International Journal of Medical Sciences And Clinical Research

VOLUME Vol.05 Issue09 2025
PAGE NO. 67-70
DOI 10.37547/ijmscr/Volume05Issue09-12

Glaucoma: Neuroprotection And Early Diagnosis

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Received: 31 July 2025; **Accepted:** 28 August 2025; **Published:** 30 September 2025

Abstract: Glaucoma is one of the global public health problems. This disease is one of the main causes of irreversible blindness worldwide. Despite progress in therapy and increased effectiveness of methods and measures to reduce intraocular pressure (IOP) and surgical methods, the disease remains poorly controlled due to asymptomatic course in the early stages and poor coverage of early diagnosis, especially in countries with poorly developed economies.

According to WHO, in 2020, glaucoma caused blindness in 3.61 million people and severe visual impairment in 4.14 million, especially in people over 50 years of age. Given that glaucoma is incurable but potentially controllable, early diagnosis and neuroprotective strategies aimed at preserving the optic nerve are of particular importance.

Scientific novelty: This article is devoted to the analysis of modern approaches to neuroprotection in glaucoma, issues of early diagnostics and the potential for integrating these areas into public health strategies. If glaucoma is considered not only as an ophthalmological but also as a neurodegenerative disease based on multifactorial death of retinal ganglion cells (RGC), this shifts the emphasis from exclusively hypotensive therapy to the need for neuroprotective strategies, which reflects the modern vector in the pathogenesis and treatment of glaucoma.

A conclusion is made about the relevance of developing and implementing neuroprotection methods and in-depth screening to improve the effectiveness of combating glaucoma at early stages. The need for a combined approach to treatment adapted to the molecular mechanisms of damage in a particular patient is substantiated, which corresponds to the modern paradigm of personalized medicine.

Keywords: Glaucoma, intraocular pressure, primary open-angle glaucoma, retinal ganglion cells, neuroprotection, mitotherapy, optical coherence tomography, flicker noise mapping, artificial intelligence.

Introduction: Glaucoma is a heterogeneous group of progressive optic neuropathies that cause degradation of the optic nerve and irreversible vision loss. The most common form of the disease is primary open-angle glaucoma (POAG), which accounts for a significant proportion of cases. According to WHO data for 2020, about 80 million people worldwide suffered from glaucoma, of which about 60 million had POAG. In 2025, according to estimates by the World Glaucoma Association (WGA), the number of patients worldwide reached 78 million, and by 2040 this sad figure is expected to exceed 100 million.

Despite the widespread use of IOP-lowering therapies, glaucoma remains the second leading cause of blindness after cataracts. In 2020, the disease resulted in total blindness in 3.61 million people (8.39% of all cases of blindness) and severe visual impairment in 4.14 million (1.41% of all cases of moderate and severe vision loss). The prevalence of glaucoma-related blindness is particularly high in high-income countries (up to 26.1%) and in sub-Saharan Africa, where the highest age-standardized incidence rates are recorded.

From 2000 to 2020, the age-standardized prevalence of glaucomatous blindness among people aged 50 years and over decreased by 26% in men and 21% in women, but the prevalence of moderate and severe vision loss increased (especially among women +7.3%). This reflects not only the demographic transition but also the insufficient effectiveness of current early detection systems.

The difficulty in diagnosing glaucoma is its asymptomatic course in the early stages. In high-income countries, up to 50% of cases remain undetected, while in low- and middle-income

countries, this figure reaches 90%. In this regard, there is an increasing demand for mass screening programs and the development of neuroprotective strategies aimed at preserving the structures and functions of the optic nerve even with the remaining risk of progression.

Review of neuroprotective strategies in glaucoma

Glaucoma should also be considered as a neurodegenerative disorder in which retinal ganglion cells (RGCs) and their axons are damaged. Neuroprotection is a set of methods aimed at preventing or slowing down the death of neurons regardless of the level of intraocular pressure (IOP).

