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Review

Role of ocular blood flow in normal tension glaucoma

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ABSTRACT

Background: Normal tension glaucoma (NTG) is a multifactorial disease in the pathogenesis of which intraocular pressure (IOP)-independent factors play a key role.
Main text: There is considerable evidence that impairment of the ocular blood flow (OBF) is involved both in the onset and progression of this disease. With the development of the hypothesis of OBF in NTG, various imaging techniques have been developed to evaluate the OBF and blood vessels. Moreover, vascular dysregulation, which is a main factor in Flammer syndrome, was frequently observed in NTG patients. Disturbed OBF leads to increased oxidative stress, which plays an important role in the pathogenesis of glaucomatous optic neuropathy. These results suggested that IOP-independent management may provide alternative treatment options for NTG patients.
Conclusions: In this review, we mainly focus on the mechanisms of the abnormal OBF in NTG.

1. Introduction

Glaucoma is a group of disorders characterized by cupping of the optic nerve head (ONH) and visual field damage.[1] As the leading global cause of irreversible blindness, it is predicted that globally the number of those with glaucoma will increase to 111.8 million by 2040, the majority of whom will be in Asia and Africa.[2] Glaucoma can be classified as open-angle glaucoma or angle-closure glaucoma according to the morphology of the anterior chamber angle. The common characteristics of all forms of glaucoma are the loss of retinal ganglion cells (RGCs), thinning of the retinal nerve fiber layer (RNFL), and increasing excavation of the optic disc.[3] Open-angle glaucoma comprises the majority of cases in the United States and Western Europe, whereas angle-closure glaucoma predominates in China and other Asian countries.[4] Normal tension glaucoma (NTG), a special subtype of primary open-angle glaucoma (POAG), is a progressive optic neuropathy with an intraocular pressure (IOP) within the normal range.[5] In the absence of the major risk factor for glaucoma, that is, an elevated IOP, NTG presents a clinical challenge.

NTG is a form of multifactorial optic neuropathy whose etiology remains strongly debated. To date, no single factor has been able to fully explain its pathogenesis. The main factors contributing to NTG-related glaucomatous optic neuropathy (GON) include vascular factors and ocular blood flow (OBF), the translaminar pressure gradient, and immune and genetic factors.[6–8] These factors can lead to RGC loss and axonal damage through several pathways. Among the various risk factors besides IOP, vascular factors have been recognized as a significant component in NTG pathogenesis, because many studies have found that the vascular structures of NTG patients are altered or dysregulated.[6] In 1959, Harrington first noted that impaired blood flow can cause optic nerve vulnerability to glaucomatous damage, even at a statistically normal IOP setting.[9] Subsequently, various research groups have discussed the vascular theories of glaucoma, particularly in NTG.

The aim of this review is to summarize the current understanding of risk factors for NTG and briefly describe the technologies for clinical measurements of OBF. The role of the vascular factors and OBF in NTG pathogenesis and some of the new treatments will also be discussed.

2. Risk factors for NTG

To identify risk factors for GON, most researchers tend to focus on NTG patients. In NTG, factors other than IOP are likely to have a clearer role in GON. It should be noted that the risk factors for GON in NTG also play a role in high tension glaucoma (HTG), but at a lower frequency. A

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meta-analysis showed that disc hemorrhage, myopia, sex, aging, and some systemic vascular diseases were prognostic for NTG progression.[10]

2.1. Intraocular pressure

Clinical studies have shown that IOP is the main risk factor in the development and progression of both HTG and NTG.[11,12] Although reducing IOP does not always prevent NTG development, it does slow it in many cases.[13] With the exception of the IOP level, the IOP fluctuation also appears to be related with the development of NTG. Lee et al. found that IOP fluctuation is related to the structural deterioration in NTG, particularly with progressive thinning of the peripapillary RNFL.[14] However, the relationship between IOP fluctuations and glaucoma progression remains greatly debated.[15]

2.2. Ethnic origin

In general, as damage occurs or progresses at a lower IOP, there will be a higher probability of additional risk factors being involved. In Asia, the prevalence of POAG is approximately 2.34%.[16] The proportion of NTG varies for different countries. In previous epidemiological studies in Asia, NTG accounted for the majority (52%–92%) of open-angle glaucoma,[17] while in Western countries, NTG comprises approximately 30% of POAG patients.[18] This variation may be caused by both genetic and environmental components.

