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ORIGINAL STUDY

Association Between Plasma Endothelin-1 and Severity of Different Types of Glaucoma

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Purpose: Endothelin-1 (ET-1) has been suggested to play an important role in the pathogenesis of glaucoma. Herein, we studied whether increased levels of plasma ET-1 are associated with changes in the visual field and changes in optical coherence tomography (OCT)-measured retinal nerve fiber layer (RNFL) thickness in patients with different types of glaucoma.

Patients and Methods: Plasma concentration of ET-1 was determined in 31 patients with primary open-angle glaucoma, 18 patients with normal tension glaucoma, 16 patients with primary angle-closure glaucoma, and in 37 normal controls. In all participants, visual field testing was performed and OCT was used to measure RNFL thickness. The correlation between mean ET-1 level and changes in the visual field (mean deviation, dB) and changes in OCT-measured RNFL thickness in 1 randomly selected eye from each patient in each group was then evaluated.

Results: The ET-1 level was 3.27 ± 1.25 pg/mL in the primary open-angle glaucoma group (-14.09 ± 8.76 dB), 3.12 ± 1.46 pg/mL in the normal tension glaucoma group (-8.87 ± 6.15 dB), $2.58 \pm .22$ pg/mL in the primary angle-closure glaucoma group (-14.55 ± 10.2 dB), and 1.53 ± 1.49 pg/mL in the control group. Although mean ET-1 levels were significantly higher in all 3 of the glaucoma groups than in the control group, there was no significant difference in ET-1 level among the 3 glaucoma groups. In addition, no significant correlation was found between levels of plasma ET-1 and structural or functional changes in patients with different types of glaucoma.

Conclusions: There was no correlation between plasma levels of ET-1 and severity of glaucoma. The role ET-1 plays in the pathogenesis of glaucoma remains to be determined.

Key Words: ET-1, glaucoma severity, RNFL thickness, glaucoma type

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Endothelin-1 (ET-1) is a potent vasoconstrictor and has been suggested to play an important role in the pathogenesis of glaucoma.[1–13] However, the role ET-1 plays in different types of glaucoma is unclear[3–9] and its association with glaucoma severity has not yet been determined. Although some studies have shown that increased plasma ET-1 levels are associated with the development and severity of normal tension glaucoma (NTG) and high-tension primary open-angle glaucoma (POAG),[3,4,9] other studies have shown a lack of association between ET-1 levels and the development of those 2 types of glaucomatous optic neuopathy.[5–8] Few studies have evaluated the role of ET-1 in primary angle-closure glaucoma (PACG), which is an important glaucoma type in Chinese populations. To better understand the differences in the pathogenesis of PACG and POAG, several studies have compared the variability in structural and functional damage between those 2 types of glaucoma.[14–17] In our previous study, we found there was no significant difference between the POAG and PACG eyes as far as various GDx VCC-measured retinal nerve fiber layer (RNFL) parameters were concerned.[14] In addition, Sihota et al[18] found that optical coherence tomography (OCT) may serve as a useful diagnostic modality in distinguishing a normal optic disc from a glaucomatous one. OCT is a noninvasive, noncontact, transpupillary imaging technology that has been demonstrated to provide objective, quantitative, and reproducible structural measurements of RNFL thickness.[14–18] In this study, we investigated whether the levels of plasma ET-1 differed between patients with different types of glaucoma, namely POAG, NTG, and PACG, and studied whether increased levels of plasma ET-1 are associated with changes in the visual field and changes in OCT-measured RNFL thickness in patients with different types of glaucoma.

PATIENTS AND METHODS

This prospective, cross-sectional study included 102 study patients (65 patients with glaucoma and 37 normal controls). The patients with clinically diagnosed glaucoma, including 31 with POAG, 18 with NTG, and 16 with PACG, received regular treatment in the Department of Ophthalmology, China Medical University Hospital (CMUH). Patients with normal eyes were volunteers from the staff at the CMUH. All procedures were performed according to the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants, and the study was approved by the Institutional Review Board of the CMUH.

Each participant underwent a complete ophthalmic examination, including slit-lamp biomicroscopy, gonioscopy, pachymetry, Goldmann applanation tonometry, stereoscopic examination of the optic disc and fundus, and standard automated perimetry (30-2 mode, Humphrey Field Analyzer, model 750, HFA; Carl Zeiss Meditec, Inc.).

