

Original article

Intraocular pressure changes after the treatment of age-related knee osteoarthritis with glucosamine sulfate

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Abstract

Background: Glucosamine is widely prescribed for age-related knee osteoarthritis (OA) treatment because of its effectiveness and safety profile. However, there was a study reporting that glucosamine was associated with an increase in intraocular pressure (IOP) in patients with glaucoma. The effect of IOP elevation in non-glaucomatous population is still inconclusive. **Purpose:** To compare the change of IOP between treatment for age-related knee OA with and without glucosamine sulfate in non-glaucomatous patients. **Methods:** This is a prospective comparative study. Age-related knee OA patients were enrolled and divided into two groups depending on indications for glucosamine sulfate treatment. Twenty patients were treated with oral glucosamine sulfate and twenty other patients were treated with other medications. IOP was measured before glucosamine sulfate treatment, 2, 4, 8, 12, 24 weeks after glucosamine sulfate treatment, and 2 weeks after stopping glucosamine sulfate treatment. The change in IOP was compared between the two groups. **Results:** Forty patients were included in the study. The mean age was 67.24±8.45 years. There was no difference in patients' characteristics between the two groups except for age which the glucosamine sulfate group was younger (63.33 vs 70.75, $p = 0.005$). In the glucosamine sulfate group, the baseline IOP was 13.96±1.82 mmHg. IOP increased statistically significantly from the baseline 2 weeks after starting glucosamine supplementation (+0.93±1.21 mmHg, $p = 0.005$). There was no statistical change in IOP compared to the baseline in other visits including the visit after glucosamine sulfate withdrawal. In the non-glucosamine group, the baseline IOP was 14.16±2.57 mmHg. There was no change of IOP in any visit. **Conclusion:** There was a statistically significant increase in IOP 2 weeks after taking glucosamine sulfate. There was no statistical change in IOP compared to the baseline in other visits including the visit after glucosamine sulfate withdrawal.

Keywords: ● Osteoarthritis ● Knee osteoarthritis ● Glucosamine sulfate ● Intraocular pressure

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นิพนธ์ต้นฉบับ

การเปลี่ยนแปลงของความดันโลหิตในผู้ป่วยโรคข้อเข่าเสื่อมจากความชราหลังได้ รับยาเกลือโคซามีนซัลเฟต

อิศราพร ตริลิทธิ ปิยาวดี นิมิตรโชติชัย รวีวรรณ ชุนถนอม วัลลภ เอี่ยมสมบูรณ์ และ พรพรรณพี พูนฤณารถ
กองจักษุกรรม โรงพยาบาลพระมงกุฎเกล้า

