

Clinical science

Effects of ambient temperature on intraocular pressure in patients with stable primary open-angle glaucoma under medical treatment

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ABSTRACT

Aims To investigate the effects of ambient temperature on intraocular pressure (IOP) in patients with stable primary open-angle glaucoma (POAG) under medical treatment.

Methods This retrospective study analysed longitudinal IOP data via Goldmann applanation tonometer of POAG patients treated at the Kyoto Prefectural University of Medicine Hospital from 2012 to 2023. Inclusion criteria were no history of ophthalmic surgeries, no change in medications, age ≥ 40 years and ≥ 3 visits/year for ≥ 3 years. Data were analysed using a linear mixed-effects model with individual eyes as the random effect. Fixed effects included age, mean deviation of Humphrey Visual Field Perimetry, corneal curvature radius, central corneal thickness (CCT), axial length, mean blood pressure (mBP), heart rate, ambient temperature, atmospheric pressure, relative humidity, wind speed, precipitation, sunshine duration, sex, glaucoma type, glaucoma stage, number of eye-drops used, season, time of day and weather.

Results A total of 2655 IOP measurements from 154 eyes of 77 patients (mean age: 65.8 years; mean observation period: 5.2 years) were analysed. IOP was negatively correlated with ambient temperature (estimate = -0.029 ; $p=0.003$) and positively correlated with mBP (estimate = 0.021 ; $p<0.001$). CCT tended to be associated with IOP. The number of eye-drops used, glaucoma type, and time of day had a significant effect, and season tended to have an effect, on IOP fluctuation.

Conclusions In patients with stable POAG under medical treatment, ambient temperature showed a significant and negative correlation with IOP after correction for the effects of other confounding and possibly correlating factors.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Fluctuations in intraocular pressure (IOP) have been observed in both normal subjects and primary open-angle glaucoma (POAG) patients. Unlike in normal subjects, it remains unknown how specific climatic factors affect IOP in POAG patients under medical treatment.

WHAT THIS STUDY ADDS

⇒ A significant negative correlation was found between IOP and ambient temperature in patients with stable POAG under medical treatment after correction for other confounding factors.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The relationship between IOP and ambient temperature in patients with stable POAG under medical treatment should be considered in a comprehensive POAG treatment strategy.

INTRODUCTION

Glaucoma is a group of progressive optic neuropathies in which a slow progressive degeneration of retinal ganglion cells and their axons are common factors that result in a distinct appearance of the optic disc and a concomitant pattern of vision loss¹ that eventually affects the patient's visual acuity and vision-related quality of life. Numerous previous studies on the specific prognostic factors for the progression of glaucoma-related visual field loss have indicated that intraocular pressure

(IOP) is the only factor that is treatable,² and several randomised controlled trials have also illustrated the importance of IOP reduction to control the progression of visual field loss.^{3–5} Hence, it is widely known that good IOP is vital for the proper shape and optical properties of the eyeball. To fulfil this need, a normal healthy eyeball maintains an IOP within a range of between 10 and 20 mm Hg by dynamic equilibrium between aqueous humour (AH) production and outflow and episcleral venous pressure.⁶ However, various factors reportedly have an effect on IOP, including seasonal factors,^{7–22} diurnal factors,^{8–10,23–25} ophthalmic factors,^{9,11,16,19,26} systemic factors,^{8,9,11,15,16,26,27} and various lifestyle-related situations such as exercise, dietary habits and even body posture.²⁸ The IOP fluctuation observed in both normal healthy subjects^{7–17} and medically treated primary open-angle glaucoma (POAG) patients^{18–22} can partly be explained by climatic change. For example, warm weather can cause vasodilation and upregulation of metabolic processes that can reflect the dynamic role they have in aqueous production, as well as in regulating aqueous outflow.¹³ Moreover, ambient temperature



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can affect IOP via the widely known correlation between IOP and blood pressure (BP),^{8 9 11 15 16 26 27} as well as between ambient temperature and BP.^{29 30} As a result of the correlation between atmospheric pressure (AP) and IOP,^{14–16} variation of AP might also be one of the factors directly related to IOP fluctuation. Dry conditions in winter months¹⁹ or a change in a subject's exposure time to light^{10 13} or ultraviolet light³¹ could also be factors involved in seasonal IOP fluctuation through various biological mechanisms.

