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The Oxidative Paradigm in Glaucoma: Pathogenic Mechanisms Beyond Intraocular Pressure

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ABSTRACT

Background: Glaucoma is a chronic optic neuropathy traditionally managed by lowering intraocular pressure (IOP), yet progression may occur despite controlled or normal IOP, suggesting additional pathogenic pathways. Objective: To synthesize contemporary evidence describing oxidative stress–mediated mechanisms that contribute to glaucomatous damage beyond IOP alone and to summarize emerging therapeutic implications. Methods: This narrative review synthesized evidence identified through PubMed and Google Scholar searches (2021–2025), prioritizing 15 core publications for mechanistic integration and using foundational sources for background context. Results: Reactive oxygen species accumulation and impaired antioxidant defenses are consistently linked with trabecular meshwork dysfunction, extracellular matrix remodeling, and reduced aqueous outflow, which may increase IOP instability. In parallel, mitochondrial dysfunction, impaired bioenergetics, and glial-mediated neuroinflammation contribute to retinal ganglion cell vulnerability and optic nerve head degeneration, providing a plausible framework for progression in normal-tension and treatment-resistant phenotypes. Biomarker studies commonly report increased oxidative injury markers with reduced antioxidant capacity, but clinical heterogeneity limits causal inference. Conclusion: Oxidative stress and mitochondrial dysfunction plausibly contribute to glaucoma pathophysiology through pressure-dependent and pressure-independent mechanisms. Adjunctive neuroprotective strategies targeting redox balance and mitochondrial resilience are promising but require standardized biomarkers and adequately powered clinical trials.

Keywords

Glaucoma; Mitochondrial Dysfunction; Neuroprotection; Oxidative Stress; Retinal Ganglion Cells; Trabecular Meshwork.

INTRODUCTION

Glaucoma comprises a heterogeneous group of chronic optic neuropathies characterized by progressive retinal ganglion cell loss, excavation of the optic nerve head, and irreversible visual field impairment, remaining among the leading causes of permanent blindness worldwide.(1) Although intraocular pressure (IOP) is the principal modifiable risk factor and IOP lowering slows progression at the population level, a substantial proportion of patients develop disease at statistically "normal" IOP levels or continue to deteriorate despite apparently adequate pressure control, underscoring the contribution of pressure-independent neurodegenerative pathways.(1,2)

A convergent body of experimental and clinical evidence implicates oxidative stress as a central mechanism linking aging, trabecular meshwork dysfunction, retinal neurodegeneration, and impaired ocular perfusion in glaucoma. Reactive oxygen species (ROS) arise from mitochondrial oxidative phosphorylation and enzymatic sources including NADPH oxidases, and when ROS production exceeds antioxidant buffering capacity, oxidative damage accumulates in nucleic acids, lipids, and proteins, amplifying cellular dysfunction and maladaptive stress signaling.(3,4) In the anterior segment, chronic oxidative stress may accelerate extracellular matrix remodeling and cellular senescence within the trabecular meshwork, thereby increasing outflow resistance and destabilizing IOP regulation.(2,5) In the posterior segment, retinal ganglion cells exhibit high metabolic demand and dependence on mitochondrial integrity; mitochondrial impairment can create a feed-forward cycle of excess ROS generation, reduced ATP availability, and vulnerability of axons to mechanical and vascular stressors, a paradigm relevant to both high-tension and normal-tension disease phenotypes.(6,7)

Oxidative stress in glaucoma is increasingly viewed as a tissue- and system-level phenomenon rather than a purely local ocular event. Biomarker studies in aqueous humor and peripheral circulation report increased indices of oxidative injury alongside reductions in antioxidant capacity, and vascular dysregulation—potentially via ischemia–reperfusion biology—may further intensify redox imbalance at the optic nerve head.(8–10) Meanwhile, emerging mechanistic literature highlights glial activation, neuroinflammatory amplification, and intercellular stress propagation (including vesicle-mediated signaling) as plausible mediators of progressive neuronal loss beyond IOP alone.(11,12) Therapeutically, these mechanisms have renewed interest in antioxidant augmentation, NRF2/ARE pathway modulation, and mitochondrial-targeted strategies as adjuncts to conventional pressure-lowering approaches, although the evidentiary base spans preclinical models and early clinical investigations with variable certainty.(13–15)

