

New directions in the treatment of normal tension glaucoma

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Glaucoma is a progressive optic neuropathy that causes characteristic changes of the optic nerve and visual field in relation to intraocular pressure (IOP). It is now known that glaucoma can occur at statistically normal IOPs and prevalence studies have shown that normal tension glaucoma (NTG) is more common than previously thought. While IOP is believed to be the predominant risk factor in primary open angle glaucoma (POAG), IOP-independent risk factors, such as vascular dysregulation, are believed to play an important part in the pathogenesis of NTG. Though certain distinguishing phenotypic features of NTG have been reported, such as an increased frequency of disc hemorrhages, acquired pits of the optic nerve and characteristic patterns of disc cupping and visual field loss, there is much overlap of the clinical findings in NTG with POAG, suggesting that NTG is likely part of a continuum of open angle glaucomas. However, IOP modification is still the mainstay of treatment in NTG. As in traditional POAG, reduction of IOP can be achieved with the use of medications, laser trabeculoplasty or surgery. Studies now show that the choice of medication may also be important in determining the outcomes of these patients. Though it is likely that future treatment of NTG will involve modification of both IOP and IOP-independent risk factors, current efforts to develop IOP-independent neuroprotective treatments have not yet proven to be effective in humans.

Key words: Intraocular pressure, low tension glaucoma, neuroprotection, normal tension glaucoma, risk factors

Glaucoma is a progressive optic neuropathy with characteristic clinical changes of the optic nerve and functional visual field deficits, which are in part, related to intraocular pressure (IOP). Historically, glaucoma was believed to be a disease of elevated IOP, that could lead to blindness if left untreated.^[1] Though von Graefe first described “amaurosis with excavation” and postulated that glaucoma could occur in the absence of elevated IOP as early as 1857,^[2] it was not until Schnabel later confirmed these findings in 1908 that this concept started to gain public acceptance.^[3] However, the notion of “normal tension” glaucoma did not become commonplace until the latter part of the 20th century.^[4] The Baltimore Eye Survey has since revealed that about half of all patients diagnosed with primary open angle glaucoma (POAG) in their study population had an initial IOP of less than 21mmHg at the time of diagnosis and approximately 20% had an IOP of less than 21mmHg on each of their first three visits suggesting that normotensive eye disease may be more common than previously thought.^[5,6]

Subsequent population-based studies have shown that the prevalence of glaucoma in the presence of an IOP in the statistically normal range is much more common than once believed. On average, these studies show that normal tension glaucoma (NTG) occurs in roughly 30 to 40% of all patients diagnosed with a glaucomatous visual field defect.^[5,7,8] For reasons that are unclear, Asian populations appear to be especially susceptible to NTG, with the Japanese Tajimi study showing the prevalence of POAG to be 3.9% in their

study population, of which 92% had an IOP of 21 mmHg or less.^[9] Similar findings were shown in Korea, where a recent prevalence study in the rural Korean town of Sangju showed that an IOP of less than 21 mmHg was found in 94.4% of cases with open angle glaucoma (OAG).^[10] Early diagnosis in these cases can be particularly challenging, since tension-based screening modalities are less helpful in this setting and delayed diagnosis can have significant individual and public health consequences as a result.

Differences with primary open angle glaucoma

By definition, NTG differs from POAG only in that the IOP is consistently less than 21 mmHg.^[11] It has been postulated that POAG and NTG represent a continuum of open angle glaucomas on opposite ends of a spectrum, with IOP being the primary causative risk factor in the former and IOP-independent risk factors being more important in the latter.^[11] Clinically, it is important to distinguish pure forms of POAG and NTG on each end from “mixed” disease in the middle of the spectrum. In the case of POAG, IOP reduction remains the focus of treatment. However, IOP reduction alone may be less effective in treating “mixed” or “normal tension” disease.

