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Intraocular pressure response to perceived stress in juvenile-onset open-angle glaucoma

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Running head: IOP and perceived stress

List of abbreviations and acronyms:

EGMT: Early Manifest Glaucoma Trial

IOP: intraocular pressure

JOAG: juvenile-onset open-angle glaucoma

ONH: optic nerve head

POAG: primary open-angle glaucoma

PSS: perceived stress scale

RGC: retinal ganglion cell

SD: standard deviation

VF: visual field

MD: mean deviation

Précis

High perceived stress from academic pressure is associated with intraocular pressure elevation and reduced fluctuation in juvenile-onset open-angle glaucoma patients. Personalized stress assessment and relief strategies may serve as an adjunct therapy in glaucoma.

Abstract

Objective: To evaluate the effect of higher perceived stress, resulting from academic pressure, on intraocular pressure (IOP) in juvenile-onset open-angle glaucoma (JOAG) patients compared to healthy individuals.

Participants and Methods: The study included 48 university students aged 18 to 27, comprising 24 JOAG patients on antiglaucoma eyedrops and 24 healthy controls. In an examiner-blind pretest-posttest design, participants' IOP was measured weekly using Goldmann tonometry during three follow-up visits at the beginning and end of the academic semester. Perceived Stress Scale (PSS) scores were also evaluated at these two time points to capture the contrast in perceived stress between periods of low and high academic pressure.

Results: Baseline PSS score at the semester's start was lower in both groups (14.1 ± 1.9 in glaucoma vs. 13.5 ± 2.4 in control) and significantly increased by the end of the semester (29.2 ± 2.1 vs. 28.5 ± 1.3; $p<0.001$), indicating increased perceived stress. Concurrently, IOP rose from 22.01 ± 5.87 mmHg to 25.08 ± 5.84 mmHg in the glaucoma group and from 11.36 ± 2.03 mmHg to 13.65 ± 2.11 mmHg in the control group. Factorial analysis revealed a significant interaction between stress and JOAG [$F(1,94)=15.94$, p=0.001], partial $\eta 2 = 0.08$, with stress having a greater increase on IOP in the glaucoma group (+3.10 mmHg) compared to the control group (+2.23 mmHg) [$t(94)=4.457$, $p<0.001$].

Conclusions: Higher perceived stress significantly increases IOP, especially in JOAG patients, suggesting personalised stress management as a potential adjunct therapy for patients.

Keywords: perceived stress; stress relief therapy; intraocular pressure; glaucoma.

Introduction

Primary open-angle glaucoma (POAG), a leading cause of global blindness, is characterized by the progressive degeneration of retinal ganglion cells (RGCs), culminating in optic nerve head (ONH) damage and disruption of the visual pathway, and ultimately, vision loss.[1] As per the World Health Organization's estimates, approximately 76 million individuals were afflicted with glaucoma in 2020, a figure projected to increase to 111.8 million by 2040, due to population growth and aging.[2] Currently, elevated intraocular pressure (IOP) is the only known modifiable risk factor for RGC death and the progression of glaucoma.[3] High IOP contributes to glaucoma by compressing retinal capillaries, causing chronic ischemic injury, and impairing axoplasmic transport, leading to axonal injury in the RGCs.[4] Glaucoma treatment aims to lower IOP, typically via medication, laser therapy, or surgery.[3] While medical treatment generally slows down glaucoma progression by lowering IOP, younger patients (<40 years) with juvenile-onset primary open-angle glaucoma (JOAG)—a subtype of POAG associated with more severe disease—stand a greater risk of end-of-life visual disabilities.[5] This underscores the importance of exploring potential factors associated with IOP elevation in JOAG patients.