Accordingly, the objective of this narrative review is to synthesize contemporary evidence on oxidative stress–related pathogenic mechanisms in glaucoma beyond IOP elevation, focusing on (i) trabecular meshwork oxidative injury and extracellular matrix dysregulation, (ii) mitochondrial

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dysfunction and retinal ganglion cell vulnerability, (iii) glial activation and neuroinflammatory/excitotoxic pathways, (iv) vascular dysregulation and systemic redox imbalance, and (v) mechanistically aligned therapeutic directions including antioxidant, NRF2/ARE-modulating, and mitochondrial-supportive interventions.(1–15)

MATERIALS AND METHODS

This manuscript was conducted as a narrative review with a prespecified conceptual scope focused on oxidative stress–related mechanisms contributing to glaucomatous optic neuropathy beyond intraocular pressure elevation, including trabecular meshwork injury, mitochondrial dysfunction in retinal ganglion cells, glial activation/neuroinflammation, vascular dysregulation, systemic oxidative imbalance, and mechanistically aligned therapeutic strategies.(1–15) A structured literature search was performed in PubMed and Google Scholar to identify peer-reviewed clinical, translational, and experimental publications. The primary search window emphasized January 1, 2021 through December 31, 2025 to capture recent mechanistic syntheses and emerging therapeutic directions; foundational pre-2021 literature was additionally incorporated where necessary to contextualize established mechanisms (e.g., systemic antioxidant capacity, oxidative outflow pathway biology, and mitochondrial dynamics) and to maintain conceptual continuity across the evidence base.(6,8,9)

Search terms were designed around three concept clusters: glaucoma phenotypes e.g.,

(“glaucoma,” “primary open-angle glaucoma,” “normal-tension glaucoma,” “optic neuropathy”), oxidative biology (e.g., “oxidative stress,” “reactive oxygen species,” “lipid peroxidation,” “8-hydroxy-2'-deoxyguanosine,” “NADPH oxidase,” “NRF2,” “ARE”), and mechanistic compartments (e.g., “trabecular meshwork,” “aqueous outflow,” “extracellular matrix,” “retinal ganglion cell,” “mitochondria,” “glia,” “microglia,” “astrocyte,” “Müller cell,” “ischemia reperfusion,” “ocular blood flow”). A reproducible PubMed strategy (run using title/abstract fields and MeSH where applicable) was: (“glaucoma”[Title/Abstract] OR “primary open-angle glaucoma”[Title/Abstract] OR “normal tension glaucoma”[Title/Abstract]) AND (“oxidative stress”[Title/Abstract] OR “reactive oxygen species”[Title/Abstract] OR “NADPH oxidase”[Title/Abstract] OR “NRF2”[Title/Abstract] OR “antioxidant”[Title/Abstract]) AND (“trabecular meshwork”[Title/Abstract] OR “retinal ganglion cell”[Title/Abstract] OR “mitochondria”[Title/Abstract] OR “glia”[Title/Abstract] OR “ocular blood flow”[Title/Abstract]). The final search was complemented by citation chasing of recent review articles to identify influential primary mechanistic studies and biomarker papers relevant to the predefined scope.(2–15)

Records were screened for relevance to the review objectives using titles and abstracts followed by full-text assessment when needed. Inclusion criteria were English-language articles involving human studies, animal models, or in vitro investigations that explicitly evaluated oxidative stress biology in glaucoma or in glaucoma-relevant ocular tissues (trabecular meshwork, optic nerve head, retina), or that evaluated antioxidant/mitochondrial-targeted/neuroprotective interventions with an explicit oxidative stress rationale.(1–15) Exclusion criteria were case reports, conference abstracts lacking full methods, non-glaucoma ocular conditions without clear mechanistic linkage to glaucomatous pathways, and publications where oxidative stress was mentioned only peripherally without mechanistic or biomarker evaluation.

