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Acs priekšējās kameras dziļuma,
tilpuma un intraokulārā šķidruma
metaboloma saistība ar lēcas cietību
kataraktas pacientiem

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Anotācija

Katarakta ir multifaktoriāla slimība un viens no galvenajiem akluma cēloņiem pasaulē. Tās patoģenēze ir cieši saistīta ar oksidatīvā stresa inducētu redoksbalansa zudumu, proteīnu agregāciju, vielmaiņas ceļu pārstrukturēšanos un enerģētiskās homeostāzes traucējumiem. Šī pētījuma mērķis bija izvērtēt intraokulārā šķidruma metabolīta profila izmaiņas pacientiem ar dažādu kataraktas brieduma pakāpi, kā arī analizēt biometriskos datus – priekšējās kameras tilpumu (ACV), dziļumu (ACD) un to potenciālo saistību ar lēcas cietību.

Metabolomikas analīzē tika konstatēts, ka pacientiem ar cietākām kataraktām raksturīgas izmaiņas mitohondriju β -oksidācijas produktos, tostarp palielināta acilkarnitīnu akumulācija un samazināta glutathiona (GSH) pieejamība. Taurīns kā neproteīnogēna aminoskābe un būtisks intraokulārais osmolīts sekmē GSH uzņemšanu šūnās un stabilizē šūnu redokssistēmu. Ar vecumu taurīna koncentrācija samazinās, kas korelē ar oksidatīvā stresa pieaugumu un kataraktas progresiju.

Lai gan biometriskie parametri, piemēram, ACV un ACD, kopumā neuzrādīja statistiski nozīmīgu korelāciju ar lēcas cietību, pacientiem ar pseidoeksfoliācijas sindromu (PEXS) tika novērotas izteiktas strukturālās atšķirības – samazināts ACD, ACV un acs ass garums. Šie parametri liecina par paaugstinātu priekšējā segmenta nestabilitāti un lielāku intraoperatīvo komplikāciju risku. Tika validēta arī jauna formula ACV aprēķināšanai, izmantojot WTW, CCT un ACD, kas ļauj precīzi noteikt ACV bez dārgas aparātūras.

Pētījuma rezultāti atklāja būtiskas izmaiņas triptofāna metabolismā un kinurenīna ceļa aktivāciju, kas korelē ar GSH deficītu, NAD^+ pieejamību un oksidatīvā stresa marķieru pieaugumu. Šīs izmaiņas liecina par iespējamām līdzībām ar citām proteīnu agregācijas slimībām, tostarp Alcheimera un Parkinsona slimību, kurās līdzīgi tiek novērota NAD^+ izsīkšana, mitohondriju disfunkcija un iekaisuma aktivācija.

Šis darbs sniedz jaunas zināšanas par kataraktas patoģenēzes molekulārajiem mehānismiem un iezīmē iespējamus biomarķierus slimības progresijas noteikšanai. Rezultāti uzsver metabolītiski mērķētas terapijas potenciālu – kombinējot NAD^+ prekursoru, taurīna un antioksidantu papildināšanu – kā iespējamu profilaktisku un ārstniecisku stratēģiju. Identificētā metode ACV aprēķināšanai var tikt izmantota arī resursu ierobežotos apstākļos, uzlabojot ķirurģiskās riska stratifikācijas iespējas.

Atslēgvārdi: katarakta, metabolomika, intraokulārais šķidrums, glutathions, taurīns, kinurenīna ceļš, acilkarnitīni, ACV, ACD, pseidoeksfoliācijas sindroms, redoksbalanss, proteīnu agregācija.

Abstract

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

Cataracts are multifactorial diseases and remain one of the leading causes of blindness worldwide. Its pathogenesis is closely linked to oxidative stress-induced redox imbalance, protein aggregation, restructuring of metabolic pathways, and disruption in energy homeostasis. The aim of this study was to evaluate changes in the intraocular fluid metabolite profile in patients with varying degrees of cataract maturity and to analyse biometric data-namely, anterior chamber volume (ACV), anterior chamber depth (ACD), and their potential association with lens hardness.

Metabolomic analysis revealed that patients with harder cataracts exhibited distinct alterations in mitochondrial β -oxidation products, including increased accumulation of acylcarnitines and reduced availability of glutathione (GSH). Taurine, a non-proteinogenic amino acid and a key intraocular osmolyte, facilitates GSH uptake into cells and stabilises cellular redox systems. With ageing, taurine concentrations decline, correlating with increased oxidative stress and cataract progression.

Although biometric parameters such as ACV and ACD did not show a statistically significant correlation with lens hardness overall, patients with pseudoexfoliation syndrome (PEXS) demonstrated marked structural differences – including decreased ACD, ACV, and axial length. These changes indicate increased anterior segment instability and a higher risk of intraoperative complications. A novel formula for ACV estimation was also validated, based on WTW, CCT, and ACD measurements, enabling accurate volume assessment without the need for expensive imaging equipment.

The study further identified significant alterations in tryptophan metabolism and activation of the kynurenine pathway, which were associated with GSH depletion, reduced NAD⁺ availability, and elevated markers of oxidative stress. These findings suggest mechanistic parallels with other protein aggregation disorders, such as Alzheimer's and Parkinson's diseases, where NAD⁺ depletion, mitochondrial dysfunction, and inflammatory activation are similarly observed.

This work provides novel insights into the molecular mechanisms underlying cataract pathogenesis and highlights potential biomarkers for disease progression. The findings support the therapeutic potential of metabolically targeted interventions – such as supplementation with NAD⁺ precursors, taurine, and antioxidants – as viable prophylactic and treatment strategies.

The validated ACV estimation method may also be of clinical utility in resource-limited settings, improving surgical risk stratification and treatment planning.

Keywords: cataract, metabolomics, intraocular fluid, glutathione, taurine, kynurenine pathway, acylcarnitine, anterior chamber volume (ACV), anterior chamber depth (ACD), pseudoexfoliation syndrome, redox balance, protein aggregation.

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Darbā izmantotie saīsinājumi

3-HK	3-hidroksikinurenīns
ACD	Priekšējās kameras dziļums
ACV	Priekšējās kameras tilpums
BH ₄	Tetrahidrobiopterīns
DNS	Dezoksiribonukleīnskābe
FGF2	Fibroblastu augšanas faktors-2
GSH	Glutathions (reducētā forma)
IDO	Indoleamīn-2,3-dioksigenāze
IFN- γ	Interferons-gamma
KAT	Kinurenīna aminotransferāze
KYN	Kinurenīns
KYNA	Kinurēnskābe
LEC	Lēcas epitēlija šūnas
NADPH	Nikotīnamīda adenīna dinukleotīda fosfāts (reducētā forma)
NAD ⁺	Nikotīnamīda adenīna dinukleotīds
NO	Slāpekļa oksīds
PEXS	Pseidoeksfoliācijas sindroms
ROS	Reaktīvās skābekļa sugas
TauT	Taurīna transportieris
TI	Ticamības intervāls
UV	Ultravioletais starojums

Ievads

Aptuveni 95 miljoni cilvēku visā pasaulē cieš no kataraktas (Liu et al., 2017). Katarakta ir vadošais akluma cēlonis, veidojot aptuveni pusi no novēršamā akluma gadījumiem globālā mērogā (Javitt et al., 1996). Malaizijas nacionālā acu pārskata dati par 1996. gadu liecina, ka katarakta bija galvenais akluma iemesls (39 %), kam seko tīklenes slimības (24 %) (Zainal et al., 2002). Šī patoloģija joprojām ir viena no galvenajām oftalmoloģijas problēmām gan attīstītajās, gan jaunattīstības valstīs (Cedrone et al., 1999). Lai gan dažādos pasaules reģionos novērojama saslimstības samazināšanās, kataraktas izraisītā akluma izplatība un tās ietekme uz populāciju paliek augsta (Lee & Afshari, 2017). Jaunattīstības valstīs 90 % no visiem dzīves gadu zaudējumiem invaliditātes dēļ ir saistīti ar kataraktas izraisītu aklumu (Nam et al., 2015).