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Patients with a best-corrected visual acuity of <20/40, a spherical equivalent outside ± 5.0 diopters, and a cylinder correction >3.0 diopters in either eye were excluded. In addition, patients with eyes with coexisting retinal disease, uveitis or nonglaucomatous optic neuropathy (GON), and patients with a clinical history of systemic vascular or circulatory disorders, including hypertension, heart disease, renal disease, or diabetes mellitus were excluded from this study.

Normal control eyes were defined as eyes with a normal-looking optic disc head and an intraocular pressure (IOP) ≤21 mm Hg in patients with a normal visual field result and without a history of increased IOP. A normal visual field was defined as a mean deviation (MD) and pattern SD within 95% confidence limits, and a glaucoma hemifield test result within normal limits.

Glaucomatous eyes were defined as those with GON and evidence of visual field loss. GON was defined as a cup-to-disc asymmetry between fellow eyes of >0.2, rim thinning, notching, excavation, or RNFL defect. Visual field reliability criteria included fixation losses and false-positive and false-negative rates of <20%. The evaluation of glaucomatous visual field defects was made based on the following liberal criteria: 2 or more contiguous points with a pattern deviation sensitivity loss of $P < 0.01$, or 3 or more contiguous points with sensitivity loss of $P < 0.05$ in the superior or inferior arcuate areas, or a 10 dB difference across the nasal horizontal midline at 2 or more adjacent locations and an abnormal result on the glaucoma hemifield test.[19] Inclusion criteria for the patients with POAG included an initial IOP >21 mm Hg as measured by Goldmann applanation tonometry, the presence of an open angle on gonioscopy, stereoscopic evidence of optic disc excavation typical of GON, and a reproducible glaucomatous visual field defect in the absence of any other abnormalities to explain the defect. Inclusion criteria for the patients with NTG included no evidence of IOP higher than 21 mm Hg, the presence of open anterior chamber angle, glaucomatous changes in the optic nerve head (ONH), corresponding visual field damage, and the absence of alternate causes of optic neuropathy. Inclusion criteria for the patients with PACG included the following: (1) definitive gonioscopic findings demonstrating at least 180 degrees of peripheral anterior synechiae; (2) an IOP of more than 21 mm Hg on at least 2 separate occasions; and (3) a GON with a visual field loss consistent with optic nerve damage. All of the patients with clinically confirmed PACG experienced an acute attack (IOP >40 mm Hg) of angle closure within 5 years before enrollment into the study. The IOP in all of the patients in this study was maintained within normal limits by laser treatment, glaucoma surgery, or antiglaucoma medication during the study period.

Stratus OCT Measurements

The Stratus OCT system (Version A 4.0.1, Carl Zeiss Meditec Inc., Dublin, CA) was used to measure RNFL thickness in all of the participants in this study. The OCT protocol included a regular 3.4 mm circular scan and quality assessment of the scans was determined by an experienced examiner. Criteria for good quality scans included the following: a well-focused ocular fundus image; a signal strength >6; and the presence of a well centered circular ring around the optic disc. One eye from each patient was selected as the study eye and the average RNFL thickness values in the temporal, superior, nasal, and inferior quadrants were used as the study parameters.

Plasma ET-1 Measurement

Venous blood samples were obtained after 30 minutes of rest in a sitting position. Plasma was immediately separated by centrifugation and frozen at −80°C. The ET-1 concentration was measured using an enzyme-linked immunosorbent assay (ELISA; R&D, Inc., Minneapolis, MN). In our study, plasma ET-1 was determined from the mean of 2 wells for each plasma sample. An internal calibration was performed with purified ET-1 at different concentrations during each assay.

The perimetry and OCT examinations were all performed within a maximum period of 2 weeks. If the tests were done on the same day, the perimetry examination was done first. Blood obtained from each patient was drawn on the same day as that for visual field testing.

STATISTICAL ANALYSIS

Statistical analyses were performed on a personal computer using the statistical package SPSS (Version 18, SPSS, Chicago, IL). Differences in age, sex, refraction, MD, and RNFL thickness measured by the Stratus OCT system among groups were evaluated by analysis of variance or the Fisher exact test. One randomly selected eye from each patient was chosen for further analysis. Multiple linear regression was applied to compare the correlations between plasma ET-1 and MD (or average RNFL thickness) in normal and glaucoma groups after adjusting for the effects of all potential confounding variables (such as age and refraction).

