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IOSUD

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DOCTORAL THESIS

THE VALUE OF BIOMARKERS IN THE LACRIMAL FILM IN THE DIAGNOSIS AND PROGRESSION OF PRIMARY OPEN-ANGLE GLAUCOMA

ABSTRACT

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ABBREVIATIONS

Abbreviation	Description
AM	Before noon
ANOVA	Analysis of variance
AUC	Area under the curve
BCa	Bias-corrected and accelerated
CI	Confidence interval
CV	Coefficient of variation
dB	Decibels
ELISA	Enzyme-Linked Immunosorbent Assay
ETDRS	Early Treatment of Diabetic Retinopathy Study
GPUD	Primary open-angle glaucoma
HD-OCT	High-Definition Optical Coherence Tomography
HS	High sensitivity
LR	Likelihood ratio
IC	Confidence Interval
IFN-γ	Interferon gamma
IL-1β	Interleukin-1 beta
IL-4	Interleukin-4
IL-6	Interleukin-6
IL-10	Interleukin-10
IQR	Interquartile range
MD	Mean deviation
n	Total number of patients
NaN	Not a number
NF-κB	Nuclear factor kappa B; transcription factor
NPV	Negative predictive value
OCT	Optical coherence tomography
P10/P25/P75/P90	10th/25th/75th/90th percentiles
P-value	p-value
PGA	Prostaglandin analogs
IOP	Intraocular pressure
pg/mL	Picograms per milliliter

Abbreviation	Description
PPV	Positive predictive value
PSD	Standard deviation of the model
PSQI	The Pittsburgh Sleep Quality Index
r	Pearson's linear correlation coefficient
RGC	Retinal ganglion cells
ROC	Receptor operating characteristic
RNFL	Retinal nerve fiber layer
SD	Standard deviation
SITA	Swedish Interactive Threshold Algorithm
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TNF-α	Tumor Necrosis Factor Alpha
UKGTS	UK Glaucoma Treatment Study
α	Level/threshold of statistical significance

INTRODUCTION

1.1. Motivation for Choosing the Topic

Glaucoma is addressed in this thesis as a progressive, irreversible optic neuropathy that is often asymptomatic in its early stages. The rationale for this topic stems from the clinical gap between the onset of biological processes and the point at which structural or functional loss becomes evident through conventional investigations. This characteristic justifies the identification of additional tools capable of detecting the biological activity of the disease before irreversible visual impairment sets in.

The tear film is chosen as the biological matrix because it allows for rapid, repeated, and noninvasive sampling with minimal discomfort for the patient. The thesis is based on the premise that inflammatory mediators in tears may reflect local and systemic processes relevant to glaucoma and may complement assessments based on intraocular pressure, OCT, and perimetry.

1.2. Importance and Relevance of the Research Topic at the National and International Levels

The relevance of this topic is underscored by the epidemiological burden of glaucoma, recognized as one of the leading causes of irreversible blindness. Increased life expectancy and an aging population are driving up the number of affected patients, and late diagnosis is associated with reduced independence, a lower quality of life, and increased costs for healthcare systems.

At the national level, the relevance of this research is underscored by the need for accessible and reproducible methods that can be integrated into outpatient practice. A platform of tear biomarkers could support early detection, risk stratification for disease progression, and the identification of biological or therapeutic complications, especially in settings where access to comprehensive ophthalmologic monitoring is uneven.

1.3. Scientific Objectives and Research Aims

The overall objective of this study is to evaluate the value of inflammatory biomarkers in the tear film for the diagnosis, risk stratification, and monitoring of the progression of primary open-angle glaucoma. The thesis aims to integrate molecular information with established clinical and paraclinical parameters.

The main objectives include identifying molecular signatures associated with glaucoma, validating the relationship between cytokines and structural progression, developing a composite index of inflammatory stability, and integrating modifiable factors—particularly sleep—into the risk model. The research directions aim to move from isolated biomarkers to integrated panels and scores compatible with precision medicine.

1.4. Significance and Anticipated Impact

The significance of this work goes beyond a purely descriptive scope, as it proposes a translational approach to glaucoma in which molecular data can become clinical tools. The anticipated impact lies in improving early detection, personalizing monitoring, and tailoring therapeutic interventions based on the patient's actual biological risk.

By utilizing the tear film, this thesis contributes to the development of a noninvasive assessment paradigm that complements OCT, perimetry, and tonometry. Looking ahead, the results may support the development of rapid tests, multimodal predictive algorithms, and interventional studies focused on the inflammation-neurodegeneration axis.

GENERAL PART

CHAPTER 1. OCULAR ANATOMY AND PHYSIOLOGY

1.1. Anatomy of the Eyeball

This chapter provides a foundation for understanding glaucoma by presenting the anatomical elements relevant to the mechanisms of neuroretinal damage and to the interpretation of tear biomarkers. The eyeball is described as an integrated optical and neurovascular system in which mechanical, vascular, neural, and secretory structures contribute to the maintenance of homeostasis.

1.1.1. The Layers of the Eyeball

The fibrous layer, vascular layer, and neural layer are analyzed in relation to their functional roles. The sclera and cornea provide mechanical support and protection; the uvea contributes to vascularization and the production of aqueous humor; and the retina contains retinal ganglion cells, the primary target of glaucomatous lesions. The biomechanical properties of the sclera and cornea are directly relevant to the transmission of intraocular pressure to the optic nerve head.

1.1.2. Refractive Media

The cornea, aqueous humor, lens, and vitreous humor are presented as refractive media, but also as structures involved in ocular homeostasis. The aqueous humor plays a nutritional and pressurizing role, and the composition of the vitreous humor may reflect retinal and inflammatory processes. However, the need for invasive access to these compartments justifies focusing on tears as a more feasible source of biomarkers.