Pasaules Veselības organizācijas un *Global Burden of Disease* 2020. gada dati liecina, ka katarakta veido aptuveni 45,5 % no visiem globālajiem akluma gadījumiem pieaugušajiem vecumā virs 50 gadiem, kā arī 38,9 % no vidēji smagiem vai smagiem redzes traucējumiem tajā pašā vecumgrupā (Steinmetz et al., 2021). Šie rādītāji apliecina ilgstošu tendenci – katarakta joprojām ir galvenais redzes zuduma cēlonis pasaulē, īpaši Ķīnā, Dienvidāzijā un Dienvidaustrumāzijā, kur prevalences līmenis būtiski pārsniedz globālo vidējo (Chua et al., 2015).

Pētījumi liecina, ka kataraktas radīto invaliditāti mērīto dzīves gadu skaits no 1990. līdz 2021. gadam praktiski dubultojies, turpinot būt sevišķi aktuālam jautājumam valstīs ar zemāku attīstības līmeni, – tas norāda uz nepieciešamību uzlabot ārstēšanas pieejamību (Li et al., 2025). *Global Burden of Disease Study* 2019. gada pārskats rāda, ka invaliditātes pielāgoto dzīves gadu skaits, kas saistīts ar kataraktu, pieauga no 3,49 miljoniem (95 % TI 2,48–4,72 miljoni) līdz 6,68 miljoniem (95 % TI 4,76–9,01 miljoni) no 1990. līdz 2019. gadam (Fang et al., 2022). Ņemot vērā pasaules iedzīvotāju skaita pieaugumu, novecošanu un aklumu izraisošo slimību izplatības palielināšanos, tiek prognozēts, ka cilvēku skaits ar aklumu vai vidēji smagiem redzes traucējumiem (tostarp kataraktu) palielināsies no 338,3 miljoniem 2020. gadā līdz 535 miljoniem 2050. gadā, neskatoties uz globālajiem centieniem mazināt slimību slogu un uzlabot acu veselības pakalpojumu pieejamību (Bourne et al., 2017).

Katarakta ir lēcas skaidrības zudums, kas klīniskajā praksē izpaužas ar šādiem simptomiem: redzes asuma samazināšanos (Hurst & Douthwaite, 1993); miglošanās sajūtu (Skiadaresi et al., 2012); paaugstinātu jutību pret spilgtu gaismu (Shandiz et al., 2011); dubultošanos, skatoties ar vienu aci (Records, 1980); lasīšanas grūtībām (Pesudovs & Coster, 1998); kā arī izteiktāka lēcas brieduma stadijā – intraokulārā spiediena paaugstināšanos (Flocks et al., 1955) un galu galā redzes zudumu (Han et al., 2023).

Kataraktu nav iespējams efektīvi ārstēt ar farmakoloģiskiem līdzekļiem (Harding, 2001). Vienīgā pierādītā un klīniski efektīvā ārstēšanas metode ir apduļķotās lēcas daļas

ķirurģiska ekstrakcija un intraokulārās mākslīgās lēcas implantācija (Davis, 2016). Tādēļ ķirurģija ir galvenā ārstēšanas pieeja kataraktas gadījumā, un tā ir kļuvusi par vienu no visbiežāk veiktajām ķirurģiskajām procedūrām pasaulē (Moshirfar et al., 2024). Mūsdienās kataraktas operācija tiek uzskatīta par ne vien biežāko, bet arī vienu no efektīvākajām medicīniskajām procedūrām, ko raksturo augsta redzes funkcijas atjaunošanas efektivitāte un salīdzinoši zems komplikāciju risks (Rossi et al., 2021). Tomēr, neraugoties uz augsti attīstītu tehnoloģiju un plašu pieejamību attīstītajās valstīs, daudzviet jaunattīstības reģionos operācija joprojām nav pietiekami pieejama. Zema sabiedrības informētība par slimību, nepietiekama veselības aprūpes infrastruktūra un ierobežotas ekonomiskās iespējas veicina novēlotu slimības atklāšanu un palielina ar kataraktu saistītā akluma izplatību (Cetinel et al., 2014).

Pētījumos atklāts, ka kataraktas operācija pusmūža vecuma pacientiem var būt saistīta ar paaugstinātu mirstības risku, iespējams, kopējo veselības traucējumu un hronisku blakusslimību dēļ, kas šajā vecumgrupā ir biežāk sastopamas (K. Negahban & K. Chern, 2002). Šie novērojumi aktualizē jautājumu par to, vai kataraktu galvenokārt izraisa novecošanās procesi vai tomēr būtiskāka nozīme ir oksidatīvajam stresam un hroniskiem iekaisuma mehānismiem (Li et al., 2024). Liela daļa kataraktas patoģenēzē iesaistīto strukturālo un funkcionālo izmaiņu rodas vai pastiprinās oksidatīvā stresa, ultravioletā (UV) starojuma, osmotiskā disbalansa un citu šūnu bojājošu faktoru ietekmē (Richardson et al., 2020). Katarakta nereti rodas arī kā viena no izpausmēm plašāku vielmaiņas traucējumu vai ģenētisku sindromu gadījumā, piemēram, cukura diabēta, galaktozēmijas, hipokalciēmijas vai mitohondriālo slimību kontekstā (Kambiz Negahban & Kenneth Chern, 2002). Šādos gadījumos tās klīniskā gaita un izpausmes var būt atšķirīgas no vecuma kataraktas, kas nosaka nepieciešamību pēc individualizētas pieejas diagnostikā un ārstēšanā.

Kopš modernās medicīnas attīstības aizsākumiem vecums tiek uzskatīts par galveno kataraktas riska faktoru (Sperduto, 1994). Tomēr klīniskajā praksē nereti tiek novērota ievērojama intraindividuāla variabilitāte, kad vienāda vecuma pacientiem var būt būtiski atšķirīgs lēcas apduļķošanās pakāpes līmenis (Hashemi et al., 2020). Novecošanās ir definēta kā process, kas pakāpeniski samazina organisma spēju pretoties bojājumiem, saslimšanām un vides stresa faktoriem. Tas izpaužas daudzos fizioloģiskos līmeņos, tostarp elpošanas ritmā, redzes asuma samazināšanās, asinsspiediena svārstībās un ķermeņa stājas regulācijā, kā arī būtiski paaugstina mirstības risku un ietekmē reprodukcijas funkcijas. Pētījumi apstiprina, ka novecošanās process galvenokārt ir saistīts ar uzkrājošiem šūnu un molekulāriem bojājumiem, kurus izraisa oksidatīvas reakcijas, brīvo radikāļu un citu reaktīvu skābekļa formu ietekme, kā arī cukuru un reaģējošu aldehīdu mijiedarbība un spontānas kļūdas metabolismā (Sadowska-Bartosz & Bartosz, 2014). Novecošanas procesā kristāliskās lēcas šķiedras

pakāpeniski bojājas dažādu bioloģisko un fizikālo faktoru ietekmē, tostarp UV starojuma, oksidatīvā stresa, deaminācijas, racemizācijas un posttranslācijas modifikāciju, piemēram, fosforilācijas, rezultātā (Lampi et al., 1998; Ma et al., 1998). Lēcas caurspīdīguma zudums jeb opacitāte tiek uzskatīts par kristalīnu olbaltumvielu strukturālo izmaiņu sekām – to nepareizu salocīšanos un agregāciju (Goulet et al., 2011). Šis process sākotnēji kalpo kā šūnas aizsardzības mehānisms, novēršot toksisku proteīnu monomēru uzkrāšanos, taču ilgtermiņā tas veicina šķiedru struktūras degradāciju un lēcas funkcionālā caurspīdīguma zudumu (Flaugh et al., 2006; Moreau & King, 2012). Tādējādi kataraktas patoģenēze lielā mērā ir saistīta ar proteostāzes zudumu un traucētu olbaltumvielu homeostāzi, kas šo procesu padara atkarīgu ne vien no hronoloģiskā vecuma, bet arī no individuāliem vielmaiņas, ģenētiskajiem un vides faktoriem (Taylor & Davies, 1987).