Although previous studies investigating the correlation between IOP and climatic factors in the general population^{14 15 17} or non-glaucoma subjects³² found a significant correlation between ambient temperature and IOP fluctuation after adjustment for other possible confounding factors, there has been a paucity of published literature on the effects of ambient temperature or other climatic factors on the IOP in POAG patients being followed under a strict medical treatment course.

Taking into consideration all possible confounding factors that reportedly have an influence on IOP fluctuation,^{7–27 31 32} the purpose of this present study was to investigate the effects of ambient temperature on IOP measurement findings longitudinally recorded in patients with stable POAG under medical treatment.

METHODS

Subjects

In this retrospective study, we reviewed the medical records of POAG patients treated at KPUM between January 2012 and December 2023 who met the following inclusion criteria: (1) patient age over 40 years, (2) at least three clinical visits annually for more than 3 years and (3) no history of ophthalmic surgeries, including cataract surgery. The following criteria were used for the diagnosis of POAG: (1) glaucomatous optic disc change with corresponding visual field loss, (2) open angle observed via gonioscopic examination and (3) no other causes possibly affecting IOP. Normal-tension glaucoma (NTG) was defined as an IOP of ≤ 21 mm Hg without medication at the initial examination and during the follow-up examinations, while the remaining patients were classified as high-tension glaucoma (HTG). The glaucoma stage was defined by the Hodapp-Parrish-Anderson mean deviation (MD) classification as follows: (a) Mild: MD > -6 dB, (b) Moderate: MD -6 to -12 dB and (c) Severe: MD < -12 dB. In addition, all subjects had to have used one to four antiglaucoma eye-drop medications daily, with the regimen being identical for both eyes without any change in the prescriptions during the study period. The eye-drop regimens were as follows: (a) 1-drop regimen (patients using a prostaglandin F (FP) receptor agonist (FP agonist)), (b) 2-drop regimen (patients using a beta-adrenergic blocker (β blocker) in addition to FP agonist), (c) 3-drop regimen (patients using a carbonic anhydrase inhibitor (CAI) in addition to FP agonist and β blocker) and (d) 4-drop regimen (patients using an alpha (α)2 agonist or a Rho kinase inhibitor in addition to FP agonist, β blocker and CAI) (online supplemental table 1). All IOP measurements were taken between the hours of 09:00 and 18:00.

Ophthalmic and systemic data

The following ophthalmic and systemic data were included in the analysis. (a) IOP measured using a Goldmann applanation tonometer (GAT), (b) MD of Humphrey Visual Field Perimetry (Carl Zeiss Meditec, Jena, Germany) findings measured with the 30–2 SITA Standard program at the time closest to the final GAT-IOP measurements, (c) corneal curvature radius (CCR) measured

with an autorefractometer (KP-8100PA; Topcon Corporation, Tokyo, Japan), (d) central corneal thickness (CCT) measured with a specular microscope (SP-2000P; Topcon Corporation) and (e) axial length (AL) measured with the IOLMaster 700 Biometer (Carl Zeiss Meditec, Jena, Germany) at the time closest to the initial GAT-IOP measurements. Systolic BP (SBP), diastolic BP (DBP) and heart rate (HR) were measured concurrently with IOP measurements. Mean BP (mBP) was calculated from SBP and DBP according to the following formula: $mBP = DBP + 1/3 (SBP - DBP)$. Only IOP measurement findings with all available ophthalmic and systemic data (ie, MD, CCR, CCT, AL, mBP and HR) were used for the final analysis.

Climatic data

Climatic data of the city of Kyoto were obtained from the Japan Meteorological Agency website (<https://www.jma.go.jp/jma/indexe.html>), and it included hourly ambient temperature ($^{\circ}\text{C}$), AP (hPa), relative humidity (RH (%)), wind speed (WS (m/s)), daily precipitation (DP (mm)) and sunlight duration (SunDur (hour)). Weather was categorised into three groups, that is, fine, cloudy and rainy, based on the official Japan Meteorological Agency daily weather forecast.

