

## SYSTEMATIC REVIEW

## The Use of Glucosamine and The Increase of IOP: a Literature Review

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**ABSTRACT**

**Background:** Glucosamine is an amino monosaccharide that can directly stimulate the synthesis of glycosaminoglycans in the cartilage. It has been widely used as an osteoarthritis treatment. However, several literatures show the possible side effects of glucosamine, such as increased intraocular pressure (IOP). **Objective:** The objective of this study was to determine if there was any correlation between the use of glucosamine and the increase in IOP. **Material and Method:** This was a descriptive qualitative study that implied a systematic review design. The study sample consisted of patients with osteoarthritis (OA) and glaucoma in Iran, Indonesia, Thailand, the USA, and India between 2013 and 2018. The literature search was conducted on a database (PubMed and Google Scholar) and selected using inclusion and exclusion criteria. **Discussion:** The research identified 5 studies on the use of glucosamine and the increase of IOP. Two articles provide significant results on the correlation between the use of glucosamine and the increase of IOP ( $P < 0.05$ ). In addition, two studies showed significant IOP reduction outcomes after discontinuation of glucosamine ( $P < 0.05$ ). A case series indicated an increase in IOP during the 6<sup>th</sup> month of glucosamine use but still at normal value. **Conclusion:** Many other factors contribute to IOP growth, other than the use of glucosamine. Therefore, a large-scale randomized clinical trial or a multicentre cohort study using the same parameters is still needed to improve the quality of the subsequent systematic review.

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**BACKGROUND**

Glucosamine is an amino monosaccharide that essential constituent of chondroitin and keratin sulfate and directly stimulate the synthesis of glycosaminoglycans (GAGs) in the cartilage (Nagaoka, et al, 2012). It can be naturally found in the human body or in a synthetic form. In an in vitro study, glucosamine can help to stimulate synovial fluid production, inhibit cartilage destruction and promote

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healing (Lim, et al., 2019). In addition to cartilage, glycosaminoglycans also contribute in maintaining a normal outflow resistance at the iridocorneal angle of the eye (Pescosolido, et al., 2012).

Glucosamine has been widely used as an osteoarthritis treatment. It was reported that glucosamine effectively reduces joint pain, improves joint stiffness, and reduces the possibility of total knee replacement (TRA) (Jerosch, 2011). A large study showed that glucosamine sulfate (capsule) and glucosamine hydrochloride (sachet) combined with chondroitin sulfate capsule provide meaningful analgesia in knee osteoarthritis patients (Reginster, et al., 2012).

Some literature reported the side effects of glucosamine usage. It has no serious adverse effects but could include digestive symptoms (dyspepsia, nausea, vomiting, diarrhea) (William & Ampat, 2022). Regardless of its positive impact on improving joint health, there are still a few debates about its ocular side effects. A study by (Esfandiari, et al., 2017) showed increased ocular pressure in 34% of patients compared to the placebo group. A different study conducted by Kusumawardhany (2017) showed a significant decrease in ocular pressure after glucosamine discontinuation. A study conducted by Murphy, et al., (2013) showed an increase in ocular pressure in a glucosamine user group and a decrease in ocular pressure in a group that had recently stopped their glucosamine consumption.

The increase in ocular pressure is possibly caused by excessive glycosaminoglycans (GAG) deposits in trabecular meshwork that could obstruct aqueous humor outflow (Pescosolido, et al., 2012). Other theories show that the release of glycosaminoglycans (GAG) could cause an osmotic effect, and absorb more water to the anterior chamber of the eye, which could lead to swelling, pore size reduction, and causing aqueous humor outflow resistance that could end in increased intraocular pressure (IOP) and glaucoma (Kusumawardhany, 2017). GAGs contribute to several roles in the human cornea such as in corneal hydration, corneal transparency and thickness, and structural integrity (Pacella, et al., 2015). Consuming GAG may exacerbate the accumulation of extracellular matrices in the eye and reduce the function of trabecular meshwork (Vranka, et al., 2015).

Along with the increasing use of glucosamine as complementary medicine, especially in treating joint disease, the risk of its side effects also increases. So far, there is no systematic review registered in PROSPERO on the impact of glucosamine use on increasing intraocular pressure, so a systematic review of the previous related studies is needed. If proven, it is expected that the results of this study could be additional data for clinicians and other health workers to be more selective and careful in the administration of glucosamine, especially to patients with a history of increased intraocular pressure.

## OBJECTIVE

The objective of this study was to determine if there was any correlation between the use of glucosamine and the increase in IOP.

## MATERIAL AND METHOD

This was a descriptive qualitative study that applied a systematic review design. It was aimed to identify, assess, and interpret all findings from previous research on the selected topic and to answer predefined research questions. This research was conducted in Surabaya, Indonesia, on May 2<sup>th</sup> 2021. We used the PICO model (presented in Table 1) to help define our clinical questions. The study population was patients who consumed glucosamine.