Lēca ir avaskulāra, caurspīdīga optiskā struktūra, kas sastāv no augsti organizētiem, optiski sincitiāliem šūnu slāņiem un pilda būtisku lomu gaismas fokusēšanā uz tīkleni (Delaye & Tardieu, 1983). Tā kā lēcai trūkst asinsvadu apgādes, tajā ir izveidojusies iekšējā jonu cirkulācijas sistēma, kas cieši saistīta ar šķidruma kustību un nodrošina efektīvu vielu mikrocirkulāciju (Mathias et al., 2007). Lēcas caurspīdīgumu nodrošina šķiedru šūnas ar augstu kristalīnu olbaltumvielu koncentrāciju, kas īsā attālumā ir sakārtotas augstā strukturālā organizācijā (Chiou et al., 1988).

Būtiska loma lēcas strukturālās un funkcionālās integritātes uzturēšanā ir lēcas epitēlija šūnām (LEC) – vienīgajam dzīvotspējīgajam šūnu slānim pieaugušas lēcas iekšienē (Bassnett & Šikić, 2017). Šīs šūnas nodrošina aktīvu jonu transportu, piedalās antioksidantu sintēzē, uztur osmotisko un metabolisko līdzsvaru, kā arī kalpo par priekštečiem jaunu šķiedru šūnu diferenciācijai lēcas ekvatoriālajā zonā (Andley, 2008). LEC ir īpaši uzņēmīgas pret oksidatīvā stresa iedarbību, un to funkcionālais traucējums tiek uzskatīts par vienu no agrīnajiem notikumiem kataraktas patoģenēzes kaskādē (Liu et al., 2022). Oksidatīvais stress rodas, ja tiek izjaukts līdzsvars starp reaktīvo skābekļa sugu (ROS) veidošanos un to neitralizēšanu ar antioksidantu sistēmām. Lai gan fizioloģiskos apstākļos ROS darbojas kā signālmolekulas, to pārmērīga uzkrāšanās, ko var izraisīt gan endogēni (piemēram, mitohondriji, NADPH oksidāzes, endoplazmatiskais tīkls), gan eksogēni (UV starojums, smagie metāli) avoti, bojā dezoksiribonukleīnskābi (DNS), lipīdus un proteīnus. Lai mazinātu šo bojājumu risku, šūnas aktivizē iekšējos antioksidatīvos mehānismus, bet ārējie antioksidanti tiek pētīti kā potenciāli aizsarglīdzekļi. Oksidatīvais stress ir nozīmīgs faktors daudzu hronisku slimību attīstībā, un tā modulēšana tiek uzskatīta par būtisku mērķi efektīvu terapeitisko stratēģiju izstrādē (Aranda-Rivera et al., 2022).

Patoloģiskos apstākļos, tostarp hroniska oksidatīvā stresa, hiperglikēmijas vai UV starojuma ietekmē, šūnu pretstresa mehānismi pavājinās, kā rezultātā veidojas bojātu proteīnu agregāti, traucēta intracelulārā homeostāze un tiek iniciētas strukturālas izmaiņas visā lēcā. LEC gadījumā endoplazmatiskā tīkla stresa aktivācija izraisa salocīto olbaltumvielu atbildes ieslēgšanos, ROS veidošanos un galu galā šūnu nāvi – šie procesi ir novēroti arī eksperimentālos galaktosēmijas modeļos pirms kataraktas klīniskas izpausmes (Mulhern et al., 2007). Novecošanas gaitā LEC funkcionālā kapacitāte pakāpeniski samazinās, kas var novest pie nozīmīgiem sintēzes un transporta traucējumiem. Tā rezultātā lēcas iekšējie slāņi kļūst īpaši neaizsargāti pret oksidatīvo, osmotisko un proteotoksisko bojājumu, kas veicina proteīnu agregāciju, šķiedru šūnu deģenerāciju un kodolveida kataraktas attīstību. Tādējādi tiek pamatoti uzskatīts, ka LEC disfunkcija ir viens no centrālajiem patoģenētiskajiem mehānismiem ar vecumu saistītas kataraktas gadījumā (Yanshole et al., 2019).

Kristalīni ir galvenās strukturālās olbaltumvielas cilvēka lēcā, veidojot līdz pat 90 % no kopējās šķiedru šūnu proteīnu masas (Surguchev & Surguchov, 2010). To augstā koncentrācija un telpiski organizētā struktūra nodrošina lēcas caurspīdīgumu, minimālu gaismas izkliedi un augstu gaismas laušanas spēju. Kristalīni tiek iedalīti trijās galvenajās grupās: α -, β - un γ -kristalīnos (Andley, 2007).

α -kristalīniem, īpaši αA un αB apakšvienībām, papildus strukturālajai funkcijai piemīt molekulārā šaperona aktivitāte, kas novērš citu olbaltumvielu denaturāciju un agregāciju (Derham & Harding, 1999). Šī aizsargfunkcija ļauj lēcai saglabāt optiskās īpašības arī novecošanas un šūnu stresa apstākļos. α -kristalīni piedalās arī citoskeleta stabilizācijā, apoptozes inhibēšanā un šūnu rezistences palielināšanā pret oksidatīviem un citiem stresoriem (Kamradt et al., 2005). Pētījumi liecina, ka α -kristalīnu aktivitāte nav ierobežota tikai ar lēcas šķiedru šūnām – tie aktīvi funkcionē arī LEC un ārpus acs, tostarp tīklenē, miokardā, smadzenēs un skeleta muskuļos (Srinivasan et al., 1992). α -kristalīna gēnu mutācijas izmaina lēcas refrakcijas indeksa gradienta struktūru, sekmējot caurspīdīguma zudumu, savukārt lokāla oksisterola savienojumu lietošana uzlaboja refrakcijas profila regularitāti 61 % gadījumu un samazināja opacitātes pakāpi 46 % pelēm (Wang et al., 2022).

β -kristalīni galvenokārt veido polimērus, kas piedalās šķiedru šūnu citoskeleta organizācijā, savukārt γ -kristalīni ir blīvas, kompaktas monomēru struktūras, kas nodrošina lēcas kodola augsto blīvumu un precīzu gaismas laušanu (Serebryany & King, 2014). β un γ kristalīni – ir starp stabilākajiem un visilgāk funkcionējošajiem proteīniem cilvēka organismā, taču ar vecumu tie var pārvērsties lielas molekulas agregātos, kas izkļiedē gaismu un veicina kataraktas attīstību, neraugoties uz α -kristalīnu šaperona klātbūtni lēcā (Bari, 2021).

