Med & Health Jan 2026; 21(1): 175-190 https://doi.org/10.17576/MH.2026.2101.10

ORIGINAL ARTICLE

Intraocular Pressure, Intracranial Pressure, Translaminar Pressure Difference and Related Factors in Primary Open Angle Glaucoma

TECK CHEE CHENG[1,3], RONA ASNIDA NASARUDDIN[1,3], SHAMSUL AZHAR SHAH[2,3], JEMAIMA CHE-HAMZAH[1,3]*

[1]Department of Ophthalmology, Faculty of Medicine, Universiti Kebangsaan Malaysia, 56000 Cheras Kuala Lumpur, Malaysia
[2]Department of Community Health, Faculty of Medicine, Universiti Kebangsaan Malaysia, 56000 Cheras, Kuala Lumpur, Malaysia
[3]Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia, 56000 Cheras, Kuala Lumpur, Malaysia

Received: 21 November 2024 / Accepted: 04 February 2025

ABSTRAK

Kajian ini bertujuan untuk menyiasat dan membandingkan hubungan antara tekanan intrakranium (ICP), tekanan bola mata (IOP) dan perbezaan tekanan translamina (TLPD) dalam kalangan pesakit yang menghidapi penyakit glaukoma bertekanan tinggi (HTG) dan populasi normal. Pesakit yang baru menghidapi HTG dan subjek normal tanpa penyakit mata telah direkrut untuk kajian ini. Semua peserta kajian menjalani ukuran tekanan darah, kadar denyutan jantung, berat badan, ketinggian dan pemeriksaan mata secara menyeluruh termasuk ujian tahap penglihatan, ukuran IOP, pemeriksaan cakera saraf optik, analisa ketebalan saraf mata di sekeliling cakera saraf optik dan peta ketebalan makula, ujian medan visual ukuran panjang bola mata serta ketebalan tengah kornea. ICP telah dikira menggunakan formula ICP (mmHg) = (0.44 x Indeks jisim badan (kg/m²)) + (0.16 x Tekanan darah diastolik (mmHg))-(0.18 x Umur (tahun)) - 1.91. TLPD diperoleh melalui hasil tolak ICP daripada IOP. Pesakit HTG mempunyai median IOP lebih tinggi [26.00 (24.00-34.00) mmHg vs. 13.00 (10.00-14.00) mmHg], median ICP lebih rendah [8.19 (6.86-10.28) mmHg vs. 11.31 (8.91-12.36) mmHg], median TLPD lebih tinggi [18.64 (15.27-26.19) mmHg vs. 1.72 (0.27-4.62) mmHg] berbanding dengan subjek normal. Tiada kolerasi diperhatikan antara IOP dan ICP. Walau bagaimanapun, IOP didapati mempunyai kolerasi dengan TLPD dalam kedua-dua kumpulan pesakit HTG ($r = 0.911$, $p < 0.001$) dan subjek normal ($r = 0.758$, $p < 0.001$). TLPD mempunyai korelasi negatif dengan ICP ($r= -0.525$, $p=0.012$) dalam kalangan subjek sihat. ICP yang lebih rendah di kalangan pesakit HTG menunjukkan kemungkinan ICP memainkan peranan dalam perkembangan glaukoma. Kajian lanjut perlu dijalankan bagi menyiasat kesan ICP terhadap perkembangan glaukoma dan juga pengurusan bagi rawatan penyakit tersebut.

Kata kunci: *Glaukoma; glaukoma sudut terbuka primer; perbezaan tekanan translamina; tekanan bola mata; tekanan cecair serebrospinal; tekanan intrakranium*

Correspondence: Jemaima Che-Hamzah. Department of Ophthalmology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia. Tel: +603-91455984 E-mail: jemaima@hctm.ukm.edu.my

ABSTRACT

This study aims to investigate and compare the relationship between intracranial pressure (ICP), intraocular pressure (IOP) and translaminar pressure difference (TLPD) in high-tension glaucoma (HTG) patients and healthy individuals. Newly diagnosed HTG patients and healthy subjects without ocular comorbidities were recruited. All participants underwent blood pressure, heart rate, body weight, height and comprehensive ocular examinations, including best-corrected visual acuity, IOP measurement, optic nerve head assessment, peripapillary retinal nerve fibre layer and macular imaging, visual field testing, axial length and central corneal thickness measurements. ICP was estimated using the formula: Cerebrospinal fluid pressure (mmHg) = (0.44 x Body Mass Index (kg/m^2)) + (0.16 x Diastolic Blood Pressure (mmHg))-(0.18 x Age (years)) - 1.91. TLPD was calculated by subtracting the estimated ICP from the IOP. Compared to healthy subjects, HTG patients had significantly higher median IOP [26.00 (24.00-34.00) mmHg vs. 13.00 (10.00-14.00) mmHg], lower median ICP [8.19 (6.86-10.28) mmHg vs. 11.31 (8.91-12.36) mmHg], and higher median TLPD [18.64 (15.27-26.19) mmHg vs. 1.72 (0.27-4.62) mmHg]. There was no correlation between IOP and ICP; however, IOP was significantly correlated with TLPD in both groups, HTG ($r = 0.911$, $p < 0.001$) and non-glaucomatous ($r = 0.758$, $p < 0.001$). In healthy subjects, TLPD was moderately and negatively correlated with ICP ($r = -0.525$, $p = 0.012$). The lower ICP observed in HTG patients suggests that ICP may be associated with the development of glaucoma. Further research is needed to explore the impact of ICP on glaucoma progression and disease management.

Keywords: Cerebrospinal fluid pressure; glaucoma; intracranial pressure; intraocular pressure; primary open angle glaucoma, translaminar pressure difference

INTRODUCTION

Glaucoma is a progressive optic neuropathy characterised by distinctive cupping of the optic disc due to degeneration of the retinal nerve fiber layer (RNFL) and corresponding visual field defects. It is a leading cause of irreversible blindness worldwide (Quigley & Broman 2006). The most common type of glaucoma is primary open-angle glaucoma (POAG), which is defined by chronic, progressive glaucomatous optic neuropathy in the presence of an open, normal-appearing anterior chamber angle and the absence of other underlying ocular conditions. POAG encompasses two subtypes with overlapping features: normal-tension glaucoma (NTG), where optic nerve damage occurs within the normal intraocular pressure (IOP) range, and high-tension glaucoma (HTG), where optic nerve damage is associated with elevated IOP exceeding the normal range (Pruzan & Myers 2015).

Multiple risk factors may be involved in the optic nerve head damage in glaucoma including advancing age, family history of glaucoma, myopia, African ancestry and thin central cornea (Weinreb & Tee Khaw 2004). However, the only modifiable risk factor is IOP and increased IOP is highly associated with the development of POAG (Leske et al. 2003). However, there are IOP-independent risk factors which may induce POAG by triggering the apoptotic process of the retinal ganglion cells such as abnormality in peripheral vascular regulation, hypotension, mechanical factors like lamina cribrosa (LC) defects and weakness, as well as increased sensitivity of the optic nerve to normal IOP (Flammer et al. 1999; Turgut & Turgut 2017). Most recently, researchers suggested that intracranial pressure (ICP) might have a big role in the glaucoma development (Jonas 2011; Ren et al. 2010).

Thus, we embarked on a research to investigate the relationship between ICP, IOP and translaminar pressure difference (TLPD) in HTG patients and healthy individuals. We also studied the correlations between IOP, ICP and TLPD, as well as ocular and systemic parameters in HTG patients. Lumbar puncture (LP) is the gold standard for measuring cerebrospinal fluid (CSF)

pressure but it is an invasive procedure. Hence, we used a formula to estimate the ICP in our study subjects (Jonas et al. 2015). This formula had been validated in Asian population.

