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Association between Ocular Perfusion Pressure, Pressure to Cornea Index and Open-Angle Glaucoma – A Case-Control Study

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A B S T R A C T

INTRODUCTION

Glaucoma is a progressive eye condition with numerous risk factors, including advanced age, elevated intraocular pressure (IOP), familial predisposition, elevated systolic and low diastolic blood pressure, and decreased central corneal thickness. The study aimed to examine the mean ocular perfusion pressure and pressure cornea index in newly diagnosed glaucoma patients and compare these parameters with those of healthy individuals without glaucoma.

MATERIALS AND METHODS

The study investigated the association between IOP and factors in patients with primary open angle glaucoma (POAG) compared to control subjects. It involved 52 participants, divided into two groups: 26 recently diagnosed POAG and 26 healthy subjects without glaucoma. The study was approved by the Institutional Ethics Committee and included informed consent and clinical examinations. The age range of the participants was between 41 and 70 years, and both sexes were represented in the study.

RESULTS

The study found that POAG subjects had significantly higher mean values of mean ocular perfusion pressure (MOPP) compared to control subjects. The older age group was found to be more prone to developing glaucoma. The mean values of PCI in POAG subjects were also significantly higher than those in control subjects.

CONCLUSION

Integrating systemic blood pressure management can optimize ocular perfusion and slow disease progression. Furthermore, incorporating pressure cornea index into glaucoma diagnostic algorithms may assist in predicting disease progression and guiding treatment decisions.

INTRODUCTION

Glaucoma, a multifactorial disease, is a complex and progressive eye condition that can lead to irreversible vision loss if not properly managed. There are many risk factors associated with glaucoma's development and progression. Significant risk factors include advanced age, elevated intraocular pressure (IOP), familial predisposition, elevated systolic and low diastolic blood pressure, and decreased central corneal thickness. Emerging research has also highlighted the significance of mean arterial pressure with the advancement and course of glaucoma [1].

The two categories of theories explaining IOP-induced ganglion cell injury in glaucoma are the vascular (ischemic) theory and the mechanical (axonal) theory. The vascular theory says that high IOP changes the shape of the lamina cribrosa by squeezing blood vessels, which can change the microcirculation of the optic nerve. This alteration in blood flow can reduce the ocular perfusion pressure (OPP), leading to hypoxia. In response to hypoxia, autoregulatory mechanisms attempt to maintain normal blood flow, but if these mechanisms fail, ischemia can occur. Further impairment including excitotoxic damage from the release of glutamate or glycine from damaged neurons, and oxidative damage from the excessive release of nitric oxide and other reactive oxygen species can result from ischemia. These variables are responsible for causing ganglion cell injury and optic nerve impairment.

The mechanical theory states that an elevated IOP, especially over an extended period, subjects the posterior structures of the eye, particularly the lamina cribrosa, to mechanical stress and strain. The weakest spot in the pressured eye is the lamina cribrosa, where the optic nerve fibres leave the eye. Elevated IOP can compress, deform, and restructure the lamina cribrosa, resulting in mechanical injury to the axons and disruption of axonal transport. This can disrupt the backward transport of crucial nourishing substances to retinal ganglion cells, resulting in optic nerve damage. Both theories highlight the complex interplay between mechanical and vascular factors in glaucoma pathogenesis. Understanding these theories is crucial for developing effective treatment strategies to manage glaucoma and prevent further damage to the optic nerve [2].

The assessment of the overall adequacy of blood perfusion to organs and tissues relies heavily on the measurement of mean arterial pressure (MAP). MAP is a critical parameter for evaluating the efficiency of blood perfusion throughout the body. Changes in MAP in turn regulate OPP. The delicate balance between MAP and IOP is crucial for maintaining adequate blood flow to the optic nerve and other structures within the eye. Disturbances in this balance, such as a decrease in MAP or an increase in IOP, can potentially lead to compromised ocular perfusion and contribute to the pathogenesis of glaucoma. A decrease in MAP due to systemic hypotension or reduced ocular perfusion pressure can lead to inadequate blood supply, increasing the optic nerve's vulnerability to damage. Conversely, an increase in IOP, which may result from impaired aqueous humor drainage, can further exacerbate the compromised ocular perfusion. In addition to the direct impact on ocular perfusion, alterations in MAP can also influence the autoregulatory mechanisms within the eye. When MAP decreases, the compensatory mechanisms that regulate ocular blood flow may become overwhelmed, further contributing to compromised perfusion to the optic nerve [3].