Acs lēca ir dinamisks orgāns, kas turpina augt visa mūža garumā, nepārtraukti pievienojot jaunas šķiedru šūnas perifērijā, kamēr iekšējie slāņi – embrioloģiski agrīnās šķiedras – saglabājas strukturāli nemainīgi. Šāda koncentriskā šķiedru slāņošanās nosaka lēcas anatomisko dalījumu kodolā un korteksā (Ruan et al., 2020). Lai uzturētu optisko skaidrību, lēca ir atkarīga no efektīvas antioksidatīvās aizsardzības sistēmas, kurā galvenie komponenti ir glutations, askorbīnskābe un enzīma superoksīda dismutāze (Lou, 2003). Glutaciona līmeņa pazemināšanās tiek uzskatīta par vienu no agrīnajiem bioķīmiskajiem rādītājiem, kas liecina par kataraktas veidošanos, un tā potenciāli var derēt kā agrīnas diagnostikas bioloģiskais marķieris (Giblin, 2000).

Lēcas šūnu vielmaiņa tiek uzturēta, pateicoties pastāvīgai intraokulārā šķidruma cirkulācijai, kas nodrošina barības vielu piegādi un vielmaiņas galaproduktu izvadīšanu. Šis šķidrums tiek sintezēts ciliārā ķermeņa *pars plicata* epitēlijā un cirkulē caur zīlīti uz priekšējo kameru, no kurienes primāri tiek novadīts caur trabekulāro tīklu un Šlēma kanālu, ieplūstot acs vēnu drenāžas sistēmā (Grüb & Mielke, 2004). Intraokulārais šķidrums darbojas kā būtiska transporta sistēma, kas piegādā glikozi, aminoskābes un elektrolītus, vienlaikus palīdzot uzturēt osmotisko līdzsvaru un veicinot oksidatīvā metabolisma blakusproduktu izvadīšanu (Goel et al., 2010; Mathias et al., 2007). Tā kā lielākajai daļai lēcas šķiedru šūnu trūkst mitohondriju, enerģijas ražošana tajās balstās galvenokārt uz anaerobo glikolīzi, padarot šūnas īpaši jutīgas pret hipoksiju un glikozes piegādes traucējumiem (Shui & Beebe, 2008). Šķidruma sastāva vai plūsmas traucējumi, kas var rasties oksidatīvā stresa vai vielmaiņas disbalansa rezultātā, veicina šūnu tūsku, proteīnu agregāciju un intracelulāras homeostāzes zudumu, kas savukārt var novest pie lēcas opacitātes attīstības – kataraktai raksturīgā procesa (Dammak et al., 2023).

Intraokulārais šķidrums ir dzidrs, ūdenim līdzīgs bioloģisks šķidrums, kas aizpilda acs priekšējo un mugurējo kameru. Tā sastāvu galvenokārt veido ūdens (98–99 %), kā arī elektrolīti (nātrijs, kālijs, hlorīdi, bikarbonāti), organiskās vielas (aminoskābes, glutations, askorbīnskābe, urīnviela, laktāts), olbaltumvielas (piemēram, imūnglobulīni, transformējošais augšanas faktors beta 2, α -melanocītus stimulējošais hormons) un gāzes (skābeklis, oglekļa dioksīds) (Bansal et al., 2021; Chen et al., 2025). Fizioloģiski intraokulārajam šķidrumam ir vairākas būtiskas funkcijas: tas palīdz uzturēt acs iekšējo spiedienu, nodrošina trofiku avaskulārajiem audiem, tostarp radzenei, lēcai un stiklveida ķermenim, kā arī piedalās vielmaiņas galaproduktu un toksisko metabolītu izvadē (Tram et al., 2021). Šķidruma kvantitatīvās un kvalitatīvās izmaiņas ir saistītas ar vairākām oftalmoloģiskām patoloģijām. Piemēram, glaukomas gadījumā šķidruma aizplūšanas traucējumi var novest pie intraokulārā spiediena paaugstināšanās (Ofri, 2002), savukārt iekaisuma procesos, piemēram, uveīta, šķidrumā bieži konstatē iekaisuma

šūnas un paaugstinātu olbaltumvielu saturu (Kalsy et al., 1990). Tādējādi intraokulārā šķidruma sastāva izpēte sniedz nozīmīgu informāciju par acs iekšējās vides stāvokli un ļauj netieši izvērtēt vielmaiņas procesus tajos audos, kurus šis šķidrums apgādā un aizsargā.

Priekšējās kameras tilpums (ACV) un dziļums (ACD) ir nozīmīgi acs priekšējā segmenta biometriskie rādītāji, kas atspoguļo intraokulārās anatomijas telpisko konfigurāciju un potenciāli ietekmē intraokulārā šķidruma cirkulācijas efektivitāti (Lei et al., 2022). Šie parametri ir dinamiski un pakļauti izmaiņām dažādu oftalmoloģisku patoloģiju gadījumā, tostarp kataraktas, glaukomas un pseidoeksfoliācijas sindroma kontekstā. Ņemot vērā, ka lēca fizioloģiski aug visa mūža garumā, pakāpeniski palielinoties tās biezumam (Cheng et al., 2019), priekšējās kameras telpa progresīvi samazinās, izraisot ne tikai mehāniskas izmaiņas intraokulārā šķidruma plūsmas raksturā, bet arī iespējamu vielmaiņas produktu uzkrāšanos ap lēcu.

Šādi lokāli mikrovides traucējumi var būt nozīmīgi modulatori kataraktas patoģenēzē, īpaši situācijās, kad tiek ietekmēta oksidatīvā bilance vai metabolītu izvadmekānismi. Tādēļ priekšējās kameras telpas izvērtēšana var sniegt vērtīgu ieskatu intraokulārā šķidruma dinamikā un tās iespējamā ietekmē uz lēcas stāvokli (He et al., 2016). Papildus intraokulārā šķidruma metaboloma analīze ļauj identificēt specifiskus metabolītus, kuru klātbūtne korelē ar lēcas brieduma pakāpi, tādējādi piedāvājot potenciālus biomarkierus kataraktas attīstības prognozēšanai (Yanshole et al., 2019). Mūsdienu attēldiagnostikas un šķidruma analīzes metodes nodrošina augstas precizitātes ieskatu intraokulārajā mikrovidē, atklājot mehānismus, kas iepriekš bija pieejami tikai postmortālā histoloģijā.

Lai gan vielmaiņas traucējumi bieži tiek saistīti ar specifiskiem metabolītiem, piemēram, cukura diabēts ar glikozes līmeņa izmaiņām vai sirds un asinsvadu slimības ar holesterīna metabolismu, ir būtiski apzināties, ka bioķīmiskie procesi nenotiek izolēti, bet ir savstarpēji cieši saistīti un ietekmē viens otru (Poznyak et al., 2020). Šāda sistēmiska izpratne ir īpaši nozīmīga mūsdienu vielmaiņas pētījumos, jo organisma metaboliskā homeostāze balstās uz kompleksu ceļu līdzsvaru, kur pat nelielas izmaiņas vienā posmā var atstāt plašas sekas citviet. Straujā analītiskās ķīmijas attīstība, īpaši spektrometrijas un augstas izšķirtspējas šķidruma hromatogrāfijas jomā, ļauj vienlaikus identificēt un kvantificēt plašu endogēno metabolītu spektru, izmantojot vienu vai vairākas metabolomikas platformas (Lamers et al., 2003). Šīs metodes nodrošina iespēju iedziļināties vielmaiņas ceļu mijiedarbībā, ļaujot interpretēt gan fizioloģiskas, gan patoloģiskas izmaiņas cilvēka organismā vai audos. Lai izprastu atsevišķu metabolītu koncentrācijas noviržu bioloģisko nozīmi un, vēl būtiskāk, paredzētu iespējamus korektīvos pasākumus uztura, farmakoloģijas vai dzīvesveida jomā, ir nepieciešama padziļināta izpratne par vielmaiņas ceļu funkcionēšanu un savstarpējo regulāciju (German et al., 2005).

