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Effect of glucosamine on intraocular pressure

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Abstract

Glucosamine is the most common nutrition supplement used in the United States. It is promoted not only as a pain reliever but also a therapy to slow osteoarthritis. Although studies with 3,800 patients with osteoarthritis of the knee or hip found that glucosamine was no better than placebo, it continues to be used for these two indications due to its perceived safety. However, reports of an increased intraocular pressure are alarming, especially in glaucoma. Glycosaminoglycans play a key role in the physiology of the cornea, conventional outflow of aqueous humor and the retina. In theory, long-term treatment with glucosamine could reach a concentration that impacts the morphology and function of ocular tissues. We recommend ophthalmologists counsel glaucoma patients about the potential risks of glucosamine and encourage cessation in uncontrolled intraocular pressure.

Keywords: Glucosamine, intraocular pressure, glaucoma, osteoarthritis, medication side effects.

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Introduction

Nutritional supplements are intended to provide nutrients that may otherwise not be consumed in sufficient quantities in a regular diet, including vitamins, minerals, proteins, amino acids or substances. Their use has increased since the 1970s and is now reported by 49% of the US population. Glucosamine is the most commonly prescribed supplement for OA[1] as an attempt to slow disease progression.[2,3] Glycosaminoglycans (GAGs) are the main constituent of the cartilage and are also abundant in corneal stroma and contribute morphological and functional characteristics to the trabecular meshwork of conventional outflow pathway.[4,5]

While the outflow capacity of the TM is partially regulated by the content of GAGs in the trabecular meshwork and could be directly affected by exogenous GAGs,[6] applanation tonometry measurement is also affected by GAG-induced changes in the biomechanical properties of the cornea.[5,7]

Since both glaucoma and OA are age-related morbidities, any systemic glucosamine consumption for osteoarthritis has potential to also affect glaucoma in the same individual.[8]

Glycosaminoglycans

Glycosaminoglycans (GAGs) are a family of highly sulfated, complex, polydisperse linear polysaccharides that display various important biological roles.[9] GAGs are categorized based on the difference of repeating disaccharide units; the most common GAG structures are chondroitin sulfate, dermatan sulfate, heparan sulfate, keratan sulfate, hyaluronic acid, and heparin.[9]

GAGs are integral components of basement membranes and interact with many extracellular matrix (ECM) components, including laminin, collagen, and fibronectin and are essential for cell adhesion and migration.[10] This interaction determines the architecture and permeability of the basement membrane.[11] Cartilage in the joint is mainly composed of type II collagen and glycosaminoglycans. Negatively charged GAGs absorb water and sodium and contribute to the viscosity and resistance to compression and shear stress of cartilage.[12]

Glucosamine is an amino monosaccharide and an essential constituent of chondroitin and keratin sulfate, a principal GAG in cartilage. It was first thought that glucosamine works by providing building blocks for the repair of the ECM of cartilage. However, anti-inflammatory and anti-catabolic effects have also been attributed to it.[13]

Despite these roles, the effectiveness of glucosamine to treat OA is debated. A recent meta-analysis of ten randomized clinical trials with a total sample size of 3803 patients found no significant differences in joint pain reduction or joint space narrowing between placebo and glucosamine.[14]

The Glucosamine/Chondroitin Sulfate (CS) Arthritis Intervention Trial (GAIT)— the largest clinical trial examining the efficacy of glucosamine and CS in OA compared celecoxib, glucosamine, CS, the combination of glucosamine and CS, and placebo in a multi-center double-blind randomized study.[15] A total of 1583 individuals with symptomatic OA were randomly assigned to receive daily doses of 1500 mg of glucosamine, 1200 mg of CS, both glucosamine and CS, 200 mg of celecoxib, or placebo for 24 weeks. The primary outcome measure was an at least 20% reduction in pain from baseline enrollment, measured using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale. OA patient groups were stratified by severity of knee pain at baseline into mild, moderate and severe. Glucosamine, CS, or their combination therapies were not significantly different from placebo in pain reduction ($p>0.05$). Among the moderate to severe pain stratum group of patients, however, the combination of glucosamine and CS was significantly better than placebo in treating OA.

Despite such limited evidence glucosamine remains a popular treatment, partly due to its reputation for safety. Almost one in five Americans with OA takes glucosamine and the sales approached $730 in 2004.[16]

Glycosaminoglycans and the eye

GAGs are the most abundant heteropolysaccharides in the human eye.[17] They are a key constituent of the extracellular matrix and act as a filler substance between cells and fibers in tissues. Here, they bind to proteoglycans, matrix proteins, and hyaluronan and form larger complexes.

