Plasma endothelin-1 and endothelin-A receptor concentrations in patients with primary open-angle glaucoma

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**ABSTRACT**

Endothelin-1 (ET-1) is a potent vasoconstrictor and is considered to have a key role in the regulation of ocular perfusion and glaucoma pathogenesis. High ET-1 and ET$_A$-receptor levels are reported in patients with primary open-angle glaucoma (POAG). We compared the mean plasma ET-1 and ET$_A$-receptor concentration of controls with patients with normal and advanced POAG stage, and assessed the correlation with the visual field parameters. The study included a total of 25 participants, aged 45–83 years: 25 (controls), 22 (early glaucoma) and 28 (advanced glaucoma). The plasma concentration of ET-1 and ET$_A$-receptor was determined by enzyme-linked immunosorbent assay. The RNFL thickness was evaluated with spectral-domain optical coherence tomography. The mean ET-1 concentration was lower in the control group (4.88 ± 1.75 pg/mL) than in the early and advanced POAG group (6.33 ± 2.38 and 6.34 ± 1.56 pg/mL). Statistically significant difference was found between the mean ET-1 concentrations in controls and glaucoma patients (p = 0.029 – early glaucoma, p = 0.018 – advanced glaucoma), and no significant difference was observed between the two POAG groups (p = 0.998). The mean ET$_A$-receptor concentration was highest in the control group (1209.28 ± 314.48 pg/mL) and the differences between the three groups were significant. Significant relationship was found only between ET-1 and RNFL. This study demonstrated the role of ET-1 in glaucoma pathogenesis based on the observed significant high ET-1 and ET$_A$-receptor plasma levels in POAG patients. A new therapeutical approach needs to be considered in some patients.

**Introduction**

Endothelin-1 (ET-1) is one of the three isoforms of endothelin. This hormone is among the most powerful vasoconstrictors [1]. It was discovered by Yanagisawa et al. in 1988 [2] and for the first time was isolated, described and cloned using porc aortic endothelial cells.

It is a peptide consisting of 21 amino acids and originates from the vascular endothelial cells with the help of endothelin-converting enzyme (ECE). ET-1 affects the target cells by connecting with two receptors, type A (ET$_A$) and type B (ET$_B$) [3]. Vascular endothelial cells are the main source of endothelin, but a variety of other cell types also participate in its production, like the endothelium of renal tubules, glomerular mesangium, cardiac myocytes, glia, pituitary gland, macrophages, mast cells, etc. [4]. There are two types of ECE: ECE-1 and ECE-2. ECE-1 is a membrane-linked metalloproteinase, which releases both intra- and extra-proendothelin-1 in basic pH medium and structurally refers to the neutral endopeptidases. ECE-2 has acidic pH optimum and acts as an intracellular enzyme [5].

ET$_A$ receptor is expressed on the smooth muscle cells of the vessels and causes their contraction through an influx of Ca$^{2+}$ followed by vasoconstriction. Two subtypes of ET$_B$ receptor are distinguished. ET$_{B1}$ is expressed on the vascular endothelial cells and mediates direct vasodilatation through NO release and its transit to the smooth muscle cells with subsequent relaxation. The other subtype, ET$_{B2}$, is situated on the smooth muscle cells and mediates direct vasoconstriction [3,6].

Lungs and kidneys are mainly responsible for the ET-1 plasma clearing, so in cases of lung and kidney diseases, the plasma levels of ET-1 increase. Besides the local paracrine function in the vascular tonus regulation, ET-1 has an impact on the development of atherosclerosis and cardiovascular diseases [5,7]. The plasma ET-1 concentration suffers dynamics also in many adrenal diseases, like primary aldosteronism, pheochromocytoma, hypocorti- cism and hypercorticism [8].
It is also known that ET-1 has a role in the pathogenesis of acute renal failure, following renal ischemia. Increased levels of ET-1 are found in acute renal failure, hypertension, heart failure, ischemic heart disease, Prinzmetal angina, pulmonary hypertension, Raynaud’s disease, subarachnoid hemorrhage, cerebral vasospasm, migraine and diabetes [5,9].