MATERIALS AND METHODS

This comparative cross-sectional study enrolled consecutive patients who were newly diagnosed as HTG with IOP more than 21 mmHg when they were presented to the Ophthalmology outpatient clinic, Hospital Canselor Tuanku Muhriz (HCTM) from 1st November 2018 to 31st December 2020. Ethical approval was obtained from the Universiti Kebangsaan Malaysia Research and Ethics Committee (JEP-UKM-2019-097). The study was conducted in accordance with the Malaysian Guidelines for Good Clinical Practice (GCP) and Declaration of Helsinki. All participants provided written informed consent prior to enrollment in the study.

Eligible participants were 18 years of age or older and able to independently sign the informed consent form. Patients with newly diagnosed HTG were recruited. Exclusion criteria such as orbital or ocular trauma history, recent cataract surgery within 6 months, previous ocular surgery such as vitreoretinal surgery, corneal transplantation, glaucoma surgery and phakic intraocular lens (IOL) implantation. Patients with active ocular infection, inflammatory disease or any other ocular diseases that might interfere with IOP measurements were excluded as well. Patients with history of neurological diseases which affected the ICP estimation such as space occupying lesions, meningoencephalitis or seizures were also excluded. For the non-glaucomatous group, subjects were age-matched and gender-matched to the patients in the HTG group. Subjects were healthy individuals without ocular comorbidities, aged 18 and above, and able to sign informed consent. Exclusion criteria included subjects with evidence of glaucoma or glaucoma suspects which was defined as suspicious optic discs, a cup-to-disc ratio larger than 0.7, asymmetric cupping of 0.2 or greater, and/ or IOP of 22 mmHg or more.

At study visit, medical and ocular histories were collected and measurements of weight, height, blood pressure (BP), heart rate (HR) and body mass index (BMI) were performed by the investigator (C.T.C). All participants underwent a comprehensive ophthalmic examination including the following assessments: best-corrected visual acuity (BCVA) measured using a Snellen chart, anterior segment examination via slit lamp biomicroscopy (Slit lamp BP 900, Haag-Streit, Koniz, Switzerland), IOP measurement using Goldmann applanation tonometry (GAT), anterior chamber angle evaluation using Goldmann 2-mirror gonio lens (Volk, OH, USA) and dilated fundus and optic nerve evaluation using 78D and 90 D (Volk, OH, USA). Additionally, participants underwent the following diagnostis tests: central corneal thickness (CCT) measurements using spectral domain optical coherence tomography (SD-OCT, Spectralis, Heidelberg, California, USA), visual fields testing with a Humphrey Field analyser (HFA) using 24-2 Sita-Standard strategy (Carl Zeiss, San Diego, USA), peripapillary and macular retinal nerve fibre layer evaluation using SD-OCT and axial length measurement (IOL Master 700, Carl Zeiss, San Diego, USA). For BCVA, Snellen fractions were converted into logMAR equivalents.

All IOP measurements were conducted by a team of two investigators (an operator and a reader). The operator managed the slit lamp, tonometer and the instrument dial, while the reader was responsible for reading and recording the results. The average IOP value was calculated from two readings. If the two measurements differed by more than 2 mmHg, an additional reading was obtained. If both eyes met the eligibility criteria, the right eye was chosen for the study.

Subsequently, ICP was calculated using a formula suggested by Jonas et. al. (2015). The formula was derived using a multivariate analysis of CSF pressure obtained from LP as a dependent variable and BMI, age and diastolic blood pressure (DBP) as independent variables. CSF pressure (mmHg) = [0.44 x BMI (kg/m2)] + [0.16 x DBP (mmHg)] - [0.18 x Age (Years)] - 1.91.

The measured CSF pressure obtained from the LP was found to be not significantly differed from the calculated CSF pressure from the formula (Jonas et al. 2014a). This formula was chosen to estimate ICP of the study subjects instead of performing LP which is an invasive procedure although it is the gold standard measurement of ICP. TLPD was obtained by subtracting ICP from IOP (TLPD = IOP - ICP).

Sample size was calculated using Power and Sample Size Calculation software version 3.0, January 2009 (Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, TN, USA). The study had 80% power to detect a difference in ICP of 3.1 mmHg assuming two-sided tests to control the overall significance level at 5% with the sample size of 22 patients per group. Therefore, the total number of subjects needed for this study was 44 subjects which consisted of 22 patients in the HTG group and 22 patients in the non-glaucomatous group.

Data was analysed with Statistical Package for Social Science (SPSS) Version 22.0 (SPSS Inc., Chicago, IL, USA) for Windows. Kolmogorov-Smirnov test was done to test normality and we found that the data was not normally distributed. Descriptive statistics were employed for demographic data and clinical characteristics. Categorical data were expressed as frequencies and percentages, whereas continuous data was presented as median and interquartile range. As the demographic data was normally distributed, the relationship between continuous data between both groups was analysed using independent t-test such as age. Meanwhile, categorical data such as gender and race were calculated using Chi-square. Comparisons of ICP, IOP and TLPD in both HTG group and normal group were analysed using Mann-Whitney U test. Spearman's correlation was used to assess the relationship between IOP, ICP and TLPD with systemic and ocular parameters in both groups. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The study recruited a total of 44 participants, comprising 22 patients with HTG and 22 healthy controls. The overall mean age was 67.27 $\pm$ 8.75 years, with the HTG group having a mean age of 68.23 $\pm$ 9.63 years and the non-glaucomatous group having a mean age of 66.32 $\pm$ 7.88 years. The majority of participants in both groups were male. The HTG group had a higher proportion of individuals of Chinese ethnicity compared to the non-glaucomatous group, which had a higher proportion of Malay participants. Demographic data were presented in Table 1. Statistical analysis revealed no significant differences in gender, age

TABLE 1: Demographic data for the study population

	Total subjects	HTG subjects	Healthy subjects	p-value
Number of patients	44	22	22	
Mean age, years (SD)	67.27 (8.75)	68.23 (9.63)	66.32 (7.88)	0.476*
Range	51-89	54-89	51-83	
Gender (%)				
Male	27 (61.36%)	14 (63.64%)	13 (59.09%)	0.757**
Female	17 (38.64%)	8 (36.36%)	9 (40.91%)	
Race (%)				
Malay	23 (52.28%)	10 (45.45%)	13 (59.09%)	0.295**
Chinese	19 (43.18%)	12 (54.55%)	7 (31.81%)	
Indian	1 (2.27%)	0 (0%)	1 (4.55%)	
Others	1 (2.27%)	0 (0%)	1 (4.55%)	

HTG: High tension glaucoma; SD: Standard deviation
*Independent T-test; **Chi-square test

TABLE 2: Characteristics complarison between high tension glaucoma (HTG) and healthy subjects