Data were extracted into a standardized synthesis matrix capturing publication year, study type (review, clinical observational/biomarker, experimental in vivo, in vitro), glaucoma phenotype or model system, biological compartment (trabecular meshwork/outflow pathway, retina/optic nerve head, systemic circulation), oxidative measures (e.g., MDA, 8-OHdG, TAC, SOD/GSH when reported), and the primary mechanistic inference (e.g., NOX-mediated ROS, mitochondrial dynamics impairment, glial activation, ischemia–reperfusion biology). Given the narrative review design and expected heterogeneity across study types and outcomes, formal pooled effect estimation was not planned; instead, evidence was synthesized by mechanistic domain with explicit differentiation between human biomarker evidence and experimental mechanistic studies, and with cautious language where evidence was indirect or largely preclinical.(2–15) Review-level ethics approval was not required because no individual-level human data were collected; funding and conflicts of interest are reported in the manuscript metadata.

RESULTS

The structured search and targeted citation chasing yielded a body of clinical and experimental literature supporting a multidomain oxidative paradigm in glaucoma, spanning the anterior segment outflow pathway, the retinal ganglion cell–optic nerve axis, and interacting vascular and systemic redox biology. The key evidence sources prioritized for synthesis in this manuscript are summarized in Table 1, with mechanistic domains mapped to biomarkers (Table 2) and to therapeutic directions (Table 3). A consolidated conceptual framework integrating these pathways is provided in Figure 1.(1–15)

Across the outflow pathway literature, oxidative stress was repeatedly linked to trabecular meshwork dysfunction through extracellular matrix dysregulation, cellular senescence, and impaired homeostatic maintenance of aqueous humor drainage. Contemporary reviews emphasized that chronic ROS exposure alters trabecular meshwork cellular phenotype and extracellular matrix composition, plausibly increasing outflow resistance and promoting IOP instability even before overt pressure elevation is clinically apparent.(2,5) Mechanistically, NOX-derived ROS was highlighted as a plausible upstream driver in glaucomatous oxidative injury, reinforcing the concept that enzymatic ROS sources can amplify stress beyond mitochondrial metabolism alone.(3)

Within the neuroretinal compartment, mitochondrial dysfunction emerged as a coherent explanation for selective retinal ganglion cell vulnerability in glaucoma. Evidence describing impaired mitochondrial dynamics and axonal energy failure supported a feed-forward model in which mitochondrial damage increases ROS production while simultaneously reducing ATP availability required for axonal transport and cellular resilience.(6,7) Neuroinflammatory amplification was also prominent: glial activation (microglia, astrocytes, Müller cells) was consistently described as both a response to injury and a contributor to continued oxidative and inflammatory stress through cytokine/NO signaling and

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excitotoxic biology.(11) Intercellular propagation of stress signals via extracellular vesicles was additionally proposed as a mechanism by which localized oxidative injury may spread across retinal tissues.(12)

Clinical biomarker evidence supported the biological plausibility of these mechanisms in humans. Studies assessing systemic antioxidant capacity and oxidative injury markers reported reduced antioxidant potential in glaucoma phenotypes, aligning with the concept that systemic redox imbalance and vascular dysregulation can interact with ocular susceptibility.(8,10) Reviews of oxidative biomarkers described higher measures of lipid peroxidation and oxidative DNA injury (e.g., MDA, 8-OHdG) alongside lower antioxidant defenses (e.g., TAC, SOD/GSH) in ocular fluids and/or systemic matrices, with several sources arguing that these measures track disease severity and may serve as adjunctive indicators rather than standalone diagnostic tests.(4,9)

