• Review Article •

Systemic diseases to the mechanism of primary open angle glaucoma

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Abstract

● Primary open angle glaucoma (POAG) is a complex neurodegenerative disorder involving genetic susceptibility, environmental factors, and systemic abnormalities, whose pathogenesis has not been fully elucidated. Based on baseline intraocular pressure (IOP), POAG is classified into two subtypes: high-tension glaucoma (HTG) and normal-tension glaucoma (NTG). This review summarizes and integrates recent research advances, focusing on the roles of systemic disorders including cardiovascular, endocrine, neurodegenerative, and autoimmune diseases, as well as obstructive sleep apnea-hypopnea syndrome (OSAHS), in the onset and progression of POAG from an integrated eye-brain-body axis perspective. Current evidence suggests that optic nerve damage in POAG involves multiple interconnected pathological pathways, such as IOP-related mechanical stress, hemodynamic disturbances, impaired neurovascular coupling, microvascular dysfunction, oxidative stress, and chronic inflammation. Among them, dysfunctions of the eye–brain axis, gut–eye axis, and ocular lymphatic–glymphatic system serve as key regulatory networks that mediate and integrate the aforementioned pathological processes. The two subtypes display distinct pathogenic features: HTG is primarily driven by elevated IOP, whereas NTG relies more on IOP-independent mechanisms and is more susceptible to systemic influences. This integrative perspective deepens our understanding of POAG pathogenesis and provides a novel theoretical foundation for early diagnosis, multidimensional intervention, and precision therapy.

● **KEYWORDS:** primary open angle glaucoma; normal-tension glaucoma; systemic diseases; eye-brain axis; gut-eye axis; ocular lymphatic-glymphatic system; optic nerve injury
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INTRODUCTION

Primary Open Angle Glaucoma: Epidemiology, Pathogenesis, and Systemic Associations

Epidemiology Glaucoma is a group of chronic neurodegenerative diseases characterized pathologically by progressive loss of retinal ganglion cells (RGCs), accompanied by typical optic atrophy and visual field defects. It is also one of the leading causes of irreversible visual impairment worldwide. Currently, the global number of people living with glaucoma approaches 95 million, of whom approximately 10 million develop at least unilateral blindness due to disease progression. With global population aging, the disease burden will continue to rise, and the worldwide number of glaucoma patients is projected to increase to 111.8 million by 2040[1]. As the most common subtype of glaucoma, primary open angle glaucoma (POAG) affects around 65 million people globally[2]. It has an insidious onset and slow progression, often with no obvious symptoms in the early stage. Most patients present with moderate to severe optic nerve injury at diagnosis, which not only results in irreversible visual loss but also imposes a substantial social and economic burden and severely impairs patients' quality of life.

Pathogenesis The pathogenesis of POAG is complex. Although elevated intraocular pressure (IOP) constitutes the core risk factor, it is not the sole determinant. Clinically, POAG is categorized into high-tension glaucoma (HTG) and normal-tension glaucoma (NTG) according to IOP levels[3]. These two

subtypes exhibit distinct pathological features. Accordingly, an individualized target IOP should be established in clinical practice by integrating the severity of optic nerve damage, progression risk, and systemic comorbidities[4]. Target IOP is defined as the highest safe IOP threshold that prevents or delays further optic nerve injury, and it also serves as a key indicator for evaluating therapeutic efficacy and the inhibitory effects on pathological signaling pathways.

The core pathogenesis of POAG involves two major pathways: IOP-dependent and IOP-independent mechanisms. IOP-dependent mechanisms center on increased aqueous outflow resistance in the trabecular meshwork, disturbed trans-laminar cribrosa pressure difference (TLCPD), and biomechanical remodeling of the optic disc. These mechanisms exert mechanical stress on the axons of RGCs and trigger apoptotic pathway activation, including caspase family activation and upregulation of BCL2-interacting mediator of cell death (BIM) protein. IOP-independent mechanisms encompass neurodegenerative changes, vascular hemodynamic abnormalities, and immune-inflammatory responses. Among these, mitochondrial dysfunction, neurovascular uncoupling, and microglial activation play crucial roles in RGC injury. In addition, dysregulated autophagy is involved in the regulation of both pathways[1-2,5-6]. Twenty-four-hour IOP fluctuation (≥10 mm Hg), as an independent risk factor, further exacerbates pathological progression by inducing repeated mechanical stretch of the optic nerve and activating oxidative stress and inflammatory responses[7]. In recent years, bidirectional regulation of the eye-brain axis, systemic inflammatory transmission mediated by the gut-eye/gut microbiota-immune axis, and dysfunction of the ocular lymphatic-glymphatic system have emerged as important systemic regulatory networks. These networks transmit pathological signals between systemic and local tissues. Genetic factors [such as myocilin (*MYOC*) and optineurin (*OPTN*) gene variants] and systemic disorders including diabetes mellitus and obstructive sleep apnea-hypopnea syndrome (OSAHS) aggravate subtype-specific injury through the above pathways. HTG is predominantly IOP-dependent, whereas NTG is mainly IOP-independent[1-2,6]. These factors ultimately interact and converge to cause irreversible apoptosis of RGCs and optic nerve degeneration, mediating the progression of POAG.

Multisystem interactions POAG is not an isolated ocular disease, but may be influenced by the combined effects of genetic susceptibility, environmental exposure, and systemic multisystem abnormalities. In this context, the eye–brain–body axis may serve as an integrative framework to describe the potential bidirectional associations and shared mechanisms between systemic status and ocular pathology. However, this framework does not imply a unidirectional, independent, or definitive causal relationship between systemic diseases and POAG. Some comorbidity associations may arise from shared upstream drivers, such as aging, genetic susceptibility, vascular dysregulation, metabolic stress, chronic inflammation, mitochondrial dysfunction, and susceptibility to neurodegeneration. Therefore, the associations of Alzheimer's disease (AD), diabetes mellitus, and other systemic disorders with POAG may reflect either the influence of systemic disease states on the ocular microenvironment or common pathological backgrounds involving neurodegeneration, microvascular injury, inflammation, or metabolic abnormalities, rather than a simple linear causal relationship.

Current evidence suggests that various systemic diseases or systemic pathological states are associated, to varying degrees, with the risk and progression of POAG. Cardiovascular diseases, such as hypertension, hypotension, and atherosclerosis, may increase the risk of optic nerve ischemia, hypoxia, and RGC injury by disturbing ocular hemodynamic homeostasis, ocular perfusion pressure, and optic nerve head microcirculation[8]. Metabolic and endocrine disorders, such as diabetes mellitus and thyroid dysfunction, may affect the ocular microenvironment through hyperglycemia-related microvascular injury, oxidative stress, metabolic dysregulation, altered aqueous humor dynamics, and local inflammatory responses[9]. Neurodegenerative diseases, including AD and Parkinson's disease (PD), may share overlapping pathological backgrounds with POAG, such as impaired proteostasis, mitochondrial dysfunction, neuroinflammation, and disrupted axonal transport[10]. In addition, abnormal immune responses associated with autoimmune diseases and chronic intermittent hypoxia related to OSAHS may also contribute to optic nerve injury through inflammatory amplification, vascular dysregulation, and oxidative stress[11-12]. Within these multisystem associations, the eye–brain axis, gut–eye/gut microbiota–immune axis, and ocular lymphatic–glymphatic system may represent three major regulatory pathways for explaining the potential links between systemic status and POAG-related optic nerve injury. These pathways are not isolated from one another; rather, they may interact under the background of vascular, metabolic, immune, and neurodegenerative injury, collectively forming a theoretical basis for understanding the systemic associations of POAG. Clarifying the causal direction of these pathways, their disease-specific roles, and their relative contributions across different POAG subtypes may further elucidate the complex pathogenesis of POAG and provide a basis for risk stratification, interdisciplinary management, and individualized intervention.

