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Is There Any Role for the Choroid in Glaucoma?

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Abstract

The choroid is part of the uveal tract and is a heavily vascularized bed that also contains connective tissue and melanin pigment. Given the role of the choroidal vasculature in the blood supply of the anterior laminar and prelaminar regions of the optic nerve head, the peripapillary choroid might be a relevant target for investigation in patients with glaucoma. The purpose of this paper is to critically review the current understanding of potential role of the choroid in the pathogenesis of glaucomatous damage.

Keywords

Choroid; glaucoma; choroidal blood flow; enhanced depth imaging

Introduction

Glaucoma is a multifactorial optic neuropathy characterized by progressive neurodegeneration of retinal ganglion cells (RGCs) and their axons, and retinal nerve fiber layer (RNFL) attenuation, a specific pattern of damage to the optic nerve head (ONH), and visual field (VF) loss.[1-3] Glaucoma is one of the most common causes of blindness in industrialized world.[4] However, the exact mechanism of glaucomatous damage remains controversial.[5] Some of the ocular structures, such as ONH,[6-8] lamina cribrosa (LC),[9-12] RNFL[13-15], sclera[16,17] and ONH microcapillaries[18-22] have been studied more extensively than the others in glaucoma. The impact of different pressure gradients on the incidence and progression of glaucoma have also been studied extensively.[23-29]

The choroid has the highest perfusion rate compared with any other vascular bed within the human body.[30] Approximately 70-80% of the ocular blood flow (OBF) is due to choroidal vasculature.[31] The choroidal blood flow (ChBF) is autoregulated via neurohumoral and local mechanisms.[28] Vascular factors may have a significant contribution in the pathogenesis of a subgroup of glaucoma patients. Therefore, the choroid deserves to be considered as a potential player, particularly in patients with normal-tension glaucoma (NTG), in those with evidence of vasospasm and in angle-closure cases.[32]

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In glaucomatous optic neuropathy the primary site of damage is at the optic nerve head, resulting in the damage to nerve fibers, and consequently secondary changes in the retinal ganglion cells. Some studies have shown that the optic nerve head is primarily supplied by the peripapillary choroid.[33] Hence, the relationship between the peripapillary choroidal circulation and glaucomatous optic neuropathy is of great importance. It has been proposed that peripapillary choroidal atrophy is a late degenerative change in glaucoma due to the chronic circulatory derangement.[34] Given the role of the choroidal vasculature in the blood supply of the anterior laminar and prelaminar regions of ONH, the peripapillary choroid might be a relevant target for investigation in patients with glaucoma.[35-38]

The purpose of this paper is to review the current understanding of potential role of the choroid in the pathogenesis of glaucomatous damage.

The Choroid

The choroid is a vascularized and pigmented tissue that is extended from the ora serrata anteriorly to the optic nerve posteriorly.[30] Apart from blood vessels that fill most of the choroid, the rest is composed of stroma that surrounds the blood vessels. The choroidal stroma contains connective tissue and dense melanin pigment. Using swept-source optical coherence tomography (SS-OCT) in a healthy population, it was shown that choroidal thickness (Ch.T.) was 286 ± 43.5 μm in the first decade of life and decreased to 229.7 ± 66.1 μm in the seventh decade.[39] The choroid is consisted of five layers; starting from the retinal side: Bruch's membrane, the capillary bed or choriocapillaris, Haller's layer, Sattler's layer and Supra-choroidal space. Haller's layer is composed of large arteries and veins, while Sattler's layer is consisted of medium and small arterioles that feed the capillary network of choriocapillaris and venules.[40] The choroid is also an important part of the uvea system that plays a key role in intraocular pressure (IOP) regulation via vasomotor control of BF and uveoscleral outflow, which has been described in most species.[41] The uveoscleral drainage varies depending on the age and the type of animal model studied.[42-46]