Emerging evidence indicates that individuals experiencing high levels of stress, or those diagnosed with anxiety and depression, exhibit a higher prevalence and accelerated progression of glaucoma.[6,7] Berchuck et al's landmark clinical study, which followed 3,259 glaucoma suspects over four years, found that those with anxiety and depression at baseline had a 16-27% higher risk of progressing to glaucoma compared to their cohorts without any such stress-related disorders.[6] Particularly in patients with Flammer syndrome, which is often associated with emotional stress, sudden deterioration in the visual field may occur due to the progression of glaucoma.[8] The association between glaucoma and psychological stress is further complicated by the fact the diagnosis of glaucoma itself can cause emotional stress, further increasing the risk of disease progression.[9] Potential stressors in glaucoma patients include treatment costs, lack of disease awareness, and visual disability from advanced glaucoma stages.[10] Also, it was reported that RGC loss of over 15% from glaucoma was associated with depression due to disrupted circadian rhythms and sleep.[11]

In recognition of these associations, there is growing interest in understanding how stress-induced psychophysiological responses affect IOP. Emerging data, primarily from lab-simulated stress tests on healthy subjects, supports the link between psychological stress and increased IOP.[12–14]. For example, Jimenez and Vera found that a 90-minute high-stress academic test significantly elevated IOP values in healthy university students compared to a less stressful test.[13] Similarly, Vera et al. found increased IOP values correlated with public speaking anxiety.[14] Other researchers have also noted a slight increase in IOP following a 10-minute stressful task, consisting of an interview speech and math assignment.[12] However, the impact of psychological stress on IOP in patients with POAG, or JOAG, remains unclear due to limited data from studies with small sample sizes, which only explored acute IOP changes following stress events.[15–17] Since IOP is dynamic and fluctuates throughout the day, acute changes in IOP may have limited relevance to glaucoma development and progression compared to sustained IOP elevation.[18,19] Therefore, understanding the effect of a real-life stress encountered in everyday life on long-term IOP changes could provide a more accurate picture of the course of psychological stress-induced IOP in glaucoma progression.

This information could help healthcare providers understand the psychological impact of stress on glaucoma patients and incorporate appropriate stress management and relaxation techniques into treatment plans. The current study hypothesizes that academic pressure-induced psychological stress significantly contributes to chronic IOP elevation in patients with JOAG.

Methods

Study Setting and Ethics

Ethics approval for the study was granted by the Institutional Review Board (UCCIRB/CHAS/2023/74). All participants provided written informed consent after understanding the study procedures, risks, and benefits. An experienced examiner measured all IOPs to minimize corneal abrasion risk. The ophthalmic equipment, including the Goldmann tonometer, was sterilized before and after each use to prevent disease spread. The study adhered to the Declaration of Helsinki's ethical principles for medical research involving human subjects.

Study Design, Sample Size, and Eligibility

A pretest-posttest interventional design was employed to investigate the IOP response to perceived stress induced by academic pressure, a common everyday life stressor.[20] Our study involved tertiary students from the University of Cape Coast, chosen due to a recent survey indicating uniformly high-stress levels primarily from academic pressure. [21] The study included two groups: physician-diagnosed JOAG patients (Glaucoma Group) and healthy individuals without glaucoma (Control Group). JOAG diagnosis followed the recommended criteria,[22–24] with the median age at diagnosis of 19 years. Both structural and functional signs of glaucomatous damage were to be present, including ONH damage (indicated by a cup-to-disk ratio > 0.5 or disc asymmetry ≥ 0.2), visual field test defects (by either an abnormal glaucoma hemifield test or a pattern deviation consistent with glaucoma), Goldmann tonometry (IOP before treatment > 21 mmHg), and gonioscopy (showing open anterior chamber angle). Additionally, a definite diagnosis of JOAG was made after ruling out the co-existing of any potential secondary cause, including steroid use, trauma, pigmentary glaucoma, uveitic glaucoma, and the presence of any neuro-ophthalmic disease.[25] The classification of glaucoma severity was based on visual field outcomes, adhering to the criteria set forth by the Glaucoma Staging System.[26]