1.1.3. The Optic Nerve

The optic nerve is the critical region in glaucomatous neuropathy. The axons of ganglion cells traverse the lamina cribrosa, an area exposed to mechanical stress, impaired perfusion, and disruption of axonal transport. The vulnerability of this region explains the development of papillary cupping and RNFL thinning, a key structural parameter in disease monitoring.

1.1.4. Ocular Adnexa

The ocular adnexa—particularly the eyelids, conjunctiva, lacrimal glands, and drainage system—are relevant to the production and stability of the tear film. The lacrimal functional unit connects the ocular surface, tear secretion, and local immunity, which explains why inflammatory or therapeutic changes can influence the composition of tear samples.

1.2 Ocular Physiology

Ocular physiology is characterized by the mechanisms of aqueous humor production and drainage, the regulation of intraocular pressure, and the role of the blood-ocular barriers. These processes explain both the basis for hypotensive treatment and the limitations of an exclusively pressure-based interpretation of glaucoma.

1.2.1. Dynamics of Aqueous Humor

Aqueous humor is produced by the ciliary body and drained via the trabecular and uveoscleral pathways. The balance between production and drainage determines intraocular pressure, and increased resistance in the trabecular meshwork contributes to ocular hypertension and stress on the optic nerve.

1.2.2. Intraocular Pressure

Intraocular pressure remains the primary modifiable risk factor and the main therapeutic target in glaucoma. However, its measurement is influenced by corneal thickness and biomechanics, diurnal variations, and individual susceptibility of the optic nerve. This complexity explains why some patients experience disease progression despite apparently controlled pressure levels.

1.2.3. Blood-Ocular Barriers

Hemato-ocular barriers control molecular transfer between the systemic circulation and the ocular compartments. In glaucoma, changes in permeability and barrier dysfunction may facilitate the involvement of inflammatory mediators in neurodegenerative processes, thereby indirectly influencing the composition of the ocular fluids available for analysis.

1.3. The Tear Film

The tear film is analyzed as a dynamic biological fluid with diagnostic relevance. It serves as an interface between the ocular surface, the local immune system, and the external environment, providing a practical substrate for the assessment of inflammatory biomarkers.

1.3.1. Structure and Composition

The tear film consists of mucin, aqueous, and lipid layers, containing proteins, electrolytes, lipids, mucins, immunoglobulins, cytokines, and metabolites. Its complex composition explains its potential to reflect both local ocular changes and systemic processes affecting the eye.

1.3.2. Functions and Dynamics

Tears provide protection, lubrication, nutrition, antimicrobial defense, and the removal of metabolic waste. Continuous renewal through blinking and drainage makes repeated sampling possible, but requires standardization of the timing and conditions of collection to avoid preanalytical variability.

1.3.3. Homeostasis of the Ocular Surface

Ocular surface homeostasis depends on the balance between tear secretion, epithelial integrity, eyelid function, the mucosal immune system, and tear film stability. Disruption of this balance can alter biomarker levels and must be taken into account when interpreting results obtained from tears.

CHAPTER 2. GENERAL CONCEPTS ABOUT GLAUCOMA

2.1. Glaucoma—a Progressive Ophthalmic Condition

Glaucoma is defined as a group of optic neuropathies characterized by the progressive degeneration of retinal ganglion cells and their axons. Its irreversible nature, slow progression, and frequent absence of symptoms in the early stages lead to delayed diagnosis and underscore the need for sensitive tools for early detection.

2.1.1. Romania and Southeast Europe

In Romania and Southeast Europe, the impact of glaucoma is exacerbated by an aging population, the prevalence of chronic diseases, and disparities in access to complex ophthalmological examinations. Monitoring intraocular pressure and screening patients at risk requires methods that are simple, reproducible, and adaptable to current clinical practice.

2.1.2. European-Level Repercussions and Implications for Health Care Systems

At the European level, glaucoma generates significant direct and indirect costs, proportional to the severity of the disease and the need for monitoring, treatment, and rehabilitation. The increasing prevalence among older adults calls for preventive strategies and selective screening for high-risk individuals.

2.1.3. Global Context: Asia, Africa, and the Americas

The global burden of the disease varies across regions due to differences in demographic distribution, population structure, and access to healthcare services. Asia contributes through the large number of people affected, Africa through high rates of prevalence and severity, and the Americas through significant costs associated with visual care and rehabilitation.

2.1.4. Demographic Shift and Implications for Healthcare

Demographic transition is leading to an increase in the number of elderly patients, a group in which the risk of glaucoma is substantially higher. Health care systems must respond through longitudinal monitoring, access to multimodal diagnosis, and the identification of patients at risk of rapid disease progression.

2.1.5. Economic Impact: From the Individual Burden to Health Care Systems

The economic impact includes medical costs, lost productivity, the need for care, social adjustments, and a decline in quality of life. Early detection and treatment are justified not only clinically but also economically, as preventing advanced vision loss reduces the long-term burden.

2.2. Pathophysiological Complexity and Diagnostic Challenges

Glaucoma involves mechanical stress, vascular dysfunction, oxidative stress, inflammation, excitotoxicity, and mitochondrial dysfunction. Current diagnosis is multimodal, but tonometry, perimetry, and OCT capture different aspects of the disease and may miss very early biological stages. This limitation supports the integration of molecular biomarkers.

2.3. Toward a High-Performance Diagnosis

A high-performance diagnosis requires combining pressure, structural, functional, and molecular parameters. This thesis advocates an approach in which tear biomarkers do not replace established methods but rather complement them by indicating inflammatory activity and the biological risk of disease progression.

2.3.1 Molecular Approaches to Diagnosis

Molecular biomarkers can support risk stratification, early detection, monitoring of treatment response, and identification of patients whose disease progresses independently of intraocular pressure. Advances in proteomics and immunoassays have expanded the ability to assess molecules in small tear samples.

2.3.2 Paradigms of precision medicine: individualizing glaucoma care

Precision medicine involves tailoring monitoring and treatment to the patient's biological, genetic, structural, and behavioral phenotype. In glaucoma, this approach is necessary because the clinical course is heterogeneous, and intraocular pressure alone does not explain the prognosis.

