Correlation of Endothelin-1 Concentration in Aqueous Humor with Intraocular Pressure in Primary Open Angle and Pseudoexfoliation Glaucoma

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Purpose. Endothelin-1 (ET-1) has been found in elevated concentrations in the aqueous humor of glaucoma patients. Indirect evidence from animal studies suggests that ET-1 might directly influence intraocular pressure (IOP). The aim of this study was to determine whether ET-1 concentrations in aqueous humor of cataract and glaucoma patients correlate with IOP.

Methods. Aqueous humor and blood samples from patients with either cataract (control, n = 38), primary open angle glaucoma (POAG, n = 35), or pseudoexfoliation glaucoma (PEXG, n = 21), without other ocular or systemic disease, were collected during routine cataract surgery or trabeculectomy. ET-1 concentration was determined by an ET-1 ELISA kit. IOP was measured preoperatively by standard Goldmann applanation tonometry. All statistical analysis was performed using commercial predictive analytics software.

Results. Both IOP and ET-1 concentration in aqueous humor were significantly increased in POAG (23.4 ± 6.8 mm Hg, 5.9 ± 2.9 pg/mL) and PEXG (24.3 ± 8.8 mm Hg, 7.7 ± 2.1 pg/mL) compared with control (15.0 ± 2.9 mm Hg, 4.3 ± 2.4 pg/mL). No difference was detected for plasma ET-1 concentrations. IOP and ET-1 in the aqueous humor were significantly correlated (R = 0.394, R² = 0.155, P < 0.001), although no correlation was found between IOP and ET-1 in blood plasma or between ET-1 in aqueous humor and ET-1 in plasma.

Conclusions. In this study, a small but highly significant correlation between IOP and the ET-1 concentration in the aqueous humor was found. Although no causative relationship can be deduced from this, ocular ET-1 effects on IOP control may merit further investigation. (Invest Ophthalmol Vis Sci. 2012;53:7356–7364) DOI:10.1167/iovs.12-10216

Endothelin-1 (ET-1), one of three endothelin isoforms, is one of the most potent vasoconstrictors known. The 21 amino acid peptide is produced ubiquitously by the vascular endothelium by cleavage from a prepro-endothelin through endothelin converting enzymes (ECEs). ET-1 acts on target cells via two receptors. The ETₐ receptor (ETAR) is typically expressed on vascular smooth muscle cells (SMCs) and causes contraction of these cells through the influx of calcium ions. Contraction can also be caused through activation of the ETₐ receptor (ETBR), when it is expressed by SMC. ETₐ receptors expressed on endothelial cells conversely can indirectly contribute to vasodilation via activation of nitric oxide synthases (NOS) and release of nitric oxide (NO), which diffuses to the vascular SMC and causes relaxation.¹

ET-1 is mainly cleared from the blood stream by the extensive vascular beds of the lungs and kidneys. Renal and pulmonary diseases are therefore often associated with systemic increases of the peptide. Apart from its mostly local paracrine function in regulating vascular tone, ET-1 is also involved in various aspects of the development of atherosclerosis and cardiovascular disease.²,³

ET-1 naturally occurs in the eye, where it is produced by the nonpigmented ciliary epithelium and released into the aqueous humor.¹ Both of its receptors are expressed by various ocular tissues, including the iris and ciliary muscle, trabecular meshwork, ocular vasculature, and retinal and optic nerve astrocytes, strongly indicating a physiological function for ET-1 in the eye.⁴,⁵ However, the precise nature of its role remains unclear.

ET-1 has also been implicated in the pathogenesis of glaucoma, after having been shown to be increased in the aqueous humor of glaucoma patients.⁸,⁹ The peptide has since been linked to retinal ganglion cell death by a number of different pathways. It was shown that intravitreal injection of ET-1 had a direct effect on both anterograde¹⁰ and retrograde¹¹ axonal transport in retinal ganglion cells (RGCs), and results in a dose- and time-dependent RGC loss in rats.¹² These effects might in part be attributed to vasoconstriction in microvasculature of the optic nerve head (ONH) and retina, as shown by several groups, who were able to provoke optic cup enlargement and optic nerve damage by an ET-1–induced ischemia in different animal models.¹³–¹⁶ Another mechanism for optic nerve head damage has been proposed by Prasanna et al.,¹⁷ who demonstrated an increased proliferation of astrocytes isolated from human ONH upon exposure to ET-1. Glial activation and fibrosis may in turn contribute to hypoperfusion, thus rendering the ONH more vulnerable to increased IOP.