Table 1 Demographic data of the subjects

Number of eligible eyes (subjects)	154 (77)
Women men	43/34
NTG/POAG	100/54
Stage of glaucoma (mild/moderate/severe)	82/25/47
Number of eye-drops used (1/2/3/4)	82/18/32/22
Patient age at end point (years)	65.8 (10.1)
Observation period (years)	5.2 (2.3)
Mean deviation (dB)	−9.1 (8.4)
Corneal curvature radius (mm)	7.7 (0.3)
Central corneal thickness (μm)	527.3 (38.4)
Axial length (mm)	25.4 (1.9)
Number of intraocular pressure measurements	2655
Season (spring/summer/autumn/winter)	679/646/687/643
Time of day (09:00–12:00/12:00–15:00/15:00–18:00)	932/850/873
Weather (fine/cloudy/rain)	1183/1101/371
Intraocular pressure (mm Hg)	12.5 (2.9)
Women men	12.3 (2.6)/12.7 (3.1)*
NTG POAG	11.8 (2.4)/13.8 (3.3)*
Stage of glaucoma (mild/moderate/severe)	12.6 (3.0)/12.5 (2.9)/12.5 (2.8)
Number of eye-drops (1/2/3/4)	12.4 (2.7)/13.9 (2.9)/13.3 (2.8)/11.3 (2.9)*
Season (spring/summer/autumn/winter)	12.8 (2.7)/12.1 (2.8)/12.4 (3.0)/12.9 (3.0)*
Time of day (09:00–12:00/12:00–15:00/15:00–18:00)	12.9 (3.0)/12.5 (2.8)/12.2 (2.9)*
Weather (fine/cloudy/rain)	12.4 (2.8)/12.6 (3.1)/12.5 (2.7)
Mean blood pressure (mm Hg)	93.0 (13.8)
Heart rate (bpm)	75.4 (13.0)
Mean (SD).	
* $p < 0.05$ by ANOVA.	
ANOVA, analysis of variance; NTG, normal-tension glaucoma; POAG, primary open-angle glaucoma.	

Statistical analysis

To investigate factors associated with IOP, a general linear mixed-effects model was used. The response variable was IOP, and each eye of each patient was treated as a random effect. Fixed effects included patient age, MD, CCR, CCT, AL, mBP, HR, ambient temperature, AP, RH, WS, DP and SunDur as continuous variables, and sex, glaucoma type (NTG and HTG), glaucoma stage (mild, moderate and severe), number of eye-drops used daily (ie, 1, 2, 3 and 4), season (Spring (March through May), Summer (June through August), Autumn (September through November) and Winter (December through February)), time of day (ie, 09:00–12:00, 12:00–15:00 and 15:00–18:00) and weather (fine, cloudy and rainy) as categorical variables.

Variables were selected according to the following criteria: continuous variables that were significantly correlated with IOP in univariable regression analysis and categorical variables where the mean IOP differed significantly between categories by analysis of variance (ANOVA). All statistical analyses were performed using JMP Student Edition V.18 (SAS) statistics software. A $p < 0.05$ was considered statistically significant.

Moreover, the same analysis was performed replacing the hourly ambient temperature, AP, RH and WS with daily average of each climatic factor, and subgroup analyses were performed for each category including the glaucoma type, the glaucoma stage and the number of eye-drops used.

RESULTS

The demographic data of the patients are shown in [table 1](#). Of the total 3671 IOP measurements obtained from 184 eyes of 92 POAG patients who met the inclusion criteria, 2655 measurements obtained from 154 eyes of 77 patients in whom complete systemic and ophthalmic data were available were included in the final analysis. A flow diagram of the patients is shown in the online supplemental figure.

Scatterplot graphs of the relationship between IOP and mBP, or IOP and ambient temperature, are shown in [figure 1a,b](#). Box-and-whisker plots of average IOP by glaucoma stage, number of eye-drops used, season and time of day are shown in [figure 2a–d](#), respectively. Among the ordinal variables, a strong and highly

significant positive correlation was observed between the glaucoma stage and the number of eye-drops used. This association was confirmed by both Kendall's rank correlation coefficient τ_b ($\tau_b = 0.621$, 95% CI 0.598 to 0.643, $p < 0.001$) and Spearman's rank correlation coefficient ($\rho = 0.692$, 95% CI 0.668 to 0.716, $p < 0.001$) (online supplemental table 2). Pearson's correlation coefficient between IOP and each continuous variable is outlined in online supplemental table 3. For example, we found that HR, WS and DP were not significantly correlated with IOP ($p = 0.16$, $p = 0.10$ and $p = 0.24$, respectively). Furthermore, ANOVA showed no statistically significant difference in average IOP among the glaucoma stages ($p = 0.85$) and weather groups ($p = 0.22$). Consequently, HR, WS, DP, glaucoma stage and weather were excluded from the multivariable analysis. Regarding multicollinearity, a high correlation was observed only between RH and SunDur ($r = -0.723$). Thus, these variables were included in separate models. Since the results for other variables were very similar between the models with and without SunDur, only the results of the model including SunDur are presented in [table 2](#).

