Clinical and Experimental Vision and Eye Research (2026), 8 (1) 7-11

COMMENTARY

From Pressure to Protection: Reframing Glaucoma as a Multifactorial Optic Neuropathy

Shibal Bhartiya[1-3], Jay Bhargav[4]

[1]Clinical Director, Ophthalmology; Program Director, Community Outreach & Wellness Marengo Asia Hospitals; Program Director, Marengo Asia International Institute of Neuro & Spine, Gurgaon and Faridabad, India; [2]Research Collaborator, Mayo Clinic, Jacksonville, Florida, USA; [3]Founder, Vision Unlimited, Gurgaon, India; [4]Musgrove Park Hospital, Taunton, Somerset, UK.

Keywords:

glaucoma, intraocular pressure, optic neuropathy, neuroprotection, retinal ganglion cells, nicotinamide, normal-tension glaucoma, patient communication, biomarkers glaucoma progression, glaucoma as neurodegenerative disease

Address for correspondence:
Shibal Bhartiya,
Marengo Asia Hospitals, Sector 56,
Gurgaon, Haryana, 122011, India.
E-mail: drshibalbhartiya@gmail.com

doi: 10.15713/ins.clever.114

Abstract

Glaucoma is classically understood and managed through the lens of intraocular pressure (IOP) reduction. Landmark clinical trials have firmly established IOP lowering as the only intervention with proven efficacy in slowing disease progression, and this evidence base rightly underpins contemporary treatment.

However, a strictly pressurecentric explanation of glaucomatous optic neuropathy is no longer scientifically tenable. Accumulating evidence implicates biomechanical vulnerability of the optic nerve head, vascular perfusion dynamics, mitochondrial dysfunction, neuroinflammatory signalling, and progressive neurodegeneration as co-determinants of retinal ganglion cell (RGC) fate. These mechanisms account for the substantial proportion of patients who progress despite apparently well-controlled IOP, and for the clinical heterogeneity that pressure measurements alone cannot explain.

This commentary argues that reframing glaucoma, in both research paradigms and in clinical communication with patients. as a multifactorial optic neuropathy characterised by variable susceptibility and continual neuronal loss is not merely a semantic preference, but a practical necessity. Situating IOP reduction within a broader strategy of optic nerve protection, while integrating metabolic, vascular, and neuroprotective considerations, better aligns clinical practice with contemporary scientific understanding.

Introduction

Glaucoma remains the leading cause of irreversible blindness worldwide, projected to affect 112 million individuals by 2040.[1] Characterised by progressive loss of retinal ganglion cells (RGCs) and their axons, glaucomatous optic neuropathy produces structural cupping of the optic disc and corresponding visual field defects that are, by the time they are clinically detectable, already significantly advanced.[2] Intraocular pressure (IOP) has historically been both the defining risk factor and the principal therapeutic target in glaucoma, a framework reinforced by decades of clinical trials demonstrating that pressure reduction demonstrably slows disease progression.[3,4,5]

Yet experienced clinicians encounter, with regularity, patients who continue to deteriorate despite achieving target IOP, and patients who tolerate significant pressure elevation without apparent structural compromise. This variability is not an anomaly to be dismissed; it is a signal that the pressure paradigm, while necessary, is not sufficient. Glaucoma is increasingly recognized as a neurodegenerative disease in which mechanical load interacts with vascular, metabolic, and inflammatory vulnerabilities to determine individual susceptibility.[2,6]

This commentary makes the case that reframing glaucoma as a multifactorial optic neuropathy has implications not only for research and therapeutic development, but for how specialists communicate with patients, and for whether those patients, faced with a chronic, asymptomatic disease, will remain engaged in lifelong care.[7]

The IOP Paradigm: Its Foundations and Its Limits

The centrality of IOP in glaucoma management rests on firm clinical trial evidence. The Ocular Hypertension Treatment Study (OHTS) demonstrated that topical hypotensive therapy significantly reduced the incidence of primary open-angle glaucoma among patients with elevated IOP.[4] The Early Manifest