2.3.3. Technological Integration: Artificial Intelligence and Multimodal Approaches

Artificial intelligence can integrate OCT imaging, visual field, intraocular pressure, and molecular data, identifying risk patterns that are difficult to detect using conventional methods. In the future, multimodal predictive models may transform tear biomarkers into operational components of clinical decision-making.

2.3.4. Sample Accessibility and Clinical Translation

Tears offer clear clinical advantages: noninvasive collection, repeatability, high patient acceptance, and compatibility with rapid testing platforms. Implementation requires standardization, multicenter validation, and the integration of results into a simple workflow for the ophthalmologist.

CHAPTER 3. PRIMARY OPEN-ANGLE GLAUCOMA

3.1. Epidemiology

Primary open-angle glaucoma is the predominant form of glaucoma and represents a major cause of irreversible blindness. Its prevalence increases with age, and demographic projections indicate a significant rise in the number of cases over the coming decades. This reality makes primary open-angle glaucoma a public health issue and justifies intensified diagnostic research.

3.1.1. Socioeconomic Impact and Quality of Life

The impact of AMD is multifaceted: patients gradually lose their visual field, mobility, and independence, while society bears significant medical and social costs. Quality of life is diminished by the fear of blindness, dependence, limitations on daily activities, and the risk of accidents.

3.1.2. Trends and Future Prospects

Future trends include an increase in prevalence, the development of genetic risk scores, the use of artificial intelligence, and the identification of clinically valid molecular biomarkers. The overall direction is a shift from late diagnosis to early detection, individualized prognosis, and preventive intervention.

3.2. Pathophysiology

The pathophysiology of GPUD is presented as an integrated cascade: mechanical stress at the optic nerve head affects axonal transport and perfusion; vascular dysfunction causes hypoxia and metabolic stress; neurodegeneration is amplified by mitochondrial dysfunction, oxidative stress, and glial activation; chronic inflammation perpetuates the damage.

3.3. Etiopathogenesis

The etiopathogenesis is multifactorial, combining nonmodifiable factors—such as age, family history, and genetic susceptibility—with modifiable factors—such as intraocular pressure, vascular status, inflammation, comorbidities, and certain lifestyle factors. This complexity explains the variability in therapeutic response.

3.3.1 Risk Factors

Risk factors include advanced age, elevated intraocular pressure, family history, race, myopia, reduced corneal thickness, vascular dysfunction, diabetes, hypertension, sleep apnea, and genetic susceptibility. These factors can accumulate, resulting in individual vulnerability profiles.

3.3.2 Mechanical Theory: The Point of Initiation

The mechanical theory explains the damage through the transmission of intraocular pressure to the lamina cribrosa, leading to tissue deformation, axonal compression, and impaired neurotrophic transport. Even moderate pressure fluctuations can become harmful in patients with increased biomechanical susceptibility.

3.2.3. Vascular theory: the propagation mechanism

The vascular theory emphasizes the role of insufficient ocular perfusion, impaired vascular autoregulation, and recurrent ischemia. Impaired microcirculation at the optic nerve head may amplify mechanical damage and explain disease progression in normal-tension or therapeutically controlled glaucoma.

3.3.4. Neurodegenerative theory: metabolic consequences

The neurodegenerative component involves ganglion cell apoptosis, mitochondrial dysfunction, glutamate excitotoxicity, and the spread of damage from the cell body to the axon and synapses. Glaucoma is thus conceptually similar to other chronic neurodegenerative diseases.

3.3.5. The role of inflammation: amplification and perpetuation of damage

Chronic low-grade inflammation is interpreted as an amplifying mechanism. Microglia activation, proinflammatory cytokines, complement, and oxidative stress create feedback loops that sustain neurodegeneration. This component justifies the study of tear cytokines as markers of biological activity.

CHAPTER 4. CLINICAL AND PARACLINICAL DIAGNOSIS OF GLAUCOMA

4.1. Clinical Course

The progression of glaucoma is slow and insidious, with progressive damage to the optic nerve and visual field. Early stages may be asymptomatic, and patients often present when structural loss is already significant. The clinical examination assesses the optic disc, the cup-to-disc ratio, peripapillary hemorrhages, and signs of ocular surface damage.

4.2. Paraclinical Diagnosis

Paraclinical diagnosis is based on tonometry, perimetry, OCT, and pachymetry, each of which provides complementary information. Correct interpretation requires correlating the results and repeating the tests over time, as progression may be structural, functional, or mixed.

4.2.1. Tonometry

Tonometry estimates intraocular pressure, a major risk factor and therapeutic target. The measured value must be interpreted in the context of corneal thickness and biomechanics, diurnal variation, and individual risk. Controlling IOP reduces progression but does not prevent it.

4.2.2. Computerized Perimetry

Computerized perimetry assesses visual function by identifying visual field defects. Indices such as MD and PSD are useful for assessing severity and progression; however, the test is influenced by patient cooperation, the learning effect, and test-retest variability. Defects may become apparent only after significant neuronal loss has already occurred.

4.2.3. Optical Coherence Tomography

OCT quantifies the thickness of the RNFL and other retinal structures, playing a central role in early diagnosis and monitoring progression. The technique allows for objective, repeatable, and non-contact assessment, but is limited by artifacts, segmentation errors, signal quality, and the ceiling or floor effect in advanced stages.

4.2.4. Pachymetry

Pachymetry measures central corneal thickness, a parameter relevant for interpreting IOP and assessing risk. A thin cornea can lead to underestimation of pressure and is associated with increased susceptibility to disease progression, thereby integrating the biomechanical component into clinical decision-making.

4.3. Multimodal Paraclinical Integration

Multimodal integration involves the simultaneous assessment of structure, function, pressure, biomechanics, and clinical context. Tear biomarkers can add a molecular dimension to this assessment, helping to detect inflammatory activity that precedes changes visible through imaging or functional methods.