Using G*Power software and considering a *t*-test, the study's sample size was determined. An effect size of 0.45,[17] alpha error of 0.05, and power of 0.80 were used, indicating a minimum of 32 eyes (16 participants per group) was adequate to detect significant IOP differences before and after academic stress intervention. From the start, 52 students were randomly selected and recruited into the two groups (26 per group) using the medical records from the Eye Clinic operated on the university campus. However, only 48 participants remained at the end of the final follow-up visit. Participants were subjected to vision and ocular health examinations, including direct ophthalmoscopy to evaluate the cup-to-disk ratio. The exclusion criteria encompassed individuals with unaided visual acuity worse than 6/18, other ocular diseases (excluding glaucoma in the Glaucoma Group), history of glaucoma surgery, use of certain medications (such as steroids and contraceptives), ocular trauma, pregnancy, habitual coffee consumption, severe or advanced glaucomatous optic neuropathy,[24] and poor adherence to antiglaucoma medication as determined by the Medication Adherence Questionnaire.[27] Since the study was structured to create a clear contrast in stress levels at two distinct time points, participants with Perceived Stress Scale (PSS) scores of 27 or above before academic stress exposure were excluded. Additionally, to control for the variable of severe visual impairment, participants with advanced glaucomatous optic neuropathy were omitted to focus solely on the effects of academic stress on stress levels. All participants were restricted to using preservative-free 0.5% topical timolol maleate drops twice daily and were confirmed to be free of any ocular surface disorders, to minimize external stress influences further. After fulfilling these criteria, selected participants were then enrolled for the subsequent follow-up procedures.

Assessment of Main Outcome Measures

The study protocol was structured into two phases: the pre-stress phase and the post-stress phase. During the pre-stress phase, spanning the first three weeks of the academic semester with generally less academic activity, participants' IOP was measured in both eyes at one-week intervals, and the 10-item Perceived Stress Scale (PSS) questionnaire was administered to assess their perceived stress levels. Also, during the post-stress phase, marked by heightened academic pressure in the last three weeks of the semester, IOP was measured weekly and perceived stress was reassessed.

The PSS questionnaire is a psychological tool designed to measure participants' self-reported stress levels by assessing their thoughts and feelings over the past month. Each question is scored on a scale of 0 (never) to 4 (very often), yielding a total possible score range of 0 to 40. Participants' PSS scores are then categorized as low stress (0-13), moderate stress (14-26), or high stress (27-40).[28] The instrument consists of two subscales: Perceived helplessness (items 1, 2, 3, 6, 9, 10) assesses an individual's sense of control over circumstances and emotions, and lack of Self-efficacy (items 4, 5, 7, 8) evaluates their perceived problem-solving ability. In clinical practice and research, a high PSS score correlates with elevated cortisol levels and is associated with depressive and anxiety disorders.[29,30]

IOP measurements were conducted using a Keeler applanation tonometer (Keeler Ltd, UK). In brief, 0.5% Amethocaine eye drops (Bausch & Lomb) were applied to anesthetize the ocular surface, followed by the staining of the ocular surface with a fluorescein strip (Medical Equipment India, New Delhi). Each IOP recorded represented the average of three measurements per visit. Participants refrained from consuming caffeine and engaging in strenuous physical activity for 24 hours prior to the measurements,[31,32] which were consistently taken between 9 a.m. and 12 noon. All IOPs were measured in the dry season, starting January to April.

Data Analysis

Statistical analysis of data and graphical presentation were performed using GraphPad Prism (Version 7.0; San Diego, CA, USA). Both eyes were included in the analyses. IOP fluctuation was defined as the standard deviation (SD) of the IOPs taken on the three different visits, either before or after academic stress, as reported previously.[19] By 2x2 mixed factor ANOVA followed by Sidak's multiple comparison tests, the interactive effect of psychological stress and the presence of glaucoma on IOP changes or IOP fluctuation was analyzed. To compare data within a group, we utilized paired *t*-tests. Paired *t*-tests were used for within-group comparisons, while independent *t*-tests were used for between-group comparisons. A p-value of less than 0.05 was considered statistically significant.