Characteristics	HTG subjects Median (IQR) (n = 22)	Healthy subjects Median (IQR) (n = 22)	p-value
Systolic blood pressure (mmHg)	140.00 (128.00-163.75)	149.50 (135.00-160.25)	0.250
Diastolic blood pressure (mmHg)	74.50 (65.00-79.50)	82.00 (77.50-88.50)	0.002
Heart Rate (bpm)	69.00 (57.25-75.75)	62.50 (59.00-70.00)	0.860
Weight (kg)	60.17 (51.33-73.38)	64.40 (58.64-75.99)	0.127
Height (m)	1.58 (1.53-1.65)	1.59 (1.57-1.62)	0.605
Body mass index (kg/m^2)	23.20 (20.88-27.12)	25.74 (23.94-28.79)	0.064
Best corrected visual acuity (LogMAR)	0.18 (0.18-0.48)	0.18 (0.00-0.18)	0.001
Intraocular pressure (mmHg)	26.00 (24.00- 34.00)	13.00 (10.00-14.00)	<0.001
Vertical cup:Disc ratio	0.80 (0.70-0.90)	0.35 (0.30-0.40)	<0.001
Central corneal thickness (µm)	524.50 (507.75-557.00)	534.50 (508.25-557.25)	0.751
Axial length (mm)	24.32 (23.10-25.38)	23.90 (22.98-24.48)	0.181
Peripapillary Retinal Nerve Fibre Layer (pRNFL)			
Global RNFL thickness (µm)	57.00 (40.75-80.25)	101.00 (95.50-106.00)	<0.001
Nasal RNFL thickness (µm)	46.50 (21.75-60.00)	72.00 (59.00-79.50)	<0.001
Temporal RNFL thickness (µm)	61.50 (44.75-75.50)	72.50 (68.75-81.00)	0.008
Superonasal RNFL thickness (µm)	56.50 (38.75-92.00)	105.50 (95.50-123.00)	<0.001
Superotemporal RNFL thickness (µm)	84.00 (49.50-116.00)	140.50 (129.75-149.00)	<0.001
Inferonasal RNFL thickness (µm)	60.50 (29.75-81.00)	116.00 (107.25-131.00)	<0.001
Inferotemporal RNFL thickness (µm)	61.50 (49.50-103.00)	147.00 (138.50-159.00)	<0.001
Macular Thickness (MT)			
Central MT (µm)	266.50 (248.50-288.50)	258.50 (249.75-277.75)	0.833
Nasal MT (µm)	325.00 (293.75-332.00)	333.50 (317.00-347.25)	0.039
Temporal MT (µm)	307.50(274.00-316.50)	319.50 (307.75-333.00)	0.003
Superior MT (µm)	319.00 (282.50-330.50)	329.50 (322.75-339.25)	0.030
Inferior MT (µm)	308.50 (275.50-320.75)	325.00 (308.00-340.75)	0.007
Humphrey visual field parameter			
Median deviation (MD)	-15.28 (-29.14- -6.47)	-2.17 (-4.12- -1.58)	<0.001
Pattern standard deviation (PSD)	6.13 (3.50-8.87)	2.08 (1.70-2.75)	<0.001

HTG: High tension glaucoma; IQR: Interquartile range
Mann-Whitney test. Significant p-value <0.05.

or ethnicity between the two groups ($p > 0.05$).

Table 2 summarised the characteristics of the study participants and comparison between both the HTG and non-glaucomatous groups. DBP was lower in the HTG subjects [(74.50 (65.00-79.50) mmHg)] compared to healthy subjects [(82.00 (77.50-88.50) mmHg)] in our study ($p = 0.002$). There were no significant differences in the systolic blood pressure (SBP), HR, body weight, BMI and height between both groups ($p > 0.05$).

Subjects with HTG were found to have poorer vision ($p = 0.001$), increased cup: disc ratio ($p < 0.001$) and higher IOP ($p < 0.001$) than

the healthy subjects. Some of the HTG patients presented late with poorer vision with a range of 0.18 to 1.00 in logMAR. However, there were no statistically significant differences in central cornea thickness (p = 0.751) and axial length (p = 0.181) among both groups. All peripapillary retinal nerve fibre layer (pRNFL) including global, nasal, temporal, superonasal, superotemporal, inferonasal and inferotemporal RNFL thickness were significantly lower in HTG compared to healthy subjects (p < 0.05). Macular thickness including nasal (p = 0.039), temporal (p = 0.003), superior (p = 0.030), inferior macula (p = 0.007) thickness were also lower in HTG compared to healthy subjects.

As shown in Table 3, IOP was significantly higher in HTG [26.00 (24.00-34.00) mmHg] compared to the non-glaucomatous group [13.00 (10.00-14.00) mmHg] with p < 0.001. On the other hand, ICP was found to be significantly lower (p = 0.001) in HTG [8.19 (6.86-10.28) mmHg] than in the non-glaucomatous group [11.31 (8.91-12.36) mmHg]. Therefore, the HTG group had a higher median TLPD [18.64 (15.27-26.19) mmHg] in comparison to the non-glaucomatous group [1.72 (0.27-4.62) mmHg] with p-value less than 0.001.

TABLE 3: Measurements of intraocular pressure (IOP), intracranial pressure (ICP) and translaminar pressure difference (TLPD) in high tension glaucoma (HTG) and healthy subjects

Variables	HTG subjects (n = 22)	Healthy subjects (n = 22)	p-value
IOP (mmHg) Median (IQR)	26.00 (24.00-34.00)	13.00 (10.00-14.00)	<0.001
ICP (mmHg) Median (IQR)	8.19 (6.86-10.28)	11.31 (8.91-12.36)	0.001
TLPD (mmHg) Median (IQR)	18.64 (15.27-26.19)	1.72 (0.27-4.62)	<0.001

HTG: High tension glaucoma; IQR: Interquartile range; IOP: Intraocular pressure; ICP: Intracranial pressure; TLPD: Translaminar pressure difference
Mann-Whitney test. Significant p-value <0.05.

Spearman's correlation was done. There was no correlation between IOP and ICP in both HTG and non-glaucomatous groups with p-value of 0.634 and 0.698 respectively as shown in Figure 1(a) and Figure 1(b). On the other hand, TLPD was found to be strongly positive correlated with IOP in HTG (r = 0.911, p < 0.001) and non-glaucomatous group (r = 0.758, p < 0.001) as shown in Figure 1(c) and Figure 1(d), respectively. Correlation between TLPD and ICP among HTG subjects did not reach a significant level (r = -0.225, p = 0.313) as shown in Figure 1(e). However, TLPD was moderately negatively correlated with ICP in healthy subjects (r = -0.525, p = 0.012) as shown in Figure 1(f).

The correlations of ocular and systemic parameters with IOP, ICP and TLPD in both groups were further investigated. The results were summarised in Table 4. IOP was negatively correlated with age (r = -0.504, p = 0.017) and BMI (r = -0.492, p = 0.020) in HTG subjects. No factors were observed to be correlated with IOP in healthy subjects.

The analysis revealed several interesting correlations between ICP and various factors in both the HTG and non-glaucomatous groups. In both groups, ICP was negatively correlated with age and BCVA (HTG: r = -0.535, p = 0.010; r = 0.437, p = 0.042, respectively; non-glaucomatous: r = -0.717, p < 0.001; r=-0.477, p = 0.025, respectively). Conversely, ICP showed a positive correlation with body weight in both the HTG (r = 0.465, p = 0.029) and non-glaucomatous (r = 0.488, p = 0.021) groups.

In the non-glaucomatous group, there were additional positive correlations between ICP

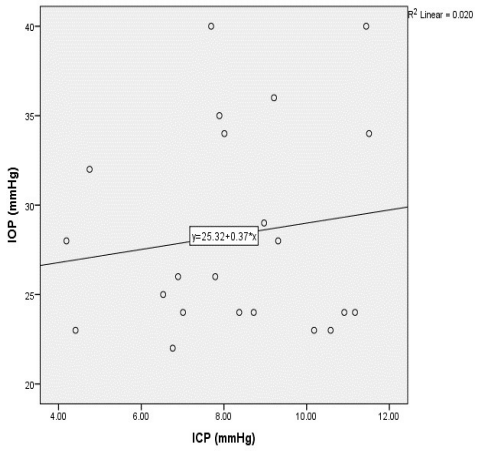

FIGURE 1(a): Scatter plot showed distributions of intraocular pressure (IOP) and intracranial pressure (ICP) in patients with high tension glaucoma (HTG). There was no significant correlation (r = 0.108, p = 0.634).

