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Preventable Risk Factor of Glaucoma

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ABSTRACT

Introduction: Glaucoma contributes of cases of number of irreversible blindness worldwide, with estimates reaching 112 million cases by 2040. About 50% remain unaware in the early stages of this disease unless there is already a visual disturbance or an acute attack.
Methods: This is an observational literature review. This study uses the PubMed and Google Scholar databases. The keywords searched were: Glaucoma risk factors, retinal ganglion cell damage, intraocular pressure, neuroprotection for glaucoma, metabolic disease and glaucoma. The inclusion criteria were original cohort studies, case-control studies, Randomized Controlled Trial (RCT), systematic review, and meta-analysis in the last decade in English. Non-English articles were excluded.
Results: The main preventable risk factors of glaucoma are increased intraocular pressure, oxidative stress, and metabolic syndrome. for every 1 mmHg increase in intraocular pressure there will be a loss of retinal nerv fiber layer of ~0.05µm to ~0.13µm per year. Controlling intraocular pressure with medications or laser/surgery can reduce intraocular pressure by 20-70%. Oxidative stress damage retinal ganglion cell particularly in normo-tension glaucoma, regardless of intraocular pressure. Metabolic syndrome increases oxidative stress thereby exacerbating retinal ganglion cell damage. The use of citicoline and nicotinamide has been widely proven to slow down retinal ganglion cell damage in glaucoma. The relationship between blood pressure with the progression of glaucoma is still debated.
Conclusion: Preventing the progression of glaucoma is important by controlling the preventable risk factors, including increased intraocular pressure, oxidative stress and metabolic syndrome. By decreasing intraocular pressure, damage to retinal ganglion cells slows down. Oxidative stress damages retinal ganglion cells regardless of intraocular pressure. Metabolic syndrome increases oxidative stress, thereby exacerbating retinal ganglion cell damage.

Keywords: Glaucoma; intraocular pressure; oxidative stress

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Introduction

Glaucoma is one of the leading causes of blindness worldwide, ranking first as a cause of irreversible blindness. In the age range above 40 years, the number of glaucoma sufferers is generally around 3.5%. This number is estimated to reach around 112 million people by 2040. Glaucoma is a disease that causes damage to retinal ganglion cells, resulting in decreased visual acuity. Approximately 50% of glaucoma sufferers are unaware of this condition in the early stages until vision loss or an acute attack occurs. Primary Open Angle Glaucoma (POAG) has the highest incidence compared to other subtypes[1].

Glaucoma risk factors are multifactorial. There are both preventable and non-preventable factors. The non-preventable risk factors of glaucoma were identified, including a family history, anterior chamber depth, corneal thickness, axial length, myopia or hyperopia, advanced age, race, and gender. This article will discuss the main preventable glaucoma-related factors to achieve optimal treatment results, including increased intraocular pressure, oxidative stress, hypertension and metabolic syndrome[2,3].

Methods

This study is an observational literature review. This study used PubMed and Google Scholar databases. The keywords searched were: Glaucoma risk factors, retinal ganglion cell damage, intraocular pressure, neuroprotection for glaucoma, metabolic disease and glaucoma. The inclusion criteria were original cohort studies, case-control, Randomized Controlled Trial (RCT), systematic review, and meta-analysis in the last decade in English. Non-English articles were eliminated. The author carefully reviewed the selected articles to examine the topic.

Review and Discussion

Intraocular Pressure

Intraocular pressure (IOP) is determined by the production and disposal of aqueous humor, which is produced by the nonpigmented ciliary body. The lamina cribrosa, which functions to support Retinal Ganglion Cells (RGCs) as they exit the eyeball, is very vulnerable to changes in IOP. When IOP increases, the lamina cribrosa will experience pressure and RGC damage will occur. In addition to mechanical damage, high IOP will also disrupt the blood supply to the optic nerve, causing the optic nerve to lack nutrition. In addition, increased IOP will produce glutamate which will trigger Reactive Oxygen Species (ROS) which cause oxidative stress that ends in mitochondrial damage and cell damage. Therefore, in individuals with neurotrophic deficiencies will be more sensitive to a slight increase in IOP. Every 1 mmHg increase in IOP, there will be a loss of Retinal Nerv Fiber Layer (RNFL) of ~0.05μm per year in general, and ~0.13µm in progressive cases. Thus, IOP control is the most important factor in the management of glaucoma. The normal IOP target is 10-21 mmHg[4].

