REVIEW ARTICLE

# Ocular and Systemic Factors Associated with Glaucoma

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## Abstract

Glaucoma is one of the leading causes of irreversible blindness in the world. Although numerous factors have been implicated in the pathogenesis of glaucoma, the main focus of management still remains lowering the intraocular pressure (IOP) by medical or surgical therapy. However, a major challenge is that many glaucoma patients continue to progress despite good control of IOP. In this regard, the importance of other coexisting factors that may contribute to disease progression needs to be explored. Ophthalmologists need to be aware of ocular risk factors and the impact of systemic diseases and their medications, along with lifestyle modifications on the course of glaucomatous optic neuropathy and adopt a holistic approach in treating the eye as well as the patient to alleviate the suffering from glaucoma in a comprehensive manner.

**Keywords:** Disorder, Glaucoma, Intraocular pressure, Systemic disease.

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## Introduction

Though IOP remains to be the best established and most modifiable risk factor, glaucoma is best considered a progressive optic neuropathy representing the final outcome of a number of disorders. As per the current knowledge, the etiopathogenesis of glaucoma may involve either one or a combination of the following major mechanisms:

- Mechanical damage/barotrauma (IOP-related).
- Vascular (decreased blood supply to optic nerve head).
- Biochemical (decreased levels of neurotrophic factors/increase in levels of neurotoxins/mitochondrial dysfunction).

There is increasing evidence that factors not limited and related to the IOP have a significant role in the etiopathogenesis as well as the progression of glaucoma.[1] We need to approach glaucoma as a systemic disease and look at each system of the human body and its impact on glaucoma. This article aims to agglomerate all the risk modifiers/stressors associated with primary open and angle closure glaucoma, which together constitute a cumulative biological risk of causation/progression of glaucomatous damage.

## Epidemiological Factors

### Age

Age is a significant modifier of the relationship between IOP and retinal nerve fiber layer (RNFL) loss over time and older patients are more likely to have glaucoma progression than younger patients at similar IOP.[2] This may be related to mitochondrial dysfunction, inability to handle oxidative damage, vascular alterations, and changes in the biomechanics of the optic nerve head with advancing age.[3]

### Race

Higher prevalence, earlier presentation, and faster progression of primary open-angle glaucoma (POAG) in African and Hispanic populations can be due to thinner corneas, larger optic nerve heads, and a higher prevalence of vascular diseases such as diabetes and hypertension.[4] Asians are more susceptible to primary angle closure glaucoma (PACG) due to the risk of having narrow angles.[5]

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### Inheritance and Family History

Glaucoma is a polygenic disease with an estimated heritability of 70%.[6] First-degree relatives of glaucoma patients have a 22% lifetime risk of glaucoma as compared to 2.3% among those with no family history. About 10% of siblings of glaucoma patients have glaucoma compared to 0.7% of siblings of those without glaucoma.[7] The novel loci for adult-onset glaucoma include the following: POAG, [ABCA1, AFAP1, GMDS, PMM2, TGFBR3, FNDC3B, ARHGEF12, growth arrest-specific protein 7 (GAS7), FOXC1, ATXN2, TXNRD2]; PACG, (EPDR1, CHAT, GLIS3, FERMT2, DPM2-FAM102); and exfoliation syndrome (XFS) glaucoma (calcium voltage-gated channel subunit α1 A).[8] Sixteen genomic regions have been associated with POAG, eight with PACG and two with XFS. Molecular and cellular events caused by mutations in myocilin, organ procurement and transplantation network, and TANK-binding kinase 1 have been suggested to have a role in early onset glaucoma.[8] Transmembrane and coiled-coil domains 1 and GAS7 mutations can effect neuron regeneration along with IOP elevation. p38 mitogen-activated protein kinases are common pathways involved in neurodegenerative

diseases and glaucoma.[9] For PACG, a positive family history is a major risk factor and screening first-degree relatives is an effective way of detecting glaucoma in a population.[10]

### Socioeconomic Status

A poor socioeconomic status has been associated with greater severity of glaucoma at presentation in multiple studies.[10] Lifelong glaucoma medications, follow-up visits, travel expenses, and loss of wages pose an economic burden on the patients. A study done on the Indian population found out-of-pocket expenses on antiglaucoma medications ranging from 0.3% in the high-income group to 123% of the monthly gross income in the low-income group.[11] Medical therapy should therefore be customized according to the socioeconomic status, availability of drugs and the facilities for access to healthcare, especially travel time to the healthcare facility. The educational status of the patient plays an important role in compliance, understanding the need for lifelong medications, and timely follow-ups.[12]

### Body Mass Index (BMI)

Obesity was considered a risk factor for increased IOP. However, patients with normal-tension glaucoma (NTG) tended to be rather slim, and most subjects with low BMI had lower blood pressure (BP) and often had cold extremities.[13]

## Ocular Factors (Table 1)

### Corneal Thickness

An ocular hypertension study demonstrated that eyes with thinner corneas are at a higher risk of developing glaucoma. Thinner corneas are also associated with more rapid progression and increased severity of visual field loss. However, this is probably due to the underestimation of IOP in thinner corneas and is not a true independent risk factor.[14,15]

### Biomechanical Factors

Corneal hysteresis is a biomechanical index that measures corneal viscoelastic dampening, that is, the cornea's ability to absorb and dissipate pressure. Low corneal hysteresis is associated with progressive optic nerve damage and visual field loss at relatively low pressures and poses an independent risk factor for glaucoma.[16,17] However, it is important to note that corneal hysteresis is not a static property like corneal thickness or lens thickness. It is higher in eyes with high IOP and reduces as IOP is controlled.

