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Review Article

Glaucoma: Pathogenesis, Screening, and Management

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ABSTRACT

A class of optic neuropathies known as glaucoma is defined by gradual loss of retinal ganglion cells (RGCs) and degradation of the visual field. Despite successful intraocular pressure (IOP)-lowering treatments, it continues to be a major cause of permanent blindness globally.

Millions of people worldwide suffer from glaucoma, which is a major cause of irreversible blindness. It includes a collection of progressive optic neuropathies that are frequently linked to high intraocular pressure and are characterized by loss of retinal ganglion cells and degradation of the visual field. Because of its complicated pathophysiology, varied presentations, and requirement for lifetime care, glaucoma management is still difficult despite advancements in our understanding of the condition. A thorough review that summarizes the most recent findings, highlights significant developments, and suggests areas in need of additional research is desperately needed given the multidisciplinary scope and quickly changing nature of glaucoma research. The goal of this review was to provide a thorough understanding of glaucoma categorization, pathogenesis, screening, and management choices for ophthalmologists, researchers, and healthcare providers.

Keyword: glaucoma, classification, pathogenesis, screening, management.

INTRODUCTION

About 80 million individuals worldwide suffer from glaucoma, which is one of the main causes of permanent blindness and a major public health concern [20]. The number of people with glaucoma worldwide is expected to increase to 111.8 million by 2040 [84]. It includes a collection of disorders that, in spite of their

varied manifestations and underlying causes, eventually cause harm to the optic nerve (ON), retinal ganglion cells (RGCs), and progressive vision loss. Due to the intricacy of glaucoma's pathophysiology and the variety of glaucoma types, a large and constantly growing body of research has been conducted to better understand the disease's causes, risk factors, diagnostic techniques, and available treatments [91].

Because the aqueous humor applies more force per area than normal to the interior surface of the eye, glaucoma is closely linked to elevated intraocular fluid pressure (IOP). Blockages in the eye's trabecular meshwork (TM), which normally serves to drain aqueous fluid from the anterior chamber, may induce glaucoma. IOP rises as a result of aqueous humor buildup brought on by poor drainage. It has been demonstrated that anomalies in the extracellular matrices of the retina and lamina cribrosa are present in glaucomatous eyes with elevated intraocular pressure. These abnormalities lead to impaired function of the optic nerve and consequently worse visual acuity [90].

Numerous risk variables, such as age, gender, smoking history, race, and high intraocular pressure, are linked to glaucoma. According to reports, men are 36% more likely than women to have glaucoma [85]. Age-related increases in glaucoma risk have also been demonstrated [58]. Only 2.2% of white people over 40 have glaucoma, compared to 5.7% of Black people [42]. It is important to note that glaucoma frequently goes untreated, possibly as a result of limited access to glaucoma screening and treatment. According to earlier studies, about 50% of glaucoma patients go undiagnosed [86]. Establishing procedures for screening people for glaucoma risk factors globally is crucial to addressing this public health emergency.

Overview of Glaucoma Types and Classification

A class of progressive optic neuropathies known as glaucoma is characterized by loss of retinal ganglion cells (RGCs) and damage to the optic nerve (ON), which results in permanent vision loss. Anatomical and pathophysiological features, especially the drainage angle (where the cornea and iris meet) and the presence or absence of high IOP, are the main factors used to categorize it.

The drainage angle stays open in open angle glaucoma (OAG), but the trabecular meshwork (TM), the eye's drainage system, gradually deteriorates over time, leading to an increase in intraocular pressure. OAG usually develops gradually and may not show any signs until the ON has been seriously damaged. OAG accounts for between 70% and 90% of all instances of glaucoma. When the drainage angle is blocked or narrowed, angle-closure glaucoma (ACG) develops, which frequently results in an abrupt rise in intraocular pressure and quick, severe symptoms. ACG and OAG are also possible main conditions. Trauma, drugs (such corticosteroids), inflammation, malignancies, or diseases like pigment dispersion or pseudo exfoliation can all lead to secondary glaucoma [28].

Primary congenital glaucoma and other pediatric glaucomas have different causes and manifestations. This type, which causes increased IOP in infancy and presents as buphthalmos, corneal edema, and ON damage, is caused by developmental abnormalities of the anterior chamber angle (ACA), usually resulting from neural crest-derived tissue digenesis [1]. Axenfeld-Rieger syndrome, Peter's abnormality, and other ocular or systemic syndromes that further impair aqueous outflow are frequently linked to secondary developing glaucomas [41]. The categorization of glaucoma aids in comprehending its many causes and directs focused diagnostic and treatment approaches (Figure 1).

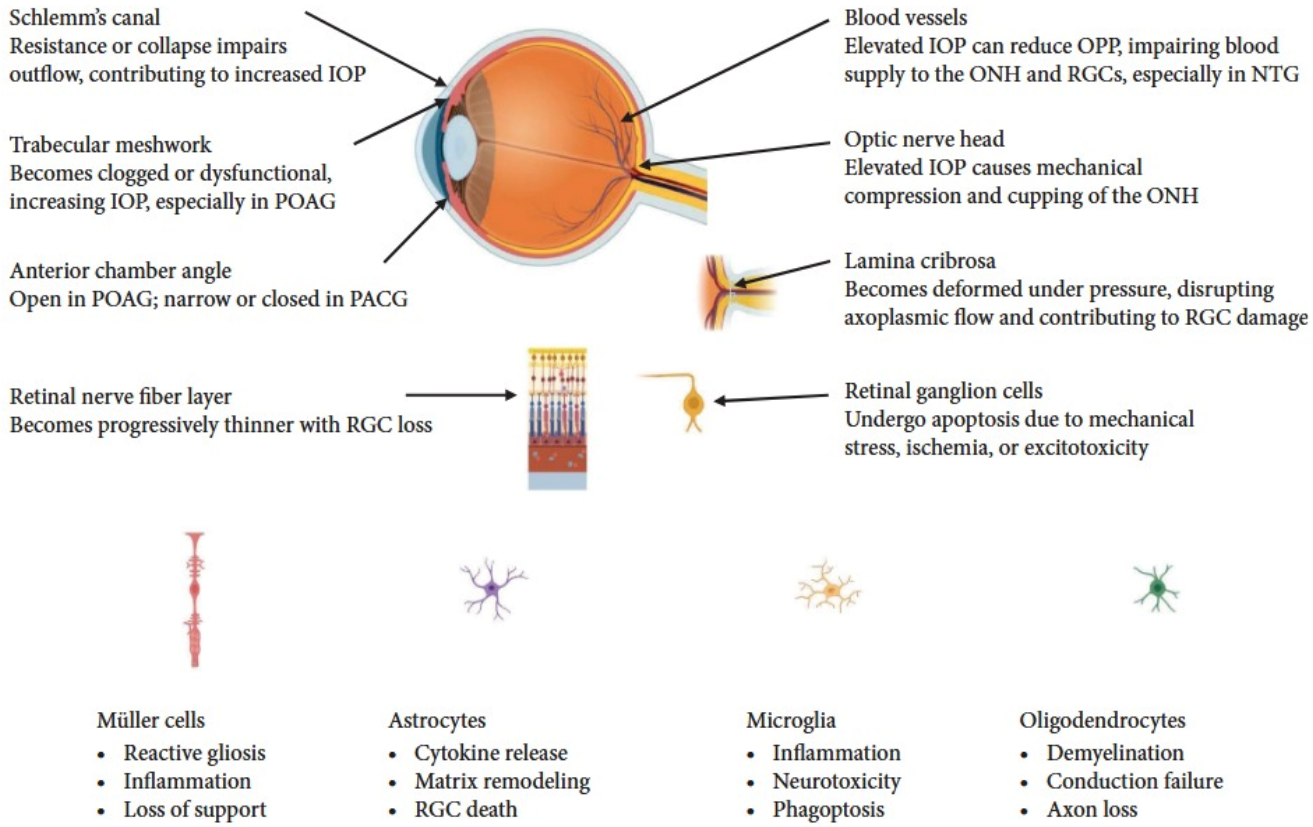

Figure 1: Glial cells are among the many ocular structures impacted by glaucoma, which is mostly caused by increased intraocular pressure and/or decreased ocular blood flow. Intraocular pressure (IOP); normal-tension glaucoma (NTG); optic nerve head (ONH); ocular perfusion pressure (OPP); primary angle-closure glaucoma (PACG); primary open-angle glaucoma (POAG); and retinal ganglion cell (RGC)l **[89].**

