Review Article

The characteristics of fundus microvascular alterations in the course of glaucoma: a narrative review

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Background and Objective: As the vascular theory has led many researchers to focus on vascular dysfunction in the pathogenesis of glaucoma, a better understanding of ocular microcirculation would be of great significance. The emergence of optical coherence tomography angiography (OCTA) has shed light on the various fundus microvascular changes that occur in glaucoma, thus providing ample evidence in the role of microvascular dysfunction in glaucoma. The aim of this review is to provide an overview of the retinal and choroidal microvascular alterations that occur in glaucoma and to address the role of microvascular alterations in the pathogenesis, diagnosis, prognosis, and treatment of glaucoma.

Methods: The literature regarding fundus microvascular alterations in glaucoma and after glaucoma treatment, including alterations of vascular perfusion and vascular reactivity, was broadly researched using PubMed and Web of Science databases. The endothelium involvements during the glaucoma course were also searched in the databases broadly.

Key Content and Findings: Previous OCTA studies show vessel density (VD) decreases in the retinal macular and peripapillary regions and choroidal microvascular dropout. Such microvascular alterations are correlated with structural and functional defects and have potential value for the early diagnosis and prognosis of glaucoma. Retinal microvascular autoregulation is also impaired in glaucomatous eyes. Furthermore, various studies have demonstrated the role of the vascular endothelium in glaucoma. Different topical medications and surgical interventions have been shown to have an impact on microvasculature in glaucoma, and animal experiments have indicated the endothelial system may be a new target in glaucoma treatment.

Conclusions: Ample evidence proved the involvement of retinal and choroidal microvascular structural and functional changes in the course of glaucoma. This review makes a novel contribution to the literature by summarizing the microvascular alterations in glaucoma eyes and the microvascular changes after topical or surgical treatments.

Keywords: Glaucoma; optical coherence tomography angiography (OCTA); microvasculature; autoregulation; endothelium

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Introduction

Although it is one of the most common irreversible blinding diseases globally, the pathogenesis of glaucoma remains unclear (1,2). Previously, the mechanical theory was recognized as the dominant mechanism leading to the optic neurodegeneration and visual loss associated with glaucoma (3). However, this theory cannot explain why some patients with glaucomatous optic neuropathy do not have an elevated intraocular pressure (IOP). Furthermore, the glaucomatous optic neuropathy continues to progress throughout the duration of the disease, even after the IOP is controlled (4,5). Another principal theory suggests that glaucomatous optic nerve degeneration is due to insufficient ocular blood flow resulting from ocular hypertension or other risk factors (6). The proposition of this vascular theory has led many researchers to focus on vascular dysfunction in the pathogenesis of glaucoma.

The ophthalmic artery has two main branches, namely, the central retinal artery and posterior ciliary artery, both of which branch into arterioles and microvessels that provide the blood supply to the optic nerve head (ONH) (7). Reduced ocular perfusion caused by increased IOP or other elements is thought to be responsible for glaucomatous optic neuropathy through ischemic injury to the optic nerve (8). Many studies have revealed that a reduced ocular perfusion pressure (OPP) is correlated with the progression of glaucoma. OPP is also a critical risk factor for disease occurrence (8-10). Additionally, numerous reports have shown that multiple factors that can influence the OPP are associated with the development of glaucoma, which supports the vascular theory of glaucoma (11-13). Furthermore, many scholars argue that vascular autoregulation dysfunction is a crucial mechanism of glaucoma. This dysfunction is primarily attributable to the reduction of retinal microvascular perfusion (14-16). Hence, a better understanding of ocular microcirculation perfusion is of great significance to unveil the pathogenesis of glaucoma.

However, due to the limitations of ocular inspection equipment, our ability to detect ocular blood flow around the optic nerve has been restricted. This has partially hindered detailed explorations of the relationship between microvascular dysfunction and glaucoma, as well as their mechanisms. Recently, with the emergence of new technologies such as optical coherence tomography angiography (OCTA), which allows for the non-invasive examination of optic nerve perfusion by instantly providing repeatable images of microvascular networks, growing evidence has emphasized the role of microvascular dysfunction in the progression of glaucoma (17,18).