บทคัดย่อ

บทนำ ปัจจุบันมีการใช้เกลือโคซามีนอย่างแพร่หลายในการรักษาโรคข้อเข่าเสื่อมจากความชรา มีรายงานพบว่าเกลือโคซามีนทำให้ความดันโลหิตสูงขึ้นในผู้ป่วยโรคข้อเข่าเสื่อม โดยที่ผลกระทบในประชากรทั่วไปยังไม่สามารถสรุปได้ **วัตถุประสงค์** เพื่อเปรียบเทียบการเปลี่ยนแปลงของความดันโลหิตระหว่างการรักษาโรคข้อเข่าเสื่อมจากความชราโดยใช้และไม่ใช้เกลือโคซามีนซัลเฟตในผู้ป่วยที่ไม่ได้เป็นโรคข้อเข่าเสื่อม **วิธีการศึกษา** เป็นการศึกษาเปรียบเทียบ ผู้ป่วยโรคข้อเข่าเสื่อมจากความชราถูกแบ่งเป็นสองกลุ่มโดยข้อบ่งชี้สำหรับการใช้ยาเกลือโคซามีนซัลเฟต ซึ่ง 20 รายได้รับเกลือโคซามีนซัลเฟตและอีก 20 รายได้รับยาชนิดอื่น ทุกคนได้รับการวัดความดันโลหิตก่อนการให้ยา และสัปดาห์ที่ 2, 4, 8, 12, 24 หลังให้ยา รวมทั้ง 2 สัปดาห์หลังจากหยุดยา แล้วเปรียบเทียบการเปลี่ยนแปลงของความดันโลหิตระหว่างสองกลุ่ม **ผลการศึกษา** คุณลักษณะของกลุ่มตัวอย่างไม่แตกต่างกัน ยกเว้นอายุซึ่งกลุ่มเกลือโคซามีนมีอายุน้อยกว่า (63.33 ปีและ 70.75 ปี, $p = 0.005$) กลุ่มเกลือโคซามีนซัลเฟตมีความดันโลหิตก่อนการให้ยาเท่ากับ 13.96 ± 1.82 มม.ปรอท และมีความดันโลหิตเพิ่มขึ้นอย่างมีนัยสำคัญที่ 2 สัปดาห์หลังใช้เกลือโคซามีนซัลเฟต ($+0.93 \pm 1.21$ มม.ปรอท, $p = 0.005$) ไม่พบการเปลี่ยนแปลงของความดันโลหิตในการตรวจครั้งอื่น รวมถึงหลังหยุดเกลือโคซามีนซัลเฟต ในกลุ่มที่ไม่ใช้เกลือโคซามีนซัลเฟตไม่พบการเปลี่ยนแปลงของความดันโลหิตตลอดการศึกษา **สรุป** ความดันโลหิตเพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติที่ 2 สัปดาห์หลังรับประทานเกลือโคซามีนซัลเฟต และไม่มีการเปลี่ยนแปลงในการตรวจครั้งอื่น รวมถึงหลังหยุดเกลือโคซามีนซัลเฟต

คำสำคัญ: ● โรคข้อเข่าเสื่อม ● ข้อเข่าเสื่อม ● เกลือโคซามีนซัลเฟต ● ความดันโลหิต

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Introduction

Nowadays, a tendency to knee osteoarthritis (OA) continues to rise in the aging population. In Thailand, more than 6 million people are affected and 50 percent of them are older than 65 years¹. Daily life is disturbed by its limited activity due to pain and deformity of knees. Erosion of bone cartilage from a decrease in proteoglycans affects the movement of joints. Glucosamine is an amino monosaccharide and essential constituent of chondroitin and keratin sulfate, a substance for glycosaminoglycans (GAGs) synthesis in the cartilage². Therefore, the initiation of glucosamine supplementation for OA was introduced³ and became the most commonly prescribed symptomatic slow-acting drug for osteoarthritis (SYSADOA). In Australia, there was a survey of 266,884 participants who answered the questions regarding consumption of glucosamine, of which 58,630 participants (22%) indicated that they had taken glucosamine for 4 weeks before the survey⁴. There was evidences suggesting that glucosamine was effective and affected the disease progression^{5,6}. It also carried a high safety profile⁷.

Not only the main component of the cartilage but glucosamine is also found as a component of corneal stroma and trabecular meshwork^{8,9}. A study reported the association between glucosamine and increased intraocular pressure (IOP) in patients with glaucoma¹⁰. A relationship between the change of IOP and glucosamine intake in the non-glaucomatous population, which is the majority of patients who take that medicine, is controversial^{11,12}. The nature of IOP change is also unknown. Elderly people are already at risk of developing glaucoma. High IOP is also a strong risk factor for both glaucoma incidence and glaucoma progression¹³. The risk of developing open-angle glaucoma in a healthy population has been shown to increase by 16% per 1-mmHg increase in IOP¹⁴.

In this study, we compared the change of IOP between

the treatment of age-related knee osteoarthritis with and without glucosamine sulfate in non-glaucomatous patients. We also assessed the nature and risk factors of the change of IOP in patients treated with glucosamine sulfate.