RESULTS

Patient characteristics are listed in Table 1. The mean age of participants in the control group was 51.97 ± 17.06 years and the mean age of patients with POAG was 48.94 ± 16.77 years. The mean age of patients with NTG was 47.06 ± 14.78 years and that of patients with PACG was 64.56 ± 9.83 years. Although there was a significant difference in age and sex among the 4 groups, only age differed significantly among the 3 glaucoma groups. The ET-1 level was 1.53 ± 1.50 pg/mL in the normal group, 3.27 ± 1.26 pg/mL in the POAG group, 3.12 ± 1.48 pg/mL in the NTG group, and 2.58 ± 1.24 pg/mL in the PACG group. Although the level of plasma ET-1 was higher among the patients with glaucoma than among participants in the control group, there was no significant difference in ET-1 among 3 glaucoma groups.

To further compare the functional and structural measurements among the 4 groups, 1 randomly selected eye from each patient was chosen for further analysis. As shown in Table 1, the average MD was −1.58 ± 1.06 dB in the control group, −14.09 ± 8.76 dB in POAG group, −8.87 ± 6.15 dB in NTG group, and −14.55 ± 10.2 dB in PACG group. Although there were significant differences in visual field severity, refraction status and RNFL thickness among the 4 groups, there was no significant difference in RNFL thickness and visual field severity among the 3 glaucoma groups. To better understand the difference between POAG and PACG, multiple comparisons were done and the results show that only age and refraction were significant.

TABLE 1. Comparisons of Demographic Data Among 4 Groups/3 Glaucoma Groups

	Normal (N = 37)	POAG (N = 31)	NTG (N = 18)	PACG (N = 16)	*P* (4 Groups)	*P* (3 Groups)‡
Age (y)	51.97 ± 17.06	48.94 ± 16.77* (*P* = 0.417)§	47.06 ± 14.78 (*P* = 0.265)§	64.56 ± 9.83* (*P* = 0.003)§	0.006*	0.001*
Sex (Male/female)	19/18	27/4	12/6	10/6	0.015†	0.113†
ET-1 (pg/mL)	1.53 ± 1.50	3.27 ± 1.26 (*P* < 0.001)§	3.12 ± 1.48 (*P* < 0.001)§	2.58 ± 1.24 (*P* = 0.010)§	< 0.001*	0.239*
One randomly selected eye						
MD, mean ± SD (dB)	−1.58 ± 1.06	−14.09 ± 8.76	−8.87 ± 6.15	−14.55 ± 10.2	< 0.001*	0.082*
PSD, mean ± SD (dB)	1.43 ± 1.30	9.27 ± 4.20	8.05 ± 4.76	6.70 ± 3.39	< 0.001*	0.140*
Refraction, mean ± SD (Diopters)	−0.67 ± 1.67	−2.96 ± 2.14‖	−3.50 ± 2.19	1.64 ± 0.44‖	< 0.001*	< 0.001*
Average RNFL thickness (μm)	107.77 ± 8.95	69.89 ± 21.47	76.30 ± 18.27	71.67 ± 23.50	< 0.001*	0.593*
Temporal quadrant thickness (μm)	81.86 ± 17.04	59.84 ± 26.41	63.89 ± 23.12	60.38 ± 21.78	< 0.001*	0.848*
Superior quadrant thickness (μm)	132.65 ± 16.82	85.61 ± 30.01	92.94 ± 25.69	79.94 ± 33.82	< 0.001*	0.448*
Nasal quadrant thickness (μm)	79.35 ± 19.65	58.48 ± 12.94	66.00 ± 11.08	58.50 ± 12.13	< 0.001*	0.095*
Inferior average thickness (μm)	137.27 ± 15.45	75.68 ± 28.07	82.17 ± 32.37	87.63 ± 37.95	< 0.001*	0.464*

*ANOVA
†Fisher exact test
‡Three glaucoma groups
§Compared with normal group (by multiple regression)
‖Significant difference between POAG and PACG by post hoc tests of ANOVA.
ANOVA indicates analysis of variance; ET-1, endothelin-1; MD, mean deviation; NTG, normal tension glaucoma; PACG, primary angle-closure glaucoma; POAG, primary open-angle glaucoma; PSD, pattern SD; RNFL, retinal nerve fiber layer.