Open-angle glaucoma and angle-closure (closed-angle) glaucoma are the two general categories of glaucoma.The area in the anterior chamber between the posterior surface of the cornea and the anterior surface of the iris is known as the iridocorneal "angle." This is where aqueous fluid is typically absorbed into the episcleral venous circulation, mostly through the trabecular meshwork and, to a lesser extent, the uveal and scleral tissue (see Figure 2) **[38].**

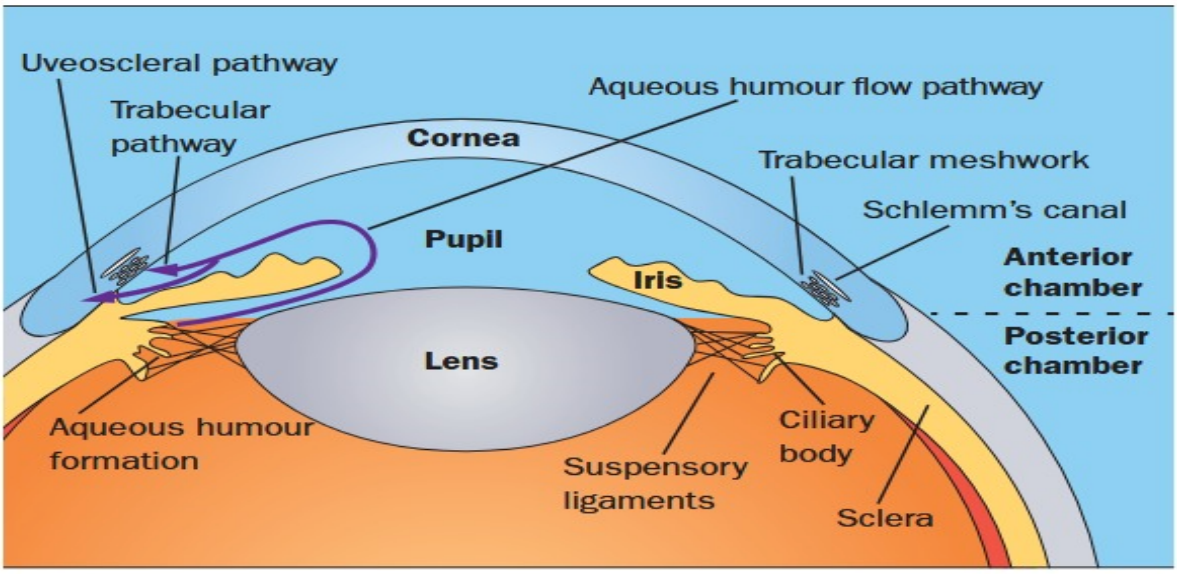

Figure 2: Production and drainage of aqueous fluid[38].

Glaucoma Pathogenesis

It is unclear if optic axon malfunction at the optic nerve head causes apoptosis of retinal ganglion cells (RGC) or if RGC dysfunction and/or death causes optic nerve dysfunction. Does an increase in IOP lead to alterations in RGC somas that ultimately result in apoptosis, or does it cause damage at the RGC axons in the ONH first?

Since elevated IOP alters the eye locally, it makes sense that retrobulbar regions would be less impacted and exhibit fewer alterations. This hypothesis is supported by examinations of retrobulbar regions in elevated IOP models, which have not revealed extracellular accumulations comparable to those observed in the eye [62].

It has been hypothesized that elevated IOP can have detrimental effects by creating a hypoxic environment in the eye after ocular blood flow is reduced (Xu et al., 2019). A decrease in ocular perfusion as a result of reduced blood flow frequently precedes glaucomatous neurodegeneration. Furthermore, normal tension glaucoma is an example of how not all glaucoma patients have increased intraocular pressure. Both increased and normal IOP circumstances might result in ischemia and histological glaucomatous abnormalities. The degeneration of retinal ganglion cells is what unites these disorders. The inner surface of the retina contains the somas of retinal ganglion cells. After passing through the layer of retinal nerve fibers, the axons of RGCs come unite at the optic disc to create the optic nerve. According to research on human patients, damage occurs simultaneously to RGC somas and their axons in the retinal nerve fiber layer [91]. These results suggest that the main site of damage in glaucoma is the retina.

On the other hand, the lamina cribrosa, a structure in the optic nerve head that supports the axons leaving the eye, frequently exhibits early alterations. RGC nerve fibers go via a network of pores in the lamina cribrosa (LC), the mesh-like connective tissue in the optic nerve head, before coming together to form the optic nerve. Supportive glial cells are found along the optic nerve to sustain communication between RGC axons and to offer cellular support. These areas are frequently home to astrocytes, which preserve the health of RGC axons by maintaining ion balances in the extracellular space and remodeling the extracellular environment in addition to performing other maintenance tasks. Astrocyte function surrounding the lamina cribrosa declines in glaucomatous eyes, leading to harmful extracellular matrix remodeling. Pathologic investigations of glaucomatous optic nerve heads in humans and monkeys have revealed several anomalies, including extracellular depositions of collagens and components of the basement membrane [33]. These aberrant deposits have been discovered in laminar pores that were formerly home to RGC axon clusters [62]. When assessing the cup-to-disc ratio (CDR), the aggregation of these depositions can be clinically recognized as optic cupping. CDR is frequently used to gauge the advancement of glaucoma. When the optic cup occupies a greater proportion of the optic disc area than usual, the CDR rises. Increased empty space in the optic nerve head is indicated by elevated CDR. It should not be assumed that glaucoma pathogenesis takes place in the optic nerve head, even if an elevated cup-to-disc ratio is frequently clinically noted in the early stages of glaucoma. Although doctors are currently unable to observe retinal cell layers at the level where changes occur, pathological changes in retinal layers may occur before ONH changes. Further understanding of the start of glaucoma disease may come from the future development and application of clinical instruments to assess retinal cellular alterations.

It seems that the area of the optic nerve head supported by the lamina cribrosa is more vulnerable to variations in intraocular pressure. This region is special because it is the only part of the central nervous system where RGC axons are primarily dependent on surrounding astrocytes to maintain cellular health because they do not have direct contact with local

capillaries [12]. It has been shown that isolated human ONH cells from the lamina crib Rosa express and release neurotropic receptors, suggesting one of their functions in supporting retinal ganglion cells [56].

Local Retinal Changes in Early Stages of Glaucoma

The optic nerve head is not the only organ affected by elevated IOP. As was previously mentioned, an increase in intraocular pressure causes cellular stress, which leads to the activation and hypertrophy of retinal astrocytes. We investigated the retinal location of astrocytic hypertrophy after the experimental rise of IOP using rat glaucoma models. To detect the presence of normal and hypertrophied astrocytes, flat-mounted retinas were immunostained using antibodies against glial fibrillary acidic protein (anti-GFAP), an intermediate filament protein expressed in astrocytes (Figure 3).

Retinal astrocytes start to hypertrophy and their end feet on the blood vessels grow in number and size within 48 hours of excessive IOP (25 mm Hg; normal IOP is 15–16 mmHg) (Figure 3). This indicates hypoxia. Astrocyte hypertrophy was shown to be increased in the same direction as optic axons. The astrocytic structures are thought to be choking optic axons. Importantly, we discovered that astrocyte hypertrophy was shown in the first 24 to 48 hours after IOP elevation in the experimental animal model, whereas optic disc cupping happens several weeks after initial exposure to elevated IOP. Within a week of the IOP being raised, a number of alterations were seen, such as retinal astrocyte hypertrophy, mutant superoxide dismutase overexpression, and osmotic imbalance caused by overexpression of aquaporin [42]. Furthermore, astrocytic end feet are more prevalent on the retinal arteries, a sign of cellular stress. When retinal metabolic stress is present, astrocytes start producing ATP, which causes Ca++ waves to spread and ultimately apoptosis..