Results

Demographic and baseline data

The glaucoma and control groups comprised 24 participants (i.e., 48 eyes) each. The age range of the glaucoma group was 18 to 27 years, with a mean age of 21.71 ± 2.49 years, compared to 18 to 25 years, with a mean age of 21.29 ± 2.31years in the control group ($t(46) = 0.600$, P = 0.551). Regarding the sex distribution, there were 10 (41.7%) males and 14 (58.3%) females in the glaucoma group as compared to 6 (25%) males and 18 (75%) females in the controls ($\chi^2(1)$ = 0.221). The glaucoma group and the control group showed a significant difference in the cup-to-disc ratio, with the glaucoma group averaging 0.62±0.12 compared to the control group's 0.24±0.10 ($t(46) = 11.718$, $P < 0.001$). Glaucoma staging, determined by visual field (VF) loss, categorized 19 patients with mild glaucoma (mean deviation (MD) ≥-5 dB) and 5 with moderate glaucoma (VF MD < -5 to -12 dB). Across the glaucoma group, the average VF MD was -4.36±5.93 dB in right eyes and -4.24±5.24 dB in left eyes. Other clinical characteristics of JOAG in the glaucoma group are presented in **Table 1.**

Impact of perceived stress on IOP

Before academic stress exposure, baseline PSS scores were similar in both glaucoma and control groups (14.1 ± 1.9 vs 13.5 ± 2.4, $t(46)=0.960$, $p=0.342$). Post-stress, PSS scores significantly rose relative to baseline in the glaucoma ($t(23)=32.402$, $p<0.001$) and control groups($t(23)=30.479$, $p<0.001$), with no notable difference between them (29.2 ± 2.1 and 28.5 ± 1.3, $t(46) =1.346$ $p=0.185$), indicating increased perceived stress levels. **Figure 1A** illustrates the comparable PSS scores (comprising two subscales) between the groups pre- and post-stress.

Concurrently, there was an increase in IOP observed in both groups. **Table 2** presents the mean IOP for each visit before and after stress exposure. In the glaucoma group, the overall mean IOP rose from 22.01 ± 5.87 mmHg to 25.08 ± 5.84 mmHg, while in the control group, it increased from 11.36 ± 2.03 mmHg to 13.65 ± 2.11 mmHg. A factorial analysis showed significant main effect for perceived stress, [$F (1, 94) = 730.87, p < 0.001$], partial $\eta^2 = 3.51$; a significant main effect for glaucoma presence, [$F (1, 94) = 153.71, p < 0.001$], partial $\eta^2 = 59.55$; and a significant interaction between psychological stress and glaucoma presence, [$F (1, 94) = 15.94, p = 0.001$], partial $\eta^2 = 0.08$. Following up with the Sidak's multiple comparisons *post hoc* tests showed that higher perceived stress significantly elevated the IOP relative to the baseline in the glaucoma ($p <0.001$) and control ($p <0.001$) groups (**Figure 1B**). A comparison between groups, however, showed that the magnitude of IOP increase in the glaucoma group (+3.10 mmHg) was significantly greater than that in the control group (+2.23 mmHg) ($t (94) =4.457, p < 0.001$, **Figure 1C**).

IOP fluctuation before and post-stress

Due to the finding of IOP elevation following psychological stress, we investigated the extent of IOP fluctuation by analyzing the SD of IOPs (SD-IOP) measured on three different visits before and following academic stress in the glaucoma and control groups. The SD-IOP (mmHg) recorded in the glaucoma group was 0.92±0.47 and 0.63±0.27 before and post-stress academic stress, respectively, compared to 0.73 ±0.45 and 0.66 ±0.26 in the control group (**Figure 1D**). A factorial analysis revealed a significant main effect for psychological stress (F (1, 94) = 10.31, $p=0.002$, partial $\eta2 = 5.479$), indicating that stress influenced IOP fluctuation. However, there was no significant main effect for glaucoma presence ($F (1, 94) = 2.166$, $p=0.144$, partial $\eta2 = 0.9614$) or interaction between stress and glaucoma presence ($F (1, 94) = 3.50$, $p=0.065$, partial $\eta2 = 1.859$).