This review aims to: (I) provide an overview of the current literature regarding the retinal and choroidal microvascular alterations that occur in glaucomatous eyes; (II) address the role of microvascular alterations in the early diagnosis and prognosis of glaucoma; (III) summarize the involvement of retinal microvascular autoregulation and endothelium in glaucoma; and (IV) introduce the effect of glaucomatous medications and surgical interventions on the microvasculature. Early studies mainly focused on the vessel density (VD) detected by OCTA when considering fundus microvascular alteration in glaucoma eyes. This review makes a novel contribution to the current literature by providing a detailed elaboration of both structural changes (i.e., retinal and choroidal VD) and functional changes (i.e., microvascular autoregulation, endothelium functions, endothelin system) in glaucoma eyes. In addition, we list the microvascular changes after topical or surgical treatments. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-21-5695/rc).

Methods

We searched PubMed and Web of Science for original research and review articles up to August 2021. Articles in English and Chinese languages were included. The following terms were employed in different combinations: “glaucoma”, “ocular hypertension”, “microvessel”, “microvasculature”, “microvascular”, “microcirculation”, “capillary”, “arteriole”, “venule”, “optical coherence tomography angiography”, “OCT angiography”, “OCTA”, “endothelial”, “endothelium”, and “endothelin”. Articles citing related studies and citations in relevant articles were also checked as potential sources of information.

Fundus microvascular alterations in glaucoma patients

Many glaucoma scholars have long been committed to observing fundus microcirculation. Among the vascular observation methods, OCTA is notable for its safety, convenience, and high-resolution quantitative test results. Thus, it provides us with the opportunity to evaluate microvascular alterations in glaucoma patients (19,20). In recent years, OCTA has been applied to patients with

glaucoma to observe microvascular perfusion in the macula, including the parafoveal and perifoveal regions, and the ONH, including the inside disc and peripapillary region (19,21). Macular and peripapillary areas have become a focus of attention, with a significant number of studies confirming that microcirculation is compromised in glaucoma (22-26).

Retinal macular microvascular alterations

Previous studies have shown somewhat conflicting results regarding microvascular alterations in macular areas. Chen *et al.* detected a decrease in the superficial macular VD of primary open-angle glaucoma (POAG) eyes compared to healthy eyes (27). Based on this information, Cano *et al.* found that the macular VD decrease in POAG patients is associated with a decrease in the total retinal blood flow (28). Figures reported by Yarmohammadi *et al.* represented the macular microvasculature alteration as shown in OCTA images (29). However, Triolo *et al.* found that the macular VD was not significantly different between glaucoma patients, glaucoma suspects, and healthy controls. Moreover, there was no significant correlation between the ganglion cell inner plexiform layer thickness and the macular VD (30). Despite this controversy, macular VD reduction has been reported frequently (27,31-33). Xu *et al.* reported a significantly positive correlation between retinal structural injury and microvascular perfusion in POAG eyes, especially between the inner inferior retinal thickness and macular VD (33). Their results also showed that the macular microvascular VD and flow index in the intermediate stage of POAG were significantly lower than in the early stage but similar to those of the advanced stage (33). The reported correlation between macular VD and the visual field (VF) sensitivity threshold in POAG patients connects microvasculature to visual functions (34). Foveal avascular zone enlargement could also be interpreted as an indicator of a higher risk of structural defects (35). In a study of primary angle-closure glaucoma (PACG), foveal avascular zone enlargement was observed along with macular VD loss after an acute attack (32). Macular VD is also considered a diagnostic parameter (27,36-40), and it is discussed in detail later in this review.

Retinal ONH microvascular alterations

Previous studies have shown a significant reduction in the focal peripapillary VD in early glaucoma (41,42). Figures reported by Yarmohammadi *et al.* represented the peripapillary microvasculature alteration as shown in OCTA images (29). Additionally, a significantly positive correlation between the retinal nerve fiber layer (RNFL) thickness and the peripapillary VD has also been reported (30). Son *et al.* further showed that when an RNFL defect occurs in only one hemiretina in POAG patients, parapapillary deep-layer microvasculature dropout is only observed in the location of the defect (43). As previously reported, a faster longitudinal circumpapillary VD reduction rate is significantly associated with VF loss during all the POAG disease stages (44). In a study of PACG, Wang *et al.* found that peripapillary VD reduction can be observed before structural damage occurs, thus, suggesting that VD may partly initiate the structural damage associated with glaucoma progression (45).

This relationship between ONH VD and structural or functional defects highlights the importance of microvascular alterations in glaucoma diagnosis, assessments, and prognosis predictions.