### Optic Nerve Head

An ocular hypertension study concluded that a larger vertical or horizontal cup disc ratio is a predictor of the development of glaucoma. However, it is largely believed that it is an indicator rather than an independent risk factor for glaucoma.[18] Disc hemorrhages are an important risk factor for glaucoma progression. The presence of acquired optic pits is a rare risk factor for glaucoma.[19]

### Refractive Error

People with hyperopia are at a higher risk of angle closure glaucoma.[20] The neuroretinal rim (NRR) thinning detection might be delayed in a small hyperopic disc. Myopia is considered a risk factor for POAG and it is postulated that myopic eyes are more susceptible to IOP-induced damage due to anomalous connective tissue organization. Anomalous, large, or tilted discs in myopia make the correct detection of NRR thinning difficult. Reduced RNFL thickness and peripapillary blood flow in myopia may also contribute to faster progression of glaucomatous damage.[21,22] A recent meta-analysis evaluating 24 studies concluded that for each unit increase in myopia, the risk of glaucoma increases by almost 20%.[23] Myopia has been demonstrated to be a greater risk factor in Asians than in white patients.[24]

## Systemic Diseases/Conditions (Table 1)

### Central Nervous System (CNS)

#### *Neurodegenerative Diseases*

Just like other neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), glaucoma is also characterized by loss of specific neuron subset.

Alzheimer's disease is the most common cause of dementia in the elderly population. Various population-based studies have shown an increased prevalence of glaucoma is seen to occur in patients with Alzheimer's and those with cognitive impairment.[25,26] In the presence of cognitive decline, there are challenges in the diagnosis of glaucoma as well as the detection of progression using visual field-testing.[27] Chronic glaucoma has been shown to induce deposition of β-amyloid peptide and hyperphosphorylated tau proteins, considered hallmark of Alzheimer's disease, in the lateral geniculate body.[28] Few studies have also pointed to an increased risk of developing dementia in patients with OAG with advanced cupping.[29] RNFL and optic disc changes may serve as early biomarkers of dementia in the future. It is imperative for an ophthalmologist to enquire about any cognitive decline in glaucoma patients, as these can coexist and need to be tackled separately.

Some studies have shown a higher incidence of glaucoma in patients with PD when compared with the normal population.[30] Neurodegeneration in PD results in low systemic dopamine levels. In the eye, dopamine is present in a subtype of amacrine cells in the inner plexiform layer and has a supposed role in IOP regulation through its receptors on the ciliary body epithelium.[31] Dopamine is also proposed to have an antiapoptotic role. Postmortem tests have shown a lower level of dopamine in the retina of PD patients.[32]

Amyotrophic lateral sclerosis (ALS) has a lower concentration of calcium in both central serous fluid and aqueous. Just like in upper and lower motor neurons affected in ALS, signal transmission in retinal ganglion cells (RGC) is also adenosine triphosphate (ATP) driven, which is provided by mitochondria in the astrocytes surrounding the optic nerve. It is postulated that low calcium concentration leads to ionic stress and subsequent premature astrocyte apoptosis, ultimately resulting in the dysfunction of RGC.[33] Mutations in optineurin, a neuroprotective protein seen in the trabecular meshwork, retina, and brain, have shown a link with OAG and ALS.[34,35]

#### *Stroke*

While interpreting visual fields, caution must be exercised in patients with a history of stroke, as these patients can have field defects due to cerebral damage.[36] However, an increased risk of stroke was found in patients with glaucoma in a 10-year follow-up study.[37] This may be explained in part due to common risk factors for both diseases like diabetes mellitus and hypertension. However, a higher risk of stroke development has also been seen in patients without any comorbidities.[38]