CHAPTER 5. INFLAMMATORY BIOMARKERS IN THE EVALUATION OF PRIMARY OPEN-ANGLE GLAUCOMA

5.1. The Molecular Signature of Glaucomatous Neuroinflammation

This chapter argues that glaucoma involves a molecular signature of neuroinflammation, manifested by microglial activation, cytokine release, oxidative stress, and extracellular remodeling. This signature may be detectable in tears and may provide information about disease activity.

5.2. Cytokines in the pathophysiology of glaucoma: modulators of the inflammatory cascade

Cytokines are studied as modulators of the relationship between mechanical injury, ischemia, glial activation, and neuronal death. They are not interpreted in isolation but as elements of a network in which the pro-inflammatory-anti-inflammatory balance influences axonal vulnerability.

5.2.1. Molecular Basis of Cytokine Function

Cytokines are signaling proteins involved in cell-to-cell communication, immune activation, and the regulation of inflammation. Through specific receptors and pathways such as NF-κB, they modulate the expression of inflammatory genes, cell survival, and the stress response.

5.2.2. Integration with the pathophysiology of glaucoma

In glaucoma, cytokines may mediate the transition from initial insult to progressive degeneration. Elevated levels of proinflammatory mediators may signal microglial activation and axonal damage, while regulatory cytokines may reflect the body's attempt to limit inflammation.

5.2.3. Regulatory Networks and Therapeutic Implications

Cytokine networks can become self-sustaining, suggesting that future therapies might target not only intraocular pressure but also the modulation of inflammation. Identifying inflammatory profiles can guide patient selection for neuroprotective or anti-inflammatory interventions.

5.3. The Cytokine Network: Specific Roles in Glaucomatous Neuroinflammation

The cytokine network represents the set of mediators evaluated collectively. This thesis focuses on IL-1β, IL-6, TNF-α, IFN-γ, IL-4, and IL-10, considering that their clinical value stems from their integrated, longitudinal interpretation in relation to the RNFL.

5.3.1. Interleukin-1β: Primary Regulator of Inflammatory Activation

IL-1β is presented as an upstream mediator associated with inflammasome activation and the initiation of the inflammatory response. Its elevation may indicate a local environment conducive to microglial activation and the amplification of neuroinflammation.

5.3.2. Interleukin-6: a dual mediator of protection and pathology

IL-6 plays a dual role, as it can be involved in both adaptive responses and the perpetuation of inflammation. Its interpretation depends on context, duration, and association with other mediators, and is particularly relevant in longitudinal analyses.

5.3.3. Tumor Necrosis Factor-α: A Central Mediator of Neuronal Death

TNF-α is described as a mediator with neurotoxic potential, involved in cellular apoptosis, axonal dysfunction, and the maintenance of inflammation. Elevated levels may indicate a more aggressive biological risk profile.

5.3.4. Interferon-γ: Orchestrator of Adaptive Immune Responses

IFN-γ reflects the involvement of adaptive immunity and the interaction between cellular responses and the ocular environment. In the context of glaucoma, it may contribute to the polarization of the inflammatory response and to communication between immune and glial cells.

5.3.5. Interleukin-4: anti-inflammatory and neuroprotective mediator

IL-4 is considered an anti-inflammatory mediator, with a potential role in limiting immune activation and promoting a reparative phenotype. Its relationship to pro-inflammatory cytokines may provide insight into the balance between protection and aggression.

5.3.6. Interleukin-10: Key Regulator of Inflammatory Resolution

IL-10 plays a major role in the resolution of inflammation and in the control of the immune response. Its levels may suggest the patient's ability to counterbalance chronic inflammation, and IL-10 dynamics become relevant in the interpretation of longitudinal profiles.

5.4. The Tear Film as a Biomarker Platform: Technical Innovation Meets Clinical Need

The tear film is presented as an ideal platform for biomarkers due to its accessibility, safety, repeatability, and compatibility with modern detection methods. This approach addresses the clinical need for rapid and noninvasive assessment of disease activity.

5.4.1. Biological Basis and Technical Advantages

Tears contain relevant proteins and immunological mediators, and small volumes can be analyzed using ELISA, multiplex assays, or emerging platforms. Noninvasive collection allows for longitudinal monitoring, which is necessary for progressive diseases such as glaucoma.

5.4.2. Clinical Evidence and Interpretive Challenges

Clinical evidence supports changes in the inflammatory profile in glaucoma patients, but interpretation is influenced by sample heterogeneity, treatments, age, ocular surface area, and analytical methods. This thesis addresses these challenges through a longitudinal design and quality control.

5.4.3. Technical Standardization and Quality Assurance

Standardization of collection, storage, extraction, and analysis is essential for the validity of tear biomarkers. Quality control must include the timing of collection, the absence of ocular stimuli, the handling of values below the limit of detection, and verification of reproducibility.

5.4.4. Clinical Implementation and Future Directions

Clinical implementation requires validated cut-off values, rapid tests, acceptable costs, and integration with OCT and perimetry. Future directions include multicenter validation, tear biosensors, and multimodal predictive algorithms.

5.5. Integration of Inflammatory Biomarkers into Precision Care for Glaucoma

Biomarkers can help stratify patients based on their inflammatory profile, structural risk, and response to treatment. In precision medicine, a patient with a persistent pro-inflammatory profile may require more frequent monitoring and evaluation of complementary interventions.

5.6. Research Gaps and Scientific Rationale

The main gaps include a lack of longitudinal studies, a lack of standardization, small cohort sizes, and insufficient correlation with OCT parameters. This thesis is justified by the attempt to overcome these limitations by analyzing cytokines over time and relating them to RNFL dynamics.

Global Perspectives: Addressing Gaps and Implementation Challenges

From a global perspective, tear biomarkers can reduce disparities in access if they are transformed into simple and accessible tests. Successful implementation depends on external validation, cost, staff training, and adaptation to healthcare systems with varying resources.