Minor increases in intraocular pressure and blood pressure have minimal impact on the blood flow in the front part of the optic nerve. Even in conditions of high oxygen levels (hyperoxia) and high carbon dioxide levels (hypercapnia), the body's autoregulatory mechanisms maintain blood flow. Autoregulation ensures a consistent or nearly consistent blood flow despite varying perfusion pressures. However, in cases of inadequate autoregulation, an increase in intraocular pressure (IOP) could potentially decrease the optic nerve perfusion. The autonomic tone can often shield the eye from temporary increases in systemic blood pressure. However, in the presence of systemic hypertension, the autonomic nervous system's regulation may fail [4].

The most reliable way to measure intraocular pressure is via a Goldmann applanation tonometer, or GAT. GAT estimates IOP by measuring the force that is required to flatten the central cornea. In addition to mean arterial pressure and intraocular pressure, another important factor to consider in the evaluation and management of glaucoma is central corneal thickness. The central corneal thickness (CCT) and various other factors such as the axial length of the eyeball, the central curvature of the cornea, and corneal rigidity primarily influence the

measurement of IOP by GAT [5]. Corneas thicker than normal requires a greater force to flatten, resulting in an overestimation of IOP, whereas thinner corneas require less force to flatten, resulting in an underestimation of IOP. Research has demonstrated that CCT can significantly influence intraocular pressure measurement and may have implications for the development and progression of glaucoma. Several studies have highlighted the association between thinner central corneal thickness and a higher risk of glaucoma progression. This underscores the importance of accounting for central corneal thickness when assessing and monitoring patients with glaucoma.

Among different groups of people, individuals with healthy eyes typically have a central corneal thickness (CCT) of around 540µm. We can also classify CCT as thin, normal, or thick. Ultrasound pachymetry is the most common method used for CCT measurement. It utilizes ultrasound energy to measure CCT.Multiple characteristics, including race, age, gender, diurnal fluctuation, and diabetes, affect CCT. As one age, there is a demonstrated correlation between the decrease in CCT and the occurrence and development of glaucoma. Researchers have identified myopia as a significant risk factor for glaucoma.

Recent investigations have found that patients with ocular hypertension have larger central corneas compared to the average thickness, while patients with normal tension glaucoma have thinner central corneas than the average thickness. We evaluated these measurements using ultrasonic pachymetry [6]. After accounting for deviations from normal in corneal thickness (CCT), a considerable proportion of patients with ocular hypertension exhibit normal intraocular pressures (IOPs). Conversely, when considering CCT, patients with normal tension glaucoma exhibit higher IOPs, a condition known as "high-pressure glaucoma". It is crucial to quantify CCT in all individuals with ocular hypertension or glaucoma.

No direct correction of Goldmann Applanation Tonometry(GAT) by central corneal thickness(CCT) is possible. We can integrate GAT IOP and CCT using a pressure-to-cornea index [PCI = IOP/CCT^3 in mm]. We propose a PCI in the range of 120–140 as the upper normal limit. PCI in the range below 100 is usually observed in normal subjects. The significance of central corneal thickness in glaucoma care extends beyond its impact on intraocular pressure measurement.

Understanding the intricate relationship between MAP and ocular perfusion in the context of glaucoma is pivotal for healthcare providers involved in the care of individuals with this condition. By integrating systemic blood pressure management into the care of individuals with glaucoma, healthcare providers can strive to optimize ocular perfusion and mitigate the risk of glaucomatous progression. While CCT serves as an additional parameter to consider when evaluating the overall health of the cornea and its potential influence on disease progression when integrated with IOP as PCI. Our study aimed to examine the mean ocular perfusion pressure and pressure cornea index in newly diagnosed glaucoma patients and compare these parameters with those of healthy individuals without glaucoma.

