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Association of Anterior Chamber Depth, Volume, and Intraocular Fluid Metabolome with Lens Hardness in Cataract Patients

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Abbreviations used in the Thesis

3-HK	3-Hydroxykynurenine
ACD	Anterior chamber depth
ACV	Anterior chamber volume
BH_4	Tetrahydrobiopterin
CI	Credibility interval
FGF2	Fibroblast growth factor 2
GSH	Glutathione (reduced form)
IDO	Indoleamine 2,3-dioxygenase
KAT	Kynurenine aminotransferase
KYN	Kynurenine
KYNA	Kynurenic acid
LEC	Lens epithelial cells
NAD^+	Nicotinamide adenine dinucleotide
NADPH	Nicotinamide adenine dinucleotide phosphate (reduced form)
NO	Nitric oxide
PEXS	Pseudoexfoliation syndrome
ROS	Reactive oxygen species
TauT	Taurine transporter
UV	Ultraviolet radiation

Introduction

Approximately 95 million people worldwide suffer from cataracts (Liu et al., 2017). Cataract is the leading cause of blindness, accounting for about half of all cases of preventable blindness globally (Javitt et al., 1996). Data from the Malaysian National Eye Survey for 1996 indicate that cataract was the main cause of blindness (39 %), followed by retinal diseases (24 %) (Zainal et al., 2002). This pathology remains one of the major ophthalmological problems in both developed and developing countries (Cedrone et al., 1999). Although a decrease in incidence has been observed in different regions of the world, the prevalence of cataract-induced blindness and its impact on the population remain high (Lee & Afshari, 2017). In developing countries, 90 % of all disability-adjusted life years lost are associated with blindness caused by cataracts (Nam et al., 2015).

Data from the World Health Organization and the *Global Burden of Disease 2020* indicate that cataract accounts for approximately 45.5 % of all cases of global blindness in adults over 50 years of age, as well as 38.9 % of moderate to severe visual impairment in the same age group (Steinmetz et al., 2021). These figures reflect a longstanding trend – cataract remains the leading cause of vision loss worldwide, particularly in China, South Asia, and Southeast Asia, where prevalence levels significantly exceed the global average (Chua et al., 2015).

Studies indicate that the number of disability-adjusted life years attributable to cataracts nearly doubled from 1990 to 2021, remaining a particularly pressing issue in countries with lower levels of development – highlighting the need to improve treatment accessibility (Li et al., 2025). The *2019 Global Burden of Disease Study* report shows that disability-adjusted life years associated with cataracts increased from 3.49 million (95 % CI 2.48–4.72 million) to 6.68 million (95 % CI 4.76–9.01 million) between 1990 and 2019 (Fang et al., 2022). Considering global population growth, ageing, and the rising prevalence of vision-impairing conditions, it is projected that the number of people with blindness or moderate to severe visual impairment (including cataract) will rise from 338.3 million in 2020 to 535 million in 2050, despite global efforts to reduce disease burden and improve access to eye care services (Bourne et al., 2017).

Cataract is the loss of lens transparency, which clinically manifests with the following symptoms: decreased visual acuity (Hurst & Douthwaite, 1993); a sensation of blurred vision (Skiadaresi et al., 2012); increased sensitivity to bright light (Shandiz et al., 2011); monocular diplopia (Records, 1980); reading difficulties (Pesudovs & Coster, 1998); and, in more advanced stages of lens maturity, elevated intraocular pressure (Flocks et al., 1955) and, ultimately, vision loss (Han et al., 2023).

Cataracts cannot be effectively treated with pharmacological agents (Harding, 2001). The only proven and clinically effective treatment is the surgical extraction of the opacified lens and implantation of an intraocular artificial lens (Davis, 2016). Therefore, surgery is the primary treatment approach for cataracts and has become one of the most commonly performed surgical procedures worldwide (Moshirfar et al., 2024). Today, cataract surgery is considered not only the most frequent but also one of the most effective medical procedures, characterised by a high success rate in restoring visual function and a relatively low risk of complications (Rossi et al., 2021). However, despite highly developed technology and wide availability in developed countries, surgery remains insufficiently accessible in many developing regions. Low public awareness of the disease, inadequate healthcare infrastructure, and limited economic resources contribute to delayed diagnosis and increase the prevalence of cataract-related blindness (Cetinel et al., 2014).

Studies indicate that cataract surgery in middle-aged patients may be associated with an increased risk of mortality, possibly due to overall health impairments and chronic comorbidities that are more prevalent in this age group (K. Negahban & K. Chern, 2002). These observations raise the question of whether cataracts are primarily driven by ageing processes or whether oxidative stress and chronic inflammatory mechanisms play a more significant role (Li et al., 2024). Many of the structural and functional changes involved in cataract pathogenesis arise from or are exacerbated by oxidative stress, ultraviolet (UV) radiation, osmotic imbalance, and other cell-damaging factors (Richardson et al., 2020). Cataracts also frequently occur as one manifestation of broader metabolic disorders or genetic syndromes, such as diabetes, galactosemia, hypocalcaemia, or mitochondrial diseases (Kambiz Negahban & Kenneth Chern, 2002). In such cases, the clinical course and presentation may differ from age-related cataracts, underscoring the need for an individualised approach in diagnosis and treatment.

Since the advent of modern medicine, age has been considered the primary risk factor for cataract development (Sperduto, 1994). However, clinical practice often reveals significant intra-individual variability, where patients of the same age may exhibit markedly different levels of lens opacity (Hashemi et al., 2020). Ageing is defined as a process that gradually reduces the body's ability to resist damage, disease, and environmental stressors. It manifests across numerous physiological systems, including respiratory rhythm, visual acuity decline, blood pressure fluctuations, and postural regulation, while also significantly increasing mortality risk and affecting reproductive function. Studies confirm that the ageing process is primarily associated with the accumulation of cellular and molecular damage caused by oxidative reactions, the effects of free radicals and other reactive oxygen species, interactions

with sugars and reactive aldehydes, and spontaneous metabolic errors (Sadowska-Bartosz & Bartosz, 2014). During ageing, the crystalline lens fibres gradually deteriorate under the influence of various biological and physical factors, including UV radiation, oxidative stress, deamination, racemisation, and post-translational modifications such as phosphorylation (Lampi et al., 1998; Ma et al., 1998). The loss of lens transparency, or opacity, is considered a consequence of structural changes in crystallin proteins – their misfolding and aggregation (Goulet et al., 2011). Initially, this process serves as a protective cellular mechanism, preventing the accumulation of toxic protein monomers, but over time it contributes to fibre structure degradation and the loss of functional lens transparency (Flaugh et al., 2006; Moreau & King, 2012). Thus, cataract pathogenesis is largely associated with a loss of proteostasis and disrupted protein homeostasis, making this process dependent not only on chronological age but also on individual metabolic, genetic, and environmental factors (Taylor & Davies, 1987).