Materials & Methods

This is a prospective comparative study. Age-related knee OA patients visiting Phramongkutklao hospital were enrolled in the present study and divided into two groups depending on indications for glucosamine sulfate treatment as in Thailand's National List of Essential Medicines. The indications for glucosamine sulfate treatment were primary osteoarthritis knee, age at least 56 years, Kellgren-Lawrence stage 2-3 in radiologic test, no improvement despite of a 3-month-conservative treatment or having a complication, renal or hepatic disorders, no use of non-steroidal anti-inflammatory drugs (NSAIDs) for more than 2 weeks, no treatment with SYSADOA such as diacerein. The treatment regimen was 1,500 mg of glucosamine sulfate supplement for 24 weeks. All patients have undergone a completed ophthalmic examination before enrolling in the study. Exclusion criteria included glaucoma or glaucoma suspected patients, steroid users, unable to follow up, having corneal diseases that affect IOP measurement, coma, and history of hyaluronic injection to the joint. Glaucoma and glaucoma suspected patients were identified by history and medical document review or having a high IOP and/or abnormal finding on gonioscopy and/or glaucomatous cupping of optic discs on ophthalmic examination.

Twenty patients were treated with oral glucosamine sulfate and twenty other patients were treated with NSAIDs or total knee arthroplasty. Pre-treatment data included patient age, gender, central corneal thickness (CCT), underlying diseases and medications, and family history of glaucoma. IOP was measured by Goldman

applanation tonometer 2 weeks before glucosamine sulfate supplementation, on the first day starting glucosamine sulfate supplementation, 2, 4, 8, 12, 24 weeks after glucosamine sulfate supplementation, and 2 weeks after stopping glucosamine sulfate supplementation.

A single physician masked to the treatment groups performed a general ophthalmic examination on every visit. The IOP of the right eye was measured 3 times using Goldmann applanation tonometry during 10.00-12.00 a.m. The average IOP was calculated before recording in the data collective form. The baseline IOP was the average of the IOP on the first and second visits to minimize the effect of normal IOP variation.

This study adhered to the tenets of the Declaration of Helsinki and its later amendments or comparable ethical standards. It was approved by the Institutional Review Board (IRB), Royal Thai Army Medical Department. The reference number was R115h/58. Informed written consent was obtained from all participants. To ensure that patient confidentiality was maintained, all data retrieval was performed by the principal investigator using a password-secured computer. Each patient's record form was assigned a subject ID code and did not contain any identifying information. All identifiable data was encrypted. Data will not be used for any other purposes than those described in the study protocol. The authors declared they had no financial interests.

Statistical analysis

The estimated sample size for two samples with repeated measurements was 20 in each group to have 90% power to detect IOP change. To compare the variables in the baseline, the chi-square test and independent samples t-test were analyzed for participant variables. The change of IOP was compared between the two groups using a 2-way repeated-measures analysis of variance with a 2-tailed t-test. All statistical analyses were performed by STATA. A *p*-value of 0.05 was considered statistically significant.

Results

Forty patients were enrolled in this study, 31 patients were female. The mean age was 67.24 ± 8.45 years (55-85). Twenty-eight patients (70%) had diabetes mellitus. The mean CCT was 534.55 ± 33.96 microns (443-600). No one had a family history of glaucoma.

The participants were classified into 2 groups according to glucosamine sulfate treatment and all of them could follow up every visit. The average age of patients was the only different characteristic between the two groups. The age of the glucosamine sulfate group was 63.33 ± 7.21 (56-79) and 70.75 ± 8.08 (55-85) ($p = 0.005$) of the non-glucosamine group (Table 1).

In the glucosamine sulfate group, all patients received a full course of glucosamine sulfate treatment and no one had complications. The baseline IOP was 13.96 ± 1.82 mmHg. IOP increased statistically significantly from the baseline 2 weeks after starting glucosamine supplementation (0.93 ± 1.21 mmHg, $p = 0.005$). Many patients in the glucosamine sulfate group experienced IOP elevation while the IOP of all patients in the non-glucosamine group did not change (Figure 1). There was no statistical change compared to the baseline in other visits including the visit after glucosamine sulfate withdrawal (Table 2). We could not identify risk factors of IOP change in patients treated with glucosamine sulfate.