Systemic endothelial dysfunction with increased plasma concentrations of ET-1 have also been proposed to negatively influence ocular perfusion and are considered a potential risk factor for normal tension glaucoma (NTG). As shown in a small patient group by Emre et al.,¹⁸ elevated ET-1 concentrations in plasma might be associated with the progression of glaucomatous visual field defects in spite of normal or normalized IOP.

All of this evidence has in recent years sparked interest in the antagonism of the ocular effects of ET-1 for the treatment of glaucoma.¹⁹,²⁰ One area of controversy is the role of ET-1 in the physiology and pathophysiology of IOP control. Despite numerous
functional studies on the ocular effects of endothelin isomers and their receptors, no comprehensive understanding of the role of ET-1 in physiological IOP control has been reached. Experimental evidence from various animal models is often contradictory, showing either pressure lowering or increasing effects upon exposure to ET-1.

Indirect evidence from cell cultures and functional experiments in native bovine tissue suggest that the trabecular meshwork (TM) shows smooth-muscle-like contractility. ET-1 is capable of causing contraction of trabecular meshwork, thus decreasing the intertrabecular space and thereby increasing outflow resistance and IOP. No direct contraction of native human tissue could be shown yet, but primary cultures of human TM cells showed ET-1-induced gel contraction, thus implicating ET-1 as a potential source of elevated IOP in glaucoma patients. On the other hand, ET-1 also causes contraction in the ciliary muscle, by exerting force via the scleral spur and tendrils reaching into the TM, thereby decreasing the meshwork and, therefore, decreasing outflow resistance and IOP (much like muscular substances do). Since both tissues, TM and CM, express both ET-receptor subtypes and ET-1 is found in the aqueous humor, it appears reasonable to assume that ET-1 does influence IOP through affecting the balance between the functionally antagonistic contractile forces of these tissues. The matter is further complicated by the observation that ET-1 inhibits the Na+/K+-ATPase in the nonpigmented ciliary epithelium cells in culture. In vivo this would mean a decrease in aqueous humor production and IOP as well.

Based on the experimental evidence alone, it cannot conclusively be decided which of these effects on IOP prevails. Moreover, it has never been investigated in humans, whether IOP and ET-1 concentration in aqueous humor are in fact associated as suggested by the animal models. The purpose of this study, therefore, was to test whether ET-1 concentrations in aqueous humor or blood plasma are directly correlated with intraocular pressure in otherwise healthy glaucoma patients and cataract controls.

Materials and Methods

Blood samples as well as aqueous humor samples were obtained from patients undergoing routine cataract surgery or trabeculectomy in our clinic, after written consent was given. Approval by the local ethics committee was granted (App. no.: 837.198.06 [5296]), all tenets of the Declaration of Helsinki were observed. IOP was measured using standard Goldmann applanation tonometry in an upright position before the surgery.

Inclusion Criteria

Patients that were scheduled for either cataract surgery or trabeculectomy were screened for their suitability for this study and allocated to one of three study groups based on the following inclusion criteria:

Control patients had a cataract without any other ocular diseases, trauma, or previous surgery and were included in the study if IOP was lower than 21 mm Hg during all measurements, optic nerve head as well as visual field or Heidelberg retinal tomograph examination showed no abnormalities, and there was no family history of glaucoma. Patients with a recorded history of primary open angle glaucoma (POAG) were included if they had characteristic optic nerve and visual field damage, their highest measured IOP was greater than 24 mm Hg, and the characteristic pseudoxofoliation material was found during the slit-lamp exam.

Topical glaucoma medication was discontinued and switched to a acetazolamide regiment at least 4 weeks prior to trabeculectomy.

Exclusion Criteria

Endothelin-1 has been implicated as contributor to a variety of different diseases. Plasma concentrations of the peptide have been found to be increased up to 10-fold in cardiovascular diseases, primary pulmonary hypertension, vasospastic disorders, but also in patients with renal failure or solid tumors (for reviews, see Jain et al. and Shah). To ensure that the observed increases in ET-1 in glaucoma patients in previous studies were due to ET-1 concentrations in blood plasma we excluded patients with any other condition that might be related to an increase in ET-1 plasma concentration.