The lens is an avascular, transparent optical structure composed of highly organised, optically syncytial layers of cells and plays a crucial role in focusing light onto the retina (Delaye & Tardieu, 1983). Due to the absence of blood vessels, the lens has developed an internal ionic circulation system closely linked to fluid movement, which ensures efficient microcirculation of nutrients (Mathias et al., 2007). Lens transparency is maintained by fibre cells with a high concentration of crystallin proteins, which are arranged over short distances in a highly organised structural pattern (Chiou et al., 1988).

Lens epithelial cells (LECs) – the only viable cell layer within the adult lens – play a crucial role in maintaining the structural and functional integrity of the lens (Bassnett & Šikić, 2017). These cells mediate active ion transport, participate in antioxidant synthesis, maintain osmotic and metabolic balance, and serve as progenitors for the differentiation of new fibre cells in the equatorial zone of the lens (Andley, 2008). LECs are particularly susceptible to oxidative stress, and their functional impairment is considered one of the early events in the cataract pathogenesis cascade (Liu et al., 2022). Oxidative stress arises when the balance between the generation of reactive oxygen species (ROS) and their neutralisation by antioxidant systems is disrupted. Under physiological conditions, ROS act as signalling molecules, but excessive accumulation – which can be induced by both endogenous sources (e.g., mitochondria, NADPH oxidases, endoplasmic reticulum) and exogenous sources (UV radiation, heavy metals) – damages DNA, lipids, and proteins. To mitigate this risk, cells activate intrinsic antioxidant mechanisms, while exogenous antioxidants are being investigated as potential protective agents. Oxidative stress is a key factor in the development of many chronic diseases, and its modulation is considered a critical target for the development of effective therapeutic strategies (Aranda-Rivera et al., 2022).

Under pathological conditions, including chronic oxidative stress, hyperglycaemia, or UV exposure, cellular stress-response mechanisms become weakened, resulting in the formation of damaged protein aggregates, disrupted intracellular homeostasis, and the initiation of structural changes throughout the lens. In LECs, endoplasmic reticulum stress activation triggers the unfolded protein response, ROS generation, and ultimately cell death – processes that have also been observed in experimental galactosemia models prior to the clinical manifestation of cataracts (Mulhern et al., 2007). During ageing, the functional capacity of LECs gradually declines, which can lead to significant impairments in protein synthesis and transport. Consequently, the deeper layers of the lens become particularly vulnerable to oxidative, osmotic, and proteotoxic damage, promoting protein aggregation, fibre cell degeneration, and the development of nuclear cataracts. Therefore, LEC dysfunction is widely recognised as one of the central pathogenic mechanisms in age-related cataract formation (Yanshole et al., 2019).

Crystallins are the primary structural proteins in the human lens, constituting up to 90 % of the total protein mass in fibre cells (Surguchev & Surguchov, 2010). Their high concentration and spatially organised structure ensure lens transparency, minimal light scattering, and high refractive power. Crystallins are classified into three main groups: α-, β-, and γ-crystallins (Andley, 2007).

α-Crystallins, particularly the αA and αB subunits, possess molecular chaperone activity in addition to their structural role, preventing the denaturation and aggregation of other proteins (Derham & Harding, 1999). This protective function allows the lens to maintain its optical properties even during ageing and cellular stress. α-Crystallins also participate in cytoskeletal stabilisation, apoptosis inhibition, and enhancing cellular resistance to oxidative and other stressors (Kamradt et al., 2005). Studies indicate that α-crystallin activity is not limited to lens fibre cells – they are also active in LECs and extra lenticular tissues, including the retina, myocardium, brain, and skeletal muscles (Srinivasan et al., 1992). Mutations in α-crystallin genes alter the structure of the lens refractive index gradient, promoting loss of transparency, while local administration of oxysterol compounds improved refractive profile regularity in 61 % of cases and reduced opacity levels by 46 % in mice (Wang et al., 2022).

β-Crystallins primarily form polymers that contribute to the organisation of the fibre cell cytoskeleton, whereas γ-crystallins are dense, compact monomeric structures that provide the high density of the lens nucleus and precise light refraction (Serebryany & King, 2014). Both β- and γ-crystallins are among the most stable and long-lived proteins in the human body; however, with ageing, they can aggregate into high-molecular-weight complexes that scatter

light and promote cataract formation, despite the presence of α-crystallin chaperones in the lens (Bari, 2021).

The ocular lens is a dynamic organ that continues to grow throughout life, continuously adding new fibre cells at the periphery, while the inner layers – embryologically early fibres – remain structurally unchanged. This concentric layering of fibres determines the anatomical division of the lens into the nucleus and cortex (Ruan et al., 2020). To maintain optical clarity, the lens relies on an effective antioxidant defence system, whose main components are glutathione, ascorbic acid, and the enzyme superoxide dismutase (Lou, 2003). A decrease in glutathione levels is considered one of the earliest biochemical indicators of cataract formation and may potentially serve as a biological marker for early diagnosis (Giblin, 2000).

Lens cell metabolism is maintained through continuous circulation of the aqueous humour, which supplies nutrients and removes metabolic waste products. This fluid is synthesised by the ciliary body pars plicata epithelium and circulates through the pupil into the anterior chamber, from where it is primarily drained via the trabecular meshwork and Schlemm's canal into the ocular venous drainage system (Grüb & Mielke, 2004). The aqueous humour functions as a vital transport system, delivering glucose, amino acids, and electrolytes, while helping maintain osmotic balance and facilitating the removal of byproducts of oxidative metabolism (Goel et al., 2010; Mathias et al., 2007). Since most lens fibre cells lack mitochondria, energy production in these cells relies primarily on anaerobic glycolysis, rendering them particularly sensitive to hypoxia and disruptions in glucose supply (Shui & Beebe, 2008). Disturbances in the composition or flow of aqueous humour, which may result from oxidative stress or metabolic imbalance, promote cellular swelling, protein aggregation, and loss of intracellular homeostasis, which in turn can lead to the development of lens opacity – a hallmark of cataract formation (Dammak et al., 2023).

The aqueous humour is a clear, water-like biological fluid that fills the anterior and posterior chambers of the eye. Its composition consists primarily of water (98–99 %), as well as electrolytes (sodium, potassium, chloride, bicarbonate), organic compounds (amino acids, glutathione, ascorbic acid, urea, lactate), proteins (e. g. immunoglobulins, transforming growth factor beta 2 (TGF-β2), α-melanocyte-stimulating hormone), and gases (oxygen, carbon dioxide) (Bansal et al., 2021; Chen et al., 2025). Physiologically, the aqueous humour serves several essential functions: it helps maintain intraocular pressure, provides trophic support to avascular tissues, including the cornea, lens, and vitreous body, and participates in the removal of metabolic waste and toxic metabolites (Tram et al., 2021). Quantitative and qualitative changes in the aqueous humour are associated with various ophthalmic pathologies. For instance, in glaucoma, impaired fluid outflow can lead to increased intraocular pressure

(Ofri, 2002), whereas in inflammatory conditions such as uveitis, the fluid often contains inflammatory cells and elevated protein levels (Kalsy et al., 1990). Therefore, studying the composition of the aqueous humour provides valuable information about the state of the intraocular environment and allows indirect assessment of metabolic processes in the tissues it nourishes and protects.