Glaucoma Trial (EMGT) confirmed that IOP reduction slowed visual field progression in early glaucoma.[5] Perhaps most instructive, the Collaborative Normal-Tension Glaucoma Study showed that even in eyes with statistically normal IOP, pressure reduction was associated with a reduced rate of visual field deterioration. This observation simultaneously validated IOP lowering, and exposed the complexity it could not fully resolve.[8]

These trials collectively anchored IOP reduction as the cornerstone of glaucoma therapy, influencing not only treatment decisions but also the language clinicians use with patients. IOP became, in effect, the scorecard of disease control. This has been both a strength and a liability.

The limitations of a purely pressure-centric model are not trivial. A significant proportion of patients in the EMGT continued to progress despite a 25% reduction from baseline IOP.[5] Structural progression detected by optical coherence tomography (OCT) can precede measurable visual field loss, decoupling the two most common surrogate endpoints used in clinical monitoring.[9] Corneal biomechanical properties, specifically corneal hysteresis, correlate with visual field deterioration independently of IOP, suggesting that tissue resilience rather than pressure magnitude may be the critical variable in some patients.[10] Meta-analytic evidence supports the conclusion that glaucomatous damage cannot be fully explained by pressure parameters alone.[11]

Normal-tension glaucoma (NTG), in which characteristic optic neuropathy develops at statistically normal pressures, is perhaps is perhaps the most direct refutation of a purely mechanical model.[12] In Asian populations, NTG may account for 30–40% of all glaucoma diagnoses, a prevalence that demands explanation beyond the pressure axis.[6]

Mechanisms Beyond Pressure: The Biological Complexity of Glaucomatous Injury

Understanding why some optic nerves fail under apparently modest pressure loads while others survive significant elevation requires engagement with several intersecting pathogenic pathways.

Optic nerve head biomechanics

The lamina cribrosa, the fenestrated collagenous plate through which RGC axons exit the eye, represents the primary site of glaucomatous injury.[13] Mechanical stress across this structure is determined not by IOP alone, but by the translaminar pressure gradient between intraocular and intracranial cerebrospinal fluid pressures.[13] Connective tissue composition, scleral rigidity, and parapapillary morphology, particularly in myopic eyes, modify the biomechanical response to equivalent pressure loads.[14] Progressive remodelling of the lamina cribrosa has been proposed as a mechanism underlying glaucomatous cupping, independent of acute pressure events.[15] This biomechanical heterogeneity helps explain why a single numerical IOP threshold cannot define safety for all eyes.

Vascular dysregulation and nocturnal vulnerability

Ocular perfusion pressure, the difference between mean arterial pressure and IOP, is an independent risk factor for glaucoma development and progression.[16] Nocturnal hypotension, particularly in patients receiving antihypertensive therapy, may critically reduce optic nerve head perfusion during sleep, with evidence linking exaggerated nocturnal blood pressure dipping to accelerated visual field loss.[17] Obstructive sleep apnoea has emerged as a clinically significant, frequently unrecognised contributor to glaucoma progression, plausibly mediated through intermittent hypoxia, oxidative stress, and impaired vascular autoregulation.[18] Flammer syndrome, primary vascular dysregulation, renders the optic nerve especially vulnerable to ischaemic stress through unstable, dysregulated perfusion.[19] These data collectively suggest that glaucoma progression reflects dynamic neurovascular strain over a 24-hour cycle, not a static snapshot of daytime IOP.