ET-1 is normally found in the eye, where it is produced by the non-pigmented ciliary epithelium and is released into the intraocular liquid [10]. Its receptors are expressed upon various structures, like iris, ciliary muscle, trabecular meshwork (TM), vasculature, retinal and optic nerve astrocytes, which determines the physiological role of ET-1 in the eye [11–13].

After establishing increased levels of ET-1 in the anterior chamber fluid of glaucoma patients, ET-1 has also been considered to play a role in the pathogenesis of glaucoma [14]. ET-1 is associated with retinal ganglion cells death. It has been proved that the intravitreal application of ET-1 in rats has a direct effect upon the anterochamber and retrograde axonal transport in the ganglion cells and causes dose- and time-dependent death [15–17]. These effects can partly be explained by the caused vasoconstriction of the optic disc and retinal microvessels. Some studies, using different animal models, could successfully provoke an optic disc impairment and enlargement of the excavation through ET-1 induced ischemia [18,19]. Another damaging mechanism of ET-1 on the optic disc is proposed by Prasanna et al. [12,20]. It states that the increased proliferation of astrocytes under the influence of ET-1 causes hypoperfusion, which makes the optic disc more vulnerable to the intraocular pressure (IOP).

General endothelial dysfunction with increased plasma ET-1 concentration has also been considered to have a negative impact on the eye perfusion and to be a risk factor for normal tension glaucoma (NTG). Emre et al. [21] report a group of patients with normal or compensated IOP whose progression in the visual field defect could be associated with increased plasma concentration of ET-1.

The role of ET-1 in the physiology and pathophysiology of the IOP control is still contradictive. Indirect evidence in experimental cell cultures shows that TM has contractility similar to that of smooth muscles. ET-1 is capable of causing contraction of TM and, thus, a decrease in the intertrabecular space with an increase in the resistance of the intraocular fluid outflow. ET-1 also causes contraction of the ciliary muscle and tension on the TM [22]. Since the elucidation that TM and ciliary body express both receptor subtypes for ET-1 and that ET-1 is present in the intraocular fluid, it has been suggested that ET-1 has influence on the IOP by affecting the balance between the functionally antagonistic contractile forces of these tissues. A mechanism of control on IOP has also been considered, namely inhibition of the Na+/K+-ATPase in the non-pigmented ciliary epithelial cells in cultures. In vivo this could mean decreased production of intraocular fluid and, hence, a decrease of IOP [22].

ET-1-induced glaucomatous optic neuropathy has been reported in the eyes of a variety of model animals: rabbits, primates, mice and rats [23]. Intraocular ET-1 injections induce chronic ischemia of the optic nerve that causes retinal ganglion cell-specific death and glaucomatous cupping of the optic nerve head (ONH). A recent meta-analysis [24] shows that statistically significantly high ET-1 plasma levels in glaucoma patients are associated with significantly higher risk for NTG and POAG.

The aim of this study was to compare the mean plasma concentration of ET-1 and its ET A-receptor between a control group and patients with early and advanced stage of primary open-angle glaucoma (POAG) with raised IOP and to evaluate the correlation and the degree of relationship with circumpapillary and macular retinal nerve fibre layer (cpRNFL and mRNFL) thickness changes.

Materials and methods

In this prospective study, which was approved by the Ethics Committee at the Medical University of Sofia, 75 patients were investigated for ET-1 and ET A-receptor plasma levels. We obtained informed consent forms from all participants included in the clinical research. The patients’ age ranged from 45 to 82 years. The gender distribution was 21 men and 54 women. They were divided into three groups:

Group 1 (controls): 25 volunteers aged 45–71 years;
Group 2 (early stage of POAG): 22 patients aged 45–82 years;
Group 3 (advanced stage of POAG): 28 patients aged 45–82 years.

