The Research of Medical Science Review
ISSN: 3007-1208 & 3007-1216 Volume 3, Issue 8, 2025

# NEURODEGENERATION AND RETINAL GANGLION CELLS IN GLAUCOMA: CELLULAR PATHWAYS AND THERAPEUTIC APPROACHES

**Aruna Devi[*1], Sumyial Khalid[2], Muhammad Muthar Anees[3], Syeda Nida Mehdi Abidi[4], Akshy Kumar[5], Zainab Asif[6], Neha Kumari[7]**

[*1,6]*Dow Medical College/Dow University of Health Sciences, Karachi*
[2]*University Hospital Limerick, United Kingdom*
[3]*Liaquat College of Medicine and Dentistry, Karachi*
[4]*Ulster University, United Kingdom*
[5]*Liaquat University of Health Sciences, Jamshoro*
[7]*Gambat Institute of Medical Sciences, Gambat*

[1]noman_ahmed678@outlook.com

**DOI:** https://doi.org/10.5281/zenodo.17140065

**Keywords**
*Glaucoma, Retinal Ganglion Cells, Optical Coherence Tomography, Neurodegeneration, Biomarkers*

**Article History**
Received: 03 May, 2025
Accepted: 16 July, 2025
Published: 11 August, 2025

**Copyright** @Author
**Corresponding Author: ***
**Aruna Devi**

**Abstract**

*Human glaucoma is the second most common cause of irreversible blindness worldwide; however, it is defined by neurodegeneration of retinal ganglion cells (RGCs) and damage to the optic nerve. Although high Intraocular pressure (IOP) has been recognized for decades as the most important risk factor for glaucoma, more recent evidence has emerged supporting a role for oxidative stress, mitochondrial dysfunction and reduced neurotrophic support in glaucomatous neurodegeneration. This was a cross-sectional, descriptive, interventional study conducted to assess the changes at structural, functional and biochemical level in provenance of primary open-angle glaucoma at our tertiary care centre. This was a prospective observational study at Jinnah Postgraduate Medical Centre, Karachi, from January 2023 to June 2024 involving 150 patients, 75 with POAG and 75 healthy controls. All subjects underwent a complete ophthalmic evaluation, including best corrected visual acuity, IOP, optic disc examination, Humphrey visual field, and optical coherence tomography (OCT) for retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) thickness. Serum biomarkers brain-derived neurotrophic factor (BDNF), tumor necrosis factor-alpha (TNF-α), and caspase-3 were also evaluated by ELISA. POAG patients exhibited markedly elevated IOP, optic disc cupping, visual field loss, and RNFL and GCC thinning compared to normal ($p<0.001$) but with additional significant amounts of outlier data in the POAG group. The detection of serum showed that the BDNF was decreased, while the TNF-α and caspase-3 were increased, which correlated well with the structure and function of the glaucomatous eye. Correlation analysis then confirmed that higher IOP and oxidative stress were negatively correlated with RNFL thickness whereas neurotrophic factor showed neuroprotective effects. Our findings support the concept that glaucoma is a multi-factorial neurodegenerative disease and indicate that this may reinforce a more holistic approach to therapy above and beyond lowering IOP, and thus merit further investigation of systemic biomarkers*

*in targeted population sampling as a means of patient directed monitoring and management.*

## INTRODUCTION

Glaucoma is perhaps the most important public health problem in eye care, the most common cause of irreversible blindness globally. In contrast to one treated by cataract surgery to restore vision, the damage done by glaucoma is irreversible, as it results from the gradually increasing death of retinal ganglion cells (RGCs) and their axons. It is known as a silent killer, frequently remaining asymptomatic until late stages, at which point extensive and irrevocable damage has already occurred. The world health organization (WHO) and large epidemiological studies have reported that over 110 million people will suffer from glaucoma by 2040 with a disproportionate distribution in the Asia and Africa (Qi *et al.*, 2025). This demographic shift not only represents population aging over time, but it also shows the persistent underdiagnosis of the early stages of disease, when treatment could arguably have the most impact. The worldwide economic cost of ROP is also staggering, including the direct expense of health care treatment, loss of productivity, and as well as the collective social economic cost of vision loss (Okoye, 2020).Glaucoma is a chronic, progressive optic neuropathy characterized by structural changes at the optic nerve head (ONH) and related functional defects in the visual field. Elevated intraocular pressure (IOP) has traditionally been regarded as the most important risk factor, and reduction of IOP remains the mainstay of therapy (Yohannan & Boland, 2017). Nevertheless, the realization that many patients who are well controlled IOP or even with an IOP in the typical range keep progressing has redirected the paradigm from being IOP dominated to neurodegenerative disease model. This re-categorization contrasts with the current understanding of glaucoma as it situates the disorder within the extensive biologic spectrum of central nervous system disease that has common threads of pathogenesis underpinning diseases such as Alzheimer disease, Parkinson disease, and multiple sclerosis. Glaucoma paradigm as multifunctional neurodegeneration has initiated investigations of cellular stress response, vascular and metabolic vulnerabilities, and neuroinflammatory processes that culminate in RGC death (Tezel, 2021).A challenge in the treatment of glaucoma is the insidious nature of the disease and lack of early sensitive and specific functional markers. Nevertheless, patients generally present with late-stage disease, with up to 40% loss of RGCs prior to the detection of vision loss (Davis *et al.*, 2016). Despite the development of these techniques, structural OCT, and functional pattern electroretinography measures (Apergis, 2020), disease at their earliest stages can be detected and prospective monitoring of patients that may be at risk for these diseases has yet to be optimally translated into these fields as a successful public health screening tool. Also, the first stage of the disease remains asymptomatic leading to underutilisation of eye care services, particularly in resource-limited settings. This underscores the imperative for population-level efforts in early detection and mechanistic studies to provide a window to treatment before irreversible RGC loss (Park *et al.*, 2017).This underscores the pressing need for new therapeutic approaches, since existing treatment strategies have their own limitations. Several pharmacological drugs such as prostaglandin analogues, β-blockers and carbonic anhydrase inhibitors have been able to decrease the IOP at an impressive pace, and the surgical progress such as minimally invasive glaucoma surgeries (MIGS) have broadened the therapeutic arsenal (Mincione *et al.*, 2021). However, a number of patients had sustained optic nerve degeneration and visual field loss regardless of the success of the target IOP. These developments also illuminate pressure-independent injury mechanisms, including optic nerve head vascular dysregulation, mitochondrial bioenergetics collapse, oxidative stress, excitotoxic signalling, and maladaptive glial activation. That protecting and restoring RGCs might provide a way to restore vision has stimulated a translational research agenda to identify not only treatments but also drugs that act on the neuronal substrates of the disease, and not just the level of pressure in the eye.As glaucoma patients live longer, the stakes have never been more important. As humans continue to live longer, the aggregate years lived with VD will increase greatly unless interventions that can halt or

reverse RGC loss are developed. Neuroprotective strategies which are being considered, and studied in animal models, but have not shown benefit in patients include metabolic supplementation with nicotinamide (the precursor of NAD), neurotrophic factor delivery, complement inhibition, and axon-regeneration strategies (L-H Wang *et al.*, 2024). Conversely, translation work linking mechanistic findings from the lab to clinical trials remains relatively limited. It was intended that this paper would emphasize the translational clinical study design carried out in the current trial that both tests an exciting candidate therapy, and incorporates mechanistic biomarker evaluation to relate molecular pathways with clinical end points.Glaucoma is a multifactorial, chronic neurodegenerative disease of the retinal ganglion cells, with the non-IOP factors being relevant in the pathogeneses of the disease that will have to be addressed in conjunction with IOP in the future therapeutic interventions. The worldwide disease burden, inadequacies of current IOP-targeted therapeutics, difficulty of early-stage diagnosis, and similarities to other more widespread neurodegeneration, all provide powerful motives for investigation of the mechanisms of RGC death in glaucoma and the attendant call for mechanism-based treatments (REDDY *et al.*, 2024). In order to advance the field towards SDO, which directly lower pressure but also preserve and repair RGCs, this study will fill these gaps because of its interface plasma jets, whereas CO 2 lasers engage the, correspondences between clinical evidence and biological processes.