2.3. Myopia

In Asians, the high prevalence of high myopia may be partly responsible for the high incidence of NTG.[18] Myopia has been demonstrated to be a risk factor associated with glaucoma progression.[19,20] However, some other studies indicated that this may not be the case.[21,22] Lee et al. found that these contradictions were attributable to different study populations. In addition, they suggested that progression of NTG and optic disc changes may observably influence glaucomatous eyes with myopia but have no effect on emmetropia or hyperopia.[14] The underlying mechanism linking NTG and myopia remains unclear. One possible explanation is that an increase in the myopic axial length may increase the sensitivity of myopia to glaucomatous damage.[23]

2.4. Age and sex

Age is a statistically important clinical risk factor for the severity of glaucoma in NTG eyes.[17] This could, in theory, indicate that older individuals may display increased vulnerability to glaucomatous damage. NTG occurs more often in women.[24] This also fits to the observation that the Flammer Syndrome is more common in females.[25]

2.5. Disc hemorrhage

It has been reported that disc hemorrhage is an important negative prognostic factor for NTG and may be a marker of progressive damage to the RNFL, leading to deterioration of visual field function.[26] Nonetheless, the mechanism underlying the onset of disc hemorrhage has not been fully elucidated. Furlanetto et al. demonstrated that a history of migraine, narrower baseline neuroretinal rim width, systemic β-blockers usage, low mean systolic blood pressure, and low mean arterial ocular perfusion pressure (OPP) are risk factors for disc hemorrhage development in NTG, which emphasizes the importance of IOP-independent factors in the pathogenesis of NTG disc hemorrhage.[27] Disc hemorrhages, which are a sign of partial vascular abnormalities, tend to be associated with NTG.[28] In addition, Nitta et al. found that the occurrence of disc hemorrhage may contribute to structural deterioration and the reduction of the radial peripapillary capillary vessel density in NTG patients.[29] On the one hand, Quigley et al. demonstrated that disc hemorrhage is caused by microvascular disruption during back-bowing of the lamina cribrosa.[30] On the other hand, other reports showed that systemic vascular diseases, including migraine, diabetes, and hypertension, can cause optic disc damage and increase the incidence of disc hemorrhage.[31,32] With respect to diabetes, previous studies have shown that it may increase the risk for open-angle glaucoma.[33,34] These observations are supported by the evidence of impaired autoregulation during NTG development.[35,36] In summary, these results suggest that OBF plays an important role in NTG.

3. Anatomy and clinical measurements of ocular blood flow

3.1. Anatomy of the optic nerve blood supply

The blood supply of the eye primarily arises from the ophthalmic artery, which is a branch of the internal carotid artery. The ONH is the main structure affected in glaucomatous optic atrophy. The superficial nerve fiber layer of the ONH is mainly supplied by the branches from the central retinal artery. The prelaminar region, immediately posterior to the nerve fiber layer, is mainly supplied by branches from the short posterior ciliary arteries and vessels originating from the arterial circle of Zinn-Haller.[35,37,38] OBF reduction might be a key factor in GON pathogenesis in NTG.[39] Previous studies showed that glaucoma patients have a reduced OBF in various ocular tissues, including the retina, choroid, iris, and optic nerve, particularly in cases of NTG.[35,40] Xu et al. determined and compared the changes in the retinal vasculature in HTG and NTG by optical coherence tomography angiography (OCTA), and found that the density of perfused retinal vessels was significantly more reduced in NTG than in HTG eyes.[41]

3.2. Assessment of ocular blood flow

A variety of different methods for measuring OBF have been described in previous research, including laser speckle flowgraphy, color Doppler imaging (CDI), Doppler Fourier domain optical coherence tomography (Doppler FD-OCT), fluorescein angiography, and OCTA among others.[37] Although many techniques have advanced in recent years, there remains no gold standard. Each technique measures different aspects of OBF, but each has certain limitations.