In the control group, healthy volunteers without eye or general diseases were selected. Patients with early and advanced POAG were selected according to the following inclusion criteria: best corrected visual acuity ≥0.2; refraction error in the following range ±4.00 dph and ±1.00 dcyl; IOP above 21 mmHg IOP measured with a Goldmann tonometer; anterior chamber angle III–IV grade of the Shaffer classification; glaucoma damages in
the eye fundus; visual field defects typical for glaucoma and corresponding to that in the ONH. Patients with POAG were divided into early and advanced stage glaucoma group according to the severity of the visual field defect in the Hodapp–Parish–Anderson classification recommended by EGS (European Glaucoma Society). All pathological conditions outside the inclusion criteria were excluded, especially general diseases evidenced by elevated plasma levels of ET-1. Arterial hypertension was not defined as an exclusion factor, because of the wide age range of the participants in this study.

All patients underwent a standard ophthalmic examination, which included: detailed case and family history of ocular and general diseases; refraction and best corrected visual acuity measurement; biomicroscopy; contact central corneal thickness measurement; Goldmann tonometry; indirect gonioscopy using Goldmann lens; indirect fundus biomicroscopy using lens – 90 dpt; Standard automated perimetry (SAP) with Humphrey Field Analyzer–HFA II (Carl Zeiss Meditec, Dublin, CA, USA), algorithm SITA Standard, pattern 24-2. Only reliable damages.

Parrish Analyzer dard automated perimetry (SAP) with Humphrey Field age range of the participants in this study.

Results and discussion

The total number of participants included in the present study was 75, aged 45–83 years, with a mean age of 63.4 ± 8.6 years. The descriptive statistics are shown in Table 1.

The mean ET-1 plasma levels (Table 2) were higher in patients with POAG (6.33 and 6.34 pg/mL) than in healthy controls (4.88 pg/mL). What is more, the mean levels of ET-1 were almost the same in patients with glaucoma: early stage (6.33 pg/mL) and advanced stage (6.34 pg/mL). Maximum ET-1 plasma concentration was found in the advanced glaucoma group (8.44 pg/mL), and minimum concentration in the early glaucoma group (0.43 pg/mL). The mean ETA-receptor plasma concentration was found to be highest in the control group (1209.28 pg/mL) and lower in the glaucoma patients (673.44 pg/mL), and in patients with advanced POAG they were higher (992.28 pg/mL).

Table 1. Descriptive statistics.

| Group          | Gender | N (%) | Mean age ± SD |
|----------------|--------|-------|---------------|
| 1  Controls    | M 6 (27.3) | 56.5 ± 8.8 |
| 45–71 years    | F 19 (35.8) |         |
| All            | 25 (33.3) |         |
| 2  Early stage of POAG | M 5 (22.7) | 66.9 ± 8.5 |
| 45–82 years    | F 17 (32.1) |         |
| All            | 22 (29.3) |         |
| 3  Advanced stage of POAG | M 11 (50.0) | 66.8 ± 8.46 |
| 45–82 years    | F 17 (32.1) |         |
| All            | 28 (37.0) |         |
| Total: 75 (100%) | M 22 (100) | 63.4 ± 8.6 |
|               | F 53 (100) |         |

N, number of participants.

*Mean values with standard deviation (±SD).
The application of inter-group comparative analysis demonstrated a statistically significant difference in the mean ET-1 plasma concentrations between controls and patients with POAG ($p = 0.029$, early POAG; $p = 0.018$, advanced stage) (Table 3). The statistical analysis showed no significant difference in the mean ET-1 concentrations between groups with early and advanced glaucoma stage ($p = 0.998$). Statistically significant differences in the mean ETA-receptor plasma levels were observed between controls and patients with glaucoma ($p < 0.001$, early stage; $p = 0.021$, advanced stage), as well as between the two glaucoma groups ($p = 0.001$).

