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ENDOTHELIN-1 ROLE IN HUMAN EYE: A SYSTEMATIC REVIEW

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ABSTRACT

Background: *Endothelin-1 (ET-1) is a potent vasoactive factor implicated in development of diabetic retinopathy, which is commonly associated with retinal edema and hyperglycemia. Although the vasomotor activity of venules contributes to the regulation of tissue fluid homeostasis, responses of human retinal venules to ET-1 under euglycemia and hyperglycemia remain unknown and the ET-1 receptor subtype corresponding to vasomotor function has not been determined.*

The aim: *This study aims to show endothelin-1 role in human eye.*

Methods: *By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

Result: *In the PubMed database the results of our search brought up 44 articles, whereas the results of our search on SagePub brought up 95 articles. The results of the search conducted for the last year of 2013 yielded a total 15 articles for PubMed and 42 articles for SagePub. The result from title screening, a total 4 articles for PubMed and 12 articles for SagePub. In the end, we compiled a total of 8 papers. We included five research that met the criteria.*

Conclusion: *ET-1 (vasoconstrictor, mitogenic, pro-oxidative, and proinflammatory) is one of the most potent vasoconstrictors in the body and its action has a dual effect: on the one hand, it acts on receptors of ECs and pericytes; on the other hand, it has a mitogenic effect on VSMCs.*

Keyword: *Endothelin-1, vasoactive, eye.*

INTRODUCTION

The endothelin system is a family of three ligands (EDN1, 2, and 3, also known as ET-1, 2, and 3) and two G-protein coupled receptors (EDNRA and EDNRB, also known as ET-A and ET-B). The canonical role of the endothelin system is to regulate blood flow and vasoconstriction. Potent vasoconstriction occurs when EDN ligands bind to EDNRA, which is highly expressed by vascular mural cells, including smooth muscle cells and pericytes. EDNRB is expressed by vascular endothelial cells, and is thought to mediate vasorelaxation in response to ligand binding. Many organ systems, including the central nervous system, use the endothelin system to maintain normal physiology.[1,2]

As with many signaling systems that have a physiological role, endothelin signaling has also been broadly implicated in the pathophysiology of numerous diseases, including retinal diseases and glaucoma. EDN ligands and receptors are known to be expressed by glaucoma-relevant cell types. EDN ligands have been shown to be expressed by retinal and optic nerve macroglia and myeloid-derived cells, while both EDN receptors are expressed by retinal neurons (including RGCs) and macroglia. Endothelin signaling has been hypothesized to play a role in human glaucoma. Levels of EDN ligand were found to be higher in the aqueous humor and plasma of glaucoma patients. Changes in blood flow have been documented in human and animal models of glaucoma, and it is hypothesized that these changes could be important factors in the development and progression of glaucoma. Animal models of ocular hypertension have also indicated a potential role for endothelin signaling in glaucoma. *Edn* ligands and receptors were significantly upregulated in retinas and optic nerve heads of ocular hypertensive DBA/2J mice before the onset of glaucomatous neurodegeneration. Similar patterns of endothelin system upregulation were found in models of acutely induced ocular hypertension and after glaucoma-relevant optic nerve crush. EDN ligands are sufficient to cause RGC death— intravitreal injection or transgenic overexpression of EDN ligands caused significant RGC loss and axonal degeneration. Caspase 3 activation in RGCs and later RGC loss after EDN1 exposure was dependent upon JUN activation, similar to RGC death after glaucoma-relevant injuries including optic nerve crush and ocular hypertension. Importantly, pan-antagonism of EDN receptors with Bosentan or Macitentan conferred significant protection from glaucomatous neurodegeneration in DBA/2J ocular hypertensive mice. Thus, targeting endothelin signaling may have potential as a neuroprotective treatment for glaucoma.[1,3]