Vielmaiņas izmaiņas ir ne tikai novērojamas eksperimentāli, bet arī detalizēti analizējamas, izmantojot mūsdienīgas analītiskās metodes, kas sniedz iespēju izprast to ietekmi uz konkrētiem bioķīmiskajiem ceļiem un šūnu funkcionālajiem mehānismiem. Šādas pieejas iespējamība balstās uz faktu, ka bioķīmisko procesu izpēte jau vairāk nekā gadsimtu ir bijusi viens no galvenajiem virzieniem dabas zinātņu attīstībā (German et al., 2005).

Darba mērķis

Pētījuma mērķis ir raksturot priekšējās kameras dziļuma un tilpuma, kā arī intraokulārā šķidruma metaboloma atšķirības kataraktas pacientiem atkarībā no lēcas cietības pakāpes.

Darba uzdevumi

Primāri uzdevumi:

1. Analizēt intraokulārā šķidruma metaboloma sastāva atšķirības pacientiem ar dažādu lēcas cietības pakāpi.
2. Novērtēt priekšējās kameras dziļuma un tilpuma parametrus atkarībā no lēcas cietības pakāpes.
3. Izpētīt statistiskās asociācijas starp lēcas cietības pakāpi, intraokulārā šķidruma metabolītu profilu un priekšējās kameras biometriskajiem rādītājiem.

Sekundāri uzdevumi:

1. Analizēt intraokulārā šķidruma metaboloma sastāva izmaiņas pacientiem ar pseidoeksfoliācijas sindromu.
2. Raksturot intraokulārā šķidruma metaboloma īpatnības pacientiem ar glaukomu.
3. Novērtēt intraokulārā šķidruma metaboloma atšķirības pacientiem ar cukura diabētu.

Darba hipotēzes

- Pacientiem, kuru priekšējās kameras dziļums un tilpums ir lielāks, novērojama ātrāka augstākas cietības pakāpes kataraktas attīstība.
- Kataraktas pacientiem ir raksturīgs specifisks intraokulārā šķidruma metabolītu profils, kas korelē ar lēcas cietības pakāpi.

Darba novitāte

Pētījuma novitāte slēpjas potenciālā ieguldījumā padziļinātā kataraktas patofizioloģijas izpratnē, īpaši koncentrējoties uz intraokulārā šķidruma sastāva analīzi. Pētījums sniegs jaunas zināšanas par biomarkšiem, kas var būt pamats precīzākai kataraktas diagnostikai, slimības prognozēšanai un personalizētas ārstēšanas pieejas izstrādei. Identificējot bioķīmiskus un molekulārus rādītājus, kas saistīti ar kataraktas progresēšanu, darbs sekmēs klīniskās prakses pilnveidi un potenciāli aizkavēs redzes zudumu.

Ņemot vērā, ka katarakta ir proteīnu agregācijas slimība, pētījuma rezultāti var sniegt būtisku ieguldījumu arī citu ar proteostāzes zudumu saistītu patoloģiju izpratnē. Starp šīm slimībām īpaši izceļamas neirodeģeneratīvās saslimšanas, piemēram, Alcheimera slimība, Parkinsona slimība un amiotrofā laterālā skleroze, kur proteīnu nepareiza salocīšanās un agregācija veido patoloģiju pamatu. Pētījuma laikā iegūtā informācija par intraokulārā šķidruma metaboliskajiem un antioksidatīvajiem raksturlielumiem var pavērt jaunas iespējas šo sistēmisko slimību agrīnai diagnostikai un molekulārai terapijai, stiprinot starpdisciplināro pieeju proteīnu agregācijas slimību pētniecībā.

Šī novatoriskā pieeja ne tikai veicina progresu oftalmoloģijā, bet arī piedāvā plašāku sabiedrības veselības ieguvumu, sekmējot personalizētu medicīnu un starpnozaru sadarbību hronisku deģeneratīvu slimību risināšanā.

Personīgais ieguldījums

Šis pētījums ietver tiešu klīnisko un pētniecisko darbu ar kataraktas pacientiem. Es personīgi veicu kataraktas operācijas. Operāciju laikā tika savākts intraokulārais šķidrums, nodrošinot augstu paraugu kvalitāti un sterilitāti turpmākai bioķīmiskai analīzei. Paralēli ķirurģiskajai darbībai piedalījās arī iegūto datu apstrādē, tostarp pacientu klīniskā profila izvērtēšanā, laboratorisko rezultātu analīzē un to sasaistē ar kataraktas patoģenētiskajiem rādītājiem.

Ētiskie aspekti

Ētiskās uzraudzības nodrošināšanu veica Rīgas Stradiņa universitātes Ētikas komiteja (apstiprinājuma Nr. 2-PEK-4/307/2023, datēts ar 2023. gada 21. martu), un pētījumu atļāva veikt Paula Stradiņa klīniskā universitātes slimnīca. Visi pētījuma dalībnieki sniedza rakstisku informēto piekrišanu, un pētījums tika veikts pilnībā atbilstoši Helsinku deklarācijā (Association, 2025) noteiktajiem ētikas principiem.

Diskusija

Priekšējās kameras tilpuma un dziļuma ietekme uz kataraktas cietības pakāpi

Mūsu pētījuma rezultāti neuzrādīja statistiski nozīmīgas saistības starp acu biometriskajiem parametriem un lēcas cietības pakāpi. Lai gan ir pierādīts, ka ar vecumu lēca kļūst biezāka, galvenokārt proteīnu agregācijas un strukturālu izmaiņu dēļ, mūsu dati neliecināja par šādu procesu ietekmi uz ACV vai ACD. Kaut arī ACV mērīšana vēl nav iekļauta klīniskajā rutīnā, tā tiek arvien biežāk atzīta par daudzsoļu rādītāju dažādu acu slimību diagnostikā, ārstēšanā un ķirurģiskā plānošanā (Coakes et al., 1979). ACV kvantitatīva novērtēšana var sniegt būtisku ieguldījumu glaukomas diagnostikā un kontroles uzlabošanā, kataraktas ķirurģijas stratēģijas izvēlē, refraktīvās ķirurģijas kandidātu izvērtēšanā, kā arī priekšējā segmenta patoloģiju izpētē.

No visām analizētajām pacientu grupām visizteiktākās biometriskās atšķirības tika konstatētas pacientiem ar pseidoeksfoliācijas sindromu (PEXS). Šajā grupā novērotais samazinātais ACD, ACV un īsāks acs gareniskais garums varētu būt saistīts ar lēcas priekšēju nobīdi un zonulu struktūras pavājināšanos (Hayashi et al., 2024). Šie faktori potenciāli palielina lēcas mobilitāti, dislokācijas risku un stiklveida ķermeņa zudumu kataraktas ķirurģijas laikā, uzsverot nepieciešamību pēc rūpīgas preoperatīvas novērtēšanas šiem pacientiem.