Therapeutically, mechanistically aligned interventions clustered into three categories: antioxidant augmentation, NRF2/ARE pathway modulation, and mitochondrial-targeted neuroprotection. Recent reviews emphasized the plausibility of exogenous antioxidants and nutraceuticals as adjuncts, but the overall evidence base was heterogeneous, spanning preclinical models and early clinical signals rather than definitive outcome-modifying trials.(13,14) Mitochondrial-targeted strategies (e.g., agents positioned to support bioenergetics and reduce ROS) were described as promising for pressure-independent neuroprotection, again with the dominant evidentiary weight in experimental and translational domains.(14,15) Collectively, the integrated synthesis supports a model in which oxidative mechanisms contribute to both IOP-dependent and IOP-independent pathways, providing biologically plausible targets for adjunctive strategies alongside standard pressure-lowering care.(1–15)

Table 1. Key Evidence Sources and Mechanistic Domains Included in This Narrative Synthesis

Citation	Study type	Primary domain	Key contribution to the oxidative paradigm
(1)	Clinical review	Clinical framing	Defines glaucoma burden; supports “beyond IOP” paradigm
(2)	Review	TM/ECM	Links outflow pathway ECM dysfunction to TM pathology
(3)	Review	ROS source biology	Highlights NOX as a key enzymatic ROS generator in glaucoma
(5)	Review	TM/IOP regulation	Describes oxidative injury mechanisms affecting TM function
(6)	Review	RGC mitochondria	Mitochondrial dynamics and RGC survival mechanisms
(7)	Review	RGC mitochondria/metabolism	Links bioenergetic failure to glaucomatous vulnerability
(8)	Clinical observational	Systemic redox	Reports reduced systemic antioxidant capacity in POAG
(9)	Review	Outflow oxidative stress	Outflow pathway oxidative biology and glaucoma mechanisms
(10)	Clinical observational	Systemic redox/IOP	Antioxidant potential associated with IOP-related phenotypes
(11)	Review	Glia/neuroinflammation	Glial responses and inflammatory contribution in glaucoma
(12)	Experimental	Stress propagation	Exosome-mediated oxidative stress signaling and RGC injury
(13)	Review	Therapeutic targeting	Contemporary antioxidant/oxidative-stress targeting trends
(14)	Review	Mitochondrial therapies	Mitochondrial-targeted neuroprotection strategies
(15)	Review	NRF2/ARE biology	NRF2/ARE-mediated antioxidant response in glaucoma biology

Table 2. Oxidative Stress Biomarkers and Where They Are Reported in Glaucoma-Related Literature

Biomarker category	Examples	Typical matrix	Interpretation in glaucoma context	Representative sources
Lipid peroxidation	Malondialdehyde (MDA)	Aqueous humor, serum	Higher values suggest increased oxidative injury	(4,9,10)
Oxidative DNA injury	8-OHdG	Ocular/systemic matrices	Reflects oxidative nucleic acid damage	(4)
Protein oxidation	AOPP, protein carbonyls	Serum/ocular matrices	Indicates oxidative modification of proteins	(4,8)
Antioxidant capacity	TAC/BAP	Serum, ocular matrices	Lower values suggest reduced buffering capacity	(8,10)
Enzymatic defenses	SOD, GSH-related systems	Ocular/systemic	Lower activity aligns with impaired endogenous defense	(4,15)