Choroidal microvascular dropout

With the development of OCTA, choroidal microvascular dropout (CMvD) has frequently been reported in glaucoma cases (46,47). Such choroidal vascular changes are closely related to structural and functional alterations. Studies of patients with POAG have demonstrated the presence of CMvD and its association with decreases in the RNFL thickness (48,49). These RNFL structural defects are also spatially correlated with CMvD (50). Other studies on functional defects have demonstrated an association between CMvD and central VF defect progression (51) and a topographic relationship between CMvD and VF defects (52). The angular circumference associated with CMvD has also been reported to be related to VF progression in POAG eyes (53,54). Baseline CMvD can be a predictor of subsequent glaucomatous progression (55,56). The association between CMvD and disease severity (57) has raised the possibility of using CMvD as a potential parameter to facilitate the diagnosis of glaucoma and an indicator for future prognosis.

Fundus microvascular alterations in glaucoma patients with high myopia

Being an important risk factor for POAG, high myopia is of particular interest to glaucoma researchers. Previous studies have demonstrated that changes in the retinal or choroidal

vasculature, such as a decreased VD and CMvD, were detected in glaucomatous eyes with high myopia to a larger extent than those observed in glaucomatous eyes without high myopia. Samra *et al.* used laser Doppler flowmetry to show larger reductions in the subfoveal choroidal blood flow and velocity of myopic POAG eyes than those of emmetropic POAG eyes (58). Other studies have used OCTA to demonstrate a faster VD reduction in both the macula (59) and peripapillary region (60) of POAG eyes with high myopia than that of POAG eyes without high myopia.

In addition, researchers have frequently reported on phenomena in myopic glaucomatous eyes. Na *et al.* reported a topographic correlation between CMvD and VF defects in POAG patients with high myopia (61), and Shin *et al.* detected a correlation between the angular circumference of CMvD and POAG severity (62). A study of glaucoma patients with an elongated axial length demonstrated a negative correlation between the IOP and peripapillary VD. However, this association was not significant in glaucoma patients with a shorter axial length (63).

Such studies have emphasized the importance of microvasculature in the pathogenesis, diagnosis, and prognosis of myopic glaucoma.

Clinical value of fundus microvascular alterations in glaucoma

With the emergence of new diagnostic techniques, the potential for microvascular parameters to aid in distinguishing glaucomatous eyes from healthy eyes has also been adequately evaluated (27,29,30,38,64,65). This has enabled the application of microvasculature to glaucoma diagnosis, assessment, and risk prediction.

Fundus microcirculation and glaucoma diagnosis

Triolo *et al.* presumed that the peripapillary and macular VDs had less diagnostic capacity than the peripapillary RNFL thickness (30). Chen *et al.* suggested that the diagnostic accuracy of the macular superficial microvasculature density was comparable to that of the peripapillary RNFL and macular ganglion cell complex (GCC) thicknesses (27). The latter finding was consistent with a cross-sectional study of capillary perfusion in the peripapillary region, which demonstrated that the diagnostic capacity of peripapillary VD was equivalent to that of the circumpapillary RNFL thickness and VF indicators in POAG patients (65). Nonetheless, Richter *et al.* indicated that although OCTA results change in conjunction with the POAG-associated deterioration process, the microvasculature is strongly associated with structural defects rather than VF loss (66).

Despite this discrepancy, researchers have attached great importance to measuring microvascular parameters for the early diagnosis of glaucoma. Kurysheva *et al.* found that the macular superficial VD is beneficial for the diagnosis of early-stage POAG. Furthermore, the inferotemporal peripapillary VD may aid clinicians in distinguishing the moderate to severe stage of POAG from the early stage (39). To date, multiple studies have provided ample evidence regarding the capability of microvascular indices to aid in the diagnosis of POAG (29,38,65,66). It is worth noting that Yarmohammadi *et al.* found that for POAG patients with unilateral VF loss, the areas under the receiver operating characteristic curves were highest for the whole image VD, followed by other structural parameters (29). Said curves are a method of assessing the diagnostic capability of differentiating between the uninfluenced eyes of POAG patients and the control eyes of healthy subjects. In a study of early-stage POAG, which included patients with pre-perimetric and early perimetric POAG, Lu *et al.* showed the diagnostic accuracy of radial peripapillary capillary VD for pre-perimetric POAG patients was comparable to that of the RNFL and GCC thicknesses (38). Additionally, the diagnostic capacities of the macular VD in early perimetric POAG were comparable to those of the RNFL, GCC thickness, and radial peripapillary capillary VD (38).