Retinal microvascular abnormalities might be present in the capillary bed that we were not able to evaluate. Following 1 month of diabetes, animal models of diabetes demonstrated increased retinal ET-1 expression where increased resistance in the distal capillary bed was observed. Consistently, Polak *et al* have shown that intravitreal administration of exogenous ET-1 leads to reductions in retinal blood flow and ischemic-type properties in healthy participants. Additionally, recent *in vivo* models by Cheung *et al* demonstrate that overexpression of endogenous ET-1 by endothelial cells induces mild transient inner retinal ischemia. Altogether, accumulating results suggest that diabetes-induced increases in ET-1 in the ocular tissue may be functionally important in early microcirculatory disruptions in DR. In addition, it is important to note that although ET-1 is a strong regulator of retinal blood flow, it is one of many factors that may directly or indirectly influence blood flow abnormalities in diabetes. It is possible that alteration in TRBF is not directly related to ET-1 alone but also involves the activation of other vasoactive factors, including nitric oxide (NO). Further studies are required to characterize the role of aqueous ET-1 and other factors that may mediate retinal hemodynamic abnormalities in diabetes. Nonetheless, our results have extended these findings by showing disturbances in ocular ET-1 expression occur at the same time as retinal microcirculatory disruptions in early diabetes.[4]

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we compare and contrast of endothelin-1 role in human eye. It is possible to accomplish this by researching or investigating endothelin-1 role in human eye. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine about the endothelin-1 role in human eye. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2013, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used " Endothelin-1 role in human eye." as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: *(("*Endothelin-1*"[MeSH Subheading] OR "*Endothelin-1 in eye*"[All Fields] OR "*Effects of endothelin-1*" [All Fields]) AND ("*Mechanism of endothelin-1*"[All*

Fields] OR " Endotheline-1 and reactive oxygen *"[All Fields]) AND ("*effects of endothelin-1 in human eye' *All Fields]) OR ("*Mechanism of endothelin-1 in human eye" *[All Fields]))* used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