Anterior chamber volume (ACV) and depth (ACD) are important biometric parameters of the anterior segment of the eye, reflecting the spatial configuration of intraocular anatomy and potentially influencing the efficiency of aqueous humour circulation (Lei et al., 2022). These parameters are dynamic and can change in various ophthalmic pathologies, including cataract, glaucoma, and pseudoexfoliation syndrome. Considering that the lens physiologically grows throughout life, gradually increasing in thickness (Cheng et al., 2019), the anterior chamber space progressively decreases, leading not only to mechanical alterations in the pattern of aqueous humour flow but also to potential accumulation of metabolic products around the lens.

Such local microenvironmental disturbances can act as significant modulators of cataract pathogenesis, particularly in situations where oxidative balance or metabolite clearance mechanisms are affected. Therefore, assessing the anterior chamber space can provide valuable insights into aqueous humour dynamics and its potential impact on lens status (He et al., 2016). In addition, analysis of the aqueous humour metabolome allows for the identification of specific metabolites whose presence correlates with the degree of lens maturation, thus offering potential biomarkers for predicting cataract progression (Yanshole et al., 2019). Modern imaging and fluid analysis techniques provide highly precise insights into the intraocular microenvironment, revealing mechanisms that were previously accessible only through postmortem histology.

Although metabolic disturbances are often associated with specific metabolites – for example, diabetes with altered glucose levels or cardiovascular diseases with cholesterol metabolism – it is essential to recognise that biochemical processes do not occur in isolation but are closely interconnected and influence one another (Poznyak et al., 2020). Such a systemic understanding is particularly important in modern metabolic research, as the organism's metabolic homeostasis relies on the balance of complex pathways, where even small alterations in one node can have widespread effects elsewhere. The rapid development of analytical chemistry, especially in mass spectrometry and high-resolution liquid chromatography, enables the simultaneous identification and quantification of a broad spectrum of endogenous metabolites using one or more metabolomics platforms (Lamers et al., 2003). These methods provide the opportunity to delve into metabolic pathway interactions, allowing interpretation of

both physiological and pathological changes in human tissues or the organism as a whole. To understand the biological significance of deviations in individual metabolite concentrations – and, more importantly, to anticipate potential corrective interventions in nutrition, pharmacology, or lifestyle – an in-depth understanding of metabolic pathway functioning and their regulatory interplay is required (German et al., 2005).

Metabolic changes are not only observable experimentally but also can be analysed in detail using modern analytical methods, offering insight into their impact on specific biochemical pathways and cellular functional mechanisms. The feasibility of such approaches is supported by the fact that the study of biochemical processes has been a central focus of natural sciences development for over a century (German et al., 2005).

Aim of the study

The aim of this study is to characterise the differences in anterior chamber depth and volume, as well as the intraocular fluid metabolome, in cataract patients according to lens hardness.

Objectives

Primary objectives:

1 To analyse the differences in intraocular fluid metabolome composition in patients with varying degrees of lens hardness.
2 To assess anterior chamber depth and volume parameters according to lens hardness.
3 To investigate statistical associations between lens hardness, intraocular fluid metabolite profiles, and anterior chamber biometric parameters.

Secondary objectives:

1 To analyse changes in intraocular fluid metabolome composition in patients with pseudoexfoliation syndrome.
2 To characterise intraocular fluid metabolome features in patients with glaucoma.
3 To evaluate intraocular fluid metabolome differences in patients with diabetes mellitus.

Hypotheses

- Patients with greater anterior chamber depth and volume exhibit faster progression of higher-grade lens hardness cataracts.
- Cataract patients possess a specific intraocular fluid metabolite profile that correlates with lens hardness.

Novelty of the study

The novelty of this study lies in its potential contribution to a deeper understanding of cataract pathophysiology, particularly through the analysis of intraocular fluid composition. The research will provide new insights into biomarkers that may serve as a basis for more precise cataract diagnosis, disease prognosis, and the development of personalised therapeutic approaches. By identifying biochemical and molecular indicators associated with cataract progression, this work aims to enhance clinical practice and potentially delay vision loss.

Given that cataract is a protein aggregation disorder, the study's findings may also provide valuable insights into other proteostasis-related pathologies. Notably, these include neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, where protein misfolding and aggregation underpin pathogenesis. Data obtained on intraocular fluid metabolic and antioxidant characteristics may open new avenues for early diagnosis and molecular therapy of these systemic diseases, strengthening interdisciplinary approaches to protein aggregation disorders research.

This innovative approach not only promotes advancements in ophthalmology but also offers broader public health benefits by supporting personalised medicine and cross-disciplinary collaboration in addressing chronic degenerative diseases.

Personal contribution

This study involves direct clinical and research work with cataract patients. I personally performed cataract surgeries, during which intraocular fluid was collected, ensuring high-quality and sterile samples for subsequent biochemical analysis. In parallel with the surgical procedures, I participated in data processing, including evaluation of patients' clinical profiles, analysis of laboratory results, and their correlation with cataract pathophysiological indicators.

Ethical considerations

Ethical oversight was provided by the Ethics Committee of Rīga Stradiņš University (approval No 2-PEK-4/307/2023, dated March 21, 2023), and the study was authorised by Pauls Stradiņš Clinical University Hospital. All study participants provided written informed consent, and the research was conducted in full accordance with the ethical principles outlined in the Declaration of Helsinki (Association, 2025).

Discussion

Influence of Anterior Chamber Volume and Depth on Lens Hardness

The results of our study did not show statistically significant associations between ocular biometric parameters and lens hardness. Although it has been established that the lens thickens with age, primarily due to protein aggregation and structural changes, our data did not indicate an impact of these processes on anterior chamber volume (ACV) or anterior chamber depth (ACD). While ACV measurement has not yet been incorporated into routine clinical practice, it is increasingly recognised as a promising parameter for the diagnosis, management, and surgical planning of various eye diseases (Coakes et al., 1979). Quantitative assessment of ACV may provide valuable contributions to glaucoma diagnosis and monitoring, cataract surgery strategy selection, evaluation of refractive surgery candidates, and the study of anterior segment pathologies.

Among all analysed patient groups, the most pronounced biometric differences were observed in patients with pseudoexfoliation syndrome (PEXS). In this group, the reduced ACD, ACV, and shorter axial eye length may be associated with anterior displacement of the lens and weakening of the zonular structures (Hayashi et al., 2024). These factors potentially increase lens mobility, the risk of dislocation, and vitreous loss during cataract surgery, emphasising the need for careful preoperative evaluation in these patients.