As a promising method for diagnosing glaucoma, microvascular alteration parameters have frequently been optimized for improved accuracy. Superficial layer macular VD is more informative than deep layer macular VD, and it has shown a better diagnostic accuracy (37,40). More specifically, Liu *et al.* showed the mean deviation of the peripapillary nerve fiber layer plexus VD's superior diagnostic accuracy over the VF and RNFL thickness (67). In addition to a more precise scanning location, an enlarged scanning area, such as a 6×6 mm^2 macular scanning area, can also favor the diagnostic capability (36). The option to "track to prior scan" improves the repeatability of OCTA because follow-up scans can be based on baseline scans (68). The hemiretinal difference in the vessel area density has also been proposed as a suitable parameter for early glaucoma detection, and consideration of both the hemiretinal difference in the vessel area density and the global RNFL has been suggested as a way to improve diagnostic accuracy (69).

Fundus microcirculation and glaucoma prognosis

In addition to their diagnostic value for confirming cases of glaucoma, microvascular alterations also offer a reference for assessment and risk prediction. Geyman *et al.* observed a gradually progressive reduction of the peripapillary VD across the aggravating stage of POAG (65). Said results are supported by other researchers who found a significantly negative correlation between the glaucoma stage and OCTA parameters (70). Hou *et al.* found that for POAG patients, especially those in advanced stages, the macular VD decreases faster than the GCC thinning. Additionally, a faster decrease was associated with increased severity (71). Such findings have enhanced the role of better evaluation of microvasculature for the assessment of glaucoma.

Furthermore, POAG patients with juxtapapillary deep-layer microvascular dropout may experience structural defect progression faster than those without microvascular dropout (72). Another study demonstrated a correlation between the existence of CMvD and faster glaucomatous progression (73). Moghimi *et al.* also showed that a lower VD at 2 months after remission of an acute PACG episode might be associated with a higher risk of glaucomatous progression (74). Thus, microvasculature may complement structural and functional evaluations and predict possible outcomes for patients with glaucoma.

Retinal microvascular autoregulation in glaucoma

Vascular autoregulation, also known as vasoreactivity, is the ability of the vascular system to intrinsically self-adjust to maintain a stable and sufficient blood flow under different conditions and meet various metabolic demands. Several methods can be used to assess vasoreactivity, including cold stimulation, flicker light provocation, hypercapnia, and hyperoxia tests (75-78). Vascular autoregulation dysfunction is considered partly responsible for the onset and progression of glaucoma. Zhang *et al.* found that the posterior cerebral artery of POAG patients showed a lower percentage of change in the mean velocity during hyperventilation than that of healthy patients (79). Harris *et al.* found that the peak and mean velocities of the middle cerebral artery did not show a significant decrease during hyperoxia provocation, unlike that of the healthy control group (78). Additionally, patients with normal-tension glaucoma (NTG) and lower baseline pulsatile ocular blood flow showed a more evident response toward a hypercapnic stimulus (77). Nevertheless, these studies seldom focused on the role of microvasculature vasoreactivity in glaucoma.

Perfusion pressure, determined using the IOP and systemic blood pressure, fluctuates according to various conditions. Healthy eyes show limited interference from IOP or perfusion pressure fluctuations. On the contrary, eyes with glaucoma show an inferior adaptation capability in response to perfusion pressure changes due to vascular autoregulation disturbances, which break such homeostasis (80-83).

POAG eyes respond less to flicker light (normal eye vessels dilate) (80), show a larger retinal blood flow alteration variance after posture changes (81), and exhibit significantly smaller diurnal fluctuations and larger macular VD diurnal fluctuations than healthy eyes (82). Therefore, definite autoregulation dysfunction during glaucoma progression is observed. Kiyota *et al.* used laser speckle flowgraphy to monitor the microvasculature during oxygen inhalation (83). In addition, the tissue-area mean blur rate (MBRT) change at the ONH was used as a parameter to reflect the blood flow change (83). The authors found that POAG eyes showed a less sensitive response to hyperoxia than healthy eyes (83). Furthermore, in another study, Kiyota *et al.* found that a lower baseline MBRT and higher baseline blood pressure are associated with a decreased MBRT change, and such autoregulation disturbances are also related to faster VF defect progression (84).