Aside from IOP, subtle clinical differences can help distinguish POAG from NTG. Examination of the optic disc in NTG tends to reveal a narrower neuroretinal rim for a given amount of visual field loss, particularly inferiorly and inferotemporally.^[12] Disc hemorrhages and beta zone peripapillary atrophy are also more frequent findings in NTG, with the presence of disc hemorrhages being a significant poor prognostic indicator.^[13,14] At the disc margin, peripapillary crescents and halos are seen more commonly as areas of absent retinal pigment epithelium with localized cupping sometimes

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occurring in this region.^[15] These focal areas of cupping may represent acquired pits of the optic nerve (APON), which are more prevalent in the setting of “low” or “normal” tension glaucoma.^[16,17] APON tend to occur in the inferior optic disc and have been associated with a greater frequency of disc hemorrhages as well as an increased risk of glaucoma progression.^[17,18] Visual field deficits associated with APON tend to occur near fixation, much like the paracentral scotomas that often accompany NTG patients [Figs. 1 and 2].^[17] Studies have shown that visual field defects in NTG tend to be closer to fixation, deeper and more focal when compared to those that occur in high tension POAG.^[19,20] Despite these differences, reported clinical observations of POAG and NTG are conflicting, suggesting that there is likely some overlap of the underlying mechanism of glaucomatous optic neuropathy in the spectrum between these two entities.^[11]

Pathophysiology of normal tension glaucoma

The pathogenesis of NTG remains unclear and it is believed that the interaction of a variety of systemic factors may be involved in the onset and progression of this disease. Harrington in 1959 was the first to suggest that impaired blood flow causes the optic nerve to be susceptible to glaucomatous damage even in the setting of statistically normal IOPs.^[21] Shortly thereafter, Haas suggested that there may be reduced resistance of the optic nerve head to IOP in the setting of vascular insufficiency.^[22] Subsequently, reduced peripapillary retinal blood flow has also been demonstrated in NTG.^[23] More than just a simple lack of perfusion however, damage to the optic nerve head in NTG is now thought to be the result of vascular dysregulation causing repeated reperfusion injury to the optic nerve.^[24] In 1968, Johnson and Drance introduced the concept of perfusion pressure suggesting that systemic hypotension could be a contributing etiologic factor in NTG,^[25] and this has been supported by more recent studies as well.^[26-28] Specifically, a diastolic ocular perfusion pressure of less than 55mmHg has been associated with a 2 to 6 fold increase in the prevalence of OAG.^[29,30] In addition, the increased frequency of disc hemorrhages in NTG appears to be a strong indicator pointing toward a vascular etiology in the optic nerve damage that occurs in these patients.^[11]

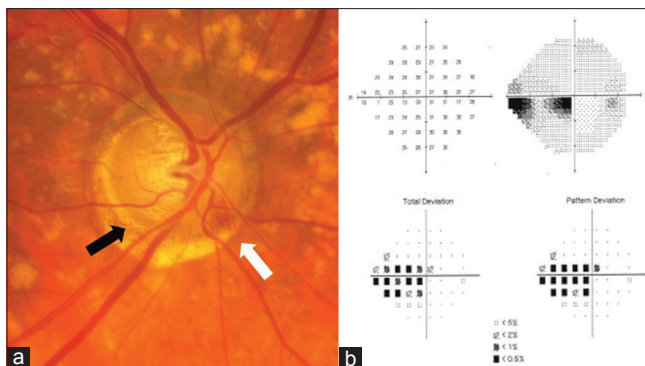


Figure 1: (a) Right optic nerve with an inferotemporal acquired pit of the optic nerve indicated by the black arrow. A disc hemorrhage is also seen in the inferonasal region (white arrow). (b) Standard automated perimetry shows a corresponding superior paracentral arcuate defect with an inferior paracentral arcuate secondary to superior rim narrowing