Figure 1 shows the comparisons of the correlations between plasma ET-1 and MD (dB) in normal and glaucoma groups without adjusting for the effects of age and refraction. Figure 2 shows the comparisons of the correlations between plasma ET-1 and average RNFL thickness in normal and glaucoma groups without adjusting for the effects of age and refraction. Multiple linear regression models were constructed to measure the age-adjusted and refraction-adjusted effects of ET-1 level on MD (dB)/average RNFL thickness in normal controls and patients with different types of glaucoma (Table 2). Compared with the normal group, the change of ET-1 level per dB is not significant in each of glaucoma group (POAG vs. normal, NTG vs. normal, PACG vs. normal: 0.315, 0.333, 0.226 pg/mL/dB, respectively). Compared with the normal group, the change of ET-1 level per micron is not significant in each of glaucoma group (POAG vs. normal, NTG vs. normal, PACG vs. normal: 0.004, 0.018, 0.025 pg/mL/μm, respectively).

Table 3 shows the correlation between plasma ET-1 level and MD/RNFL thickness parameters in each group. There were no significant correlations between ET-1 level and functional measurements (MD, pattern SD) or structural measurement (RNFL thickness) in each group.

DISCUSSION

Glaucoma is an optic neuropathy associated with progressive RNFL thinning and remodeling of the ONH and a corresponding pattern of visual field loss.[13] Increased IOP is the most important risk factor for glaucoma, but the

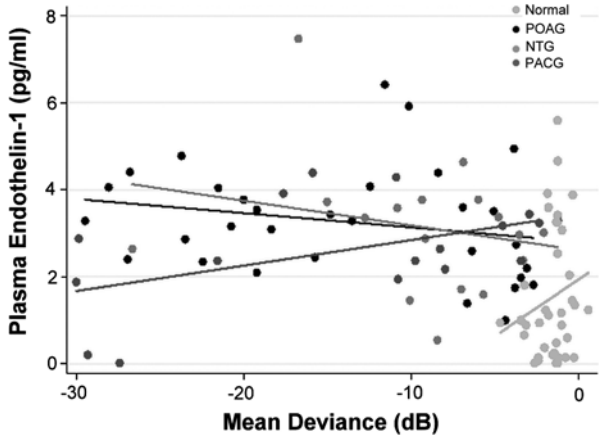

FIGURE 1. Comparisons of the correlations between plasma endothelin-1 and mean deviation in normal and glaucoma groups without adjusting for the effects of age and refraction.

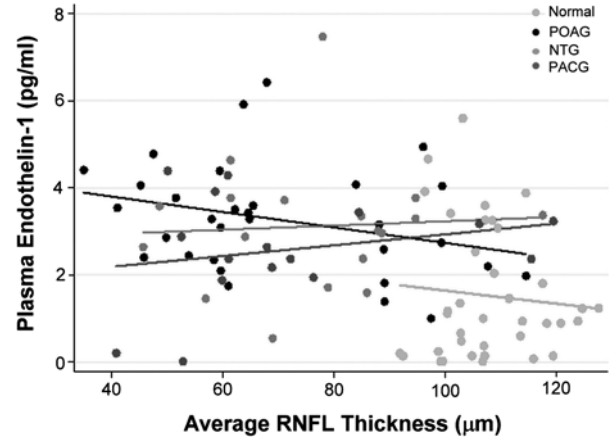

FIGURE 2. Comparisons of the correlations between plasma endothelin-1 and average retinal nerve fiber layer (RNFL) thickness in normal and glaucoma groups without adjusting for the effects of age and refraction.

TABLE 2. Compare the Correlations Between Plasma ET-1 Level and MD/Average RNFLThickness After Adjusting the Effects of Age and Refraction Using the Multiple Linear Regression, Based on 1 Randomly Selected Eye

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Parameter	β	Standard Error	Wald χ^2	*P*
Age	0.006	0.0113	0.282	0.595
Refraction	−0.038	0.0966	0.157	0.692
PACG vs. Normal	1.439	0.7515	3.669	0.055
NTG vs. Normal	0.618	0.6904	0.802	0.371
POAG vs. Normal	0.771	0.6306	1.494	0.222
MD	0.282	0.2169	0.282	0.193
PACG × MD*	−0.226	0.2201	0.157	0.304
NTG × MD*	−0.333	0.2230	3.669	0.135
POAG × MD*	−0.315	0.2183	0.802	0.149
Age	0.005	0.0111	0.192	0.661
Refraction	−0.050	0.0971	0.265	0.606
PACG vs. Normal	−1.160	2.9685	0.153	0.696
NTG vs. Normal	−0.347	3.0366	0.013	0.909
POAG vs. Normal	1.399	2.8254	0.245	0.621
AveRNFL	−0.013	0.0252	0.275	0.600
PACG × AveRNFL*	0.025	0.0293	0.725	0.394
NTG × AveRNFL*	0.018	0.0307	0.361	0.548
POAG × AveRNFL*	−0.004	0.0275	0.018	0.893

*Interaction terms between group and MD/AveRNFL (Average RNFL thickness).