The lymphatic lacunae of the choroid are of special interest to scientists.[41,47] It has been shown that choroid contains large membrane-lined lacunae, in birds and to a lesser degree in primates, and these fluid reservoirs, act as the lymphatic drainage that change the volume and thickness of choroid over a span of few days.[41] Schroedl and colleagues[48] suggested that the normal adult human choroid does not contain typical lymph vessels, but is endowed with a significant number of Lymphatic vessel endothelial hyaluronic acid receptor (LYVE-1) positive macrophages. These cells may be involved in choroidal hyaluronic acid metabolism or contribute to temporary formation of lymphatic channels under inflammatory conditions. The lacunae also play a role in Ch.T. adjustments in response to retinal defocus.[41,49] In human studies, lymphatic channels have been also identified in the human ciliary body.[48,50] The presence of distinct lymphatic system in the uveal system is suggestive of the role of these channels in fluid outflow and IOP regulation via the uveoscleral pathway.[42,50,51]

Choroidal Blood Flow

The choroid is supplied by the posterior ciliary arteries, branching from the ophthalmic artery.[52,53] The drainage of the choroidal circulation is mainly through vortex veins.[52] The capillary bed, or choriocapillaris, is located adjacent to the RPE and is the source of blood supply to the photoreceptors.[52] The endothelium of the choriocapillaris is fenestrated, glial cells are absent, and there is a lack of intermediate filaments in choroidal pericytes, contributing to lack of myogenic choroidal autoregulation and more dependence on the neural regulation.[40] The choroidal vessels are richly innervated.[40,41] Choroidal circulation is characterized by very high flow and low oxygen extraction so the systemic hypoxia and elevated intraocular pressure lead to decreased oxygen pressure in the choroid.[54] Since choroidal blood flow is not regulated metabolically, systemic hypoxia and elevated IOP lead to decreased oxygen tension in choroid and oxygen consumption in photoreceptors, and the choroidal oxygen tension increases considerably in retinal vascular occlusions and retinal detachment cases.[54]

The involvement of the peripapillary choroid in blood supply of the ONH has been discussed extensively. The peripapillary choroid supplies both prelaminar and retrolaminar regions of the ONH.[33] The prelaminar portion receives its arterial supply via direct branches of the short posterior ciliary arteries and vessels originating from the arterial circle of Zinn-Haller. Branches of the short posterior ciliary arteries may course through the choroid to supply the prelaminar region.[55]

It seems that the choroid as an important vascular bed might affect the peripapillary region, and it might also have an impact on the uveoscleral outflow and IOP modulation in primary open angle glaucoma (POAG).[56-59] During fluorescence fundus angiography in glaucoma, it was found that fluorescence was reduced at the optic disc, and peripapillary choroid.[60-62] In another study by Laatikainen,[63] delayed or deficient filling of the peripapillary choroid was reported in 60% of glaucomatous eyes. These findings are suggestive of the involvement of the selective choroidal vasculature, especially the peripapillary part, in GON.

Choroidal blood flow constitutes 85% of the ocular blood flow, and is the source of nutrients for outer retina. Choroidal blood flow regulation is important for the regulation of the temperature and the volume of the eye.[53] Total human OBF is estimated to be 1 mL/min, most of which runs through the uveal tract, specifically the choroid.[64] Several mediators contribute to the regulation of OBF, including, nitric oxides [NOs], endothelin-1 [ET-1] and metabolic mediators such as protons [H+], carbon dioxide [CO2] and oxygen [O2].[64] Similar to peripheral vasculature, the choroidal vasculature receives a rich innervation from both sympathetic and parasympathetic pathways. Cholinergic and adrenergic receptors have been found in the choroidal vasculature assuming to play a role in ChBF regulation.[65-67]

Neuronal NOs synthase has been found to be associated with perivascular nerve fibers in the choroid.[68] Endothelial NO has been found in choriocapillaris endothelium, and in endothelial cells of large choroidal blood vessels.[68] The NO formed during endothelial dysfunction negatively affects ocular hemodynamic abnormalities that appear to trigger generation and development of various eye diseases including glaucoma.[69]