In 2006, Kunimatsu et al. [25] reported their results from examination of the ET-1 plasma concentration using an immunoenzyme method in three groups of patients: control group (19 subjects), POAG (18 patients) and NTG (30 patients) aged under 60 years. The mean ET-1 plasma concentration value in our cohort was higher than that in the Japanese patients both in the control and glaucoma groups. Kunimatsu et al. [25] found a higher ET-1 plasma level in patients with POAG as compared to the control group ($1.33 \pm 0.50$ pg/mL), but with no statistical significance, unlike our results (Table 4). In 1997, Tezel et al. [14] and, in 2003, Nicolela et al. [9] also did not find significant differences in the ET-1 plasma concentration between healthy and POAG patients as well (Table 4).

In 2012, Cellini et al. [26] examined the ET-1 plasma concentration in 20 controls compared to 20 POAG patients (Table 4). Their results, similar to ours, showed not only higher ET-1 plasma concentration, but also a statistically significant difference between the concentration in healthy and glaucoma patients: $1.75 \pm 0.25$ pg/mL vs. $2.83 \pm 0.28$ pg/mL ($p < 0.001$).

All but one study of the ET-1 plasma concentration found no statistical significance in the difference between healthy and POAG patients. It is possible for the results to have been compromised by imprecise inclusion and exclusion criteria, for numerous endocrine and cardiovascular diseases could influence the ET-1 plasma concentration. The ET-1 plasma levels could also be influenced by the general condition of the patient, whether active or calm, lying down in bed or sitting in a chair.

In 2016, Li et al. [24] performed a meta-analysis in order to combine and summarize the results from several studies analyzing ET-1 plasma levels in NTG patients (7 studies, 212 NTG, 164 controls) and POAG (5 studies, 160 POAG, 174 controls), and also to clarify the association between ET-1 plasma levels and the risk for the mentioned types of glaucoma. They found statistically significant higher ET-1 plasma concentrations in glaucoma patients than in the control group, with a 0.63 pg/mL mean difference ($p = 0.02$) in the POAG group, and 0.60 pg/mL ($p = 0.007$) in the NTG patients. This has been the first meta-analysis so far to investigate the association between ET-1 plasma concentrations and glaucoma. The results showed that statistically significantly high ET-1 plasma levels in glaucoma patients

### Table 2. Mean, maximum and minimum plasma concentration of ET-1 and ETA-receptor.

| Group                  | Parameter (pg/mL) | N   | Mean SD  | Min | Max  |
|------------------------|-------------------|-----|----------|-----|------|
| Controls               | ET-1              | 25  | 4.88     | 1.75| 2.05 |
|                        | ET$_A$-receptor   | 25  | 1209.28  | 314.48| 774.97|
| Early stage of POAG    | ET-1              | 22  | 6.33     | 2.38| 0.43 |
|                        | ET$_A$-receptor   | 22  | 673.44   | 283.02| 261.24|
| Advanced stage of POAG | ET-1              | 28  | 6.34     | 1.56| 3.34 |
|                        | ET$_A$-receptor   | 28  | 992.28   | 264.22| 506.17|

Note: Mean values with standard deviation (±SD); N, number of participants.

### Table 3. Inter-group dispersion analysis.

| Parameter | Controls vs. early POAG | Controls vs. advanced POAG | Early vs. advanced POAG |
|-----------|-------------------------|---------------------------|-------------------------|
| ET-1      | $p = 0.029$             | $p = 0.018$               | $p = 0.998$             |
| ET$_A$-receptor | $< 0.001$     | $p = 0.021$               | $p = 0.001$             |