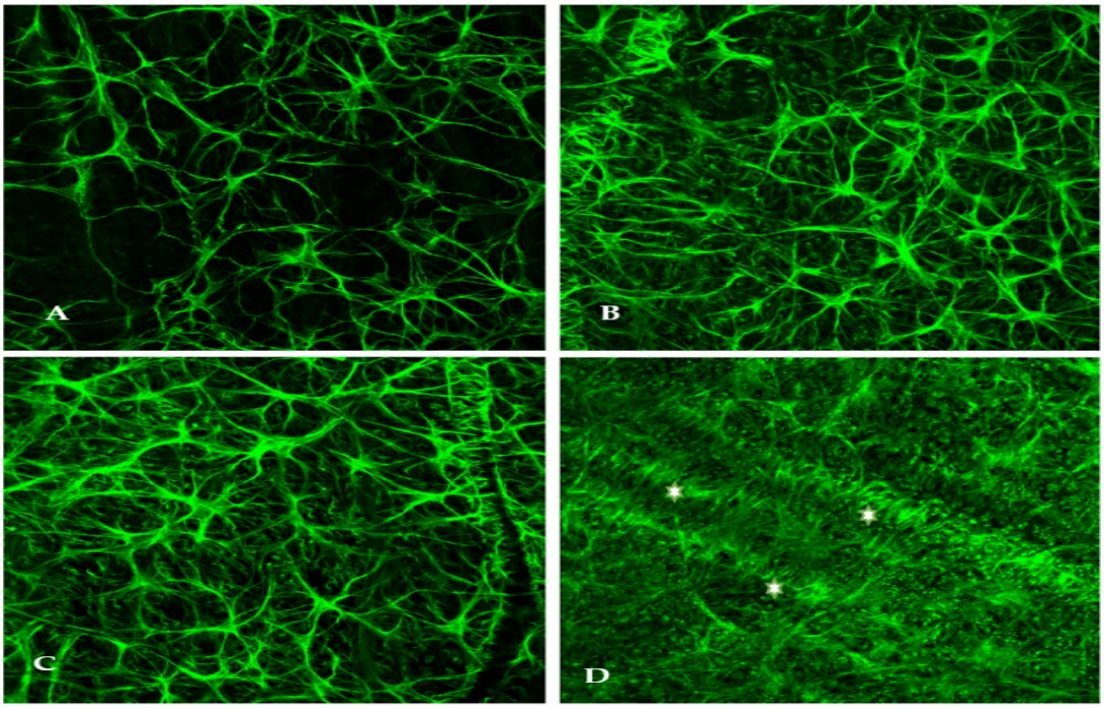

Figure 3: Labelled astrocytes are visible in flat-mounted rat retinas stained with antibodies against glia fibrillary acidic protein (GFAP) at mid-retinal sites. (A) A typical control retina. (B) Four days following an increase in IOP. (C) Seven days following an increase in IOP. (A–C) were captured with a 40X objective. (D) Seven days following an increase in IOP, identical to (C), but captured with a 10X lens. Within four days following an increase in IOP, high levels of GFAP expression and astrocytic hypertrophy emerged. The stars in (D) indicate areas where bundles of optic fibers travel. Astrocyte

proliferation is in line with the axons of retinal ganglion cells [42].

The health of retinal ganglion cell somas' axons in the ONH won't matter because the axons will surely degenerate as a result of continuously high IOP and stress-related alterations. The idea that glaucomatous neurodegeneration starts in the retina and progresses to the optic nerve head is further supported by this. As demonstrated, regions of high astrocyte density also include vast bundles of axons, so strangling is still a possibility even though astrocyte hypertrophy is not always the cause of RGC axon mortality. A study of astrocyte morphology in the early stages of glaucoma supports these findings. Smaller astrocyte processes start to proliferate and penetrate regions close to retinal ganglion cell axons [50].

How are retinal ganglion cells harmed by elevated intraocular pressure? The intraocular pressure is kept between 10 and 20 mmHg higher than the surrounding air pressure. During activities like flying and diving, changes in the external pressure of the environment might cause vision deterioration [39]. A glutamate excitotoxicity mechanism of glaucomatous neurodegeneration has been linked to transient receptor potential channel vanilloid 4 (TRPV4). Both mammalian bipolar cells and retinal ganglion cells carry the pressure-sensitive receptor TRPV4. The TRPV4-linked cation channel opens as a result of mechanical membrane movement brought on by pressure changes [25]. Glutamate release onto retinal ganglion cell synapses is probably increased on retinal bipolar cells by TRPV4-induced cation inflow. This is corroborated by a study by Gao et al. [25], which showed that retinal ganglion cells showed dose-dependent death after prolonged exposure of mouse retinas to TRPV4 agonists. Additionally, research has demonstrated that TRPV4 increases the minimum stimulation required for the RGC to activate as well as the rate at which retinal ganglion cells fire [25]. Another potential mechanism for the pathophysiology of glaucoma is TRPV4-mediated glutamate excitotoxicity of RGCs in response to high IOP. Furthermore, this mechanism is consistent with the pattern of visual loss seen with glaucoma. RGC death in the retinal periphery causes peripheral vision to deteriorate in the early stages of glaucoma vision loss. Glutamate released by bipolar cells may cause excitotoxicity in RGCs. While there is less signal convergence in the central retina, retinal ganglion cells in the periphery regions of the retina that correlate to peripheral vision get convergent inputs from several bipolar cells [80].

As the thickness of the retinal nerve fiber layer diminishes, glaucomatous degeneration can also be seen. Glaucomatous visual field abnormalities are directly associated with RGC dysfunction and weakening of the retinal nerve fiber layer [66]. Furthermore, there is compelling evidence that one of the first tissues to be impacted by an increase in intraocular pressure is retinal tissue. High-resolution angiograms have shown that poor perfusion starts in the retina and spreads to nearby regions like the choroid. While choroid vascular area density reaches 50% of baseline at 70 mmHg, local perfusion, measured as vascular area density, first declines in the retina and reaches a level 50% of baseline at only 60 mmHg [94].

Artificial Intelligence and Digital Health

Artificial intelligence (AI) has shown previously unheard-of promise in glaucoma diagnosis, disease progression prediction, and surgery evaluation. AI improves clinical decision-making through more precise analysis, treatment strategy optimization, and individualized patient management thanks to technological breakthroughs. It is a useful tool for enhancing glaucoma care results because of its capacity to integrate multimodal data and identify subtle disease trends.

• Diagnosis of Glaucoma

In order to analyze fundus photos, Phene et al. [67] created a deep learning model, trained it on a sizable dataset, and verified its effectiveness across several cohorts. By recognizing important characteristics such an elevated cup-to-disk ratio, RNFL abnormalities, and neuroretinal rim notching, the model

successfully identified referable glaucomatous optic neuropathy (GON). Notably, it outperformed several glaucoma experts. This AI model has the potential to improve early detection and decrease missed diagnoses in glaucoma screening and diagnostic support, especially in situations with limited resources. In the meantime, Chiang et al. [16] achieved an AUC of 0.99 by using wide-field OCT to concurrently record three-dimensional structures of the macula and optic nerve head. Another work (contribution 8) used a ConvNeXt_Base model in conjunction with a convolutional block attention module (CBAM) to diagnose glaucoma in high myopia. The results showed an AUC of 0.894, indicating the viability of large-scale, quick screening using deep learning. To further enhance the model's generalizability, the study also highlighted the necessity of incorporating more varied datasets, such as OCT and visual field test findings. Recent research (contribution 9) has shown that Few-Shot Learning (FSL) in conjunction with wide-field optical coherence tomography angiography (WF-OCTA) can greatly improve diagnostic accuracy even in data-scarce scenarios, addressing the issue of AI diagnostic performance requiring large datasets. For example, the AUC reached 0.93 with data from just 195 eyes, surpassing the 0.80 AUC of conventional deep learning techniques. This demonstrates how AI tools can promote innovative imaging diagnosis.