Three Key Regulatory Networks Underlying the Systemic Associations of POAG

Eye–brain axis: bidirectional regulation and transsynaptic injury between the eye and central nervous system The eye–brain axis serves as a dynamic regulatory network linking the eye and the central nervous system (CNS). *Via* coordinated neural transmission, immune-inflammatory responses, substance transport and metabolic pathways, it establishes a bidirectional pathological injury cycle of the eye–brain axis in POAG. On one hand, pathologically elevated IOP in POAG increases TLCPD, directly compressing optic nerve fibers, impairing axoplasmic transport, and inducing RGC apoptosis. This injury propagates centrally along the visual pathway through anterograde transsynaptic degeneration, manifesting as volume atrophy and neuronal loss in the lateral geniculate nucleus (LGN), thereby transmitting ocular damage to the CNS. On the other hand, structural and functional disturbances in the CNS may retrogradely injure the retinal nerve fiber layer (RNFL) and RGCs *via* retrograde transsynaptic degeneration, thus exacerbating POAG progression. Neuronal dysfunction and atrophy in the visual cortex or LGN disrupt retrograde signal transmission and neurotrophic support, leading to impaired axoplasmic transport in RGCs and progressive RNFL thinning. This ultimately results in compromised survival signaling and triggers RGC apoptosis, establishing a brain-to-eye injurious feedback loop[13-15].

At the molecular level, elevated IOP activates retinal glial cells. Inflammatory factors such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α) released by these cells disrupt the blood-retinal barrier and penetrate the blood-brain barrier, which further activates microglia and astrocytes in the brain and forms a positive feedback loop of neuroinflammation. Meanwhile, abnormally deposited amyloid-β protein (Aβ) and phosphorylated tau protein (p-Tau) in POAG can diffuse bidirectionally through the AQP4-dependent ocular lymphatic system (cerebrospinal fluid-perivascular space transport pathway). This process not only exacerbates RGC injury but also impairs GABAergic neurotransmission in the visual cortex, leading to reduced neural specificity[13,16]. Furthermore, aberrant mammalian target of rapamycin (mTOR) signaling, disturbed lipid metabolism, and impaired autophagy, which serve as shared pathological mechanisms of the eye–brain axis, can simultaneously trigger RGC apoptosis and cerebral cortical metabolic dysfunction. These abnormalities manifest as decreased mitochondrial ATP synthesis efficiency and imbalanced oxidative stress in the visual cortex[17].

With respect to systemic disease associations, the eye–brain axis enables multisystem crosstalk through shared molecular pathways. POAG and AD share 18 overlapping differentially expressed genes, suggesting high molecular homology and common core pathological mechanisms including disturbed lipid metabolism[17]. Associations with PD and multiple sclerosis involve abnormal α-synuclein aggregation and immune-mediated demyelinating injury, respectively. Metabolic diseases such as diabetes can disrupt the homeostasis of the retinal neurovascular unit *via* the eye–brain axis, synchronously inducing retinal neural damage and brain structural and functional abnormalities[13]. In summary, bidirectional pathological transmission and molecular abnormalities mediated by the eye–brain axis form a bidirectional regulatory network between the eye and the central nervous system in POAG.

Gut–eye/gut microbiota–immune axis: a potential pathway linking systemic immune status to ocular neuroinflammation The gut–eye axis and gut microbiota–immune axis have recently been proposed as potential systemic pathways linking gut dysbiosis, systemic immune dysregulation, and ocular neuroinflammation in POAG. This pathway is not limited to diabetes-related mechanisms, but may also participate in the interactions between autoimmune diseases, metabolic abnormalities, other systemic disorders, and POAG[18-21]. Current evidence suggests that gut dysbiosis may affect systemic immune homeostasis through a cascade involving intestinal mucosal barrier disruption, peripheral immune activation, and amplification of inflammatory signaling. After impairment of the intestinal mucosal barrier, lipopolysaccharides (LPS), microbial metabolites, and other microbe-associated molecular patterns may enter the circulation and induce peripheral T-cell activation. Meanwhile, these signals may also modulate immune responses against autoantigens, such as heat shock proteins (HSPs), through molecular mimicry or cross-reactive immune responses, thereby further altering the balance among Th1/Th17 and Treg cell subsets[20,22]. Gut microbiota-derived metabolites, including short-chain fatty acids and bile acids, may also indirectly contribute to ocular neuroinflammation and optic nerve injury by regulating immune cell polarization, vascular endothelial function, microglial reactivity, and the expression of pro-inflammatory cytokines such as IL-6 and TNF-α[18,21].

However, the role of the gut–eye/gut microbiota–immune axis in POAG and other retinal diseases remains an emerging and incompletely understood field[23-25]. Ocular tissues are characterized by relative immune privilege, in which the blood–retinal barrier, blood–aqueous barrier, and local immunoregulatory microenvironment jointly restrict the direct entry of peripheral immune cells and circulating inflammatory mediators into the eye[26]. Therefore, direct evidence remains limited regarding how gut-derived inflammatory factors, microbial metabolites, or immune cell signals cross or modulate these barriers and ultimately affect RGCs, the

optic nerve head, and the retinal micro-environment. Current studies mainly suggest several possible pathways. First, gut dysbiosis may induce systemic low-grade inflammation and influence the reactivity of retinal microglia through peripheral immune activation or circulating inflammatory mediators. Second, microbial metabolites may indirectly affect ocular tissues by regulating vascular endothelial function, blood-retinal barrier stability, or immune cell phenotypes[23-25]. Third, under conditions of intraocular pressure-related stress, diabetes mellitus, chronic inflammation, or barrier dysfunction, peripheral immune signals may be more likely to participate in intraocular inflammatory responses. Most available evidence is derived from animal experiments, indirect mechanistic inference, non-POAG ocular disease models, and limited clinical association studies; therefore, it is not yet sufficient to demonstrate a definitive directional causal relationship between gut-derived signals and POAG progression[23-25].

From the perspective of POAG subtypes, the gut microbiota–immune axis may be more closely involved in non-IOP-dependent injury, particularly in patients with concomitant autoimmune abnormalities, metabolic dysregulation, or chronic low-grade inflammation. Its role may mainly be reflected in peripheral immune activation, T-cell-related responses, amplification of neuroinflammation, and increased vulnerability of RGCs[20,22,26]. At present, there is no direct evidence demonstrating that this pathway has clearly distinct patterns of involvement between NTG and HTG[27]. Therefore, the role of the gut microbiota–immune axis across different POAG subtypes should still be regarded as a potential explanation based on existing mechanistic studies, rather than an established subtype-specific mechanism. In HTG, whether this pathway may indirectly contribute to IOP-related injury by affecting trabecular meshwork inflammation, the aqueous humor microenvironment, or aqueous humor outflow resistance remains to be further investigated[20-21].

In terms of clinical translation, probiotic supplementation, dietary modification, and other interventions targeting the gut microbiota should currently be considered potential research directions rather than established therapeutic strategies[18,21]. Future studies should integrate longitudinal cohorts, gut microbiota sequencing, serum and aqueous humor metabolomics, immune cell phenotyping, intraocular inflammatory factor profiling, and assessment of blood-retinal barrier function to clarify whether alterations in the gut microbiota represent upstream drivers of POAG, disease-associated changes, or indirect markers of systemic inflammatory status[20-21].

Ocular lymphatic–glymphatic system: a key link connecting IOP-dependent and IOP-independent pathways

A growing body of evidence has confirmed that dysfunction of the ocular lymphatic-glymphatic system serves as a key pathogenic mechanism linking IOP-dependent and IOP-independent pathways in POAG, providing a new perspective for elucidating its pathogenesis[28-33]. This system consists of Schlemm's canal [which expresses lymphatic endothelial markers such as Prox-1 and vascular endothelial growth factor receptor (VEGFR)-3], conjunctival lymphatic vessels, and optic nerve meningeal lymphatic vessels. Its core functions include aqueous humor drainage and metabolic waste clearance. Impaired function of this system increases aqueous outflow resistance and constitutes an important pathological basis for elevated IOP in HTG[29,32]. In contrast, the glymphatic system, which relies on aquaporin 4 (AQP4) and perivascular spaces of the optic nerve, is primarily responsible for the directed clearance of neurotoxic substances including β-amyloid. Dysfunction of this component is particularly prominent in NTG and can accelerate apoptosis of RGCs[28,31].