These include the following: cardiovascular diseases, Grade II (as classified by the New York Heart Association), previous stroke or myocardial infarction, vasospastic disorders (e.g., migraine, Prinzmetal’s Angina, Raynaud’s Syndrome), autoimmune diseases, malignant tumors, pulmonary diseases (including asthma, chronic obstructive pulmonary disease, chronic bronchitis, primary pulmonary hypertension), insulin-dependent diabetes mellitus, and all kidney disorders.

Patients with a history of ocular disease other than those specified in the inclusion criteria, as well as patients with ocular manifestations of other diseases, such as diabetic or hypertensive retinopathy, were excluded from the study. Patients who had undergone previous ocular surgery (including refractive and cataract surgery) were also excluded.

Based on these inclusion and exclusion criteria, we screened approximately 2300 patients scheduled for either cataract surgery or trabeculectomy in our clinic over the course of 2 years. In all, 110 patients were included in the study.

Preoperative Medication

In all patients scheduled for trabeculectomy all topical glaucoma medication was discontinued 30 days before surgery. In our clinic, this is standard procedure to avoid bleb failure due to eye drop–related disturbance of conjunctival wound healing or postoperative scarring. For the purpose of the presented study, this procedure also ensured that all trabeculectomy patients were treated similarly and potential influences of topical glaucoma medication on ET-1 concentration in aqueous humor were minimized. The expected increase in IOP was dampened by application of a systemic carbonic anhydrase inhibitor during this period. Five days prior to surgery, dexamethasone eye drops were added. Perioperative topical medication was similar to that of patients who underwent phacoemulsification: gentamicin to prevent infection and diclofenac to avoid inflammation. Atropin or scopolamin was used for mydriasis. Of the 56 glaucoma patients included in the study, 13 were scheduled for phacoemulsification and thus treated like the control group. There were no combination surgeries performed during this study.

Handling of Samples and ET-1 ELISA

Blood samples (3 mL) were taken just prior to surgery, placed on ice, and immediately brought to the laboratory where they were centrifuged for 5 minutes at 4°C. The supernatant plasma was then transferred into a separate sample tube and stored at –80°C, the entire process taking no more than 10 minutes. During surgery, approximately 100 μL of aqueous humor was collected and also stored at –80°C for later use.

ET-1 was measured using a sandwich ELISA kit (Assay Designs, Ann Arbor, MI) according to the protocol of the provider. In brief, 100 μL of diluted aqueous humor and plasma samples were pipetted into 96-well plates precoated with a monoclonal antibody that is specific for human ET-1 and does not cross-react with other isomers or species. After 30 minutes of incubation at 37°C, the wells were emptied and washed...
several times with the provided washing buffer. A second ET-1–specific enzyme-coupled detection antibody was then added to the wells and incubated at 37°C for another 30 minutes. After thoroughly washing off any excess antibody, a substrate was added to the wells and incubated at room temperature for 30 minutes in the dark. After the incubation time, the reaction was terminated by adding 100 μL “stop solution” to each well; the intensity of the color compound was measured using a multwell plate reader (Multiskan Ascent, Thermo Fisher Scientific GmbH, Schwerte, Germany).

To determine and correct for intertest variability between the used ELISA plates, all samples were prepared and measured on the same day and with the same ET-1 standard preparation. Technical replicates showed a within-plate difference of an average of 5.7% and 8.8% between-plate variation of the known ET-1 standard samples. Cross-reactivity with the other endothelin isomers was determined to be 5.9% for ET-2 and 3.2% for ET-3.

Statistical Analysis

Unless stated otherwise, all data are presented as mean ± SD.

All statistical analyses were performed using a commercial predictive analytics software (SPSS 16 software; SPSS, Inc., Chicago, IL). Univariate ANOVA was used to determine group differences for the measured parameters. In the case of statistically significant differences, Bonferroni-corrected post hoc comparisons were used to locate the source of the difference. Pearson’s correlation coefficient (R) was calculated for the analyses of the associations between ET-1 in the aqueous humor, blood plasma, and intraocular pressure. To correct for multiple testing, we used the sequentially rejective Bonferroni procedure described by Holm (also referred to as Holm-Bonferroni correction).