**Table 1:** Risk factors of glaucoma (beyond IOP)

| | |
|---|---|
| | *Epidemiological factors* |
| Age | Older patients are more likely to have glaucoma progression than younger patients at the same level of IOP |
| Race | • Higher risk of POAG in African and Hispanic population<br>• Higher risk of PACG in Asians |
| Family history/inheritance | Glaucoma is a polygenic disease with an estimated heritability of 70%. First-degree relatives of glaucoma patients have a 22% lifetime risk of glaucoma |
| Socioeconomic status | Lower socioeconomic and educational status is associated with greater severity of glaucoma at presentation |
| BMI | Low BMI associated with NTG |
| | *Ocular factors* |
| Corneal thickness | Thin corneas have a higher risk of glaucoma progression |
| Biomechanical factors | Low corneal hysteresis is associated with faster glaucoma progression |
| Optic nerve head | • A larger cup-to-disc ratio is an important predictor for the development and progression of glaucoma<br>• Disc hemorrhages point towards a higher risk of glaucoma |
| Refractive error | • Myopia is associated with the risk of POAG<br>• Hypermetropic eyes have a higher risk of angle closure glaucoma |
| | *Systemic factors* |
| | *CNS* |
| Neurodegenerative diseases | • Increased prevalence of glaucoma in patients with Alzhiemer's disease and increased variation in the visual field in patients with cognitive impairment<br>• Patients of PD and amyotrophic lateral sclerosis have a higher prevalence of glaucoma |
| Stroke | Careful interpretation of the visual field changes in patients with CNS involvement; increased risk of stroke in patients with glaucoma |
| Psychiatric disorders | Tricyclic antidepressants and antipsychotics can precipitate acute angle closure glaucoma |
| Migraine | Increased incidence of NTG as well as POAG |
| Personality | Glaucoma patients demonstrate more negative personality traits such as type A personality, anxiety, and depression |
| TLPD | The positive association between it and visual field defects in glaucoma |
| | *Cardiovascular system* |
| Vascular dysregulation | • Flammer's syndrome: unstable blood flow leads to oxidative damage<br>• Secondary vascular dysregulation seen in autoimmune conditions such as rheumatoid arthritis, giant cell arthritis, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis, and Crohn's disease, etc. can also increase the risk of glaucoma<br>• Vasospasms in diseases that can be risk factors of glaucoma include Behcet's disease, Buerger's disease, preeclampsia, homocysteinemia, head injury, sickle cell disease, porphyria, Susac syndrome, mitochondriopathies, arteriosclerosis, antiphospholipid syndrome, and drugs |
| Hypertension and hypotension<br>Ischemic heart disease<br>Dyslipidemia | • Antihypertensives causing hypotension as well as hypotension per se causes reduced ocular perfusion: progression of glaucoma<br>• Calcium channel blockers increase the risk of POAG<br>• Systemic β-blockers are to be avoided at night to prevent nocturnal hypotensive episodes and subsequent decrease in optic nerve perfusion.<br>Atherosclerosis, autonomic dysfunction, and endothelial dysfunction cause optic disc perfusion abnormalities |
| | *Respiratory system* |
| Chronic obstructive pulmonary disease<br>Obstructive sleep apnea<br>Interstitial lung disease | • Risk factor for NTG<br>• CPAP leads to a rise in IOP<br>• The use of steroids for treatment is associated with the risk of glaucoma |
| | *Renal Disease* |
| End-stage renal disease | Uremic state due to lower glomerular filtration rates has been associated with raised IOP independently |
| | *Endocrine system* |
| Diabetes | Increased rate of ganglion cell loss |
| Sex hormones | • Late menarche and early menopause resulting in low estrogen is a risk factor for glaucoma<br>• The use of oral contraceptive pills increases the risk of glaucoma<br>• Injections of testosterone can lead to a transient rise in IOP |

*Contd…*

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| | |
|---|---|
| | *Endocrine system* |
| Thyroid disease | • Graves' disease<br>• Hypothyroidism<br>• History of treatment of thyroxine<br>• History of thyroid surgery |
| Pituitary adrenal disease | Cushing syndrome is associated with increased IOP |
| Growth hormone disorders | Acromegaly has a high risk of glaucoma |
| | *Gastrointestinal diseases* |
| Infection | HP infection was found to be associated with POAG |
| Oral health | Loss of teeth associated with increased risk of glaucoma |
| | *Immune system* |
| Toll-like receptor proteins and tumor necrosis factor | Immune-mediated mechanisms associated with accelerated ganglion cell apoptosis in glaucoma |
| Dietary factors | • The inverse relationship between body mass index and OAG<br>• Low niacin level associated with OAG<br>• Increased intake of iron and low intake of vitamin A associated with increased risk of glaucoma |
| Lifestyle/work factors | • Smoking<br>• Caffeine<br>• Lateral decubitus position during sleeping<br>• Weightlifting<br>• Occupations such as trumpet blowers, glass blowers, etc.<br>• Excessive lid wiping/massaging; wearing swimming goggles; deep sea diving<br>• Wearing tight collar shirts and ties<br>• Performing yoga involving head-down positions<br>• Excessive smartphone use in low-light conditions<br>• Sleep-wake disturbances, prolonged sleep latency |
| Pollutants | • Prolonged exposure to high particulate matter concentration in air<br>• Heavy metals such as lead, cobalt, cadmium, and mercury |
| Drugs causing angle closure | • Sulfa based drugs such as acetazolamide, topiramate, cotrimoxazole, and hydrocholorothiazide<br>• Adrenergic agents are used either locally in the form of phenylephrine drops, nebulized salbutamol, and nasal ephedrine or systemically in the form of epinephrine for anaphylactic shock<br>• Cholinergic agents e.g., pilocarpine<br>• Anticholinergic agents e.g., atropine and tropicamide drops<br>• Selective Serotonin Reuptake Inhibitors, tricyclic and tetracyclic antidepressants, benzodiazepines, disopyramide, and antipsychotics<br>• Anticonvulsants e.g., topiramate; Antiparkinsonians e.g., cabergoline, orphendrine, trihexiphenadryl<br>• Periocular botox (botulinum toxin)<br>• H1 receptor blockers, e.g., brompheniramine and chlorpheniramine; H2 receptor blockers, e.g., cimetidine and ranitidine<br>• Recreational drugs like cocaine and ecstasy<br>• Anticoagulants (risk of suprachoroidal hemorrhage)<br>• Latanoprost (ciliochoroidal effusion in Sturge Weber)<br>• Non-steroidal anti-inflammatory drugs-mefenamic acid<br>• Anesthetic agents like succinylcholine, ketamine, atropine, scopolamine, muscle relaxants, ephedrine, and epinephrine |
| Drugs causing OAG | • Steroids, especially glucocorticoids<br>• Antineoplastic drugs like docetaxel, paclitaxel, and imatinib<br>• Eye ointments– due to Toxic Anterior Shock syndrome, trabeculations, and fibrin deposition |

### *Personality*

Glaucoma patients tend to demonstrate more negative personality traits such as emotional fluctuation and instability and to be less trusting, helpful, responsive, forgiving, hardworking, reliable, hearted, optimistic, active, and ambitious. They also demonstrate a higher tendency of hypochondria, hysteria, and type A personality.[39]

### *Anxiety and Depression*

Increased incidences of anxiety and depression have been found in patients with glaucoma.[40] Glaucoma medication, such as topical blockers and carbonic anhydrase inhibitors, can also cause depression. Anxiety and depression can adversely impact the patient's ability to follow treatment regimens. Therefore, these need to be identified and managed separately in coalition with a

psychologist psychiatrist to encourage treatment adherence and provide the patient with a better quality of life. Psychological stress can lead to elevation of IOP and history to elicit recent stressors must be taken from a glaucoma patient.

