ApoE4, + blood-brain-barrier, + lifespan, + mortality, + safety

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

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