Furthermore, our results highlight that the stability of ACV and ACD, even in cases of progressive cataract, may reflect the eye's compensatory mechanisms within the anterior segment. These observations suggest that anterior chamber biometric parameters may not serve as early markers of cataract progression but rather as secondary factors influencing intraoperative risk. This is particularly important for surgical planning, as minor changes in ACV or ACD may become clinically relevant only in combination with other risk factors, such as zonular weakness or the presence of PEX. Such an interpretation indicates that the value of biometric data lies not only in a direct correlation with lens hardness but also in its ability to complement the patient's individual risk profile prior to cataract surgery.

Although the initial hypothesis proposed a strong correlation between glaucoma and ACV parameters, this assumption was not confirmed in our study. Nevertheless, the literature describes studies in which the relationship between ACV and intraocular pressure is considered a potential predictor of treatment efficacy, particularly in patients receiving therapy with prostaglandin analogues (Scott et al., 2021). Additionally, ACV is recognised as an important risk factor in predicting primary angle-closure glaucoma (Pakravan et al., 2012).

An important contribution of our study is the testing and validation of an ACV calculation formula using available biometric data. The developed method allows for

the estimation of ACV without the need for expensive equipment such as Pentacam or AS-OCT. This provides significant advantages in resource-limited settings, where access to advanced technologies is restricted. Implementing such alternative approaches in clinical practice could promote broader use of ACV measurements and improve the accessibility of diagnosis and treatment for ocular diseases on a global scale.

Metabolomic differences in patients with varying lens hardness

Metabolic processes as a basis of cataract pathogenesis

Glutathione (GSH) is the main intracellular antioxidant in lens tissues, playing a crucial role in protecting crystallins from oxidative damage and maintaining the oxidative-reducing balance within cells (Jiao et al., 2023; Truscott & Friedrich, 2016). GSH functions both as a direct ROS scavenger and as a coenzyme in various enzymatic detoxification pathways, including glutathione peroxidase and glutathione-S-transferase systems (Deng et al., 2025). Additionally, GSH participates in the reduction of protein disulphide bonds, helping preserve structural integrity (Georgiou-Siafis & Tsiftsoglou, 2023; Giustarini et al., 2017). Reduced GSH levels lead to oxidative protein modifications, misfolding, and cross-linking, gradually disrupting lens fibre transparency and promoting opacity progression – the main pathogenic mechanism of cataract (Truscott, 2005). Taurine, one of the dominant non-protein amino acids present in the aqueous humour, complements GSH's antioxidant activity by stabilising cell membranes, inhibiting excessive calcium influx, and regulating osmotic balance (Froger et al., 2014). Furthermore, taurine has been shown to enhance intracellular GSH uptake, providing an additional mechanism for cellular protection against oxidative stress (Baliou et al., 2021). Taurine levels in lens tissues decrease with age, correlating with increased oxidative burden and higher risk of cellular damage. This dynamic may represent a key mechanism driving age-related changes in lens tissues (Singh et al., 2023). The interaction between GSH and taurine illustrates a synergistic antioxidant network essential for maintaining the structural and functional integrity of the lens.

The third essential component – nicotinamide adenine dinucleotide (NAD^+) – is not only a central cofactor in cellular energy metabolism, participating in glycolysis, the tricarboxylic acid cycle, and oxidative phosphorylation, but also indispensable for maintaining redox homeostasis (Pehar et al., 2018; Xiao et al., 2018). Changes in the NAD^+/NADH ratio or a reduction in total NAD^+ levels can disrupt cellular biological balance and promote the development of various processes, including ageing, neurodegenerative diseases, and tumour formation (Amjad et al., 2021). NAD^+ is also required for the synthesis of the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH), which is critically important

for the regeneration of GSH from its oxidised form glutathione (GSSG), thereby ensuring effective cellular protection against oxidative stress (Lu, 2013). During ageing, NAD^+ reserves become depleted, impairing these protective mechanisms and promoting alternative metabolic pathways, including tryptophan catabolism via the kynurenine pathway (Kincaid & Berger, 2020). This metabolic shift leads to the accumulation of potentially toxic intermediates, such as 3-hydroxykynurenine (3-HK) and xanthurenic acid, which are associated with increased cell death and structural alterations (Wang et al., 2025).

The metabolite profile changes observed in our study in the aqueous humour indicate significant destabilisation of cellular energy and redox balance systems, which closely correlate with lens hardness and the stage of cataract progression. In particular, alterations in mitochondrial β-oxidation end products, such as acetylcarnitine levels, suggest impaired fatty acid transport and incomplete ATP synthesis (Merritt et al., 2018). This energy deficit, especially under the hypoxic conditions of the lens nucleus, promotes increased oxidative stress and diminishes the cell's ability to protect crystallin proteins from denaturation and aggregation, thereby facilitating the development of lens opacification.

These mechanisms create a pathophysiological cycle: protein damage caused by oxidative stress drives intensive GSH consumption and depletion. As GSH levels decrease, redox balance is disrupted, which in turn reduces NAD^+ availability. NAD^+ deficiency further enhances tryptophan metabolism via the kynurenine pathway, leading to the accumulation of potentially toxic intermediates such as 3-HK. These metabolites induce cell death in LECs and fibre cells, resulting in impaired lens structural integrity and progressive loss of transparency.

These findings reinforce the notion that cataract is not merely a passive, age-related structural change but rather a biochemically active, dynamically progressing pathology that could potentially be modulated through targeted metabolic interventions, including taurine, NAD^+ precursors, vitamin B_6, and GSH analogues.

Taurine

Taurine is a sulphur-containing amino acid found at high concentrations in tissues exposed to elevated oxidative stress, including the ocular lens, myocardium, and central nervous system. In the lens, taurine and total protein concentrations decrease with advancing cataract stage, although this decline is not directly correlated with age (Anthrayose & Shashidhar, 2004). Taurine is taken up from the bloodstream, and its tissue levels largely depend on dietary intake, particularly from animal-derived sources such as meat, fish, and dairy products (Duan et al., 2023). Its antioxidant properties involve neutralising free radicals and stabilising cell membrane structure and function (Jong et al., 2021). Taurine plays a particularly

important role in LECs, which are exposed to prolonged UV radiation and associated oxidative damage. Beyond osmolarity regulation, taurine acts as a metabolic modulator, participating in calcium homeostasis, inflammatory processes, and apoptosis regulation (Ripps & Shen, 2012).

Taurine was first identified in 1827, isolated from ox bile, and its name is derived from the Latin word *taurus* (Tiedemann & Gmelin, 1827). Today, taurine is produced industrially, typically using cysteine as a starting material, without relying on animal-derived sources. Experimental studies have shown that taurine effectively mitigates oxidative stress-induced cellular damage by promoting intracellular GSH uptake and stabilising the cell's redox balance (Hansen et al., 2010). These properties make taurine an important protective factor against oxidative stress-mediated damage, contributing to the prevention of cataract pathogenesis.