Table 1. PICO formula

Characteristics of PICO	Search Terms
Population	Patients who consume glucosamine
Intervention	Glucosamine WITH/WITHOUT Glucosamine discontinuation
Control	Placebo OR without glucosamine
Outcome	Intraocular pressure

The study sample included patients with OA and glaucoma in Iran, Indonesia, Thailand, the USA, and India from 2013-2018. The inclusion criteria of the study were journal in English/Indonesian. The population was patients who consumed glucosamine with or without discontinuation. The outcome was IOP measurement. Original and full text-articles were included in this study. The research design was a randomized clinical trial, case series or cohort, with research year in 2011-2021. Non-full text articles were excluded in this study. The literature search was carried out on a database (PubMed and google scholar), and we conducted a screening process of duplication followed by selection using inclusion and exclusion criteria.

Literature searches were carried out in databases (PubMed) and (ScienceDirect) by selecting journals based on the year of publication from 2013 to 2018. Search for articles or journals using keywords and boolean operators (AND, OR NOT or AND NOT) to expand or narrow the search, making it easier to search. The keywords in this systematic review consist of (Glucosamine OR Glycosaminoglycans) AND (IntraocularPressure OR IOP or Ocular Hypertension). The data that had been collected was managed using the PICO (Population, Intervention, Comparison, and Outcome) method. All articles collected were then processed using the PRISMA flow diagram to sort the inclusion and exclusion characteristics of the articles obtained accordingly. The chosen articles were assessed with the Joanna Brigg Institute (JBI) critical appraisal checklist.

## RESULT AND DISCUSSION

Table 2 shows the result of every study analyzed in this review. Esfariandi's study in Iran used a double mask randomized clinical trial to find out the effect of glucosamine consumption on IOP, and found a significant increase of IOP in 34.1% of the patients who had glucosamine supplementation and 12.5% of patients who had placebo. The significant increase in IOP was  $>2$  mmHg from the examination. The study also showed that the average age that had increased IOP was 66 years old. The study concluded that glucosamine supplementation caused a significant increase in IOP especially for the elderly patient (Esfandiari & Loewen, 2019).

The study conducted by Kusumawardhani (2017) measured IOP using a case series method and found a significant reduction in IOP after discontinuation of glucosamine compared to during glucosamine consumption ( $P = 0.013$ ). The study also found an increase in IOP after consumption of glucosamine compared to before consumption of glucosamine, but the difference was not significant ( $p = 0.527$ ). The study concluded that glucosamine supplementation reversed intraocular pressure, which decreased significantly after discontinuation.

Yuenyongviwat, et al, (2019) randomized control trial study measured the IOP of patients supplemented by 1500 mg glucosamine sulfate every day for 6 months and then discontinued for 3 months. The result found no differences in IOP between the control and experimental group during the 6th week, 3rd month, and 6th month measurement after glucosamine supplementation ( $p = 1.0$ ;  $p = 2.4$ ; and  $p = 0.82$ ). The study also found no differences in IOP during the 9th month after discontinuation of glucosamine ( $p = 0.29$ ). The study concluded that glucosamine had no significant effect on Intraocular pressure.

Murphy, et al., (2013) used a cohort method to measure the IOP of patients who had discontinued their glucosamine supplementation. The study found a significant decrease in IOP in both eyes after discontinuation of glucosamine ( $p < 0.001$ ). The average decrease of IOP in the right eye is from  $19.88 \pm 3.67$  to  $17.16 \pm 3.29$ , and in the left eye is from  $2.42 \pm 3.05$  to  $17.57 \pm 2.81$ . The study concluded glucosamine was a risk factor for the increase of intraocular pressure.

The case series study of Suhasini measured the IOP of 100 patients within 3 different age groups; 20-40 years old, 40-60 years old, and  $>60$  years old, who were consuming glucosamine for at least 6 months. The study found no increase in IOP during the 3rd month after glucosamine supplementation. Patient's IOP increased by 2 mmHg during the 6th month of glucosamine supplementation, but the IOP was still in normal value. The increase in IOP was found in 34 patients who all belonged to the 40-60 years old age group. The study concluded that glucosamine was relatively safe to be used for patients with osteoarthritis with frequent intraocular pressure monitoring (Suhasini, et al, 2018).