The retinal, choroidal, and retrobulbar vascular beds vary in their autoregulatory properties.[70-72] However, the interaction of these vascular systems may play an important role in keeping the ONH healthy.[70] In the early 1970s, contrary results were reported in the regulatory behavior of ChBF during experimental manipulation of ocular perfusion pressure (OPP). Alm and Bill[73] concluded that choroid had no autoregulation in cats; however, Weiter et al.[74] showed some level of choroidal autoregulatory ability. Several publications using Doppler flowmetry demonstrated that the choroid maintains its blood flow level over a wide range of OPP in both human[75] and rabbits.[76-78] Since then, several studies have shown that many glaucoma patients suffer from impaired autoregulation and reduced or unstable ChBF circulation, specifically in those with visual field deterioration.[70,79-81]

Major differences have been observed in the regulatory behavior of ONH blood flow and ChBF during experimental manipulation of IOP and OPP.[65,82,83,84] It has been demonstrated that ET-1 is elevated in most cases of vascular dysregulation, including glaucoma,[85-88] and that the inhibition of ET receptors increases ChBF and ONH BF in patients with glaucoma and healthy controls.[86] It has also been shown that the ONH BF maintains a much better autoregulation compared with choroid during provocative IOP elevation.[65,89,90] Choroidal blood flow depends on OPP because it depends on absolute mean arterial pressure (MAP) and IOP.[91] Boltz and colleagues investigated whether such behavior is also evident in the ONH of healthy subjects. They found a complex regulation of ONHBF during combined changes in MAP and IOP. They identified myogenic mechanisms underlying ONH autoregulation, and indicated that ONHBF regulation is better during an increase in MAP than during an increase in IOP. While myogenic mechanisms are stronger in the ONH and retinal blood flow, the neural control of vascular tone is stronger in the choroid.[91]

Since choroidal vessels are hidden by the RPE, the measurement of ChBF is specifically challenging. This explains the reason for why the BF of the choroidal circulation has been evaluated indirectly in the past.[40] Pulsatile ChBF[92], indocyanine green angiography (ICGA)[93], laser speckle flowgraphy[94], laser Doppler flowmetry (LDF)[95-98], and scanning laser Doppler flowmetry[99] have all been used for clinical studies of human ChBF measurement. Schemetterer and colleagues[100] reported that laser interferometrically measured fundus pulsation amplitude (FPA) can be also considered as a valid relative index for pulsatile ChBF. They showed that FPA at the neuroretinal rim and at the cup is influenced by retinal and choroidal circulation.[100]

Although these techniques have provided significant information about the mechanisms of ChBF, none of them has proven to be capable of measuring the absolute BF rate. Miura et al.[101] recently used Doppler OCT at wavelength of 1,020 nm in combination with pulse oximetry to measure ChBF. They showed that pulse synchronization of Doppler OCT at 1020 nm is capable of accurate quantitative assessment of the in vivo absolute BF velocities in the choroidal vessels in human subjects.[101] A significant decrease in subfoveal ChBF has been reported in both glaucoma patients and myopic subjects.[102-104]

Choroidal Thickness

The choroid is a dynamic structure and its thickness depends on several factors.[103,105-108] Older age,[34,36,109-112] higher IOP,[32] higher myopia,[107,113-118] and longer axial length (AL) are associated with thinner choroid.[100,118-122] Some studies have demonstrated that the mean Ch.T. to be significantly thinner in NTG eyes compared with healthy eyes.[35] Thicker Ch.T. has been reported in end-stage POAG compared to age-matched healthy controls.[56] There are several justifiable factors that contribute to the conflicting findings; such as different measurement techniques and the dynamic and variable nature of the choroid in post mortem eyes. The choroidal shrinkage due to sample fixation during preparation in in-vitro samples and the lack of blood perfusion during the preparation of the ocular specimens affect the Ch.T. measurements. In addition, histologic studies have been relatively small, and the correction for age and axial length was not made in some studies.