The study results highlight taurine's crucial cytoprotective role under cellular stress conditions, particularly through its ability to mitigate the consequences of oxidative damage, which is essential for maintaining the structural and functional integrity of various tissues, including the lens (Ma et al., 2021). Taurine also contributes to cellular homeostasis by modulating the balance between autophagy and apoptosis – two key mechanisms responsible for eliminating damaged organelles and proteins, as well as enabling adaptive responses to stress (El Idrissi & Trenkner, 2003; Jong et al., 2011). Taurine and its halamines (taurine chloramine and taurine bromamine) exhibit significant anti-inflammatory and cytoprotective effects by neutralising myeloperoxidase-derived oxidants at sites of inflammation, thereby reducing oxidative stress and tissue damage (Marcinkiewicz & Kontny, 2014). Experimental evidence further demonstrates that taurine can attenuate mitochondria-induced apoptosis by inhibiting caspase cascade activation (Schaffer et al., 2010). This protective effect is particularly critical in lens fibre cells, where cell loss is irreversible due to the lack of proliferative or regenerative capacity, positioning taurine as a potentially valuable therapeutic target for mitigating cataract pathogenesis.

Experimental animal studies indicate that taurine supplementation provides significant protection for the lens against oxidative and osmotic damage. Its protective effect is closely linked to the maintenance of GSH levels, a mechanism central to cataract pathogenesis. Taurine administration in experimental models normalised GSH concentrations and reduced malondialdehyde levels – a byproduct of lipid peroxidation – demonstrating its antioxidant activity (Sevin et al., 2021). Taurine also has the ability to neutralise free radicals and protect lens proteins from glycation, the uncontrolled binding of sugars to proteins, which is a key mechanism driving cataract development (Devamanoharan et al., 1997). For example, in a Pacific Spring rat model where lenses were exposed to high glucose concentrations (55.6 mM) to mimic diabetic cataract formation, supplementation with 30 mM taurine prevented

the reduction of GSH levels and decreased protein carbonylation, a marker of oxidative damage (Son et al., 2007). Similar protective effects were observed in a rabbit model with GSH deficiency, where taurine significantly preserved the structural integrity of the lens (Malone et al., 1993).

Another important mechanism of taurine's action is its ability to preserve mitochondrial functional integrity. Taurine stabilises components of the mitochondrial respiratory chain and reduces ROS generation within the mitochondrial matrix, thereby preventing the initiation of lipid peroxidation cascades (Seneff & Kyriakopoulos, 2025). This mitochondrial protective effect is particularly significant, given that mitochondria serve simultaneously as a primary source of ROS and a major target for oxidative damage (Kuznetsov et al., 2022).

Taurine not only possesses antioxidant properties but also exerts significant neuromodulatory and neurotropic effects, influencing the functional state of various ocular structures, including the lens, retina, and ciliary body cells (Wu & Prentice, 2010). In the context of lens physiology, taurine's osmoregulatory function is particularly important, as it stabilises cell volume and helps prevent the development of intracellular oedema (Trachtman et al., 1988). This mechanism is crucial given its relevance to cataract progression, especially in metabolic disorders such as diabetic or hyperosmolar cataracts.

Interestingly, the age-related decline in taurine concentration is observed not only in the anterior segment of the eye but also systemically – in plasma and the brain – highlighting its potential as a biomarker of biological ageing. Studies across various species, including mice, non-human primates, and humans, have shown that taurine levels gradually decrease with age, while supplementation in model organisms positively influences lifespan, suggesting a possible role of taurine in the ageing process (Singh et al., 2023). Experimental models demonstrate that taurine supplementation not only mitigates age-associated physiological changes but also enhances ATP synthesis efficiency, maintains telomere stability, and improves cellular survival (Mashyakhy et al., 2021; Sheikh & Iqbal, 2023). However, studies conducted by the National Institutes of Health indicate that taurine cannot be considered a universal ageing biomarker, as its concentration changes vary across populations; in humans, taurine levels show only weak correlations with functional health, including muscle strength and metabolic parameters (Fernandez et al., 2025).

Taurine also influences oncogenic cells. It can inhibit the proliferation of lung cancer cells and tumour growth by inducing apoptosis through the PUMA–Bax pathway and suppressing Bcl-2, suggesting potential anticancer effects, at least in preclinical settings (Tu et al., 2018). Leukemic stem cells are unable to synthesise taurine endogenously and therefore acquire it from the bone marrow microenvironment via the taurine transporter (TauT);

this interaction promotes glycolysis and supports malignant cell proliferation. Researchers at the *University of Rochester* have shown that TauT inhibition in vivo suppresses leukemic cell expansion and significantly extends survival, highlighting new potential therapeutic avenues (Sharma et al., 2025). Taurine, abundantly present in neutrophils, reacts with myeloperoxidase-generated hypochlorous acid to form taurine chloramine, reducing oxidative damage and limiting excessive neutrophil degranulation (Kim et al., 2020). This antioxidative and anti-inflammatory action may also be relevant for protecting lens tissues in the context of cataract development.

These findings suggest that taurine functions not merely as a passive antioxidant but as an active regulator, maintaining cellular structural and functional integrity – particularly within the ocular lens microenvironment, where disruptions in redox balance can rapidly impair visual quality. Consequently, maintaining taurine levels, especially in older individuals, could serve as a prophylactic or therapeutic strategy for cataract management, particularly when combined with other redox-modulating compounds such as NAD^+ precursors or agents that stimulate GSH synthesis.

NAD^+ Deficiency and the Tryptophan–Kynurenine Metabolic Pathway

NAD^+ is a central coenzyme in cellular bioenergetics and redox regulation (Braidy & Liu, 2020). Its functions extend beyond the classical role as an electron acceptor in oxidative phosphorylation – NAD^+ is also involved in DNA repair and maintenance of mitochondrial function and serves as a substrate for NAD^+-dependent enzymes, such as sirtuins and poly-ADP-ribose polymerases, which are actively engaged in cellular stress response mechanisms (Houtkooper et al., 2012).

With ageing, NAD^+ levels physiologically decline, leading to mitochondrial dysfunction, loss of redox balance, and weakening of cellular defence mechanisms (McReynolds et al., 2020). In lens cells, these changes manifest as reduced GSH regeneration due to limited NADPH synthesis from $NADP^+$, as well as a diminished capacity to neutralise oxidative stress.

NAD^+ can also be synthesised via the Preiss-Handler pathway, in which nicotinic acid is converted into nicotinamide mononucleotide and subsequently into NAD^+ (Bieganowski & Brenner, 2004). One of the main endogenous NAD^+ biosynthesis routes is the kynurenine pathway, which is activated under cellular stress, inflammation, or oxidative damage (Ogbechi et al., 2020). In this pathway, the enzyme indoleamine-2,3-dioxygenase (IDO) regulates the conversion of tryptophan to KYN, which is further metabolised into NAD^+ and other intermediates such as 3-HK, kynurenic acid (KYNA), and quinolinic acid (Savitz, 2020).