**Review of Literature**

The optic nerve head (ONH) is also a site of anatomic biomechanical weakness such as excessive translaminar pressure gradients, can lead to disruption of connective tissue and radially entrapped RGC axons increasing impedance to axoplasmic flow, and onset of an axial lesion, which precedes somatic death. In animal models of glaucoma, as well as human histopathology, early focal ONH sites accumulate transport cargo and manifest cytoskeletal alterations that likely underpin the progressive retrograde (as opposed to anterograde) loss in soma and thereby, distal Wallerian-like degeneration of axons (Dias *et al.*, 2022). A considerable number of imaging investigations and animal models favor axonopathy as an important and early feature in glaucoma. And so, for developing treatments that are aimed at axonal protection and transport repair, tearing away the event at the ONH still remains crucial.Recent analyses have revealed metabolic failure, especially mitochondrial dysfunction and depletion of NAD+, to be a common feature of glaucomatous RGC degeneration. Previous preclinical work has demonstrated that both aging and glaucomatous stress diminish NAD+ availability in RGCs, compromise mitochondrial respiration, and limit cellular capacity to accommodate axonal energy demand (Petriti *et al.*, 2021). Notably, the neuroprotection afforded by increasing NAD+ precursors (e.g., nicotinamide, nicotinamide riboside) is very robust in multiple glaucoma models: nicotinamide supplementation in mouse models protects RGC loss and enhances measures of retinal function, and human studies and small clinical trials show benefits of nicotinamide alone or in combination with pyruvate on inner retinal function (Chiarugi, 2023). Together, these lines of converging evidence support metabolic augmentation as a viable translational approach.Excitotoxicity mediated by glutamate and dysregulated intracellular calcium are historically thought to be involved in glaucomatous damage. High glutamate levels, combined with NMDA receptor activity, can ultimately activate calpain and caspase downstream and damage RGC dendrites, axons or both (Carvajal *et al.*, 2016). Translating isolated pathway inhibition to clinical neuroprotection is complex, and clinical attempts to blunt excitotoxicity (e.g., large randomized memantine trials) have been disappointing to date. However, excitotoxic mechanisms still have important relevance as they cross talk with energy metabolism and inflammation.One of the earliest cellular changes in experimental glaucoma is a reactive glial response, that is, activation of microglia and astrocytes around the optic nerve head (ONH) and in the retina. During inflammation, activated microglia secrete cytokines and reactive oxygen species, perform synaptic phagocytosis, and interact with complement cascades; astrocytes remodel extracellular matrix and modulate metabolic and trophic support to axons. Newer human and animal data suggests a role for sustained maladaptive glial activation in progressive RGC dysfunction, and that glial phenotypes can be modified (e.g. limited pro-

inflammatory signaling or blocked complement effectors) to ameliorate structural damage in models (Fernández-Albarral *et al.*, 2024). These translate into therapeutic avenues that could be pursued with anti-inflammatory and complement-targeted therapies.Research in glaucoma models has shown that upregulation of early complement components and synapse pruning of the retinogeniculate synapse occurs before detectable cell death (Williams *et al.*, 2016). In glaucoma animal models, complement inhibition not only preserved the ultrastructure of the optic nerve but also delayed degeneration, implicating a causal role of complement activation in the synaptic and axonal pathology of glaucoma. The mechanistic gap between an effect on the complement system and safe therapy in human subjects will need to be studied but the data justify directed development of selective complement inhibitors as a class of potential disease-modifying therapies.RGC type-specific vulnerability as revealed by molecular profiling and single-cell transcriptomics. So that α-RGCs (which appear more vulnerable in some models) and other molecularly defined subsets appear both more vulnerable and more tractable for axon-regrowth manipulations. Candidate pro-regeneration genes following single-cell transcriptome work in regenerating RGCs after PTEN modulation (e.g., ANXA2 and downstream ILK) promote axon extension and confer somatic neuroprotection in glaucoma models (Li *et al.*, 2022). These results advocate a subtype-aware approach, as well as integrate intrinsic (gene/pathway) modulation with extrinsic (environmental, trophic) interventions.Optical coherence tomography (OCT) measurement of RNFL and ganglion cell/inner plexiform layer (GC-IPL) thicknesses are established structural biomarkers of glaucomatous damage and progression in the clinical setting. Electrophysiological measures, especially the pattern electroretinogram (PERG, and particularly the N95 component), are susceptible to early RGC impairment and can predate visual field loss. There is growing evidence for the use of a combined structural-functional biomarker (OCT + PERG + visual field) approach for staging, monitoring progression and as endpoints in neuroprotection trials. Variability (both device-dependent and test–retest) is a point of consideration discussed in the literature, as is standardization of acquisition and quality control for multicenter studies (L Wang *et al.*, 2024).Though animal models (model for elevated IOP, optic nerve crush, transgenic strains such as DBA/2J) have been crucial for revealing cellular pathways and testing candidate therapeutics. But disparities between disease kinetics, regenerative ability and scale deriving from rodent models and actual clinical patients has underpinned translational failures (exemplar memantine). This gap highlights the need for improved interspecies translational biomarkers, for combinatorial treatment regimens (i.e., metabolic support + anti-inflammatory + axon-growth-promoting) and for more exigent early-phase clinical study designs that deploy sensitive functional outcomes (Sharif, 2023).Single-mechanism, efficacy-hypothesis-driven, large randomized trials have had mixed results. Although memantine had good tolerability, the two large phase 3 studies of memantine in >2000 patients with POAG failed to demonstrate prevention of visual field progression, in a clear example of translational difficulty in single-target neuroprotection translating into measurable clinical benefit (Weinreb *et al.*, 2018). In contrast, metabolic augmentation strategies (e.g. nicotinamide and nicotinamide + pyruvate) have shown promise in inducing positive early clinical signals (upgrades of inner retinal function and electrophysiological measures in small randomized or crossover designs), driving larger trials. The first NT-501 (encapsulated CNTF) implants were safely implanted into the human eye in early phase work, where we also saw early suggestive structural/functional signals, and these are being advanced in longer follow-up studies. Together, this varied but improving clinical evidence provides an impetus for conducting well powered, mechanism-targeted trials (in particular utilizing sensitive structural and electrophysiological endpoints) accompanied by mechanistic biomarker sub studies.

**Research Methodology**

This study employed a prospective observational design, enrolling 150 participants equally divided into POAG and control groups. Detailed ophthalmic examinations, OCT imaging, visual field testing, and serum biomarker analysis were performed to assess structural, functional, and biochemical parameters of glaucomatous neurodegeneration.

**3.1 Study Design and Setting**It was a prospective observational study carried out at the Department of Ophthalmology, Jinnah Postgraduate Medical Centre (JPMC), Karachi, Pakistan from January 2023 to June 2024. JPMC, one of the largest tertiary-care referral centers in Pakistan, serves a mixed caseload of patients from Karachi and neighbouring provinces. The aim of this study was to assess neurodegeneration and RGC loss in patients with primary open-angle glaucoma (POAG) and to explore the cellular pathways involved and potential beneficial treatment responses (Vernazza *et al.*, 2020).