• Prediction of Disease Progression

Beyond diagnosis, AI has drawn interest in forecasting the course of glaucoma. According to Mohammadzadeh et al.[60], the AUC for predicting visual field development increased to 0.894 when RNFL thickness was integrated with a set of three optic disk pictures (ODPs) using ResNet-152. In a different study, Mohammadzadeh et al. [61] analyzed the baseline and the most recent ODP using ResNet-50, obtaining an AUC of 0.926 with outstanding sensitivity and specificity. Additionally, AI applications have incorporated genetic screening (contribution 10). For example, adding certain single-nucleotide polymorphisms (SNPs) of the LOXL1 gene, like rs2165241 and rs1048661, to risk models for exfoliation glaucoma (PXG) increased the model's AUC by 10. This illustrates how more accurate, individualized treatment plans can be made possible by combining genetic testing with AI. Furthermore, a substantial causal association between type 2 diabetes (T2D), fasting glucose (FG) levels, and the risk of POAG was found by another study (contribution 11) using Mendelian randomization analysis. POAG risk was observed to be increased by T2D (OR = 1.06), with FG having an even greater effect (OR = 1.19). These findings imply that metabolic imbalance could be a factor in the development of glaucoma. The accuracy of AI-based glaucoma progression models should be improved by adding systemic and genetic risk variables found in genome-wide association study (GWAS) and Mendelian randomization (MR) research, given the growing relevance of AI in disease prediction (contribution 11).

Evaluation of Surgical Outcomes

AI has great promise for assessing glaucoma surgical results. Birla et al. [9] employed machine learning algorithms to analyze preoperative and intraoperative characteristics in trabeculectomy for juvenile open-angle glaucoma (JOAG). The primary factors influencing five-year postoperative success rates were found to be age, preoperative IOP, Tenon's capsule thickness, mitomycin C (MMC) usage, and surgical procedures. The study demonstrated that three distinct algorithmic models achieved accuracy rates of 86.45%, 87.47%, and 87.44%, with average AUC values of 0.876, 0.926, and 0.922, using an IOP reduction ≥ 50% as the success criterion. These models performed exceptionally well in differentiating successful from unsuccessful cases.

However, Banna et al. [5] assessed how well various machine learning models—such as random forest, support vector machine, artificial neural network, and logistic regression—performed in forecasting one-year surgical success rates for patients with refractory

glaucoma. With an accuracy of 68% and an AUC of 0.74, the results demonstrated that random forest fared the best. The study also discovered that the results of trabeculectomy may be impacted by systemic health variables, such as a history of myocardial infarction.

Using data from electronic health records (EHRs), Barry and Wang [6] created a number of models that forecast the results of several glaucoma procedures, such as trabeculectomy, MIGS, and drainage device implantation. With an accuracy of 75.5% and an AUC of 76.7%, the random forest model outperformed the other models in the study, which included 2398 surgical cases. Notably, the model showed a higher predictive ability for postoperative IOP control (AUC = 86%), but a comparatively lower ability to predict surgical failure or increased postoperative medication requirements. This suggests that different AI models may be needed to optimize the results for different prediction targets.

Improving AI model performance requires integrating multidimensional data, particularly when taking into consideration a variety of patient features, such as systemic health issues. AI has demonstrated significant promise in increasing surgical success rates and lowering postoperative complications, providing a route toward individualized patient care. Clinical practice is nevertheless hampered by issues including data standards, privacy issues, and the difficulty of processing multimodal data. To fully realize AI's promise in glaucoma

Screening Glaucoma

Screening and diagnosis of Glaucoma

Damage to the optic nerve and retinal nerve fiber layer is the hallmark of glaucoma, a chronic progressive optic neuropathy that can result in permanent loss of peripheral or central vision. The only known modifiable risk factor is intraocular pressure. A family history of glaucoma, non-white race, and advanced age are additional significant risk factors. Patients may be predisposed to glaucoma by a number of systemic medical disorders and drugs, such as topiramate, corticosteroids, anticholinergics, and some antidepressants. Open-angle and angle-closure glaucoma are the two main types of glaucoma. Perimetry, optical coherence tomography, and intraocular pressure measurements are diagnostic tests used to detect glaucoma and track the disease's progression. Reducing intraocular pressure is a key component of glaucoma treatment. This can be accomplished using laser and incisional surgical methods, as well as several classes of glaucoma drugs [82].

Primary open angle glaucoma (POAG)

Examining the anterior chamber angle structure and categorizing the condition as open or closed angle glaucoma is the most fundamental way to classify glaucoma. Both open and closed angle glaucoma can be further divided into primary and secondary etiologies, with secondary glaucoma arising from trauma, other ocular or systemic diseases, or the use of specific medications. In North America, POAG is the most prevalent type of the illness. It is defined as the onset of glaucomatous optic neuropathy in the absence of an underlying etiology[23]. Although it can be quite asymmetric, the disease is typically bilateral. The definition of glaucoma no longer includes elevated intraocular pressure (IOP); in fact, it is estimated that up to 50% of people with POAG have IOPs less than 22 mmHg at presentation. Despite this, intraocular pressure continues to be the most significant modifiable risk factor for glaucoma and a major predictor of the development of visual loss [22]. In fact, the likelihood of developing optic nerve injury increases with increasing IOP. On the other hand, reducing IOP can considerably postpone the development of glaucoma and minimize the chance of its progression [51].

POAG is frequently characterized to as a "silent thief of vision" because it is primarily asymptomatic, but if the condition is identified early on, vision loss may be halted. According to a 2010 World Health Organization report, 7.6 million persons have glaucoma-related blindness: 3.3 million from ACG and 4.3 million from OAG. According to Quigley and Broman [71], there will be 5.9 million blind persons from OAG and 11.5 million blind people from glaucoma by 2020.Due in part to

the substantial population expansion in these regions, the most of this increase in blindness is expected to occur in Asia and Africa [85].

According to Heijl et al. [32], POAG often progresses slowly, but a tiny percentage of patients will do so quickly. Understanding the natural history helps determine the proper follow-up intervals for individuals with or at risk of glaucoma, as well as the extent of potential harm if treatment is postponed. One group of patients with early to moderate glaucoma who had not yet begun therapy was included in both the Collaborative Normal Tension Glaucoma Study (CNTGS) and the Early Manifest Glaucoma Trial (EMGT) [55]. According to both investigations, people with high tension POAG (HTG) advanced significantly more quickly than people with normal tension glaucoma (NTG) [32].

The high pressure group (HTG) in the EMGT had a median time to glaucoma development of 3.5 years, while the NTG group had a median duration of 5 years. Exfoliation syndrome patients typically advanced far more quickly and earlier than those with primary open angle glaucoma. However, there was a few that advanced rather quickly in both the HTG and NTG groups [32]. Early detection of "rapid progressors" is crucial for initiating or changing treatment quickly and aggressively to stop more vision loss. Additionally, the EMGT discovered that, generally speaking, older people had much faster progression rates (-1.48dB/year) than younger people (-0.60dB/yr), underscoring the possibility that progression rates may fluctuate with time. Furthermore, not everyone experienced progression; after six years, roughly 75% of the HTG cohort and 56% of the NTG cohort made progress. On the other hand, 93% of exfoliation syndrome patients made progress [32].

50% of eyes with NTG showed deterioration after 5 to 7 years, according to the CNTGS, which examined the natural history of untreated glaucoma with IOP under 21 mmHg and discovered a progression rate comparable to the EMGT. Once more, the majority advanced slowly, but the rate of decline varied greatly, ranging from -0.2dB/year to -2.0dB/year. The latter is a catastrophic pace that is expected to cause severe functional impairment in a comparatively short amount of time [32].