Retinal ganglion cells (RGCs) are neurons located in the inner layer of the retina that receive visual information from photoreceptors (via bipolar cells) and transmit it to the brain via axons that form the optic nerve. In glaucoma, RGCs gradually degenerate and die, leading to irreversible vision loss. The underlying mechanisms of RGC loss in glaucoma involve a complex interaction of various pathological processes, including neurotrophin depletion, excitotoxicity, oxidative stress, mitochondrial dysfunction, inflammation, and apoptosis.

Neurotrophins such as ciliary neurotrophic factor (CNTF) and brain-derived neurotrophic factor (BDNF) play a critical role in the survival and maintenance of RGCs. In glaucoma, deprivation of these neurotrophins leads to RGC degeneration due to impaired axonal transport and receptor expression.

Excitotoxicity, primarily due to elevated levels of the neurotransmitter glutamate, results in overactivation of N-methyl-D-aspartate (NMDA) receptors on RGCs, causing a harmful influx of calcium ions that triggers apoptotic pathways. Although the role of glutamate in glaucoma is complex and not fully understood, it is clear that its dysregulation significantly contributes to RGC death.

Oxidative stress is another major factor in glaucomatous neurodegeneration. An imbalance between reactive oxygen species (ROS) production and the body's antioxidant defenses leads to oxidative damage to retinal ganglion cells (RGCs), affecting proteins, lipids, and DNA. Oxidative stress can be exacerbated by mitochondrial dysfunction, since RGCs have high energy requirements and any impairment of mitochondrial function can lead to energy deficit, further reducing cell viability. Cytochrome release from damaged mitochondria into the cytoplasm is a key event activating the apoptotic pathway in RGCs.

Inflammation also plays a major role in the development of glaucoma, with proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) elevated in the retina and optic nerve head. These cytokines can induce RGC apoptosis either directly or by enhancing excitotoxicity and oxidative stress. In addition, retinal glial cells, including astrocytes, Müller cells, and microglia, are involved in both protective and detrimental responses in glaucoma. Although they can promote debris clearance and produce neurotrophic factors, their overactivation can lead to chronic inflammation and further RGC damage.

In this regard, antioxidant protection can be reasonably considered as a promising direction of neuroprotective therapy in glaucoma. This is confirmed by both experimental data and a number of clinical studies. Such drugs as CoQ10, resveratrol and N-acetylcystein neutralize oxidative stress - an important factor in neurodegeneration in glaucoma.

Endogenous antioxidant systems (e.g., superoxide dismutase, catalase, glutathione) are weakened with age and by chronic hypoxic stress in glaucoma. Exogenous antioxidants can compensate for this deficit and reduce RGC damage.

These include CoQ10 (ubiquinone), which improves mitochondrial function and reduces apoptosis (currently being studied in eye drops and systemic use). Vitamins C and E, lutein, curcumin, resveratrol, melatonin, glutathione, and alpha-lipoic acid also exhibit antioxidant and neuroprotective properties.

Thus, antioxidant therapy, especially in combination with other targets such as excitotoxicity inhibitors, neurotrophins and anti-inflammatory agents, may have an important place in personalized glaucoma treatment in the future.

Glutamate antagonists. Excess glutamate has a neurotoxic effect. In this regard, the experimental drug memantine, which blocks NMDA receptors, showed a neuroprotective effect in preclinical models, but did not achieve significant clinical efficacy in the completed Allergan study (NCT00168350).

Memantine is a voltage-dependent, low-affinity, non-competitive NMDA receptor antagonist that selectively binds to activated glutamatergic receptors, reducing excessive glutamatergic activity, calcium influx, and activation of pro-apoptotic cascades without affecting normal neurotransmission, thereby protecting RGCs from excitotoxic injury. In animal models, memantine has demonstrated promising neuroprotective effects.

Although preclinical studies have shown promising results, large-scale clinical trials have failed to confirm significant benefits of memantine in the treatment of glaucoma. Two double-blind, placebo-controlled, multicenter phase III clinical trials (NCT00141882 and NCT00168350) involving 2,296 patients with POAG

over four years failed to show that memantine slowed visual field progression compared to placebo.