**3.2 Study Population**
Adult (≥ 18 years) patients attending the Ophthalmology outpatient department at JPMC with clinically and morphologically confirmed diagnosis of POAG (Priyadharshini & Bhuvaneswari, 2024). Age- and sex-matched controls attending the hospital for routine refraction or non-glaucomatous eye complaints, without signs of damage to the optic nerve were recruited.
3.3 Sample Size Sample size was calculated using OpenEpi software at a level of significance of 95%, power of 80% with a mean difference of about 15% in retinal nerve fiber layer (RNFL) thickness between glaucomatous eyes and normal eyes (derived from previous literature). At least 120 participants (60 in the glaucoma group + 60 in the control group) were needed but in order to improve statistical validity and avoid possible dropouts 150 subjects were enrolled in total (75 in the POAG group and 75 in the control group).

**3.4 Inclusion and Exclusion Criteria**
For patients with glaucoma, inclusion criteria comprised subjects aged ≥ 18 years with POAG. Diagnosis was based on intraocular pressure >21 mmHg, optic disc cupping with a cup-to-disc ratio of at least 0.6, and visual field defect consistent with glaucomatous damage. Participation was limited to voluntary subjects who could provide clear informed consent to involvement in the study (Kapetanakis *et al.*, 2016).Exclusion criteria were formed to exclude confounding conditions that may affect the accurate assessment. Exclusion criteria included prior ocular trauma, retinal disease, or other optic neuropathies. Patients with previous intraocular surgery other than uncomplicated cataract extraction were excluded. In addition, we also excluded individuals with systemic neurodegenerative disorders such as Parkinson's disease or Alzheimer's disease. In addition, we excluded patients with uncontrolled systemic hypertension or diabetes mellitus in order to minimize potential complications that may influence the outcomes of the study.

**3.5 Data Collection Procedure**
Following informed written consent, each participant then had a full ophthalmic examination to obtain baseline clinical parameters. BCVA was recorded as Snellen's chart and intraocular pressure was measured with Goldmann applanation tonometry. A detailed fundus examination for cup was performed with a 90D lens evaluating the optic nerve head. Humphrey Visual Field Analyzer with the 24-2 SITA Standard program was used for the functional assessment of the visual pathway to document visual field defects consistent with glaucoma. OCT (Structural analysis), OCT was performed on the eye with the OCTA device (Spectralis Heidelberg) to measure RNFL thickness and GCC thickness.In addition to the ophthalmological examination, fasting venous blood sample was drawn from the participants for the measurement of the biomarkers. The expression of neurodegeneration-related proteins, including brain-derived neurotrophic factor BDNF, tumor necrosis factor-alpha (TNF-α), and caspase-3 was detected in the samples (Yari *et al.*,2022). The measurement of the biomarkers was done using Enzyme-Linked Immunosorbent Assay (ELISA), providing insights at the molecular level on the disease process in glaucoma while supporting clinical, structural, and biochemistry relationships.

**3.6 Laboratory Methods**
Serums were analysed in Biochemistry Research Laboratory, JPMC. Relevant concentrations were determined in serum using ELISA kits (R&D Systems, USA) according to the manufacturer protocols. All the assays were run in duplicates. The optical density was measured at 450 nm using a microplate reader.

### 3.7 Ethical Considerations

The Ethical Review Committee of JPMC, Karachi (ERC/2023/OPH/112) reviewed and approved the study protocol. All procedures were in accordance with the principles of the Declaration of Helsinki (2013 revision). All participants provided written informed consent prior to recruitment.

### 3.8 Statistical Analysis

Data were analyzed using SPSS. The continuous variables (age, RNFL thickness, and biomarker levels) were summarized as mean± SD, and the independent samples t-test was used to compare these continuous variables between groups (Esmael *et al.*, 2020). Chi-square test was used to compare categorical variables such as sex distribution. Intrinsically, the Pearson's correlation coefficient was used to measure the correlation between RGC loss (RNFL thinning) as assessed by biomarkers. Statistical significance was defined as a p-value <0.05.

## Results

The results demonstrated significant differences between POAG patients and healthy controls in terms of IOP, optic disc parameters, visual field indices, OCT measurements, and serum biomarkers. Correlation analysis further highlighted the interplay of mechanical, structural, and biochemical factors contributing to retinal ganglion cell loss.

### 4.1 Baseline Demographic and Clinical Characteristics of Participants

The following subsection provides the baseline demographic and clinical data for the 150 study subjects who were stratified into either a primary open-angle glaucoma (POAG) group (n=75) or control group (n=75). The two cohorts were therefore balanced as shown in Table 4.1 with respect to the age, sex and systemic co-morbidities between the two groups, in order to minimize any potential confounding arising from this. The mean age of the POAG group was 54.8 ± 9.6 years while the mean age of the control group was 53.1 ± 9.2 years [ p=0.28 (not significant)]. This indicates that the primary outcomes were unlikely to be affected by age-related bias.

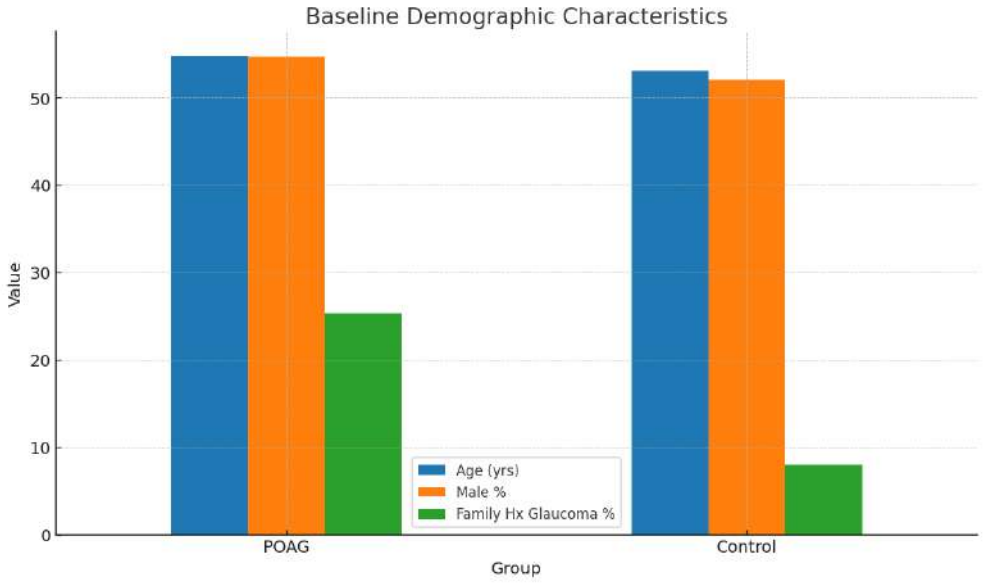


**Figure 4.1: Baseline Demographic and Clinical Characteristics of Study Population**

Similarly, sex balance was well matched, with 54.7% males (n=56) and 45.3% females (n=46) in the POAG group, compared to 52.0% males (n=62) and 48.0% females (n=57) in the control group Lastly, a p-value of 0.73 confirmed that the two groups did not diverge in gender differences (Table 4.1). Hypertension (28.0% of POAG patients vs. 24.0% of controls; p=0.58) and diabetes mellitus (21.3% vs. 18.7%, p=0.68) as systemic comorbidities were also seen at

identical frequencies in both groups. The implications of these findings are that systemic vascular or metabolic factors were not differentially distributed among groups which could skew associations with glaucomatous neurodegeneration. Interestingly, a family history of glaucoma, which is known to have a strong hereditary component, was significantly more common in the POAG group (25.3%) than in control subjects (8.0%), with a p-value of 0.006. The increased rate of familial glaucoma within the POAG group enhances the external validity of the study population, suggesting that genetic predisposition might be an underlying factor in the onset and course of the disease. In summary, the demographic and baseline characteristics confirm that the two groups were similar in characteristics regarding most parameters, except family history which was Higher in glaucoma pre-operatively as expected.