Neurodegeneration, mitochondrial dysfunction, and trans-synaptic degeneration

RGC death in glaucoma occurs primarily through apoptotic pathways triggered by axonal injury at the level of the optic nerve head.[20] Critically, this process may continue after IOP has been successfully lowered, implying that secondary neurodegenerative mechanisms are self-propagating once initiated.[20] Mitochondrial dysfunction occupies a central position in this cascade: RGCs have exceptionally high metabolic demands given the non-saltatory conduction along unmyelinated axons traversing the retina, making them disproportionately vulnerable to any energy deficit.[21] Age-related decline in nicotinamide adenine dinucleotide (NAD+) levels has been documented in the retina, rendering RGCs increasingly susceptible to IOP-related stress. This is a metabolic precipice that shifts with age.[22]

Glaucomatous neurodegeneration does not terminate at the optic disc. Neuroimaging and post-mortem studies have documented structural and functional changes within the lateral geniculate nucleus and visual cortex, classifying glaucoma unambiguously as a central neurodegenerative disorder.[23] This systemic neurological dimension has important implications for how the disease is staged, monitored, and ultimately treated.

Neuroinflammation and oxidative stress

Microglial activation occurs early in experimental glaucoma models, with activated microglia releasing pro-inflammatory cytokines and reactive oxygen species that amplify RGC stress in a self-perpetuating cycle of neuronal injury.[24,25] A systematic review and meta-analysis confirmed significant alterations in oxidative and anti-oxidative stress markers in patients with chronic glaucoma, supporting a mechanistic role for redox imbalance in disease pathogenesis.[26] Whether neuroinflammation is a primary driver or a secondary consequence of axonal injury remains debated; what is not debatable is that glaucomatous optic neuropathy involves active biological signaling, not passive mechanical degeneration alone.

Neuroprotection: From Concept to Cautious Optimism

The recognition of glaucoma as a multifactorial neuropathy has stimulated considerable interest in therapeutic strategies that preserve RGC structure and function independently of IOP reduction.[27] The translational challenge has been formidable: multiple agents that demonstrated robust neuroprotective effects in animal models have failed to replicate these benefits in human trials, highlighting the gap between preclinical promise and clinical proof.[28] Disease heterogeneity, slow progression rates, and trial design limitations compound the difficulty of detecting meaningful neuroprotective signals.

Nicotinamide (vitamin B3) represents the most clinically proximate neuroprotective candidate. As a precursor to NAD+, nicotinamide supports mitochondrial function and neuronal energy homeostasis. Williams et al. demonstrated that NAD+ supplementation conferred robust, dose-dependent protection against RGC degeneration in aged mouse models of glaucoma, with effects independent of IOP at lower doses, a critically important observation.[29] Early-phase clinical trials have reported improvements in inner retinal electrophysiological function with high-dose nicotinamide supplementation, and an ongoing randomised controlled trial of nicotinamide riboside is designed to assess structural and functional endpoints.[30,31] There has been considerable interest in the use of nicotinamide as a candidate for neuroprotection in glaucoma. Even though robust clinical evidence is still being established, the mechanistic rationale is compelling and the therapeutic window appears safe.[22]

Brimonidine has long been discussed as a potential neuroprotectant, with some clinical data suggesting reduced visual field progression relative to timolol despite equivalent IOP control.[32] These findings remain contested and do not constitute definitive evidence of pressure-independent neuroprotection. They do, however, illustrate both the clinical appetite for such therapies and the evidentiary standards they must meet.

Systemic agents with neuroprotective potential have more recently attracted interest. Glucagon-like peptide-1 (GLP-1) receptor agonists, widely used in metabolic medicine, exhibit anti-inflammatory, anti-apoptotic, and mitochondrial stabilising properties in central nervous system models.[33] Emerging epidemiological data suggest associations between GLP-1 receptor agonist use and reduced glaucoma incidence among patients with diabetes, though these observations are confounded by metabolic and vascular covariates and require prospective validation.[34] This intersection between systemic metabolic health and optic nerve resilience, reflected also in the potential roles of aerobic exercise, dietary antioxidants, and sleep quality on neurovascular homeostasis, extends the therapeutic frame well beyond the eye drop bottle.[35]

The evolving interest in ageing biology itself as a modifiable parameter in glaucoma is worth noting. Glaucoma is, fundamentally, an age-related noncommunicable disease. Strategies that attenuate the biological processes of ageing, mitochondrial decline, cellular senescence, systemic inflammation, may influence the trajectory of glaucomatous neurodegeneration in ways that IOP reduction alone cannot.[36]

The Communication Problem: Why Language Matters

The clinical consequences of a pressure-only explanatory model extend beyond the laboratory. When a patient with glaucoma is told their pressure is "well-controlled," the implicit message is that the disease is under control. If that patient subsequently learns, at a follow-up visit, that their visual field has deteriorated, the cognitive dissonance is profound. This can erode trust, reduce adherence, and generate justified confusion about the nature of the disease.