Mroczkowska *et al.*, recently demonstrated subclinical vascular abnormalities at both the micro- and macro-vascular level using dynamic retinal vessel analysis in newly diagnosed NTG patients.^[31] Other observations suggestive of vascular and perfusion abnormalities include the increased prevalence of such systemic conditions like obstructive sleep apnea (OSA), migraine headaches and Raynaud’s phenomenon in patients with NTG.^[11,32-36] With regard to OSA, it is unclear whether treatment with continuous positive airway pressure (CPAP) decreases the risk of progression of NTG. However, nasal CPAP has been shown to cause an elevation of IOP, though the clinical significance of this finding remains to be seen.^[37,38]

More recently, elevated aqueous and plasma levels of endothelin-1 (ET-1) have been linked to glaucoma.^[39-44] ET-1 is an endothelium-derived vasoconstrictor protein which acts as a potent endogenous vasoconstrictor, mainly on small vessels.^[43-45] In the eye, ET-1 is synthesized and released from the ciliary processes and is believed to be involved in the modulation of ocular blood flow.^[43,46] Preclinical studies have shown that intravitreal injections of ET-1 can cause hypoperfusion of the optic nerve head as well as retinal ganglion cell apoptosis in a similar manner to axotomy and other models of glaucoma.^[47-49] These findings suggest that upregulation of ET-1 may be involved in the pathogenesis of NTG, where vascular dysregulation and other IOP-independent mechanisms seem to contribute. It is not surprising then, that studies have shown a correlation between systemic endothelial vascular cell dysfunction and vascular dysregulation in the setting of NTG and elevated ET-1.^[45,50,51] Recent reports have also linked NTG and elevated ET-1 with heart rate variability and subclinical inflammation.^[51,52]

Along these lines, the excitotoxic inflammatory cytokine tumor necrosis factor-alpha (TNF- α) has been shown to be upregulated by ischemic and pressure-loaded glial cells resulting in subsequent retinal ganglion cell death and reduction of TNF- α may be neuroprotective.^[53-55] This finding suggests that there could be an underlying subclinical and highly localized inflammatory process that contributes to

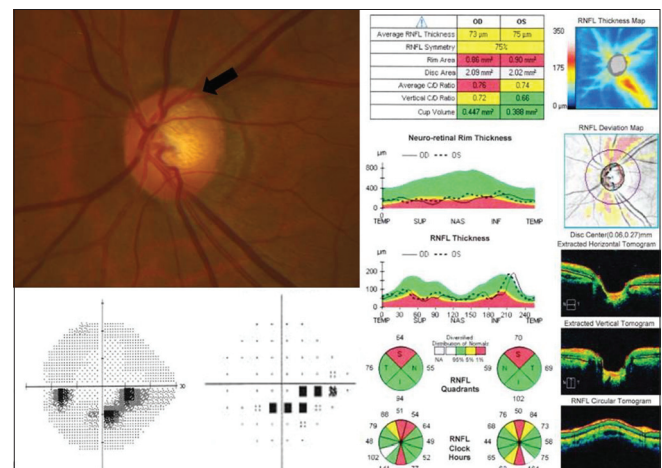


Figure 2: Early acquired pit of the optic nerve occurring in the superotemporal optic nerve head of the left eye (black arrow). Optical coherence tomography of the retinal nerve fiber layer shows thinning corresponding to the region of the APON. The visual field shows an inferior paracentral arcuate defect consistent with these findings

glaucomatous optic neuropathy. It is not surprising therefore, that some have postulated a relationship between autoimmune dysfunction and NTG. Cartwright and colleagues found that 30% of NTG patients had one or more immune-related diseases compared to only 8% of controls with ocular hypertension.^[56] An increased incidence of autoantibodies and paraproteinemia have also been demonstrated in patients with NTG.^[57-59] More specifically, an analysis of autoantibody repertoires in the sera of patients with glaucoma by Joachim and colleagues found IgG antibody patterns against retinal antigens in POAG and NTG patients,^[60] and these antigen bands were identified in a subsequent study to be α B-crystallin, vimentin and heat shock protein 70.^[61]