SPECIAL SECTION

CHAPTER 6. MATERIALS AND METHODS

6.1. Overall Study Design

The study is structured as a longitudinal, observational, prospective clinical trial conducted over 24 months, with repeated assessments at 0, 6, 12, 18, and 24 months. The design investigates the relationship between inflammatory biomarkers in the tear film, OCT structural parameters, and relevant clinical or behavioral factors.

6.2. Study Population and Cohort Structure

The cohort included patients with treated primary open-angle glaucoma, patients with suspected glaucoma or untreated glaucoma, and a healthy control group. Inclusion and exclusion criteria were designed to minimize confounding factors such as ocular or systemic inflammatory conditions, recent surgical interventions, anti-inflammatory medication, and poor OCT image quality.

6.3. Ophthalmic Clinical Protocol

The protocol included visual acuity, biomicroscopy, tonometry, gonioscopy, fundus examination, computerized perimetry, and OCT assessment. IOP was treated as an important clinical variable but not as the sole determinant of progression.

6.4. OCT Equipment and Protocol

Structural assessment was based on spectral-domain OCT, using a standardized protocol for the optic disc and RNFL. Only scans with adequate signal, correct centering, absence of major artifacts, and proper segmentation were accepted. The primary structural variable was RNFL thickness and its rate of longitudinal change.

6.5. Collection and Processing of the Tear Film

The tear film was collected using sterile Schirmer strips prior to any ophthalmic procedures that could have altered tear composition. Samples were processed according to standard protocol, refrigerated, centrifuged, and stored at low temperature until biomarker analysis.

6.6. Biomarkers and derived variables

The biomarkers analyzed were IL-1β, IL-6, TNF-α, IFN-γ, IL-4, and IL-10. Derived variables included proinflammatory burden, indicators of immune balance, and the Inflammatory Stability Index, designed to reflect the persistence of an inflammatory profile over time.

6.7. Data Management and Quality Control

The data were organized longitudinally, with checks for consistency, units of measurement, missing values, and values below the limit of detection. Quality control covered the preanalytical, analytical, and postanalytical phases to enhance the reproducibility of the results.

6.8. Statistical Analysis Methods

Statistical analysis included mixed models with random effects, multivariate regressions, Tobit models for censored values, bootstrapping, permutation tests, cross-lagged panel models, ROC analyses, survival models, and Bayesian analyses. Statistical significance was interpreted in the context of effect size and modeling robustness.

6.9. Software Platforms Used

Data processing was performed in R and specialized packages for data manipulation, longitudinal models, ROC analysis, survival analysis, Bayesian modeling, and internal validation. The software platforms supported the reproducibility and traceability of the analytical workflow.

6.10. Ethical Considerations and Data Protection

The study adhered to the ethical principles applicable to observational clinical studies, informed consent, and the protection of personal data. The noninvasive nature of tear collection reduced the risk to participants, and clinical monitoring was integrated into the standard ophthalmologic evaluation.

CHAPTER 7. DYNAMICS OF THE CORRELATION BETWEEN CYTOKINES AND GLAUCOMA PROGRESSION

7.1. Introduction

This chapter investigates the temporal relationship between tear cytokines and structural glaucomatous progression. The central premise is that inflammation does not merely occur as an epiphenomenon but may also precede and predict RNFL thinning, offering a window for early intervention.

7.2. Materials and Methods

The analysis was based on the previously described longitudinal cohort, with repeated clinical evaluations, OCT scans, and tear samples. The objective was to correlate the evolution of pro- and anti-inflammatory biomarkers with RNFL dynamics and treatment status.

7.2.1. Study Design and Cohort Structure

The longitudinal design allowed for the estimation of intra-individual changes and comparisons between groups. The cohort structure enabled the analysis of differences between treated, untreated, or suspected patients and healthy controls, reducing reliance on isolated cross-sectional measurements.

7.2.2. Parameters Analyzed

The main parameters were tear cytokine levels, RNFL thickness, RNFL thinning rate, intraocular pressure, and progression phenotype classification. Cytokines were interpreted both individually and as part of an inflammatory network.

7.2.3. Statistical analysis

We used longitudinal mixed models, correlations, time-lagged models, directionality analyses, and robustness checks. This approach was appropriate for distinguishing simultaneous relationships from predictive ones.

7.3. Results and Discussion

The results indicate that the lacrimal inflammatory profile differs between groups and is associated with structural progression. The pro-inflammatory signal was more pronounced in patients at risk for glaucoma and in those who were untreated, while treatment was associated with a more favorable structural and inflammatory profile, without completely normalizing the risk.

7.3.1. Cohort Profile and Baseline Inflammatory Status

The baseline profile suggested a biological difference between glaucoma patients and controls. Proinflammatory mediators were interpreted as an expression of local immune activation, and regulatory mediators as indicators of compensatory capacity. This distinction supports the value of the tear film for stratification.

7.3.2. Dynamics of the retinal nerve fiber layer

The RNFL decreased over time, but the rate of decline differed between groups. The course in controls was consistent with physiological aging, whereas untreated patients showed a more pronounced thinning trend. Antihypertensive treatment reduced, but did not eliminate, the risk of progression.

7.3.3. The Relationship Between Cytokines and the Retinal Nerve Fiber Layer

IL-1β, IL-6, and TNF-α were associated with RNFL loss, supporting the involvement of the inflammatory cascade in neurodegeneration. IL-10 and IL-4 were interpreted as potential regulatory mediators, and the ratio of pro- to anti-inflammatory components was more informative than measuring them in isolation.

7.3.4. The Inflammatory Response in Relation to RNFL Thinning

Time-lagged analysis supported the existence of a 6–12-month window during which cytokines can predict RNFL thinning. This observation has important clinical implications, as it may allow for intensified monitoring before structural loss becomes evident on OCT.