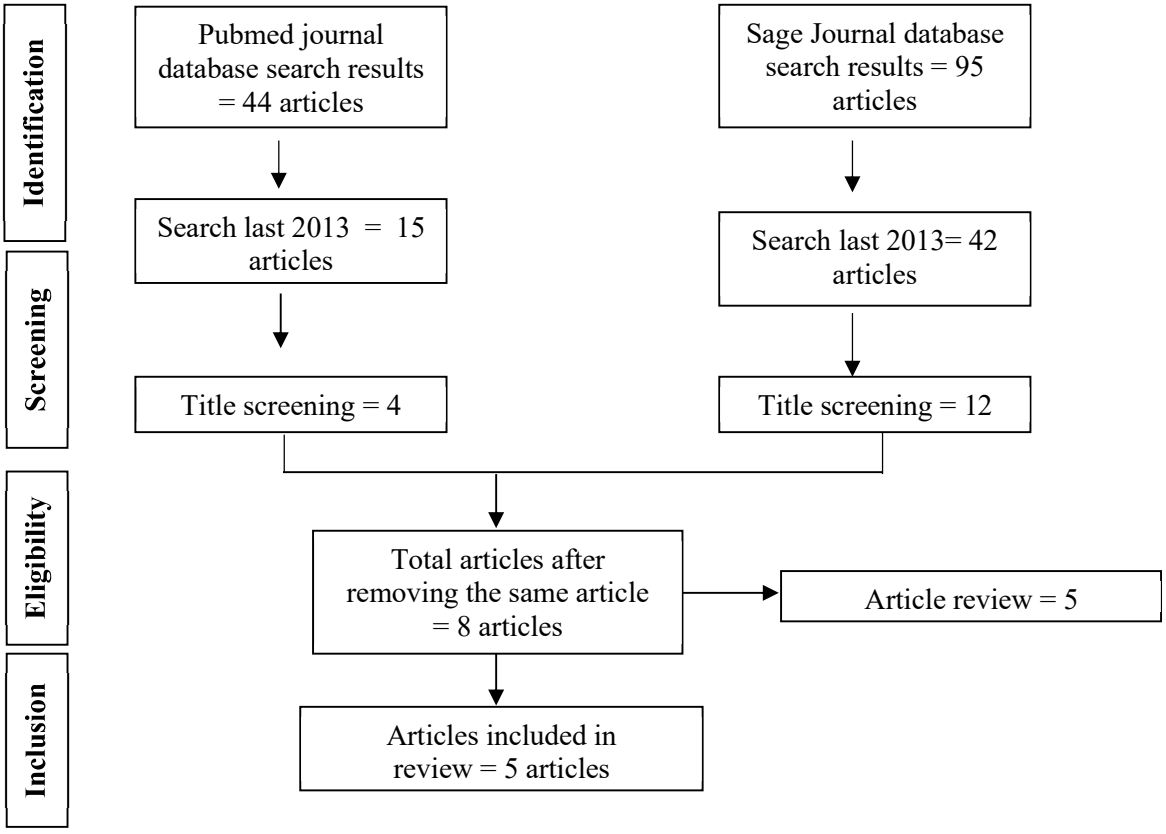

Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 44 articles, whereas the results of our search on SagePub brought up 95 articles. The results of the search conducted for the last year of 2013 yielded a total 15 articles for PubMed and 42 articles for SagePub. The result from title screening, a total 4 articles for PubMed and 12 articles for SagePub. In the end, we compiled a total of 8 papers. We included five research that met the criteria.

Lommatzsch, C *et al* (2022)[5] showed glaucoma patients with predominantly early or mild stages of glaucoma were included. We expected perimetry to not have shown many visual field defects, whereas RNFL changes could be observed by performing OCT, and promising results regarding sensitivity and specificity of the OCT GSS have been demonstrated. As perimetry remains the current gold standard in glaucoma monitoring, this technique should nevertheless be included in future studies, as well as expansion of the patient population to patients with more advanced stages of glaucoma and more individuals with NTG and XFG. The expansion and re-evaluation of the initial patient population at a later point of time would also allow to determine the sensitivity and specificity of plasma ET-1 as a diagnostic index. The blood samples were taken while the patients were under general anaesthesia. An increase in plasma ET-1 level during surgical operations has been demonstrated. However, the ET-1 level increases gradually after 2 h of surgery and declines slowly thereafter. In the current study all samples were obtained within the first 10 min after onset of anaesthesia. Thus, an influence of anaesthesia on the ET-1 level is unlikely.

Kang, HM *et al* (2021)[6] showed aqueous ET-1 level at baseline was not significantly correlated with mean BCVA and mean CMT at baseline and at 12 months in both the patients with CRVO and those with BRVO. As our results imply, ET-1 may not directly affect functional and anatomical outcomes, although it seems to be involved in the pathogenesis of CRVO and BRVO. Because disease itself and various complications associated with CRVO or BRVO such as foveal ischemia, macular edema, and vitreous hemorrhage are associated with functional and anatomical outcome in CRVO and BRVO, ET-1 may not directly affect clinical outcomes. However, if ET-1 is involved in the pathogenesis of CRVO and BRVO, prevention or early intervention for these diseases may be beneficial to preserve vision in these patients. Thus, further studies are warranted to investigate the possible impact of ET-1 in the clinical outcome in the patients with CRVO and those with BRVO. The mean aqueous humor ET-1 level was significantly higher in CRVO than BRVO or normal controls. After IVB, aqueous ET-1 levels in both the CRVO group and the BRVO group were significantly reduced.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Lommatzsch, C *et al*., 2022[5]	Germany	A prospective monocentric study	98 eyes	Eyes of patients with cataract (n = 30) or glaucoma (n = 68) were examined with optical coherence tomography (OCT) and OCT-angiography (OCT-A; AngioVue™-RTVue-XR; Optovue, Fremont, California, USA). The peripapillary and the macular vessel density (VD) values were measured. Inferior and superior retinal nerve fibre layer (RNFL) thickness loss was used for further OCT staging. Aqueous humour of the examined eye and plasma were sampled during cataract or glaucoma surgery and analysed by means of ELISA to determine their ET-1 level. Glaucoma eyes are characterised by reductions in RNFL thickness and VD that correlate significantly with the OCT GSS score. Peripheral and ocular ET-1 level were significantly elevated in patients with glaucoma and correlate positively with the OCT-GSS score of the entire study population. Peripapillary and macula VD of glaucoma patients correlates negatively with plasma ET-1 levels.
Kang, HM *et al*., 2021[6]	Korea	A prospective study	80 subjects	At baseline, the mean aqueous ET-1 level was 12.7±3.6 pg/mL in the CRVO group, 8.0±2.3 pg/mL in the BRVO group, and 2.0±0.9 pg/mL in