Of recent interest has been the possible role of intracranial and cerebrospinal fluid (CSF) pressure in NTG. For reasons that are still unclear, patients with NTG have been shown to have a lower CSF pressure than the normal population.^[62,63] One possible explanation comes from animal studies demonstrating that the pressure gradient across the lamina cribosa can vary independently of IOP.^[64,65] It is believed that lower CSF pressures increase translaminal pressure, that may contribute to glaucomatous optic neuropathy.^[66] In addition, a positive linear relationship between CSF pressure and body mass index (BMI) has been reported suggesting that individuals with a lower BMI may be at increased risk of developing glaucoma in part, due to lower CSF pressures.^[66] Consistent with this observation, several studies have also shown that increased BMI may be protective for glaucoma.^[67-70]

Diagnosis and evaluation

Diagnostic evaluation of NTG should always begin with a thorough medical history and review of systems. Such a history may be helpful in alerting the clinician to the possibility of nonglaucomatous causes of optic neuropathy, such as ocular trauma or a history of central nervous system (CNS) pathology. It is not uncommon for such patients to communicate a history of cold extremities, migraine headaches, systemic hypotension, or other signs of vascular dysregulation.

A comprehensive eye examination, including gonioscopy, should then be performed to rule out potential secondary causes of glaucoma. Differentiation between high tension and normal tension glaucoma can be difficult based on a single IOP measurement and as a result, a diurnal curve can be helpful to detect episodes of elevated IOP outside of routine clinic visits when the IOP appears to be in the statistically normal range. CNS imaging or neuro-ophthalmic consultation is usually unnecessary in the presence of classic findings, such as APON or optic disc hemorrhages with corresponding visual field defects. As with high-tension glaucoma however, further work-up should be considered in the presence of asymmetric disease or visual field defects suggestive of a compressive CNS lesion or other nonglaucomatous processes.

A systemic evaluation for potentially contributing conditions, such as OSA or Raynaud's phenomenon, is often valuable in cases of disease progression refractory to IOP-lowering therapy. The diagnosis of NTG can even be diagnostic in some patients who were previously unaware of the presence of contributing systemic disease. As IOP-independent risk factors are believed to be significant contributors in the pathogenesis of NTG, coordination with

the patient's internist to pursue further evaluation with sleep studies or 24 h ambulatory blood pressure monitoring may be insightful in select cases. Because NTG is a disease entity in which non-ocular systemic abnormalities are believed to play a significant role in disease progression, optimization of potential IOP-independent factors, such as modification of a treatment regimen for systemic hypertension in order to alleviate nocturnal hypotension can be helpful in slowing the progression of their eye disease. When the rate of disease progression remains unchanged despite optimization of both IOP and IOP-independent risk factors, the diagnosis of NTG should be reevaluated and a work-up for nonglaucomatous causes of vision loss considered.

Current treatment

IOP remains the only proven modifiable risk factor for the treatment of glaucoma. However, it was not until the Collaborative Normal-Tension Glaucoma Study (CNTGS) that the significance of IOP reduction in the setting of statistically normal IOPs was confirmed. This multicenter, clinical trial demonstrated that a 30% reduction in IOP decreased the long-term risk of progression from 35 to 12%.^[71,72] It should be noted that topical beta blockers were not used and over half of all of the patients in CNTGS were able to achieve their goal IOP reduction without the use of surgery or laser trabeculoplasty. However, the study did show a greater risk of needing cataract surgery in the treatment group compared to the control group as well as faster rates of progression in women and in those patients with migraine headaches or disc hemorrhages.^[73] In addition, approximately half of untreated patients did not show signs of progression over five to seven years, suggesting that the benefit of IOP reduction may be quite variable among NTG patients.^[74]