These metabolites can serve protective roles, but when excessively accumulated, they may damage proteins, induce apoptosis, and destabilise the lens microenvironment (Savitz et al., 2015). Studies in transgenic mice with elevated IDO expression in the lens demonstrate that increased enzyme activity promotes KYN accumulation, induces lens epithelial cell apoptosis, and accelerates cataract formation (Mailankot et al., 2009).

In our study, in the early stage of cataract (SPONCS 2), we observed significantly elevated IDO activity, likely reflecting a compensatory response to increasing oxidative stress and UV exposure. These results suggest that lens epithelial cells initially activate alternative NAD^+ biosynthesis pathways to restore energy homeostasis and maintain cellular structural integrity. However, as cataract progression advances, IDO activity decreases, likely due to lens epithelial cell apoptosis and reduced enzyme expression.

At the same time, it was observed that the levels of kynurenine derivatives, particularly 3-HK, increase in the late stages of cataract (SPONCS 4–5), reaching maximum concentration. These compounds are recognised as phototoxic, pro-apoptotic, and pro-oxidative factors, whose accumulation can promote crystallin denaturation, cross-linking, and a reduction in lens transparency (Korlimbinis & Truscott, 2006). Interferon gamma (IFN-γ) stimulates IDO expression in lens epithelial cells by activating the JAK–STAT1 pathway, which promotes the production of kynurenine, especially 3-HK. These metabolites induce oxidative stress and apoptosis, representing an important mechanism in cataract development associated with chronic inflammation (Mailankot & Nagaraj, 2010).

Fibroblast growth factor-2 (FGF2) is important for lens fibre cell differentiation. Kynurenine inhibits FGF2-induced crystallin and MIP26 expression in mouse lens epithelial cells by suppressing Akt and ERK1/2 phosphorylation, without affecting FGF2 receptor binding. These findings suggest that KYN can disrupt fibre cell differentiation by blocking the production of essential proteins (Mailankot et al., 2010). Immunohistochemical analyses confirm the expression of kynurenine aminotransferases (KAT I–III) in the lens extracellular matrix already in the early stages of cataract, indicating active involvement of the kynurenine pathway in cellular adaptation and degeneration processes (Rejdak et al., 2013).

Such metabolic dynamics highlight the importance of the kynurenine pathway in cataract pathogenesis, and its modulation – such as IDO inhibition or stimulation of KAT activity – may serve as a potential therapeutic approach. Moreover, not only the absolute NAD^+ level but also the quality of its biosynthetic pathway and the associated metabolite profile are critical factors in cataract development. Therefore, a strategy combining supplementation with NAD^+ precursors, such as nicotinamide riboside, with modulation of IDO activity or 3-HK formation could offer a novel metabolism-based approach for cataract prevention and therapy.

KAT activity as a biomarker and therapeutic target

KAT is a key enzyme in the tryptophan–kynurenine metabolic pathway that catalyses the conversion of KYN into KYNA, a metabolite with pronounced neuroprotective, antioxidant, and photoprotective properties. KYNA absorbs UV-A radiation (315–400 nm) and can act as a photosensitiser, forming a triplet state ($^3KNAH^-$) capable of reacting with other biomolecules. KYNA has been detected in human lens tissue at concentrations of approximately 1–2 μM/mg, and upon UV exposure, it can participate in oxidative modifications of proteins, potentially contributing to cataract development (Morozova et al., 2023). Under UV radiation, KYNA transitions to a triplet state and undergoes self-oxidation, generating reactive radicals that covalently bind to amino acids such as tryptophan and tyrosine. These findings indicate that KYNA can mediate protein modifications in living tissues and may play a role in UV-induced damage mechanisms (Morozova et al., 2023). In human and rat cataract models, increased KYNA concentrations and activation of KAT I/II expression have been observed, correlating with cataract severity (Zarnowski et al., 2005; Zarnowski et al., 2007). Elevated KYNA levels have also been detected in the plasma of multiple sclerosis patients, suggesting a potential protective role against excitotoxic damage (Hartai et al., 2005). Kynurenine pathway metabolites – KYN, 3-HK, and their glycosides – function as endogenous UV filters in the lens, absorbing harmful radiation and providing photoprotection. However, their increased binding to crystallins with age, coupled with potential photosensitising effects, may promote oxidative damage and contribute to cataractogenesis (Zarnowski et al., 2005).

KAT activity is crucial for maintaining lens transparency and structural integrity, as it regulates the balance between protective and potentially toxic kynurenine pathway metabolites. Our study data indicate that KAT activity reaches its peak in the early stage of cataract (SPONCS 2), when the lens can still actively counteract oxidative stress and direct kynurenine metabolism toward protective pathways. This elevated activity likely reflects a compensatory adaptive mechanism by which cells attempt to neutralise ROS induced by UV radiation and maintain redox balance.

However, as the disease progresses, our data show a gradual decline in KAT activity, particularly in SPONCS 4–5 stages. This regressive trend may be due to a decrease in pyridoxal 5′-phosphate (the active form of vitamin B_6), which is essential for KAT catalytic function (Whittaker, 2016), or structural enzyme damage caused by oxidative stress (Francisqueti et al., 2017). Enzyme function can also be impaired by post-translational modifications, such as nitrosylation (Song et al., 2011) or carbonylation (Ortuño-Sahagún et al., 2014), which are associated in the literature with the loss of various cellular functions during ageing.

Such KAT dysfunction leads to a reduction in KYNA synthesis, thereby decreasing photoprotective defence and increasing the likelihood that KYN is redirected into alternative pathways, such as 3-HK or quinolinic acid production. Both of these metabolites have pro-oxidative and pro-apoptotic effects and can crosslink crystallins, destabilising their structure and promoting lens opacity.

Interestingly, while other kynurenine pathway enzymes, such as kynurenine monooxygenase, appear relatively stable across different cataract stages, KAT exhibits the most pronounced activity gradient. This indicates KAT's particular sensitivity to microenvironmental changes, making it a potential indicator of metabolic alterations during cataract progression.

Thus, KAT can be considered not only a potential biomarker but also a target for therapeutic intervention strategies. In the early stage of the disease, supplementation with pyridoxal 5′-phosphate or KYNA analogues could be considered to enhance cellular protection against photo-oxidative damage. In later stages, approaches that reduce 3-HK accumulation or neutralise its effects – such as inhibiting caspase activation or promoting crystallin stabilisation – would be valuable.

Metabolic Differences in Patients with Various Ophthalmic Pathologies

Changes in Patients with PEXS

Our study results indicate that PEXS is associated with pronounced metabolic disturbances that promote cell death via the ferroptosis mechanism – a regulated, iron-dependent form of cell death characterised by lipid peroxidation and oxidative stress-induced cellular dysfunction. (Chen et al., 2021). Identified metabolic profiles, including elevated levels of cysteine and citrulline, as well as alterations in ubiquinone metabolism, suggest a weakening of antioxidant defence systems, particularly involving dysfunction of the glutamine–cystine antiporter (system Xc^-) (de Baat et al., 2023). These observations emphasise that PEXS cannot be reduced solely to morphological changes in the anterior segment but rather reflects systemic disturbances in cellular metabolism and redox balance, which may be crucial for a deeper understanding of disease pathogenesis and the development of potential new therapeutic strategies (Scharfenberg & Schlötzer-Schrehardt, 2012).