### *Migraine*

Both migraine and vasospasm are risk factors for glaucomatous field damage. Migraine has been seen to occur with more frequency in patients with NTG.[41] The most commonly accepted pathophysiological mechanism of vascular dysregulation or vasospasm may be the common link between glaucoma and migraine. A meta-analysis by Chang Xu et al. revealed a statistically significant relationship between migraine and POAG (RR = 1.24; 95% CI = 1.12–1.37). They found that the risk of developing POAG was 24% higher risk in migraine patients, as compared to those who had never suffered from migraine. This included both POAG and NTG patients.[42] In addition, migraine, as a comorbidity may confound glaucoma diagnosis and monitoring. This is because the visual sensory symptoms of migraine may impact the results of standard tests of visual function, including visual fields, electrophysiology, and ocular imaging. It is important to remember that these abnormalities may persist between migraine events (the interictal period), even when patients are asymptomatic and seemingly healthy. There is sufficient evidence to suggest an increased prevalence of migraine in patients with glaucoma, especially those with NTG, further confounding the association. The results of glaucoma investigations in these patients, therefore, require careful attention during interpretation.[43]

### *Translamina Cribrosa Pressure Difference (TLPD)*

This refers to IOP change relative to orbital cerebral spinal fluid pressure (CSFP). A positive association has been seen between TLPD and visual field defects in glaucoma. Raised CSFP has been demonstrated in POAG patients. In cases with dysregulated cerebrospinal fluid hemodynamics, raised CSFP can result in the accumulation of toxic compounds at the optic nerve head, leading to retinal ganglion cell loss.[44]

### *Sleep Cycle Disturbances*

Patients with advanced glaucoma may potentially exhibit disturbed circadian rhythms due to altered melatonin cycles. Melatonin is responsible for the arousal system, as well as thermoregulation.[45,46] Patients with altered vascular regulatory mechanisms often report long sleep onset times.

## Cardiovascular System

### *Vascular Dysregulation*

Patients of primary vascular dysregulation syndrome, aka Flammer syndrome, have an increased incidence of NTG and can experience a sudden worsening of scotoma when exposed to cold temperatures.[47] Unstable perfusion (under perfusion followed by reperfusion) in these conditions leads to oxidative damage.[48]

Secondary dysregulation can be seen in autoimmune conditions such as rheumatoid arthritis, giant cell arthritis, multiple sclerosis, systemic lupus erythematosus, ulcerative colitis, Crohn's disease, etc. Higher circulating endothelin levels here lead to reduced choroidal and optic nerve blood flow.[49] Though these conditions are very often known to cause secondary glaucoma, their association with primary open or angle closure glaucoma is not established at present and needs to be explored.

Other causes of secondary vasospasms, which can be risk factors of glaucoma, include Behcet's disease, Buerger's disease, preeclampsia, homocysteinemia, head injury, sickle cell disease, porphyria, Susac syndrome, mitochondriopathies, arteriosclerosis, antiphospholipid syndrome, and drugs.[50]

### *Hypertension*

Systemic hypertension and glaucoma are seen to frequently coexist together with similar mechanisms postulated in the pathogenesis of both diseases.[51] Both are associated with dysregulation of blood flow.

Patients of systemic hypertension, on treatment with oral hypotensives, may be at a higher risk for increased progression of optic neuropathy in glaucoma suspects as compared to age-matched normotensives.[52] The odds of diagnosing glaucoma in patients on calcium channel blockers and α-blockers, and the angiotensin-converting enzyme was more than with other class of drugs used for hypertension.[51,53] In a recent database analysis, of all systemic medications, calcium channel blockers, especially amlodipine, were most strongly associated with an increased risk of POAG.[54] These drugs decrease BP without impacting IOP. This reduces the ocular perfusion pressure, which may result in an increased risk of glaucoma. Therefore, β-blockers are the preferred class of drugs for the treatment of hypertension in patients with glaucoma. However, topical β-blockers should not be prescribed to patients already on systemic therapy as no added benefit would be seen. β-blockers should be avoided at night to prevent nocturnal hypotensive episodes and a subsequent decrease in optic nerve perfusion.

### *Hypotension*

The blood flow to the optic nerve is determined by the ocular perfusion pressure (OPP). Mean OPP is the difference between the mean arterial BP and the IOP. The systolic and diastolic OPP can similarly be determined by subtracting the IOP from the systolic and diastolic BP values, respectively. Many authors agree that cardiovascular disease, low blood, and perfusion pressures are independent predictors for the long-term progression of the glaucomatous optic neuropathy.[55]

Leske et al. have reported that the risk of OAG in subjects with a diastolic OPP <50 mm Hg is four times that of those with an OPP of 80 mm Hg.[56] In addition, lower systolic perfusion pressure has been shown to more than double the relative risk of OAG, while a lower diastolic perfusion pressure <55 mm Hg more than triples this value.[57]

Therefore, it is beneficial to do BP recording at the time of IOP phasing, especially in patients of NTG, and those who continue to progress despite achieving target IOP control. Some patients may also require 24-hour BP monitoring to look for nocturnal BP dips.