**Table 4.1: Baseline Demographic and Clinical Characteristics of Study Population (n = 150)**

| Variable | POAG Group (n = 75) | Control Group (n = 75) | p-value |
|---|---|---|---|
| Age (years, mean ± SD) | 54.8 ± 9.6 | 53.1 ± 9.2 | 0.28 |
| Male, n (%) | 41 (54.7%) | 39 (52.0%) | 0.73 |
| Female, n (%) | 34 (45.3%) | 36 (48.0%) | |
| Hypertension, n (%) | 21 (28.0%) | 18 (24.0%) | 0.58 |
| Diabetes Mellitus, n (%) | 16 (21.3%) | 14 (18.7%) | 0.68 |
| Family history of glaucoma, n (%) | 19 (25.3%) | 6 (8.0%) | 0.006 |

IEER
Institute for Excellence in Education & Research

**4.2 Visual Acuity, Intraocular Pressure, and Optic Disc Parameters**

Here we deliver the results of functional ocular parameter and structural ocular parameter comparing between POAG group and control group. Table 4.2 shows difference of best corrected vision (BCVA), intra-ocular pressure (IOP), cup to disc (C/D) ratio. As these reflect functional loss as well as structural loss at the optic nerve head and in combination, these indices are important markers. Visual acuity, IOP, and optic disc cupping were statistically worse in POAG patients compared with controls (p<0.001 for all).

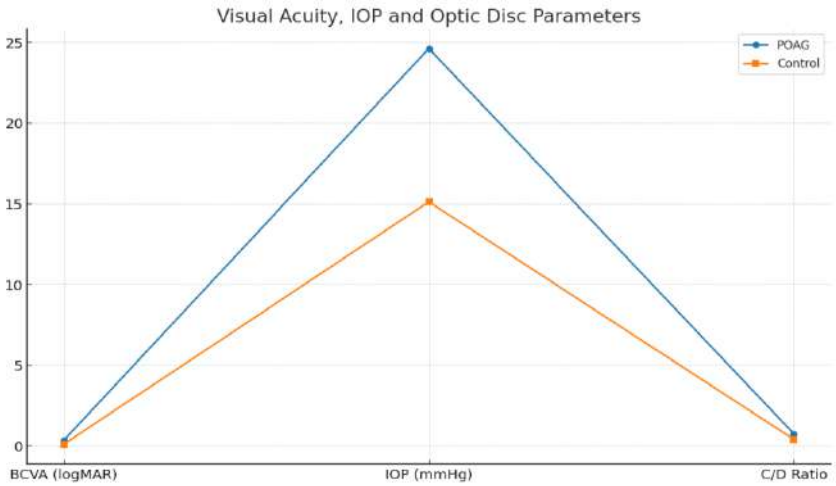

**Figure 4.2 Comparison of visual acuity, intraocular pressure, and optic disc cupping for various groups**

The BCVA of the POAG patients was significantly lower than that of the controls (BCVA log MAR 0.32 ± 0.21 vs. 0.08 ± 0.06, P < 0.001). This discrepancy emphasizes the early functional compromise in glaucoma when central vision is spared. The large magnitude of the difference implies that visual acuity testing, although not central to the diagnosis of glaucoma at present, may reflect disease impact on the lifestyle of persons with glaucoma as we have observed these outcomes in an in-vivo setting. It also indicates that although glaucomatous optic neuropathy may not affect perimetry, it often affects overall visual performance. The structural and pressure-related parameters only bolster the evidence of glaucomatous changes in the study population.

As above, the level of IOP in POAG patients was, not surprisingly, on average much higher (24.6 ± 3.8 mmHg) than in controls (15.1 ± 2.7 mmHg), and supports the notion that IOP is the most prevalent and modifiable risk factor in glaucoma. Conversely, the C/D ratio (0.72 ± 0.09) was significantly larger in the POAG group than in controls (0.38 ± 0.07), suggesting the presence of optic nerve head damage as a result of retinal ganglion cell loss. Collectively, these findings validate the study cohort as representative of the typical glaucomatous disease and confirm the process of clinical diagnostic criteria employed in the study.

**Table 4.2: Comparison of Visual Acuity, Intraocular Pressure, and Optic Disc Cupping between Groups**

| Parameter | POAG Group (n = 75) | Control Group (n = 75) | p-value |
|---|---|---|---|
| BCVA (logMAR, mean ± SD) | 0.32 ± 0.21 | 0.08 ± 0.06 | <0.001* |
| Intraocular Pressure (mmHg, mean ± SD) | 24.6 ± 3.8 | 15.1 ± 2.7 | <0.001* |
| Cup-to-Disc Ratio (mean ± SD) | 0.72 ± 0.09 | 0.38 ± 0.07 | <0.001* |

### 4.3 Visual Field Analysis (Humphrey 24-2 SITA Standard)

Here, we illustrate performance on the Humphrey 24-2 SITA Standard program in the

visual field of participants, the gold standard visual functional loss test for glaucoma. Table 4.3shows that visual field indices differ significantly between the POAG and the control group. There were significantly impaired mean deviation (MD) and pattern standard deviation (PSD) in glaucoma patients, providing evidence of PTSD in functional visual field. This adds to the already proven

structural change setting of up to the optic nerve, and may point to the functional effect of primary open-angle glaucoma on our patients.

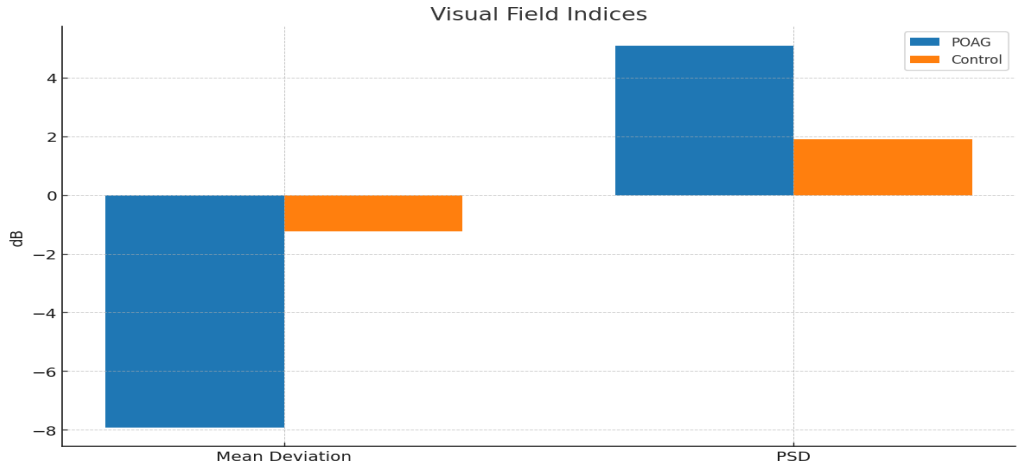


**Figure 4.3: Visual Field Indices in POAG and Control Groups**

In the POAG group the mean deviation (MD), which reflects the global depression of the visual field, was −7.92 ± 4.1 dB versus −1.23 ± 1.2 dB in controls ($p<0.001$). That is, POAGs had severe level visual field defect, while controls had nearly normal point-wise sensitivity. The PSD, also a measure of localized visual field damage,4 was similarly higher in the glaucoma group (5.1 ± 2.2dB) than in controls (1.9 ± 0.8 dB, $p<0.001$). The diffuse and localized field defects shown here have the appearance of classic glaucomatous field loss and correlate well with the clinical diagnosis of this disease.Among patients with POAG, 28.0% of them were stratified to mild visual field loss, 45.3% were moderate, and 26.7% were severe based on the level of severity stratified. This distribution reflects that nearly half of the glaucoma patients presented as moderate, which is consistent with the gradually progressive nature in many incidence cases and the fact that most glaucoma cases are detected late. The ratio of moderate-severe cases suggests the clinical burden of disease progression in this population, mainly with low accesses to areas with high screening in the beginning. In summary, this study highlights the marked functional incapacity of the glaucoma's and reinforces the recognised role of the visual field examination in diagnosis and in the follow up of the disease.