Treatment to achieve the IOP target can be with drugs or laser/surgery. Classes of drugs that are used include prostaglandin analog (increase aqueous humor outflow through the uveoscleral pathway), beta-blockers (reduce aqueous humor production by the ciliary body), alpha-adrenergic agonists (reduce aqueous humor production and improve outflow through the uveoscleral pathway), oral carbonic anhydrase inhibitors (CAI), and mannitol or glycerol (for acute glaucoma attacks)[4].

If drug therapy is insufficient or laser facilities are available, so interventions may be necessary. Argon laser (ALT) and especially Selective Laser Trabeculoplasty (SLT) improve trabecular drainage and can lower IOP by 20-30%. A study conducted over six years, presented at the annual meeting of the American Academy of Ophthalmology (AAO) in 2024, found that with selective laser trabeculoplasty therapy, POAG experiences 29% slower progression compared to using eye drops. Previous studies found that selective laser trabeculoplasty is equally effective as eye drops. AAO recently published the results of an Ophthalmic Technology Assessment of selective laser trabeculoplasty, stating that this laser therapy can be used as a primary treatment for POAG, allowing most patients to be free of glaucoma eye drops, or in combination with eye drops. However, SLT's effectiveness decreases over time, with IOP control reaching 70% at 6 months post-procedure, and then dropping to 27% after 2 years. This procedure can be repeated[5].

MIGS (Minimally Invasive Glaucoma Surgery), provides faster recovery and lower risks in POAG. MIGS uses micro-invasive procedures such as *iStent*, *Hydrus*, *CyPass*, or excimer laser trabeculostomy. This procedure increases aqueous humor outflow through the trabecular meshwork and reduces the risk of fibrosis. This procedure is intended for POAG, especially for mild to moderate degrees. One study showed a reduction in IOP of >20% over a four-year period and reduced the need for glaucoma medications. This procedure is very safe and can be combined with cataract surgery. The combination of MIGS and phacoemulsification can reduce the need for glaucoma eye drops[6].

Trabeculectomy and drainage Implants are creating a fluid outflow pathway through the sclera into the subconjunctival space in advanced cases. This procedure is used when laser treatment is ineffective on primary or secondary open-angle glaucoma. The risks of trabeculectomy include bleb leakage, postoperative fibrosis, infection, and hypotonic maculopathy. The incidence of bleb leakage, hyphema, and hypotonic maculopathy after drainage implants is lower compared to trabeculectomy, but there is a greater risk of concurrent cataracts, diplopia/strabismus, and tube erosion. The success rate of both procedures is about 70-90%[7].

Laser Peripheral Iridotomy (LPI) is the first-line therapy for angle-closure glaucoma. Generally used for angle-closure glaucoma with pupillary block, by making a small hole in the iris so that aqueous humor can flow to the anterior chamber. LPI can prevent acute angle-closure glaucoma attacks and prevent the adhesion of the iris to the trabecular meshwork. In a study using Spectral Domain Anterior Segment Optical Coherence Tomography (SD AS-OCT) on 22 eyes that underwent laser iridotomy, an increase in Angle Opening Distance (AOD), Trabecular Iris Space Area (TISA), Anterior Chamber Depth (ACD), Anterior Chamber Width (ACW), and Anterior Chamber Area (ACA) was found after one week of laser iridotomy. The effectiveness of LPI is about 65-70% in reducing IOP[8].

Oxidative Stress

Oxidative stress occurs when there is an imbalance between free radicals and antioxidants. Oxidative stress results in impaired tissue stabilization, DNA and protein damage, and particularly damage to cells in the trabecular meshwork, optic nerve head, lamina cribrosa, and RGCs, which are responsible for glaucoma progression, particularly in glaucoma with normal IOP. Glaucoma with increased IOP also involves increased glutamate, which triggers ROS and cell damage, leading to apoptosis through the caspase pathway (a protease that breaks down cells). The NADPH Oxidase (NOX) enzyme is also involved in producing ROS in response to inflammation. Damaged mitochondria produce ROS, which further exacerbates mitochondrial damage. In addition to directly causing RGCs apoptosis, ROS can also induce RGCs apoptosis through NF-kB activation (an inflammatory response). One study found that antioxidants such as glutathione, superoxide dismutase, and catalase decreased, accompanied by increased oxidative stress markers such as MDA (lipid damage) and nitrotyrosine in the serum and tears of glaucoma patients. Controlling oxidative stress is a new therapeutic target, alongside controlling IOP in glaucoma patients. One of the agents that is currently being researched a lot is citicoline, nicotinamide (vitamin B3), and vitamin D3 supplementation, which are neuroprotective compounds that can protect the structure and function of neurons, and indirectly can reduce the negative impact of oxidative stress[9, 10].