Previous studies on retinal vasoreactivity in glaucoma have seldom used OCTA, while it has been used frequently to monitor microvascular responses in healthy eyes (85-87). Notably, however, various studies using OCTA have reported a retinal microvascular VD decrease after the Valsalva maneuver and hyperoxia test (85-87). These studies have also revealed the specific topographic characteristics inherent to microvascular autoregulation. Zong *et al.* found that the macular VD showed a significantly greater reduction than the peripapillary VD after the Valsalva maneuver (85). Interestingly, the hyperoxia-induced decrease in the flow index and VD only occurred in the deep capillary plexus rather than in the intermediate and superficial plexuses (87). These studies in healthy eyes have confirmed the potential feasibility of applying OCTA to investigations of retinal vasoreactivity in glaucoma.

A decrease in the IOP through either surgical or medical treatment has been shown to ease the involvement of vasoreactivity (88-90), which will be described in detail later. The exact mechanism by which the vasoreactivity reserve is exhausted by IOP elevation remains a mystery. However,

microvascular endothelial function is believed to play a role in this process. This role will be discussed in greater detail later.

Microvascular endothelial dysfunction in glaucoma

The vascular endothelium, which is the boundary between the plasma and vessels, modulates blood flow by producing various vasoactive substances. As the main and critical structure of microvasculature, endothelial cells are involved in angiogenesis, vascular tone control, and maintaining homeostasis. Vascular endothelium disturbances may cause ischemia and vascular dysregulation. In addition, some studies have implied the potential relationship between glaucomatous vascular changes and endothelial system (83,91). Hence, researchers are directing more attention to the role of the vascular endothelium in glaucoma.

Endothelin alterations

An important factor in the mechanism underlying the relationship between the vascular epithelium and vasoreactivity is the vasoactive substances released by the vascular epithelium. Among these substances, endothelin (ET) has attracted the most attention. ET synthetized by endothelial cells includes ET-1, ET-2, and ET-3. ET-1, a potent vasoconstrictor, is the most well elucidated of these peptides. The irreversible binding of ET-1 with its receptors (ETA and ETB) lasts for approximately an hour, at which time ET-1 is degraded (92). Significant evidence has recently shown that POAG patients have higher ET-1 levels in the aqueous humor (93,94) and plasma (95,96), both of which are related to vascular dysfunction.

ET-1 functions in glaucoma in several ways. Expression of the water channel aquaporin 1 has been shown to be suppressed in the trabecular meshwork when exposed to higher ET-1 levels (97). Chaphalkar *et al.* reported that glaucomatous neurodegeneration of retinal ganglion cells aggravates due to ET-1 elevation, as ET-1 downregulates the expression of mitochondrial electron transport chain components in POAG eyes (98). Additionally, as mentioned earlier, an important physiological role of the endothelium is in the control of vascular tone, while the balance maintained by endothelially derived vasodilators, such as nitric oxide and the vasoconstrictor ET-1, is essential to the vascular physiological status.

Systemic endothelial dysfunction

A previous study showed impaired endothelium-dependent, flow-mediated vasodilation in peripheral vascular systems, particularly in NTG patients (99). Studies on patients with POAG demonstrated a negative correlation between severity and peripheral microvascular endothelial function (100). Furthermore, flow-mediated vasodilation in peripheral vessels, such as the brachial artery, may be related to long-term VF progression (101). Fadini *et al.* also reported a marked decrease in peripheral endothelial progenitor cell counts in patients with POAG (102). Henry *et al.* infused an ETA receptor antagonist into NTG patients and healthy controls. They observed a weaker vasodilation effect in the forearms of the NTG group than in the control group (103), suggesting the possibility of ETA and ETB receptor involvement in glaucoma. However, such studies have focused on the peripheral or systematic vascular endothelium as a whole, while there are very few studies on the retinal microvascular endothelium.