Dysfunction of lymphatic-like endothelial cells in Schlemm's canal and the glymphatic system is accompanied by characteristic molecular regulatory disorders, which further induce multiple pathological phenotypes in the ocular lymphatic-glymphatic system. First, structural and functional impairment of Schlemm's canal occurs. Downregulation of the VEGFR-3 signaling pathway reduces Prox-1 expression and causes loss of the endothelial lymphatic phenotype. In addition, dysregulation of the angiopoietin-TIE2 pathway aggravates aqueous outflow dysfunction[29-30]. Second, clearance function of the glymphatic system is disrupted. TNF-α mediates loss of AQP4 polarity in astrocytic endfeet. Meanwhile, an unbalanced translaminar cribrosa pressure gradient activates integrin-β1 signaling. These changes impair retrograde clearance of β-amyloid and promote pathological remodeling of perivascular spaces, ultimately leading to accumulation of toxic metabolites in the retinal and optic nerve microenvironment. Furthermore, in the DBA/2J mouse model of glaucoma, defects in the lamina cribrosa barrier and enlargement of perivascular spaces synchronously enhance anterograde and retrograde transport in the ocular glymphatic system, causing disordered fluid exchange between the eye and cranial cavity and promoting toxic metabolite accumulation. This pathological process is distinct from glymphatic decline associated with physiological aging[31-33].

Dysfunction of this system interacts closely with multiple systemic factors. For instance, hyperglycemia in diabetes directly damages lymphatic endothelial cells, while optic nerve hypoperfusion caused by cardiovascular diseases further impairs glymphatic clearance. Both act to accelerate the development and progression of POAG by exacerbating dysfunction of the ocular lymphatic-glymphatic system[30,32]. Meanwhile, gut microbiota-derived metabolites also regulate

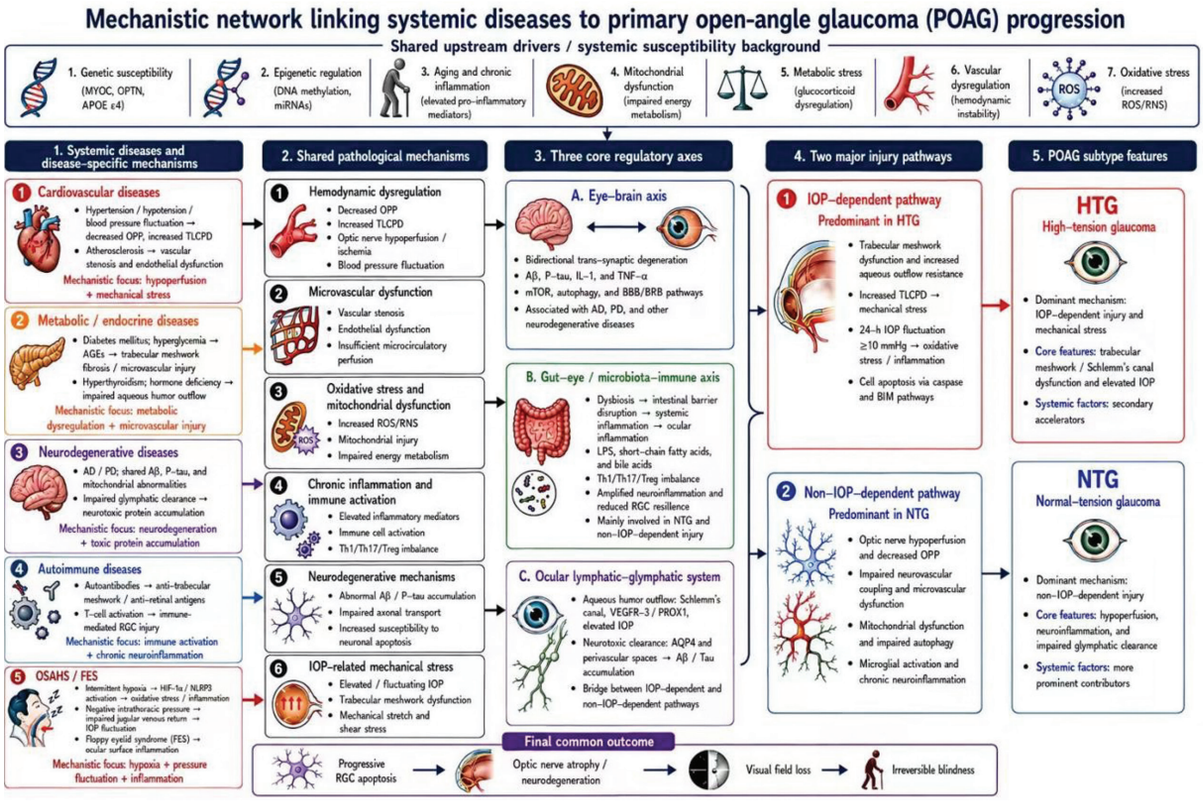

Figure 1 Potential mechanistic links between systemic diseases and POAG progression This schematic summarizes potential systemic associations and mechanistic links in POAG progression. Shared upstream susceptibility factors and systemic diseases may contribute through overlapping vascular, metabolic, immune-inflammatory, neurodegenerative, and IOP-related mechanisms, which can be organized within the eye–brain axis, gut–eye/microbiota–immune axis, and ocular lymphatic–glymphatic system. These processes may converge on IOP-dependent injury, more prominent in HTG, and non-IOP-dependent injury, more relevant to NTG. Arrows indicate proposed associations rather than established unidirectional causal relationships. POAG: Primary open angle glaucoma; HTG: High-tension glaucoma; NTG: Normal-tension glaucoma; IOP: Intraocular pressure; OPP: Ocular perfusion pressure; TLCPD: Trans-lamina cribrosa pressure difference; RGC: Retinal ganglion cell; ROS: Reactive oxygen species; RNS: Reactive nitrogen species; AGEs: Advanced glycation end products; AD: Alzheimer's disease; PD: Parkinson's disease; Aβ: amyloid-β; P-tau: Phosphorylated tau; IL-1: Interleukin-1; TNF-α: Tumor necrosis factor-α; mTOR: Mechanistic target of rapamycin; BBB: Blood–brain barrier; BRB: Blood–retinal barrier; LPS: Lipopolysaccharide; Th1: T helper 1 cell; Th17: T helper 17 cell; Treg: regulatory T cell; VEGFR-3: Vascular endothelial growth factor receptor 3; PROX1: Prospero homeobox protein 1; AQP4: Aquaporin-4; OSAHS: Obstructive sleep apnea-hypopnea syndrome; FES: Floppy eyelid syndrome; HIF-1α: Hypoxia-inducible factor-1α; BIM: Bcl-2-like protein 11; *MYOC*: Myocilin; *OPTN*: Optineurin; APOEε4: Apolipoprotein E ε4 allele.

lymphatic endothelial and glymphatic functions, contributing to the establishment of a systemic pathogenic network[18] (Figure 1).

CARDIOVASCULAR DISEASES

Epidemiological Association RGC apoptosis is the core pathological feature of optic nerve injury in POAG, in which impaired ocular blood flow is a key factor driving optic nerve dysfunction. As the core provider of ocular blood supply, the cardiovascular system can exacerbate ocular hypoperfusion and optic nerve ischemia–hypoxia through multiple pathways—including hemodynamic disturbances, an imbalanced translaminar cribrosa pressure gradient, and disruption of the vascular microenvironment—thereby inducing RGC apoptosis and accelerating POAG progression, with a particularly pronounced impact on NTG[34-35].

Abnormal blood pressure and atherosclerosis are critical cardiovascular factors mediating ocular blood flow abnormalities, both of which have established epidemiological associations with POAG. Abnormal blood pressure exhibits a "U-shaped" association with POAG: hypertension increases the risk of POAG by 22%, and its genetic susceptibility further elevates the disease risk [odds ratio (OR)=1.83, 95% confidence interval (CI): 1.25–2.67][36-37]. Hypotension shows subtype specificity: a nocturnal systolic blood pressure drop>15% and a daytime diastolic blood pressure ≤63 mm Hg are strong risk factors for NTG. Fluctuations in 24h blood pressure and excessive nocturnal blood pressure reduction (>20%) also reduce ocular perfusion pressure and accelerate optic nerve damage[37-38], indicating that excessively high, low, or highly variable blood pressure all increase POAG onset

and progression risk *via* distinct pathways. Atherosclerosis is closely linked to POAG: the risk of atherosclerosis in glaucoma patients and the risk of POAG in atherosclerosis patients are both significantly higher than in their respective control groups (both $P<0.001$), demonstrating a bidirectional association that is particularly prominent in individuals aged 65y and older[39]. Current studies have confirmed that both abnormal blood pressure and atherosclerosis are independent risk factors for the onset and progression of POAG[38-39].