7.3.5. The Interaction Between Inflammation, Treatment, and Progression Phenotypes

Patients were categorized into progression phenotypes, ranging from stable to rapid progressors. Persistent pro-inflammatory profiles were associated with higher risk, and treatment shifted some patients toward more favorable phenotypes, without completely eliminating individual biological variability.

7.3.6. Analytical Robustness and Additional Checks

Robustness checks, including alternative models and sensitivity analyses, supported the stability of the conclusions. The relationship between cytokines and RNFL did not depend exclusively on single statistical hypotheses, which strengthens the translational interpretation of the results.

7.4. Preliminary Conclusions and Implications for Therapy

This chapter concludes that ocular inflammation has predictive value for structural progression. Incorporating cytokines into patient monitoring may help identify those who require more frequent follow-ups, optimize treatment, and, in the future, guide neuroprotective or anti-inflammatory interventions.

CHAPTER 8. INFLAMMATORY STABILITY INDEX AND RNFL DYNAMICS

8.1. Introduction

This chapter proposes a shift from assessing absolute cytokine levels to analyzing their stability over time. The Inflammatory Stability Index was designed to distinguish persistent inflammation from transient fluctuations, based on the assumption that stable-high profiles have greater prognostic significance.

8.2. Materials and Methods

The same longitudinal cohort was used, with repeated cytokine and RNFL data. The ISI was calculated by relating the proinflammatory load to temporal variability, allowing for the classification of patients into inflammatory phenotypes.

8.2.1. Study Design and Cohort Structure

The 24-month design allowed for the assessment of inflammation persistence and its relationship with structural progression. The group structure enabled the evaluation of treatment effects and the comparison of inflammatory profiles among controls, treated patients, and untreated patients.

8.2.2. Parameters Analyzed

Pro-inflammatory and anti-inflammatory cytokines, the annual rate of RNFL change, intraocular pressure, clinical variables, and ISI phenotypes were analyzed. ISI values allowed for the identification of low-volatile, intermediate, and high-stable profiles.

8.2.3 Statistical analysis

The analyses included regressions, mixed models, Tobit models, bootstrap methods, permutation tests, ROC analyses, panel models, and structural survival models. Emphasis was placed on the stability of the effects and the clinical utility of the risk thresholds.

8.3. Results and Discussion

The results showed that the stability of inflammation is a more robust predictor than a single measurement. Patients with high ISI exhibited higher structural risk, and persistent inflammation was associated with more densely interconnected cytokine networks.

8.3.1 Cohort Profile and Baseline Inflammatory Status

At baseline, inflammatory profiles differentiated the clinical groups, with glaucoma patients exhibiting a higher pro-inflammatory burden. However, the true value of the ISI emerged from the analysis of its persistence over time, not just from baseline levels.

8.3.2 Dynamics of the retinal nerve fiber layer

RNFL dynamics confirmed the existence of individual variation in progression. Structural thinning was more pronounced in patients with a stable-high inflammatory phenotype, suggesting that persistent inflammation influences the rate of axonal degeneration.

8.3.3. The Relationship Between Cytokines and the Retinal Nerve Fiber Layer

The cytokine-RNFL relationship was strengthened by incorporating temporal stability. IL-1β, IL-6, and TNF-α contributed to defining the proinflammatory burden, while IL-10 provided information on immune regulatory capacity. ISI synthesized these dimensions into a practical indicator.

8.3.4. Temporal Evolution of the Inflammatory Signal

Stable, high-level inflammation suggested persistent activation of the inflammatory axis, which may be more relevant to neurodegeneration than transient episodes. This observation supports the utility of repeated biomarker monitoring, rather than a single measurement.

8.3.5. The Interaction Between Inflammation, Treatment, and Progression Phenotypes

The treatment was associated with more favorable profiles, but did not completely eliminate the risk of inflammation. Patients with high ISI may represent a group that requires more frequent structural monitoring and evaluation of complementary interventions.

8.3.6. Analytical Robustness and Additional Tests

Sensitivity analyses confirmed that the relationship between ISI and RNFL progression remains stable across alternative models. This robustness supports the use of ISI as a stratification tool, provided that external validation is conducted on independent cohorts.

8.4. Preliminary Conclusions and Implications for Therapeutic Management

This chapter demonstrates that not only the intensity but also the stability of inflammation matters for the progression of glaucoma. ISI can contribute to a risk-based monitoring algorithm, in which stable-high-risk patients are evaluated more frequently and may benefit from earlier interventions.

CHAPTER 9. SLEEP, INFLAMMATION, AND RNFL DYNAMICS

9.1. Introduction

This chapter adds a modifiable factor—sleep—to the biological model of glaucomatous progression. The premise is that sleep deprivation can amplify systemic and local inflammation, impairing repair mechanisms, clearance, and neurovascular homeostasis.

9.2. Materials and Methods

The study integrated data on sleep duration and quality with tear biomarkers and RNFL dynamics. The objective was to evaluate how sleep interacts with inflammation and treatment in determining structural risk.

9.2.1. Study Design and Cohort Structure

The longitudinal cohort was analyzed based on sleep parameters, inflammatory status, and RNFL changes. This structure allowed for the investigation of a model in which behavioral factors influence the inflammation-neurodegeneration axis.

9.2.2. Parameters Analyzed

The parameters included sleep duration, sleep quality scores, tear cytokines, ISI, RNFL, intraocular pressure, and treatment status. Sleep deprivation was interpreted as a potential amplifier of the pro-inflammatory profile.

9.2.3. Statistical Analysis

Regression models, mediation analyses, longitudinal models, and sensitivity analyses were used to evaluate the relationship between sleep, inflammation, and RNFL progression. The analyses examined both the direct effect and the indirect effect mediated by inflammation.

9.3. Results and Discussion

The results suggest that sleep deprivation is associated with higher levels of proinflammatory mediators and faster structural progression. This relationship is not interpreted as a simple association, but rather as part of a pathophysiological chain in which insufficient sleep increases inflammatory activation, which in turn accelerates RNFL loss.