				the control group (P<0.001). After IVB, the mean aqueous level of ET-1 was 3.4±1.9 pg/mL (0.5–6.9 pg/mL) in the CRVO group and 1.8±1.0 pg/mL (0.3–3.2 pg/mL) in the BRVO group (P = 0.008). The mean aqueous ET-1 level was significantly reduced in both the patients with CRVO and those with BRVO (P<0.001).
Khuu, LA *et al*., 2017[4]	Canada	Case control study	30 participants	Aqueous ET-1 was significantly elevated in the NPDR group compared with the control group (3.5±1.8 *vs* 2.2±0.8, *P*=0.02). TRBF was found to be significantly reduced in the NPDR group compared with the control group (34.5±9.1 *vs* 44.1±4.6 μl/min, *P*=0.002). TRBF and aqueous ET-1 were not correlated within the NPDR group (*r*=−0.24, *P*=0.22). In a multivariate analysis, high A1c was associated with reduced TRBF and aqueous ET-1 levels across control and NPDR groups (*P*<0.01).
Powierza, K *et al*., 2021[7]	Poland	Cross-sectional study	17 participants	Statistically significant difference between ET-1 concentration in patients with chronic idiopathic uveitis and controls was found 1.33 (1.22; 1.48) vs 1.93 (1.1; 3.11), p = 0.008). No correlations were found between ET-1 concentration and age, either in chronic idiopathic uveitis patients or controls. Nine out of 17 patients presented with anterior uveitis, 5 with posterior and 3 with panuveitis. There were no differences in ET-1 concentration between anterior, posterior and panuveitis (p = 0.634), and in terms of grade of inflammation.
Kang, HM *et al*., 2022[8]	Korea	Prospective study	85 subjects	Advanced DR group included 40 eyes (47.1%), whereas early DR group did 19 eyes (22.4%), and control group (26 eyes, 30.5%). Mean aqueous ET-1 level was 10.1±4.1 pg/mL (6.0–21.0 pg/mL) in advanced DR group, 1.9±0.7 pg/mL (0.6–2.8 pg/mL) in early DR group, and 2.1±1.0 pg/mL (0.7–3.9 pg/mL) in control group (P < 0.001). Advanced DR group was further subdivided into severe

				nonproliferative DR (15 eyes, 12.8%) and proliferative DR (25 eyes, 34.3%). Mean aqueous ET-1 level was 10.1±4.3 pg/mL (6.0–20.1 pg/mL) in patients with severe nonproliferative DR, and 10.0±4.0 pg/mL (6.0–21.0 pg/mL) in those with proliferative DR (P = 0.928) at baseline. Mean ET-1 level at 1 month after intravitreal injection was 2.5±1.0 pg/mL (0.3–4.8 pg/mL) in patients with severe proliferative DR and 2.9±1.7 pg/mL (1.0–7.0 pg/mL) in those with proliferative DR (P = 0.443). Mean aqueous ET-1 level was significantly reduced in both groups (P < 0.001, respectively).

Khuu, LA *et al* (2017)[4] showed the importance of the mechanisms by which ET-1 modulates vasculopathy has been highlighted by non-ocular studies as well, where endothelial dysfunction plays a role. For instance, impaired endothelial macrovascular and microvascular reactivity to endogenous ET-1 has been demonstrated in patients with early glucose intolerance and non-insulin-dependent type II diabetes. Recently, Ahlborg *et al* showed that treatment using a dual ET antagonist in patients with insulin resistance improved insulin sensitivity, renal blood flow, and resistance, indicating an important role for endogenous ET-1 in endothelial dysfunction. Thus, the augmented ET-1 production and activity represents retinal vascular endothelial dysfunction, which is an early phenomenon in diabetes.