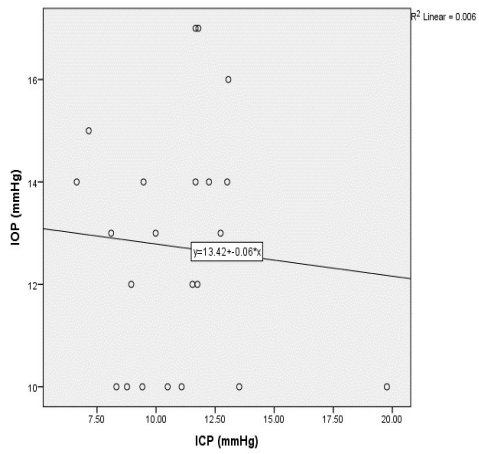

FIGURE 1(b): Scatter plot showed distributions of intraocular pressure (IOP) and intracranial pressure (ICP) in healthy subjects. There was no significant correlation (r = 0.088, p = 0.698).

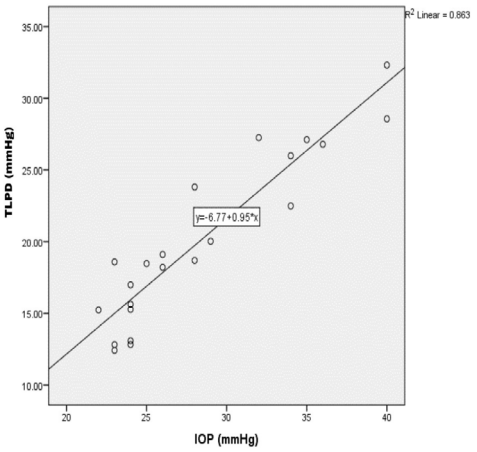

FIGURE 1(c): Scatter plot showed distributions of translaminar pressure difference (TLPD) and intraocular pressure (IOP) in patients with high tension glaucoma (HTG). There was a significantly positive correlation (r = 0.911, p < 0.001).

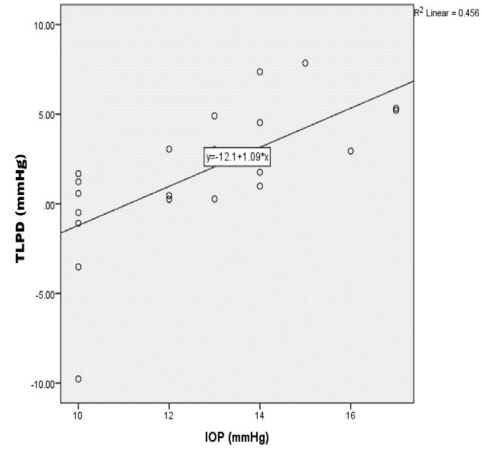

FIGURE 1(d): Scatter plot showed distributions of translaminar pressure difference (TLPD) and intraocular pressure (IOP) in healthy subjects. There was a significantly positive correlation (r = 0.758, p < 0.001).

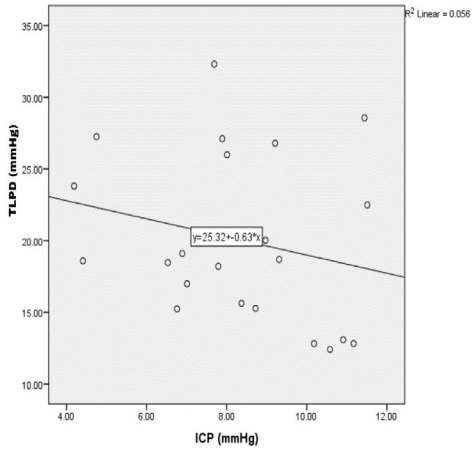

FIGURE 1(e): Scatter plot showed distributions of translaminar pressure difference (TLPD) and intracranial pressure (ICP) in patients with high tension glaucoma (HTG). There was no significant correlation (r = -0.225, p=0.313)

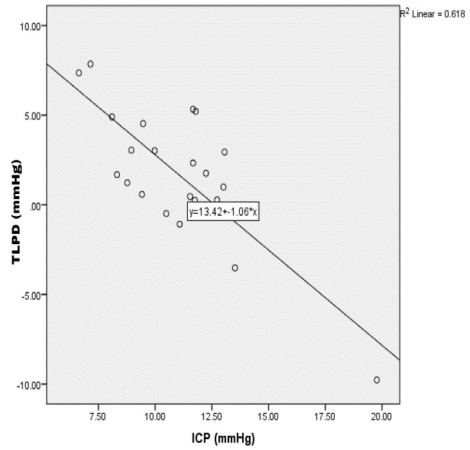

FIGURE 1(f): Scatter plot showed distributions of translaminar pressure difference (TLPD) and intracranial pressure (ICP) in healthy subjects. There was a significantly negative correlation (r = -0.525, p = 0.012)

and DBP (r = 0.542, p = .009), BMI (r = 0.668, p = 0.001), and inferotemporal RNFL thickness (r = 0.567, p = 0.006). Notably, the correlation between ICP and inferotemporal RNFL thickness remained significant even after Bonferroni correction. However, a negative correlation was found between ICP and BCVA (r = -0.477, p = 0.025) in this group. Interestingly, no such correlations were observed between ICP and the aforementioned factors in the HTG group.

In glaucoma patients, TLPD was observed to be negatively correlated to body weight (r= -0.446, p = 0.038), BMI (r = -0.601, p = 0.003) and axial length (r = -0.453, p = 0.034). In healthy subjects, DBP and inferotemporal RNFL thickness was found to be significantly negative correlated with TLPD (r = -0.471, p = 0.027 and r = -0.452, p = 0.035, respectively).

DISCUSSION

The current research has demonstrated that in patients with HTG, IOP is the only modifiable risk factor. However, ICP may also play a significant role in the development and progression of POAG from ocular hypertension (OHT) (Berdahl et al. 2008b). Our study findings indicate that HTG subjects exhibit statistically higher IOP, lower ICP, and greater TLPD compared to healthy controls. Interestingly, there was no correlation observed between IOP and ICP, but TLPD was found to be strongly and positively correlated with IOP in both the patient and control groups.

Several studies have also shown that ICP was significantly lower in patients with HTG and NTG as compare with the normal population (Berdahl et al. 2008a; Berdahl et al. 2008b; Ren et al. 2010; Siaudvytyte et al. 2014). A retrospective study by Berdahl et al. (2008a)comparing ICP in subjects with HTG, NTG, and OHT with age-matched control subjects found that ICP was lower in HTG and NTG but was elevated in OHT. On the other hand, ICP was reported to be higher in patients with OHT which was thought to be a protective mechanism in glaucoma progression (Berdahl et al. 2008a; Berdahl et al. 2008b). Ren et al. (2010) showed that TLPD was significantly higher in HTG and NTG compared to a non-glaucomatous group. They also found that the non-glaucomatous subjects have a higher CSF pressure compared to those with glaucoma. The lower the ICP or the higher the TLPD, the

TABLE 4: Correlations between intraocular pressure (IOP), intracranial pressure (ICP), translaminar pressure difference (TLPD) and other study parameters in high tension glaucoma (HTG) and healthy subjects