Autonomic dysfunction may also contribute to visual field progression, especially in patients with NTG.[58] In the absence of other risk factors, a heart rate variability assessment to look for autonomic dysregulation could be helpful.[59]

Since low BP as well as nocturnal dipping, may increase the probability of visual field deterioration, an increase in BP in patients with hypotension may decrease glaucoma progression, even though the evidence of this effect is not concrete. In cases with progression despite good IOP control, the BP may be increased with an increase in the salt intake or low-dose fludrocortisone (0.1 mg/2 per week). The latter is known to cause

a mild increase in BP, reduce night-time dips and also improve the autoregulation of ocular blood flow indirectly. Vasoconstrictive drugs which increase BP, however, are contraindicated since they may adversely impact glaucoma by decreasing the optic nerve hypoplasia perfusion.[60,61]

## Ischemic Heart Disease

### *Cardiologist's Perspective*

Patients with glaucoma have a higher incidence of ischemic heart disease than those without glaucoma.[62] Flammer and Flammer AJ, in their review of "The eye and the heart," have addressed the concept that the two organs share a lot of common characteristics and are exposed to the same intrinsic and environmental influences leading to atherosclerosis, autonomic dysfunction, and endothelial dysfunction leading to a decrease in blood flow to both organs. Therefore, these vascular changes manifesting as glaucoma may be an early indicator of ischemic heart disease and prove helpful from a cardiologist's perspective.[63]

### *Ophthalmologist's Perspective*

Topical medications can reach systemic concentrations and upto 80% of timolol has been shown to be systemically absorbed. The systemic side effects of β-blockers can manifest in the form of dysrhythmias or impaired cardiac output.[64]

A history of ischemic heart disease or a heart block in the patient should preclude the physician from using topical β-blockers for glaucoma management.

The Blue Mountains Eye study has reported higher cardiovascular mortality in subjects using topical β-blockers.[65] Although the reports on cardiovascular mortality are conflicting, and caution should be exercised while prescribing them; the patient should be explained to occlude the punctum to prevent systemic absorption and follow up regularly with a cardiologist. Topical β-blockers may also cause Raynaud's phenomena in predisposed individuals.[66]

## Dyslipidemia

Topical β-blocker therapy has an adverse effect on the lipid profile. Triglyceride and values have been shown to increase by 12% and 8%, respectively, while high-density lipoprotein (HDL) cholesterol levels decreased by 9% after β-blocker therapy.[67] The changes result from the inhibition of lipoprotein lipase by β-blockers, causing a reduction in HDL and elevated triglyceride levels.[68] There is little evidence about the effect of topical antiglaucoma agents, including prostaglandins (PGs), on serum lipid levels. The production of endogenous PGs may be decreased by a diet deficient in essential fatty acids or, on the contrary, increased by dietary supplementation of the same. PGE2 and PGD2 have been shown to suppress the secretion of very low-density lipoprotein in primary rat hepatocyte cultures but do not impact lipid metabolism in any other way.

Long-term oral statins (atorvastatin, simvastatin, lovastatin, and fluvastatin) have been demonstrated to have a protective effect on OAG.[69] Patients with >24 months of statin use had a lower risk of OAG. This may be attributed to increased aqueous outflow caused by rho-kinase activity inhibition and reduced retinal ganglion cell death, as seen in mouse models.[70] Similarly, non-statin cholesterol-lowering agents have also been known to reduce the risk of OAG. On the contrary, few authors have reported an increase in the risk of OAG with a high dosage of statins. In a Taiwanese population-based study, a 1.2-fold increased risk of OAG was found in patients with a high dose of statin (>120 defined daily doses/year).[71]

Therefore, close monitoring of lipid profiles and close collaboration with a physician is essential.

## Respiratory System

### *Chronic Obstructive Airway Disease*

Asthma and chronic obstructive pulmonary disease are two common chronic diseases in the elderly, affecting the same age group as glaucoma. Although no association has been found between glaucoma and obstructive airway disease, the use of topical β-blockers for glaucoma can increase the risk of worsening symptoms or an acute attack due to systemic absorption.[72,73] β-blockers should be avoided in such patients as much as possible. If absolutely necessary, spirometry should be considered in susceptible individuals before starting β-blocker therapy for glaucoma.[74]

Inhalational steroids should be avoided in these patients as glaucoma patients can be steroid responders. Steroid use can cause a rise in IOP in previously controlled patients.

### *Obstructive Sleep Apnea (OSA)*

The OSA causes a decrease in arterial oxygen saturation and a rise in carbon dioxide saturation during sleep and results in transient hypoxia and increased vascular resistance.[75] The reduction of OPP, and the consequent reduction in the oxygen supply to the optic nerve results in glaucomatous damage. A recent review by Chaitanya et al. has identified OSA as a major risk factor for glaucoma, especially in patients with normal IOP.[76] Obese glaucoma patients with progressive disease despite well-controlled IOPs, as well NTG patients, must be evaluated for OSA and other sleep disorders. A simple history of snoring, excessive daytime sleepiness, or lethargy can give a clue to the diagnosis.[77]

However, continuous positive airway pressure (CPAP) therapy, which is the primary modality of treatment for OSA has been shown to raise IOP and greater diurnal fluctuations, thereby triggering further glaucomatous damage.[78] Therefore, a comprehensive ophthalmic examination is mandatory at every follow-up for these patients.

### *Interstitial Lung Disease*

A history of systemic steroid use may be present in patients with interstitial lung disease and could be a risk factor for raised IOP.