Results from the follow-up Sidak's multiple comparison tests indicated a significantly lower SD-IOP post-stress relative to the baseline in the glaucoma group (*p*=0.001), but not in the control group (*P*=0.572).

Discussion

Elevated IOP is an important modifiable risk factor for the prevention of glaucoma onset and progression.[33,34] Due to the high incidence of psychological stress and anxiety disorders in glaucoma patients, understanding how psychological stress impacts IOP remains crucial. While a recent study suggested a correlation between the two,[9] a cause-and-effect relationship is yet to be established. To the best of our knowledge, this is the clinical study to examine the relationship between psychological stress and IOP changes in JOAG patients over a 3-week period using a quasi-experimental design. The most significant finding was the interaction between perceived stress and the presence of glaucoma, indicating that the impact of psychological stress on IOP varies between individuals with glaucoma and those without the sight-threatening disease.

In JOAG patients, we observed a significant average increase in IOP, specifically 3.10 mmHg, when comparing baseline IOP measurements to post-exam measurements. A similar trend was observed in the control group, with an average IOP increase of 2.29 mmHg. Although this increase may seem modest, it is clinically significant in glaucoma management when considered in the long term. Consistently, both clinical trials and extensive population-based studies have robustly established that chronic elevation of IOP significantly increases the risk of glaucoma progression.[35,36] For instance, the Early Manifest Glaucoma Trial (EGMT) found that the risk of glaucoma progression increased by 13% for every 1 mmHg increase in baseline IOP over an 8-year follow-up period.[36] Thus, over an extended period even the modest elevation in IOP of 3.10 mmHg in glaucoma patients could increase the risk of glaucoma progression by 39%. Comparatively, the absolute increase in IOP was significantly greater in glaucoma patients; yet, when evaluated as a percentage change from baseline, the control group experienced a more substantial relative increase, at 20.2%, compared to a 13.9% increase in treated glaucoma patients. This indicates that the higher baseline IOP in glaucoma patients is a key factor in their pronounced absolute IOP rise under stress. It is important to consider, though, that these glaucoma patients were undergoing treatment with topical antiglaucoma medication, which likely moderated the IOP increase to some degree. The study outcome underscores the importance of stress management strategies and regular IOP monitoring in glaucoma patients to minimize disease progression risk. Recent studies using only either glaucoma patients or controls already reported acute IOP elevation following short exposure to psychological stress.[12–17] Our current study, therefore, reveals that the impact of chronic stress could be even worse in glaucoma patients, who already have higher IOP.

As with many physiological measures, the IOP in normal eyes varies within a particular range during the day, and may also vary when recorded at the same time of the day on different visits. In the glaucoma population, however, IOP fluctuates by a larger degree compared to normal healthy population without glaucoma. This explains why our glaucoma patients on treatment recorded a slightly higher SD-IOP than the control group at the baseline (0.92 vs. 0.73 mmHg). Reports from studies in different populations suggest that IOP fluctuation may increase the risk of glaucoma progression, although others have refuted this notion.[18,19,35] This study notably demonstrates that high stress levels stabilize IOP, despite its elevated state. The paradoxical role of stress in both elevating IOP and reducing its fluctuations—and the implications for glaucoma progression—demands further investigation. Kim et al.[18] observed in their review that among populations with lower mean IOPs, greater IOP fluctuations were linked to glaucoma progression. However, in cases with higher mean IOPs, such as those in the EMGT, the detrimental effects of IOP fluctuation were not evident.[37] This finding underscores the complex relationship between IOP levels, their fluctuations, and the risk of glaucoma progression, highlighting the need for more nuanced research in this area.

