Beyond Intraocular Pressure

Rethinking Normal-Tension Glaucoma Through Biomechanics, Cellular Resilience and Neuroprotection

5.1 When Pressure Is Not Enough

For decades, glaucoma has been regarded primarily as a pressure-related disease. Elevated intraocular pressure (IOP) remains the most important modifiable risk factor, and lowering IOP is currently the only treatment strategy consistently proven to slow disease progression. This paradigm has transformed ophthalmic care and preserved the vision of millions of patients worldwide.

Nevertheless, one fundamental question remains unanswered.

Why do retinal ganglion cells continue to degenerate in many patients whose intraocular pressure has always remained within the statistically normal range?

Normal-tension glaucoma (NTG) represents one of the most compelling challenges to the traditional pressure-centered concept of glaucoma. Particularly in East Asian populations, NTG accounts for a substantial proportion of primary open-angle glaucoma, suggesting that elevated IOP alone cannot fully explain the mechanisms underlying progressive optic nerve damage.

Rather than viewing NTG simply as “glaucoma without elevated pressure,” it may be more appropriate to regard it as an opportunity to broaden our understanding of glaucomatous neurodegeneration. Pressure remains an important determinant of mechanical stress on the optic nerve; however, it may represent only one component of a far more complex biological process.

Emerging evidence from ophthalmology, neuroscience, vascular biology and aging research suggests that retinal ganglion cell survival is influenced by multiple interacting factors. Ocular biomechanics, axial length, vascular regulation, mitochondrial function, oxidative stress, immune responses and cellular energy metabolism may all contribute to the vulnerability—or resilience—of the optic nerve.

From this perspective, glaucoma may be understood not solely as a disease of pressure, but as a disease of tissue susceptibility. Two individuals exposed to the same intraocular pressure may not experience the same biological response because the resilience of their optic nerve differs. Understanding the determinants of this resilience may become one of the most important scientific challenges in glaucoma research over the coming decades.

This Vision Paper does not propose a new disease model, nor does it question the established importance of lowering intraocular pressure. Instead, it offers a hypothesis-generating conceptual framework intended to stimulate interdisciplinary discussion. The central proposition is that future research may benefit from integrating pressure-related mechanisms with broader biological concepts, including biomechanics, mitochondrial health, vascular homeostasis and neuroprotection.

The purpose is not to replace existing paradigms, but to complement them.

Perhaps the most important question is therefore no longer:

“How high is the intraocular pressure?”

but rather:

“Why does one optic nerve remain resilient while another progressively degenerates under apparently similar conditions?”

Answering this question may not only improve our understanding of normal-tension glaucoma but also provide broader insights into neurodegeneration, healthy aging and the preservation of neuronal function throughout life.

5.2 Japan Changed the Question: Why Myopia May Matter More Than We Think

One of the most remarkable observations in glaucoma epidemiology originates from Japan. Unlike many Western populations, where elevated intraocular pressure has traditionally dominated clinical attention, the majority of patients diagnosed with primary open-angle glaucoma in Japan present with intraocular pressure within the statistically normal range. This observation has fundamentally influenced Japanese glaucoma research and has shifted scientific interest toward mechanisms beyond pressure alone.

At the same time, Japan is among the countries with the highest prevalence of myopia worldwide. Over recent decades, increasing axial length has become a defining characteristic of large parts of the population, particularly among younger generations. While myopia is primarily recognized as a refractive condition, its anatomical consequences extend far beyond optical correction.

Axial elongation changes the geometry of the entire posterior segment of the eye. The sclera becomes thinner, the optic nerve head is exposed to altered biomechanical forces, and the lamina cribrosa may undergo structural remodeling. These changes do not necessarily cause glaucoma by themselves; however, they may influence the mechanical environment in which retinal ganglion cell axons function throughout life.

This raises an important conceptual question.

If two individuals have identical intraocular pressure but fundamentally different optic nerve anatomy due to differences in axial length, should the biological impact of the same pressure be expected to be identical?

From a biomechanical perspective, the answer may not necessarily be yes.

Pressure is a physical force, but the response to that force depends on the properties of the tissue that receives it. The optic nerve head is not a rigid structure. Its architecture, connective tissue composition, scleral biomechanics and lamina cribrosa characteristics may determine how mechanical stress is distributed and tolerated over decades.

This concept shifts attention from pressure alone toward biological vulnerability.

Rather than asking whether intraocular pressure is statistically normal, future research may increasingly need to ask whether the optic nerve is structurally capable of tolerating that pressure over an entire lifetime.