3.2.1. Color Doppler imaging

CDI is a widely used method for the analysis of parameters of the retrobulbar vasculature, including blood flow velocities, the pulsatility index, and the resistive index.[42] Although CDI is an outstanding approach to assess the large arteries, it has limitations in quantifying vessel diameters and calculating total RBF.[43] Matthiessen et al. suggested that CDI measurements had a good reproducibility, and proved that CDI appears to be an appropriate method for examining retrobulbar blood flow velocities both in clinical practice and research.[44] Numerous studies have evaluated ocular hemodynamics by CDI in POAG and NTG patients.[45,46] These reports confirmed, to some extent, the changes in the retrobulbar flow velocity in glaucoma.

3.2.2. Doppler Fourier domain optical coherence tomography

OCT is a noninvasive technique with high-resolution cross-sectional imaging, and is commonly used in glaucoma evaluation.[47] Recently, with the development of Doppler FD-OCT, visualization and quantification of blood flow have become possible. OCT can also detect the Doppler shift of reflected light, which provides information regarding flow and movement.[48] The speed of OCT imaging has been greatly improved due to the development of Fourier domain techniques.[49] The main advantage of this technique is the ability to rapidly measure the total retinal blood flow.[50] There are still some limitations of Doppler FD-OCT, including phase wrapping artifact in vessels with high blood flow velocities and measurement errors caused by eye motion. Wang et al. found that the total retinal blood flow significantly decreased in eyes with glaucoma and the deficit in blood flow correlated well with the severity of the visual field loss as shown by Doppler FD-OCT.[51] This new technique can

routinely measure total retinal blood flow in a clinical setting. It will be helpful in diagnosing and treating optic nerve and retinal diseases related to poor blood flow.

3.2.3. Fluorescein angiography

Angiography visualizes the penetration of fluorescent dye through ocular vessels. Fluorescein angiography has traditionally been used to assess the microvascular supply of the prelaminar region of the optic disc and the peripapillary choroid.[52] It has advantages related to investigating the retinal circulation in more detail as well as the ONH circulation, but has limitations in analyzing choroidal circulation.[35,42] A number of studies have used fluorescein angiography for the qualitative and quantitative evaluation of angiography, showing the hemodynamic changes in patients with POAG, NTG, or primary angle-closure glaucoma.[53,54] Plange et al. found that the retinal arteriovenous passage time was prolonged in NTG patients.[55] In addition, retinal hemodynamics was correlated with OPP and systemic blood pressure (BP), which may reflect impaired autoregulation in NTG.

3.2.4. Optical coherence tomography angiography

OCTA is a relatively newly developed imaging technique that allows the detection of blood flow through the motion contrast generated by erythrocytes. It allows noninvasive visualization of the microcirculation in the ONH, peripapillary retina, and macula.[56] OCTA can provide quantitative, rapid, and detailed information about the microvasculature, and has thus emerged as a promising method for glaucoma assessment and management.[57] Liu et al. first reported that a lower peripapillary vessel density were found in glaucomatous eyes compared with normal eyes by OCTA.[58] Scripsema et al. also found a significant decrease of peripapillary capillary densities in NTG eyes when compared with normal eyes.[59] It appears that the vascular density decreased with the increase of glaucoma severity. Some differences were found between the NTG and POAG eyes, suggesting that there may be pathophysiological differences with different effects on the area around the ONH and peripapillary. Additional studies are required to elucidate these differences.[60] Current OCTA studies support its potential in clinical practice for the diagnosis and staging of glaucoma and in evaluating its progression, thereby providing a better understanding of its pathogenic mechanisms.