Studies on patient-provider communication in glaucoma consistently show that vision-related quality of life is discussed in a minority of consultations, and that patients frequently lack understanding of the chronic, asymptomatic nature of their condition.[37] Adherence to topical glaucoma therapy remains poor across populations, estimated at below 50% in some series, with implications for disease control that are directly attributable to inadequate patient education.[38] Patient-centred care, including shared decision-making and explicit quality-of-life discussion, has been shown to improve adherence and satisfaction.[7]

Reframing glaucoma as a condition of optic nerve vulnerability, one in which IOP is a critical but not sole determinant, offers patients a more accurate explanatory model. Patients who understand that progression can occur despite controlled IOP, that their age, vascular health, and sleep patterns are relevant, and that monitoring is as important as treatment are better positioned to engage meaningfully with lifelong care.

This does not mean presenting patients with the full complexity of glutamate excitotoxicity or the translaminar pressure gradient. It means shifting the clinical narrative from "your pressure is fine" to "we are protecting your optic nerve", a subtle but important reorientation of therapeutic purpose.

From Pressure Control to Optic Nerve Protection: A Broader Framework

The transition proposed here is not a rejection of IOP-based management. Pressure reduction remains the only intervention with conclusive evidence of efficacy, and target IOP: individualised on the basis of optic nerve morphology, disease severity, rate of progression, and life expectancy, will remain the operational anchor of clinical decision-making.[3] What is proposed is a contextualisation: IOP reduction as one component of a multi-domain strategy for optic nerve protection, rather than as the sum total of therapeutic ambition.

This broader framework has several practical implications. First, it supports more holistic patient assessment, including cardiovascular risk profiling, sleep history, and vascular autoregulatory status, as part of glaucoma management, not as a curiosity of the academic literature.[18,19] Second, it validates research investment in neuroprotective and metabolic therapies, providing a scientific rationale that pressure-centred models cannot offer.[27] Third, it aligns clinical practice with the reality of glaucoma as a neurodegenerative disease of the central nervous system; one that should, in principle, benefit from the translational lessons of Alzheimer's disease, Parkinson's disease,

and other neurodegenerative conditions in which multi-target approaches are increasingly standard.[23]

Precision medicine, the individualisation of treatment based on biological, genetic, and clinical profiling, is already reshaping other areas of chronic disease management. Glaucoma's inherent heterogeneity makes it a natural candidate for such approaches. Genomic determinants of optic nerve susceptibility, biomarkers of neuroinflammation, and imaging-based measures of structural resilience are all active areas of investigation that presuppose a multifactorial disease model.[2,39]

Conclusion

Glaucoma has long been explained through the language of pressure. That language is not wrong. It is incomplete. Glaucomatous optic neuropathy emerges from the interaction of mechanical load, vascular vulnerability, metabolic insufficiency, and neuroinflammatory amplification in a retinal ganglion cell population that is, in many patients and at many ages, already at the edge of its bioenergetic tolerance.[21,22]

Reframing glaucoma as a multifactorial optic neuropathy, in research, in clinical practice, and in patient communication, is not a counsel of therapeutic pessimism. It is an honest acknowledgement that preserving vision over a lifetime may require more than a single mechanism of action, and more than a single number on the tonometer. The future of glaucoma care is not the abandonment of pressure lowering; it is the elevation of pressure lowering to its proper status as a necessary but not sufficient component of comprehensive optic nerve protection.[3,27,36]