More recently, the Low-Pressure Glaucoma Treatment Study (LoGTS) has raised questions about the choice of drug therapy in NTG. LoGTS was a prospective, randomized clinical trial which compared the use of timolol with brimonidine as monotherapy for NTG. Not unlike CNTGS, there was a preponderance of females and optic disc hemorrhages in the LoGTS study population.^[75] After a mean follow-up of approximately 30 m, brimonidine-treated patients were less likely to have visual field progression compared to timolol-treated patients (9.1 and 39.2%, respectively) despite similar reductions in IOP by both drugs.^[76] These results suggest the possibility that either brimonidine is neuroprotective or timolol is neurodestructive when used as monotherapy for NTG. The high rate of brimonidine discontinuance (28.3%) secondary to drug-related adverse events during the course of the study should be noted when interpreting these findings.

The current gold standard for medical glaucoma therapy is the prostaglandin analogues. The prostaglandin analogues are the single most effective agent in reducing IOP with adequate diurnal control.^[77] Prior to the introduction of prostaglandin analogues, beta blockers were considered the first-line pressure-lowering agents used in the treatment of POAG. However, topical beta blockers have the potential for significant systemic side effects, such as nocturnal hypotension, that may be of particular concern in NTG. As mentioned, LoGTS suggests that beta blockers may even have a deleterious effect in NTG.^[76] Hayreh and colleagues also found topical

beta blockers to be an independent risk factor for visual field progression by aggravating nocturnal arterial hypotension in NTG patients.^[78] In contrast, alpha agonists, specifically brimonidine, have been shown to be neuroprotective in animal models of optic nerve and retinal injury.^[79] With the exception of the prostaglandin analogues, the commonly used classes of anti-glaucoma medications depend largely on reducing aqueous production (as opposed to increasing aqueous outflow) to lower IOP. Because aqueous production naturally decreases while asleep,^[80] it is believed that aqueous suppressants have little effect on nocturnal IOP. There is a single report, however, that topical carbonic anhydrase inhibitors may provide better diurnal IOP control than timolol, although these findings have yet to be duplicated.^[81] The value of nocturnal IOP reduction remains unclear as there are currently little data to support its clinical significance in glaucoma patients.

Because NTG patients have baseline IOPs in the statistically normal range, it is often difficult to achieve IOPs in the single digits with medications alone. Nonmedical options for treating NTG are the same as those used to treat “high pressure” open angle glaucoma. Laser trabeculoplasty has been found in recent studies to provide better diurnal control than some of the commonly used ocular hypotensive agents.^[82,83] However, the Early Manifest Glaucoma Trail (EMGT) found that the combination of the beta blocker, betaxolol and argon laser trabeculoplasty had no significant IOP-lowering effect in NTG patients with a baseline IOP of 15mmHg or less, suggesting that laser trabeculoplasty may have a limited role in the treatment paradigm of NTG.^[84]

Glaucoma filtering surgery is indicated when adequate control cannot be achieved with medical therapy or laser trabeculoplasty. Because the target IOP is often lower in NTG than in POAG, NTG patients are at greater risk for ocular hypotony and related complications, such as hypotony maculopathy, post-operatively.^[85] Despite the potential complications associated with filtration surgery, trabeculectomy remains the most effective method of achieving low IOPs. In addition, trabeculectomy has been shown to blunt diurnal and nocturnal IOP fluctuations even in the setting of postural changes.^[86,87] Because IOP remains relatively constant in the presence of a well-functioning bleb and is not dependent on patient compliance for adequate control, it is the authors' experience that progression in NTG patients is often reduced even if similar IOP reductions were achieved previously with medications. Aqueous shunts are another surgical option which have become increasingly popular in the past decade and especially so after the recent Tube Versus Trabeculectomy (TVT) study.^[88] The TVT study compared the outcomes and complication rates of tube shunt surgery using the Baerveldt-350 implant with trabeculectomy in eyes with a previous history of glaucoma or cataract surgery. After five years, tube shunt surgery was associated with a lower failure rate and fewer complications than trabeculectomy in previously operated eyes.^[89,90] It should be noted that the TVT study did not demonstrate superiority of tube shunts over trabeculectomy as primary glaucoma surgery and such a trial is currently in progress. A similar comparison of trabeculectomy with the Ahmed glaucoma valve using more stringent criteria for success (IOP \leq 18 mmHg and reduction of IOP \geq 20% from baseline) showed that trabeculectomy had a significantly higher 5 year cumulative probability of success compared