4. The role of ocular blood flow in NTG

Some studies have shown that an inadequate blood supply can lead to RGC loss.[61–63] Chronic ischemia and reperfusion damage have been considered to be involved.[35] The reduction of OBF is the result of multiple factors. Some experts have focused on OPP, which is an important parameter that determines the perfusion of the ONH.[64–66] OPP is calculated as arterial BP minus IOP. This calculation was primarily based on animal studies.[67] It was based on two assumptions: that the ratio of the arterial BP in the eye to the BP at the arm is constant, and that RVP is equal to the IOP. From today's point of view, however, neither of these is quite correct. Although the calculation of PP described above was not optimal, there is a significant correlation between PP and glaucoma progression. Besides, when assessing the risk status of an individual patient, separate consideration of RVP, BP, and IOP is more meaningful and helpful.[68] As summarized in several reviews, low BP compromises the OPP at the optic disc and thus leads to glaucomatous damage.[35,36]

Systemic hypotension has been demonstrated to be a clear risk factor for glaucomatous damage.[69] In the Baltimore Eye Study, after 9 years of follow-up, a cohort study indicated that risk factors for POAG development were lower systolic BP, systolic OPP, diastolic OPP, and mean OPP.[70] Previous studies have also shown that a low partial pressure (PP), particularly a fluctuating PP, is considered to be a risk factor for GON development.[66,71] A fluctuating OPP can lead to an instable OBF and oxygen supply and, therefore, to oxidative stress, which may be of relevance in glaucoma pathogenesis.[72] Charlson et al. suggested that the duration and magnitude of the nocturnal BP decline, particularly when 10 mmHg lower than the daytime BP, were risk factors for visual field deterioration in NTG patients.[73] In a prospective longitudinal study of 65 NTG patients, a low nocturnal diastolic OPP at baseline was proposed to be an important predictive factor for visual field deterioration at 5 years.[74] A retrospective study aimed to investigate the long-term clinical course of NTG patients.[75] It was found that a low OPP may exacerbate the progression of visual field loss. The dipping pattern was also associated with glaucomatous visual field deterioration, and a more pronounced dipping was associated with greater visual field deterioration. NTG patients exhibit significantly greater nocturnal BP dips, which may in turn lead to OPP fluctuation with ischemic episodes at the ONH, and were associated with the progressive visual field defect.[76] Consequently, systemic hypotension, particularly nocturnal BP dips, may play an important role in disease progression in NTG individuals. However, not all patients with a low BP will progress.[77] Whether or not an impairment occurs as a result of a low BP depends on its autoregulation.

Orgul et al. reported that 65% of NTG patients with systemic hypotension suffered from vasospasms.[78] This suggests that there is an association between low BP and vasospastic disorders, which may reflect the additional effect of vascular dysregulation. The blood flow is not only determined by the PP, but also local resistance. An increase in vein resistance will increase venous pressure, thereby reducing the PP.[79] There are complex interactions between OBF and OPP with local flow resistance, and the response to a reduction in OPP is the regulation of resistivity. There is evidence that in patients with low BP, a reduction in OPP reduces OBF owing to autoregulatory changes and defective adaptations.[40] Ramli et al. found that the nocturnal supine BP parameters and OPP in the NTG group were significantly lower than in normal controls.[80] Their findings indicated that there may be defective autoregulatory mechanisms in NTG patients. Lindeman et al. revealed that alterations in BP combined with the heart rate suggest impaired BP regulation in glaucoma patients, particularly NTG patients.[81] These results implied that vascular regulation or dysregulation may play an important role in the GON pathogenesis. Barbosa-Breda et al. compared a large cohort of NTG and POAG patients using several different vascular-related devices, and found that NTG patients displayed more signs of vascular dysfunction.[82]

5. Vascular dysregulation

It has been suggested that vascular dysregulation is a major factor in GON pathogenesis in NTG.[83,84] Some NTG patients displayed changes in OBF autoregulation; moreover, they also showed more extensive vascular dysfunction known as primary vascular dysregulation (PVD). Primary vascular dysregulation syndrome, which was first proposed by Josef Flammer, describes a phenotype comprising PVD together with a cluster of associated symptoms and signs that can occur in healthy subjects and those with disease.[79] This syndrome was then later renamed "Flammer Syndrome" by K. Konieczka et al..[85]