Insulin. The mTOR pathway is critical for RGC energy metabolism, with insulin serving as a major activator of both mTORC1 and mTORC2. Insulin crosses the blood-brain/retinal barrier and influences neuronal survival, neurotransmission, and glucose uptake. Impaired insulin signaling has been implicated in neurodegenerative diseases, including glaucoma. Studies show that insulin enhances glucose transport, promotes dendritic regeneration, and maintains neuronal survival. Activation of mTORC1/2 is vital for insulin-mediated dendritic repair and synapse restoration in RGCs, making insulin a promising therapeutic target.

Intranasal insulin has emerged as a promising method to cross the blood-brain barrier without causing systemic side effects such as hypoglycemia. Studies of intranasal insulin in Alzheimer's disease and mild cognitive impairment have shown it to be a safe and effective way to target insulin signaling in neurodegeneration. Although clinical trials in glaucoma have not yet been conducted, preclinical data suggest that exogenous insulin may help preserve RGCs. A phase I study of topical insulin eye drops in glaucoma has been conducted and has shown safety in patients with glaucoma.

Overall, intranasal and topical insulin represents a promising strategy for the treatment of neurodegenerative diseases, although further studies are needed to confirm its efficacy.

Mitochondrial Targeted Therapy and Transplantation

Mitochondria are essential for bioenergetics and play key roles in calcium regulation, cell signaling, apoptosis, and synaptic maintenance. RGCs, with their large dendritic trees and unmyelinated axons in the retina, rely heavily on mitochondria to meet their high metabolic demands. As a result, these cells are highly susceptible to mitochondrial dysfunction, as seen in diseases such as Leber hereditary optic neuropathy (LHON) and autosomal dominant optic atrophy. In glaucoma models, mitochondrial abnormalities appear before optic nerve degeneration, suggesting that metabolic stress plays a key role in RGC injury and degeneration.

Mitochondrial transplantation, or mitotherapy, involves the transfer of functional mitochondria into cells with mitochondrial dysfunction, offering potential treatment for diseases associated with mitochondrial dysfunction. Studies have shown promising results in animal models, including improved oxidative metabolism, neuroprotection, and axonal repair in RGCs. In vitro studies in humans have also demonstrated the ability of mitotherapy to restore cellular function in diseases such as LON. Factors such as the source and delivery of mitochondria influence the success of mitochondrial transplantation, both of which require further study.

Modern methods of early diagnosis of glaucoma

High-tech imaging techniques and artificial intelligence (AI) algorithms play a key role in the early detection of glaucoma, allowing for the detection of minimal deviations from the norm at the structural and functional levels. These include optical coherence tomography (OCT), which measures the thickness of the retinal nerve fiber layer (RNFL) and ganglion cell complex, identifying early subclinical changes.

OCT is a non-invasive technology based on interferometry principles, allowing to obtain retinal sections with micron resolution. OCT angiography (OCTA) provides visualization of microcirculation in the retina and optic disc (an important biomarker of glaucomatous ischemia). Decreases in RNFL and GCC thickness can be detected long before changes appear on standard perimetry, which makes OCT particularly valuable for early diagnosis.

It is important that modern devices (e.g. Cirrus HD-OCT, Spectralis OCT) have automatic segmentation and allow dynamic monitoring of disease progression. OCTA also allows differentiating glaucoma from other neuro-ophthalmological conditions with similar morphological features.

Although standard automated perimetry (SAP) remains the "gold standard" for visual field assessment, it is only sensitive in later stages of the disease when 30-40% of ganglion cells have already been lost. In this regard, flicker-noise mapping is considered as a more sensitive method for assessing visual functions, allowing the detection of subclinical and unstable areas in the visual field, even before they are recorded by traditional methods. Short-wavelength stimulus perimetry (SWAP) and multifocal electroretinography (mfERG) are also used to assess the functional activity of individual retinal areas.

