Laporan Hasil Penelitian

THE ASSOCIATION BETWEEN GLUCOSAMINE SUPPLEMENTATION AND INCREASED INTRAOCULAR PRESSURE IN PATIENTS WITH OPEN ANGLE GLAUCOMA

Rini Kusumawar Dhany [1]
[1)] Dosen Fakultas Kedokteran Universitas Wijaya Kusuma Surabaya
Staf Departemen Mata RSU Dr.Wahidin Soediro Husodo Mojokerto

Submitted : March 2017 | Accepted : June 2017 | Published : July 2017

ABSTRACT

It is postulated that the excessive deposits of glycosaminoglycans in the trabecular meshwork will restrict the outflow of aqueous humor. In addition, another theory suggests that an increasing of glycosaminoglycans release into the aqueous causes an osmotic effect, drawing more water into the anterior chamber, thus causing swelling, a decreasing of pore size and eventually increased to outflow resistance. These mechanisms may be able to induce an increase thickness of the pore lining and/or decrease outflow, then resulting in increase of intraocular pressure (IOP). We observed a total of 13 patients with open-angle glaucoma (6 men and 7 women with mean age 62+3 yearsold) that still consume a glucosamine supplement associated with their osteoarthritis disease. We measured IOP before, on 7th day after glucosamine consumption and after discontinuation. The IOP measurements were performed at least 3 times within 2 years, and no associated with a changing in glaucoma medications or eye surgery. We found a significant decreased of IOP after discontinuation of glucosamine rather than during glucosamine supplementation (P = 0.013). The IOP was also increase during glucosamine consumption compared with before supplementation, however the difference was not significant (P = 0.527). Insignificant difference also we found in the IOP after discontinuation compared with before supplementation. Our study showed a reversible effect of glucosamine supplementation for increasing IOP. A discontinuation of glucosamine consumption significantly reduced intraocular pressure. However, the possibility about a permanent damage associated with a prolonged use of glucosamine consumption is not eliminated. It is suggested to observe the IOP patients who choose a supplementation with glucosamine.

Keywords : Glucosamine, Glaucoma, Intraocular Pressure
Correspondence : rininugroho@gmail.com

ABSTRAK

Diduga bahwa deposit glycosaminoglycans yang berlebihan dalam jaring trabekular akan membatasi arus keluar aqueous humor. Selain itu, teori lain menunjukkan bahwa peningkatan glikosaminoglikan dilepaskan ke dalam aqueous menyebabkan efek osmotik, menarik lebih banyak air ke dalam ruang anterior, sehingga menyebabkan pembengkakan, penurunan ukuran pori-pori dan akhirnya meningkat menjadi hambatan arus keluar. Mekanisme ini mungkin dapat menginduksi peningkatan ketebalan lapisan pori dan / atau penurunan aliran keluar, kemudian menghasilkan peningkatan tekanan intraokular (IOP). Kami mengamati total 13 pasien dengan glaukoma sudut terbuka (6 pria dan 7 wanita dengan usia rata-rata 62 + 3 tahun) yang masih mengkonsumsi suplemen glukosamin yang terkait dengan penyakit osteoarthritis mereka. Kami mengukur IOP sebelumnya, pada hari ke 7 setelah konsumsi glukosamin dan setelah penghentian. Pengukuran IOP dilakukan minimal 3

kali dalam 2 tahun, dan tidak terkait dengan perubahan pada pengobatan glaukoma atau operasi mata. Ditemukan penurunan IOP yang signifikan setelah penghentian glukosamin daripada suplementasi glukosamin (P = 0,013). IOP juga meningkat selama konsumsi glukosamin dibandingkan dengan sebelum suplementasi, namun perbedaannya tidak signifikan (P = 0,527). Perbedaan yang tidak signifikan juga kita temukan dalam IOP setelah penghentian dibandingkan dengan sebelum suplementasi. Studi kami menunjukkan efek reversibel suplementasi glukosamin untuk meningkatkan IOP. Penghentian konsumsi glukosamin secara signifikan mengurangi tekanan intraokular. Namun, kemungkinan tentang kerusakan permanen yang terkait dengan penggunaan glukosamin berkepanjangan tidak dihilangkan. Disarankan untuk mengamati pasien IOP yang memilih suplemen dengan glucosamine.

Keywords **:** Glukosamin, Glaukoma, Tekanan Intraocular
Correspondence : rininugroho@gmail.com

BACKGROUND

Normal aqueous outflow of the eye is regulated by the content of glycosaminoglycans (GAGs). Researchers postulate that the excessive deposits of GAG in the trabecular meshwork restrict the outflow. Another theory suggests that an increasing release of GAG into the aqueous causes an osmotic effect, drawing more water into the anterior chamber, thus causing swelling, a decrease in pore size, and eventually increase resistance to outflow. Either of these proposed mechanisms could lead to increase thickness of the pore lining and/or decreased outflow, resulting in increased intraocular pressure (IOP). Excessive glucosamine molecules may similarly elevate IOP (Knepper et al., 1996). In this study, we examine the relationship between glucosamine supplementation and increased IOP in patients with open angle glaucoma.