ET-1 indicates endothelin-1; MD, mean deviation; NTG, normal tension glaucoma; PACG, primary angle-closure glaucoma; POAG, primary open-angle glaucoma; PSD, pattern SD; RNFL, retinal nerve fiber layer.

pathogenesis of glaucoma is multifactorial and unclear.[2,13] The role increased IOP plays in glaucomatous change remains to be elucidated.[2] Studies have shown that some patients might not develop glaucomatous changes despite increased IOP, whereas other patients show evidence of glaucomatous changes in the absence of increased IOP.[2,20,21] Ischemia and vascular dysregulation have been implicated in the pathogenesis of GON, and ET-1 has been demonstrated to be a key player in regulation of ocular perfusion and perhaps in the overall pathogenesis of glaucoma.[1,2,10–13,21] In this study, we found that although the mean level of ET-1 was higher in all of the glaucomatous groups than in the control group, there were no significant differences in mean ET-1 level among the 3 types of glaucoma (POAG, 3.27 ± 1.25 pg/mL, −14.09 ± 8.76 dB; NTG, 3.12 ± 1.46 pg/mL, −8.87 ± 6.15 dB; and PACG, 2.58 ± 1.22 pg/mL, −14.55 ± 10.2 dB). The results indicate a possible association between ET-1 and the development of glaucomatous changes.

Gazzard et al[15] compared the correlation between visual field loss and pretreatment IOP in the pathogenesis of PACG and POAG and found that increased IOP played a more important role in optic nerve damage in PACG than in POAG and that other, less pressure-dependent mechanisms were responsible for the development of POAG. Another important finding is that IOP reduction might not fully prevent progression of NTG disease, which indicates that factors other than increased IOP are involved in the pathogenesis of NTG.[21] Therefore, NTG and POAG represent a continuum of open-angle glaucoma, in which a certain level of IOP is the predominant causative risk factor in POAG, whereas additional IOP-independent factors are involved in the pathogenesis of NTG.[21] Therefore, it is fair to say that there is considerable overlap between POAG and NTG.[10] To further understand the role ET-1 plays in POAG and PACG, 1 recent study have tried to investigate the levels of ET-1 and nitric oxide (NO) in the aqueous humor and plasma in the 2 groups of glaucoma patients.[22] They speculated that ET-1 and NO may represent as a result of glaucoma damage but may not be a leading cause for it. Although the current result shows some association between ET-1 and glaucoma, it is not appropriate to conclude the role ET-1 plays in glaucoma at this moment too. AQ5

Few studies have investigated the association between ET-1 and the severity of glaucoma. In this study, we found no correlation between ET-1 level and structural and functional changes among the 3 types of glaucoma. In addition, the correlation between ET-1 and structural/functional measurements was not consistent in each glaucoma group. Possible reasons for this might be related to the small sample size, relatively large standard deviation of ET-1 level, and more advanced stages of glaucomatous eyes in our study.[8,9]

There are some limitations in this study. First, the small sample size in the NTG and PACG groups might have influenced the statistical outcome. Second, selection bias of

TABLE 3. The correlations Between Structural/Functional Parameter and Plasma Endothelin-1 in Each Group