References

1. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology. 2014;121(11):2081–2090
2. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. JAMA. 2014;311(18):1901–1911
3. Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M, et al. Early manifest glaucoma trial group. reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2002;120(10):1268–1279
4. Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, Miller JP, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120(6):701–713
5. Leske MC, Heijl A, Hyman L, Bengtsson B. Early Manifest Glaucoma Trial: design and baseline data. Ophthalmology. 1999;106(11):2144–2153
6. Killer HE, Pircher A. Normal tension glaucoma: review of current understanding and mechanisms of the pathogenesis. Eye (Lond). 2018;32(5):924–930
7. Bhartiya S. Patient centricity and the ethics of glaucoma care. J Curr Glaucoma Pract. 2020;14(2):68–71
8. Anderson DR; Normal Tension Glaucoma Study. Collaborative normal tension glaucoma study. Curr Opin Ophthalmol. 2003;14(2):86–90
9. Schuman JS, Kostanyan T, Bussel I. Review of longitudinal glaucoma progression: 5 years after the Shaffer Lecture. Ophthalmol Glaucoma. 2020;3(2):158–166
10. Susanna BN, Ogata NG, Jammal AA, Susanna CN, Berchuck SI, Medeiros FA. Corneal biomechanics and visual field progression in eyes with seemingly well-controlled intraocular pressure. Ophthalmology. 2019;126(12):1640–1646
11. Hoang TT, Anh BV, Subramanian P. Is glaucoma a two-pressure-related optic neuropathy? A systematic review and meta-analysis. Turk J Ophthalmol. 2024;54(2):83–89
12. Drance S, Anderson DR, Schulzer M; Collaborative Normal-Tension Glaucoma Study Group. Risk factors for progression of visual field abnormalities in normal-tension glaucoma. Am J Ophthalmol. 2001;131(6):699–708
13. Sigal IA, Ethier CR. Biomechanics of the optic nerve head. Exp Eye Res. 2009;88(4):799–807
14. Wang YX, Panda-Jonas S, Jonas JB. Optic nerve head anatomy in myopia and glaucoma, including parapapillary zones alpha, beta, gamma and delta: histology and clinical features. Prog Retin Eye Res. 2021;83:100933
15. Downs JC, Roberts MD, Sigal IA. Glaucomatous cupping of the lamina cribrosa: a review of the evidence for active progressive remodeling as a mechanism. Exp Eye Res. 2011;93(2):133–140
16. Kim KE, Oh S, Baek SU, Ahn SJ, Park KH, Jeoung JW. Ocular perfusion pressure and the risk of open-angle glaucoma: systematic review and meta-analysis. Sci Rep. 2020;10(1):10056
17. Ramli N, Nurull BS, Hairi NN, Mimiwati Z. Low nocturnal ocular perfusion pressure as a risk factor for normal tension glaucoma. Prev Med. 2013;57 Suppl:S47–S49
18. Vasu P, Wagner IV, Lentz PC, Gumaste P, Abubaker Y, Ang BCH, et al. Obstructive sleep apnea as a potentiator of primary open-angle glaucoma and necessity for interventional therapy. Ophthalmol Glaucoma. 2025;8(6):553–559
19. Konieczka K, Flammer J. Treatment of glaucoma patients with Flammer syndrome. J Clin Med. 2021;10(18):4227
20. Wang X, Sun L, Han X, Li Z, Xing Y, Chen X, et al. The molecular mechanisms underlying retinal ganglion cell apoptosis and optic nerve regeneration in glaucoma (Review). Int J Mol Med. 2025;55(4):63
21. Ju W-K, Perkins GA, Kim K-Y, Bastola T, Choi W-Y, Choi S-H. Glaucomatous optic neuropathy: mitochondrial dynamics, dysfunction and protection in retinal ganglion cells. Prog Retin Eye Res. 2023;95:101136
22. Bhartiya S. Niacinamide and neuroprotection: the glaucoma holy grail. J Curr Glaucoma Pract. 2022;16(3):141–143
23. Kosior-Jarecka E, Pankowska A, Polit P, Stepniewski A, Symms MR, Koziol P, et al. Volume of lateral geniculate nucleus in patients with glaucoma in 7 Tesla MRI. J Clin Med. 2020;9(8):2382