In non-glucosamine group, the baseline IOP was 14.16 ± 2.57 mmHg. IOP did not change significantly from the baseline in any visits.

Discussion

This study found that IOP increased statistically significantly from the baseline at 2 weeks after starting glucosamine sulfate supplementation. There was no statistical change compared to the baseline in other visits including the visit after glucosamine sulfate withdrawal.

The introduction of glucosamine supplement in

Table 1 Demographic characteristics of the 2 groups

	Glucosamine (n = 20)	Non-glucosamine (n = 20)	Total (n = 40)	p-value
Gender				
Male	5 (25)	4 (20)	9 (22.5)	0.573
Female	15 (75)	16 (80)	31 (77.5)	
Underlying disease				
Diabetes mellitus	5 (25)	7 (35)	12 (30)	0.632
Age				
Mean±SD	63.33±7.21	70.75±8.08	67.24±8.45	0.005*
Median (min-max)	60.5 (56-79)	69.5 (55-85)	66 (55-85)	
Central corneal thickness				
Mean±SD	542.56±29.91	527.35±36.47	534.55±33.96	0.171
Median (min-max)	542 (501-584)	526 (443-600)	536.5 (443-600)	

Notes: Continuous variables were reported as mean ± SD (range) while categorical variables were reported as number (%). Statistical analysis was chi-square test and independent Sample t -test. P-value of 0.05 was considered statistically significant.

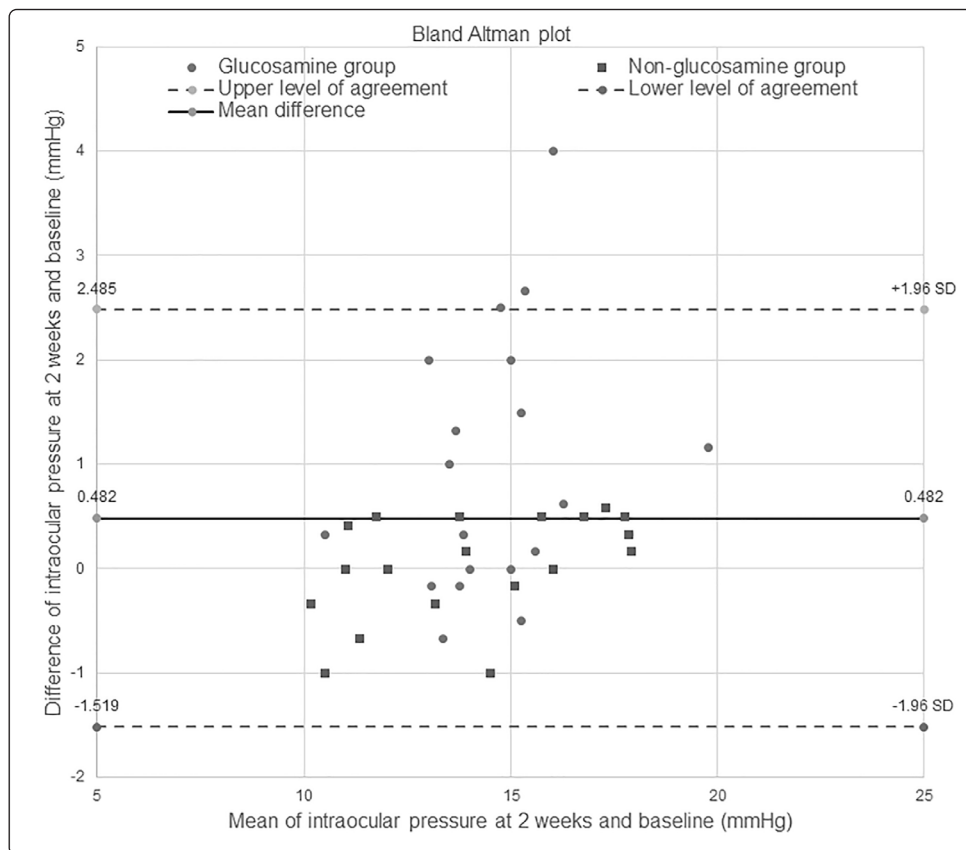


Figure 1 Bland-Altman plot of the intraocular pressure (IOP) change of both groups at 2 weeks after starting glucosamine sulfate, x-axis Mean of the IOP at 2 weeks after starting glucosamine Eyes in glucosamine group tended to have IOP rising while IOP was almost unchanged in the non-glucosamine group.