9.3.1. Cohort Profile and Baseline Sleep-Inflammation Status

The baseline profile revealed differences between patients with adequate sleep and those with sleep deprivation. The latter group exhibited a more unfavorable inflammatory profile, suggesting an interaction between sleep behavior, immune status, and neuroretinal vulnerability.

9.3.2. RNFL Dynamics and Sleep Deprivation

Sleep deprivation was associated with a more pronounced decline in RNFL. This relationship supports the hypothesis that sleep contributes to the maintenance of neurovascular homeostasis and that its disruption may accelerate degenerative processes.

9.3.3. The Relationship Between Sleep, Inflammation, and RNFL

Analyses have shown that inflammation mediates a significant portion of the relationship between sleep and RNFL. Mediators such as IL-6 and TNF-α may represent the biological link between sleep deprivation and glaucomatous progression.

9.3.4. Temporal Evolution of the Inflammatory Signal

Over time, patients with insufficient sleep tended to maintain a more persistent pro-inflammatory profile. This persistence aligns with the ISI concept and suggests that sleep may influence the stability of the inflammatory response.

9.3.5. Clinical stratification and treatment impact

Incorporating sleep into clinical stratification suggests that antihypertensive treatment may be less effective in the context of an inflammatory profile exacerbated by sleep deprivation. Personalized management of glaucoma could include sleep counseling and screening for sleep disorders.

9.3.6 Analytical Robustness and Further Validation

Further analyses supported the stability of the association between sleep deprivation, inflammation, and RNFL. Limitations include the self-reported nature of some sleep parameters and the lack of objective monitoring for all participants, indicating the need for future studies using actigraphy or polysomnography.

9.4. Preliminary Conclusions and Implications for Treatment

This chapter concludes that sleep should be considered a modifiable factor in glaucoma risk assessment. Optimizing sleep may serve as a complementary intervention to ocular treatment, particularly in patients with a high inflammatory profile and accelerated structural progression.

CHAPTER 10. INTEGRATED DISCUSSIONS

10.1. Integrated Analysis of Key Results

The integrated discussions bring together the three main themes of this special section into a unified model. Cytokines predict RNFL decline, the stability of inflammation quantifies the persistence of risk, and sleep functions as a modifiable factor that can amplify or attenuate the inflammatory process.

10.1.1. Synthesis of Key Findings

The main findings support the value of the tear film as a biomarker platform, the relevance of proinflammatory cytokines to structural progression, and the utility of the ISI for risk stratification. Furthermore, sleep complements the model by introducing a modifiable systemic variable.

10.1.2. Connections Between Temporal Dynamics, Inflammatory Stability, and Modifiable Factors

From a temporal perspective, the inflammatory signal precedes RNFL thinning; from a stability perspective, persistent inflammation is more important than isolated episodes; from the perspective of modifiable factors, sleep deprivation may sustain the proinflammatory environment. These components describe a coherent biological chain: insufficient sleep—persistent inflammation—cytokine coupling—RNFL progression.

10.1.3. Validation of Initial Hypotheses

The central hypothesis—that low-grade chronic inflammation detectable in the tear film contributes to glaucoma progression—is supported by longitudinal results. The validation is temporal, quantitative, and mechanistic, although it requires confirmation in larger, independent cohorts.

10.2. A Unified Analysis of the Pathophysiology of Glaucoma

This thesis proposes a unified analysis in which intraocular pressure remains important but is integrated with inflammation, neurodegeneration, vascularization, and systemic factors. This framework explains the progression observed in patients whose intraocular pressure appears to be well-controlled.

10.2.1. Integrated Conceptual Model

The conceptual model integrates mechanical stress, vascular dysfunction, ocular inflammation, cytokine stability, and sleep. The RNFL becomes the ultimate structural manifestation of these interactions, and ocular biomarkers can signal the activity of the process before measurable damage occurs.

10.2.2. Clinical Translation

Clinical translation involves integrating biomarkers into a decision-making algorithm that complements standard ophthalmologic evaluation. Patients with high inflammatory signals, elevated ISI, or sleep deprivation can be monitored more frequently and evaluated for therapeutic optimization.

10.3. Implications for Precision Medicine in Glaucoma

Precision medicine in glaucoma is based on combining intraocular pressure, structural, functional, molecular, and behavioral information. This thesis argues that inflammatory profiles can serve as additional criteria for tailoring follow-up and treatment.

10.3.1. Stratification of patients based on inflammatory phenotypes

Inflammatory phenotypes allow for the differentiation of patients with low, intermediate, and high risk of disease progression. The stable-high phenotype is the most clinically relevant, as it reflects persistent inflammation and is associated with a higher structural risk.

10.3.2. Integration of lifestyle factors into personalized management

Lifestyle factors, particularly sleep, can influence the inflammatory environment and response to treatment. Personalized management may include sleep assessment, apnea screening, behavioral counseling, and management of inflammatory or vascular comorbidities.

10.3.3. Decision Algorithm for Clinical Implementation

The proposed algorithm would combine OCT, IOP, perimetry, tear biomarkers, ISI, and sleep assessment. Patients with high biological risk would benefit from quarterly or semiannual monitoring, while those with a stable profile and low risk could be followed at longer intervals.

10.4. Limitations of the current study

Limitations of the study include cohort size, the single-center design, the biological variability of tears, and the observational nature of the study. These limitations call for caution in generalizing the findings and require external validation.

10.4.1 Methodological Limitations

Methodological limitations relate to sample size, censored values, possible residual confounding, and the lack of randomization. Statistical models have mitigated these issues but cannot eliminate them entirely.

10.4.2 Limitations of External Validity

External validity is limited by the cohort's structure and the specific characteristics of the recruitment center. The results must be confirmed in different populations with varying disease severity, diverse treatments, and multiple comorbidities.

10.4.3. Technical Limitations

Technical limitations include the sensitivity of analytical platforms, variability in tear collection, limitations of OCT, and imaging artifacts. Protocol standardization and quality control are essential for reducing these effects.