Turklāt mūsu rezultāti izgaismo, ka ACV un ACD stabilitāte pat progresējošas kataraktas gadījumā var atspoguļot acs mehānismus priekšējā segmenta kompensācijai. Šie novērojumi norāda, ka priekšējās kameras biometriskie rādītāji var nebūt agrīns kataraktas progresijas marķieris, bet drīzāk sekundārs faktors, kas ietekmē intraoperatīvo risku. Īpaši nozīmīgi tas ir ķirurģiskajā plānošanā, jo nelielas izmaiņas ACV vai ACD var kļūt klīniski nozīmīgas tikai kombinācijā ar citiem riska faktoriem, piemēram, zonulu vājumam vai PEXS klātbūtni. Šāda interpretācija liecina, ka biometrisku datu vērtība slēpjas ne tikai tiešā korelācijā ar lēcas cietību, bet arī to spēju papildināt pacienta individuālo riska profilu pirms kataraktas operācijas.

Lai gan sākotnēji tika izvirzīta hipotēze, ka glaukomi būs cieša korelācija ar ACV parametriem, šis pieņēmums mūsu pētījumā netika apstiprināts. Tomēr literatūrā aprakstīti pētījumi, kuros ACV un intraokulārā spiediena attiecība tiek aplūkota kā potenciāls ārstēšanas efektivitātes prognozētājs, īpaši pacientiem, kuri saņem terapiju ar prostaglandīnu analogiem (Scott et al., 2021). Tāpat ACV tiek atzīts par būtisku riska faktoru primārās aizvērtas kakta glaukomas prognozēšanā (Pakravan et al., 2012).

Svarīgs mūsu pētījuma ieguldījums ir ACV aprēķina formulas pārbaude/validācija, izmantojot pieejamus biometriskos datus. Izstrādātā metode ļauj novērtēt ACV bez nepieciešamības pēc dārgas aparatūras, piemēram, *Pentacam* vai *AS-OCT*. Tas sniedz būtiskas

priekšrocības ierobežotu resursu apstākļos, kur piekļuve modernām tehnoloģijām ir ierobežota. Šādas alternatīvas pieejas ieviešana klīniskajā praksē var veicināt ACV plašāku izmantošanu un uzlabot acu slimību diagnostikas un ārstēšanas pieejamību globālā mērogā.

Metaboloma atšķirības pacientiem ar dažādu lēcas cietības pakāpi

Metaboliskie procesi kā kataraktas patoģenēzes pamats

Glutathions (GSH) ir galvenais intracelulārais antioksidants lēcas audos, kura funkcija ir būtiska kristalīnu aizsardzībā pret oksidatīvo bojājumu, un tas spēlē nozīmīgu lomu šūnu oksidatīvā un reducējošā līdzsvara nodrošināšanā (Jiao et al., 2023; Truscott & Friedrich, 2016). GSH darbojas gan kā tiešs ROS neitralizētājs, gan kā koenzīms dažādos fermentatīvos detoksikācijas ceļos, tostarp glutathiona peroksidāzes un glutathiona-S-transferāzes sistēmās (Deng et al., 2025). Tāpat GSH piedalās olbaltumvielu disulfīdu saišu reducēšanā, palīdzot saglabāt to strukturālo integritāti (Georgiou-Siafis & Tsiftoglou, 2023; Giustarini et al., 2017). Samazināts GSH līmenis noved pie proteīnu oksidatīvām modifikācijām, nepareizas salocīšanās un šķērssaistīšanās procesiem, kas pakāpeniski izjauc šķiedru šūnu caurspīdīgumu un veicina opacitātes progresēšanu – galveno kataraktas patoģenētisko mehānismu (Truscott, 2005). Taurīns – viena no dominējošajām aminoskābēm, kas neietilpst proteīnos, bet ir klāt intraokulārajā šķidrumā, – papildina GSH antioksidatīvo darbību, stabilizējot šūnu membrānas, inhibējot pārmērīgu kalcija iekļūšanu šūnā un regulējot osmotisko līdzsvaru (Froger et al., 2014). Turklāt pierādīts, ka taurīns veicina GSH intracelulāro uzņemšanu, tādējādi nodrošinot papildu mehānismu šūnu aizsardzībai pret oksidatīvo stresu (Baliou et al., 2021). Taurīna koncentrācijas samazināšanās lēcas audos ar vecumu korelē ar pieaugošu oksidatīvo slodzi un paaugstinātu šūnu bojājumu risku. Šī dinamika var būt kā viens no izšķirošajiem mehānismiem novecošanai raksturīgo izmaiņu veicināšanā (Singh et al., 2023). Abu molekulu – GSH un taurīna – mijiedarbība ilustrē sinerģisku antioksidatīvo tīklu, kas ir būtisks lēcas strukturālās un funkcionālās integritātes uzturēšanā.

Trešais būtiskais komponents – nikotīnamīda adenīna dinukleotīds (NAD^+) – ir ne tikai centrāls kofaktors šūnas enerģijas metabolismā, iesaistoties glikolīzē, trikarbonskābju ciklā un oksidatīvajā fosforilācijā, bet arī neaizvietoājams redoksreakciju homeostāzes uzturēšanā (Pehar et al., 2018; Xiao et al., 2018). Izmaiņas NAD^+/NADH attiecībā vai kopējā NAD^+ līmeņa samazināšanās var izjaukt šūnas bioloģisko līdzsvaru un veicināt dažādu procesu attīstību, tostarp novecošanu, neirodeģeneratīvas slimības un audzēju veidošanos (Amjad et al., 2021). NAD^+ ir nepieciešams nikotīnamīda adenīna dinukleotīda fosfāta reducētās formas (NADPH) sintēzei, kas savukārt ir kritiski svarīgs GSH atjaunošanai no tā oksidētās formas, nodrošinot efektīvu šūnu aizsardzību pret oksidatīvo stresu (Lu, 2013). Novecošanās procesā novērojama

NAD⁺ rezervju izsīkšana, kas kavē šos aizsargmehānismus un veicina alternatīvu metabolisma ceļu, tostarp triptofāna katabolismu pa kinurenīna ceļu (Kincaid & Berger, 2020). Šī metabolisma pārbīde izraisa potenciāli toksisku starpproduktu, piemēram, 3-hidroksikinurenīna (3-HK) un ksanturenīnskābes, uzkrāšanos, kas saistīti ar paaugstinātu šūnu bojāeju un strukturālām izmaiņām (Wang et al., 2025).

Mūsu pētījumā konstatētās metabolītu profila pārmaiņas intraokulārajā šķīdumā liecina par būtisku šūnu enerģētiskās un redoksbalansa sistēmu destabilizāciju, kas cieši korelē ar lēcas cietības pakāpi un kataraktas progresēšanas stadiju. Jo īpaši izmaiņas mitohondriju β-oksīdācijas gala produktos, piemēram, acetilkarnitīnu koncentrācijā, liecina par traucētu taukskābju transportu un nepilnīgu ATP sintēzi (Merritt et al., 2018). Šāds enerģijas deficīts, īpaši lēcas kodola hipoksiskajos apstākļos, veicina oksidatīvā stresa pastiprināšanos un samazina šūnas spēju aizsargāt kristalīnu proteīnus no denaturācijas un agregācijas, tādējādi sekmējot opacitātes attīstību.

Šie mehānismi veido patofizioloģisku ciklu: oksidatīvā stresa radīti proteīnu bojājumi veicina intensīvu GSH patēriņu un tā izsīkumu. Samazinoties GSH koncentrācijai, tiek traucēta redoksbalansa uzturēšana, kas savukārt samazina NAD⁺ pieejamību. NAD⁺ deficīts pastiprina triptofāna metabolismu pa kinurenīna ceļu, veicinot potenciāli toksisku starpproduktu, piemēram, 3-HK, uzkrāšanos. Šie metabolīti inducē šūnu bojāeju LEC un šķiedru šūnās, kā rezultātā pasliktinās lēcas strukturālā integritāte un progresē tās caurspīdīguma zudums.