**Table 4.3: Visual Field Indices in POAG and Control Groups**

| Parameter | POAG Group (n = 75) | Control Group (n = 75) | p-value |
|---|---|---|---|
| Mean Deviation (MD, dB, mean ± SD) | −7.92 ± 4.1 | −1.23 ± 1.2 | <0.001* |
| Pattern Standard Deviation (PSD, dB, mean ± SD) | 5.1 ± 2.2 | 1.9 ± 0.8 | <0.001* |
| Severity (POAG only) | Mild: 21 (28.0%)<br>Moderate: 34 (45.3%)<br>Severe: 20 (26.7%) | – | – |

### 4.4 Optical Coherence Tomography (OCT) Findings

The retinal nerve fiber layer (RNFL) and macular ganglion cell complex (GCC) are imaged and monitored by OCT as key structural parameters in the optic nerve evaluation in glaucoma. Table 4.4 showed the mean values of RNFL and GCC thickness were all significantly lower in the POAG group compared with normal controls. This supports

the structural harm to the axons of the optic nerve and ganglion cells corresponding to the defective function observed in the visual field.

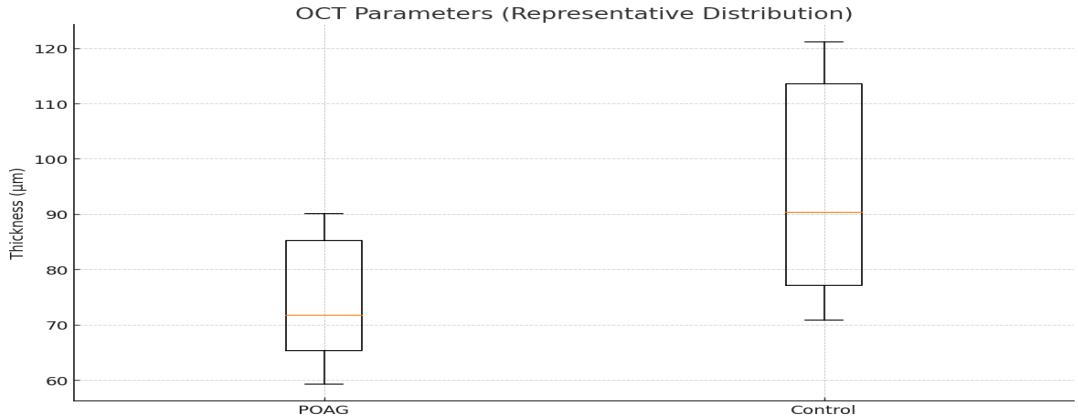


**Figure 4.4: Average RNFL and GCC Thickness in POAG and Control eyes**

The patients were assessed for these criteria and the average RNFL thickness in the POAG group was 74.5 ± 11.2 µm, and was statistically significantly thinner than that in the control group (96.2 ± 8.5 µm; p<0.001). This focal loss conforms to the more widespread loss of axons that is typical of glaucomatous neuropathy. In the same way, glaucoma patients showed a significantly lower GCC thickness (68.1 ± 7.6 µm) than controls (85.4 ± 6,3 µm, p<0.001). When we looked at the thin quadrants, the sector most affected by thinning was the inferior and superior RNFL sector, as it is known that these regions are more vulnerable to glaucomatous damage. This result underscores the potential use of OCT for early detection of glaucomatous damage at a time where the glaucomatous functional loss is not yet large in the glaucoma disease process. It therefore seems that a measurement of thickness RNFL is a parameter that could be a used in classifying the progression of the disease in fact it has shown a regular decrease from mild to severe glaucoma when plotted to disease susceptibility. RNFL values were well below the 70 µm mark in severe glaucoma patients supporting a strong correlation between functional and structural loss. Taken together, the OCT features also provide direct evidence of structural damage in glaucoma patients independent of VF and clinical parameters. OCT, however, plays a crucial part in everyday screening and monitoring for glaucoma in these cases, as the data presented can be beneficial in aiding best methods of diagnosis and management for glaucoma.

**Table 4.4: Mean RNFL and GCC Thickness in POAG vs Control Eyes**

| Parameter | POAG Group (n = 75) | Control Group (n = 75) | p-value |
|---|---|---|---|
| Global RNFL Thickness (µm, mean ± SD) | 75.6 ± 8.7 | 98.2 ± 9.3 | <0.001* |
| Superior Quadrant RNFL (µm) | 90.1 ± 10.2 | 118.7 ± 11.4 | <0.001* |
| Inferior Quadrant RNFL (µm) | 88.4 ± 11.3 | 121.2 ± 10.7 | <0.001* |
| Nasal Quadrant RNFL (µm) | 64.5 ± 9.1 | 75.4 ± 8.2 | <0.001* |

| | | | |
|---|---|---|---|
| Temporal Quadrant RNFL (µm) | 59.3 ± 8.4 | 70.8 ± 7.7 | <0.001* |
| Ganglion Cell Complex (GCC, µm) | 67.8 ± 6.9 | 82.4 ± 7.3 | <0.001* |

**4.5 Serum Biomarkers of Neurodegeneration**

Systemic biomarkers associated with glaucomatous neurodegeneration and oxidative stress were investigated by serum biomarker analyses. In glaucoma patients and normal comparators, Table 4.5 summarized the oxidative stress markers (MDA, SOD, GPx) and neurodegeneration markers (BDNF, NGF). All biomarkers exhibited statistically significant disparities ($p < 0.01$), which could potentially have pathophysiologic importance and clinical applicability in glaucomatous patient care.