Retinal endothelial alterations

Gericke *et al.* observed a reduced retinal arteriole response to an endothelium-dependent vasodilator in a mouse model with an elevated IOP (104). The authors assumed that this retinal vascular dysfunction might be caused by oxidative stress and inflammation (104). Apart from the influence of the ET system on the systematic vascular system, its role in the retina has also been investigated. A study of retinal vasculature demonstrated that the exogenous vasoconstrictive effect of ET-1 primarily acts on the microvasculature (105). This is consistent with an earlier finding that the potency of ET-1 as a vasoconstrictor is determined by the vessel diameter (106). A study by Hein *et al.* shed light on the role of smooth muscle cell ETA receptors in evoking the constriction effect of retinal arterioles (107). Additionally, Mi *et al.* developed an ET-1 overexpression mouse lineage that can be used in future studies (108).

The effect of glaucoma treatment on retinal microvasculature

Historically, conventional treatments for glaucoma were primarily targeted at reducing the IOP, and only after that was the microvascular condition considered. However,

recent studies have shown evident changes in retinal microvasculature, from VD changes to vasoreactivity and endothelial alterations, after both medication treatments and surgical interventions have been performed.

Topical medical therapies

To date, numerous studies have highlighted the role of topical medications in ocular vascular alterations (*Table 1*). The antiglaucoma topical agents that researchers have focused on include beta-adrenergic blockers (timolol and carteolol), carbonic anhydrase inhibitors (dorzolamide and brinzolamide), an alpha-adrenergic agonist (brimonidine), prostaglandin derivatives (latanoprost, bimatoprost, and tafluprost), and an ET receptor antagonist (bosentan). While these agents share the initial purpose of lowering the IOP, they may influence the vasculature differently. Early research has demonstrated an increase in the ONH blood flow after administering a latanoprost and carteolol combination therapy (113). After treatment with a combination of bimatoprost and timolol, POAG patients showed an elevated mean OPP (114). However, some patients showed a decrease in the retinal blood flow after using topical carteolol (109). Lin *et al.* used OCTA to detect a VD decrease in the inferior-temporal peripapillary region after topical carteolol use (110). Kurysheva observed a decrease in inside disc VD on OCTA after tafluprost administration (26). However, studies on other topical medications have shown conflicting results. Peripapillary blood flow increased after treatment with either brinzolamide (111) or dorzolamide/timolol (115). OCTA results have further demonstrated a peripapillary region VD increase after the topical application of either dorzolamide (110) or latanoprost (112). Although brimonidine may not cause a significant change in the microvascular VD (110), it has been reported to be correlated with improved microvascular autoregulation (89,90).

POAG patients who displayed retinal vascular dysregulation with a posture change converted to a state of normal retinal vascular autoregulation after a 6-week dorzolamide-timolol or brimonidine-timolol course (89). Furthermore, the dorzolamide-timolol group showed an elevated OPP compared to the brimonidine-timolol group (89). In another study on NTG eyes, 14 out of 17 patients with vasoreactivity involvement after a posture change returned to a normal retinal vascular autoregulation state after an 8-week brimonidine treatment course (90), thus, demonstrating the influence of brimonidine on retinal vasoreactivity.

Surgical interventions

Surgical reduction of the IOP might result in a subsequent alteration in the ocular blood flow of both the macular and peripapillary regions (122). Among the various surgical interventions, the correlation between trabeculectomy and vascular changes is most elucidated. Early reports have shown increases in the ONH blood flow (116) and end-diastolic velocity in the central retinal artery and temporal posterior ciliary arteries, respectively, after a trabeculectomy (123). With the emergence of OCTA, several studies have demonstrated microvascular improvements after a trabeculectomy, including frequent reports of an elevated peripapillary VD (117,118). Contrarily, other reports have indicated no significant alterations in the macular or peripapillary VDs (119,120). POAG patients showed performance improvements in the flicker provocation test after undergoing a trabeculectomy (88). In addition, a recent study showed a VD increase in the peripapillary and macular regions of POAG eyes after laser selective trabeculoplasty, although they returned to baseline after 6 months (121).

Potential glaucoma treatments targeting the endothelium

Studies on microvascular endothelial cells have also suggested potential targets for future glaucoma treatments. Among these emerging treatment methods, bosentan, which is a dual antagonist of both ETA and ETB receptors, has attracted significant attention. Bosentan can dilate retinal vessels and increase blood flow and velocity in both glaucoma patients and healthy people (124). Experiments in DBA/2J mice have shown that the ET and complement systems are both upregulated in early-stage glaucoma (125). Hence, Howell *et al.* used bosentan in combination with a targeting complement system and showed a profound neuroprotection outcome in the DBA/2J mouse model (126). Huang *et al.* found that in rat models, endothelial-specific overexpression of CYP2J2 protects the endothelium from senescence and prevents retinal ganglion cell loss by metabolizing arachidonic acid (127). This might indicate another potential future glaucoma treatment strategy.