Power analysis for significant correlations was performed using a statistical power analysis program (G*Power 3.1 software, provided by the Department of Experimental Psychology, Heinrich-Heine-University Düsseldorf, Germany).

RESULTS

Descriptive Analysis

Of more than 2300 patients screened in our hospital, only 110 patients met all the inclusion and exclusion criteria and agreed to participate in the study. Of these patients, 15 had to be excluded from the statistical analysis because of missing values. In these cases, either too little or no aqueous humor could be obtained. One further patient was excluded because of an extreme outlier at 796.2 pg/mL of ET-1 in blood plasma. This high value was most likely the result of an error when drawing the blood sample. Later repeat measurements on new blood samples drawn on two occasions after the study confirmed a normal ET-1 plasma level in this patient.

Of the remaining 94 patients, 38 were included in the cataract control group, 35 were allocated to the POAG group, whereas 21 patients suffered from PEX glaucoma. Typical fundus photographs for the glaucoma groups are shown in Figure 1. There was no difference between the patient groups with regard to age, sex, or the laterality of the eyes included in the study (see Table 1).

Comparisons between Groups for IOP and ET-1 Concentrations in Aqueous Humor and Blood Plasma

Both mean IOP and ET-1 concentration in aqueous humor were significantly increased in the POAG (23.4 ± 6.8 mm Hg, 5.9 ± 2.9 pg/mL) and PEXG (24.3 ± 8.8 mm Hg, 7.7 ± 2.1 pg/mL) group compared with the cataract group (15.0 ± 2.9 mm Hg, 4.3 ± 2.4 pg/mL) (Figs. 2, 3). Individual IOP and ET-1 in aqueous humor were significantly correlated (Pearson’s correlation coefficient $R = 0.394$, $R^2 = 0.155$ $P < 0.001$, power = 0.82; Fig. 4) in the overall study population. Within-group correlation showed a similar trend. However, the correlations were not significant (Fig. 5).

No difference in mean could be detected in plasma ET-1 concentrations: 4.7 ± 3.2 and 5.0 ± 2.0 pg/mL in POAG and PEXG versus 5.7 ± 5.2 pg/mL in cataract (Fig. 6, Table 2). There was no correlation between ET-1 in blood plasma and IOP across the entire study population (Fig. 7) nor within groups (data not shown). There was no correlation between ET-1 in blood plasma and in aqueous humor, respectively (Fig. 8).

To test whether differences in preoperative treatment between types of surgery affected the ET-1 concentration in aqueous humor, ET-1 levels were compared between glaucoma patients who underwent trabeculectomy ($n = 43$) and glaucoma patients who underwent phacemulsification ($n = 13$). There was no statistical difference between these two groups (6.5 ± 2.7 vs. 6.6 ± 3.1 pg/mL; $P = 0.958$; Fig. 9). Additionally, correlation coefficients between IOP and ET-1 in aqueous were comparable to that of the total study population, both within the trabeculectomy group ($R = 0.369$, $R^2 = 0.136$; $P = 0.025$; $P_{adj} = 0.091$; $n = 43$; Fig. 10) and in the entire glaucoma group ($R = 0.282$, $R^2 = 0.079$; $P = 0.045$; $P_{adj} = 0.136$; $n = 56$). After correction with the Holm-Bonferroni procedure, these correlations could not be considered statistically significant, however.

Table 1. Patient Characteristics of the Study Groups

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>POAG</th>
<th>PEXG</th>
<th>Statistics</th>
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<tbody>
<tr>
<td>No. of patients</td>
<td>38</td>
<td>35</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>69.7 ± 8.3</td>
<td>65.1 ± 12.4</td>
<td>71.4 ± 7.4</td>
<td>$P = 0.281$ (ANOVA)</td>
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<td>Sex (male/female)</td>
<td>20/18</td>
<td>19/16</td>
<td>7/14</td>
<td>$P = 0.248$ (chi-square)</td>
</tr>
<tr>
<td>Eye (OD/OS)</td>
<td>21/17</td>
<td>15/20</td>
<td>8/13</td>
<td>$P = 0.469$ (chi-square)</td>
</tr>
<tr>
<td>No. of glaucoma medications</td>
<td>0</td>
<td>2.7 ± 1.4</td>
<td>2.2 ± 1.5</td>
<td>$P &lt; 0.001^*$ (ANOVA)</td>
</tr>
<tr>
<td>Procedure (Phako/TE)</td>
<td>38/0</td>
<td>6/29</td>
<td>6/15</td>
<td>$P &lt; 0.001^*$ (chi-square)</td>
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* Indicates statistical significance.
DISCUSSION