Core Mechanisms

IOP-dependent injury mechanism: cardiovascular abnormalities exacerbate aqueous outflow resistance and intraocular pressure dysregulation Cardiovascular dysfunction disturbs aqueous humor homeostasis and IOP through multiple pathways, thereby exacerbating IOP-dependent optic nerve injury. Hypertension disrupts the balance between aqueous humor production and drainage *via* dual pathways. On one hand, it increases ciliary body blood flow and capillary perfusion pressure, directly promoting excessive aqueous humor formation. On the other hand, it elevates episcleral venous pressure and increases aqueous outflow resistance, indirectly reducing aqueous humor drainage. Together, these effects drive elevated IOP[40]. Abnormal blood pressure also impairs autonomic nervous system function, further destabilizing aqueous humor dynamics. It both increases aqueous production and reduces outflow efficiency, amplifying the IOP-elevating effect. It may also induce dysfunction of the ocular lymphatic-glymphatic system, worsening aqueous drainage and forming a vicious cycle with elevated IOP[30,41]. Atherosclerosis promotes trabecular meshwork cell apoptosis *via* oxidized low-density lipoprotein (ox-LDL). It also inhibits endothelial nitric oxide synthase (eNOS) activity and reduces nitric oxide (NO) production, impairing aqueous outflow at both cellular and molecular levels. These pathological effects act synergistically with hypertension to aggravate IOP dysregulation, ultimately inducing RGC injury through mechanical stress and mediating IOP-dependent damage in POAG[42].

Besides elevating baseline IOP, cardiovascular abnormalities can significantly amplify 24h IOP fluctuations (normal range<8 mm Hg). When IOP fluctuation exceeds 10 mm Hg, optic nerve damage can occur independently of absolute IOP level. Repetitive mechanical stretching disrupts the axonal cytoskeleton of RGCs in the optic nerve head and triggers oxidative stress and inflammatory responses. Inflammatory mediators can propagate to the central nervous system *via* the eye–brain axis, further exacerbating neurodegenerative changes[7]. This mechanism is particularly prominent in HTG. By reinforcing IOP-dependent injury pathways, cardiovascular diseases markedly accelerate mechanical stress-mediated RGC apoptosis and axonal degeneration[42].

Non-IOP-dependent injury mechanism: cardiovascular abnormalities mediate optic nerve perfusion and functional disturbance Non-IOP-dependent mechanisms represent a core pathway through which cardiovascular diseases exacerbate POAG injury, with a particularly pronounced effect on the NTG subtype. These mechanisms act synergistically *via* optic nerve hypoperfusion, vascular dysregulation, and neuroinflammation, with hypoperfusion and ischemia–hypoxia of the optic nerve head (ONH) as the central event. Hypertension induces microvascular remodeling characterized by retinal arteriosclerosis, vascular wall thickening, and luminal stenosis. Hypotension directly reduces ocular perfusion pressure [ocular perfusion pressure (OPP)=mean arterial pressure−IOP)]. Nocturnal blood pressure dips and non-dipping hypertension further lower OPP and worsen ONH ischemia–hypoxia at night. Atherosclerosis mediates carotid artery stenosis. Together, these factors lead to chronic ischemia–hypoxia of the ONH, whose severity is directly determined by the compensatory capacity of the ocular collateral circulation, which also influences the rate of optic nerve degeneration and clinical outcome. Sustained ischemia–hypoxia disrupts energy metabolic homeostasis in RGCs and activates the mitochondria-mediated apoptotic pathway, ultimately promoting programmed RGC death[41-44].

Meanwhile, vascular regulation and endothelial dysfunction serve as key intermediate steps in this injury process.

Chronic hypertension impairs the autoregulatory capacity of ocular vessels to maintain blood flow homeostasis, rendering them unable to mount adaptive compensatory responses to fluctuations in blood pressure and IOP. Atherosclerosis further induces microvascular endothelial dysfunction, characterized by reduced vasodilatory responses to acetylcholine, thereby disrupting ocular blood flow homeostasis, worsening ischemia, and impairing trabecular meshwork function[42]. In addition, systemic inflammation triggered by gut dysbiosis can infiltrate the eye *via* the gut–eye axis, further damaging the vascular endothelium, exacerbating endothelial dysfunction, and aggravating optic nerve hypoperfusion[20]. Persistent hypoperfusion not only impairs the clearance of neurotoxic substances by the ocular lymphatic–glymphatic system, leading to the accumulation of inflammatory cytokines and neurotoxic agents that in turn worsen vascular endothelial injury and hypoperfusion, but also indirectly compromises aqueous humor drainage *via* impaired trabecular meshwork function, forming a vicious cycle between hypoperfusion and abnormal IOP[31,42].

At the molecular level, vascular endothelial dysfunction promotes the infiltration of inflammatory cells and cytokines into the ONH region, activates the nuclear factor-kappa B

(NF-κB) pathway, upregulates the expression of IL-6 and TNF-α, and aggravates local neuroinflammation and vascular endothelial injury. Meanwhile, atherosclerosis promotes vascular smooth muscle cell proliferation and luminal stenosis *via* the platelet-derived growth factor (PDGF)-BB/PDGFRβ pathway, further worsening optic nerve hypoperfusion. These events ultimately form a persistent injury cycle of vascular remodeling–hypoperfusion–RGC apoptosis[42].

Pressure gradient imbalance mechanism (TLCPD disturbance): dual injury from optic nerve mechanical stress and hypoperfusion TLCPD refers to the pressure gradient between IOP and intracranial pressure (ICP). It serves as a key mechanical mechanism linking cardiovascular abnormalities to pathological damage in POAG. Its homeostasis is jointly regulated by systemic blood pressure, IOP, and ICP. Once disturbed, TLCPD imbalance exacerbates ONH injury through synergistic effects of mechanical stress and vascular insufficiency, and this pathological process is closely associated with cardiovascular abnormalities[45-46].

Finite element modeling by Mao *et al*[45] confirmed that elevated TLCPD significantly increases biomechanical strain in ONH tissue, with the prelaminar neural tissue and lamina cribrosa representing the most vulnerable regions. At the same TLCPD level, mechanical stretch injury induced by elevated IOP is significantly more severe than that caused by reduced cerebrospinal fluid pressure (CSFP), which is highly correlated with ICP. Cardiovascular abnormalities represent a major trigger of TLCPD dysregulation. Hypertension increases IOP *via* vascular remodeling in the trabecular meshwork, directly increasing TLCPD and exposing the lamina cribrosa to excessive mechanical stress, leading to structural damage to RGC axons[42,45]. Abnormal blood pressure rhythms, such as nocturnal hypotension and non-dipping hypertension, combined with reduced vascular elasticity and luminal stenosis caused by atherosclerosis, jointly decrease OPP. These changes act synergistically with TLCPD imbalance to further aggravate ONH hypoperfusion, which can result in ischemic ONH injury even with normal IOP[42].

Dual injury mediated by TLCPD imbalance exhibits distinct subtype-specific patterns in POAG, with cardiovascular abnormalities involved throughout the entire pathological process. In HTG, TLCPD imbalance is mainly driven by elevated IOP, with mechanical stress as the core injury mechanism. Cardiovascular abnormalities further amplify this mechanical damage by increasing IOP[45-46]. In NTG, IOP remains within the normal range, and TLCPD disturbance mostly arises from reduced CSFP and postural ICP fluctuations. Blood pressure fluctuations and impaired vascular autoregulation caused by cardiovascular abnormalities act synergistically with mild TLCPD elevation, accelerating RGC apoptosis and optic nerve degeneration *via* a combined mechanism of mild mechanical stress injury and optic nerve hypoperfusion. In addition, systemic blood pressure can indirectly modulate TLCPD homeostasis by regulating OPP. Nocturnal ICP fluctuations and abrupt ICP reduction caused by upright posture further exacerbate TLCPD imbalance[46]. Vascular endothelial dysfunction and carotid artery stenosis resulting from cardiovascular diseases worsen optic nerve hypoperfusion, establishing a persistent dual-injury cycle with TLCPD disturbance. This constitutes an important systemic pathological basis for POAG, particularly NTG[42].