In the multivariable analysis, significant positive associations with IOP were found for mBP (estimate (Est)=0.021 (SE=0.004, 95% CI 0.014 to 0.029, $p < 0.001$)), while a significant negative association with IOP was found in ambient temperature (Est=-0.029 (SE=0.008, 95% CI -0.045 to -0.014, $p = 0.003$)). CCT tended to associate with IOP (Est=0.012 (SE=0.005, 95% CI 0.003 to 0.021, $p = 0.17$)). Among the categorical variables, glaucoma type, number of eye-drops used and time of day had a significant effect ($p < 0.001$, $p < 0.001$ and $p = 0.022$, respectively), and season also tended to have an effect on IOP fluctuation ($p = 0.15$). [Table 3](#) shows the analysis findings for each element in the categorical variables, glaucoma type, number of eye-drops used and time of day. IOP was higher in HTG, 2-drop regimen and 15:00–18:00 compared with NTG, 4-drop regimen and 09:00–12:00 (Est=2.522 (SE=0.405, 95% CI 1.721 to 3.323, $p < 0.001$), Est=3.561 (SE=0.739, 95% CI 2.097 to 5.024, $p < 0.001$) and Est=0.366 (SE=0.103, 95% CI 0.165 to 0.568, $p < 0.001$), respectively).

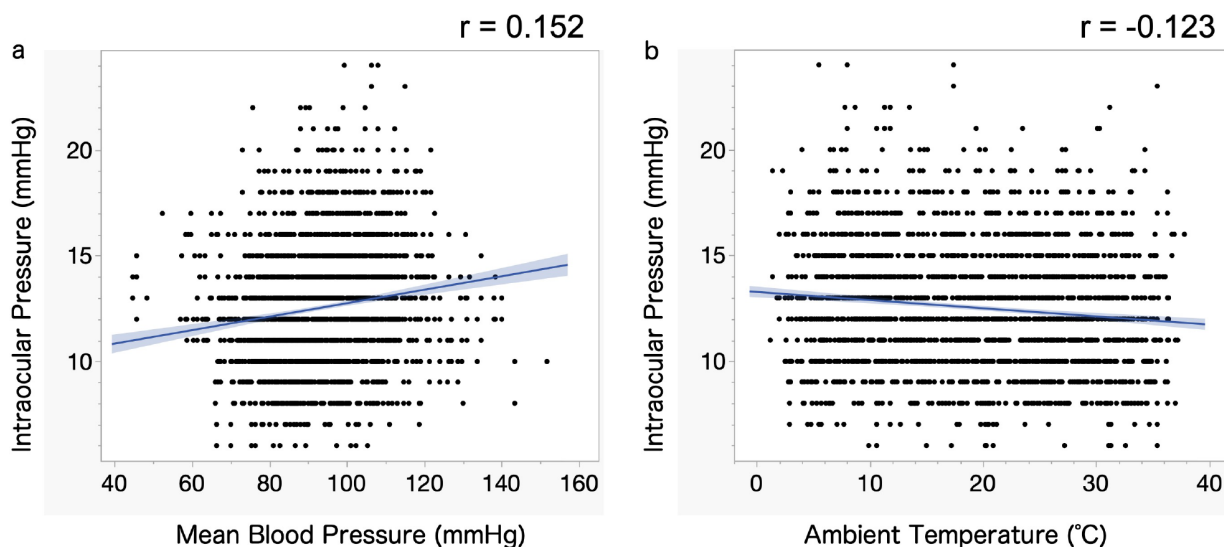


Figure 1 Scatterplot graphs of the relationship between intraocular pressure (IOP) and (a) mean blood pressure (mBP) and (b) ambient temperature (AT). Pearson's correlation coefficients between IOP and mBP, and IOP and AT, were 0.152 ($p < 0.001$) and -0.123 ($p < 0.001$), respectively. The approximation formulas used were $y = 0.032x + 9.573$ (where y is IOP and x is mBP) and $y = -0.039x + 13.280$ (where y is IOP and x is AT), respectively.