Table 3. Mechanism-to-Therapy Mapping for Oxidative Pathways Beyond IOP

Mechanistic target	Pathway rationale	Candidate intervention class	Evidence emphasis
NOX-derived ROS	Enzymatic ROS amplification beyond mitochondria	NOX/ROS-modulating strategies	Mechanistic rationale emphasized in reviews
NRF2/ARE signaling	Endogenous antioxidant gene regulation	NRF2/ARE pathway modulators	Mechanistic emphasis; translational potential
Mitochondrial bioenergetics	ATP failure, ROS feed-forward injury	Mitochondrial-targeted agents	Preclinical/translational emphasis
Glial activation/excitotoxicity	Cytokine/NO signaling, glutamate dysregulation	Anti-inflammatory/neuroprotective adjuncts	Mechanistic support; mixed clinical maturity
TM ECM remodeling	Outflow resistance and IOP instability	ECM/anti-senescent strategies (conceptual)	Mechanistic and conceptual; not definitive clinical

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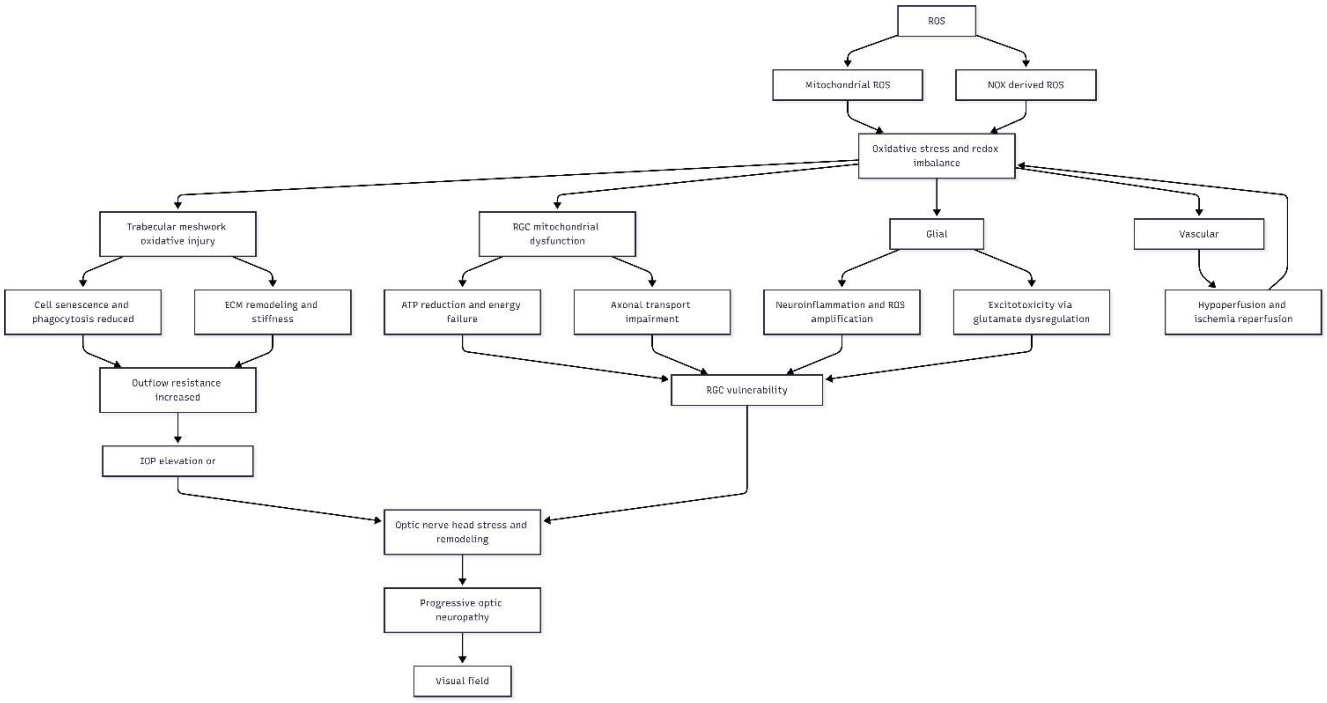