Citicoline is a precursor for the synthesis of phosphatidylcholine and sphingomyelin, which are then useful in repairing RGCs membranes and optic nerve axons damaged by oxidative stress or chronic ischemia. This is important for reducing the vulnerability of RGCs to mechanical stress such as increased IOP. In vitro studies have found that citicoline prevents cell membrane damage and apoptosis of RGCs caused by oxidative stress. Citicoline increases levels of acetylcholine, dopamine, and serotonin in the central nervous system. This increase in neurotransmitters helps improve overall visual function. A study of Pattern Electroretinogram (PERG) and Visual Evoked Potentials (VEP) showed improvements in glaucoma patients receiving citicoline therapy. An experimental study found that citicoline supplementation reduced mitochondrial dysfunction, a major pathway for RGCs death. Citicoline also increases glutamate uptake by astrocytes, decreases NMDA activity, and increases glutamate transporter expression. Citicoline has anti-apoptotic effects through modulating the expression of anti-apoptotic proteins (Bcl-2) and decreasing the expression of pro-apoptotic proteins (Bax, caspase-3). These effects reduce the progressive degeneration of RGCs and increase the survival of retinal neurons exposed to chronic stress due to elevated IOP Citicoline also improves neuroplasticity by supporting the expression of neurotrophic factors such as Brain-Derived Neurotrophic Factor (BDNF) which is important for the regeneration of the visual pathway. In a clinical study, it was found that glaucoma patients who received long-term citicoline therapy experienced improvements in visual function and slowed visual field decline. In several studies, it was found that adjuvant therapy with citicoline can improve visual fields. In a study, oral administration of citicoline 500 mg/day with a treatment cycle of 120 consecutive days, followed by a 60-day break, for 2 years was reported to slow the decline in RNFL and Ganglion Cell Complex (GCC) thickness, as well as improve visual fields. In a study of the administration of 2% liposomal citicoline drops as an adjunct therapy in POAG patients, retinal function was improved and glaucoma progression was reduced[11-13].

Nicotinamide (vitamin B3) is a precursor of Nicotinamide Adenine Dinucleotide (NAD+). NAD+ is a coenzyme that helps improve optic nerve mitochondrial dysfunction, increasing cellular energy reserves (ATP), reducing oxidative stress, and increasing resistance to oxidative stress. Clinical trials are currently being conducted on the use of nicotinamide as a neuroprotector for the management of glaucoma in many countries. In a laboratory study, oral administration of nicotinamide resulted in 93% of the samples not developing glaucoma. Additionally, in a randomized controlled study involving 32 individuals with open-angle glaucoma, it was found that oral supplementation with calcium pyruvate 3 grams/day for 9 weeks led to an average increase of 8 test locations in the visual field compared to placebo. In line with this research, a 12-week clinical trial in Australia with 57 participants receiving nicotinamide supplementation of 3 grams/day found an improvement in retinal function assessed by electroretinography. One study found that the combination of nicotinamide and pyruvate improved short-term visual function in glaucoma patients already receiving IOP-lowering therapy. However, longer-term trials are needed to assess broader effects.[14-16]

Vitamin D3 has also been shown to influence aqueous humor production and outflow through the trabecular meshwork. Vitamin D3 acts through the vitamin D receptor (VDR), which interacts with the TGF-β2/SMAD pathway in trabecular meshwork cells. VDR activation can inhibit SMAD2/3 phosphorylation and reduce the expression of profibrotic genes (such as fibronectin, α-SMA, and collagen). This has the potential to reduce excessive ECM deposition, decrease resistance to aqueous humor outflow, and ultimately lower IOP. Experimental studies have shown that vitamin D3 reduces ECM remodeling and oxidative stress in TM cells. In animal models, vitamin D3 can lower IOP, reduce RGCs loss, and provide a protective effect on the optic nerve. Furthermore, vitamin D3 has a neuroprotective effect on the optic nerve. A study in monkeys found that vitamin D3 supplementation can reduce intraocular pressure. However, the benefits of vitamin D supplementation for glaucoma are still controversial and require further research.[17,18]