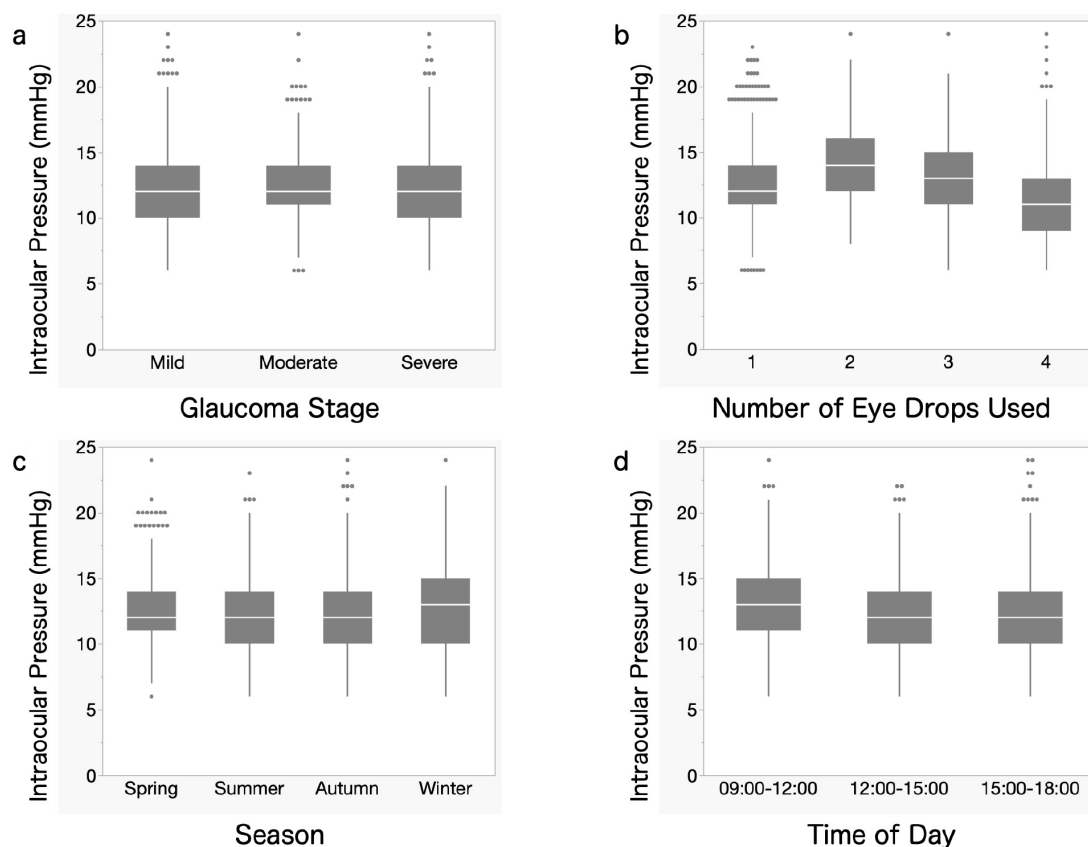


Figure 2 Box-and-whisker plots of the average IOP of (a) each glaucoma stage, (b) each number of eye-drops used, (c) per season and (d) at specific times of day. The average IOP (SD) of the mild, moderate and severe stage was 12.6 (3.0), 12.5 (2.9) and 12.5 (2.8) mm Hg, respectively, of the 1-drop, 2-drop, 3-drop and 4-drop regimens used was 12.4 (2.7), 13.9 (2.9), 13.3 (2.8) and 11.3 (2.9) mm Hg, respectively, in Spring, Summer, Autumn and Winter was 12.8 (2.7), 12.1 (2.8), 12.4 (3.0) and 12.9 (3.0) mm Hg, respectively, and at 09:00–12:00, 12:00–15:00 and 15:00–18:00 was 12.9 (3.0), 12.5 (2.8) and 12.2 (2.9) mm Hg, respectively. In regard to the time of day, average IOP at 09:00–12:00 was the highest; however, in the general linear mixed-effects model after adjusting for confounding factors, IOP at 15:00–18:00 was relatively higher. IOP, intraocular pressure.