The normal aqueous outflow of the eye is affected by the content of GAGs, in particular in the juxtacanalicular part of the trabecular meshwork[18,19] in a process termed funneling.[20] The trabecular meshworks of primates contain significant amounts of the major glycosaminoglycan found in the ECM of other tissues.[4] Side chains of glycosaminoglycans interact to form a system of entangled chains of polyanionic macromolecules, hence, act like a gel and are an important contributor to outflow resistance.[5]

It has been shown that high level of tumor growth factor beta 2 (TGFb2) in glaucomatous aqueous stimulates trabecular cells to secrete a high level of GAGs, which cross-links proteins to complexes not degradable by metalloproteinases.[21] Histologic evaluation of trabecular meshwork in steroid-induced

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glaucoma shows GAG in the TM. Although myocilin is the most characteristic ECM component for glucocorticoid-induced glaucoma,[22] additional ECM and constriction of the trabecular spaces can be observed in sensitive subjects even after a short course.[23]

Exogenous GAG is also shown to stimulate cultured human trabecular meshwork cells to produce more GAG as a positive feedback mechanism.[24]

Clinical studies on the effect of glucosamine on IOP

In a small retrospective study, Murphy et al. noted oral glucosamine supplement was associated with a significant but reversible rise in pressure.[8] They observed that poorly controlled glaucoma patients had controlled IOP once glucosamine supplementation was discontinued, and IOP increased in those patients with glaucoma who received glucosamine supplement for their OA condition. Shortcomings acknowledged by the authors included variability in glucosamine dosage and length of treatment, compliance, and brand variability. Furthermore, as GAG are also abundant in the corneal stroma,[25] any change in its concentration could lead to IOP measurements error as applanation tonometry is influenced by biomechanics of the cornea. While this study found an association between taking glucosamine and increased eye pressure, it did not establish a cause-and-effect relationship.

To address the shortcomings of mentioned study, we conducted a randomized clinical trial to explore the possible role of glucosamine supplement in the rise of IOP in patients with OA.[26] Eighty-eight patients with osteoarthritis who attended a rheumatology clinic were included. Patients with eye diseases that might affect the biomechanics of the cornea, including a history of ocular surgery, corneal scar, and dystrophies were excluded. Forty-four patients were randomly assigned to take 750 mg glucosamine three times a day for 3 months and 44 patients to take gelatinous capsules filled with sugar as a placebo on the same schedule.

The rise in the IOP was significantly larger at 3-month follow-up visit in the glucosamine group. In the glucosamine group, 34% of patients had an IOP increase of more than 2 mm HG compared to 23.5% of patients in the placebo group. Additionally, the mean age in those with increases of 2 mm Hg IOP or more was 66 years, compared to 57.7 years in patients who had increases of less than 2 mm Hg. Accumulation of extracellular matrix and thickening of the basement membrane could be aggravated by the exogenous use of GAG and compromise the reduced function of the trabecular meshwork. This is supported by histology that demonstrated age-related structural and functional changes including loss of cellularity, collagen and

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extracellular matrix accumulation, thickening, and fusion of trabecular sheets.[6,27] Age is also shown to be a risk factor for steroid-induced ocular hypertension.[23] The risk of ocular hypertension was not associated with diabetes mellitus, cardiovascular disease or gender. The results of our study showed that while glucosamine causes a statistically significant increase in IOP in patients with osteoarthritis, corneal biomechanics remain unchanged within 3 months of glucosamine supplement therapy. These results suggest that glucosamine supplementation could cause a trabecular meshwork selective change after 3 months.

There is no study concerning the pharmacokinetics of glucosamine in the trabecular meshwork. In OA, the glucosamine concentration in synovial fluid after oral administration is 500-fold less than the level expected to have a therapeutic effect on joint space narrowing[28] but it is possible that oral supplement reaches problematic levels in the TM instead. Another theory to explain why IOP might be more affected than joint parameters in OA is that high concentrations of GAG in aqueous could draw more water into the anterior chamber due to an osmotic effect, thus inducing swelling and pore size compromise, leading to a reduced outflow.[5]

Conclusions

Although the effect of Glucosamine on osteoarthritis is debated and recent studies indicate a placebo effect, it is unlikely that patients will discontinue as any alleviation is a benefit. However, the recent clinical association between glucosamine use and an IOP elevation is concerning and matches older laboratory studies. We recommend ophthalmologists share this information with their glaucoma patients and alert them to the potential dangers of nutritional supplements that are not regulated by the FDA. Glycosaminoglycans should be discontinued in glaucoma patients with an uncontrolled IOP.

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