The extracellular matrix (ECM) of the trabecular meshwork (TM) is thought to be important in regulating intraocular pressure (IOP) in both normal and glaucomatous eyes. IOP is regulated primarily by a fluid resistance to aqueous humor outflow. However, neither the exact site nor the identity of the normal resistance to aqueous humor outflow has been established. Whether the site and nature of the increased outflow resistance, which is associated with open-angle glaucoma, is the same or different from the normal resistance is also unclear. The ECMs of the TM beams, juxta-canalicular region (JCT) and Schlemm's canal (SC) inner wall are comprised of fibrillar and non- fibrillar collagens, elastin-containing microfibrils, matricellular and structural organizing proteins, glycosaminoglycans and proteoglycans. Both basement membranes and stromal ECM are present in the TM beams and JCT region. Cell adhesion proteins, cell surface ECM receptors and associated binding proteins are also present in the beams, JCT and SC inner wall region. The outflow pathway ECM is relatively dynamic, undergoing constant turnover and remodeling. Regulated changes in enzymes responsible for ECM degradation and biosynthetic replacement are observed. IOP homeostasis, triggered by pressure changes or mechanical stretching of the TM, appears to involve ECM turnover. Several cytokines, growth factors and drugs, which affect the outflow resistance, change ECM component expression, mRNA alternative splicing, cellular cytoskeletal organization or all of these. Changes in ECM associated with open-angle glaucoma have been identified (Acott, T. S. & Kelley M. J., 2008).

The iridocorneal angle changes are caused by glycosaminoglycans both in aging and in glaucomatous patients: (1) deposition of fibrous granular material and increased electron density of the structures close to the

iridocorneal angle; and (2) strong decrease of hyaluronic acid content and increase of sulfated glycosaminoglycans. Similar to what happens in other tissues in the body; glycosaminoglycans of the human iridocorneal angle undergo physiological and pathological changes. The trabecular meshwork is the structure responsible for the regulation of the aqueous humor outflow that is often altered in primary open-angle glaucoma patients (Pescosolido et al., 2012). To our knowledge, there are limited studies of glucosamine HCl in humans. Although some subjects do report statistically significant improvement in pain and function from products combining glucosamine HCl and other agents, glucosamine HCl by itself appears to offer little benefit to those suffering from osteoarthritis (Fox, B. A. & Stephens, M. M. 2007). A large study showing that glucosamine sulfate (GS) and chondroitin sulfate (CS) capsules or sachet preparations with glucosamine hydrochloride (GH) and CS capsules in knee osteoarthritis (OA) patients provide clinically meaningful and sustained analgesia (Reginster, J. Y., Neuprez, A., Lecart, M. P., Sarlet, N. & Bruyere, O. 2012)

METHODS

We recruited a total of 13 consecutive patients with open-angle glaucoma (6 men and 7 women with mean age 62+3 years old) at ophthalmology outpatient clinic Dr. Wahidin Soedirohusodo Mojokerto hospital. However they still require consuming a glucosamine supplement associated with their osteoarthritis disease. The IOP was measured before, on 7th day after they starting glucosamine supplementation and after discontinuation. IOP measurements were performed using Schiotz tonometry at least 3 times within 2 years, and no associated changes in glaucoma medications or eye surgery. There were 3 drop out patients because lack of glaucoma medication compliance.

Sample size :

$$n = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \sigma^2}{2}$$

$\alpha = 0.05 ; \beta = 0.1 ; n = 11$

RESULT

Tabel 1. Research Result

ID	Age (Years)	Sex	OD			OS		
			TIO -1	TIO -2	TIO -3	TIO -1	TIO -2	TIO -3
M-1	67	M	17.3	17.3	17.3	17.3	17.3	17.3
M-2	55	M	17.3	20.6	17.3	17.3	20.6	17.3
M-3	67	F	14.6	20.6	20.6	24.4	24.4	24.4
M-4	77	M	20.6	24.4	20.6	24.4	20.6	20.6
M-5	58	F	31.8	24.4	12.2	14.6	20.6	8.5
M-6	DO	F						
M-7	57	F	20.6	20.6	17.3	24.4	17.3	20.6
M-7	DO	M						
M-8	62	F	14.6	14.6	20.6	20.6	43.4	24.4
M-9	72	F	14.6	14.6	20.6			
M-10	71	M	20.6	27.2	24.4	14.6	37.2	24.4
M-11	DO	F						
M-12	58	F	14.6	14.6	14.6	20.6	37.2	24.4
M-13	71	F	8.5	37.2	20.6	8.5	37.2	17.3
M-14	55	M				17.3	17.3	17.3
M-15	50	F	37.2	27.2	23.1	37.2	19.6	19.6
W	56	L	27.2	14.6	17.3	27.2	14.6	17.3

M: male F: female
TIO-1 : before glucosamine supplementation
TIO-2 : 7th day during glucosamine supplementation
TIO-3 : glucosamine discontinuation
DO: Drop out

Normal distribution data has been tested with the Kolmogorov-Smirnov test with P> 0.05. Based on the obtained test P = 0.007 or P <0.05 significantly different and each period had been analyzed to find out more IOP differences between each period.