Šie secinājumi nostiprina pieņēmumu, ka katarakta ir nevis pasīvs, ar novecošanos saistīts strukturāls process, bet gan bioķīmiski aktīva, dinamiski progresējoša patoloģija, kuru potenciāli var modulēt, izmantojot mērķtiecīgas vielmaiņas līmeņa intervences, tostarp taurīna, NAD⁺ prekursoru, B₆ vitamīna un GSH analogiem.

Taurīns

Taurīns ir sēru saturoša aminoskābe, kas augstā koncentrācijā sastopama audos ar paaugstinātu oksidatīvā stresa risku, tostarp acs lēcā, miokardā un centrālajā nervu sistēmā. Taurīna un kopējā proteīna koncentrācija acs lēcā samazinās atkarībā no kataraktas stadijas, taču nav tieši saistīta ar vecumu (Anthrayose & Shashidhar, 2004). Taurīns lēcā tiek uzņemts no asinsrites, un tā audu koncentrācija lielā mērā ir atkarīga no uztura uzņemšanas, īpaši no dzīvnieku izcelsmes produktiem, piemēram, gaļas, zivīm un piena (Duan et al., 2023). Tā antioksidatīvās īpašības izpaužas, neitralizējot brīvos radikāļus un stabilizējot šūnu membrānas struktūru un funkcionalitāti (Jong et al., 2021). Īpaši nozīmīga taurīna loma ir LEC, kuras ir pakļautas ilgstošai UV starojuma ietekmei un ar to saistītam oksidatīvajam bojājumam. Papildus

osmolaritātes regulācijai taurīns kalpo kā metabolisks modulatora elements, iesaistoties kalcija homeostāzes, iekaisuma procesu un apoptozes regulācijā (Ripps & Shen, 2012).

Taurīns pirmo reizi tika identificēts 1827. gadā, izolējot to no bulļa žults, un tā nosaukums cēlies no latīņu vārda *taurus* (Tiedemann & Gmelin, 1827). Mūsdienās tas tiek sintezēts rūpnieciski, parasti izmantojot cisteīnu kā izejvielu, un netiek izmantoti dzīvnieku izcelsmes avoti. Eksperimentālie pētījumi liecina, ka taurīns efektīvi samazina oksidatīvā stresa inducētos šūnu bojājumus, veicinot intracelulāru GSH uzņemšanu un stabilizējot šūnas redokslīdzsvaru (Hansen et al., 2010). Šīs īpašības padara taurīnu par nozīmīgu aizsargfaktoru pret oksidatīvā stresa izraisītiem bojājumiem, kas veicina kataraktas patoģenēzi.

Pētījuma rezultāti iezīmē taurīna būtisko citoprotektīvo funkciju šūnu stresa apstākļos, īpaši saistībā ar tā spēju mazināt oksidatīvā bojājuma izraisītās sekas, kas ir nozīmīgi dažādu audu, tostarp lēcas, strukturālās un funkcionālās integritātes saglabāšanā (Ma et al., 2021). Taurīns ietekmē arī šūnu homeostāzes uzturēšanu, modulējot līdzsvaru starp autofāģiju un apoptozi – diviem būtiskiem šūnu mehānismiem, kuru uzdevums ir nodrošināt bojāto organelļu un proteīnu elimināciju, kā arī adaptīvu atbildi uz stresu (El Idrissi & Trenkner, 2003; Jong et al., 2011). Taurīns un tā halamīni (taurīna hloramīns un taurīna bromamīns) demonstrē nozīmīgu pretiekaisuma un citoprotektīvu iedarbību, jo spēj neitralizēt mieloperoksidāzes izcelsmes oksidantus iekaisuma vietās, tādējādi mazinot oksidatīvo stresu un audu bojājumus (Marcinkiewicz & Kontny, 2014). Eksperimentāli ir pierādīts, ka taurīns spēj samazināt mitohondriālās disfunkcijas inducētu apoptozi, kavējot kaspāžu kaskādes aktivāciju (Schaffer et al., 2010). Šāda aizsargiedarbība ir īpaši nozīmīga lēcas šķiedru šūnās, jo šūnu zudums tajās nav atjaunojams proliferācijas vai reģenerācijas ceļā, padarot taurīnu par potenciāli nozīmīgu terapeitisku mērķi kataraktas patoģenēzes ierobežošanā.

Eksperimentālie pētījumi ar dzīvniekiem liecina, ka taurīna papildināšana sniedz nozīmīgu aizsardzību lēcai pret oksidatīviem un osmotiskiem bojājumiem. Tā spēja aizsargāt lēcas audus ir cieši saistīta ar GSH līmeņa saglabāšanu – mehānismu, kas ir būtisks kataraktas patoģenēzē. Taurīna lietošana eksperimentālajos modeļos normalizēja GSH koncentrāciju un samazināja malondialdehīda – lipīdu peroksidācijas galaprodukta – līmeni, tādējādi norādot uz taurīna antioksidatīvo iedarbību (Sevin et al., 2021). Taurīnam piemīt arī spēja neitralizēt brīvos radikāļus un aizsargāt lēcas proteīnus no glikācijas – cukuru nekontrolētas saistīšanās ar proteīniem –, kas ir viens no kataraktas attīstību veicinošajiem mehānismiem (Devamanoharan et al., 1997). Piemēram, *Pacific Spring* žurku modelī, kur lēcas tika pakļautas augstai glikozes koncentrācijai (55,6 mM), lai imitētu diabētiskas kataraktas attīstību, 30 mM taurīna papildināšana novērsa GSH līmeņa samazināšanos un samazināja proteīnu karbonilāciju – oksidatīva bojājuma marķieri (Son et al., 2007). Līdzīgas aizsargājošas īpašības taurīns

demonstrēja arī GSH deficīta izraisītā trušu modeli, kur novērota būtiska lēcas strukturālās integritātes saglabāšanās (Malone et al., 1993).

Vēl viens nozīmīgs taurīna iedarbības mehānisms ir tā spēja saglabāt mitohondriju funkcionālo integritāti. Taurīns stabilizē mitohondriju elpošanas ķēdes komponentus un samazina ROS veidošanos mitohondriju matricā, tādējādi kavējot lipīdu peroksidācijas kaskādes iniciāciju (Seneff & Kyriakopoulos, 2025). Šī mitohondriju aizsargfunkcija ir īpaši nozīmīga, ņemot vērā, ka mitohondriji vienlaikus ir gan ROS ģenerācijas vieta, gan oksidatīvā bojājuma mērķstruktūra (Kuznetsov et al., 2022).

Taurīnam piemīt ne tikai antioksidatīvās īpašības, bet arī nozīmīga neurotransmisijas modulējoša un neirotropiska iedarbība, kas ietekmē dažādu acs struktūru, tostarp lēcas, tīklenes un ciliārā ķermeņa šūnu, funkcionālo stāvokli (Wu & Prentice, 2010). Lēcas fizioloģijas kontekstā īpaša nozīme ir taurīna osmoregulējošajai funkcijai, kas nodrošina šūnu tilpuma stabilizēšanu un palīdz novērst intracelulāras tūskas attīstību (Trachtman et al., 1988). Šis mehānisms ir būtisks, ņemot vērā tā saistību ar kataraktas progresēšanu, īpaši metabolisku traucējumu gadījumos, piemēram, diabētiskās vai hiperosmolārās kataraktas formās.