5.1. Flammer syndrome

Flammer syndrome occurs more prevalently among females, slender subjects, Asians, those with indoor jobs, and academics.[86] These symptoms begin to manifest in adolescence and mitigate with age. Moreover, Flammer syndrome has a hereditary component and is not caused by another disease.[85] There is currently no single gold standard for the diagnosis of Flammer syndrome. However, in clinical practice, testing may not always be necessary because there are certain signs and symptoms that clearly indicate Flammer syndrome, including: 1) Cold extremities (cold hands or feet); 2) Low BP; 3) Being exceptionally sensitive (smell, pain, vibration, high altitude, response to drugs, etc.); 4) Shifted circadian rhythm; 5) Prolonged sleep onset time; 6) Reduced feelings of thirst.[79]

Regarding the circulation, subjects with Flammer syndrome have an inborn predisposition to respond differently to all types of stimuli

(including cold, mechanical or emotional stress, and particularly stimuli related to blood vessels). The most clear pathological reaction is vasoconstriction (vasospasm). Due to vascular disorders, the response of Flammer syndrome patients to BP and IOP is also altered, resulting in instability of the OPP and OBF. Morphologically, the retinal vessels demonstrate a higher level of irregularity and are stiffer, with a reduced vasodilation occurring in response to flickering light.[87] In a provocation with hand-grip test, their choroidal vessels showed a more vasoconstrictive response compared with control subjects.[88] This complex regulatory dysfunction results in incomplete adaptation to stimului which in turn, leads to unstable ocular perfusion.

That Flammer syndrome is a risk factor for GON may explain the risk factors for NTG such as sex and ethnic origin. Indeed, Flammer syndrome is also a main cause of splinter hemorrhages at the border of the ONH, which may explain why ONH hemorrhages occur frequently in NTG patients. Optic disc hemorrhages are commonly observed in glaucoma patients, particularly in NTG, and occur more frequently in Flammer syndrome patients.[89] Josef Flammer suggested that this may be a result of a disturbed blood-retina barrier.[72,90] Subjects with Flammer syndrome also exhibit increased retinal venous pressure (RVP). High RVP can reduce the PP and therefore reduce circulation of both the retina and the ONH.[91] Such dysregulation is probably the result of a local increase in vasoactive factors, including endothelin-1 (ET-1). Compared with healthy controls, higher ET-1 levels were observed in glaucoma patients, particularly those with NTG who usually suffer from Flammer syndrome.[92,93] Moreover, Flammer syndrome in NTG is also associated with retinal astrocyte activation, increased oxidative stress, and diffuse visual field defects.[85] The complex regulatory dysfunction can lead to an incomplete adaptation to stimuli, resulting in unstable ocular perfusion. This instable blood flow leads to mild but repeated reperfusion, which contributes to glaucomatous damage through oxidative stress.[94]

5.2. Vasospasm and migraine

Migraine is currently considered to be a neurovascular syndrome, which is associated with transient vasospastic episodes, leading to the impairment of autoregulation of blood flow in the central nervous system.[95] There is an association between migraine and Flammer syndrome. Although migraine and Flammer syndrome have some common features, there are some distinct differences. Vasoconstriction is the most obvious pathological reaction in Flammer syndrome, hence, Flammer syndrome was previously classified as a vasospastic syndrome.[85] Ischemia due to vasoconstriction is considered to be a potential risk factor for the development of glaucomatous visual field damage.[79,96] Vasospasm refers to the reversible disproportionate contraction of the arteries, resulting in a temporary decrease or shortage of the blood supply to the corresponding organ. Vasospasm is common and associated with a variety of diseases, for example, in the retina, particularly in the case of migraines.[85] Previous studies have demonstrated that vasospasm leads to environmental disturbances in blood flow, increasing the vulnerability of the ONH to vascular challenges, leading to instability of perfusion, changes in ischemia, reperfusion injury, and the loss of ONH axons.[97] In addition, migraines can cause a temporary decrease of OBF.[98] Gramer et al. found a relationship between migraine and vasospasm in a large number of glaucoma patients. They also found that migraine was associated more with NTG than HTG.[99] To date, the association of migraine and NTG has been formally confirmed in many studies, with migraines being a risk factor for NTG progression.[27,100,101] Moreover, it has been reported that subjects with vasospastic disorders, including Raynaud's phenomenon, also have a prevalence of migraine.[102] Consequently, both migraine and vasospasm may be risk factors for NTG.