Characteristics	IOP				ICP				TLPG			
	HTG subjects (n = 22)		Healthy subjects (n = 22)		HTG subjects (n = 22)		Healthy subjects (n = 22)		HTG subjects (n = 22)		Healthy subjects (n = 22)	
	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value	r	p-value
Age	-0.504	0.017	-0.041	0.857	-0.535	0.010	-0.717	<0.001	-0.258	0.247	0.406	0.061
Systolic blood pressure	-0.044	0.847	-0.094	0.678	-0.010	0.964	-0.045	0.843	0.075	0.740	-0.043	0.850
Diastolic blood pressure	0.316	0.152	-0.268	0.228	0.204	0.362	0.437	0.042	0.306	0.166	-0.471	0.027
Heart rate	0.116	0.607	-0.311	0.159	0.361	0.098	-0.040	0.859	-0.048	0.832	-0.226	0.313
Weight	-0.236	0.291	0.113	0.617	0.465	0.029	0.488	0.021	-0.446	0.038	-0.181	0.419
Height	0.243	0.277	0.265	0.234	0.313	0.155	0.195	0.385	0.029	0.899	0.078	0.729
Body mass index	-0.492	0.020	0.081	0.720	0.300	0.175	0.463	0.030	-0.601	0.003	-0.174	0.437
Best corrected visual acuity	-0.419	0.052	-0.346	0.115	-0.437	0.042	-0.477	0.025	-0.189	0.399	0.029	0.897
Vertical cup:Disc ratio	-0.090	0.692	0.079	0.725	-0.211	0.347	0.034	0.879	0.035	0.878	0.033	0.885
Central corneal thickness	0.182	0.418	-0.156	0.487	0.226	0.312	0.386	0.076	0.079	0.728	-0.342	0.119
Axial length	-0.357	0.103	-0.178	0.429	0.039	0.863	0.013	0.954	-0.453	0.034	-0.211	-0.347
Global RNFL thickness	-0.151	0.503	-0.226	0.313	0.293	0.186	0.242	0.277	-0.276	0.214	-0.328	0.137
Nasal RNFL thickness	-0.173	0.440	-0.220	0.325	0.176	0.432	0.198	0.376	-0.248	0.266	-0.285	0.198
Temporal RNFL thickness	-0.172	0.444	-0.176	0.434	0.191	0.393	0.220	0.325	-0.268	0.227	-0.284	0.201
Superonasal RNFL thickness	0.023	0.920	-0.260	0.243	0.326	0.139	-0.059	0.795	-0.169	0.453	-0.134	0.551
Superotemporal RNFL thickness	-0.154	0.494	0.105	0.642	0.356	0.104	0.175	0.436	-0.272	0.220	-0.021	0.926
Inferonasal RNFL thickness	0.009	0.968	-0.261	0.241	0.222	0.320	-0.020	0.931	-0.079	0.726	-0.164	0.465
Inferotemporal RNFL thickness	-0.085	0.707	-0.064	0.776	0.115	0.610	0.567	0.006	-0.147	0.513	-0.452	0.035
Central macular thickness	-0.321	0.146	-0.496	0.061	-0.072	0.751	-0.227	0.309	-0.279	0.208	-0.164	0.465

Continued...

...continuing

Nasal macular thickness	-0.248	0.266	-0.250	0.262	-0.143	0.527	0.106	0.639	-0.283	0.201	-0.204	0.364
Temporal macular thickness	-0.241	0.281	-0.244	0.274	-0.112	0.618	0.200	0.372	-0.237	0.288	-0.337	0.125
Superior macular thickness	-0.275	0.216	-0.129	0.568	-0.001	0.998	0.333	0.130	-0.314	0.155	-0.273	0.219
Inferior macular thickness	-0.069	0.761	-0.191	0.395	-0.144	0.523	0.256	0.250	-0.086	0.702	-0.276	0.213
Mean deviation	0.102	0.650	0.036	0.874	0.231	0.301	0.347	0.113	-0.090	0.691	-0.163	0.468
Pattern standard deviation	0.084	0.709	0.281	0.205	0.228	0.308	-0.028	0.901	-0.037	0.871	0.184	0.414

HTG: High tension glaucoma; r: Correlation coefficient; RNFL: Retinal nerve fibre layer; IOP: Intraocular pressure; ICP: Intracranial pressure; TLPG: Translaminar pressure gradient
Spearman's correlation. Significant p-value <0.05.

more likely it is for an individual to develop into glaucoma (Ren et al. 2010). These results were similar to our study.

The LC, which is a mesh-like structure of the sclera, allows axons of the retinal ganglion cells to emerge out as the optic nerve. It is bathed by CSF which occupies the subarachnoid space, generating a retrobulbar pressure which is believed to be equivalent to ICP (Morgan et al. 1995). The LC deforms posteriorly and appears as optic disc cupping in glaucoma. If it deforms anteriorly, it appears as optic disc swelling in conditions like papilloedema, ocular hypotony and pseudotumour cerebri. All these diseases will lead to damage of the retinal nerve fibres (Morgan et al. 1995). This suggests that the LC is a vulnerable structure influenced by IOP and retrolaminar CSF pressure.

LC experiences two distinct pressure components: a higher IOP anteriorly and a lower ICP posteriorly (Morgan et al. 1995; Morgan et al. 1998; Morgan et al. 2008). Any imbalance between the IOP and ICP may contribute to the development of POAG (Fleischman et al. 2014). The discrepancy between the posterior-acting IOP and the anterior-acting ICP at the level of the LC creates a TLPD. Thus, the translaminar pressure gradient (TLPG) can be defined as the difference of IOP and ICP per unit thickness of LC [IOP-ICP/thickness of LC] (Berdahl et al. 2008a). An increased TLPG can lead to significant pathological deformities of the LC and impede the retrograde axonal transport, ultimately resulting in apoptosis of the retinal ganglion cells (Siaudvytyte et al. 2014; Siaudvytyte et al. 2015). TLPG is also affected by thickness of LC (Jonas et al. 2004).

The study by Fleischmann & Berdahl (2014) proposed that a net balancing force, arising from the difference between IOP and ICP, determines the TLPD. Therefore, the effect of ICP reduction is similar to IOP elevation in development of glaucoma (Fleischman & Berdahl 2014). Consequently, the researchers found that reducing ICP has a similar effect to increasing IOP in the development of glaucoma (Roy Chowdhury & Fautsch 2015; Yang et al. 2014).

One of the studies lowered the CSF in monkeys via shunt surgeries and found that 50% of the experimental monkeys developed glaucoma-like pathology after the procedure (Yang et al. 2014). Besides that, it has been reported that a patient with underlying NTG developed severe glaucoma progression after a ventriculoperitoneal shunt which demonstrated that ICP can cause development of glaucoma (Chen et al. 2016). A review article by Price et al. (2020) noting that ICP is linked to glaucoma which ICP closely correlates with retrolaminar tissue pressure. They also found that this relationship is affected by the size of optic canal, thickness of LC and lymphatic outflow from the optic nerve (Price et al. 2020).

Several studies have explored the potential relationship between IOP and ICP. While some researchers have reported a correlation between the two variables (Lashutka et al. 2004; Li et al. 2012), the majority of studies have found no such association (Czarnik et al. 2009; Han et al. 2008; Kirk et al. 2011). Importantly, these latter investigations were all conducted in subjects who underwent medically indicated lumbar puncture (LP). Similarly, our own study population did not exhibit a correlation between ICP and IOP. Furthermore, Hou et. al. (2016) performed an animal study on dogs to further investigate the potential relationship between these two pressure measurements. The ICP of the dogs was lowered by performing shunt surgery. The authors identified three key features in the relationship between ICP and IOP. First, there is an ICP-IOP dependent zone, where IOP decreases linearly with decreasing ICP. However, once ICP falls below a breakpoint of approximately 70.5 mmH_2O, IOP remains static and independent of further ICP changes. (Hou et al. 2016). This ICP-IOP independent zone explains why a normal IOP can still be harmful to the optic nerve head when ICP is abnormally low, as seen in NTG (Berdahl et al. 2008b; Ren et al. 2010; Siaudvytyte et al. 2014).

Our study also found that TLPD was correlated with IOP in both groups and ICP only in healthy subjects. There was no correlation between ICP and TLPD in the HTG group. It is postulated that TLPD in patients with HTG remains stable in ICP-IOP dependent zone because IOP decreases together with the reduction of ICP. However, when ICP falls below breaking point, IOP will not decrease further causing TLPG to increase. A raised TLPD will then lead to retinal ganglion cell axons damage which manifest as glaucoma (Hou et al. 2016; Zhang et al. 2016).