Endothelin-1 is believed to be a contributor to the pathogenesis of POAG. It has been shown to be elevated in the aqueous humor of patients with POAG by several groups. Its involvement in the regulation (and dysregulation) of IOP has been hypothesized based on animal studies. However, a direct correlation between ET-1 in aqueous humor and IOP had never been shown in humans. Although other studies have measured ET-1 in aqueous humor and linked it to different forms of glaucoma before,8,9,32–34 our study is the first to show a significant correlation between individual measurements of IOP and ET-1 in aqueous of POAG, PEXG, and cataract control patients. Despite the fact that at $R = 0.396$ the correlation coefficient is rather small, we found the association to be statistically highly significant. In our study, the coefficient of determination ($R^2$) was 0.155, which means that 15.5% of the variation of IOP could be explained or predicted by the concentration of ET-1 in the aqueous humor.35 ET-1 in blood plasma, on the other hand, does not seem to be associated with IOP. Clearly, other variables not measured in our study are necessary to explain the remaining variation in IOP.

Whether there is a causal relation between higher concentrations of ET-1 in the aqueous humor and elevated IOP cannot be determined based on our results. The fact that we found the highest concentrations in pseudoexfoliation glaucoma appears to indicate an increase in ET-1 secondary to IOP elevation. Ghanem et al.32 recently reached a similar conclusion after finding higher levels of ET-1 in the aqueous humor of patients with chronic closed angle glaucoma.
Both PEXG and CCAG often show very high IOP, which in the case of a secondary increase of ET-1 might account for the higher concentrations found in these patients in our study as well as the work reported by Ghanem et al.\textsuperscript{32} How an elevated IOP might lead to an increased release of ET-1 into the aqueous humor is currently unknown.

On the other hand, Iwabe et al.,\textsuperscript{33} who also included CCGA patients in their study, found no such elevation in this group, nor in their pooled group of various other secondary glaucoma patients. Moreover, Koliakos et al.\textsuperscript{34} have previously shown that ET-1 is elevated also in the aqueous humor of normotensive patients with exfoliation syndrome and without glaucomatous damage, suggesting a role for ET-1 in the later development of higher IOP and conversion to PEX glaucoma. Thus, the higher ET-1 concentrations found in PEX syndrome and PEX-glaucoma patients may be of different origin than that of those found in some CCAG patients. The latter might result from extreme IOP values that could be disruptive to the blood-aqueous barrier provided by the ciliary epithelium,\textsuperscript{36} which might cause unphysiological increases in ET-1. Since neither Ghanem et al.\textsuperscript{32} nor Iwabe et al.\textsuperscript{33} reported such extreme IOP peaks, however, this remains speculative.

Independent of whether ET-1 might be increased in response to an elevated IOP, recent results from a primate model suggest that ET-1 contributes to the regulation of IOP in glaucomatous eyes. Wang et al.\textsuperscript{37} reported that a single topical administration of the ETA receptor antagonist avosentan (SPP-301) in monkeys with laser-induced partial outflow obstruction led to dose-dependent, sustained lowering of IOP. Since the group did not measure ET-1 in the aqueous before or after the photocoagulation of parts of the trabecular meshwork, it remains unclear whether ET-1 was increased secondarily and to what extent such a potential increase might have contributed to the elevation of IOP in that model. The study does show, however, that antagonizing ocular actions of endothelin might be a useful strategy to treat glaucoma.