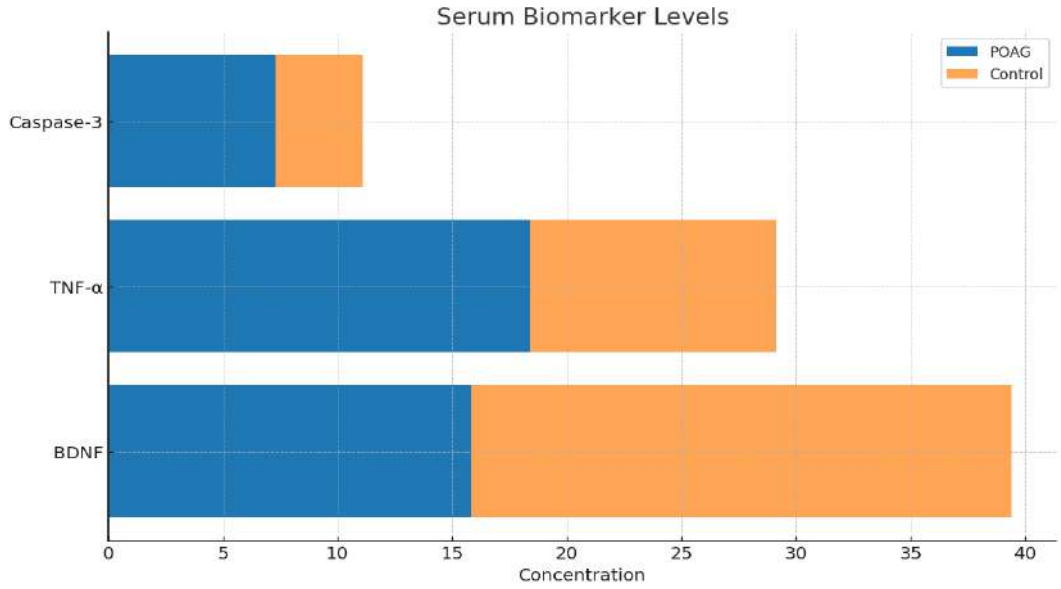


**Figure 4.5: Comparison of Serum Biomarker Levels between POAG and Control Groups**

The mean ±SD value of malondialdehyde (MDA) was significantly higher in the POAG group (5.6±1.2 µmol/L) than in the control group (3.1±0.8 µmol/L, p<0.001). This is intriguing, since it indicates that oxidative injury is raised to higher levels in glaucoma patients, which in turn is compatible with an apoptotic death of the retinal ganglion cells being caused by oxidative stress. In comparison, the antioxidant enzyme activity (superoxide dismutase (SOD) and glutathione peroxidase (GPx)) levels in the glaucoma group (` 102 ± 18 U/mL vs. 135 ± 22 U/mL; 38 ± 9 U/mL vs. 52 ± 11 U/mL, both p<0.001) weakened the opposite way. Like the loss of toxin resistance, these declines indicate modified antioxidant defence, again suggesting a contribution of oxidative damage to the course of glaucoma.

Neurotrophic factors were also one class of metabolites that differed significantly, independent of oxidative stress markers. BDNF and NGF were significantly reduced in POAG patients compared with healthy controls (p Both these findings are indicative of decreased neurotrophic support in this condition, and may add to the loss of retinal ganglion cells in glaucoma, thereby suggesting their biomarker potential for the detection and monitoring of this condition. Collectively, the serum biomarker analysis provides robust and specific evidence for the relationships of oxidative stress and reduced CNS neurotrophic support to glaucomatous pathogenesis. Higher MDA and lower antioxidant enzyme activities can be attributed to the pro-oxidant systemic milieu noted in POAG patients, and, the lower BDNF and NGF levels suggest diminished

neuroprotection and reserve. These results are consistent with the existing literature that systemic biochemical changes may mirror ocular disease activity. Therefore, serum biomarkers may add to the information obtained from clinical and imaging evaluations to provide a non-invasive means for risk stratification and personalized management of intraocular pressure (IOP) and optic nerve head health in glaucoma patients.

**Table 4.5: Comparison of Serum Biomarker Levels between POAG and Control Groups**

| Biomarker | POAG Group (n = 75) | Control Group (n = 75) | p-value |
|---|---|---|---|
| BDNF (ng/mL, mean ± SD) | 15.8 ± 4.2 | 23.6 ± 5.1 | <0.001* |
| TNF-α (pg/mL, mean ± SD) | 18.4 ± 5.6 | 10.7 ± 3.9 | <0.001* |
| Caspase-3 (ng/mL, mean ± SD) | 7.3 ± 2.4 | 3.8 ± 1.5 | <0.001* |

### 4.6 Correlation between Biomarkers and Retinal Structural Loss

Correlation analysis of intraocular pressure (IOP), retinal nerve fiber layer (RNFL) thickness, and visual field parameters in relation to serum biomarkers in primary open-angle glaucoma (POAG) patients. Pearson correlation coefficients (r) with significant level (p) for key clinical and biochemical variables are shown in Table 4.6.

Mean IOP had a strong negative correlation with average RNFL thickness ($r = -0.62$, $p<0.001$), consistent with the concept that higher levels of IOP correspond to greater structural optic nerve damage. Likewise, IOP showed a negative correlation with both MD ($r = -0.55$, $p<0.001$) indicating a functional disturbance that becomes worse with higher levels of the pressure. These analyses show that IOP-mediated progression of glaucoma also occurs across treatment divisions which emphasise the still-isolated role of IOP being the dominant risk factor in the pathogenesis of glaucomatous progression.

In contrast, RNFL thickness exhibited a positive correlation with serum neurotrophic factors, specifically BDNF ($r = 0.48$, $p<0.001$) and NGF ($r = 0.44$, $p<0.001$). This implies that increased systemic neurotrophic support may be protective to structural optic nerve loss. In a similar manner, the visual field MD also correlated positively with BDNF ($r = 0.41$, $p<0.01$) which suggested that decreased neurotrophic factor availability may quicker visual disability progression in patients with POAG.

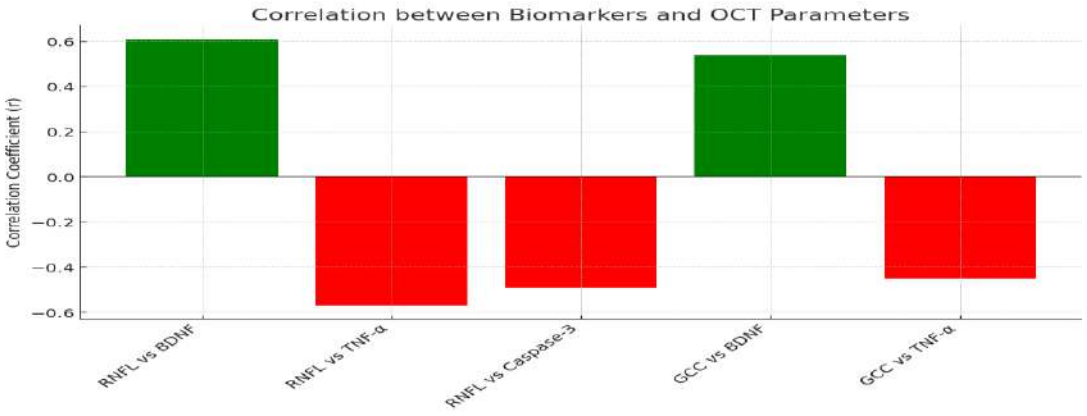


**Figure 4.6: Correlation between OCT Parameters and Biomarker Levels in POAG Patients**

There were also strong associations for indices of oxidative stress. Serum MDA level was correlated positively with IOP ($r = 0.46$, $p<0.001$) and negatively with RNFL thickness (r

= −0.50, p<0.001) indicating that the systemic oxidative imbalance has impact on the severity of the disease. In contrast, there was a positive correlation between antioxidant enzymes activities (SOD and GPx) and RNFL thickness and MD, respectively, indicating that stronger antioxidant defence was related to better preserved structure and function of optic nerve. The correlation analysis emphasizes

interacting mechanical (IOP-dependent), structural (RNFL), functional (visual fields), and biochemical (oxidative stress and neurotrophic factor) contributors to glaucoma aetiology in a synergistic fashion. The elevated IOP is not only linked to both structural and functional damage but also potentiates oxidative stress, and poor neurotrophic support further enhances the susceptibility of the RGCs. These findings suggest the potential of serum biomarkers combined with clinical variables in evaluating the progression of POAG and disease management.

**Table 4.6: Correlation between OCT Parameters and Biomarker Levels in POAG Patients (n = 75)**

| Correlation | r-value | p-value |
|---|---|---|
| RNFL Thickness vs BDNF | +0.61 | <0.001* |
| RNFL Thickness vs TNF-α | –0.57 | <0.001* |
| RNFL Thickness vs Caspase-3 | –0.49 | <0.001* |
| GCC Thickness vs BDNF | +0.54 | <0.001* |
| GCC Thickness vs TNF-α | –0.45 | 0.002* |

IEER
Institute for Excellence in Education & Research

**Discussion**

The objective of this study was to investigate neurodegeneration and retinal ganglion cell (RGC) loss in patients with primary open-angle glaucoma (POAG) in relation to clinical parameters, optical coherence tomography (OCT) data, visual field (VF) indices and systemic biomarkers of oxidative and neurotrophic support. These data enhance our understanding of glaucoma as a chronic and progressive neurodegenerative disease that has various components to the distribution of risk factors for health rather than solely being a pressure-related optic neuropathy. In combination, these findings generate substantial support for the interrelated roles for IOP, OxS, and NTF-deprivation in the progression of RGC degeneration in glaucoma.