In terms of systemic factors, we found that IOP was negatively correlated with age and BMI in HTG subjects. A previous study found that IOP increases with age until the age of 60 years old. However, after 60, IOP will drop resulting in an inverted U pattern (Wong et al. 2009). This is consistent with our study as the mean age for our study population was 68 years old. Obesity was an independent risk factor of raised IOP in a few studies (Cohen et al. 2016; Kumar et al. 2019). Meanwhile, another study found that there was no correlation between BMI and IOP (Albuquerque et al. 2013). These findings were conflicting with our findings and need further investigations.

Previous studies have shown that higher CSF pressure was related with younger age, higher BMI and hypertension (Berdahl et al. 2008b; Ren et al. 2010). Our study has also found age and weight to have correlation with ICP in both HTG and non-glaucomatous groups. For our study, ICP was derived from a formula developed by Jonas et al. (2014b). This formula was shown to be correlated with CSF pressure obtained from LP in which it reduces by 0.69 mmHg per decade (Pedersen et al. 2018). The reduction of ICP with age also coincides with the increased prevalence of glaucoma in elderly (Fleischman et al. 2012). This could possibly mean that apart from age-related structural changes in the trabecular meshwork which induce raised IOP, ICP may affect the development of POAG in elderly patients (Han et al. 2016). In fact, many studies have shown that lower ICP will lead to structural damage to the RNFL due to raised TLPD (Berdahl & Allingham 2009; Ren et al. 2010; Siaudvytyte et al. 2014). On the other hand, obesity is a crucial risk factor of idiopathic intracranial hypertension (Pedersen et al. 2018; Subramaniam & Fletcher 2017). Obese

patients tend to have a higher ICP, thus posing a possibility that obesity could potentially be a protective factor over development of glaucoma. Conflictingly, patients with obesity also tend to have higher IOP which will lead to glaucomatous optic neuropathy too (Lam et al. 2017). The relationship of obesity, IOP and ICP need to be further investigated with a larger sample size and longer duration study. Besides that, BMI and DBP were noticed to be correlated with ICP only in the non-glaucomatous group but not in the HTG group. This may be also due to the small sample size which fails to show a correlation between these factors in patients with HTG.

For factors affecting TLPD, three factors were found to be negatively correlated with TLPD in HTG subjects which were body weight, BMI and axial length. Surprisingly, our study found that TLPD was lower in patients with longer axial length. We postulated the long eyeball may affect the structure and function of the LC which is vulnerable to any changes of pressure anterior and posterior to it. Further studies shuold investigate factors affecting TLPD which may be helpful in managing glaucoma in the future.

In this study, we found that IOP, ICP and TLPD in HTG subjects have no correlation with ocular parameters such as vertical cup to disc ratio, RNFL thickness, macula thickness and Humphrey Visual Field (HVF) parameters which is similar to a previous study (Berdahl et al. 2008b). Severity and progression of the glaucoma is not dependant only on the measurement of IOP and ICP but also to other factors including duration of the disease, unmodifiable risk factors e.g. age and race, central cornea thickness, presence of pseudoexfoliation and disc haemorrhage (Leske et al. 2007).

Interestingly, inferotemporal RNFL thickness was demonstrated to be positively correlated with ICP in our healthy subjects. This could be explained by the possibility of having patients with pre-perimetric NTG among the healthy subjects in which they have normal IOP, optic disc appearance and HVF findings with a lower ICP compared to the other healthy subjects. Inferotemporal RNFL thickness is usually affected first in glaucoma due to the anatomical location of the RNFL (Chen et al. 2018). The most peripheral part of the RNFL lies deep in the retina and any changes of pressure gradient over the LC will cause early damage compared to other parts of the RNFL. These findings further emphasise the protective effects of having higher ICP and lower TLPD in individuals with normal IOP from developing glaucoma.

Our study has a few strong points compared to the previous studies. To our knowledge, our study has a fairly large population compared to the previous study (Ren et al. 2010). Siaudvytyte et al. (2014) had a study sample of only 9 subjects in each arm. Our sample size was similar to Ren et al. (2010) who used LP to measure the ICP. In addition, HTG subjects recruited in our study were newly diagnosed without administration of any anti-glaucoma medications. Studies in the past did not exclude patients who were on topical or systemic anti-glaucoma (Berdahl & Allingham 2010; Ren et al. 2010; Siaudvytyte et al. 2014). The IOP lowering drugs would have masked the real TLPD and also potentially affect the ICP estimation. Nevertheless, our study has similar results as ICP was found to be lower among patients with glaucoma. This could suggest that inclusion of patients who are on antiglaucoma medications might not affect the estimated ICP.

The estimated ICP was calculated from a formula by Jonas et al. (2014b) which consisted of BMI, DBP and age. This formula was also used by several studies to estimate indirect measurement of CSF pressure (Xie et al. 2013; Jonas et al. 2014a; Jonas et al. 2014c). By using this formula, our patients did not need to undergo LP which is an invasive procedure although it is currently the gold standard of CSF pressure measurement. The estimated ICP level was slightly lower in both glaucoma and healthy subjects (8.29 mmHg; 10.96 mmHg, respectively) compared to Berdahl et al. (2008a) (9.6 mmHg; 12.7 mmHg) and Ren et al. (2010)(11.7 mmHg; 12.9 mHg) using LP (Marek et al. 2014). The difference of ICP could also be due to difference in ethnicity of study population as this formula was derived from Chinese population compared to our study

population which consisted of three races (Malay, Chinese and Indian). Besides that, calculated ICP based on a formula which involves BMI and DBP might not be ideal as both parameters could contribute to a significant correlation.

Furthermore, "snapshot" measurement of IOP and blood pressure may not represent the real long term pressure variations. Both parameters fluctuate throughout the day and have their own diurnal variations. However, both measurements were done at sitting position which may eliminate the postural variations. CSF pressure taken from LP at left lateral decubitus position might not reflect the true CSF pressure over the optic nerve in the orbit as the IOP was taken at sitting position (Ren et al. 2010). Positional changes may affect the retrolaminar CSF pressure which subsequently affect the TLPD. In addition, both parameters were taken at the same time to avoid the circadian variation which could potentially affect the result of the study.

Another limitation is that we did not take the thickness of LC into consideration. Theoretically, a thicker LC is able to withstand a higher TLPD because of its integrity and resilience in maintaining its shape to protect the axons of retinal ganglion cells (Guidoboni et al. 2014; Marek et al. 2014). The sample size was small and skewed in the HTG population leading to non-parametric analysis. There was also a time constraint in carrying out the study as it was done during the COVID-19 pandemic. Future cohort-designed studies with larger sample size may give better evidence of the relationship between ICP and IOP. A new non-invasive method of measuring the CSF indirectly such as transcranial doppler (TCD) ultrasound may give more insight about this relationship (Siaudvytyte et al. 2015).

One of the possible implications from this study is ICP can be a guide on management of OHT. Treatment could be initiated early if estimated ICP is lower than normal population to prevent development of glaucoma. Besides that, ICP can also be taken into consideration when physicians are deciding on the target IOP. A lower target IOP might be needed in patients with lower ICP to halt the progression of RNFL and visual field loss. Perhaps in the near future, ICP can be another modifiable risk factor in management of POAG other than IOP. Certain medications can be implemented to increase ICP of glaucoma patients within a safe limit in order to slow down the disease progression. However, it requires extensive studies to understand the role of ICP in management of glaucoma.

CONCLUSION

In conclusion, ICP is associated with glaucoma. This study demonstrates that subjects with HTG exhibit higher IOP, lower ICP and higher TLPD compared to normal subjects. While no direct relationship was observed between ICP and IOP, TLPD was found to be correlated with both IOP and ICP. These findings suggest the need for further investigation into the effects of ICP on the progression of glaucoma, which may inform improved management strategies for glaucoma patients.

Author contributions: Study conceive and design: TCC, SAS, JCH; Data collection: TCC; Data analysis and interpretation: TCC, SAS; Manuscript-original draf: TCC, RAN, JCH; All authors critically review and revised the manuscript for important intellectual content and approved the final version.