Changes in IOP, and alterations in BP and OPP due to different factors could affect the Ch.T.[105-107,113,120,123] The choroid has a dynamic behavior, and a significant increase in Ch.T. happens during water drinking test (WDT) in POAG.[31,106,124,125] On the other hand, there are different perspectives regarding choroid and angle-closure glaucoma. A study found that the choroid was significantly thicker in primary angle closure glaucoma (PACG) compared with POAG and normal eyes even after adjusting for shorter axial length; and hypothesized that choroidal expansion plays a role in the development of angle closure glaucoma.[32,121] Another study conducted on PACG patients found that when the IOP was increased significantly, choroidal thinning and corresponding elongation of the optical axis happened in eyes with PACG.[126] These studies suggest that the dynamic behavior of the choroid may play a role in the angle-closure process. It is difficult to account for conflicting data, since both the choroid and IOP have fluctuations throughout the day, which may not necessarily be in concordance with each other.[105,107,123]

Different techniques have been employed for choroidal thickness measurement. Lower energy techniques such as partial coherence interferometry have been used safely in human and animal models; however, its use is limited because of the substantial intra-subject variability.[105] Laser Doppler interferometry is another technique that has allowed measurement of Ch.T. in animal models.[49,127,128] Time-domain OCT (TDOCT) systems have limited depth of penetration and are not suitable for the measurement of Ch.T. With the development of novel spectral domain OCT (SDOCT) technologies with longer wave length and better depth penetration, the so called “Enhanced Depth Imaging (EDI)” technique generates an inverted image by moving the choroid close to the zero delay to maximize the sensitivity on the outer limit of choroid, making it possible to generate high-resolution images of posterior structures.[110,118,129-131] Furthermore, eye-tracking, image-averaging technologies, and significantly improved A-scan speeds, allow high-quality and safe acquisition of cross-sectional images of the choroid.[129]

A reduction in the average or regional peripapillary Ch.T. has been reported in glaucoma.[132-134] It has been shown that glaucomatous eyes have decreased density of large choroidal vessels and choriocapillaris.[56,80,104] Choroidal thinning was also reported to be associated with a reduction in innermost choroidal vessels in POAG,[109] and choriocapillaris

in sclerotic GON.[38] Sclerotic glaucomatous damage occurs usually in the eyes with arteriosclerotic changes in the choroid accompanied by choroidal thinning.[38] On the other hand, some other studies have not been able to identify a difference in Ch.T. between glaucoma patients, and glaucoma suspects or normal subjects.[36,123] This inconsistency in the results can be explained by the possible fewer glaucomatous patients with the sclerotic damage in studies that did not find any correlation between peripapillary Ch.T. and glaucoma.

Some histological studies have shown that the choroid tends to be thinner around the ONH compared to subfoveal choroid and is nasally thinner than temporally.[110,111,118] Others have indicated that acute PACG eyes have reduced macular choroidal thickness compared with primary angle closure suspects when the IOP is reduced.[135] It has been proposed that these studies do not void the involvement of the choroid during the pathogenesis of glaucoma, but rather other mechanisms, such as inherited features, are involved more in the disease mechanism.[136] In a cross-sectional study, Mwanza et al.[137] used EDI OCT and found no significant change in Ch.T. of the eyes with advanced POAG compared to the fellow eyes with no glaucoma or with mild glaucoma. The results of this study suggested that a thinner choroid did not necessarily correlate with the glaucoma, nor was a thicker choroid a surrogate for the absence of glaucoma. Moreover, Ehrlich et al.[36] did not find any association between RNFL thickness and choroidal thickness in peripapillary region in a cohort of patients including POAG and glaucoma suspects.

Currently no imaging device is capable of automated segmentation of the choroid, making manual calculations subjective to the operator's error.

Conclusion

The choroid is a dynamic tissue. The ChBF depends on different factors such as OPP, BP, IOP, and even emotional and stress levels that may indirectly affect ChBF. The circadian rhythm and other related physiologic factors should be considered when measuring choroidal features. The relationship between the peripapillary choroidal circulation and glaucomatous optic neuropathy is of great importance. New advanced imaging technologies allow a more accurate measurement of choroidal features in the peripapillary region. Large prospective studies are required to elucidate the exact relationship between the choroid and glaucoma. Longitudinal studies that measure the dynamic nature of choroid, specifically in the peripapillary region, and account for contributing factors, are much needed to answer the question of the role of choroid in glaucoma.

Method of Search

Searching the National Library of Medicine (PubMed) for the following keywords: choroidal thickness, choroidal blood flow, choroidal vasculature, choroidal circulation, choroid in glaucoma, choroidal measurement and enhanced depth imaging. All the reviewed papers were in English. We considered the English abstract of articles that were in other languages as well.

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