with Ahmed glaucoma valves when greater reductions in IOP are necessary.^[91] As a result, trabeculectomy is likely a more suitable surgical option than glaucoma drainage devices in NTG, since it tends to achieve a lower post-operative IOP. The TVT study also found a lower mean IOP in the trabeculectomy group (12.6 ± 5.9 mmHg) compared to the tube shunt group (14.4 ± 6.9 mmHg) at five years, although this difference was not statistically significant in their study.^[89]

More recently, the concept of “non-penetrating” glaucoma surgery has gained interest for its potential to limit some of the complications associated with more invasive procedures to lower IOP. Nonpenetrating deep sclerectomy, is one example of such a procedure in which the internal wall of Schlemm's canal is excised without entering the anterior chamber. Retrospective data by Lachkar *et al.*, showed that nonpenetrating deep sclerectomy was associated with an IOP reduction of $33.73 \pm 20.9\%$ after 6 years with few complications.^[92] Subsequent prospective studies comparing nonpenetrating deep sclerectomy directly with trabeculectomy have shown similar IOP-lowering results with improved complication rates,^[93-96] suggesting that such less invasive surgical procedures may have an increasing role in the treatment of NTG and other forms of glaucoma moving forward.

Other proposed therapies

The literature clearly demonstrates that IOP modification is effective in treating NTG and that attempts to lower IOP in these patients are certainly justified. Since a significant proportion of NTG patients continue to worsen after IOP reduction, attention in recent years has shifted toward IOP-independent neuroprotective therapies. Glutamate antagonists in particular were once believed to hold promise as potential neuroprotective agents independent of IOP. Glutamate is an excitatory neurotransmitter in the CNS and retina, which is excitotoxic at high extracellular levels. Experimental models of glaucoma have shown glutamate excitotoxicity to be associated with retinal ganglion cell death,^[97,98] and the inhibition of excess glutamate by blocking its receptor, N-methyl-D-aspartate (NMDA), has been proposed as a potential therapeutic target for neuroprotection in glaucoma as a result.^[99] Memantine is a clinically useful drug in neurologic disorders, namely Alzheimer's dementia, whose principle mechanism of action is blockade of flow through the NMDA receptor.^[100] Though multiple preclinical studies demonstrated that memantine had a protective effect in animal models of glaucoma,^[101-105] a subsequent multicenter, randomized clinical trial failed to show the same effect in human glaucoma.^[106]

Unoprostone is another drug with potential neuroprotective properties in preclinical studies. Unoprostone is a prostanoid and synthetic docosanoid that is approved by the United States Food and Drug Administration for IOP reduction in OAG and ocular hypertension through increased aqueous outflow via the trabecular meshwork.^[107] Recent studies suggest that unoprostone may prolong neuronal survival independent of its ability to lower IOP, in part due to improved ocular blood flow via antagonism of ET-1.^[108,109] However, further studies are needed to determine the clinical significance of these data in humans.