## Renal Dysfunction

In the Singapore Malay Eye Study, end-stage renal disease and lower glomerular filtration rates have been associated with raised IOP independent of age, diabetes, hypertension, and other risk factors.[79] The uremic state may cause a breakdown in the homeostasis of body fluids, including the aqueous humor resulting in fluid overload and trabecular meshwork damage, causing an elevation of the IOP. Monitoring of IOP is therefore required in patients with chronic kidney disease (CKD) during every ophthalmic visit. However, no independent association has been found between CKD and glaucoma.

Caution should be exercised while using oral carbonic anhydrase inhibitors for IOP reduction in patients with CKD.[80,81] Appropriate dose adjustments and monitoring of creatinine are required while using acetazolamide. Patients should be informed about symptoms of hypokalemia and metabolic acidosis, like paresthesia, nausea, vomiting, etc., to prevent further complications.

Hemodialysis done for CKD can result in a significant increase in IOP and decrease in OPP during the procedure and thus increases the risk of glaucoma progression.[82]

## Genitourinary System

Alpha-agonists could precipitate lower urinary tract symptoms due to benign prostatic hyperplasia. A quick history in all elderly males and avoiding alpha agonists could be helpful.

Long-term use of oral carbonic anhydrase inhibitors increases the risk of stone formation.[83]

## Endocrine System

### *Diabetes Mellitus*

Significant positive association has been found between diabetes and glaucoma in a recent meta-analysis.[84] Several mechanisms have been proposed for the biological link between glaucoma and diabetes. Diabetes not only affects vascular tissues but has also been shown to compromise glial and neuronal functions, ultimately causing apoptotic RGC death.[85] The increased glucose levels in the aqueous humor in the eyes of diabetics may stimulate the synthesis and accumulation of fibronectin in the trabecular meshwork. This has been postulated to result in the depletion of trabecular meshwork cells, damaging the trabecular outflow.[86] Hence, good metabolic control is essential to prevent further damage to RGCs. The mainstay of management of diabetic macular edema is intravitreal vascular endothelial growth factor antagonists. Repeated injections of Bevacizumab were found to increase the rate of development of glaucoma. In a study done by Eadie et al., they found that the rate ratio for glaucoma was 2.48 when seven or more injections were given.[87] Damage to the trabecular meshwork and blockage of the meshwork by protein aggregates or contaminants were proposed as the causes for the same.

Furthermore, glaucoma has been called the diabetes of the brain—"Type 4 diabetes."[88] The insulin-mediated regulation of IOP and its dysregulation in mitochondrial dysfunction supports the idea of insulin hypofunctionality in glaucoma. Further research is required in this regard and this could translate to using insulin as a potential therapeutic target.

### *Sex Hormones*

Estrogen hormone is found to be protective against OAG. The estrogen hormone was found to increase the ocular blood flow by its smooth muscle relaxing action. It has been found that age-related reduction in the female sex hormone resulted in reduced ocular blood flow. Estrogen also increases the endothelial nitric oxide synthase activity, thus causing vasodilation and also affecting aqueous production and outflow. It has also been found to protect RGCs and also have a neuroprotective effect. IOP is also lower in pregnancy, especially in the third trimester, due to increased estrogen. Studies have shown that female subjects with less endogenous estrogen exposure have an increased risk of glaucoma, such as those with late menarche, early menopause, and females with a history of oral contraceptive pill use. The exact role of postmenopausal hormone supplementation in the prevention of glaucoma is still not clear. Further studies are needed to explore the role of estrogen in glaucoma as well as a neuroprotective agent.[89,90]

Testosterone injections have shown an association with transient IOP elevation. Steroids and testosterone are often taken as supplements by bodybuilders and together pose a significant risk of developing glaucoma.[91]

### *Thyroid Diseases*

Studies have reported thyroid problems in up to 12% of patients glaucoma.[92] In Graves' disease, IOP elevation may be caused by orbital congestion due to increased tissue volume and contraction of extraocular muscles over surrounding adhesions.

Multiple studies have demonstrated hypothyroidism as a significant risk factor for POAG and normalizing thyroid levels can result in reduced optic nerve damage. The potential mechanism here is the deposition of mucopolysaccharides at an angle leading to reduced aqueous outflow.[93] Higher prevalence of glaucoma has also been reported in patients receiving thyroxine and with a history of thyroid surgery.[92]

### *Pituitary Adrenal Disease*

Cushing syndrome is characterized by an excess of cortisol hormone, which can be due to the overproduction of adrenocorticotropic hormone from the pituitary gland, excess production of cortisol from a tumor of the adrenal gland, or iatrogenic exposure in the treatment of chronic asthma, rheumatoid arthritis, etc. Cortisol has a glucocorticoid-like activity which can result in OAG.[94]

### *Growth Hormone Disorders*

Open-angle glaucoma (OAG) is frequently observed in patients with acromegaly.[95] In addition to reduced outflow at the level of the trabecular meshwork, up to 80% of patients of acromegaly have OSA syndrome, which is an important risk factor for glaucoma.[96] Addison's disease has also shown an association with glaucoma.