Clinical Implications for Therapeutic Strategies Based on the above pathological associations and injury mechanisms, clinical management of POAG requires an interdisciplinary integrated strategy that achieves the dual goals of cardiovascular protection and glaucoma intervention. Routine 24-hour ambulatory blood pressure monitoring is recommended for POAG patients, especially those with the NTG subtype and those with well-controlled IOP but progressive disease. Excessive blood pressure reduction should be avoided to prevent nocturnal OPP decline, thereby balancing cardiovascular protection and the maintenance of adequate optic nerve perfusion[42]. For IOP management, in addition to mean IOP level, control of IOP fluctuation should also be emphasized. In high-risk individuals, combined with 24-hour IOP monitoring, therapeutic regimens with stable hypotensive effects and reduced diurnal fluctuation may be prioritized to achieve coordinated stability of intraocular pressure and systemic hemodynamics[47]. For POAG patients complicated by atherosclerosis or vascular endothelial dysfunction, individualized comprehensive management strategies should be developed by incorporating systemic vascular factors on the basis of conventional IOP-lowering treatment, with focused evaluation of their impacts on optic nerve perfusion and TLCPD homeostasis. Meanwhile, bidirectional screening and early combined intervention should be strengthened in populations at high risk for both cardiovascular diseases and POAG[41]. Future interdisciplinary studies are warranted to explore the clinical value of potential intervention targets such as TLCPD homeostasis regulation and vascular endothelial function improvement, so as to provide novel directions for precision therapy of POAG.

METABOLIC AND ENDOCRINE DISEASES

Diabetes Mellitus

Epidemiological association Diabetes mellitus is a highly prevalent chronic metabolic disease worldwide, and its ocular complications are not limited to diabetic retinopathy (DR). Current evidence suggests a complex association between diabetes mellitus and POAG, the strength of which may be influenced by multiple factors, including glycemic control,

disease duration, ethnic background, and differences in ocular structure. This indicates that diabetes mellitus may not merely be a concomitant comorbidity. Chronic hyperglycemia and diabetes-related metabolic abnormalities may disrupt intraocular homeostasis through microvascular injury, oxidative stress, and inflammatory responses, while the eye–brain axis, gut–eye/microbiota–immune axis, and ocular lymphatic–glymphatic system may also participate in systemic pathological regulation, collectively influencing the POAG-related ocular microenvironment[9,48]. A multicenter cross-sectional study from Ethiopia reported that the prevalence of POAG among adults with diabetes mellitus was 14.37%. Fasting plasma glucose >125 mg/dL and disease duration ≥10y were each associated with a higher risk of POAG, and this association was more pronounced in the NTG subtype[49]. Mendelian randomization studies have also suggested a positive association between type 2 diabetes mellitus (T2DM) and POAG; however, the findings are inconsistent across populations. An association between fasting glucose and POAG has been observed in European populations, whereas similar findings were not detected in East Asian populations[48,50]. This discrepancy may be related to ethnic differences in glaucoma susceptibility gene polymorphisms, such as *MYOC* and *OPTN*, as well as differences in metabolic characteristics and glycemic regulation, which may contribute to population-specific effects of hyperglycemia on ocular injury.

In addition, iris volume in patients with POAG has been reported to be positively correlated with glycated hemoglobin (HbA1c) levels, suggesting that chronic hyperglycemia may be involved in the remodeling of ocular structures such as the iris. However, the relevant studies did not adequately distinguish between HTG and NTG subtypes, and their conclusions therefore remain limited[51]. The relationship between DR and POAG also remains controversial. Longitudinal studies have shown that patients with POAG have an increased risk of developing DR over a 10y period. Meanwhile, diabetes-related microvascular lesions, vascular leakage, and retinal structural changes may also interfere with the assessment of glaucomatous optic nerve damage[52-54]. In addition to retinal factors, alterations in corneal biomechanics represent another important confounding factor. Hyperglycemia may enhance advanced glycation end products (AGEs)-mediated collagen cross-linking in the corneal stroma, resulting in increased central corneal thickness and reduced corneal hysteresis. These changes may directly interfere with the accuracy of Goldmann applanation tonometry, obscure true IOP fluctuations, and lead to misclassification between HTG and NTG, thereby ultimately reducing the reliability of related epidemiological findings[55-57]. Therefore, the association between diabetes mellitus and POAG should be interpreted comprehensively in light of study design, population differences, ocular structural changes, and potential confounding factors. Hyperglycemia and diabetes-related microvascular injury may increase the susceptibility of ocular tissues to glaucomatous damage; however, the two conditions may also share common upstream backgrounds, including aging, metabolic stress, vascular endothelial dysfunction, chronic low-grade inflammation, oxidative stress, and impaired neurovascular regulation. The disease-specific role and precise mechanisms of diabetes-related alterations in POAG remain to be further clarified.

Core Mechanisms

IOP-dependent injury mechanism: hyperglycemia increases resistance to aqueous humor outflow, thereby elevating intraocular pressure This pathway primarily affects HTG. Its core mechanism is that hyperglycemia increases aqueous humor outflow resistance and raises IOP by modulating the structure and function of the trabecular meshwork. At the molecular level, hyperglycemia elevates glucose concentration in the aqueous humor and upregulates fibrillar components (fibronectin, type IV collagen) in the trabecular meshwork *via* activation of the PI3K/Akt/mTOR signaling pathway. Meanwhile, AGEs bind to the receptor for AGEs [receptor for advanced glycation end products (RAGE)] on trabecular meshwork cells, triggering receptor-mediated signaling that promotes extracellular matrix cross-linking and fibrosis. These dual mechanisms markedly increase resistance to aqueous humor outflow[9,48]. At the cellular level, AGEs directly induce trabecular meshwork cell apoptosis and reduce phagocytic activity through activation of the caspase-3 pathway. Hyperglycemia induces hyperosmolarity and hyperviscosity in serum and aqueous humor, which suppresses passive diffusion of aqueous humor and impairs aqueous drainage by the ocular glymphatic system, further elevating IOP[9,58]. In addition, hyperglycemia may promote significant enlargement of iris volume in POAG patients (37.67±4.72 mm^3 *vs* 34.55±4.12 mm^3, P=0.01) by remodeling iris microvasculature and disturbing neuromuscular metabolism, thereby aggravating angle narrowing. This effect is more pronounced in HTG patients and indirectly contributes to IOP elevation, forming a vicious cycle among hyperglycemia, increased iris volume, elevated IOP, and impaired glymphatic drainage[51].

Non-IOP-dependent injury mechanism: synergistic damage by oxidative stress, neuroinflammation and microangiopathy This pathway represents the core mechanism underlying hyperglycemia-induced NTG injury, independent of IOP elevation. It directly damages RGCs at the molecular, cellular, and tissue levels, and acts synergistically with gut–eye axis dysregulation to accelerate disease progression.

At the molecular level, hyperglycemia mainly activates four key pathogenic pathways. First, abnormal activation of the polyol pathway occurs. High expression of aldose reductase drives extensive conversion of glucose to sorbitol, which accumulates in RGCs and causes osmotic imbalance and oxidative stress. This process also activates the AGEs-RAGE axis, induces Müller cells to release pro-inflammatory factors including IL-6 and TNF-α, inhibits the PI3K/Akt survival pathway, and initiates caspase-9-mediated mitochondrial apoptosis[58-59]. Second, the ocular lymphatic-glymphatic system is impaired. AGEs suppress the clearance of neurotoxic proteins, namely amyloid-β and Tau, exacerbating optic nerve degeneration, which also contributes substantially to mechanistic heterogeneity across populations[58]. Third, transsynaptic injury is mediated *via* the eye–brain axis. Hyperglycemia-associated central insulin resistance weakens insulin and IGF-1 receptor signaling, abnormally activates the NF-κB pathway to augment central inflammation, and promotes transsynaptic neurodegeneration through the eye–brain neural connection, thereby accelerating RGC apoptosis[60]. Fourth, systemic inflammation is driven by the gut microbiota-immune axis. Hyperglycemia induces dysbiosis, promotes lipopolysaccharide (LPS) release, and allows LPS to infiltrate the eye *via* the gut–eye axis. This activates the TLR4/NF-κB pathway, upregulates pro-inflammatory chemokines such as CXCL5 and CXCL8, and reduces the anti-inflammatory cytokine IL-2, further amplifying neural injury[58,61]. In addition, hyperglycemia activates the PDGF-BB/*PDGFRβ* pathway, driving proliferation and migration of vascular smooth muscle cells and leading to vascular lumen stenosis. This establishes a self-sustaining injury cycle of vascular remodeling-hypoperfusion-RGC apoptosis[42].