OBJECTIVES

1. The primary objective was to assess the following parameters in subjects with POAG and healthy subjects: The Goldmann Applanation Tonometer (GAT) was used to measure IOP, the digital sphygmomanometer was used to measure blood pressure (systolic and diastolic) in sitting posture, and an ultrasound pachymeter was used to measure central corneal thickness (CCT).
2. The secondary objective was to estimate, study, and compare the mean ocular perfusion pressure (MOPP) and pressure-to-cornea (PCI) index values in the above two groups.

MATERIALS AND METHODS

STUDY DESIGN

The study utilized a case-control design to assess mean ocular perfusion pressure and pressure cornea index in Open angle glaucoma subjects compared to control subjects.

SAMPLING PROCEDURE

The sample size was calculated assuming the expected mean and standard deviation of the pressure cornea index in the open-angle glaucoma subjects as σ_1(132.9, 51.4) and in the healthy volunteers as σ_0(92, 24.8), as per the previous study by Franco AM et al [7]. The other parameters considered for sample size calculation included a power of study and two-sided alpha error.

The formula used for sample size calculation:

$$N = \frac{(\mu + \vartheta)^2(\sigma_1 + \sigma_0)}{(\mu_1 - \mu_0)^2}$$

N = sample size
μ_1, μ_0 = Difference between the means (μ_1=132.9 and μ_0=92)
σ_1, σ_0 = standard deviations (σ1 = 51.4 and σ_0 = 24.8)
μ = the two-sided percentage point of the normal distribution corresponding to 100% minus the power (μ = 1.645).
ϑ = percentage point of the normal distribution corresponding to the (two-sided) significance level for significance level (ϑ = 1.960).
According to the above-mentioned calculation, each group required a sample size of 25. We will include an additional subject in the sample size to accommodate a non-participation rate or follow-up rate of approximately 5%. Hence, the final required sample size would be 26 subjects in each group.

STUDY PARTICIPANTS

The study included a total of 52 participants, divided into two groups: 26 individuals recently diagnosed with Open angle glaucoma and 26 healthy subjects without glaucoma. The study represented both sexes, with participants ranging in age from 41 to 70 years.

INCLUSION CRITERIA:

For the POAG group, 26 people had to have an open angle during gonioscopy, an abnormal optic nerve head, a normal glaucomatous visual field, an intraocular pressure (IOP) of more than 21 mmHg, and no other cause of glaucoma. We included 26 healthy subjects without glaucoma and with no history of diabetes, hypertension, family history of glaucoma or other medical illness in the control subject group.

EXCLUSION CRITERIA:

Patients younger than 40 years old, patients who didn't want to take part, patients with corneal diseases, a history of previous intraocular or corneal surgery, long-term contact lens wearers, people with secondary glaucoma or unilateral glaucoma, known allergies to topical anesthetic drugs, and people who have taken certain medications in the past.

ETHICAL CLEARANCE

The Institutional Ethics Committee on Human Subjects at Dhanalakshmi Srinivasan Medical College Hospital, Perambalur, approved the research/study under the number IECHS/IRCHS/DSMCH/Cert/514, dated 26-03-2024. We briefed subjects about the study's objectives and methods, obtained their informed written consent before the study, ensured information confidentiality, maintained respectful behaviour, allowed participants free entry and exit, and ensured data integrity to ensure voluntary participation.

DATA COLLECTION

We conducted the study on 26 subjects with POAG and 26 healthy subjects without glaucoma, all of whom were in the age group >41-70 years. We selected the subjects from the patients who visited the ophthalmology glaucoma outpatient department, along with staff members and bystanders.

Data collection involved obtaining informed written consent from the subjects and conducting detailed history-taking and measurement of blood pressure using a digital sphygmomanometer. Ophthalmic clinical examinations included gonioscopy, tonometry, inspection of the optic disc, automated perimetry, and measurement of central corneal thickness using pachymetry.