Powierza, K *et al* (2021)[7] showed ET-1 expression is disturbed in pediatric chronic idiopathic uveitis irrespective of the anatomical location and grade of inflammation. We conclude that lower ET-1 expression plays a crucial role in disturbed vascular tone control and can result in permanent visual impairment in chronic non-infectious uveitis.

Kang, HM *et al* (2022)[8] showed The mean aqueous ET-1 level was significantly higher in the eyes with advanced DR than those with early DR and the control group. The mean aqueous ET-1 level was significantly reduced after intravitreal injections in the advanced DR group. Based on our results, future studies on the exact role of ET-1 in the pathogenesis of DR and future implication for intervention would be helpful for managing DR.

DISCUSSION

Endothelin-1 (ET-1) belongs to the family of endogenous vasoconstrictor peptides. ET-1 is widely distributed in human tissues and secreted mainly by vascular smooth muscle cells (VSMC). As a result of transcription, proendothelin-1 is formed. Subsequent stimulation by hypoxia or vascular wall shear stress with the participation of an endothelin-converting enzyme leads to the formation of an active peptideET-1 exerts its effects by binding to the endothelin receptors A (ETA) and B (ETB), two cell surface proteins that belong to the G-protein-coupled receptors superfamily. Both these receptors induce various effects depending on the binding subtype of endothelin. They also differ in their affinity to each type of endothelin. The binding affinity of ET-1 to ETA is greater than that of ET-2 and ET-3, whereas all subtypes of endothelin have equal binding affinity to receptor ETB. ETA receptors are located mostly in VSMC, where they are responsible for potent vasoconstriction, cell proliferation, and a proinflammatory effect. ETB receptors include two subtypes: ETB1, which is expressed on endothelial cells and results in nitric oxide-mediated vasodilation, and ETB2, present in VSMC, which causes vasoconstriction.[6,9]

ETs act on specific receptors (ETA and ETB) which are transmembrane G-proteins described in ocular tissues and retinal vessels. ETA, selectively expressed by VSMCs, has high affinity for ET-1 and ET-2 but low affinity for ET-3 and is primarily involved in vasoconstriction. ETB, expressed on both VSMCs and ECs, is equally responsive to all isoforms and is involved in vasodilation by releasing of nitric oxide (NO) and prostacyclin (PGI_2). The gene transcription of ET-1 and ET-3, specifically in ocular tissues, has been demonstrated in vascular and extravascular sites of retina, uveal tract, and optic nerve. A remarkable physiological role of these peptides turned out to be important in control of the following physiological processes of retina and optic nerve: vascular tone, aqueous flow and neural modulation.[10,11]

ET-1 is a strong vasoconstrictor with mitogenic, pro-oxidative, and proinflammatory properties that are of significant importance in the regulation of vascular function, particularly relevant in the pathophysiology of diabetic vasculopathy.

Overproduction and increased functional effects of ET-1 are reported to be greatly altered in diabetic conditions. The ETA and ETB receptors, coupled with two distinct G-proteins, mediate the action of ET-1 on the vascular tone. For instance, ETA and ETB receptors contribute to the potent vasoconstrictor and mitogenic effect of ET-1 on VSMCs, whereas ETB receptors located in ECs provoke vascular relaxation via the release of NO and PGI_2. In diabetic patients, signaling mechanisms between ET-1 and its receptors as well as the expression of ETA and ETB are altered. The oxidative stress plays an important role: reactive oxygen species (ROS) generation leads to the synthesis of ET-1 via transforming growth factor-β and, at the same time, ET-1 increases ROS generation via NAD(P)H oxidase in ECs. However, the downregulation of ET-1 and NAD(P)H oxidase-derived superoxide caused by an increase of NO has demonstrated a sort of restoration of endothelial function.[11,12]

CONCLUSION

ET-1 (vasoconstrictor, mitogenic, pro-oxidative, and proinflammatory) is one of the most potent vasoconstrictors in the body and its action has a dual effect: on the one hand, it acts on receptors of ECs and pericytes; on the other hand, it has a mitogenic effect on VSMCs.

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