The results of the multivariable analysis using daily climatic factors were similar to those using hourly factors (online supplemental table 4). A significant negative association with IOP was found for daily ambient temperature (Est=−0.030 (SE=0.009,

95%CI −0.047 to −0.013, $p=0.008$)), as well as in hourly ambient temperature.

In the subgroup analysis according to the glaucoma stage, a significant negative association between IOP and ambient temperature was observed in patients with Severe-stage glaucoma (Est=−0.052 (SE=0.014, 95%CI −0.079 to −0.025, $p=0.002$)) (online supplemental table 5). Similarly, according to the number of eye-drops used, a significant negative

Table 2 Results of generalised linear mixed effects model analysis

Factors	Estimates (SE)	95% CI	P value*
Patient age (years)	0.035 (0.013)	0.010 to 0.060	0.08
Mean deviation (dB)	0.010 (0.028)	−0.045 to 0.065	NS
Corneal curvature radius (mm)	0.707 (0.723)	−0.724 to 2.138	NS
Central corneal thickness (μm)	0.012 (0.005)	0.003 to 0.021	0.17
Axial length (mm)	−0.017 (0.103)	−0.222 to 0.187	NS
Mean blood pressure (mm Hg)	0.021 (0.004)	0.014 to 0.029	<0.001
Ambient temperature (°C)	−0.029 (0.008)	−0.045 to −0.014	0.003
Atmospheric pressure (hPa)	−0.012 (0.007)	−0.025 to 0.002	NS
Sunlight duration (hours)	0.014 (0.010)	−0.006 to 0.035	NS
Gender			NS
Glaucoma type			<0.001
Number of eye-drops used			<0.001
Season			0.15
Time of day			0.022

NS indicates a $p>0.050$ before Bonferroni correction.
 *p value after Bonferroni correction.
 NS, not significant.

Table 3 Results of generalised linear mixed-effects model analysis for categorical variables

Factors	Estimates (SE)	95% CI	P value*
Glaucoma type (Re: NTG)			
HTG	2.522 (0.405)	1.721 to 3.323	<0.001
Number of eye-drops used (Re: 4)			
1	2.461 (0.693)	1.090 to 3.832	0.002
2	3.561 (0.739)	2.097 to 5.024	<0.001
3	2.951 (0.588)	1.787 to 4.114	<0.001
Time of day (Re: 09:00–12:00)			
12:00–15:00	0.239 (0.096)	0.050 to 0.428	0.026
15:00–18:00	0.366 (0.103)	0.165 to 0.568	<0.001

*P value after Bonferroni correction.
 HTG, high-tension glaucoma; NTG, normal-tension glaucoma.

association between IOP and ambient temperature was observed in the 3-drop regimen patients (Est = -0.058 (SE = 0.017 , 95% CI -0.091 to -0.025 , $p = 0.007$)) and in the 4-drop regimen patients (Est = -0.068 (SE = 0.022 , 95% CI -0.111 to -0.025 , $p = 0.025$)) (online supplemental table 6). The subgroup analysis to compare the impact of ambient temperature on IOP between the NTG group and HTG group revealed a significant negative correlation between IOP and ambient temperature exclusively in the NTG group. In contrast, no significant relationship was observed in the HTG group (data not shown).

DISCUSSION

In the current study, we focused on which climatic factors could contribute to IOP fluctuation in patients with stable POAG under medical treatment, and we found that among the factors examined, ambient temperature showed a significant, negative, and independent contribution to IOP fluctuation. The findings were also compatible with those in the previous studies^{15–22} indicating that IOP of POAG patients showed seasonal variation. However, in those previous studies, that relationship was evaluated only by using the average seasonal or monthly IOP, without taking into consideration the effects of factors possibly correlating with IOP measurement findings. Hence, and to the best of our knowledge, this is the first study to evaluate the relationship between ambient temperature and IOP in patients with stable POAG under medical treatment after adjusting for possible confounding effects of seasonal,^{7–22} diurnal,^{8–10} 23–25 ophthalmic⁹ 11 16 19 26 and systemic⁸ 9 11 15 16 26 27 factors.