STATISTICAL ANALYSIS

We entered the data consisting of IOP, age, systolic blood pressure (SBP), diastolic blood pressure (DBP), and central corneal thickness (CCT) between the POAG and control groups in a Microsoft Excel datasheet. Mean arterial pressure (MAP), Mean ocular perfusion pressure (MOPP) and Pressure Cornea index (PCI) were calculated from the above obtained variables. The continuous variables were represented as the mean value plus or minus the standard deviation (mean ± SD). The study aimed to determine if there were any significant differences in these variables between the two groups. We analysed the differences in means between the two groups using an independent samples 't' test. We deemed all statistical tests statistically significant if the p-value was less than 0.05.

RESULTS

The results are summarized as follows.

Table 1 shows the summary statistics of participants in the study including age, systolic and diastolic blood pressure, intraocular pressure, and central corneal thickness. Statistical tests revealed statistically significant differences between the mean values of the above-mentioned parameters. The glaucoma cases had significantly higher age, higher systolic and diastolic blood pressure, higher IOP, and lower CCT compared to that of control subjects.

Table 1: Characteristics of Study participants

Characteristics	**Summary Statistics**		
	POAG subjects(n=26)	**Control Subjects(n=26)**	**Unpaired t-test p value**
Age (in years)	56.31 ± 4.43	48.23± 6.02	<0.001**
IOP Right eye(mm of Hg)	21.54±2.8	15.66±1.93	<0.001**
IOP Left eye (mm of Hg)	21.46±2.54	15.56±1.88	<0.001**
SBP (mm of Hg)	146.62±15.87	107.46±18.22	<0.001**
DBP (mm of Hg)	99.23±7.42	84.54±8.05	<0.001**
CCT - Right eye (µm)	511.19±20.86	542.73±21.42	<0.001**
CCT - Left eye (µm)	507.81±22.38	538.92±21.73	<0.001**
Values are Mean ± Standard Deviation; IOP: Intraocular pressure; POAG: Primary Open Angle Glaucoma; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; CCT: Central Corneal Thickness; * - Correlation is significant at 0.05 level; ** - Correlation is significant at 0.01 level(2-tailed)			

Table 2 shows the comparison of mean arterial pressure (MAP), mean ocular perfusion pressure (MOPP), and pressure cornea index (PCI) in subjects with open-angle glaucoma and without glaucoma. Statistical tests revealed statistically significant differences between the two groups (p <0.001). The glaucoma cases had higher MAP, higher MOPP and higher PCI values compared to those of healthy subjects without glaucoma.

Table 2: Characteristics of Study participants

Parameter		Mean	Standard Deviation	Standard Error Mean	95% Confidence Interval of differences		t	p - value
					Lower limit	Upper limit		
MAP (mm Hg)	POAG Subjects (n=26)	115.03	9.55	1.87	111.17	118.88	7.17	<0.001**
	Control Subjects (n=26)	92.18	11.11	2.18	87.69	96.67		
MOPP (mm Hg)	POAG Subjects (n=52 eyes)	55.27	4.83	0.67	53.92	56.61	8.47	<0.001**
	Control Subjects (n=52 eyes)	45.87	5.54	0.77	44.32	47.41		
PCI	POAG Subjects (n = 52 eyes)	162.5	15.37	2.13	158.22	166.78	26.61	<0.001**
	Control Subjects (n = 52 eyes)	98.63	9.08	1.26	96.1	101.17		

POAG – Primary open angle glaucoma; MAP – Mean arterial pressure; MOPP – Mean ocular perfusion pressure; PCI – Pressure cornea index; * - Correlation is significant at 0.05 level; ** - Correlation is significant at 0.01 level(2-tailed)

DISCUSSION

In our study (Table 1), the mean values of intraocular pressure (right and left eye), age, systolic BP, and diastolic BP were significantly higher (p-value < 0.001) in the POAG subjects compared to that of control subjects. Also, there was a marked reduction in the mean CCT (right and left eye) values of the POAG subjects when compared with that of control subjects and it was also statistically significant (p-value <0.001). The mean value of the age (in years) in the POAG subjects (56.31 ± 4.43) was significantly higher (p-value = 0.000) when compared to that of the control subjects (48.23 ± 6.02). The mean values of the IOP in the POAG subjects were 21.54 ± 2.8 for the right eye and 21.46 ± 2.54 for the left eye. The above mean IOP values were significantly higher (p-value <0.001) in the POAG subjects when compared to that of the control subjects which were 15.66 ± 1.93 for the right eye and 15.56 ± 1.88 for the left eye respectively. This finding suggests that older age subjects are more prone to the risk of developing glaucoma or its incidence is more prevalent in the older age group.