These findings significantly expand the current understanding of PEXS pathophysiology, offering a conceptually new perspective on disease origin – not merely as a localised fibrillar material accumulation process, but as a systemically regulated metabolic dysfunction with potentially destructive consequences for visual function (Zenkel & Schlötzer-Schrehardt, 2014). Furthermore, the metabolic biomarkers identified in this study,

involved in ferroptosis mechanisms and oxidative stress pathways, may provide a valuable foundation for developing novel therapeutic strategies. Targeted modulation of these metabolic pathways could, in the future, support metabolomics-based, personalised approaches to PEXS patient management, potentially reducing the risk of intraoperative complications during cataract surgery.

Changes in Patients with Glaucoma

Our study identified several metabolites potentially involved in the pathogenesis of glaucoma. In the glaucoma patient group, significant increases in the concentrations of tryptophan, phenylalanine, tyrosine, leucine, and glutamine were observed, suggesting disruptions in aromatic amino acid metabolism (Lynch & Dudareva, 2020). These alterations may be linked to reduced activity of aromatic amino acid hydroxylases, which depend on tetrahydrobiopterin (BH_4) – an essential cofactor in various enzymatic processes, including nitric oxide (NO) synthesis (Kim & Han, 2020). BH_4 deficiency can arise under conditions of oxidative stress, impaired biosynthesis or recycling of BH_4, or due to polymorphisms in the methylenetetrahydrofolate reductase gene (Raghubeer & Matsha, 2021). Such metabolic disturbances may contribute to increased intraocular pressure through reduced NO bioavailability (Aliancy et al., 2017) and promote the neurodegenerative processes characteristic of glaucoma (Lionaki et al., 2022).

The identified metabolic disturbances suggest that glaucoma development may involve not only elevated intraocular pressure but also systemic factors affecting cellular metabolism, including redox imbalance and disruptions in amino acid metabolism (Wang et al., 2021). Elevated levels of glutamine and leucine may reflect cellular attempts to activate neuroprotective compensatory mechanisms, mitigating excitotoxic damage (Lotery, 2005). These findings further support the concept of glaucoma as a multifactorial neurodegenerative disease modulated by metabolic processes, with the biopterin pathway potentially playing a significant role (Eichwald et al., 2023). Consequently, future research in this area could facilitate the identification of new metabolic biomarkers and support the use of antioxidant or metabolically targeted therapies for glaucoma prevention and treatment.

Changes in Patients with Diabetes

Our study identified significant metabolic differences in the aqueous humour between patients with and without diabetes undergoing cataract extraction. In the diabetic patient group, markedly elevated concentrations of 3-HK, histamine, and octanoylcarnitine were observed, along with reduced levels of putrescine. Overall, these findings indicate disrupted tryptophan metabolism, increased oxidative stress, and potential inflammatory activity in the anterior

segment of the eye. Pathway enrichment analysis particularly highlighted activation of the kynurenine pathway, consistent with growing evidence of its involvement in diabetes-induced oxidative and neurodegenerative damage (Kozieł & Urbanska, 2023).

The obtained results confirm that diabetes-induced pathophysiological processes in the anterior segment of the eye are also reflected in the metabolic profile, providing further evidence of systemic metabolic dysregulation in these patients (Dolar-Szczasny et al., 2024). The identified metabolites may serve as potential biomarkers with possible diagnostic or prognostic significance, particularly in the context of diabetic retinopathy development or progression (Ma et al., 2024). However, given the adjustments for multiple testing and the higher error rate, these results should be interpreted cautiously and considered hypothesis-generating, requiring confirmation in independent cohort studies.

Conclusions

1 Patients with higher-grade lens hardness exhibited statistically significant differences in the aqueous humour metabolome, particularly in antioxidant systems, amino acid metabolism, and the kynurenine pathway. These results confirm the hypothesis of a specific metabolite profile depending on the stage of cataract development.

2 Anterior chamber depth and volume in our study did not show a statistically significant association with lens hardness; therefore, the hypothesis that larger ACD and ACV accelerate cataract progression was not confirmed.

3 Patients with PEXS demonstrated both pronounced biometric and metabolic changes: reduced ACD, ACV, and axial eye length, as well as a metabolome profile reflecting ferroptosis activation and impaired antioxidant defence. These results indicate that PEXS is not only a structural disorder but also a systemic metabolic dysregulation disease.

4 Glaucoma patients showed significant metabolic alterations, including increased levels of tryptophan, phenylalanine, tyrosine, leucine, and glutamine, indicating disturbed aromatic amino acid metabolism and possible BH_4 deficiency. This enhances the understanding of glaucoma as a multifactorial metabolic and neurodegenerative disease.

5 Patients with diabetes mellitus exhibited significant aqueous humour metabolome changes, including increased 3-HK, histamine, and octanoylcarnitine, along with decreased putrescine. These changes reflect activation of the kynurenine pathway, oxidative stress, and inflammatory processes in the anterior segment, and may serve as potential biomarkers for the management of diabetes-related ocular complications.

Theoretical insights into cataract metabolic mechanisms

1 Ageing and redox imbalance

With ageing, the body experiences progressive redox imbalance, as ROS production exceeds antioxidant defence capacity, leading to oxidative stress in the lens and other tissues.

2 Role of glutathione in cataract pathogenesis

The GSH system in lens epithelial cells is the primary neutraliser of oxidative stress. Depletion of GSH reserves renders lens proteins more susceptible to lipid peroxidation and other oxidative modifications, promoting crystallin denaturation and increased lens opacity.

3 Protective function of taurine

Taurine acts as an additional antioxidant and osmolyte, maintaining cellular redox balance. Adequate taurine levels optimise GSH utilisation in ROS defence and help delay early cataractogenic mechanisms.

4 Activation of the kynurenine pathway under GSH deficiency

When GSH reserves are depleted, cells activate alternative antioxidant mechanisms, including the tryptophan–kynurenine pathway. Elevated IDO and KAT activity in this pathway promotes KYNA production.

5 Accumulation of toxic intermediates – 3-HK

Insufficient availability of cofactors, such as vitamin B6, limits proper processing of kynurenine pathway metabolites, leading to pro-oxidant and phototoxic 3-HK accumulation. These toxic intermediates promote protein carbonylation, apoptosis, and further ROS generation, creating a vicious cycle that accelerates lens opacification.

6 Strategies for preserving human lens transparency

To slow cataract progression, an integrated approach is required, including:

- Restoration of GSH reserves (e.g., via GSH precursor supplementation),
- Maintaining optimal taurine levels,
- Modulating kynurenine pathway activity using IDO or KAT inhibitors, alongside cofactor restoration therapy.