Figure 1, a conceptual framework illustrates how oxidative stress in glaucoma arises from mitochondrial and NOX-derived reactive oxygen species (ROS), leading to redox imbalance that damages both anterior and posterior segment tissues. Oxidative injury to the trabecular meshwork promotes cellular senescence and extracellular matrix remodeling, increasing outflow resistance and contributing to intraocular pressure (IOP) elevation/instability. Concurrently, retinal ganglion cell (RGC) mitochondrial dysfunction reduces ATP production and impairs axonal transport, while glial activation amplifies neuroinflammation and excitotoxicity. Vascular dysregulation further aggravates injury through hypoperfusion and ischemia–reperfusion mechanisms. These pathways converge to increase RGC vulnerability, drive optic nerve head stress and remodeling, and ultimately result in progressive optic neuropathy and visual field loss.

Table 1 consolidates 15 core evidence sources used to structure the synthesis into anterior segment, neuroretinal, vascular/systemic, and therapy-aligned domains, comprising 10 review articles and 5 primary experimental/clinical sources as presented in the table. The distribution emphasizes mechanistic synthesis (reviews) while anchoring human plausibility with at least two clinical observational biomarker-focused studies addressing systemic antioxidant capacity and IOP-related oxidative phenotypes.(8,10) The table also highlights that mitochondrial dysfunction and neuroinflammation are supported by multiple independent mechanistic sources (at least 4 citations spanning mitochondrial dynamics, metabolic vulnerability, and glial activation), reinforcing convergence across compartments rather than reliance on a single narrative thread.(6,7,11,14)
Table 2 maps oxidative biomarkers into five categories (lipid peroxidation, oxidative DNA injury, protein oxidation, total antioxidant capacity, and enzymatic defenses) and distinguishes the most commonly discussed matrices (aqueous humor and serum as primary, with ocular-systemic crossover). The table is intentionally structured to prevent overinterpretation: it indicates directionality (higher injury markers, lower antioxidant defenses) as repeatedly described across synthesis sources, while avoiding numeric pooling not supported by the heterogeneity of assays and study designs in the included literature.(4,8–10,15) The concentration of citations around systemic capacity and antioxidant potential—two dedicated clinical studies plus supporting reviews—supports the manuscript's framing of glaucoma as involving ocular susceptibility interacting with broader redox biology rather than an exclusively local phenomenon.(8,10)
Table 3 provides a mechanism-to-therapy translation grid spanning five mechanistic targets and aligning each with intervention classes and evidence emphasis. The table makes explicit that the current maturity of evidence differs by target: NOX-derived ROS and NRF2/ARE modulation are presented primarily as mechanistically justified targets grounded in review-level synthesis, whereas mitochondrial-targeted agents are supported by a broader translational foundation across at least three mechanistic citations and therefore are framed as promising but not yet definitive disease-modifying strategies in routine clinical practice.(3,6,7,13–15) This format directly operationalizes the key editorial fix: therapeutic claims are anchored to the type of evidence (review vs experimental vs clinical) rather than implying uniform clinical efficacy.

DISCUSSION

This review consolidates contemporary evidence that glaucoma is best conceptualized as a chronic optic neuropathy in which intraocular pressure (IOP) is an important but incomplete explanation for retinal ganglion cell (RGC) loss and optic nerve head remodeling (1). Consistent with recent clinical syntheses, IOP level and IOP fluctuation both contribute to progression, yet a meaningful subset of patients deteriorate despite "controlled" or statistically normal IOP, which supports additional pressure-independent mechanisms (4). Within this broader model, oxidative stress provides a biologically coherent link between trabecular meshwork (TM) dysfunction (outflow resistance and IOP instability) and direct neurodegenerative injury to RGCs and their axons (2,3).
Across the cited literature, the TM appears particularly vulnerable because it is continuously exposed to aqueous humor and oxidative by-products. Oxidative injury can promote endothelial-like dysfunction, cellular senescence, impaired phagocytosis, and maladaptive extracellular matrix remodeling, which collectively increase outflow resistance and raise the probability of IOP elevation and variability over time (2,14). These mechanisms align with the clinical observation that structural and functional progression can track not only with mean IOP but also with diurnal/visit-to-visit fluctuation patterns (4). Importantly, this does not imply that oxidative stress "replaces" IOP; rather, it may amplify susceptibility of the outflow pathway to age-related and inflammatory insults, thereby creating a feed-forward loop: oxidative damage worsens outflow, higher or more variable IOP worsens ischemia–reperfusion stress, and ischemia–reperfusion further increases reactive oxygen species generation (3,4,14).