## Gastrointestinal System

Helicobacter pylori (HP) infection, already being implicated in certain ocular conditions like dry eye disease, blepharitis, and uveitis, was also found to be associated with OAG. Studies have shown an increased prevalence of HP infection in glaucoma patients as well as increased immunoglobulin G anti-HP serum levels in glaucoma patients.[97] Helicobacter organism releases proinflammatory mediators and vasoactive substances which could influence apoptotic processes as well as homeostasis in the trabecular meshwork as well as the optic nerve, thereby affecting glaucomatous optic neuropathy. The organism also releases reactive oxygen species and increases circulating lipid peroxides which act as proapoptotic signals leading to cellular death.[98] A meta-analysis showed a significant correlation between POAG and HP infection (odds ratio 3.06).[99] Kountouras et al. have also demonstrated the beneficial effect of eradicating HP infection in glaucoma patients on the IOP as well as the visual field parameters.[99] With the increasing evidence of association of HP, evaluation of patients for this infection and its appropriate treatment, would benefit glaucoma patients.

## Immune System

In recent years, the role of immune-mediated mechanisms in accelerated ganglion cell apoptosis in glaucoma has become clear. Patients with NTG have demonstrated antibodies against antigens such as heat shock proteins, neuron-specific enolase, neurofilament proteins, etc. Experimental models have shown increased expression of Toll-like receptor proteins in response to elevated IOP, which activates the innate immune system in glaucoma. Tumor necrosis factor-alpha and its receptor upregulation have been reported in subjects with glaucoma.[100]

## Musculoskeletal System

### *Arthritis*

A head-to-toe examination would help in identifying any deformity in the peripheral extremities. Small joint involvement

would point towards rheumatoid arthritis and a history of steroid use.[101] Steroid-sparing drugs and immunosuppressant therapy should be considered in such patients after consulting with the rheumatologist.

Uveitis associated with rheumatoid arthritis could add to the trabecular meshwork damage and rise in intraocular pressure.[102]

*Raynaud Phenomenon*

A history of vasospasm of extremities to cold should be elicited as that would warrant caution in using topical β-blockers. An abnormal response of the endothelium to endogenous vasoconstrictors like endothelin-1 has been implicated in the vasospastic response. This vasospasm is thought to occur in certain subsets of glaucoma, especially NTG, as shown by Nicolela et al.[103] So, there is a generalized endothelial dysfunction and could cause progression of glaucoma in the absence of other risk factors.

### Oral Health and Dentition

As expected, the number of natural teeth, periodontal disease, and root canal treatments have not been associated with POAG. However, any reported tooth loss within the past 2 years has been associated with a 1.45-fold increased risk of POAG (95% CI, 1.06e1.97). An associated diagnosis of periodontal disease increases the risk by 1.85-fold (95% CI, 1.07e3.18).

This could very well be attributed to chance and an aging demographic, still, dental pathology, particularly severe periodontitis, and must be addressed promptly.[104]

## Dietary Considerations

Body mass index (BMI) has been implicated to have an inverse relationship as an independent risk factor for OAG.[105] Studies have shown an association between dietary intake and glaucoma. Increased consumption of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) is associated with reduced glaucomatous optic neuropathy, whereas increased consumption of polyunsaturated fatty acids is associated with an increased risk of glaucoma. DHA and EPA are thought to modulate microcirculation and ocular blood flow. There was also a correlation between DHA deficit and visual field loss. These fatty acids were found to be protective against toxic damage to the RGC though the exact mechanism is still unknown.[106] Other than fatty acids, increased intake of iron and low intake of vitamin A were also associated with an increased risk of glaucoma.[107] Vitamin B3 or nicotinamide is an important precursor of nicotinamide adenine dinucleotide (NAD), which is an oxidation-reduction cofactor important in mitochondrial function and the generation of ATP. Plasma nicotinamide concentration was lower in POAG patients as compared to controls.

In mouse models of glaucoma with high IOP, mitochondrial dysfunction has been demonstrated with reduced levels of NAD in the retina. It has also been shown that high-dose supplementation of the precursor nicotinamide was associated with structural and functional preservation of the RGCs.[108,109]

## Drugs

### Drugs Causing OAG

Steroids, especially glucocorticoids, increase aqueous humor outflow resistance in a way that is analogous to the pathophysiology of POAG, the deposition of extracellular matrix, because of the inhibition of metalloproteinases.[110] Antineoplastic drugs like docetaxel, paclitaxel, and imatinib may also cause OAG.[111] Postsurgical instillation of eye ointments has also been associated with glaucoma this may be due to Toxic Anterior Shock syndrome, which results in trabeculations and fibrin deposition, decreasing the outflow facility.[112]

### Drugs Precipitating Acute Angle-closure

Sulfa-based drugs such as acetazolamide, topiramate, cotrimoxazole, and hydrochlorothiazide can lead to acute angle closure glaucoma by causing ciliary body edema and anterior displacement of the iris lens diaphragm. The same can occur due to adrenergic agent use, either locally in the form of phenylephrine drops, nebulized salbutamol, and nasal ephedrine or systemically in the form of epinephrine for anaphylactic shock. Cholinergic agents such as pilocarpine and anticholinergic agents such as atropine and tropicamide drops, tricyclic and tetracyclic antidepressants, and disopyramide can also precipitate acute angle closure. Periocular botox (botulinum toxin) used for treating blepharospasm or wrinkles can diffuse to ciliary ganglion inhibiting pupillary sphincter and precipitate an acute attack in predisposed eyes.[113] Other drugs associated which can precipitate angle closure are H1 receptor blockers such as brompheniramine and chlorpheniramine used for treating allergic reactions, H2 receptor blockers such as cimetidine and ranitidine used to treat gastroesophageal reflux and ulcers, cocaine, anticoagulants (risk of suprachoroidal hemorrhage).