Conflict of interest: The authors declare no conflicts of interest.

Funding: This research received no external funding.

Acknowledgements: The authors thank Dr Loo Lean Cheong (Universiti Kebangsaan Malaysia) for assistance in revising and editing this paper.

Ethical statement: This study was conducted in accordance with the Declaration of Helsinki and was approved by Universiti Kebangsaan Malaysia Research and Ethics Committee (Approval No.: JEP-UKM-2019-097). Written informed consent was obtained from all participants.

REFERENCE

Albuquerque, L.L., Gaete, M.I., Figueiroa, J.N., Alves, J.G. 2013. The correlation between body mass index and intraocular pressure in children. *Arq Bras Oftalmol* **76**(1): 10-2. https://doi.org/10.1590/s0004-27492013000100004.

Berdahl, J.P., Allingham, R.R. 2009. Cerebrospinal fluid pressure may play a role in reversal of cupping after glaucoma surgery. *Am J Ophthalmol* **148**(4): 623-4. https://doi.org/10.1016/j.ajo.2009.06.002.

Berdahl, J.P., Allingham, R.R. 2010. Intracranial pressure and glaucoma. *Curr Opin Ophthalmol* **21**(2): 106-11. https://doi.org/10.1097/ICU.0b013e32833651d8.

Berdahl, J.P., Allingham, R.R., Johnson, D.H. 2008a. Cerebrospinal fluid pressure is decreased in primary open-angle glaucoma. *Ophthalmol* **115**(5): 763-8. https://doi.org/10.1016/j.ophtha.2008.01.013

Berdahl, J.P., Fautsch, M.P., Stinnett, S.S., Allingham, R. 2008b. Intracranial pressure in primary open angle glaucoma, normal tension glaucoma, and ocular hypertension: A case-control study. *Invest Ophthalmol Vis Sci* **49**(12), 5412-8. https://doi.org/10.1167/iovs.08-2228

Chen, B.H., Drucker, M.D., Louis, K.M., Richards, D.W. 2016. Progression of normal-tension glaucoma after ventriculoperitoneal shunt to decrease cerebrospinal fluid pressure. *J Glaucoma* **25**(1): e50-e52. https://doi.org/10.1097/IJG.0000000000000186.

Chen, C.Y., Huang, E.J.C., Kuo, C.N., Wu, P.L., Chen, C.L., Wu, P.C., Wu, S.H., King, Y.C., Lai, C.H. 2018. The relationship between age, axial length and retinal nerve fiber layer thickness in the normal elderly population in Taiwan: The chiayi eye study in Taiwan. *PLoS One* **13**(3): 1-13. https://doi.org/10.1371/journal.pone.0194116.

Cohen, E., Kramer, M., Shochat, T., Goldberg, E., Garty, M., Krause, I. 2016. Relationship between body mass index and intraocular pressure in men and women: A population-based study. *J Glaucoma* **25**(5): e509-13. https://doi.org/10.1097/IJG.0000000000000374

Czarnik, T., Gawda, R., Kolodziej, W., Latka, D., Sznajd-Weron, K., Weron, R. 2009. Associations between intracranial pressure, intraocular pressure and mean arterial pressure in patients with traumatic and non-traumatic brain injuries. *Injury* **40**(1): 33-9. https://doi.org/10.1016/j.injury.2008.10.010

Flammer, J., Haefliger, I.O., Orgül, S., Resink, T. 1999. Vascular dysregulation: A principal risk factor for glaucomatous damage? *J Glaucoma* **8**(3): 212-9.

Fleischman, D., Berdahl, J.P. 2014. Posterior scleral biomechanics and the translaminar pressure difference. *Int Ophthalmol Clin* **54**(1): 73-94. https://doi.org/10.1097/IIO.0b013e3182aabef4.

Fleischman, D., Berdahl, J.P., Zaydlarova, J., Stinnett, S., Fautsch, M.P., Allingham, R.R. 2012. Cerebrospinal fluid pressure decreases with older age. *PLoS One* **7**(12): 1-9. https://doi.org/10.1371/journal.pone.0052664

Guidoboni, G., Harris, A., Cassani, S., Arciero, J., Siesky, B., Amireskandari, A., Tobe, L.A., Egan, P., Januleviciene, I., Park, J. 2014. Intraocular pressure, blood pressure and retinal blood flow autoregulation: A mathematical model to clarify their relationship and clinical relevance. *Invest Ophthalmol Vis Sci* **55**(7): 1-40. https://doi.org/10.1167/iovs.13-13611.

Han, X., Niu, Y., Guo, X., Hu, Y., Yan, W., He, M. 2016. Age-related changes of intraocular pressure in elderly people in southern China: Lingtou Eye Cohort study. *PLoS One* **11**(3): 2-11. https://doi.org/10.1371/journal.pone.0151766.

Han, Y., McCulley, T.J., Horton, J.C. 2008. No correlation between intraocular pressure and intracranial pressure. *Ann Neurol* **64**(2): 221-4. https://doi.org/10.1002/ana.21416.

Hou, R., Zhang, Z., Yang, D., Wang, H., Chen, W., Li, Z., Sang, J., Liu, S., Cao, Y., Xie, X., Ren, R., Zhang, Y., Sabel, B.A., Wang, N. 2016. Pressure balance and imbalance in the optic nerve chamber: The Beijing Intracranial and Intraocular Pressure (iCOP) Study. *Sci China Life Sci* **59**(5): 495-503. https://doi.org/10.1007/s11427-016-5022-9.

Jonas, J.B. 2011. Role of cerebrospinal fluid pressure in the pathogenesis of glaucoma. *Acta Ophthalmol* **89**(6): 505-14. https://doi.org/10.1111/j.1755-3768.2010.01915.x.

Jonas, J.B., Berenshtein, E., Holbach, L. 2004. Lamina cribrosa thickness and spatial relationships between intraocular space and cerebrospinal fluid space in highly myopic eyes. *Invest Ophthalmol Vis Sci* **45**(8): 2660-5. https://doi.org/10.1167/iovs.03-1363.

Jonas, J.B., Wang, N., Wang, S., Wang, Y.X., You, Q.S., Yang, D., Wei, W.B., Xu, L. 2014a. Retinal vessel diameter and estimated cerebrospinal fluid pressure in arterial hypertension: The Beijing eye study. *Am J Hypertens*, *27*(9), 1170–1177. https://doi.org/10.1093/ajh/hpu037

Jonas, J.B., Wang, N., Wang, Y. X., You, Q.S., Xie, X., Yang, D., Xu, L. 2014b. Body height, estimated cerebrospinal fluid pressure and open-angle glaucoma. The Beijing eye study 2011. *PLoS One* **9**(1): 1170-8. https://doi.org/10.1371/journal.pone.0086678.

Jonas, J.B., Wang, N., Xu, J., Wang, Y.X., You, Q.S., Yang, D., Xie, X.B., Xu, L. 2014c. Diabetic retinopathy and estimated cerebrospinal fluid

pressure. The Beijing eye study 2011. *PLoS One* **9**(5): e96273. https://doi.org/10.1371/journal.pone.0096273.

Jonas, J.B., Wang, N.L., Wang, Y.X., You, Q.S., Xie, X.B., Yang, D.Y., Xu, L. 2015. Estimated translamina cribrosa pressure difference versus intraocular pressure as biomarker for open-angle glaucoma. The Beijing Eye Study 2011. *Acta Ophthalmol* **93**(1): e7-13. https://doi.org/10.1111/aos.12480.

Kirk, T., Jones, K., Miller, S., Corbett, J. 2011. Measurement of intraocular and intracranial pressure: Is there a relationship? *Ann Neurol* **70**(2): 323-6. https://doi.org/10.1002/ana.22414.