Table 2. Journals' results summary

No.	Authors	Study	Population	Location	Case (N)	Control (N)	Result	P-value
1.	<a href="#">Esfandiari, et al., (2017)</a>	Randomized controlled trial	Patient with OA, age 36-83 years old.	Iran	44	44	Approximately 34.1% of people from the group that consumed glucosamine and 12.5% of people from the group that used a placebo, experienced a significant increase in IOP elevation ( $\geq 2$ mmHg) at the end of follow-up (P= 0.023)	0.002
2.	<a href="#">Kusumawardhany, (2017)</a>	Case series	Patients with open angle glaucoma aged 50-77 years old	Indonesia	13	-	A significant reduction in IOP was found after discontinuation of glucosamine compared to during glucosamine consumption (P= 0.013). IOP also increased during consumption of glucosamine compared to before consuming glucosamine, but the difference was not significant (P= 0.27)	Decreased IOP after stopping glucosamine consumption P = 0,013 Increased IOP during glucosamine consumption P = 0.527.
3.	<a href="#">Yuenyongviwat, et al., (2019)</a>	Randomized controlled trial	Patients with OA age 50-78 years old	Thailand	21	21	There was no difference in IOP between groups at each visit (P>0.5).	The differences in IOP in every intervention and control group are in 6 weeks (P = 1.00), in 3 months (P = 0.24), in 6 months (P = 0.82), and 9 months (P = 0.29).
4.	<a href="#">Murphy, et al., (2013)</a>	Cohort	Patient with glaucoma, age 62-90 years old.	USA	11	6	Cohort A and B concluded that patients who stopped glucosamine consumption experienced a significant decrease in IOP with the average change from 19.5 to 16.7 (Cohort A) and 20.3 to 17.3 (Cohort B) (P < 0.001)	Cohort A: Increased in IOP while consuming glucosamine P = 0.001, decreased in IOP after stopping glucosamine consumption P = 0.002 Cohort A dan B: Decreased in IOP after stopping glucosamine consumption P<0.001.
5.	<a href="#">Suhasini, et al (2018)</a>	Case series	Patients with OA, group age 20-40 years old, 40-60 years old, and >60 years old.	India	100	-	After 3 months of taking glucosamine, there was no changes in IOP. After 6 months of taking glucosamine, 34% of the patient showed an increase in IOP (2 mmHg) but still in the normal range.	-

The mechanism of glucosamine use in causing an increase in IOP was influenced by the role of glycosaminoglycans and the function of trabecular meshwork (Esfandiari & Loewen, 2019). Previous studies showed various results. Four out of five studies found an increase in IOP during glucosamine consumption although some were still within the normal range of intraocular pressure, while the remaining did not find any significant difference in IOP.

A drop in intraocular pressure following glucosamine cessation was also noted in these studies. Kusumawardhany and Murphy concluded that the mechanism of IOP reduction due to glucosamine discontinuation was similar to the discontinuation of corticosteroids (Murphy, et al., 2013; Kusumawardhany, 2017). It was found that the synthesis of glycosaminoglycans, especially hyaluronic acid, was lower in patients with glaucoma than in normal people. This was caused by negative feedback from the body due to external glycosaminoglycans supplementation. The side chain structure of glycosaminoglycans can interact with each other and cause an increase in fluid resistance in trabecular meshwork. Therefore, that makes it difficult for aqueous humor to exit the chamber. Abrupt discontinuation of glucosamine causes glycosaminoglycan levels to decrease drastically due to lower glycosaminoglycan synthesis in the body, resulting in a decrease in intraocular pressure (Esfandiari et al., 2017). One out of five studies showed no differences in the IOP between two groups. However, the patients recruited in this study were not ocular hypertension patients and might respond differently compared to other studies (Yuenyongviwat, et al., 2019). While this study used crystalline glucosamine sulfate, many studies reported differences between crystalline glucosamine sulfate and glucosamine hydrochloride that might provide different result (Kucharz, et al., 2016; Bruyère, et al., 2014; Bruyère, et al., 2018).

The increase in intraocular pressure after glucosamine use was also influenced by age. Elderly people have a higher IOP than adults do. Several studies have shown that IOP will increase with age, while other studies show that IOP decreases with age. The dynamic changes in aqueous humor, which lead to a decrease in aqueous humor production, are the cause of the decrease in IOP with age. (Baek, et al., 2015). Age-related changes to the trabecular meshwork structure resulted in a reduction in the outflow tract, which further increased IOP in the elderly. (Han, et al., 2016). Histological study showed age-related structural and functional changes including cellularity loss, collagen and extracellular matrix accumulation and thickening of trabecular sheaths (Vranka, et al., 2015). Age is also a risk factor for steroid-induced ocular hypertension. The accumulation of the extracellular matrix and thickening of the basement membrane can be worsened by glycosaminoglycan supplementation and can interfere with the function of the trabecular meshwork (Esfandiari & Loewen, 2019).

In addition to glucosamine, a study conducted in 2017 reported that ACEI and ARB use are associated with higher IOP. Other medications that are linked with IOP increase are sulfonyleurea and biguanides. However, the reports regarding this matter are still limited. Therefore, further study might be required (Ho, et al., 2017).

## CONCLUSION

From the five journals reviewed, four journals supported the systematic review hypothesis that the use of glucosamine can increase intraocular pressure while another journal stated that there was no increase in intraocular pressure after taking glucosamine. The differences in the results may occur because the studies conducted in different countries with different races and genetics, different doses of glucosamine and different duration in glucosamine consumption. Therefore, there are many other factors that contribute to the increase in intraocular pressure other than the use of glucosamine. To improve the quality of subsequent systematic reviews, large-scale randomized clinical trials or multi-center cohort studies that use the same parameters are needed.

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## Conflict of Interest

All authors have no conflict of interest.

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### Author Contribution

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