Calcium channel blockers (CCBs) are a class of drugs that have been widely used for the treatment of systemic hypertension

and other cardiovascular diseases since their introduction in the 1960s.^[110] Their primary mechanism of action involves inhibition of voltage-gated calcium channels in vascular smooth muscle, which in turn leads to decreased contractility and vasodilation. Consequently, early work by Gasser and Flammer investigated the role of peripheral vasospasm in NTG as well as the potential therapeutic application of CCBs to improve ocular perfusion.^[111-113] Subsequent reports found that centrally acting CCBs, such as nimodipine and nifedipine, improve ocular blood flow and color sensitivity in glaucoma patients.^[114-117] Low-dose nifedipine has also been shown to reverse ET-1 induced ocular hemodynamic effects.^[117] However, these effects on visual field and function are mixed, as some studies have reported functional improvement in these patients,^[118,119] while others found no effect.^[120,121] When used topically, CCBs have been shown in some animal studies to reduce IOP, although the mechanism of this action is not completely understood.^[122-125] Follow-up studies examining the effect of topical verapamil have shown only a modest reduction of IOP in normal human eyes.^[126-129] However, the potential benefits of CCBs have yet to be validated in randomized clinical trials and the side effects of CCBs, namely those related to peripheral edema, limit their tolerability in some patients. In addition, there is concern that systemic hypotension, caused by peripheral vasodilation in the case of CCBs, may exacerbate glaucomatous damage by decreasing diastolic ocular perfusion pressure to the optic nerve.

More recently, the widely used class of anti-cholesterol medications, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, more commonly known as "statins," have gained interest as a potential treatment for glaucoma. In addition to lowering lipids, statins have been shown to possess an antiapoptotic and neuroprotective effect suggesting that long-term use may reduce the risk of glaucoma.^[130-132] However, studies have demonstrated mixed results with regard to the protective effect of statins suggesting that an interventional prospective study may be helpful in elucidating the potential benefit of statins for treating NTG and other forms of glaucoma.^[132-134]

Many investigators are now examining the potential use of nutritional supplements and phytochemicals as adjunctive therapies for glaucoma. One of the more commonly studied phytochemicals is ginkgo biloba, a unique species of trees indigenous to Korea, Japan and China. Extracts from ginkgo leaves, consisting mainly of flavonoids and terpenoids, have long been used for therapeutic purposes, particularly for its purported nootropic effects on cognition and memory through a mechanism that is believed to be related to its vasorelaxant properties.^[135] Other studies have shown that ginkgo extracts may have anti-oxidative properties as well.^[136,137] With regard to glaucoma, a recent study found improved peripapillary blood flow in NTG patients consuming ginkgo biloba extract when compared to control patients.^[138] The ginkgo extract EGb761 has also been found to be neuroprotective in animal models of ischemic CNS injury,^[139,140] while human studies have reported improved visual field indices associated with consumption of ginkgo extracts in NTG patients.^[141-143] Another phytochemical currently under investigation is resveratrol - a naturally-occurring polyphenol commonly found in berries, nuts and the skin of red grapes with reported anti-oxidative and anti-inflammatory properties that may be beneficial in various

age-related conditions, including glaucoma.^[144,145] One of the ways in which resveratrol is believed to be vasoprotective is by inhibiting ET-1 synthesis.^[146] Resveratrol has also been shown to be helpful in preventing damage of trabecular meshwork cells in the setting of chronic oxidative stress.^[147] As with other potential therapies under investigation, these findings have yet to be validated in human studies, although the initial data are encouraging.

Conclusion

NTG represents a subtype of the open angle glaucomas with unique diagnostic characteristics and management challenges. While these patients present with statistically normal IOPs, it is clear that IOP modification is currently the best established target for treatment. Many theories have been proposed for the pathogenesis of NTG and there is mounting evidence that IOP-independent risk factors, such as vascular dysregulation, play an important contributing role. Recent research has shown that the choice of medications may be important in the overall prognosis of these patients as well. When medications are unable to achieve adequate stability of visual field progression and optic nerve damage, glaucoma filtering surgery remains the most proven option in the treatment paradigm of NTG. Ideally, future treatment of NTG will target both IOP and IOP-independent risk factors. Further research is still needed to develop clinically effective and useful IOP-independent neuroprotective agents for NTG.

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