AI systems trained on large data sets of OCT, color fundus photographs, and functional tests have demonstrated high efficiency in glaucoma screening and diagnosis. Deep learning algorithms can automatically interpret images and highlight pathological features that may not be obvious even to an experienced ophthalmologist. Studies have shown that the sensitivity of such models in detecting glaucoma, including its early forms, exceeds 90%.

Recently, DeepMind (Google Health) developed a model capable of classifying glaucoma based on fundus

and OCT images with an accuracy comparable to leading experts. In addition, integrated AI platforms are being developed that can predict the risk of glaucoma progression and select the optimal treatment strategy based on multimodal data (structural, functional, genetic).

Multicenter trials of deep learning-based automated diagnostic systems integrated with OCT and fundus photography conducted in 2024 showed sensitivity of 92–94%.

CONCLUSION

At the same time, most specialists are of the opinion that a comprehensive approach is necessary for the treatment of glaucoma, including both hypotensive and neuroprotective therapy. There is no universal drug and clear recommendations for the use of neuroprotective therapy at various stages and forms of glaucoma. According to many authors, such treatment should include a combination of drugs with different mechanisms of action. Research in the field of neuroprotective treatment for glaucoma remains a pressing issue and continues to this day.

There is currently no cure for glaucoma, and vision loss caused by disease progression is irreversible. However, medications and surgery can help slow or stop further vision loss. Because open-angle glaucoma is a chronic condition, lifelong monitoring is necessary and very effective.

Despite the improvement in the situation with severe blindness, the number of people with moderate visual loss continues to grow - which indicates the need for active screening, early diagnosis and treatment. Quite high hidden incidence (up to 90%) indicates the need to develop and implement new mass screening programs, especially among the elderly population.

REFERENCES

1. Aprelev A.E., Pidodniy E.A. Primary neuroprotection of glaucoma https://cyberleninka.ru/article/n/pervichnaya-neyroprotektsiya-glaukomy
2. Chuprov A.D., Aprelev A.E., Gorbunov A.A., Pidodniy E.A. Neuroprotection in glaucoma. https://science-education.ru/article/view?id=30715
3. Wang L.-H., Huang C.-H., Lin I.-C. (2024). Advances in Neuroprotection in Glaucoma: Pharmacological Strategies and Emerging Technologies. https://www.mdpi.com/1424-8247/17/10/1261
4. Pei K., Georgi M., Hill D., Lam C. F. J., Wei W., Cordeiro M. F. (2024). Review: Neuroprotective Nanocarriers in Glaucoma. Pharmaceuticals 17(9):1190. https://doi.org/10.3390/ph17091190
5. Lee H.-P., Tsung T.-H., Tsai Y.-C., Chen Y.-H., Lu D.-W. (2024). Glaucoma: Current and New Therapeutic Approaches. Biomedicines, 12(9):2000. https://doi.org/10.3390/biomedicines12092000
6. Xia Q., Zhang D. (2024). Apoptosis in glaucoma: A new direction for the treatment of glaucoma (Review). Molecular Medicine Reports 29:82. https://doi.org/10.3892/mmr.2024.13207
7. Lisa M. Young, OD, FAAO Glaucoma Facts and Stats https://glaucoma.org/articles/glaucoma-facts-and-stats?utm_source=chatgpt.com
8. Global estimates on the number of people blind or visually impaired by glaucoma: A meta-analysis from 2000 to 2020 https://www.nature.com/articles/s41433-024-02995-5?utm_source=chatgpt.com
9. Zhang J., Tian B., Tian M., Si X., Li J., Fan T. (2025). A scoping review of advancements in machine learning for glaucoma: current trends and future direction. Frontiers in Medicine 12:1573329. https://www.frontiersin.org/journals/medicine/articles/10.3389/fmed.2025.1573329/full
10. Dal Monte, M.; Cammalleri, M.; Pezzino, S.; Corsaro, R.; Pescosolido, N.; Bagnoli, P.; Rusciano, D. Hypotensive effect of a nanomicellar composition of melatonin and agomelatine in a rat model: implications for glaucoma therapy. https://pmc.ncbi.nlm.nih.gov/articles/PMC7151109/