Such a perspective does not diminish the importance of intraocular pressure. Instead, it suggests that pressure and tissue susceptibility are inseparable components of the same biological equation.

This concept may also help explain why populations with a high prevalence of axial myopia, such as Japan, have become central to research on normal-tension glaucoma. The disease may not simply reflect the absence of elevated pressure, but rather the interaction between normal mechanical load and increased structural vulnerability.

Understanding this interaction could represent one of the next major steps in glaucoma research. It encourages a broader scientific framework in which ocular biomechanics, retinal ganglion cell resilience, vascular regulation and cellular metabolism are investigated together rather than in isolation.

Within this perspective, normal-tension glaucoma becomes more than a subtype of glaucoma. It becomes a model for understanding how anatomical predisposition and biological resilience together

determine whether neural tissue remains functional—or progressively degenerates despite apparently normal clinical parameters.

5.3 Cellular Resilience: Why Retinal Ganglion Cells Survive—or Degenerate

If biomechanics helps explain why certain optic nerves are exposed to greater mechanical vulnerability, it still does not answer the central biological question: Why do some retinal ganglion cells survive for decades under similar conditions while others progressively degenerate?

The answer may lie not only in the magnitude of external stress, but also in the intrinsic capacity of neurons to adapt, maintain homeostasis and recover from chronic physiological challenges.

Retinal ganglion cells are among the most metabolically active neurons in the human body. Their long, unmyelinated axons within the retina require a continuous supply of energy to maintain axonal transport, ionic gradients and synaptic communication. This dependence makes them particularly vulnerable to disturbances in mitochondrial function, oxidative balance and cellular metabolism.

Increasing evidence suggests that glaucomatous neurodegeneration cannot be understood solely as a mechanical disorder. Instead, it appears to involve a complex interaction between mechanical stress, vascular regulation, mitochondrial function, oxidative stress, neuroinflammation and age-related decline in cellular repair mechanisms.

Within this broader framework, the concept of cellular resilience becomes increasingly relevant.

Cellular resilience describes the ability of a cell to maintain structural integrity and biological function despite continuous internal and external stress. In retinal ganglion cells, this resilience is likely determined by multiple interconnected systems, including mitochondrial ATP production, antioxidant defense mechanisms, efficient protein turnover, autophagy, immune regulation and adequate microvascular perfusion.

When these adaptive mechanisms function efficiently, neurons may tolerate mechanical stress for many years without clinically detectable damage. When resilience progressively declines, however, the same level of mechanical load may become sufficient to initiate irreversible neurodegeneration.

This perspective may help explain one of the most puzzling observations in glaucoma: similar intraocular pressure does not necessarily result in similar clinical outcomes.

The biological response appears to differ because the tissue itself differs.

From this viewpoint, intraocular pressure should not be regarded as an isolated causal factor but as one component acting upon tissue with varying degrees of biological resilience. Disease progression may therefore depend not only on the external load but also on the capacity of retinal ganglion cells to preserve mitochondrial function, regulate oxidative stress, maintain axonal transport and adapt to chronic metabolic demands.

This conceptual framework also creates an important bridge between glaucoma research and the rapidly expanding fields of aging biology and neurodegeneration. Many biological processes currently investigated in Alzheimer’s disease, Parkinson’s disease and other neurodegenerative disorders—including mitochondrial dysfunction, impaired cellular energetics, chronic low-grade inflammation and declining stress resistance—may also contribute to the progressive loss of retinal ganglion cells.

Rather than viewing glaucoma exclusively as an ocular disease, it may therefore be valuable to consider it as a localized manifestation of broader biological processes that influence neuronal survival throughout the body.

This perspective does not replace established concepts of pressure reduction. Instead, it complements them by emphasizing that preserving neuronal function may ultimately depend on understanding not

only the forces acting upon the optic nerve, but also the biological capacity of the tissue to withstand those forces.

Future research should therefore increasingly integrate ocular biomechanics with mitochondrial biology, vascular physiology, immunology and systems medicine. Such an interdisciplinary approach may help explain why retinal ganglion cells remain resilient in some individuals while progressively degenerate in others despite apparently comparable clinical conditions.

The therapeutic implications of this conceptual framework are discussed in the following chapter, where current treatment strategies and future research directions are considered in light of this broader biological perspective.

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Author's Note

This Vision Paper presents a hypothesis-generating conceptual framework intended to stimulate interdisciplinary scientific discussion. It should not be interpreted as a clinical guideline or therapeutic recommendation. Clinical decisions should always be based on current evidence, established guidelines and individual patient circumstances.

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