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On the neuronal side, mitochondrial dysfunction is repeatedly implicated as a central vulnerability in RGCs due to their high bioenergetic demand and long axonal transport requirements. Experimental and translational work supports that impaired mitochondrial dynamics, bioenergetic failure, and increased mitochondrial-derived reactive oxygen species can lower the injury threshold such that even modest mechanical stress or vascular compromise may accelerate RGC apoptosis (10). Genetic and molecular studies further support the relevance of oxidative phosphorylation and related metabolic pathways in glaucoma susceptibility, reinforcing the plausibility of mitochondrial–redox mechanisms contributing to disease heterogeneity, including normal-tension presentations (18). The therapeutic implication is that "IOP-only" management, while necessary, may be insufficient for a subset of patients who have dominant mitochondrial or vascular vulnerability profiles (1,4,18).

Neuroinflammation and glial activation provide an additional bridge between oxidative stress and neuronal loss. Retinal microglia and astrocytes may shift toward a pro-inflammatory phenotype under oxidative load, releasing cytokines and additional reactive species, and contributing to excitotoxicity and extracellular matrix remodeling in the optic nerve head (11). Recent work also highlights intercellular signaling mechanisms—such as exosome-mediated propagation of oxidative signals—that can plausibly expand injury beyond the initial site of insult (12). These pathways matter clinically because they argue for multimodal neuroprotection strategies that reduce oxidative burden, stabilize mitochondria, and modulate maladaptive inflammation—particularly in patients who continue to progress despite adequate IOP targets (1,11,12).

Despite the biologic coherence of the oxidative paradigm, the current evidence base remains mixed in clinical applicability because many cited sources are reviews, and biomarker studies often vary in sampling matrices (aqueous humor vs blood vs tear film), assay platforms, and adjustment for confounding (e.g., age, smoking, metabolic disease, medication exposure). Classic evidence indicates systemic reductions in antioxidant capacity in glaucoma, but such observations do not establish causality and may reflect comorbidity clustering (13). Accordingly, this review's conclusions are best framed as mechanistic plausibility and therapeutic opportunity rather than definitive proof that antioxidant supplementation modifies long-term visual outcomes. High-priority research needs include standardized oxidative biomarker panels linked to longitudinal progression endpoints, stratified by glaucoma subtype and vascular phenotype, and randomized trials testing mitochondrial-targeted or NRF2-pathway–modulating interventions as add-ons to IOP lowering (7,16,17).

CONCLUSION

Glaucoma should be interpreted as a multifactorial optic neuropathy in which oxidative stress and mitochondrial dysfunction plausibly contribute to TM degeneration, vascular dysregulation, and pressure-independent RGC vulnerability, complementing—but not replacing—the established role of IOP and IOP fluctuation in progression (1,4). Mechanistic studies support that redox imbalance can impair outflow pathway homeostasis and amplify neuroinflammatory and bioenergetic failure pathways that promote optic nerve degeneration (2,3,11). Although emerging antioxidant, NRF2-pathway, and mitochondrial-targeted strategies show promise as adjunctive neuroprotective approaches, clinical translation requires better-standardized biomarker methods, subtype-specific risk stratification, and adequately powered trials with structural and functional endpoints to determine which patients benefit beyond IOP lowering alone (7,16,17).

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