24. Duarte JN. Neuroinflammatory mechanisms of mitochondrial dysfunction and neurodegeneration in glaucoma. J Ophthalmol. 2021;2021:4581909
25. Ramirez AI, Fernandez-Albarral JA, Hoz R de, López-Cuenca I, Salobrar-García E, Rojas P, et al. Microglial changes in the early aging stage in a healthy retina and an experimental glaucoma model. Prog Brain Res. 2020;256(1):125–149
26. Benoist d'Azy C, Pereira B, Chiambaretta F, Dutheil F. Oxidative and anti-oxidative stress markers in chronic glaucoma: a systematic review and meta-analysis. PLoS One. 2016;11(12):e0166915
27. Tribble JR, Hui F, Quintero H, El Hajji S, Bell K, Di Polo A, et al. Neuroprotection in glaucoma: mechanisms beyond intraocular pressure lowering. Mol Aspects Med. 2023;92:101193
28. Almasieh M, Levin LA. Neuroprotection in glaucoma: animal models and clinical trials. Annu Rev Vis Sci. 2017;3:91–120
29. Williams PA, Harder JM, Foxworth NE, Cochran KE, Philip VM, Porciatti V, et al. Vitamin B3 modulates mitochondrial vulnerability and prevents glaucoma in aged mice. Science. 2017;355(6326):756–760
30. Hui F, Tang J, Williams PA, McGuinness MB, Hadoux X, Casson RJ, et al. Improvement in inner retinal function in glaucoma with nicotinamide (vitamin B3) supplementation: a crossover randomized clinical trial. Clin Experiment Ophthalmol. 2020;48(7):903–914
31. Leung CKS, Ren ST, Chan PPM, Wan KHN, Kam AKW, Lai GWK, et al. Nicotinamide riboside as a neuroprotective therapy for glaucoma: study protocol for a randomized, double-blind, placebo-controlled trial. Trials. 2022;23(1):45
32. Garudadri CS, Choudhari NS, Rao HL, Senthil S. A randomized trial of brimonidine versus timolol in preserving visual function: results from the Low-pressure Glaucoma Treatment Study. Am J Ophthalmol. 2011;152(5):877
33. Gong X, Orge FH. Glucagon-like peptide-1 receptor agonists and ocular disease: mechanisms, evidence and therapeutic perspectives. Int J Mol Sci. 2026;27(3):1432
34. Lang MV, Vasu P, Dorairaj EA, Bhartiya S, Dorairaj SK. Glaucoma risk reduction as a secondary benefit of glucagon-like peptide-1 receptor agonists: a review of emerging evidence. J Curr Glaucoma Pract. 2025;19(4):223–228
35. Saha BC, Kumari R, Onkar A, Das S, Pal T. Lifestyle modification as complementary medicine in glaucoma management. J Curr Glaucoma Pract. 2025;19(1):38–49
36. Dada T, Mahalingam K, Bhartiya S. Reversing aging and improving health span in glaucoma patients: the next frontier? J Curr Glaucoma Pract. 2024;18(3):87–93
37. Sleath B, Sayner R, Vitko M, Carpenter DM, Blalock SJ, Muir KW, et al. Glaucoma patient-provider communication about vision quality-of-life. Patient Educ Couns. 2017;100(4):703–709
38. Tsai JC. A comprehensive perspective on patient adherence to topical glaucoma therapy. Ophthalmology. 2009;116(11 Suppl):S30–36
39. Bhartiya S, Ichhpujani P, Wadhwani M. Current perspectives in tackling glaucoma blindness. Indian J Ophthalmol. 2025 Mar 1;73(Suppl 2):S189–S196

How to cite this article: Bhartiya S. Bhargav J, From Pressure to Protection: Reframing Glaucoma as a Multifactorial Optic Neuropathy. Cli Exp Vis Eye Res J 2025;8(1):7-11.

Conflicts of Interest: None. **Source of Support:** None.