High Blood Pressure

Elevated IOP and diminished ocular perfusion have been proposed as contributing factors to the development of optic neuropathy in glaucoma. Arterial blood pressure (BP) may modulate both parameters. Elevated BP has the potential to increase IOP through enhanced aqueous humor production, whereas hypotension may compromise ocular perfusion pressure (OPP), predisposing the optic nerve to ischemic injury. This complex interaction among IOP, OPP, and systemic BP is of particular clinical relevance, given the frequent co-occurrence of glaucoma and hypertension in aging populations[19].

Elevated blood pressure has been shown to affect IOP through two main mechanisms. First, elevated blood pressure increases capillary pressure within the ciliary body, thereby increasing aqueous humor production. Second, elevated blood pressure increases episcleral venous pressure, thereby inhibiting aqueous humor outflow. Optic nerve damage occurs due to mechanical and ischemic compression of the nerve fibers. Although the eye has autoregulatory mechanisms to maintain consistent perfusion, elevated endothelin-1 levels in hypertensive individuals can disrupt vascular homeostasis, thereby impairing the regulation of ocular blood flow[20].

However, the correlation between blood pressure and glaucoma remains controversial. A study in Turkey showed that individuals with hypertension had significantly higher intraocular pressure (IOP) compared with normotensive subjects. Subsequent reductions in blood pressure were associated with a significant reduction in IOP in hypertensive patients. These observations suggest that poorly controlled systemic hypertension may contribute to persistent elevations in IOP, thereby increasing the progression of glaucomatous optic neuropathy. In contrast, some studies have found no significant association between blood pressure and increased IOP. Interestingly, other research suggests that in younger individuals, hypertension may have a positive effect by increasing ocular perfusion pressure (OPP), potentially reducing the risk of glaucoma. Furthermore, individuals receiving antihypertensive therapy have been reported to have a two to threefold increased risk of developing glaucoma. This association may be related to the nocturnal administration of antihypertensive medications, which can lead to excessive drops in nighttime blood pressure and, consequently, a reduction in OPP[21,22].

Metabolic Syndrome

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities including central obesity, hyperglycemia, hypertension, and dyslipidemia. Its prevalence continues to increase and is associated with an increased risk of various diseases, including glaucoma. Insulin resistance, a core component of MetS, has been hypothesized as a potential pathophysiological link between MetS and glaucoma. Several studies have investigated the relationship between MetS and GON in individuals diagnosed with glaucoma[23].

The brain contains high densities of insulin and insulin-like growth factor-1 (IGF-1) receptors. Disruption of these signaling pathways due to insulin resistance disrupts neuronal communication and activates pro-inflammatory processes, ultimately leading to RGC degeneration. Furthermore, insulin resistance has been shown to impair cerebral blood flow and increase oxidative stress, cause microvascular dysfunction (vasculopathy), and accelerate neurodegenerative mechanisms, further contributing to optic nerve damage and the development of glaucoma. Inflammatory mediators involved include TNF-alpha, IL-1β, and nitric oxide. A study by Lee et al. found that MetS influences the incidence of POAG regardless of IOP.[23,24]

Conclusion

The main preventable risk factors for glaucoma include increased intraocular pressure, oxidative stress, and metabolic syndrome. Every 1 mmHg increase in intraocular pressure there will be a loss of retinal nerv fiber layer of ~0.05µm to ~0.13µm per year. Intraocular pressure decreases by 20-70% with medication therapy or laser/surgery. Oxidative stress damage ganglion cell particularly in normo-tension glaucoma, regardless of intraocular pressure. Metabolic syndrome increases oxidative stress thereby exacerbating retinal ganglion cell damage. The use of citicoline and nicotinamide to decrease oxidative stress is supported by many studies. As for the routine administration of vitamin D, it remains controversial. The relationship between blood pressure and glaucoma is still debated.

Conflicts of Interest

There is no conflict of interest.

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