Strong risk factors

1. Intraocular Pressure

Elevated IOP: IOP is one of the biggest risk factors for the development and progression of glaucoma, yet it is still the only one that can be easily changed [54]. Although "elevated" and "normal" IOP are difficult to distinguish, there is a well-established link between elevated IOP and optic nerve injury. Based on two standard deviations from the population mean of 15 mmHg, the conventional definition of high IOP is ≥21 mmHg. High IOP was found to be a significant risk factor for glaucoma progression in the Ocular Hypertension Treatment Study (OHTS), with a 10% relative risk for every 1 mmHg increase over baseline IOP. According to Leske et al. [51], the EMGT also discovered that IOP was a significant risk factor for advancement in those with recently diagnosed glaucoma, with a hazard ratio rising by 11% for each 1 mmHg increase in IOP. Another risk factor for primary open angle glaucoma is inter-eye asymmetry in IOP ≥2 mmHg [52]. The diagnostic importance of IOP changes detected by in-office measures is a topic of debate in the literature [30]. detection of the risk of progression is probably more significant than detection of the disease.62 The importance of IOP variation as a risk factor for glaucoma may be better understood with continuous 24-hour IOP monitoring [21].

2. Age

Increasing Age: Age is a significant risk factor for the onset and progression of POAG, according to several population-based studies [17]. According to the Baltimore Eye Survey, those over 70 have a 3.5-fold higher prevalence of POAG.9 The EMGT discovered that the prevalence of glaucoma increased with age, and the OHTS demonstrated that age above 55 was a major predictor of POAG [51]. According to Quigley et al. [70], age has also been proven to be a significant risk factor in a number of ethnic

groups, with Hispanics having the greatest prevalence of POAG among all races for people over 80.

3. Race

a. African Origin: According to **Leske et al.** [54], POAG is four to six times more common in people of African origin and in people of African descent from the US and the Caribbean than in Caucasians. Additionally, it has been proposed that African Americans are more likely to develop POAG at a younger age and to go blind as a result of the condition [75].

b. Hispanic Origin: POAG seems to be more common among Hispanics than among Caucasians, particularly among those over 60 **[70].**

c. **Asian Origin:** According to recent demographic research, POAG is more common among Asian and Asian Indian ethnic groups than previously believed, with prevalence rates that are comparable to those of Caucasians [85].North Koreans and Japanese people are more likely than Caucasians to have NTG.69, 70 POAG and NTG are growing issues that should not be disregarded, even while ACG is still a major worry among Asian ethnic groups [85].

Important risk factors

Low Blood Pressure:

• Low blood pressure and inadequate ocular blood flow have been linked to POAG, particularly NTG[59]. Regardless of baseline IOP, the EMGT discovered that low blood pressure was a significant risk factor for glaucoma advancement in individuals [55]. A patient may have low blood pressure due to overtreatment for systemic hypertension or due to a physiological condition. It is crucial to determine the kind and quantity of medication, as well as the time of day it is given, if a patient undergoing glaucoma evaluation is also receiving treatment for high blood pressure [45].

• Low ocular perfusion pressure (OPP) has been linked to progressive glaucomatous optic nerve injury by causing changes in blood flow at the optic nerve [59]. In a clinical environment, it is possible to rapidly assess diastolic ocular perfusion pressure (DOPP) to determine which patients are most likely to have low vascular perfusion to the optic nerve. This straightforward calculation is subtracting the diastolic blood pressure (DBP) from the intraocular pressure (IOP) (DOPP = DBP - IOP). According to the Baltimore Eye Survey, glaucoma prevalence was significantly correlated with low DOPP [59]. DOPP levels below 56 have been proposed as a helpful cutoff point for identifying individuals who are more likely to develop progressive glaucomatous optic neuropathy [68].

Myopia:

• High myopia: Research and meta-analyses have shown that glaucoma is much more common in those with higher myopic refractive error than in those with mild myopia or emmetropia [93]. This correlation is a risk factor for the onset and advancement of POAG. According to the underlying theory, people with higher axial length and severe myopia have less scleral support for retinal ganglion cells at the lamina cribrosa, which makes the optic nerve more vulnerable to glaucomatous injury [93].

Diabetes Mellitus:

• The literature has contradictory reports regarding the link between diabetes mellitus and glaucoma. The OHTS's surprising results revealed that those who self-reported having diabetes actually had a lower chance of developing POAG, which would imply that diabetes was not chosen as a predictive factor. Nonetheless, a 2015 meta-analysis that was published in the American Academy of Ophthalmology Journal found that a markedly higher risk of glaucoma was linked to diabetes, the length of diabetes, and raised fasting blood glucose levels. Additionally, they discovered that a slightly higher IOP was linked to diabetes and raised fasting blood glucose [95].

Vascular Dysregulation

•Two disorders that have been found to be risk factors for the onset and advancement of glaucoma are migraine and Raynaud syndrome. These disorders may be linked to poor autoregulation of blood flow to the optic nerve,

which puts the tissue at risk for hypoxia and reperfusion damage..

•Sleep Apnea: Research has indicated a connection between POAG and sleep apnea **[31].** The precise clinical relevance of this connection and whether treating sleep apnea can decrease the course of glaucoma are still unknown.

Angle-closure glaucoma (ACG)

Angle-closure glaucoma (ACG) is a collection of disorders in which the anterior-chamber angle closes either by adhesion (synechiae) or reversibly (appositional). Both acute and chronic forms of this angle closure are possible. In the acute type, the iris suddenly blocks the trabecular meshwork, usually through the pupillary block mechanism, causing the IOP to rise quickly [47].

There are various classifications for primary angle closure disease (PACD). The patients were categorized using the International Society of Geographical and Epidemiological Ophthalmology (ISGEO) categorization system. There are three phases to primary angle closure conditions. The first step, called Primary Angle Closure Suspect (PACS), is when the posterior trabecular meshwork may come into contact with the peripheral iris, potentially resulting in angle closure. An occludable drainage angle and indications that the peripheral iris is blocking the trabecular meshwork are characteristics of the second stage, Primary Angle Closure (PAC). Peripheral anterior synechiae (PAS), increased intraocular pressure (IOP), glaucomflecken (lens opacities), iris whorling (distortion of the radially orientated iris fibers), and excessive pigment deposition on the trabecular surface are some of these symptoms. When PAC is accompanied by signs of glaucoma, such as optic disc injury, the last stage, Primary Angle Closure Glaucoma (PACG), develops [34]. When angle closure increases intraocular pressure to the point where glaucomatous optic disc damage results, secondary angle closure glaucoma develops. Usually, an underlying, identifiable pathologic aetiology—such eye neovascularization or uveitis—causes this illness.

Pathogenesis

Pupillary block

This syndrome results in iris bowing and appositional closure of the angle due to an elevated pressure differential between the anterior and posterior compartments of the eye caused by restriction of aqueous flow .Aqueous humor normally passes between the anterior lens and the posterior iris on its way from the posterior to the anterior chamber of the eye. This flow is usually facilitated by a pressure differential of roughly 0.23 mmHg between these chambers. On the other hand, the iris may bow forward into a convex form when this pressure differential increases. The iris may come into contact with the trabecular meshwork due to its convexity, which could prevent aqueous humor from draining. This obstruction raises the possibility of PACG and can result in PAS. Because the pupil is closer to the anterior lens capsule in eyes with shallow anterior chambers, pupillary block is more likely to occur. Furthermore, studies have demonstrated that iris thickness can influence the pressure differential between the anterior and posterior chambers; darker irides may be more vulnerable to pupillary block, according to some research [48].

Angle crowding

The phenomenon of angle crowding causes angle closure when the iris is compressed between the trabecular meshwork and another anatomical structure. This is most noticeable in people with a plateau iris configuration, which primarily affects women between the ages of 30 and 50, particularly those who have hyperopic refractive defects. According to Wright [92], ultrasonic biomicroscopy (UBM) was used to diagnose plateau iris in 30% of eyes suspected of PAC following laser iridotomy. A broad or forward-positioned ciliary body that presses the iris root against the trabecular meshwork is a characteristic of plateau iris morphology.

Secondary angle closure glaucoma

Anterior lens movement

Primary angle closure (PAC) is mostly influenced by the lens, and more anteriorly positioned lenses increase iris convexity [19].

This is shown in diseases such phacomorphic glaucoma with progressive cataracts and choroidal growth in malignant glaucoma, such as microspherophakia and ectopia lentis [19].