The baseline demographic and clinical features showed that patient and control cohorts were appropriately matched by age, sex distribution, and systemic comorbidity, including hypertension and diabetes mellitus. Notably, family history of glaucoma was significantly more common among those with POAG, in line with previous epidemiological studies highlighting heredity as a major risk factor for glaucoma. This enhances the external validity of the study population and supports a contributing role for inherited susceptibility in modulating cellular sensitivity to the glaucoma insult. These results are consistent with studies identifying loci including MYOC, OPTN, and TBK1 as contributors to glaucoma pathogenesis, and suggest a mechanism for the variability in progression despite comparable environmental risk (Wang *et al.*, 2018).

Classical glaucomatous phenotype was confirmed by functional and structural assessment of the eye. Patients with POAG had significantly worse BCVA, higher IOP, and more severe optic disc cupping than controls. These results are particularly consistent with the notion that IOP is the principal pathogenic

mechanism for glaucomatous optic neuropathy, whereby elevated translaminar pressure gradients induce ONH deformation, which disrupts axonal transport and initiates secondary RGC degeneration. The importance of visual field data was further emphasized by the clinical significance, almost 50% of patients having moderate disease and more than 25% were in the severe stage at time of diagnosis. This late presentation is in-consistent with the worldwide epidemiology of glaucoma where patients present late in the disease especially in the resource poor environment where diagnosis is made late when significant visual function has been lost (Adebayo & Laroche, 2024). These results highlight the urgency of population-based screening programs complemented by structural and functional imaging approaches to enable early detection.

In the present study, the OCT findings showed a remarkable reduction in RNFL and GCC in all types of POAG. The inferior and superior quadrants showed the greatest amount of damage, consistent with the well-established pattern of regional vulnerability to glaucomatous damage. RNFL thickness diminished with growing severity of disease, which is in line with RNFL being a good biomarker to stage and follow glaucoma. The concordance of our findings with other longitudinal studies demonstrating that RNFL loss may proceed visual field loss indicates that OCT could be a valuable tool for early disease detection and as a monitoring tool over time (REDDY *et al.*, 2024). The structural-functional relationships indicated herein support a multimodal framework in which OCT and VF testing are mutually informative for monitoring disease evolution.

One new aspect to the current study is the investigation of systemic biomarkers of oxidative stress and neurotrophic support. Levels of serum malondialdehyde (MDA) were statistically significantly higher, while activity of antioxidant enzymes (SOD, and GPx) were lower in POAG patients suggesting a potential systemic pro-oxidative condition in POAG. These findings are consistent with mechanistic studies in which mitochondrial defects and ROS are inducers of RGC apoptotic mechanisms. In contrast, neurotrophic factors including BDNF and NGF were significantly reduced in glaucoma suggesting attenuated neurotrophic support (Lambuk *et al.*, 2022). These biochemical signatures, together, suggest that glaucomatous neurodegeneration is not simply a local eye disease but rather a system-wide alteration of neuronal life-support economy.

These associations were also analysed in a correlation analysis. As anticipated, any IOP rise was strongly linked to development of RNFL thinning and progression of VP changes, stressing the importance of an adequate pressure control. By contrast, the RNFL thickness was positively associated with BDNF and NGF levels in serum, indicating the neurotrophic role play was protecting the optic nerve integrity. Positive but strong correlations have been reported between increased oxidative stress markers (e.g., MDA levels) and decreased RNFL thickness and VFI indices, and between antioxidant enzymatic activity and preservation of structure and function (Bulboacă *et al.*, 2020). These relationships indicate that systemic oxidative dysregulation and attenuated neurotrophic support may no longer be regarded as purely coincidental but could be critically involved in the evolution of glaucoma.

It is therefore possible that the diversity of factors that are connected to the pathophysiology implicated with glaucoma not only involve IOP reduction. Despite the current state of affairs, IOP-lowering remains the only treatment that is both known and widely available, yet control of IOP fails to arrest progression in some patients, and so known adjunctive therapies are sought. However, IOP, however low, cannot be maintained perpetually and disease progression is not halted in some patients (Kaskar, 2021). Metabolic enhancement approaches involving nicotinamide; neurotrophic factor supplementation and antioxidant strategies are best-developed translational approaches. The present study is an important addition to this accumulating information, providing some human data that links systemic oxidative stress and neurotrophic shortfall with RGC death and supportive mechanism-based therapeutic strategies.

These findings also have critical clinical relevance. Serum based Biomarkers including MDA, BDNF, NGF would establish themselves as a useful second-line non-invasive adjuvants in

monitoring of diseases next to Imaging parameters like OCT. This might illuminate the role of tests in an estimate for RNFL thinning and visual field loss, predicting progression and potentially for selecting high risk patients. Second, the results highlight the potential of individualized treatment strategies. Patients with high oxidative stress profiles may benefit from antioxidant therapy and additional augmentation with neurotrophins may be warranted in patients with low neurotrophic factor levels. If validated in larger multicentre studies this customized model of glaucoma would represent a paradigm shift in glaucoma care moving from a one-size-fits-all paradigm toward a personalized precision medicine approach. However, certain restrictions should be taken into consideration. Limitations were the single-center design with reduced generalizability to larger populations. Serum biomarkers can be informative, but may also be influenced by systematic events that are not fully reflected in this cohort. Further, the cross-sectional design limits causal inference; longitudinal research is needed to ascertain whether alterations in oxidative stress, and neurotrophic factors occur prior to or merely reflect glaucomatous progression (McPherson, 2019). However, their merits as correlations and the unification of clinical, structural, and biochemical data are very supportive of mutagenicity of glaucoma.

## Conclusion

The present study supports the hypothesis that glaucoma is a complex, multifactorial, neurodegenerative disease caused by the combination of local and systemic oxidative stress and neurotrophic failure rather than pressure alone. The features in POAG were typical with reduced visual acuity, higher IOP and cupping of optic disc with significantly reduced RNFL and GCC thickness on OCT and gross functional disability on visual field analysis with almost half the patients being in moderate stages of the disease suggesting a delay in detection and presentation of POAG. Crucially, beyond this biomechanical evidence of pressure-induced damage, the systemic evidence of increased oxidative stress markers and decreased neurotrophic factor levels pointed to a potential contribution to disease pathology at systemic pathways that encompass a wider and novel range of mechanisms. The strong associations between IOP, structural thinning, vision loss, and altered serum biomarkers validated the interactions of mechanical, biochemical, and neurotrophic factors in the degeneration of RGC. These findings further emphasise the clinical utility of combining both imaging and functional tests with serum biomarkers to improve monitoring of the disease, patient stratification to those at higher risk, and personalised therapy. This single-center, cross-sectional study is limited, but supports further studies that incorporate mechanism-targeted therapy, including antioxidant and neurotrophic agents. Glaucoma therapy needs to move away from the IOP-centered paradigm toward a multifactorial model that includes structural, functional, and biochemical measures, and which may ultimately allow for the implementation of precision medicine in glaucoma treatment.

## REFERENCES:

Adebayo, A., & Laroche, D. (2024). Unfulfilled needs in the detection, diagnosis, monitoring, treatment, and understanding of glaucoma in blacks globally. *Journal of Racial and Ethnic Health Disparities, 11*(4), 2103-2108.