Table 2 Intraocular pressure change of both groups at each follow-up visit

Intraocular pressure mmHg	Glucosamine n = 20	Non-glucosamine n = 20	p-value
Baseline	13.96±1.82	14.16±2.57	0.785
2 weeks-baseline	0.93±1.21	0.03±0.49	0.005*
4 weeks-baseline	0.73±1.21	0.13±0.83	0.072
8 weeks-baseline	0.89±1.10	0.48±0.71	0.168
12 weeks-baseline	0.87±1.29	0.16±0.92	0.053
24 weeks-baseline	0.83±1.08	0.36±0.58	0.092
24 weeks-withdrawal	0.51±0.81	0.20±0.59	0.580
Baseline-withdrawal	0.31±0.97	0.16±0.78	0.168

Notes: Continuous variables were reported as mean±SD (range). Statistical analysis was 2-way repeated-measures analysis of variance with 2-tailed t test. p-value of 0.05 was considered statistically significant.

age-related knee OA treatment aimed to restore the extracellular matrix of cartilage¹⁵. It has been early reported as an effective treatment for the management of OA¹⁶. In addition, glucosamine was widely prescribed because of its safety profile¹⁷. Although a recent Cochrane review on glucosamine supplement failed to show any improvement in pain and function of knee OA-related symptoms¹⁸, it was still popularly used in knee OA patients. In many countries, glucosamine is available as an over-the-counter medication.

There was the first study reported on the association between glucosamine and an increase in IOP in patients with glaucoma¹⁰. In their study, 17 patients were recruited and divided into two groups. In the first group, the IOP was measured before and after glucosamine treatment. The second group had only IOP after the treatment of glucosamine. They found that the first group had significantly increased IOP when taking glucosamine and the second group had significantly decreased IOP when stopping glucosamine. In both groups, when they stopped glucosamine, the IOP was significantly lowered. The authors acknowledged the study's limitations including variability in glucosamine dosage and length of treatment, compliance, and brand variability.

The effect of glucosamine on IOP was confirmed by another study¹¹. They compared IOP between patients who received glucosamine supplements and placebo. Glaucoma patients were included in the study. They found a significantly higher IOP in the glucosamine group at the 3-month visit (13.5±2.3 and 13±2.7 mm Hg, $p = 0.002$). As IOP has a naturally diurnal variation, 34.1% in treatment and 12.5% in the placebo group had a clinically significant (defined as ≥ 2 mm Hg) rise in IOP. In our study, IOP change was statistically significant but not clinically significant in the non-glaucomatous population (+0.93±1.21 mmHg, $p = 0.005$). Although there was no clinically significant IOP elevation of the overall glucosamine sulfate group, we found 3 patients (15%) who had clinically significant IOP rising from the baseline (2.52±0.13 mmHg). All of those were female. The mean CCT was 545 microns (501-582). The mean age was 64.67 years (56-73). Two patients had diabetes mellitus. No one had a family history of glaucoma and all had open-angle. Only one patient had IOP rising at 2 weeks and continuously sustained until 24 weeks but returned to the baseline level after stopping the medication. We speculated that the differences in the results of the two studies were caused by different study populations, glucosamine dosage, and follow-up time.