Absolute pupillary block

It happens when 360-degree posterior synechiae, in which the iris attaches to a crystalline lens, an intraocular lens, capsular remnants, or the vitreous face, totally block the passage of aqueous humor via the pupil [72].

Without pupillary block

Angle-closure can be caused by either (a) the contraction of an inflammatory, hemorrhagic, or vascular membrane in the angle, which causes PAS, or (b) the forward displacement of the lens-iris diaphragm, which is frequently linked to anterior rotation and ciliary body enlargement. For instance, in neovascular glaucoma, the fibrovascular membrane closes the angle through synechiae (Figure 4) [72].

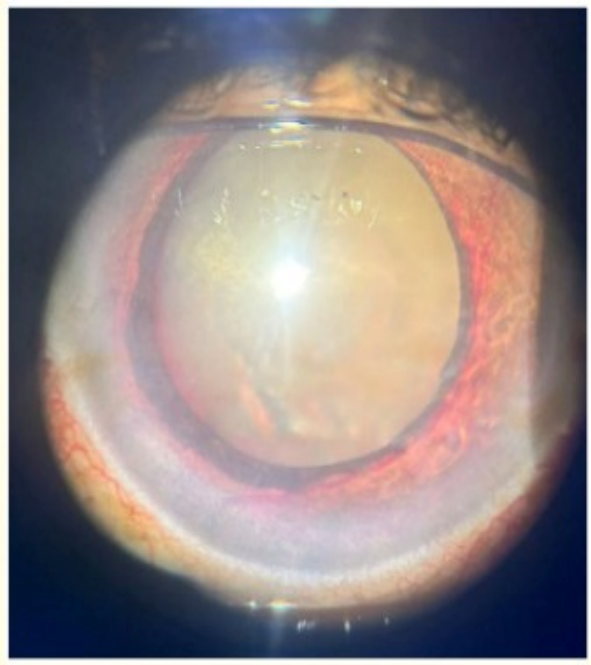

Figure 4: Shows neovascular glaucoma with florid neovascularization of Iris[72].

Management

When to consider treatment

Setting target pressures and starting therapy are the next steps in glaucoma care, which culminates in risk assessment and glaucoma diagnosis (preferably at the pre-perimetric stage). Long-term reassessments are planned according to the disease's severity, rate of advancement, risk of side effects, and patient-specific considerations like non-adherence issues . Although there is a compelling argument for starting treatment with trabeculoplasty, the traditional care strategy starts with topical medicines, then selective laser trabeculoplasty, and finally surgery [96]. The needs, values, and abilities of each patient will ultimately determine where to start, along with other considerations including access to care. It is obvious that managing any illness, especially a chronic one, takes careful thought on a number of levels. It is crucial to stay up to date on the data regarding disease diagnosis, treatment risks and benefits, therapy adherence rates, patient-reported outcome concerns, and health-related quality of life metrics .

The prevalence of ocular surface disease in the glaucoma-affected population is another crucial factor. When ocular surface illness is present, not only does adherence to topical medication probably deteriorate, but if the ocular surface disease is not properly controlled, IOP management may also suffer[7]. To lessen the exposure of the ocular surface and anterior chamber tissues to benzalkonium chloride (BAK), preservative-free (at least benzalkonium chloride-free) formulations should be taken into consideration early in the care strategy. Fixed combination treatments improve adherence while lowering preservative exposure and addressing wash-out-related issues [40]. There is currently no specific treatment for glaucoma; instead, intraocular pressure reduction is used to help lower the risk of progression.

In the end, it is up to the individual to decide how to be treated. Every individual must receive comprehensive counseling regarding the advantages and disadvantages of treatment as opposed to close observation in the absence of treatment. Make sure a family member or caregiver is able to attend, particularly for patients who may find such a decision difficult. It is advised that the counseling and informed consent process be thoroughly documented.

IOP Lowering for glaucoma

The only clinically proven way to halt the progression of glaucoma is still to lower intraocular pressure. Remember that not everyone with glaucoma has elevated IOP, and not everyone with elevated IOP (ocular hypertension; OHT) develops glaucoma. Therefore, until a threat to visual function has been established, therapy for open angle glaucoma is typically not started. This could occur when a person with a high-risk profile for the development of glaucoma is detected, or when there is verified structural damage to the optic nerve or functional loss of visual field. The ultimate objectives of treatment should be to maximize health-related quality of life (HRQoL), maintain functional vision for everyday activities, and be aware of a person-centered model to balance the individual's goals and life expectancy with their risk profile .

For the medical treatment of glaucoma, a number of pharmacological classes with several medicines in each class are currently available. Additionally, new compounds and innovative delivery methods are being continuously researched, and they will probably soon change our existing therapy algorithms. Numerous randomized clinical trials have proven the efficacy and limits of IOP-lowering therapies [53]. Each class of drug will take these aspects into account independently.

Target pressure

Choosing a "target" intraocular pressure is part of a clear management strategy that should be created before beginning treatment. The initial IOP that is expected to stabilize the disease's progression to the point where it will lessen the danger to visual function is known as the target pressure. Every patient has a different target IOP, and every eye is different as well. Our decision-making is influenced by randomized control clinical studies, which emphasize the significance of establishing a target IOP that most accurately represents the disease's stage and the possibility of reducing progression **[51].** In actuality, nonetheless, it is impossible to guarantee that keeping the target IOP will accomplish that objective. In fact, the target pressure is only a mathematical construct based on a "best guess" scenario, and the only way to accurately ascertain the rate of progression for a particular patient—which in turn determines whether the target IOP was adequate—is to analyze long-term, repeated measures of structure and function. Setting a goal pressure, however, is still a useful place to start since it establishes a fair value from which critical reevaluation can be evaluated throughout time. As a result, it's critical to remember that a target pressure is a dynamic value. It is probably not required to modify treatment to obtain that predetermined value if the measured IOP is not reaching the target but little to no indicators of progression are seen. If clinically substantial disease progression is identified, it doesn't matter if the measured IOP is at target or not [2]. Before making changes to therapy in the event of progression, adherence to treatment should be carefully considered. Figure 5 shows a simplified flow chart that illustrates how to use target IOP appropriately.

The target pressure construct has limits. Many patients have a peak IOP that is not recorded during office hours, as was previously mentioned [15]. Larger variations in IOP have been linked to the advancement of the disease and should always be taken into account when reviewing data, in addition to being crucial for determining the goal pressure [74].

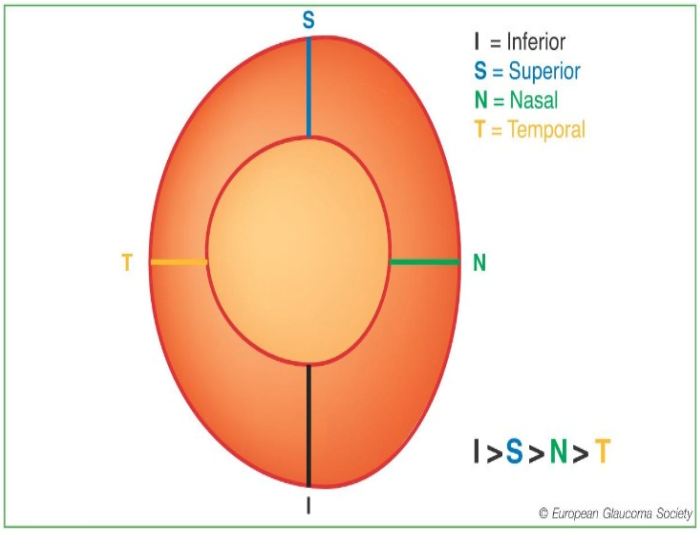

Figure 5: Monitoring glaucoma using target pressure [76].