At the cellular and tissue levels, hyperglycemia-associated systemic microangiopathy serves as a key intermediate step, with a more prominent role in NTG. Hyperglycemia activates the polyol pathway, promotes AGEs accumulation, and activates protein kinase C (PKC), exacerbating oxidative stress and inflammation and disrupting the integrity of the inner blood–retinal barrier (iBRB)[59]. Following iBRB impairment, circulating immune cells such as macrophages and lymphocytes, as well as inflammatory mediators including CXCL5 and CXCL8, infiltrate the retina, inducing persistent neuroinflammation and accelerating the loss of RGCs and their axons. Proliferative diabetic retinopathy (PDR), a severe phenotype of microvascular damage, acts as an independent risk factor for NTG [adjusted odds ratio (AOR)=4.91]. It disrupts intraocular blood flow homeostasis through retinal ischemia-hypoxia and VEGF-mediated anterior segment structural alterations. This effect is pronounced in NTG but only plays an additive role in HTG[49,62]. Meanwhile, the aqueous humor inflammatory profile differs between subtypes in diabetes-complicated POAG patients. NTG patients show significantly higher levels of CXCL5, CXCL8, and IL-1α, lower IL-2 levels, and more marked activation of the TNF-α-centered terminal inflammatory pathway compared with HTG patients. Such elevations cannot be fully explained by classic POAG inflammatory pathways, suggesting that diabetes may provide a distinct inflammatory amplification route for NTG *via* the gut microbiota–immune axis. Furthermore, ocular glymphatic system dysfunction is more severe in NTG and further aggravates neurotoxic protein accumulation. In HTG, this abnormality is only a secondary factor and contributes indirectly to injury mainly by impairing aqueous humor drainage[58].

Clinical implications for treatment A multidisciplinary strategy combining metabolic control and glaucoma intervention is required in clinical practice. For diabetic patients with a long disease course, poor glycemic control, or concurrent DR, regular glaucoma screening is recommended. Meanwhile, enhanced surveillance for DR should be performed in POAG patients with diabetes. Hypoglycemic agents may be chosen to also provide preventive benefits against POAG. Glucagon-like peptide-1 receptor agonists significantly reduce the risk of POAG in patients with T2DM (1-year RR=0.59, 2-year RR=0.50). Insulin-sensitizing agents such as metformin may exert protective effects against POAG[63]. Future studies may explore targeted interventions against AGEs accumulation, oxidative stress, and neuroinflammation, providing novel therapeutic strategies for diabetes-associated POAG.

Thyroid Dysfunction

Epidemiological association Thyroid dysfunction and related autoimmune responses may contribute to the development and progression of POAG *via* hormonal imbalance and immune inflammation. A Meta-analysis confirmed that hypothyroidism increases the risk of POAG (OR=1.64), with population heterogeneity that is more prominent in North American and Asian cohorts[64]. Thyroid autoantibodies exhibit distinct specificity in their effects on POAG. Positive anti-thyroglobulin antibody (TgAb) serves as an independent risk factor for elevated IOP (OR=21.0), whereas anti-thyroid peroxidase antibody (TPOAb) shows no significant association[65-66]. This discrepancy suggests that IOP regulation is affected not by systemic autoimmune reactions, but by local pathological mechanisms linked to specific antibodies. Furthermore, patients with thyroid-associated ophthalmopathy often present with elevated IOP and glaucomatous optic neuropathy, indicating that orbital mechanical compression and hemodynamic abnormalities also play important roles in POAG pathogenesis[67-68].

Core Mechanisms

IOP-dependent injury mechanism: impaired aqueous humor outflow mediated by hormone deficiency Deficiency of T3/T4 resulting from hypothyroidism inhibits the autophagy pathway in trabecular meshwork cells (downregulating Beclin-1/LC3II), leading to abnormal deposition of glycosaminoglycans and hyaluronic acid, which directly increases aqueous outflow resistance and elevates IOP[66]. In thyroid-associated ophthalmopathy (TAO), orbital soft tissue inflammation, fluid accumulation, and extraocular muscle hypertrophy can raise episcleral venous pressure (EVP) and reduce the effective drainage gradient across the trabecular meshwork. Meanwhile, mechanical compression can also narrow Schlemm's canal diameter, collectively aggravating impaired aqueous humor drainage[67-69]. Increased EVP and mechanical compression reinforce each other: stagnant aqueous humor worsens tissue edema, and tissue swelling further impedes venous return, ultimately forming a vicious cycle that drives sustained IOP elevation. These hemodynamic and mechanical factors play a dominant role in thyroid-related glaucoma, with effects significantly stronger than structural remodeling of the trabecular meshwork itself.

Non-IOP-dependent injury mechanism: autoimmunity and hemodynamic abnormalities Thyroid hormone deficiency impairs the regulatory effects of T3/T4 on the proliferation and migration of optic nerve vascular endothelial cells, resulting in insufficient angiogenesis and abnormal permeability of the optic disc. This subsequently exacerbates optic nerve hypoperfusion, leading to optic nerve damage through non-IOP-dependent pathways[66]. Thyroid autoimmune abnormalities can trigger local orbital chronic inflammation and the release of inflammatory mediators *via* related antibodies, further impairing optic nerve microvascular regulation and participating in the pathogenesis of POAG[65]. In patients with TAO, local chronic inflammation and microcirculatory disturbance can also exacerbate ischemic hypoxia of the optic nerve independent of IOP levels. This mechanism is particularly prominent in patients with NTG[67-68]. Optic nerve hypoperfusion and autoimmune inflammation reinforce each other, forming a degenerative vicious cycle of "insufficient perfusion–inflammatory infiltration–optic nerve damage", which constitutes an important non-IOP-dependent injury pathway in POAG.

Clinical implications for treatment In clinical practice, screening for thyroid function and autoantibodies should be emphasized in patients with POAG, especially those with NTG and those with well-controlled IOP but progressive optic nerve damage. For patients with concomitant hypothyroidism, endocrine intervention can be combined with glaucoma therapy to improve aqueous humor outflow and optic nerve perfusion. For patients with TAO and glaucoma, orbital inflammation should be controlled according to disease activity to relieve mechanical compression and elevated episcleral venous pressure. Overall, thyroid dysfunction contributes to the pathogenesis of POAG through multiple pathways, suggesting that interdisciplinary collaborative monitoring and individualized intervention may help further optimize the diagnosis and management of this disease.

NEURODEGENERATIVE DISEASES

Epidemiological Association POAG is essentially an optic neurodegenerative disease, and its pathological processes overlap with those of central neurodegenerative diseases, such as AD and PD, in several non-IOP-dependent mechanisms, including impaired proteostasis, mitochondrial dysfunction, neuroinflammation, and disrupted axonal transport. A large-scale cohort study showed that patients with POAG had an increased subsequent risk of developing AD, with an adjusted hazard ratio (aHR) of 1.31[70]. However, a definite causal relationship between POAG and PD has not yet been established. Although genetic studies have suggested local genetic overlap between the two diseases at the microtubule-associated protein tau (*MAPT*) locus on chromosome 17q21, Mendelian randomization analyses did not support a direct causal association[71]. Therefore, the association between POAG and neurodegenerative diseases is more likely to reflect shared pathological backgrounds and partial mechanistic intersections, rather than a clearly defined directional causal relationship. Whether direct mutual promotion exists between these diseases, and the direction of such causality, remain to be further clarified. Although POAG, AD, and PD share certain neurodegenerative mechanisms, they remain distinct in terms of pathological origin, predominantly affected tissues, and key downstream molecular pathways.

Core Mechanisms

IOP-dependent injury mechanism: Schlemm's canal dysfunction mediates abnormal aqueous humor drainage and indirectly damages the optic nerve Dysfunction of the ocular lymphatic–glymphatic system has emerged as a novel unifying mechanism linking AD and POAG. Its core lies in Schlemm's canal dysfunction leading to impaired aqueous humor drainage, and dysregulation of this system represents a key event mediating neural injury. This system comprises the lymphatic-like Schlemm's canal and the AQP4-dependent glymphatic system, which are responsible for the directional clearance of neurotoxic substances such as Aβ from the optic nerve and retina. Impaired Schlemm's canal function, characterized by lumen narrowing, disrupted AQP4 polarity, and disturbed perivascular space remodeling, causes obstructed aqueous outflow and elevated IOP. Concurrently, it leads to the retention and accumulation of Aβ and hyperphosphorylated

Tau protein in the optic nerve microenvironment, indirectly exacerbating retinal ganglion cell apoptosis and axonal damage, ultimately resulting in optic nerve injury through IOP-dependent pathways[28-29,33]. These mechanisms interact with the AD pathological cascade. Accumulation of neurotoxic metabolites further aggravates mitochondrial dysfunction and neurovascular dysregulation, forming a vicious cycle.