The precise mechanism underlying the increase in IOP induced by stress is not yet fully understood. But it is believed that increased secretion of cortisol hormone by the hypothalamic–pituitary–adrenal (HPA) axis in response to stress has an important influence.[12] A recent randomized controlled trial conducted on ocular hypertensive patients (n=60; IOP of 21-30 mmHg) demonstrated the effectiveness of daily one-hour sessions of mindfulness-based stress reduction therapy over a six-week period. This therapy led to a reduction in serum cortisol levels, as well as improvements in IOP, IOP fluctuation, and retinal vessel perfusion. The individuals who participated in the mindfulness-based stress reduction therapy experienced a significant decrease in IOP by 3.93 mmHg and a decline in cortisol levels by 2.54 ng/ml. Conversely, the untreated control group did not show any significant changes in either IOP or cortisol levels.[38] Moreover, a strong correlation (r=0.727; p =0.001) was observed between changes in IOP and serum cortisol levels.[38] Interestingly, a case report involving two patients suffering from Cushing's syndrome, who presented with ocular hypertension as a result of excessive cortisol production, revealed a reversal of their ocular condition after their endogenous cortisol levels returned to normal following pituitary adenoma surgical treatment.[39] Taken together, these findings strongly suggest that systemic cortisol levels play a crucial role in the regulation of IOP, and support the implementation of strategies aimed at mitigating both internal and external triggers, such as psychological stress.

Study strength and limitations

The study's major strength lies in its natural experimental design, which uses academic pressure, a common real-life stressor, to investigate psychological stress.[40] Therefore, the results, particularly the observed changes in IOP as a psychophysiological response to stress, can have wider generalizability to others in a similar setting. This study utilized a repeated study design to accurately examine the variations in IOP as a function of stress, accounting for test-retest variability within a specific psychological state. However, the natural observational nature could be a significant limitation, as it could result in participants experiencing varying degrees of academic stress due to differences in their study disciplines and individual commitment to academic work. This was mitigated by excluding participants who reported lower perceived stress levels (i.e., PSS score < 13) during the post-stress phase from the analysis. Moreover, **Figure 1A** illustrates that the two groups studied had comparable scores in the two subscales of the PSS-10. Furthermore, as a longitudinal study, there was the possibility that participants may have encountered other forms of stress unrelated to academic pressure, which could influence the perceived stress score. The specific source of stress was not identified, so attributing IOP changes exclusively to academic pressure should be approached with caution. Additionally, our study sample consisted of younger participants, with all individuals in the glaucoma group on timolol treatment for IOP reduction. Consequently, the findings may not accurately represent the IOP response in adult POAG patients, or JOAG patients who may have received surgical intervention for IOP control.

Conclusion

In conclusion, stress from academic pressure significantly affects IOP in both healthy and glaucomatous eyes, with a greater impact on the latter. Despite this, stress-induced IOP elevation in JOAG patients showed less fluctuation over time. Thus, assessing stress levels could inform the potential benefits of personalised stress relief therapy as an adjunct therapy in glaucoma management, though further longitudinal studies are needed to fully understand the impact of stress on IOP elevation, fluctuation, and glaucoma progression.

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Figure Legend

Figure 1: Impact of high academic pressure on perceived stress scale (PSS) score (A), intraocular pressure (IOP) rise (B & C), and fluctuation in glaucoma patients and controls (D). Figure 1C shows the average rise in the IOP of both eyes per participant in glaucoma and control groups following stress (*data is arranged in order of increasing magnitude*). Data is presented as mean ± standard deviation (SD). Statistical analysis involved a 2x2 mixed factor ANOVA, followed by Sidak's multiple comparison tests. ***P<0.001; **P<0.01.