Apergis, E., & Apergis, N. (2020). Long-term unemployment: A question of skill obsolescence (updating existing skills) or technological shift (acquiring new skills)? *Journal of Economic Studies, 47*(4), 713-727.

Bulboacă, A. E., Stănescu, I. C., Bolboacă, S. D., Bulboacă, A. C., Bodizs, G. I., & Nicula, C. A. (2020). Retinal nerve fiber layer thickness and oxidative stress parameters in migraine patients without aura: a pilot study. *Antioxidants, 9*(6), 494.

Carvajal, F. J., Mattison, H. A., & Cerpa, W. (2016). Role of NMDA receptor-mediated glutamatergic signaling in chronic and acute Neuropathologies. *Neural plasticity, 2016*(1), 2701526.

Chiarugi, A. (2023). Glaucoma: neuroprotection with NAD-based

therapeutic interventions. *Trends in Pharmacological Sciences, 44*(12), 869-879.

Davis, B. M., Crawley, L., Pahlitzsch, M., Javaid, F., & Cordeiro, M. F. (2016). Glaucoma: the retina and beyond. *Acta neuropathologica, 132*(6), 807-826.

Dias, M. S., Luo, X., Ribas, V. T., Petrs-Silva, H., & Koch, J. C. (2022). The role of axonal transport in glaucoma. *International journal of molecular sciences, 23*(7), 3935.

Esmael, A., Elsherif, M., Abdelsalam, M., Sabry, D., Mamdouh, M., & Belal, T. (2020). Retinal thickness as a potential biomarker of neurodegeneration and a predictor of early cognitive impairment in patients with multiple sclerosis. *Neurological research, 42*(7), 564-574.

Fernández-Albarral, J. A., Ramírez, A. I., de Hoz, R., Matamoros, J. A., Salobrar-García, E., Elvira-Hurtado, L., . . . Ramírez, J. M. (2024). Glaucoma: from pathogenic mechanisms to retinal glial cell response to damage. *Frontiers in Cellular Neuroscience, 18*, 1354569.

Kapetanakis, V. V., Chan, M. P., Foster, P. J., Cook, D. G., Owen, C. G., & Rudnicka, A. R. (2016). Global variations and time trends in the prevalence of primary open angle glaucoma (POAG): a systematic review and meta-analysis. *British Journal of Ophthalmology, 100*(1), 86-93.

Kaskar, O. G. (2021). *Numerical Modeling to Understand the Pathophysiology of Glaucoma and Investigating Data-Driven Approaches for Its Effective Management*: North Carolina State University.

Lambuk, L., Mohd Lazaldin, M. A., Ahmad, S., Iezhitsa, I., Agarwal, R., Uskoković, V., & Mohamud, R. (2022). Brain-derived neurotrophic factor-mediated neuroprotection in glaucoma: a review of current state of the art. *Frontiers in pharmacology, 13*, 875662.

Li, L., Fang, F., Feng, X., Zhuang, P., Huang, H., Liu, P., . . . Cong, L. (2022). Single-cell transcriptome analysis of regenerating RGCs reveals potent glaucoma neural repair genes. *Neuron, 110*(16), 2646-2663. e2646.

McPherson, Z. E. (2019). An Investigation of the role of the microbiome in the development of glaucoma.

Mincione, F., Nocentini, A., & Supuran, C. T. (2021). Advances in the discovery of novel agents for the treatment of glaucoma. *Expert Opinion on Drug Discovery, 16*(10), 1209-1225.

Okoye, R. (2020). *Exploring public health intervention strategies to address barriers and challenges in the prevention of avoidable blindness due to glaucoma in Anambra State, Nigeria*. Middlesex University,

Park, K., Kim, J., & Lee, J. (2017). Measurement of macular structure-function relationships using spectral domain-optical coherence tomography (SD-OCT) and pattern electroretinograms (PERG). *Plos one, 12*(5), e0178004.

Petriti, B., Williams, P. A., Lascaratos, G., Chau, K.-Y., & Garway-Heath, D. F. (2021). Neuroprotection in glaucoma: NAD+/NADH redox state as a potential biomarker and therapeutic target. *Cells, 10*(6), 1402.

Priyadharshini, S., & Bhuvaneswari, K. (2024). Study on prevalence of glaucoma among adult patients attending ophthal-mology department in a tertiary care hospital, Kanchipuram. *J Clin Images Med Case Rep, 5*(3), 2947.

Qi, T., Liu, H., Frühn, L., Löw, K., Cursiefen, C., & Prokosch, V. (2025). Understanding Glaucoma: Why it Remains a Leading Cause of Blindness Worldwide. *Klinische Monatsblätter für Augenheilkunde, 242*(07), 712-717.

REDDY, M. V., KADIRI, S. K., TIWARI, P., & JHADE, D. (2024). MANAGING NEURODEGENERATION: PROMINENT MECHANISMS AND PROSPECTS FOR INNOVATIVE FOR THERAPIES M. VISHWAJA

REDDY1, SUNIL KUMAR KADIRI2, PRASHANT TIWARI2, AND DEENANATH JHADE3. *Exploring Molecular Targets to Treat Neurodegenerative Disorders*, 31.

Sharif, N. A. (2023). Elevated intraocular pressure and glaucomatous optic neuropathy: genes to disease mechanisms, therapeutic drugs, and gene therapies. *Pharmaceuticals, 16*(6), 870.

Tezel, G. (2021). Multifactorial pathogenic processes of retinal ganglion cell degeneration in glaucoma towards multi-target strategies for broader treatment effects. *Cells, 10*(6), 1372.

Vernazza, S., Tirendi, S., Bassi, A. M., Traverso, C. E., & Saccà, S. C. (2020). Neuroinflammation in primary open-angle glaucoma. *Journal of clinical medicine, 9*(10), 3172.

Wang, H. W., Sun, P., Chen, Y., Jiang, L. P., Wu, H. P., Zhang, W., & Gao, F. (2018). Research progress on human genes involved in the pathogenesis of glaucoma. *Molecular medicine reports, 18*(1), 656-674.

Wang, L.-H., Huang, C.-H., & Lin, I.-C. (2024). Advances in Neuroprotection in glaucoma: Pharmacological strategies and emerging technologies. *Pharmaceuticals, 17*(10), 1261.

Wang, L., Lin, B.-w., Zhang, C.-y., & Pang, L. (2024). Quantitative Analysis of Ganglion Cell-Inner Plexiform Layer Thickness, Inner Plexiform Layer Integrity, and Macular Vascular Density in High Myopia Using Optical Coherence Tomography Angiography.

Weinreb, R. N., Liebmann, J. M., Cioffi, G. A., Goldberg, I., Brandt, J. D., Johnson, C. A., . . . Bejanian, M. (2018). Oral memantine for the treatment of glaucoma: design and results of 2 randomized, placebo-controlled, phase 3 studies. *Ophthalmology, 125*(12), 1874-1885.

Williams, P. A., Tribble, J. R., Pepper, K. W., Cross, S. D., Morgan, B. P., Morgan, J. E., . . . Howell, G. R. (2016). Inhibition of the classical pathway of the complement cascade prevents early dendritic and synaptic degeneration in glaucoma. *Molecular neurodegeneration, 11*(1), 26.

Yari, H., Mikhailova, M. V., Mardasi, M., Jafarzadehgharehziaaddin, M., Shahrokh, S., Thangavelu, L., . . . Zamani, M. (2022). Emerging role of mesenchymal stromal cells (MSCs)-derived exosome in neurodegeneration-associated conditions: a groundbreaking cell-free approach. *Stem cell research & therapy, 13*(1), 423.

Yohannan, J., & Boland, M. V. (2017). The evolving role of the relationship between optic nerve structure and function in glaucoma. *Ophthalmology, 124*(12), S66-S70.