Non-IOP-dependent injury mechanism: direct optic nerve damage *via* neurodegenerative pathways This mechanism represents a core shared pathway between POAG and neurodegenerative diseases including AD and PD, which directly injures the optic nerve through protein misfolding, genetic abnormalities, genetic susceptibility, and cellular dysfunction.

At the molecular level, protein misfolding serves as the central pathway. Both POAG and AD exhibit β-amyloid (Aβ) deposition and aberrant Tau phosphorylation. Retinal Aβ deposition activates microglia, releases reactive oxygen species (ROS), and suppresses expression of the neurotrophic receptor (TrkA) in RGCs, disrupting neuroprotective signaling. Excessive Tau phosphorylation, mediated by upregulation of the *TTBK1* gene, impairs microtubule architecture in RGC axons and inhibits axonal transport[72-73].

In the genetic abnormality pathway, the *TTBK1* gene acts as a key driver. As a Tau phosphorylation-related gene, it not only participates in abnormal Tau phosphorylation in AD but also mediates aberrant aggregation of α-synuclein (α-syn) associated with PD. This interferes with mitophagy *via* dysfunction of the *PINK1*/Parkin pathway, leading to impaired energy metabolism and RGC apoptosis, thereby exacerbating optic nerve damage[73]. In terms of genetic susceptibility, the *APOE* ε4 allele, a major genetic risk factor for AD, is closely associated with the risk and progression rate of POAG[74-75].

In the cellular dysfunction pathway, impaired clearance of the ocular lymphatic-glymphatic system constitutes a key event. Obstruction of this clearance pathway triggers TNF-α-mediated disruption of AQP4 polarity in astrocytic endfeet. This acts synergistically with the integrin β1 pathway activated by an abnormal TLCPD, inhibiting retrograde clearance of Aβ and causing pathological remodeling of perivascular spaces. This ultimately leads to accumulation of neurotoxic substances including Aβ and phosphorylated Tau, inducing neuroinflammation and RGCs apoptosis[31-33]. Meanwhile, mitochondrial dysfunction, neurovascular dysregulation, and other cellular cascades exacerbate energy metabolic crisis and hypoxic-ischemic injury, synergistically promoting neuronal degeneration and directly worsening optic nerve damage[76-78].

In addition, POAG and AD share core pathological pathways such as glutamate excitotoxicity and dysregulated calcium signaling. Dopaminergic imbalance associated with PD can further aggravate optic nerve damage by modulating expression of the retinal dopamine D2 receptor[79]. These shared neurodegenerative mechanisms are primarily relevant to NTG and have minimal impact on the progression of HTG.

Clinical Implications for Treatment Clinicians should recognize the comorbid association between POAG and neurodegenerative diseases such as AD and PD, and strengthen screening and monitoring for neurodegenerative disorders in patients with POAG, especially those with NTG. For IOP-dependent injury, emphasis should be placed on improving Schlemm's canal function, promoting aqueous humor drainage, and controlling IOP to reduce indirect optic nerve damage. For non-IOP-dependent injury, common neuroprotective strategies can be explored based on these shared neurodegenerative mechanisms, targeting core pathways including protein misfolding and mitochondrial dysfunction to reduce direct optic nerve injury. Meanwhile, individualized interventions should be implemented in combination with genetic risk factors and disease-specific pathological features to achieve interdisciplinary collaborative management, providing novel insights and targets for the treatment of POAG.

IMMUNE AND INFLAMMATORY DISEASES

Autoimmune Diseases

Epidemiological association The neurodegenerative process in POAG is closely linked to autoimmunity, and several clinical studies have confirmed a distinct association between these conditions. In a cross-sectional study, Lorenzo *et al*[80] reported that the prevalence of autoimmune diseases was significantly higher in patients with POAG than in controls (17.4% *vs* 10.1%), and that autoimmune disease independently increased the risk of POAG by 2.62-fold, with T cell-mediated autoimmune diseases (*e.g.*, rheumatoid arthritis, psoriasis) being particularly prominent. Using a nationwide Korean cohort study, Kim *et al*[81] further confirmed that patients with rheumatoid arthritis had a significantly increased risk of POAG (HR=1.44), with the highest risk within 2y after diagnosis (HR=1.83). Using Mendelian randomization analysis, Meng *et al*[27] established a causal relationship between ankylosing spondylitis and POAG (OR=1.28), providing genetic evidence supporting an important role of autoimmune mechanisms in POAG pathogenesis. However, the association is heterogeneous. For instance, findings regarding the link between rheumatoid arthritis and POAG have been inconsistent across studies, which may be attributed to differences in disease activity, medication use, and immune subsets. Autoimmune-mediated non-IOP-dependent injury also represents an important risk factor for NTG.

Core Mechanisms

IOP-dependent injury mechanism This mechanism is centered on B cell-mediated immune responses, which

indirectly damage the optic nerve by impairing aqueous humor drainage and elevating IOP. Autoimmune disturbance can induce gut microbiota dysbiosis and further disrupt the intestinal mucosal barrier, promoting B cells to produce anti-trabecular meshwork antibodies. These antibodies inhibit matrix metalloproteinase (MMP)-9 activity, reduce extracellular matrix degradation, and thereby increase aqueous outflow resistance, leading to elevated IOP[22,27]. This pathway is mainly involved in the pathogenesis of HTG. By exacerbating trabecular meshwork dysfunction and IOP fluctuation, it ultimately causes optic nerve injury through IOP-dependent mechanisms.

Non-IOP-dependent injury mechanism This mechanism is independent of IOP level and represents a core pathway of autoimmune-mediated optic nerve damage in POAG. It mainly involves T cell-mediated immune responses and is also a key risk factor for NTG. Gut dysbiosis can disrupt the intestinal mucosal barrier, leading to the release of retinal autoantigens (*e.g.*, HSP60) into the circulation, which activates $CD4^+$ T cells and drives their differentiation toward Th1/Th17 subsets[22,27]. Elevated IOP can further promote the infiltration of $CD4^+$ T cells into the retina. This process relies on commensal flora-mediated cross-immune responses against heat shock proteins (HSP27, HSP60). Moreover, once initiated, T cell-mediated neural damage can persist even after IOP normalization, continuing to induce RGC apoptosis[22]. Activated $CD4^+$ T cell subsets directly infiltrate the optic nerve and attack RGCs, ultimately causing direct optic nerve injury independent of elevated IOP.

Clinical implications for treatment Clinicians should strengthen POAG screening in patients with autoimmune diseases, with particular attention to monitoring optic nerve progression in those with NTG. Treatment should target both IOP control and immunomodulation. Repairing the intestinal barrier and inhibiting aberrant T-cell activation may alleviate non-IOP-dependent neural damage. For glaucoma patients with comorbid autoimmune diseases, a personalized interdisciplinary strategy combining ophthalmology and rheumatology is recommended.

OSAHS AND FLOPPY EYELID SYNDROME

Epidemiological Evidence A large body of epidemiological evidence confirms a significant association between OSAHS and POAG, independent of regional and ethnic differences. A systematic review and meta-analysis including 46 studies and over 3.3 million participants verified that patients with OSAHS have a significantly increased risk of POAG, with an unadjusted odds ratio of 3.66. After adjustment for confounders, the risk remained significantly elevated (adjusted OR=1.40; adjusted HR=1.59). This association strengthens with increasing OSAHS severity and shows distinct glaucoma subtype specificity. Patients with severe OSAHS (apnea-hypopnea index, AHI>30) carry the highest POAG risk. Furthermore, the strength of the association between OSAHS and NTG is significantly higher than that for HTG[82]. This subtype specificity indicates that OSAHS is not merely a comorbidity of POAG, but a systemic risk factor implicated in its pathogenesis, particularly playing an important role in NTG.

Key Intermediate Phenotype: Floppy Eyelid Syndrome Floppy eyelid syndrome (FES) is characterized by marked eyelid laxity, easy eversion, nocturnal lagophthalmos, and chronic ocular surface inflammation. As a key clinical phenotype linking OSAHS and POAG, FES is highly prevalent in patients with comorbid OSAHS and POAG, ranging from 25% to 64.57%, and is more common in those with severe OSAHS[83-84]. This suggests an indispensable mediating role in the pathogenic pathway of OSAHS-related glaucoma. Such mediation is achieved mainly through two interrelated mechanisms: neurotoxicity driven by ocular surface inflammation, and mechanical disturbance of IOP and optic nerve biomechanics. In addition, FES usually precedes the onset of OSAHS-related glaucoma, particularly POAG, and is positively correlated with OSAHS severity, supporting its role as an early clinical biomarker for identifying individuals at high risk of glaucoma[83-84]. This predictive value is especially prominent in NTG. Ocular surface inflammation and mechanical stress mediated by FES are highly consistent with the core pathological features of NTG. Therefore, FES screening can be used for early identification and intensified monitoring of these high-risk glaucoma patients[85-86].