10.4.4 Measures to Mitigate Limitations

Mitigation measures include a standardized protocol, strict inclusion criteria, robustness checks, longitudinal analysis, and integrated interpretation. These measures enhance the credibility of the conclusions but do not replace multicenter validation.

10.5. Fundamental Unanswered Questions

Questions remain regarding the exact causality of inflammation, the clinical thresholds of biomarkers, the impact of anti-inflammatory treatments, the role of systemic comorbidities, and the optimal way to integrate tear tests into daily practice.

10.6. Future Research Directions

Future directions aim to validate biomarkers, develop rapid tests, and move toward interventions that modulate the inflammation-neurodegeneration axis. These directions transform the thesis's findings into a program of applied clinical research.

10.6.1. Direction I: Multicenter validation of the tear biomarker panel and the inflammatory stability index

The first direction involves multicenter studies, larger cohorts, a follow-up period of at least 3–5 years, and interlaboratory standardization. The impact would be the definition of robust thresholds and increased confidence in the clinical use of the ISI.

10.6.2. Research Area II: Development of a rapid, point-of-care test based on the tear film and integration with multimodal predictive algorithms

The second direction aims to develop a rapid tear-based test compatible with ophthalmologic consultations. The test could provide an inflammatory score that can be integrated with OCT, IOP, perimetry, and sleep data, facilitating immediate clinical decision-making.

10.6.3. Research Area III: Interventional studies aimed at modifying the inflammation–neurodegeneration axis

The third direction proposes interventional studies to test whether reducing inflammation or optimizing sleep slows RNFL progression. Biomarkers would thus become not only prognostic tools but also criteria for therapeutic selection.

10.6.4. Synthesis of the Contribution of Future Research Directions to the Development of the Field

Together, these directions can transform research on tear biomarkers into a practical tool for precision medicine. They complement the current directions of this thesis through validation, technological miniaturization, and interventional testing.

CHAPTER 11. GENERAL CONCLUSIONS

11.1 Original Contributions to Scientific Knowledge

This study makes original contributions by demonstrating the longitudinal relationship between tear cytokines and RNFL, by introducing the Inflammatory Stability Index, and by integrating sleep deprivation into the model of glaucoma progression. These contributions expand the classic pressure-centered paradigm of glaucoma toward a molecular and systemic approach.

11.2. Impact on Clinical Practice

The potential clinical impact lies in identifying patients at risk of progression before evident structural damage occurs, adjusting the frequency of monitoring, and tailoring treatment based on the inflammatory phenotype. Tear biomarkers may become a complementary tool, particularly useful in patients with progression that cannot be explained by IOP.

11.3. Clinical Implications and Outlook

Clinical prospects include the development of rapid tests, multimodal algorithms, and interventions targeting modifiable factors. Assessing sleep and inflammation can complement intraocular pressure control, supporting a holistic approach to the management of patients with glaucoma.

11.4. FINAL CONCLUSIONS

The overall conclusion is that the tear film represents a valuable, accessible, and noninvasive source of biomarkers for glaucoma. Proinflammatory cytokines, their temporal stability, and their interaction with sleep provide information relevant to prognosis and monitoring.

This thesis advocates a shift from the isolated assessment of intraocular pressure toward integrated models that include OCT, visual field testing, tear biomarkers, and systemic factors. This integration may contribute to early detection, prevention of rapid progression, and personalized treatment in primary open-angle glaucoma.

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LIST OF PUBLICATIONS

Full-text articles published as first author in ISI-listed journals indexed by Web of Science

- **Neacşa, R.**; Tănase, C.; Moldovan, A.-D.; Manasia, D.; Tobă, M.-E. Sleep Deficit and Inflammatory Markers as Combined Risk Factors for Glaucoma Progression: A Prospective Longitudinal Observational Cohort Study. Int. J. Mol. Sci. 2026, 27, 1338. https://doi.org/10.3390/ijms27031338" https://www.mdpi.com/1422-0067/27/3/1338. WOS: 001688984100001

Full list of publications as first author in PubMed-indexed journals

- **Neacșa R**, Manasia D, Tănase C, Tobă ME, Moldovan AD. The Inflammatory Stability Index Correlates with Reduction in the Retinal Nerve Fiber Layer in Glaucoma. Rom J Ophthalmol. Jan–Mar 2026;70(1):85–94. doi: 10.22336/rjo.2026.12. PMID: 42146946; PMCID: PMC13178763. https://pubmed.ncbi.nlm.nih.gov/42146946/
- **Neacșa R**, Manasia D, Tănase C, Tobă ME, Moldovan AD. Progressive Inflammatory Coupling Drives Glaucoma Progression—a Longitudinal Analysis of Cytokine-RNFL Dynamics. Rom J Ophthalmol. Oct–Dec 2025;69(4):512–518. doi: 10.22336/rjo.2025.79. PMID: 41971217; PMCID: PMC13065147. https://pubmed.ncbi.nlm.nih.gov/41971217/
- **Neacșa R,** Manasia D, Tobă ME. Uncommon Therapeutic Approaches for Patients with Recurrent Central Serous Chorioretinopathy: case report and literature review. Rom J Ophthalmol. Jan–Mar 2025;69(1):17–21. doi: 10.22336/rjo.2025.04. PMID: 40330964; PMCID: PMC12049657 https://pubmed.ncbi.nlm.nih.gov/40330964/
- **Full-text articles published as a co-author in ISI-listed journals indexed in Web of Science**
- Neagu AC, Budișteanu M, Domuța ME, Gheorghe DC, Mocanu AI, Pavel DM, **Neacșa R,** Mocanu H. Syndromic congenital hypoacusis associated with premature birth and a variant of the SPEN gene: A case report and literature review. Exp Ther Med. 2025 Jun 4;30(2):151. doi: 10.3892/etm.2025.12901 https://www.spandidos-publications.com/10.3892/etm.2025.12901. WOS:001511197600001