### Table 4. ET-1 plasma concentrations in POAG patients reported in other studies.

| Reference | Controls | Glaucoma |
|-----------|----------|----------|
|           | Mean ± SD| Mean ± SD| Statistical difference |
| [9]       | 2.56 ± 1.36, N = 27 | 2.81 ± 1.29 – POAG, N = 43 | No |
| [14]      | –        | –        | No ($p = 0.07$) |
| [25]      | 1.33 ± 0.50, N = 19 | 1.58 ± 0.64 – POAG, N = 18 | No |
|           |          | 1.49 ± 0.51 – NTG, N = 30 | No |
| [28]      | 1.53 ± 1.49, N = 37 | 3.27 ± 1.25 – POAG, N = 31 | No |
|           |          | 3.12 ± 1.46 – NTG, N = 18 | No |
| [26]      | 1.75 ± 0.25, N = 20 | 2.83 ± 0.28 – POAG, N = 20 | Yes ($p < 0.001$) |

Note: Mean values with standard deviation (±SD); N, number of participants.
were associated with significantly higher risk for NTG and POAG [24].

In 2016, Kosior-Jarecka et al. [27] reported positive correlation between ET-1 plasma levels and visual field defects. Our results showed that the ET-1 plasma levels were significantly higher in patients with POAG than in the control group, although no significant difference was found between early and advanced changes in the visual field of patients with POAG. This suggested that ET-1 most probably had influence on the glaucoma pathogenesis, but not likely on the stage of POAG changes.

The analysis of the relationship between ET-1/ET<sub>A</sub>-receptor plasma levels and cpRNFL/mRNFL thickness in the present study (Table 5) showed a statistically significant negative relationship between ET-1 and mRNFL (Inf mRNFL and Total mRNFL), as well as significant correlation between ET-1 and Inf pRNFL. Close to significant correlation was observed between ET-1 levels and Total cpRNFL. No relationship between the plasma ET<sub>A</sub>-receptor concentration and any of the RNFL parameters was found. Chen et al. [28] observed higher ET-1 concentration in POAG (31 patients) and NTG groups (18 patients) as compared to a control group (37 subjects) without statistically significant difference (Table 4). Chen et al. [28] further reported a significant correlation of the ET-1 plasma concentration with structural (cpRNFL) and functional (MD) changes. Examining the correlation between ET-1 and cpRNFL, we revealed a significant negative correlation only between ET-1 and Inf pRNFL.

In 2015, Wróbel-Dudzińska et al. [29] reported a statistically significant difference between the frequency of occurrence of specific ET-1 (K198N) and ET-A receptor (C1222T, C70G and G231A) genes polymorphisms in POAG and NTG groups, indicating that the polymorphic variants have an effect on IOP levels and systemic arterial blood pressure and its regulation mechanisms in NTG patients. Thus, it is suggested that these genetic variances have an influence on vascular factors, and they, in turn, on glaucoma pathogenesis, namely, dysfunction of autoregulation mechanisms, vascular dysregulation and even endothelial dysfunction responsible for ET-1 release [29].

In order to determine the functional role of endothelin in glaucoma, Howell et al. [30] administered bosentan, to DBA/2J mice (an antagonist of the two types of endothelin receptors). Bosentan significantly reduced the incidence of glaucoma in mice: at the age of 10.5 months, 80% of treated eyes did not have glaucoma as compared with only 39% of untreated eyes [30]. It also increased the ocular blood flow in human glaucoma patients, not affecting the blood pressure [6]. These experiments strongly support a role of the endothelin system in the early pathogenesis of glaucoma in this model. Endothelin receptor antagonists could be considered promising new treatments of glaucoma.

### Conclusions

The results from this study showed statistically significant difference between the ET-1 plasma concentration in healthy and glaucoma patients. The mean ET-1 plasma concentration increased in the groups as follows: control group < early glaucoma patients < advanced glaucoma patients. The statistical analysis revealed significant difference between the ET<sub>A</sub>-receptor plasma concentrations in the three groups. The mean ET<sub>A</sub> plasma concentration increased in the groups as follows: early glaucoma patients < advanced glaucoma patients < control group. Significant correlation was found between Inf mRNFL/Total mRNFL/Inf pRNFL and ET-1. No statistical significance was revealed between the ET<sub>A</sub>-receptor concentration and RNFL. Our results supported the suggestion that ET-1 could play a role in glaucoma pathogenesis, because of the observed significantly high ET-1 and ET<sub>A</sub>-receptor plasma levels in POAG patients. Further research, including larger cohorts of patients, would be needed to explore the potential of endothelin receptor antagonists as a new approach of behaviour and treatment in some glaucoma cases.