We found a significant decreased of IOP after discontinuation of glucosamine rather than during glucosamine supplementation (P = 0.013). The IOP was also increase during glucosamine consumption compared with before supplementation, however the difference was not significant (P = 0.527). An insignificant difference also we found in the

IOP after discontinuation compared with before supplementation

Tabel 2. Statistic Analysis

Periode	Mean ± SD	Frequency	Significancy
Pre-treatment	20.3038 ± 7.39727	26	P= 0.007
Treatment	23.6538±8.27779	26	
Post-treatment	19.2269±3.90595	26	

DISCUSSION

All the patients consume a glucosamine with dosage 3x500 mg with duration of treatment 7 days. The diurnal variation could affect IOP, thus all of patients were measured during 8.00 – 12.00 a.m. The IOP was increased on 7th day after they began glucosamine supplementation compared with before glucosamine supplementation. but the difference statistically not significant. This may be caused by sample size and large deviation standard before and during treatment (7.39727 and 8.27779, respectively). The limitations of the study were the confounding factors that can affect intraocular pressure such as diet that also contain glucosamine (e.g., Lobster, Crab and Crawl fish), drug compliance, physical medication for each patient, hypertension, diabetic mellitus and myopia.

In vitro research on human eyes has found a decrease in GAG synthesis, particularly hyaluronic acid in glaucomatous eyes compared with healthy eyes (Schachtschabel DO & Binninger E. 1995). Accordingly, theories exist regarding an osmotic effect of GAGs leading to swelling and outflow resistance (Knepper PA. McLone DG, 1985). We hypothesized that the discontinuation of glucosamine supplementation reduces IOP by mechanisms similar to those of discontinuation of corticosteroid treatment, which shows a similar effect (Covell LL. 1985). Many questions are raised by glucosamine supplementation-associated IOP changes. This study shows a reversible increases effect of glucosamine supplementation- associated IOP changes and the discontinuation of glucosamine significantly reduced intraocular pressure. However, the possibility that the permanent damage associated with a prolonged use of glucosamine supplementation is not eliminated. Monitoring IOP in patients choosing to supplement with glucosamine is indicated.

REFERENCES

Acott, TS. & Kelley, MJ. (2008). Extracellular Matrix In The Trabecular Meshwork, *Exp Eye Res*, vol.86, pp.543-61.

Covell, Ll. (1958), Glaucoma Induced by Systemic Steroid Therapy, *Am J Ophthalmol.* Vol.45(1), pp.108-109.

Fox, BA., Stephens, MM. (2007), Glucosamine Hydrochloride for the Treatment of Osteoarthritis Symptoms, *Clin Interv Aging*. Vol.2, pp.599-604.

Knepper, PA., Mclone, DG. (1958-1986). Glycosaminoglycans And Outflow Pathways of The Eye And Brain, *Pediatr Neurosci*. Vol.12(4-5), pp.240-251

Knepper, PA., Goossens, W., Hvizd, M. & Palmberg, P. F. (1996). Glycosaminoglycans of The Human Trabecular Meshwork In Primary Open-Angle Glaucoma, *Invest Ophthalmol Vis Sci*, Vol. 37, pp.1360-7.

Pescosolido, N., Cavallotti, C., Rusciano, D. & Nebbioso, M. (2012), Trabecular Meshwork In Normal And Pathological Eyes, *Ultrastruct Pathol*. Vol. 36, pp. 102-7.

Pournadeali, K. N. (1999). Glucosamine Sulfate: A Review Of Efficacy For The Pharmacy *Professional. Int J Pharm Compd*, Vol. 3, pp. 428-33.

Reginster, JY., Neuprez, A., Lecart, M. P.,Salmon, FJ. (2007). Glaucoma In: Riordan-Eva, P. & Whitcher, J. P. (Eds.) *Vaughan & Asbury's General Ophthalmology Seventeenth Edition*. New York, Mcgraw- Hill Companies.

Sarlet, N., Bruyere, O. (2012). Role of Glucosamine In The Treatment For Osteoarthritis, *Rheumatol Int*, Vol. 32, pp. 2959-67.

Schachtschabel, Do., Binninger, E. (1993). Stimulatory Effects Of Ascorbic Acid On Hyaluronic Acid Synthesis Of In Vitro Cultured Normal And Glaucomatous Trabecular Meshwork Cells Of The Human Eye, *Z Gerontol.* Vol.26(4), pp.243-246.

Uitterlinden, EJ., Jahr, H., Koevoet, JL., Jenniskens, Y. M., Bierma-Zeinstra, S. M., Degroot, J., Verhaar, J. A., Weinans, H. & Van Osch, G. J. (2006). Glucosamine Decreases Expression of Anabolic And Catabolic Genes In Human Osteoarthritic Cartilage Explants, *Osteoarthritis Cartilage*, Vol.14, pp.250-7.