In addition, abnormal variations in blood vessel diameter are common in peripheral organs, including the fingers and eyes of individuals with migraine.[79,103] These blood vessel alterations are assumed to be a sign of vasospasm, or more broadly, for Flammer syndrome.[85] Retinal vascular dysregulation and poor blood flow at the ONH have been implicated in NTG; several studies have proposed that NTG and migraine have a common vasospastic mechanism.[104] Flammer syndrome subjects suffer more frequently from migraines. It has been reported that vasospasm could underlie the occlusions of the retinal vasculature in migraine patients.[105] Dadaci et al. hypothesized that the expression of neurogenic inflammation in the eye contributes to the autonomic dysfunction and alteration of ocular circulation in migraine in glaucoma.[106] It is true that autonomic nervous dysfunction is present in glaucoma, PVD, and migraine. But in these diseases, clear dysregulations were also found of the retinal blood vessels, although they are not autonomically innervated. A decreased blood flow in the ocular artery is associated with glaucoma progression. A history of migraines constitutes an important and independent risk factor for optic disc hemorrhage.[27] Furthermore, NTG patients with a concurrent history of migraine are more likely to progress in terms of visual field defects.[100] These findings indicated that the vasculature remains a potential factor in the pathogenesis of both NTG and migraine.

5.3. Reperfusion damage

A mild but recurrent BF decrease is primarily due to the fluctuation of OPP and disturbance of autoregulation, resulting in an unstable and insufficient oxygen supply, thus increasing local mitochondrial oxidative stress.[107,108] Oxidative stress is induced by an imbalance between the production of reactive oxygen species and their elimination by antioxidants, which results in damage to cellular macromolecules and ultimately leads to cellular and tissue dysfunction and even mortalit.[109] Reperfusion caused by unstable ocular perfusion is the major cause of oxidative stress, mainly occurring in the ONH. Perfusion instability is present both in patients with a high IOP or a low IOP that exceeds their ability to regulate, as well as in patients with a normal IOP or BP (if the patient has disturbed autoregulation). Disturbed autoregulation occurs predominantly in patients with Flammer syndrome. By interfering with the autoregulation, the sensitivity to a BP reduction is increased.[40,72] Increasing evidence has demonstrated that oxidative stress is involved in the loss of RGCs in NTG, and plays an important role in GON pathogenesis.[109–111]

Systemic DNA damage as the pathomechanism of glaucoma is identifiable by the markers of oxidative stress, including urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG) and total antioxidant status. Yuki et al. found that the levels of urinary 8-OHdG/creatinine were increased significantly in subjects with progressive NTG compared with patients with nonprogressive NTG.[112] Urinary 8-OHdG levels have recently been reported to be associated with the ONH circulation, particularly in early-NTG patients.[113] Mozaffarieh et al. revealed that POAG patients with PVD have a significantly higher rate of DNA breaks in circulating lymphocytes than both POAG patients without PVD and healthy controls.[114] Although many details of the relationship between oxidative stress and NTG remain strongly debated, further studies will reveal the association between DNA damage and NTG. Unlike damaged DNA, damaged proteins cannot be repaired. Wunderlich et al. suggested that the upregulation of 20S proteasome alpha-subunit levels indicated an increased oxidative stress in glaucoma patients.[115]