Among the variable fixed effects, BP also correlated with the IOP of patients with stable POAG under medical treatment, independently of other factors. A significant correlation between IOP and BP in general populations,⁸ 9 11 15 16 26 27 as well as between ambient temperature and BP,²⁹ 30 has been reported, which suggests that the observed significant correlation between IOP and ambient temperature could be attributable to the correlation between IOP and BP and between ambient temperature and BP. However, our current multivariable analysis findings indicated that ambient temperature and BP could affect IOP independently. In living organisms, a low temperature can be considered 'cold stress' that induces sympathetic nervous system activity.³³ A circadian rhythm of IOP is under the control of sympathetic and parasympathetic nerve activity, and the findings in a previous study showed increased AH formation via the administration of epinephrine or other adrenergic agonists, as well as decreased AH formation by β -adrenergic antagonists, being compatible with increased IOP due to sympathetic nervous system activity.⁶

In the subgroup analysis, we found a significant relationship between ambient temperature and IOP only in patients who had severe-stage glaucoma or who were using multiple eye-drops. Further research with larger cohorts is needed to clarify the potential relationship in mild-stage glaucoma or FP agonist monotherapy. Regarding glaucoma type, a significant negative correlation between IOP and ambient temperature was observed exclusively in the NTG group. However, since the sample size of the HTG group in our cohort was relatively small, this lack of a statistically significant correlation in the HTG group may be attributable to insufficient statistical power rather than a true absence of association.

Shamshad *et al.*³⁴ and Fabiani *et al.*³⁵ reported a positive relationship between temperature and IOP via direct warming or cooling of the eyeball, which may be inconsistent with our current findings. However, this apparent discrepancy could

possibly be explained by the difference between temperature change limited to the eyeball³⁴ 35 and temperature change in the environment affecting the entire body, and the presence of 'negative feedback' for homeostasis in the living body³⁶ which was not the case in temperature changes limited to the eyeball.³⁴ 35

In this present study, we investigated whether outdoor temperature could be correlated with IOP measured indoors, and we found a significant relationship not only for the hourly outdoor temperature but also for the daily outdoor temperature, despite the mean hourly outdoor temperature being 2.5°C higher than the mean daily outdoor temperature (ie, $19.3^{\circ}\text{C} \pm 9.2^{\circ}\text{C}$ vs $16.8^{\circ}\text{C} \pm 8.7^{\circ}\text{C}$). These findings demonstrate that outdoor temperature is reliably correlated with IOP, even when IOP is measured indoors. Moreover, this consistent finding suggests that any potential discrepancy between indoor and outdoor temperatures had a negligible impact on our primary finding. In contrast, Saeki *et al.*³⁷ reported a greater impact of indoor temperature than outdoor temperature on BP using home-based measurements. Hence, determination of the potential discrepancy between the effects of indoor and outdoor temperatures on IOP fluctuation needs to be further investigated in future studies, such as those focusing on 24-hour IOP profiles, where home-based measurements are expected to be the predominant findings used in the study.

In this study, our findings indicated that the time interval of 09:00–12:00 was a factor associated with lower IOP as compared with measurements taken at 15:00–18:00, and 50% of the subjects in our study used eye-drops other than FP agonist, that is, those subjects used ocular hypotensive drops before 09:00, in which the peak effect was expected in the late morning.

It should be noted that this study had several limitations. First, there are other factors that could have been included as explanatory variables or fixed effects. For example, since this was a retrospective study, lifestyle-related factors such as exercise or obesity,²⁸ as well as blood biochemistry³⁸ findings, could not be included in the current analysis. Those factors should be included in a future prospective study involving a larger sample size. Second, this study focused exclusively on subjects without any changes in their eye-drop regimens to exclude the confounding effects of medication changes on IOP. Investigating the impact of ambient temperature changes in patients with poorly controlled IOP is challenging, as such patients cannot be ethically maintained on a stable medication regimen without intervention, including glaucoma surgery.

In conclusion, the findings in this study revealed that ambient temperature was one of the independent factors with a significant negative correlation with IOP in patients with stable POAG under medical treatment, and that the responsiveness of IOP to ambient temperature is greater in patients with severe-stage glaucoma, which should be considered in a comprehensive POAG treatment strategy.

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