### Disclosure statement

No potential conflict of interest was reported by the authors.

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### Table 5. Correlation between mRNFL/cpRNFL and ET-1/ET<sub>A</sub>-receptor.

| Parameter           | ET-1 | ET<sub>A</sub>-receptor |
|---------------------|------|-------------------------|
| Sup mRNFL           | 0.211| 0.136                   |
| N = 75              | 0.069| 0.243                   |
| Inf mRNFL           | 0.291| 0.119                   |
| N = 75              | 0.011| 0.307                   |
| Total mRNFL         | -0.260| 0.128                  |
| N = 75              | 0.244| 0.274                   |
| Sup cpRNFL          | -0.162| 0.228                  |
| N = 75              | 0.165| 0.050                   |
| Inf cpRNFL          | -0.266| 0.154                  |
| N = 75              | 0.027| 0.187                   |
| Nax cpRNFL          | -0.176| 0.040                  |
| N = 75              | 0.131| 0.731                   |
| Temp cpRNFL         | -0.109| 0.123                  |
| N = 75              | 0.354| 0.294                   |
| Total cpRNFL        | -0.225| 0.172                  |
| N = 75              | 0.052| 0.141                   |
References

[1] Choritz L, Machert M, Thieme H. Correlation of endothelin-1 concentration in aqueous humor with intraocular pressure in primary open angle glaucoma and pseudoexfoliation glaucoma. Invest Ophthalmol Vis Sci. 2012;53(11):7336–7342.

[2] Yanagisawa M, Kurihara H, Kimura S, et al. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. Nature. 1988;332(6163):414–418.

[3] Lüscher TF, Wenzel RR. Endothelin and endothelin antagonists: pharmacology and clinical implications. Agents Actions Suppl. 1995;45:237–253.

[4] Inoue A, Yanagisawa M, Kimura S, et al. The human endothelin family: three structurally and pharmacologically distinct isopeptides predicted by three separate genes. Proc Natl Acad Sci. 1989;86:2863–2867.

[5] Jain SK, Yadava RK, Raikar R. Role of endothelins in health and disease. J Indian Acad Clin Med. 2002;3:59–64.

[6] Resch H, Karl K, Weigert G, et al. Effect of dual endothelin receptor blockade on ocular blood flow in patients with glaucoma and healthy subjects. Invest Ophthalmol Vis Sci. 2009;50(1):358–363.

[7] Shah R. Endothelins in health and disease. Eur J Intern Med. 2007;18:272–282.

[8] Kirilov G, Tomova A, Dakovska L, et al. Plazmeni niva na endotelin-1 pri bolni sas sindroma na Chushing [Plasma levels of Endothelin-1 in patients with Cushing’s syndrome]. Endocrinologia. 2001;61(1):35–41. Bulgarian.

[9] Nicolela MT, Ferrier SN, Morrison CH, et al. Effects of cold-induced vasospasm in glaucoma: the role of endothelin-1. Invest Ophthalmol Vis Sci. 2003;44(6):2565–2572.

[10] Lepple-Wienhues A, Becker M, Stahl F, et al. Endothelin-like immunoreactivity in the aqueous humour and in conditioned medium from cultured ciliary epithelial cells. Curr Eye Res. 1992;11:1041–1046.

[11] Fernández-Durango R, Rollin R, Medeiro A, et al. Localization of endothelin-1 mRNA expression and immunoreactivity in the anterior segment of human eyes: expression of ETA and ETB receptors. Mol Vis. 2003;9:103–109.

[12] Prasanna G, Krishnamoorthy R, Clark AF, et al. Human optic nerve head astrocytes as a target for endothelin-1. Invest Ophthalmol Vis Sci. 2002;43:2704–2713.