The microcirculation is mainly regulated via endothelial-derived vasoactive factors, including ET-1 and nitric oxide (NO). This regulation of endothelial cells is crucial to the ability of cells to adapt to variations in PP (autoregulation).[116] ET-1 significantly induces vasoconstriction by interacting with its receptors. Various studies demonstrated a systemic endothelium-derived vascular dysfunction in NTG.117-119 Oxidative stress leads to elevated ET-1 expression. A large number of studies have shown an elevated ET-1 level in glaucoma patients, particularly in patients with progressive neuropathy despite having a normalized IOP.120, 121 By contrast, NO primarily promotes vasodilation. Astrocyte activation leads to increased NO production, and if accompanied by a high concentration of superoxide (O2-) due to reperfusion, highly damaging peroxynitrite can be produced.122, 123

Neufeld et al. suggest that the glaucomatous ONH is exposed to excessive NO levels, which may be neurodestructive, locally, to the axons of the RGCs.124 Metalloproteinases are upregulated in the ONH of glaucoma patients. An upregulation of matrix metalloprotein-9 was found in circulating lymphocytes in NTG patients, which may be a consequence of reperfusion injury.[125]

6. Regulation of ocular blood flow

The mainstream treatment for all types of glaucoma, including NTG, is IOP reduction. The Collaborative Normal Tension Glaucoma Study demonstrated that a 30% IOP reduction may slow NTG progression.[126] Some subjects may continue to progress even if their IOP is on target, leading to the need to develop new treatments. With the advances in the understanding of NTG pathogenesis, several new therapeutic approaches have been developed, some of which are already in clinical use, while others are still under experimental research. The IOP-independent management of NTG, including vascular regulation and neuroprotection, provide alternative therapeutic options for NTG patients.

All theories regarding NTG development and the vascular etiology derive a general conclusion, that is, there is an interruption of the blood flow in the optic nerve.[127] Ischemic changes involved are not only the result of an insufficient blood flow, but also an imbalance or fluctuation of the circulation around the optic nerve, which leads to ischemia-reperfusion injury. Therefore, several drugs that act on OBF have been investigated. Gasser and Flammer first investigated the calcium channel blockers (CCBs) as potential therapeutic applications to improve ocular perfusion.[128] Since then, a range of reports found that CCBs, including nimodipine, normalize the retinal circulation together with vasospastic symptoms and increase the ONH and choroidal blood flow in NTG patients.[129,130] Nimodipine also has the capacity to reverse the effects of ET-1 on ocular blood vessels.[131] Furthermore, CCBs are also believed to have neuroprotective properties.[132] Toriu et al. reported that lomerizine protects neuronal cells against retinal neurotoxicity both in vitro and in vivo.[133] However, there is concern that a systemic hypotensive effect, via peripheral vasodilation in the case of CCBs, may exacerbate glaucomatous damage by decreasing the diastolic OPP to the optic nerve.[134] Under normal condition, the doses we used were very low that hardly ever lower BP but it does have an effect on NTG.[135] In addition, some side effects, including peripheral edema, may limit the utility of CCBs for certain patients.[136]

An additional component of NTG treatment is neuroprotection. Many researchers are currently investigating the potential use of natural substances as an adjuvant therapy for glaucoma. Ginkgo biloba extract (GBE) is a phytochemical that is widely used in medicine. Several studies suggested that, as a neuroprotective and antioxidative agent, it shows a benefit in the management of neurological and vascular conditions.[137] Chung et al. revealed the neuroprotective properties of a ginkgo extract (EGb761) in brain ischemia.[138] In clinical trials, GBE was shown to delay the progression of visual field defects in NTG patients.[139] It was also found that GBE improved peripapillary blood flow in NTG patients compared to a control group.[140] Another phytochemical currently under investigation is resveratrol, which is found in fruits and red wine, and is reported to have antioxidative and anti-inflammatory properties.[141,142] Resveratrol is currently being investigated for neuroprotective qualities in the treatment of glaucoma and other ophthalmic diseases.[143]

7. Vascular treatment

Most of the literature emphasizes that IOP lowering is the only proven glaucoma therapy, and occasionally points out that blood flow evaluation is not useful in glaucoma because of the lack of therapeutic consequences.[43] Is such a statement still fully valid?