	Normal	*r*	R^2	*P*	POAG	*r*	R^2	*P*
MD (dB)	1.940 + 0.261 X	0.183	0.034	0.277	2.807-0.033X	−0.229	0.052	0.216
PSD (dB)	1.978-0.315X	−0.272	0.074	0.104	2.595 + 0.073X	0.243	0.059	0.188
Average RNFL (μm)	3.154-0.015X	−0.090	0.008	0.598	4.509-0.018X	−0.303	0.092	0.098
Temporal (μm)	−1.402 + 0.036X	0.405	0.164	0.013	4.050-0.013X	−0.274	0.075	0.136
Superior (μm)	1.544 + 0.0001X	−0.001	< 0.001	0.994	4.169-0.011X	−0.251	0.063	0.173
Nasal (μm)	3.161-0.021X	−0.269	0.072	0.108	4.348-0.018X	−0.190	0.036	0.307
Inferior (μm)	5.689-0.030X	−0.311	0.097	0.061	4.253-0.013X	−0.290	0.084	0.114
	NTG	*r*	R^2	*P*	**PACG**	*r*	R^2	*P*
MD (dB)	2.619-0.057X	−0.235	0.055	0.348	3.435 + 0.059X	0.484	0.234	0.058
PSD (dB)	2.803 + 0.039X	0.127	0.016	0.616	2.577 + 0.001X	0.001	< 0.001	0.996
Average RNFL (μm)	2.755 + 0.005X	0.059	0.003	0.816	1.690 + 0.012X	0.236	0.056	0.379
Temporal (μm)	2.799 + 0.005X	0.079	0.006	0.757	2.519 + 0.001X	0.018	< 0.001	0.948
Superior (μm)	3.219-0.001X	−0.018	< 0.001	0.943	1.117 + 0.018X	0.500	0.250	0.048
Nasal (μm)	1.129 + 0.030X	0.225	0.051	0.368	1.768 + 0.014X	0.136	0.019	0.615
Inferior (μm)	3.036 + 0.001X	0.022	0.001	0.929	2.341 + 0.003X	0.084	0.007	0.758

MD indicates mean deviation; NTG, normal tension glaucoma; PACG, primary angle-closure glaucoma; POAG, primary open-angle glaucoma; PSD, pattern SD; RNFL, retinal nerve fiber layer.

the study population does exist in this study too. For example, the mean age of the patients in the PACG group (64.56 ± 9.83 y) was much higher than that in the other 2 glaucoma groups (POAG, 48.94 ± 16.77 y; NTG, 47.06 ± 14.78 y). In addition, in this group of patients, lens opacity might have influenced the quality of the OCT images. To have reliable RNFL thickness data, it is necessary to have strict imaging criteria, which might generate some kind of selection bias. Third, the clinical relevance of plasma ET-1 level in glaucoma remains to be clarified. Unbound ET-1 lasts < 2 minutes in plasma; therefore, the effect of ET-1 in the body lasts approximately 1 hour due to the irreversible binding of ET-1 to its receptor, ET_A and ET_B.[2,23] ET_A receptors are found in retinal and choroidal vasculature and the iris and ET_B receptors are found in retinal neurons and glial cells in addition to cilliary processes.[2,23] ET_A and ET_B receptors have also been detected in the lamina cribrosa of the ONH, suggesting that ET-1 plays a role in local extracellular matrix remodeling and vascular tone.[2] The biological effects of ET stem from both vascular and cellular effects through the interplay of both ET_A and ET_B receptors.[2,23,24] Therefore, ET-1 plasma level could not reflect the real physiological action of ET-1 in humans. We strongly believe this is the most plausible reason to result in contradictory role of plasma ET-1 level in different glaucoma type across the studies. Accordingly, the data presented in this study do not allow us to draw any conclusion about the role ET-1 plays in the pathogenesis of glaucoma.

Vascular dysregulation and altered ocular blood flow contribute to ischemic damage to the ONH and retinal ganglion cells and, therefore, play major roles in the progression of glaucoma.[25] Polak et al[26] showed that exogenous ET-1 administration resulted in significant reduction in optical nerve head and choroidal blood flow, whereas administration of BQ123, a potent ET_A receptor antagonist, attenuated the effects of ET-1. In another study, the authors found that exogenous ET-1 administration decreased retinal blood flow, but that it was attenuated by BQ123, whereas finding no change in retinal vessel diameter with ET-1 administration.[26] In addition to functioning as a vascular regulator, ET-1 has been shown to play multiple roles in the pathogenesis of glaucoma.[2] Studies have shown that ET-1 expression in ciliary bodies and trabecular meshwork plays a role in the regulation of aqueous humor outflow.[27,28] Furthermore, ET-1 has been found to be involved in retinal ganglion cell apoptosis.[29,30] Moreover, ET-1 has been linked to other glaucoma-associated effects on the optic nerve and retinal ganglion cells including astrogliosis,[31] extracellular matrix remodeling,[23] NO-induced oxidative damage,[32] disruption of anterograde axonal transport,[33] and glucocorticoid-induced ocular hypertension.[34] Therefore, ET-1 seems to be involved in the pathogenesis of GON; however, further studies are needed to establish whether ET-1 is a potential therapeutic target in the management of glaucoma.

In conclusion, we found no significant correlation between plasma ET-1 and glaucoma severity. Future studies with larger sample sizes are needed to further investigate the role ET-1 plays in the pathogenesis of glaucoma.

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