Core Mechanisms OSAHS mediates optic nerve injury in POAG through two interrelated pathways: IOP-dependent (elevated IOP) and non-IOP-dependent (chronic hypoxia and oxidative stress), forming a complex pathogenic network. OSAHS-related intermittent hypoxia and inflammatory responses predominantly drive NTG progression *via* non-IOP-dependent pathways, whereas their impact on HTG is limited to mild IOP elevation and fluctuation. The precise pathogenic mechanisms underlying OSAHS in POAG remain to be fully elucidated[87]. Furthermore, FES can further amplify these pathological effects and synergize with OSAHS to exacerbate optic nerve degeneration.

IOP-dependent injury mechanism Negative thoracic pressure generated during apneic episodes increases episcleral venous pressure and reduces aqueous outflow, resulting in transient IOP elevation[88-89]. Meanwhile, sleep fragmentation associated with OSAHS can exacerbate diurnal IOP fluctuation (≥10 mm Hg), further aggravating IOP-related optic nerve injury[90-91]. However, continuous IOP monitoring has revealed paradoxical IOP reduction during apneic events in some

patients, suggesting that mechanical factors may play only a secondary role in OSAHS-related IOP-dependent injury[88]. Furthermore, FES amplifies these OSAHS-related IOP abnormalities through local mechanical effects. FES-related eyelid laxity causes intermittent compression of the globe during sleep, inducing transient IOP elevation and increasing biomechanical stress on the lamina cribrosa. This effect is particularly prominent in NTG patients and synergistically worsens optic nerve damage[83].

Non-IOP-dependent injury mechanism OSAHS primarily damages the optic nerve through neuroinflammation and oxidative stress induced by chronic intermittent hypoxia (CIH), as well as optic nerve hypoperfusion caused by hemodynamic fluctuations. This pathway plays a central role in NTG progression[82].

The retina is characterized by high oxygen tension and constant light exposure, rendering it susceptible to tissue-specific oxidative damage even in the absence of altered systemic oxidative stress markers. Systemic hypoxia induced by recurrent apnea and hypopnea events activates the hypoxia-inducible factor (HIF)-1α/VEGF pathway and the NLRP3 inflammasome in retinal tissue, leading to massive release of pro-inflammatory cytokines (IL-1β, IL-18, TNF-α) and ROS. This directly causes RGC injury and blood–retinal barrier breakdown, ultimately accelerating optic nerve degeneration[90-92]. FES acts synergistically with OSAHS *via* ocular surface inflammation. Nocturnal lagophthalmos in FES results in persistent ocular surface exposure, triggering local sterile inflammation with markedly upregulated inflammatory mediators including IL-6, matrix metalloproteinase-9 (MMP-9), and ROS. These local factors converge with systemically induced pro-inflammatory cytokines and ROS to act on the optic nerve head, further amplifying inflammatory and oxidative damage and significantly promoting RGC apoptosis[83-86]. Furthermore, CIH impairs mitochondrial function and disrupts oxidative balance, markedly reducing the tolerance of RGCs to glaucoma-related stress. FES-associated eyelid laxity induces high expression of elastic-degrading enzymes such as MMP-9 in the tarsal plate, worsening mechanical instability of the eyelid and directly transmitting mechanical stress to deep intraocular structures. This non-IOP-dependent mechanism adds to inflammatory and oxidative injury, collectively exacerbating optic nerve degeneration[82-83].

At the hemodynamic level, nocturnal hypertension, morning hypotension associated with OSAHS, and acute IOP spikes caused by thoracic pressure fluctuations during apneic episodes can disrupt the homeostasis of ocular perfusion pressure (OPP)[84]. Obstructive sleep apnea (OSA)-induced endothelial dysfunction further impairs retinal vascular autoregulation and exacerbates hypoperfusion of the optic nerve head. The inherent vascular dysregulation in patients with POAG markedly amplifies this abnormality, leading to chronic ischemia and hypoxia of the optic nerve. This constitutes a core pathological component of non-IOP-dependent injury in NTG. In addition, severe OSA increases blood flow resistance in the posterior ciliary arteries—the main vessels supplying the optic nerve—further worsening optic nerve hypoperfusion. Together, these mechanisms mediate RGC apoptosis and injury through ischemia and hypoxia[88].

Clinical Therapeutic Implications The association between OSAHS and POAG is mediated by the synergistic effects of chronic intermittent hypoxia, neuroinflammation, hemodynamic disturbances, and FES, which provides a theoretical basis for bilateral screening and targeted intervention in high-risk populations. Continuous positive airway pressure, as the mainstay treatment for OSAHS, can ameliorate the nocturnal IOP rhythm, but may increase IOP in patients with impaired trabecular meshwork function, requiring individualized monitoring. FES is expected to serve as an adjuvant therapeutic target for glaucoma, although its intervention efficacy still needs to be verified by further research.

CONCLUSION AND PERSPECTIVES

POAG is a complex optic nerve neurodegenerative disorder whose development and progression involve not only IOP-related injury and alterations in the local ocular microenvironment, but also the combined effects of genetic susceptibility, environmental exposure, aging, and systemic factors involving multiple organ systems. The eye–brain–body framework provides a systems-level perspective for integrating the comorbid associations and potential shared mechanisms between POAG and various systemic diseases. However, this framework should not be interpreted as evidence that systemic diseases are independent direct causes of POAG. Some associations may arise from common upstream factors, including aging, vascular dysregulation, metabolic stress, chronic low-grade inflammation, mitochondrial dysfunction, and susceptibility to neurodegeneration. HTG and NTG exhibit distinct subtype-specific pathological features. HTG is primarily driven by IOP-dependent injury, whereas systemic factors often exert secondary accelerating effects. In contrast, NTG is mainly mediated by non-IOP-dependent pathways, and systemic comorbidities may have a more direct and pronounced influence on its onset and progression. Systemic pathological states, including cardiovascular dysfunction, metabolic abnormalities, neuroimmune dysregulation, and gut dysbiosis, may aggravate retinal ganglion cell injury through overlapping and interacting cascade networks. Among these mechanisms, the eye–brain axis, gut–eye/gut microbiota–immune axis, and ocular lymphatic/glymphatic system represent three emerging core regulatory pathways. These pathways connect systemic

multisystem pathological alterations with optic nerve injury, highlighting the potential mechanistic links between POAG and multiple systemic diseases, including metabolic, immune-mediated, and neurodegenerative disorders.

Current research on the relationship between systemic diseases and POAG still has several important limitations. Existing evidence is largely derived from observational studies, and causal evidence remains insufficient. In addition, heterogeneity related to ethnicity, population characteristics, and POAG subtypes has not been fully clarified. The associations of diabetes mellitus, OSAHS, PD, and other disorders with POAG remain controversial, and their disease-specific mechanisms are still unclear. Interventional studies targeting the gut microbiota, TLCPD-related mechanisms, and systemic immune-inflammatory pathways also lack reliable evidence for clinical translation. Most existing studies have focused on a single systemic disease, whereas systematic investigations into the interactive effects of multiple comorbidities and their synergistic involvement in optic nerve injury remain limited. Future studies should further distinguish the specific effects of systemic diseases on POAG from comorbid associations driven by shared upstream risk factors, and should clarify key pathological pathways in different patient subgroups.

At the clinical level, POAG management should account for subtype-specific differences while maintaining IOP control as the foundation. In HTG, greater emphasis should be placed on controlling absolute IOP levels and IOP-related mechanical injury. In NTG, more attention should be paid to IOP fluctuation, optic nerve perfusion, vascular dysregulation, and systemic comorbidities. Future strategies should integrate subtype-based IOP management with systemic disease assessment through multidisciplinary collaboration, thereby promoting early identification, precise intervention, and long-term individualized management of POAG. A systemic perspective may deepen our understanding of POAG pathogenesis and provide new research directions and a clinical basis for reducing the burden of POAG-related blindness.

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