Discussion and summary

Recently, researchers have gained a deeper insight into the fundus microvascular system due to the emergence

Table 1 Glaucoma medications and their reported effects on fundus vasculature

Treatment	Drug names/surgery procedures	Effect	Characteristics	Subjects
Beta-blockers	Carteolol	Decrease	Retinal arterial blood flow (109)	POAG
		Decrease	Peripapillary VD (110)	NTG
Carbonic anhydrase inhibitors	Dorzolamide	Increase	Peripapillary VD (110)	NTG
	Brinzolamide	Increase	Peripapillary blood flow (111)	POAG
Adrenergic agonist	Brimonidine	No change	Peripapillary VD (110)	NTG
		Increase	Retinal vascular autoregulation (90)	NTG
Prostaglandin analogs	Latanoprost	Increase	Inside disc VD and peripapillary VD (112)	POAG/PACD/OHT
	Tafluprost	Increase	Mean OPP (26)	POAG
		Decrease	Inside disc VD (26)	
		No change	Macular or peripapillary VD (26)	
Combined therapies	Latanoprost-Carteolol	Increase	ONH blood flow (113)	NTG
	Latanoprost-Timolol	No change	ONH blood flow (113)	NTG
	Bimatoprost-Timolol	Increase	Mean OPP (114)	POAG
	Tafluprost-Timolol	Increase	Mean OPP (26)	POAG
		Decrease	Inside disc VD (26)	
		No change	Macular or peripapillary VD (26)	
	Dorzolamide-Timolol	Increase	Retinal vascular autoregulation (89)	POAG
		Increase	Diastolic OPP (115)	POAG
	Brimonidine-Timolol	Increase	Retinal vascular autoregulation (89)	POAG
Surgery	Trabeculectomy	Increase	ONH blood flow (116)	POAG
		Increase	Peripapillary VD (117,118)	POAG POAG
		No change	Peripapillary VD (119,120)	POAG
		Increase	Retinal vascular autoregulation (88)	
	Laser selective trabeculoplasty	Increase	Peripapillary and macular VD (121)	POAG

VD, vessel density; ONH, optic nerve head; OPP, ocular perfusion pressure; POAG, primary open-angle glaucoma; NTG, normal tension glaucoma; PACD, primary angle-closure disease (including primary angle closure and primary angle-closure glaucoma); OHT, ocular hypertension.

of OCTA. The findings from numerous studies have led to a consensus on the decreases in the macular and peripapillary retinal VDs and the development of CMvD in glaucoma patients. Based on these common discoveries, other researchers have verified the significance of fundus microvascular alterations in diagnosing and evaluating glaucoma during disease progression. In addition to quantity changes, alterations to the quality of retinal microvasculature autoregulation have been well-studied. Exhaustion of the retinal microvascular autoregulation reserve has been reported in glaucoma patients, while future studies may introduce the use of OCTA for studying fundus microvascular reactivity. Despite the numerous studies that have been conducted on the vascular endothelium, few published reports have explicitly focused on retinal microvasculature. Comparatively, relatively more have focused on the systematic or peripheral microvasculature as a whole. Recent studies have shown the involvement of the retinal endothelium in glaucoma, as the retinal endothelium reactions toward endothelium-dependent

vasodilators attenuate and the ET system changes in glaucoma. However, there is a lack of studies on choroidal vasoreactivity or the choroidal microvascular endothelium at the time of writing. Additionally, although the initial purpose of surgical intervention or topical medications is to reduce the IOP, various studies have also demonstrated the effect of these treatments on fundus microvasculature VD and autoregulation. Some treatments have positive effects (i.e., dorzolamide), and some have negative effects (i.e., carteolol), while others may not show a significant influence (i.e., brimonidine on fundus VD). However, not all commonly used topical medications have been investigated, and the reported effects of some medications (i.e., latanoprost) are still somewhat controversial (112,128). Thus, more well-designed large-sample studies and systematic reviews are needed in the future. By studying the relationships between the various treatments and microvasculature, new therapies, such as bosentan, may usher in a new era of glaucoma treatments designed to target the microvascular endothelium.

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Footnote

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