In our study, there was no correlation between the ET-1 concentration in blood plasma and that in aqueous humor. This corroborates previous results\textsuperscript{9,32} and is well in line with the finding that the ET-1 found in aqueous humor is produced and released by the eye itself.\textsuperscript{4} Importantly, there was also no difference in mean plasma concentration between the patient groups. Thus, at least in our study population, plasma ET-1 is not likely to have contributed to the development of glaucomatous damage via effects on ocular perfusion. This may be considered a testament to the success of our very rigorous exclusion criteria, especially with regard to any type of vascular disease, and might be different in individuals with elevated plasma concentrations of ET-1. Thus, we are confident

### Table 2. Primary Parameters Measured

<table>
<thead>
<tr>
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<th>Control</th>
<th>POAG</th>
<th>PEXG</th>
<th>Statistics</th>
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<tbody>
<tr>
<td>IOP, mm Hg</td>
<td>15.0 ± 2.9</td>
<td>25.4 ± 6.8</td>
<td>24.3 ± 8.8</td>
<td>( P &lt; 0.001^* )</td>
</tr>
<tr>
<td>ET-1 in aqueous humor, pg/mL</td>
<td>4.3 ± 2.4</td>
<td>5.9 ± 2.9</td>
<td>7.7 ± 2.1</td>
<td>( P &lt; 0.001^* )</td>
</tr>
<tr>
<td>ET-1 in blood plasma, pg/mL</td>
<td>5.7 ± 5.2</td>
<td>4.7 ± 3.2</td>
<td>5.0 ± 2.0</td>
<td>( P = 0.576 )</td>
</tr>
</tbody>
</table>

* Indicates statistical significance.

### FIGURE 6. Box-and-whisker plots of ET-1 concentration in blood plasma of the studied patient groups. Circles represent outliers; black dots show extreme values. There was no significant difference between mean ET-1 concentrations.

### FIGURE 7. Scatterplot of IOP versus ET-1 in blood plasma for the whole study population; each data point represents one patient. As indicated by the linear regression, there was no correlation between the two variables.

### FIGURE 8. Scatterplot of ET-1 in aqueous humor versus ET-1 in blood plasma for the whole study population, with each data point representing one individual patient. No correlation was found.
that our results were not confounded by systemic diseases. Similarly, despite the aqueous samples being collected during different types of intraocular procedures, the strict adherence to a preoperative regimen of discontinuing topical glaucoma medication for at least 30 days sets apart our study from previous studies measuring ET-1 in aqueous humor.

Despite this, the interpretation of our results is limited by a number of factors. The samples were collected during different intraocular procedures. Although the type of anesthesia used during the operation did not seem to have an effect on the measured ET-1 concentration (data not shown), a more homogeneous study population (i.e., only patients with cataract surgery) may have yielded more exact results. Another problem may have been the time between measuring IOP and the actual operation. To avoid excessive manipulation of the eyes directly before the surgical procedure, which might have led to reactive increases of ET-1 in the aqueous humor, we measured IOP approximately 24 hours before surgery. Since neither continuous recordings of IOP nor time courses on ET-1 concentrations in aqueous humor of human subjects or patients are currently available, we cannot rule out that there may be a mismatch between the IOP measurement used for our analyses and the ET-1 concentration obtained.

Further sources of error may be the small size of the groups, as well as a strong selection bias, due to the very strict exclusion criteria. Although the data were normally distributed and there were only very few outliers, a larger study population would have yielded more precise results. Also, our study population does not reflect the typical glaucoma or cataract patient. While it was important for this study to exclude conditions that might potentially confound the results, the very common comorbidity of older patients may account for additional increases in ET-1 both in aqueous humor and blood plasma that may influence the glaucoma in ways that cannot be deduced from our study. Also, it cannot be ruled out that a faulty blood-aqueous barrier as a symptom of other ocular or systemic diseases may account for a correlation between aqueous humor and blood plasma ET-1 levels in such patients. A larger, less selective trial might overcome some of these limitations. Such a study would have the added benefit of allowing a stratification of severity of the glaucomatous damage and could potentially also show whether ET-1 is associated with the likelihood of progression of the disease.

In conclusion, our study is the first to report a highly significant, albeit small correlation between ET-1 levels in aqueous humor and IOP. Due to the large variance of ET-1 levels, its potential as a predictive marker is limited. Targeting its effects on the various tissues involved in IOP regulation, however, may be a useful approach in the treatment of glaucoma. Further studies are needed to elucidate the role of ocular actions of ET-1 in general and in the pathogenesis of glaucoma in particular.

References

7. Rao VR, Krishnamoorthy RR, Yorio T. Endothelin-1, endothelin A and B receptor expression and their pharmacological