On the contrary, a study demonstrated no association between glucosamine supplement and IOP OA patients¹². In their study, forty-two patients with OA of the knee were randomized to receive 1,500 mg of glucosamine sulfate for 6 months or the conventional treatment. There was no difference in IOP between groups during any visit. This study had a similar study protocol as our study in terms of patients' characteristics and glucosamine dosage. We found a statistically significant IOP rising at 2 weeks after taking glucosamine sulfate while the other study did not have a 2- week visit.

Glucosamine is an amino sugar and a precursor in the biochemical synthesis of GAGs. GAGs are widely known as a substance of extracellular matrix at the trabecular meshwork which is partly responsible for increased resistance to outflow¹⁹⁻²¹. Steroid-induced trabecular meshwork changes and consequent ocular hypertension is a condition that is well demonstrated related to excessive GAGs accumulation. Deposition of GAGs in the ground substance of the trabecular meshwork outflow pathways and its consequent constriction of the trabecular spaces and increased outflow resistance has been proposed to explain the rise of IOP following steroid therapy²². The osmotic forces exerted by GAGs may induce water influx into aqueous humor and edema of the trabecular meshwork, which increases the resistance to aqueous outflow⁹. In normal condition, catabolic enzymes released from lysosomes depolymerize GAGs and prevent this obstruction²³. The imbalance of GAGs deposit and degradation may lead to IOP elevation. However, the level of glucosamine in aqueous humor after taking glucosamine sulfate is unknown. We postulated that the level of glucosamine in the eye directly affected this phenomenon. We hypothesized that these mechanisms occurred within 2 weeks after starting glucosamine sulfate resulting in IOP elevation. In a normal eye, the change was minimal and usually returned to normal equilibrium

within a short time. In glaucomatous eyes which the extracellular matrix is thicker than in normal eyes and the outflow is already compromised, this effect may persist and lead to longstanding IOP elevation. Since GAGs are also abundant in corneal stroma^{8,9}, a change in their concentration could also lead to an increase in corneal thickness, which is falsely higher in IOP measurement with Goldmann applanation tonometry. We only measured the central corneal thickness at the baseline visit therefore we were unable to prove this hypothesis. However, the IOP returned to the baseline level after 2 weeks, if this mechanism existed, it was a temporary event.

This study is a prospective comparative study, conducted by a single masked physician who performed a general eye examination on every visit. Only one form of glucosamine sulfate was prescribed. We selected only the right eye of each participant for the study. IOP was calculated from multiple measurements and the baseline IOP was averaged from two visits to minimize the effect of normal IOP variation. The difference in the average age of patients between groups might not affect the IOP change. Neither recent evidence of the aging effect on IOP fluctuation nor risk factors analysis in this study was identified. This study had some limitations. The sample size was too small to identify risk factors of IOP elevation related to glucosamine sulfate supplement. We found only 3 patients who had significant IOP change. Larger sample size with various study populations is required to demonstrate the nature of IOP change and its risk factors in further study. Some investigations such as anterior segment OCT to assess anatomical angle structure may be useful for identifying the etiology of the IOP change. Measurement of glucosamine levels in aqueous humor may explain the pathophysiology of the condition.

We have compared the change of intraocular pressure in non-glaucomatous patients who were treated with and without glucosamine sulfate. In application, this study shows a statistically significant but not clinically significant increase of IOP from the baseline 2 weeks after starting glucosamine supplementation (0.93 ± 1.21 mmHg, $p = 0.005$). There was no statistical change compared to the baseline in other visits including the visit after glucosamine withdrawal. This study reported the safety of glucosamine supplementation, in terms of intraocular pressure change, which is widely prescribed for age-related knee OA patients. Although most age-related knee OA patients can take this medicine safely, there was 15% of patients experienced clinically significant IOP elevation in our study. IOP monitoring at 2 weeks after prescription may have benefits in some patients who have other risk factors of glaucoma.

Conclusion

There was a statistically significant increase in IOP 2 weeks after taking glucosamine sulfate. The amount of IOP elevation was not clinically significant in the non-glaucomatous population. There was no statistical change in IOP compared to the baseline in other visits including the visit after glucosamine withdrawal.

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