## Lifestyle Associated Risk (Table 1)

### Smoking

A direct association has been found between smoking, the number of pack years and glaucoma in an 8.5 years follow-up study by Pérez-de-Arcelus et al.[114] Smoking can cause optic nerve head damage by a variety of mechanisms like increasing oxidative stress, inflammation, and vascular compromise. Current smoking status has been strongly associated with the development of glaucoma and should be reinforced to the patient.[114]

### Caffeine

There have been conflicting results on the effect of caffeine on IOP. However, in the Blue Mountains Eye Study, an intake of ≥200 mg caffeine per day was found to raise IOP in patients with glaucoma, while no significant change was seen in patients without preexisting glaucoma.[115] Therefore, caffeinated beverages may not be recommended for patients with glaucoma or ocular hypertension.[116]

### Sleeping Posture

Lateral decubitus position is associated with an increase in IOP on the dependent side.[117] Asymmetric POAG was found to have an association with time spent sleeping in one particular lateral cubitus posture.[118]

### Activities Causing Raised IOP/IOP Fluctuations

Occupations involving high-resistance wind instruments like trumpet blowers should be avoided by patients with glaucoma as the increase in the intrathoracic pressure decreases the venous return from the head and neck causing an increase in IOP. There is evidence that both high (e.g., trumpet and oboe) and low-resistance wind musicians (e.g., clarinet and flute) experience a transient

rise in IOP while playing their instruments. This elevation is accompanied by uveal engorgement and is more in the former. In fact, high-resistance wind musicians may have a significantly greater incidence of visual field loss commensurate with cumulative life hours of playing wind instruments. This may eventually present as glaucomatous damage and its misclassification as NTG.[119,120]

Activities such as eye wiping/massaging, lid squeezing/squinting, wearing swimming goggles, deep sea diving, and tight collar shirt or tie can lead to increased IOP fluctuations.[121]

### Weightlifting

Weightlifting is associated with an increase in IOP[122] and therefore, patients with glaucoma should be advised to avoid weightlifting so as to avoid spikes in IOP.

### Yoga

Although yoga and meditation have been shown to have cerebral blood flow and are neuroprotective, yoga posture involving head-down positions should be avoided in patients with glaucoma. Yoga exercises of Adho Mukha Svanasana, Uttanasana, Halasana, and Viparita Karani have been associated with a rise in IOP, therefore, should be avoided.[123]

### Exercise

An IOP elevation has been reported with muscle exertion, increase in respiratory volumes, change in body positions (e.g., supine to sitting), and especially following the Valsalva maneuver. Physical exercise involves all of these. This increase in IOP may be further exacerbated by the sudden increase in hydration levels following exercise. On the contrary, exercise may cause an increase in aqueous outflow, decreasing the IOP. Also, people who are stronger are more likely to exercise and may have a lower risk of glaucoma.[124]

### Smartphone

Smartphone use in low light conditions has been shown to cause IOP fluctuations not only in healthy subjects but also in NTG patients on medication.[23]

### Air Pollution

Black carbon particles in the atmosphere, which are a byproduct of combustion, are associated with many health disorders, including hypertension. The biological effects are hypothesized to be due to effects on endothelial function, metal processing, and oxidative stress. It has been found that increased ambient black carbon exposure may be a risk factor for raised IOP in patients who are already predisposed to oxidative stress.[125] Chua et al. also reported that patients exposed to higher PM 2.5 concentrations were more likely to report glaucoma (odds ratio 1.06) and thinner ganglion cell inner plexiform layer thickness. They found that it exhibited a dose-response relationship with no relation to the IOP.[126] Thus, the role of air pollution in the causation of glaucoma needs to be explored further.

### Heavy Metals

Various studies have suggested that lead, cobalt, cadmium, mercury, and other heavy metals may be involved in the pathogenesis of glaucoma, mediated by oxidative stress. Heavy metal exposure can be occupational or through diet and water contamination. Higher concentrations of heavy metals in an urban environment might be associated with a higher prevalence of glaucoma in urban areas.

Cobalt has been shown to cause RGC loss and optic neuropathy.[127,128] Cadmium can cause oxidative stress by reducing glutathione levels, which can lead to vascular damage resulting in systemic disorders such as hypertension and renal damage, which can contribute to glaucoma and interfere with calcium homeostasis affecting transmission in RGCs.[129,130] Studies have shown a correlation between OAG and NTG with cadmium blood levels.[131] Lead exposure has been shown to cause RNFL thinning. It can interfere with the generation of the action potential by competitively inhibiting calcium uptake in cells.[132,133] A lower blood manganese and high aqueous zinc levels have also been shown to be associated with greater odds of glaucoma.[134]

## Conclusion

A holistic approach to treating the patient rather than just the IOP is the need of the hour. Recently the role of the allostatic load has gained recognition in defining and objectively measuring the role of multiple stressors in many diseases, including glaucoma.[135] A good history and a complete head-to-toe examination will help in identifying and possibly alleviating these stressors to benefit the patient and improve the overall quality of life. Eliciting patients' understanding of the disease and their concerns and addressing them personally will help in better adherence to treatment.[136] Simple lifestyle modifications can go a long way in better management and a better quality of life in glaucoma patients. Assessing the socioeconomic status of the family and other local factors will help in individualizing management plans and better compliance. It is important for the treating ophthalmologist "to treat the eye as well as the patient behind the eye" and adopt a holistic approach to improve the overall quality of life of glaucoma patients.

## Consent for Publication

Obtained from all the authors.

## Availability of Data and Material

All pertaining data has been provided.

The manuscript has been read and approved by all the authors, the requirements for authorship have been met, and each author believes that the manuscript represents honest work.

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