To create a somewhat accurate estimate of the baseline IOP, a sufficient number of IOP measurements must be gathered. As previously stated, 24-hour IOP tests are currently impractical in the majority of therapeutic situations, but they would be extremely helpful in evaluating a patient's condition. As a result, at least two measurements should be made as early in the morning as feasible, and at least three IOP readings should be obtained at various periods of the day. Other suggestions call for at least two to three visits with four to six measurements taken at various times of the day. After glaucoma is classified as mild, moderate, or severe (Table 1), the goal intraocular pressure (IOP) can be determined by lowering IOP more for individuals at higher risk of progression and less for those at reduced risk. The goal is often to drop IOP by as little as 20% in mild/low risk settings and as much as 50% in severe/high risk scenarios, using the highest IOP reading as a pre-treatment baseline (see Table 1). Young age is one of the other risk factors that should be taken into account [26].

Stage disease	Suggested initial target pressure	Consider lowering an additional 10% if:
Mild damage	20-30% lowering	• <50 years of age • African North American descent • Sibling with advanced glaucoma
Moderate damage	30-40% lowering	
Severe damage	40-50% lowering	

Table 1: Setting Target IOP Based on Stage of Glaucomatous Damage [26].

A THERAPY

When treating glaucoma, starting a medicinal intervention should not be done hastily. Treatment is typically continued for the rest of one's life after it begins. The following elements should be taken into account when choosing an intervention: knowledge of the treatment's effectiveness, advantages, and risks; the frequency of side effects and the emergence of treatment intolerance; the various factors influencing each patient's adherence to therapy and the risks associated with non-adherence; and the capacity to perform routine follow-up.

The monocular medication trial, which compares a treated to an untreated eye to distinguish therapeutic IOP change from spontaneous fluctuation, was used for many years in an effort to evaluate treatment efficacy [8]. The validity of this comparison relies on several presumptions, such as that each eye fluctuates symmetrically, that fluctuations are reproducible, and that the short-term reaction to therapy in one eye may reliably anticipate the long-term response of both eyes. However, researchers have recently questioned the veracity of these presumptions. To establish a reliable baseline and evaluate the effect of therapy on both eyes, it is currently recommended to take multiple IOP readings before and after treatment [43].

Selective laser trabeculoplasty (SLT) has recently been demonstrated to be a viable first-line treatment for glaucoma, whereas laser trabeculoplasty was first thought of as a treatment alternative to defer incisional surgery [96]. In fact, SLT exhibits a favorable safety profile, does away with preservative exposure and the requirement to follow a treatment plan, and has one-year efficacy data that is on par with the prostaglandin analogue class of drugs [24]. The therapy's short-term effectiveness is one of its main disadvantages, however there is evidence that some people, such as those with high baseline IOP and those who responded well to the first surgery, may benefit from repeat SLT [4]. In an effort to lessen side effects, newer types of laser trabeculoplasty are being studied [88].

First-line therapy considerations

Prostaglandin analogues

According to Ishida et al. [37], prostaglandin analogues are powerful medications that have an unparalleled ability to lower intraocular pressure (IOP) by 31 to 33%. Effectiveness during a 24-hour cycle, necessitating only one daily dosage, is the second clear benefit. Although they take three to four hours to start working, they peak about eight hours later, therefore it is best to take them at night.319 Any time of day that will enable good adherence is preferred to simply continuing the nighttime administration at the risk of poor adherence; however, nighttime use is generally advised in an effort to ensure that the peak effectiveness coincides with the early morning hours when IOP is assumed to be highest.

In contrast to many other glaucoma medications, the main mechanism of action is increased outflow facility via remodeling of intercellular spaces in the uveoscleral pathway. Although this is advantageous for the management of intraocular pressure in chronic open angle glaucoma, these drugs are generally not helpful in situations of acutely elevated IOP. Although they are rare, systemic side effects can include rash, muscle or chest pain, upper respiratory tract infections, colds, and the flu [64]. Conversely, conjunctival hyperemia, iris color changes (particularly hazel, mixed-color grey, or light brown irides), hypertrichosis, and prostaglandin-associated periorbitopathy (PAP; periocular skin pigmentation and deepening of the upper eyelid sulcus, ptosis, and appearance of enophthalmos) are common local effects [65]. The patient's adherence to therapy may be impacted if thorough counseling of their potential is not sufficiently communicated, even though the practitioner may consider these localized adverse effects to be cosmetic. It is generally not advised to use prostaglandin analogues for monocular therapy. Although people who have a history of uveitis, cystoid macular edema, or recurrent herpes simplex keratitis should exercise caution, there is no proof that these illnesses are causally related. Prostaglandin analogues should continue to be used in the treatment plan for individuals with uveitic glaucoma because of their effectiveness in reducing intraocular pressure in uveitis patients and the minimal risk of these uncommon sequelae. The prostaglandin analogues are so successful that they cannot be disregarded in the treatment of uveitic glaucoma, even though they might not be the first choice for individuals with these risks [36].

The three primary prostaglandin analogues (latanoprost 0.005%, travoprost 0.004%, and bimatoprost (a prostamide) 0.01% and 0.03%) all significantly reduce intraocular pressure, however bimatoprost may respond better overall [63].

Travoprost was created using Sofzia, a less hazardous preservative, in recognition of the need for BAK-free, if not entirely preservative-free, formulations for the ocular surface. Before concluding that the drug class as a whole is ineffective in a specific patient and switching to alternate, possibly less effective rather than concurrent agents, it may be wise to switch within the class if one agent in this class does not function as expected due to potential individual differences in receptor populations [27]. All three prostaglandin analogs are marketed as fixed-combination (FC) medicines with timolol 0.5%. There is evidence that the bimatoprost/timolol FC lowers IOP more than the other two, and these FC reduce IOP more than their individual prostaglandin analogues [57].

The proportional reduction in the frequent side effect of hyperemia in the FC products when compared to prostaglandin analogue monotherapy is also noteworthy. Tafluprost 0.0015%, a more recent medication in this family, is accessible in several countries across the globe and is probably going to be offered as an FC agent with timolol [35]. This medication's unique benefit is its preservative-free formulation, which comes in unit dose vials.

Second-line or adjunctive treatment options

Beta-adrenoceptor blocking agents

For many years, beta-blockers, also known as beta-adrenoceptor blocking medications, have

been the mainstay of glaucoma treatment. Even while once-daily or twice-daily dose significantly lowers IOP (~27%, range 19 to 29%), their usage as a first-line therapy has been effectively overtaken by prostaglandin analogue medicines because of their effectiveness in lowering IOP and relative lack of systemic adverse effects. Reduced aqueous production is the beta-blockers' main mode of action. They can be roughly classified as either cardio-selective, which preferentially targets beta-1 receptors (betaxolol 0.5% solution and 0.25% suspension), or non-selective, which targets both beta-1 and beta-2 receptors (timolol 0.25% and 0.5%, levobunolol 0.25% and 0.5%). Betaxolol is often administered twice daily, whereas the nonselective medications may only be administered once. When a once-daily dosage is provided, morning instillation is advised because aqueous production is physiologically reduced at night. In contrast to prostaglandin analogues, the majority of the anticipated IOP reduction with timolol will happen within two weeks [77].The well-known systemic side effects of beta-blockers include weariness and impotence, precipitation of heart block, and aggravation of lung diseases such asthma and chronic obstructive pulmonary disease. Stinging and diminished ocular feeling are examples of local side effects.

In this class, the beta-blocker timolol is regarded as the gold standard. Therefore, the three primary prostaglandin analogues, the alpha-adrenoceptor agonist brimonidine, and the carbonic anhydrase inhibitors (CAIs) dorzolamide and brinzolamide can all be found in fixed combination with 0.5% timolol. There is also a timolol formulation without preservatives. Betaxolol may maintain visual field as well as or better than timolol, even if it reduces IOP slightly les [29].