Kumar, A., Sharma, N., Rathee, A., Pradhan, N. 2019. Comparison of body mass index and intraocular pressure. *Int J Res Med Sci* **7**(2): 367. https://doi.org/10.18203/2320-6012.ijrms20190336

Lam, C.T.Y., Trope, G.E., Buys, Y.M. 2017. Effect of head position and weight loss on intraocular pressure in obese subjects. *J Glaucoma* **26**(2): 107-12. https://doi.org/10.1097/IJG.0000000000000573.

Lashutka, M.K., Chandra, A., Murray, H.N., Phillips, G.S., Hiestand, B.C. 2004. The relationship of intraocular pressure to intracranial pressure. *Ann Emerg Med* **43**(5): 585-91. https://doi.org/10.1016/j.annemergmed.2003.12.006.

Leske, M.C., Heijl, A., Hussein, M., Bengtsson, B., Hyman, L., Komaroff, E., Lee, P. 2003. Factors for glaucoma progression and the effect of treatment. *Evidence-Based Eye Care* **4**(4): 196-7. https://doi.org/10.1097/00132578-200310000-00007.

Leske, M.C., Heijl, A., Hyman, L., Bengtsson, B., Dong, L.M., Yang, Z., EMT Group. 2007. Predictors of long-term progression in the early manifest glaucoma trial. *Ophthalmol* **114**(11): 1965-72. https://doi.org/10.1016/j.ophtha.2007.03.016.

Li, Z., Yang, Y., Lu, Y., Liu, D., Xu, E., Jia, J., Yang, D., Zhang, X., Yang, H., Ma, D., Wang, N. 2012. Intraocular pressure vs intracranial pressure in disease conditions: A prospective cohort study (Beijing iCOP study). *BMC Neurol* **12**: 2010-3. https://doi.org/10.1186/1471-2377-12-66.

Marek, B., Harris, A., Kanakamedala, P., Lee, E., Amireskandari, A., Carichino, L., Guidoboni, G., Tobe, L.A., Siesky, B. 2014. Cerebrospinal fluid pressure and glaucoma: Regulation of trans-lamina cribrosa pressure. *Br J Ophthalmol* **98**(6): 721-5. https://doi.org/10.1136/bjophthalmol-2013-303884.

Morgan, W.H., Yu, D.Y., Alder, V.A., Cringle, S.J., Cooper, R.L., House, P.H., Constable, I.J. 1998. The correlation between cerebrospinal fluid pressure and retrolaminar tissue pressure. *Invest Ophthalmol Vis Sci* **39**(8): 1419-28. https://doi.org/10.1167/iovs.98-3908-1419

Morgan, W.H., Yu, D.Y., Balaratnasingam, C. 2008. The role of cerebrospinal fluid pressure in glaucoma pathophysiology: The dark side of the optic disc. *J Glaucoma* **17**(5): 408-13. https://doi.org/10.1097/IJG.0b013e31815c5f7c.

Morgan, W.H., Yu, D.Y., Cooper, R.L., Alder, V.A., Cringle, S.J., Constable, I.J. 1995. The influence of cerebrospinal fluid pressure on the lamina cribrosa tissue pressure gradient. *Invest Ophthalmol Vis Sci* **36**(11): 2163-4.

Pedersen, S.H., Lilja-Cyron, A., Andresen, M., Juhler, M. 2018. The relationship between intracranial pressure and age-chasing age-related reference values. *World Neurosurg* **110**: e119-23. https://doi.org/10.1016/j.wneu.2017.10.086.

Price, D.A., Harris, A., Siesky, B., Mathew, S. 2020. The influence of translaminar pressure gradient and intracranial pressure in glaucoma: A review. *J Glaucoma* **29**(2): 141-6. https://doi.org/10.1097/IJG.0000000000001421.

Pruzan, N.L., Myers, J.S. 2015. Phenotypic differences in normal vs high tension glaucoma. *J Neuroophthalmol* **35**(19): S4-S7. https://doi.org/10.1097/WNO.0000000000000297.

Quigley, H., Broman, A.T. 2006. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol* **90**(3): 262-7. https://doi.org/10.1136/bjo.2005.081224

Ren, R., Jonas, J.B., Tian, G., Zhen, Y., Ma, K., Li, S., Wang, H., Li, B., Zhang, X., Wang, N. 2010. Cerebrospinal fluid pressure in glaucoma. A prospective study. *Ophthalmology* **117**(2): 259-66. https://doi.org/10.1016/j.ophtha.2009.06.058

Roy Chowdhury, U., Fautsch, M.P. 2015. Intracranial pressure and its relationship to glaucoma: Current understanding and future directions. *Med Hypothesis Discov Innov Ophthalmol* **4**(3): 71-80.

Siaudvytyte, L., Januleviciene, I., Ragauskas, A., Bartusis, L., Meiliuniene, I., Siesky, B., Harris, A. 2014. The difference in translaminar pressure gradient and neuroretinal rim area in glaucoma and healthy subjects. *J Ophthalmol* **2014**: 937360. https://doi.org/10.1155/2014/937360.

Siaudvytyte, L., Januleviciene, I., Ragauskas, A., Bartusis, L., Siesky, B., Harris, A. 2015. Update in intracranial pressure evaluation methods and translaminar pressure gradient role in glaucoma. *Acta Ophthalmol* **93**(1): 9-15. https://doi.org/10.1111/aos.12502.

Subramaniam, S., Fletcher, W.A. 2017. Obesity and weight loss in idiopathic intracranial hypertension: A narrative review. *J Neuroophthalmol* **37**(2): 197-205. https://doi.org/10.1097/WNO.0000000000000448.

Turgut, B., Turgut, F.A. 2017. Differences between the characteristics of normal tension glaucoma and high tension glaucoma. *Adv Ophthalmol Vis*

System **7**(7): 449-51. https://doi.org/10.15406/aovs.2017.07.00250

Weinreb, R.N., Tee Khaw, P. 2004. Primary open-angle glaucoma. *Lancet* **363**(9422): 1711-20. https://doi.org/10.1016/S0140-6736(04)16257-0.

Wong, T.T., Wong, T.Y., Foster, P.J., Crowston, J.G., Fong, C.W., Aung, T. 2009. The relationship of intraocular pressure with age, systolic blood pressure, and central corneal thickness in an Asian population. *Invest Ophthalmol Vis Sci* **50**(9): 4097-102. https://doi.org/10.1167/iovs.08-2822.

Xie, X., Zhang, X., Fu, J., Wang, H., Jonas, J. B., Peng, X., Tian, G., Xian, J., Ritch, R., Li, L., Kang, Z., Zhang, S., Yang, D., Wang, N., Hou, R., Li, Z., Zhang, Z., Sang, J., Chen, W., Liu, S. 2013. Noninvasive intracranial pressure estimation by orbital subarachnoid space measurement: The Beijing Intracranial and Intraocular Pressure (iCOP) study. *Crit Care* **17**(4): R162. https://doi.org/10.1186/cc12841.

Yang, D., Fu, J., Hou, R., Liu, K., Jonas, J.B., Wang, H., Chen, W., Li, Z., Sang, J., Zhang, Z., Liu, S., Cao, Y., Xie, X., Ren, R., Lu, Q., Weinreb, R.N., Wang, N. 2014. Optic neuropathy induced by experimentally reduced cerebrospinal fluid pressure in monkeys. *Invest Ophthalmol Vis Sci* **55**(5): 3067-73. https://doi.org/10.1167/iovs.14-15244.

Zhang, Z., Wu, S., Jonas, J.B., Zhang, J., Liu, K., Lu, Q., Wang, N. 2016. Dynein, kinesin and morphological changes in optic nerve axons in a rat model with cerebrospinal fluid pressure reduction: The Beijing Intracranial and Intraocular Pressure (iCOP) study. *Acta Ophthalmol* **94**(3): 266-75. https://doi.org/10.1111/aos.12768