[13] Rao VR, Krishnamoorthy RR, Yorio T. Endothelin-1, endothelin A and B receptor expression and their pharmacological properties in GFAP negative human lamina cribrosa cells. Exp Eye Res. 2007;84:1115–1124.

[14] Tezel G, Kass MA, Kolker AE, et al. Plasma and aqueous humor endothelin levels in primary open angle glaucoma. J Glaucoma. 1997;6:83–89.

[15] Stokely ME, Brady ST, Yorio T. Effects of endothelin-1 on components of anterograde axonal transport in optic nerve. Invest Ophthalmol Vis Sci. 2002;43:3223–3230.

[16] Taniguchi T, Shimazawa M, Sasaoka M, et al. Endothelin-1 impairs retrograde axonal transport and leads to axonal injury in rat optic nerve. Curr Neurovasc Res. 2006;3:381–388.

[17] Lau J, Dang M, Hockmann K, et al. Effects of acute delivery of endothelin-1 on retinal ganglion cell loss in the rat. Exp Eye Res. 2006;82:132–145.

[18] Brooks DE, Küllberg ME, Cannon RL, et al. Functional and structural analysis of the visual system in the rhesus monkey model of optic nerve head ischemia. Invest Ophthalmol Vis Sci. 2004;45:1830–1840.

[19] Sasaoka M, Taniguchi T, Shimazawa M, et al. Intravitreal injection of endothelin-1 caused optic nerve damage following to ocular hypoperfusion in rabbits. Exp Eye Res. 2006;83:629–637.

[20] Prasanna G, Krishnamoorthy R, Yorio T. Endothelin, astrocytes and glaucoma. Exp Eye Res. 2011;93:170–177.

[21] Emre M, Orgül S, Haufschild T, et al. Increased plasma endothelin-1 levels in patients with progressive open angle glaucoma. Br J Ophthalmol. 2005;89:60–63.

[22] Choritz L, Rosenthal R, Fromm M, et al. Pharmacological and functional characterization of endothelin receptors in bovine trabecular meshwork and ciliary muscle. Ophthalmic Res. 2005;37:179–187.

[23] Sugiyama T. Involvement of Endothelin-1 in the pathophysiology of normal-tension glaucoma. Int J Ophthalmic Res. 2015;1(2):36–40.

[24] Li S, Zhang A, Cao W, et al. Elevated plasma endothelin-1 levels in normal tension glaucoma and primary open-angle glaucoma: a meta-analysis. J Ophthalmol. 2016;2016:2678017, 6 p.

[25] Kunimatsu S, Mayama C, Tomidokoro A, et al. Plasma endothelin-1 level in Japanese normal tension glaucoma patients. Curr Eye Res. 2006;31(9):727–731.

[26] Cellini M, Strobbe E, Gizzi C, et al. Endothelin-1 plasma levels and vascular endothelial dysfunction in primary open angle glaucoma. Life Sci. 2012;91:699–702.

[27] Kosior-Jarecka E, Wróbel-Dudzińska D, Łukasik U, et al. Plasma endothelin-1 single nucleotide polymorphisms of endothelin-1 and endothelin type A receptor genes as risk factors form normal-tension glaucoma. Mol Vision. 2016;22:1256–1266.

[28] Chen HY, Chang YC, Chen WC, et al. Association between plasma endothelin-1 and severity of different types of glaucoma. J Glaucoma. 2013;22(2):117–122.

[29] Wróbel-Dudzińska D, Kosior-Jarecka E, Łukasik U, et al. Risk factors in normal-tension glaucoma and high-tension glaucoma in relation to polymorphisms of endothelin-1 gene and endothelin-1 receptor type A gene. J Ophthalmol. 2015;2015:368792. 12 p.

[30] Howell GR, Macalinao DG, Sousa GL, et al. Molecular clustering identifies complement and endothelin induction as early events in a mouse model of glaucoma. J Clin Invest. 2011;121(4):1429–1444.