Alpha-adrenoceptor agonists (∞2)

Alpha-agonists, also known as selective (∞2) alpha-adrenoceptor agonist medicines, have been used for many years. IOPlowering is substantial at first (20–30%), although it may eventually decline to lesser levels (~17% reduction) [3]. Timolol 0.5% taken twice daily is thought to be roughly equal to brimonidine 0.2% taken three times daily [44]. Alpha-agonists work by reducing aqueous production and increasing outflow via the uveoscleral route [73]. Although apraclonidine (0.5%, 1.0% unit dose) was initially developed as a selective alpha-agonist, its high rates of tachyphylaxis and ocular allergy quickly caused it to lose favor as a treatment for open angle glaucoma. On the other hand, it works incredibly well to avoid IOP rises following surgery. Compared to apraclonidine, brimonidine (0.2%, 0.15%, and 0.1% in the US exclusively) is far more selective and has a reduced incidence of tachyphylaxis and allergy. Alpha-agonists have a rapid onset of action (one hour), a peak (two to three hours), and a trough (ten to fourteen hours). For this reason, if brimonidine is used as a single medication therapy, the dosage is three times daily; however, research indicates that it can be effectively lowered to twice daily when used as an adjuvant therapy [81].Fatigue or sleepiness, dry mouth, and headache are among the relatively rare systemic side effects of alpha-agonists [14]. Patients with Raynaud syndrome, orthostatic hypotension, and serious cardiovascular disease should be treated with caution. Due to serious central nervous system side effects, such as severe drowsiness and lethargy, which have been documented in newborns following even a single drop of 0.2% brimonidine, this medication is likewise not recommended for use in children [10]. Hyperemia, allergies (in up to one in four individuals), burning upon instillation, dryness, visual disruption, weeping, and eyelid edema are examples of local side effects.

Although research on the use of brimonidine has met several criteria for determining whether a medication is neuroprotective, and some studies have suggested that brimonidine preserves the visual field better than timolol, there is currently no solid proof of neuroprotection in human glaucoma [46]. Both brinzolamide 1.0% and timolol 0.5% are available in FC along with brimonidine.

Carbonic anhydrase inhibitors (CAIs)

Dorzolamide (2.0%) and brinzolamide (1.0%) are two substances that inhibit carbonic anhydrase. The CAIs are typically used as supplemental therapies because their ability to decrease IOP is much less than that of prostaglandin analogues or beta-blockers. Like alpha-agonists, they should be taken three times a day if recommended alone, but they can be taken twice as an add-on. When combined with a prostaglandin analogue taken at bedtime, morning and mid-afternoon are typically regarded as appropriate dosing periods. IOP is moderately lowered (15–20%), although one noteworthy advantage of the CAIs is their capacity to lower IOP at night. According to Quaranta et al. [69], this seems to be exclusive to the CAIs. This makes CAIs a desirable agent for those patients in whom progression is occurring despite what appears to be IOP at target, and in those patients with NTG in whom 24-hour blood pressure monitoring has demonstrated that significant nocturnal dips in blood pressure are occurring, increasing the relative risk for optic nerve non-perfusion during the night [78].

Reduced aqueous production is the CAIs' mode of action. Taste perversion and headaches are typically the systemic side effects of topically administered CAIs, with discomfort during instillation being the most commonly reported complaint. In order to prevent patients from stopping their medication out of fear that it is harming them, it is crucial to communicate this anticipated finding. Blurred vision, hyperemia, and dryness are also common [79].

The growing knowledge of the problem of sulfa medication allergies and CAIs is interesting. Dorzolamide and brinzolamide are sulfonamides, and these non-antibiotic sulfa medications contain the allergy-causing components of sulfonamide antibiotics [83]. Rather than being the result of cross-reactivity with the sulfonamide, people who have been discovered to be allergic to both sulfa antibiotics and CAIs are thought to have a predilection toward allergies in general [11]. Because of this, CAI glaucoma drops are probably safe for patients who are allergic to sulfa antibiotics.

Brinzolamide and dorzolamide are both offered as FC with 0.5% timolol. Typically, they are administered every twelve hours. Additionally, FC offers brinzolamide with brimonidine 0.2%, which is administered three times daily. Although oral medications in this class, such as acetazolamide (250 mg tablets) and methazolamide (50 mg), are rarely used to treat primary open angle glaucoma, they may be taken into consideration when a very elevated intraocular pressure needs to be acutely lowered in an emergency (or, less frequently, in preparation for a surgical procedure). Oral treatment is highly effective; after 30 minutes, there is a 30% drop in IOP, which peaks at 2 hours and lasts for 6 to 8 hours. Systemic usage of the CAIs is contraindicated in the presence of liver or kidney disease, serum electrolyte imbalance, and other less prevalent systemic diseases; these medical considerations are very different. Malaise, diarrhea, anorexia, metallic taste, and polyuria are the most frequent side effects; sadness, tiredness, and dizziness are also possible. There may be other hematologic, dermatological, and central nervous system side effects in addition to metabolic acidosis. Before giving these medications, it is advised to speak with the patient's family doctor, particularly for elderly patients and those whose medical history is unknown [11].

Muscarinic agonists

Since the year 2000, glaucoma has been treated using muscarinic agonists that act directly or indirectly. There is only one drug available on the market: pilocarpine in different concentrations and administration methods (0.25% to 10%; drops and sustained-release inserts). Pilocarpine works by increasing the scleral spur's tension, which physically opens the trabecular meshwork and increases traditional outflow. Pilocarpine has a quick beginning of action, peaking within two hours, however it only lasts for eight hours. These medications are cheap and have rare systemic side effects, but because they must be taken four times a day and have serious local side effects,

they are practically no longer used to treat open angle glaucoma. However, these medications can assist lower ocular pressure and lessen the risk of advancement when glaucoma is progressive, maximal medical therapy has been reached, and surgical options are not feasible **[87].**

After treating any acute IOP spike, pilocarpine is very crucial for primary angle closure glaucoma caused by plateau iris or pupillary block. It could be applied to pigment dispersion syndrome in an efficient (albeit uncomfortable) manner. Pilocarpine should not be used for uveitic or neovascular glaucoma, and any subsequent angle closure that results in an anterior displacement of the lens-iris diaphragm would be a relative contraindication for a miotic agent **[87].**

Future Challenges and Research Directions in Glaucoma Management

Significant progress has been made in the diagnosis and treatment of glaucoma, but there are still many important obstacles to overcome, especially when it comes to controlling severe stages and guaranteeing long-term vision preservation. Even though they are effective at reducing IOP, current treatments frequently fail to stop RGC death and ON degeneration, particularly in diseases like NTG. While surgical procedures have inherent dangers and may not be available in all contexts, drug administration faces obstacles such as ocular anatomical limits, poor patient adherence, and treatment adverse effects [49]. Due to the absence of sensitive and specific diagnostics for identifying disease in its early stages, early diagnosis is still not ideal. Furthermore, despite its potential, gene and stem cell therapies are difficult to implement in everyday practice due to issues with delivery efficiency, regeneration capacity, ethical problems, and high prices [18]. Genetic variation among patients further complicates personalized treatment, and inequities in healthcare access continue to impact results, especially in areas with limited resources. Additionally important but challenging to accomplish are patient education and long-term adherence to intricate treatment plans.

In order to halt the progression of the disease, clinical trials centered on neuroprotective medicines, enhanced drug delivery methods such as gene or nanoparticle-based therapies, and individualized therapy strategies are essential. Glaucoma management will be strengthened by increasing community-based screening, implementing AI for early diagnosis, and improving patient-centered care through customized treatment plans and adherence support. Lastly, it is anticipated that further developments in MIGS and the investigation of robotic-assisted methods would enhance surgical safety and results, lowering the overall treatment burden for patients globally.

CONCLUSION

The most common cause of permanent blindness worldwide is glaucoma. By identifying systemic illnesses and drugs that raise a patient's risk of glaucoma and recommending high-risk individuals for a thorough ophthalmologic examination, vision loss from glaucoma can be reduced. The categorization, pathophysiology, screening, and treatment options of glaucoma have all been thoroughly covered in this review. The term "glaucoma" refers to a diverse range of conditions that might manifest acutely, subacutely, or chronically. These conditions are often categorized as either open-angle or closed-angle glaucoma. The goal of all current medicinal, laser, and surgical glaucoma treatments is to reduce intraocular pressure (IOP), which is the sole modifiable risk factor. Early glaucoma diagnosis, disease progression prediction, and surgical outcome evaluations have all become more accurate because to AI and multimodal data integration. More individualized treatment plans are made possible by AI-driven methods that use genetic and systemic health data.

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