Cataract pathogenesis is closely linked to metabolic and redox dysfunctions, where GSH deficiency and accumulation of toxic kynurenine pathway intermediates play key roles. These mechanisms not only enhance oxidative stress and protein aggregation but also disrupt NAD^+ homeostasis and cellular energy metabolism, particularly under anaerobic conditions in the lens nucleus. Targeted metabolic therapies that simultaneously restore antioxidant defence systems (e.g., via GSH and taurine supplementation) and inhibit toxic intermediate formation during kynurenine or other stress pathway activation may offer an effective strategy for cataract prevention and slowing disease progression.

Proposals

Further research should focus on a deeper investigation of intraocular fluid metabolomics, integrating broader metabolite and lipid analyses. Such a multidisciplinary approach could identify novel biomarkers associated with cataract progression, particularly in more aggressive or rapidly advancing forms of the disease. Characterising metabolic changes may improve our understanding of redox imbalance, crystallin aggregation mechanisms, and cellular damage development across different cataract stages.

Special attention should be given to the kynurenine pathway and NAD^+ metabolism in lens tissues. Future studies could examine the relationship between the accumulation of toxic kynurenine pathway intermediates and crystallin structural alterations, protein aggregation, and cell death mechanisms. Simultaneously, analysing NAD^+ availability and its role in maintaining energy homeostasis is crucial, as NAD^+ depletion may exacerbate redox imbalance and increase lens epithelial cell susceptibility to oxidative damage.

At the experimental level, future studies should evaluate the efficacy of metabolically targeted therapies, such as combined taurine and GSH donor administration, as well as NAD^+ precursor supplementation. These therapeutic strategies may slow cataract progression by restoring antioxidant reserve systems and limiting toxic intermediate accumulation. Additionally, it will be important to assess the effectiveness of such interventions across different cataract stages to determine optimal preventive or therapeutic approaches.

Clinically, integrating intraocular fluid metabolite profiles as additional biomarkers could aid in early disease diagnosis and personalised surgical planning. This approach may be particularly valuable for patients with PEXS or other anterior segment instability risk factors, where timely risk stratification could reduce intraoperative complications. Accurate assessment of ACV and ACD, along with validated calculation formulas, could further enhance risk evaluation and surgical planning strategies.

Moreover, the findings and future studies have broader implications beyond ophthalmology, contributing to the understanding of other protein aggregation disorders, such as Alzheimer's and Parkinson's diseases. These conditions share similar underlying mechanisms – oxidative stress, NAD^+ depletion, mitochondrial dysfunction, and structural protein alterations. A multidisciplinary approach combining metabolomics, biochemistry, and clinical practice may pave the way for personalised, targeted strategies in cataract prevention and treatment while advancing knowledge of age-related neurodegenerative and protein aggregation disorders.

List of publications, reports and patents on the topic of the Thesis

Publications:

1. Zemitis, A., Vanags, J., Fan, J., Klavins, K., Laganovska, G. (2024) Metabolomic Disparities in Intraocular Fluid Across Varied Stages of Cataract Progression: Implications for the Analysis of Cataract Development. *J Ocul Pharmacol Ther.* 2024 Oct;40(8):477–485. doi: 10.1089/jop. 2024.0067. Epub 2024 Jul 8. PMID: 38976556.
2. Zemitis, A., Rizzuto, V., Lavrinovica, D., Vanags, J., Laganovska, G. (2024) Redefined Formula for Anterior Chamber Volume Calculation: Quantitative Analysis of Biometric Parameters Across Ocular Pathologies. *Clin Ophthalmol.* 2024 Dec 27;18:3989-3998. doi: 10.2147/OPTH.S495068. PMID: 39741797; PMCID: PMC11687106.
3. Zemitis, A., Vanags, J., Schiemer, T., Klavins, K., Laganovska, G. (2025) Aqueous humor metabolomic profiling identifies a distinct signature in pseudoexfoliation syndrome. Front Mol Biosci. 2025 Jan 23;11:1487115. doi: 10.3389/fmolb.2024.1487115. PMID: 39917180; PMCID: PMC11798801.
4. Zemitis, A., Vanags, J., Klavins, K., Laganovska, G. (2025) The Role of IDO Activity in Cataract Progression: Correlation to Age and Cataract Severity. Curr Eye Res. 2025 May 27:1–7. doi: 10.1080/02713683.2025.2506118. Epub ahead of print. PMID: 40423999.
5. Zemitis, A., Vanags, J., Klavins, K., & Laganovska, G. (2025). Assessment of Kynurenine Pathway Enzyme Activity in Ocular Diseases: Associations with Cataract, Diabetes, Glaucoma, and Pseudoexfoliation Syndrome. *Journal of Clinical Medicine*, 14(13), 4529. doi: 10.3390/jcm14134529
6. Zemitis, A., Svjascenkova, L., Bleidele, S., Veitners, A., Vanags, J., Klavins, K., & Laganovska, G. (2025). Metabolic alterations in diabetic patients: aqueous humor profiling for biomarker discovery. *Amino acids*, *57*(1), 44. doi: 10.1007/s00726-025-03476-z

Reports and theses at international congresses and conferences:

1. Dr. Artūrs Zemītis "*The role of anterior chamber depth, intraocular fluid and peripheral blood metabolome in predicting lens hardness in cataracta patiens*." Update on Cornae and External Diseases Vilnius, Lietuva 14.04.2023
2. Dr. Artūrs Zemītis *"Kataraktas īpatnības glaukomas slimniekiem."* Glaukomas ķirurģijas aktualitātes Rīga, Latvija 02.12.2022.
3. Dr. Artūrs Zemītis *"Hope for Sight: Vitrectomy in a Ukraine War Survivor after Rocket Explosion – A Case Report"* Baltic Eye Surgeons Talk Show vol.9 Rīga, Latvija 05.05.2023.
4. Dr. Artūrs Zemītis "*Tīklenes slimības*" Uzstāšanās ar mutisku referātu "Acs vielmaiņa." 24.11.2023. LAĀA sēde.
5. Dr. Artūrs Zemītis "*Metaboloms un acis*" Rīga, Latvija 16.05.2024.
6. Dr. Arturs Zemitis "*Exploring the Distinct Metabolomic Profiles within the Intraocular Fluid of Cataract Patients*" WOC 2024 Congress Vancouver, Canada 16.08.2024.
7. Arturs Zemitis, PhD. Juris Vanags, assoc. prof. Kristaps Klavins, prof. Guna Laganovska "*Evaluating the 3-Hydroxykynurenine/Kynurenic Acid Ratio as a Diagnostic Biomarker for Cataract Progression.*"
8. Arturs Zemitis, PhD. Juris Vanags, assoc. prof. Kristaps Klavins, prof. Guna Laganovska "*Metabolic Profiling of Aqueous Humour Reveals Biochemical Alterations Associated with Myopia*" SOE 2025 ePoster

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