In this study (Table 1), the mean value of the SBP in the POAG subjects (146.62 ± 15.87) was significantly higher (p-value <0.001) when compared to that of the control subjects (107.46 ± 18.22). The mean value of the DBP in the POAG subjects (99.23 ± 7.42) was significantly higher (p-value < 0.001) when compared to that of the control subjects which was (84.54 ± 8.05). In this study (Table 2), the mean value of the MAP in the POAG subjects (115.03 ± 9.55) was significantly higher (p-value <0.001) when compared to that of the control subjects (92.18 ± 11.11). The mean value of the MOPP in the POAG subjects (55.27 ± 4.83) was significantly higher (p-value < 0.001) when compared to that of the control subjects which was (45.87 ± 5.54).

Age influences the correlation between blood pressure (BP) and glaucoma, according to the Baltimore Eye Survey [8]. Hypertension has been shown to have a beneficial effect on younger people, possibly enhancing ocular perfusion pressure (OPP). However, in elderly individuals, the beneficial impact diminishes, and there is a heightened susceptibility to glaucoma. This is likely due to changes in blood vessels caused by high blood pressure, which disrupts the delivery of oxygen and nutrients. The Thessaloniki Eye Study [9] found that people who took too many blood pressure medicines had a higher chance of getting open-angle glaucoma, which is marked by increased cupping and a smaller optic disc rim area because of low ocular perfusion pressure. Elevated arteriolar or capillary resistance may be the reason for this connection. Treating high blood pressure will result in higher levels of tissue hypoxia if modifying capillary resistance is not taken into consideration.

In this study (Table 1), the mean values of the CCT in the control subjects were 542.73 ± 21.42 in the right eye and 538.92 ± 21.73 in the left eye respectively. The mean CCT in subjects with POAG was measured to be 511.19 ± 20.86 for the right eye and 507.81 ± 22.38 for the left eye which was significantly lower (p-value < 0.001) when compared to that of the control group. In this study (Table 2), the mean values of PCI in the glaucoma subjects (162.5 ±15.37) were significantly higher (p<0.001) than that of the control subjects (98.63±9.08).

Epidemiological research [10] and case-controlled investigations [11] have strongly linked a thinner CCT in glaucoma cases. Parkavan et al. [12] found that eyes with a higher central corneal thickness (CCT) display smaller optic discs, suggesting a stronger optic nerve head. According to one theory, a thin central corneal thickness may indicate a thin sclera with larger optic discs, resulting in a larger lamina cribrosa. Changes in the make-up of the connective tissue at the level of the lamina cribrosa may cause the lamina plates and the pores that surround the axons and blood vessels as they leave the eye to become more distorted [13]. Elevated stress and strain in this area might heighten the vulnerability to intraocular pressure (IOP)-related stress, rendering individuals more susceptible to developing glaucoma.

CONCLUSION

In conclusion, while elevated intraocular pressure, advanced age, high systemic blood pressure and low central corneal thickness are key factors in glaucoma development and treatment. Growing evidences suggest that vascular factors, such as blood pressure and ocular perfusion pressure, also plays a significant role. Considering systemic blood pressure management as part of glaucoma care can help optimize ocular perfusion and potentially slow disease progression. Overall, the integration of systemic blood pressure management into glaucoma care highlights the importance of considering both ocular and systemic factors in treatment strategies.

More research on how to include central corneal thickness in algorithms and how to create intelligent algorithms that account for things like central visual field defects and other eye diseases is necessary to improve the accuracy of glaucoma diagnosis. Overall, central corneal thickness is an important factor to consider in the evaluation and management of glaucoma. Furthermore, incorporating pressure cornea index into glaucoma diagnostic algorithms may assist in predicting disease progression and guiding treatment decisions.

Declaration of patient consent

Informed and written patient consent obtained from all the participants in the study.

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Nil

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

There was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI

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