Pharmacological treatment of the vascular disorders in glaucoma requires a suitable drug and controlled long-term studies showing that such treatment improves prognosis. A prerequisite for the development of such a drug by the pharmaceutical industry is an agreement in the scientific community that a vascular problem exist and is relevant to the disease. While individual investigators have described circulatory disturbances in glaucoma for decades,[35] it is only with the recent introduction of OCTA that this has become apparent to all ophthalmologists.[58]

Another point of contention has been whether the reduction in blood flow is only secondary to the glaucoma damage or increased intraocular pressure, or whether it is primary. There is no doubt that a loss of substance decreases blood flow. It is also clear that increased IOP decreases blood flow, especially when autoregulation is impaired. However, the fact that ocular blood flow disturbance often precedes visual field damage, that blood flow disturbance can be measured not only in the eye but also in other organs of glaucoma patients, and that a short-term pharmacologically induced increase in blood flow leads to a transient improvement in visual fields,[144] whereas an induced decrease in blood flow leads to a transient deterioration of visual fields,[145] speaks in favor of an additional primary vascular component.

However, in order to develop an effective drug, we also need to know the nature of the perfusion disorder in glaucoma. It is well known that low PP reduces blood flow to the eye, especially when autoregulation is disturbed and thus worsens the prognosis. The question here is which is more promising, increasing PP or improving regulation. Severe atherosclerosis can also reduce ocular perfusion, but it is hardly treatable. However, relatively new and therapeutically promising is the observation that vascular dysregulation is a common cause of NTG.[79] While smaller, uncontrolled studies have already shown that regulation can be improved,[128] larger controlled studies are imperative. We illustrate this with the example of increased RVP. The retinal veins are often dysregulated in glaucoma patients. As a result, venous pressure increases and PP decreases.[91] A first promising study has shown that this RVP can be lowered with vitamin supplementation containing L-methylfolate (Ocufolin® forte).[146,147]

While we still have a long way to go before we have a widely accepted, evidence-based vascular treatment for glaucoma, ophthalmologists already have therapeutic options other than only further lowering intraocular pressure in patients with progressive glaucoma damage despite well-controlled IOP.[135]

8. Conclusions

In summary, NTG is a multifactorial and complicated disease, the pathogenesis of which involves vascular factors. OBF is the main factor contributing to the progression of NTG-related GON. PVD, the essential component of Flammer syndrome, leads to OBF instability in the ONH, which in turn locally increases oxidative stress. The methods to evaluate OBF are developing with the greater understanding of the role of OBF in NTG. As described in this review, the novel methodologies employed have their own unique advantages and can be used as reliable measurement methods of OBF status. Recently, accumulated evidence has suggested that an association of compromised vasculature with NTG pathogenesis urges us to pay greater attention to IOP-independent therapy of NTG, in addition to decreasing the IOP.

Study Approval

Not Appliciable.

Author Contributions

The authors confirm contribution to the paper as follows: conceived and designed the review: XDW, KK, KJW, JF, KY; searched and selected references of the review: XDW, KK, XL, MC; Drafting the manuscript: XDW, KK; All authors reviewed and approved the final version of the manuscript.

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Conflict of Interest

The authors declare that they have no competing interests.

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Abbreviations

NTG	Intraocular Pressure
OBF	Ocular Blood Flow
GON	Glaucomatous Optic Neuropathy
ONH	Optic Nerve Head
RGCs	Retinal Ganglion Cells
RNFL	Retinal Nerve Fiber Layer
POAG	Primary Open-Angle Glaucoma
HTG	High Tension Glaucoma
OPP	Ocular Perfusion Pressure
CDI	Color Doppler Imaging
Doppler FD-OCT	Doppler Fourier Domain Optical Coherence Tomography
OCTA	Optical Coherence Tomography Angiography
BP	Blood Pressure
RVP	Retinal Venous Pressure
PVD	Primary Vascular Dysregulation
ROS	Reactive Oxygen Species
8-OHdG	8-Hydroxy-2'-Deoxyguanosine
ET-1	Endothelin-1
NO	Nitric Oxide
MMP	Matrix Metalloprotein
CCBs	Calcium Channel Blockers
GBE	Ginkgo Biloba Extract

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