Interesanti, ka taurīna koncentrācijas samazināšanās novecošanās procesā tiek novērota ne tikai acs priekšējā segmentā, bet arī sistemātiskā līmenī – plazmā un smadzenēs –, kas liecina par tā potenciālu kā biomarkieri bioloģiskajam vecumam. Dažādu sugu, tostarp peļu, pērtiķu un cilvēku, pētījumos ir konstatēts, ka taurīna līmenis pakāpeniski samazinās ar vecumu, savukārt tā papildināšana modeļorganismos pozitīvi ietekmē dzīvildzi, liecinot par taurīna iespējamo lomu novecošanās procesā (Singh et al., 2023). Eksperimentāli modeļi demonstrējuši, ka taurīna papildināšana ne tikai kavē novecošanai raksturīgas fizioloģiskās izmaiņas, bet arī veicina ATP sintēzes efektivitāti, nodrošina telomēru stabilitāti un uzlabo šūnu izdzīvošanu (Mashyakh et al., 2021; Sheikh & Iqbal, 2023). Tomēr Nacionālā veselības institūta veiktie pētījumi norāda, ka taurīns nevar tikt uzskatīts par universālu novecošanas biomarkieri, jo tā koncentrācijas izmaiņas dažādās populācijās ir atšķirīgas un, piemēram, cilvēkiem taurīna līmenis korelē vāji ar funkcionālo veselību, tostarp muskuļu spēku un metabolisma parametriem (Fernandez et al., 2025).

Arī onkoloģijas šūnas ietekmē taurīns. Taurīns var inhibēt plaušu vēža šūnu proliferāciju un audzēju augšanu, stimulējot apoptozi caur *PUMA–Bax* ceļu un Bcl-2 nomākšanu. Tas norāda uz potenciālu pretvēža iedarbību, vismaz preklīniskos apstākļos (Tu et al., 2018). Leikēmijas cilmes šūnas nespēj sintezēt taurīnu pašas, tādēļ tās piesaista to no kaulu smadzeņu mikrovides, izmantojot taurīna transportieri (TauT); šī sadarbība veicina glikolīzi un tādējādi veicina ļaundabīgu šūnu proliferāciju. *University of Rochester* pētnieki ir konstatējuši, ka TauT inhibīcija mūsos kavē leikēmijas šūnu izplatīšanos un ievērojami pagarina dzīvildzi, paverot

iespējas jauniem terapeitiskiem risinājumiem (Sharma et al., 2025). Taurīns, kas bagātīgi sastopams neitrofilajos leukocītos, reaģē ar mieloperoksidāzes radīto hipohloroskābi, veidojot taurīna hloramīnu, kas samazina oksidatīvo bojājumu un kavē neitrofilu pārmērīgu degranulāciju (Kim et al., 2020). Šī antioksidatīvā un pretiekaisuma iedarbība var būt nozīmīga arī lēcas audu aizsardzībā kataraktas attīstības kontekstā.

Šie aspekti liecina, ka taurīns darbojas ne tikai kā pasīvs antioksidants, bet arī kā aktīvs regulators, saglabājot šūnu strukturālo un funkcionālo integritāti, īpaši acs lēcas mikrovidē, jo oksidatīvā līdzsvara traucējumi var ātri pasliktināt redzes kvalitāti. Tādējādi taurīna koncentrācijas uzturēšana, it īpaši vecāka gadagājuma indivīdiem, potenciāli var kalpot kā profilaktisks vai terapeitisks stratēģijas elements kataraktas ārstēšanā, it sevišķi kombinācijā ar citiem redoksbalansa modulējošiem savienojumiem, piemēram, NAD^+ prekursoru vai GSH sintēzes stimulējošo līdzekļu lietošanu.

NAD^+ trūkums un triptofāna–kinurenīna metabolisma ceļš

NAD^+ ir centrāls koenzīms šūnu bioenerģētikā un redoksreakciju regulācijā (Braidy & Liu, 2020). Tā funkcijas pārsniedz tradicionālo lomu kā elektronu akceptoram oksidatīvās fosforilācijas procesā – NAD^+ piedalās arī DNS atjaunošanā, mitohondriju funkciju uzturēšanā, kā arī kalpo kā substrāts NAD^+ atkarīgajiem enzīmiem, piemēram, sirtuīniem un poli-ADP-ribozes polimerāzēm, kuri aktīvi iesaistīti šūnas stresa atbildes mehānismos (Houtkooper et al., 2012).

Ar vecumu NAD^+ koncentrācija organismā fizioloģiski samazinās, kas noved pie mitohondriju funkcijas traucējumiem, redoksbalansa zaudēšanas un šūnu aizsardzības mehānismu vājināšanās (McReynolds et al., 2020). Lēcas šūnās šīs izmaiņas izpaužas kā samazināta GSH atjaunošana, ko izraisa ierobežota NADPH sintēze no NADP^+ , kā arī samazināta spēja neitralizēt oksidatīvo stresu.

NAD^+ sintēze var notikt arī caur Preiss–Handlera ceļu, kur nikotīnskābe tiek pārvērsta nikotīnamīda mononukleotīdā un tālāk NAD^+ formā (Bieganski & Brenner, 2004). Viena no galvenajām endogēnajām NAD^+ biosintēzes shēmām ir triptofāna metabolismā iesaistītais kinurenīna ceļš, kas tiek aktivizēts šūnu stresa, iekaisuma vai oksidatīvo bojājumu kontekstā (Ogbechi et al., 2020). Šajā ceļā enzīma indoleamīn-2,3-dioksigenāzes (IDO) aktivitāte regulē triptofāna pārvēršanu par kinurenīnu (KYN), no kura tālāk sintezējas NAD^+ un citi starpprodukti, piemēram, 3-HK, kinurēnskābe (KYNA) un kvinolīnskābe (Savitz, 2020). Šie metabolīti var pildīt gan aizsargfunkcijas, gan, pārmērīgi uzkrājoties, bojāt proteīnus, inducēt apoptozi un destabilizēt lēcas mikrovidi (Savitz et al., 2015). Pētījumi ar transgēnām pelēm, kurām acs lēcā ir paaugstināta IDO enzīma ekspresija, liecina, ka šī aktivitātes

palielināšanās veicina KYN akumulāciju, izraisa lēcas šūnu apoptozi un paātrina kataraktas veidošanos (Mailankot et al., 2009).

Mūsu pētījumā agrīnajā kataraktas stadijā (SPONCS 2) tika konstatēta nozīmīgi paaugstināta IDO aktivitāte, kas, visticamāk, atspoguļo kompensatoru reakciju uz pieaugošo oksidatīvo stresu un UV starojuma ietekmi. Šie rezultāti norāda, ka LEC sākotnēji aktivizē NAD⁺ biosintēzes alternatīvos ceļus, lai atjaunotu enerģētisko homeostāzi un saglabātu šūnu struktūras integritāti. Tomēr kataraktas progresēšanas laikā tika novērota IDO aktivitātes samazināšanās, visticamāk, saistīta ar LEC apoptozi un enzīma ekspresijas samazinājumu.

Vienlaikus tika konstatēts, ka kinurenīna atvasinājumu līmenis, īpaši 3-HK, palielinās kataraktas vēlīnās stadijās (SPONCS 4–5), sasniedzot maksimālu koncentrāciju. Šie savienojumi ir atzīti par fototoksiskiem, proapoptotiskiem un prooksidatīviem faktoriem, kuru uzkrāšanās var veicināt kristalīnu denaturāciju, šķērssaistīšanu un lēcas caurspīdīguma samazināšanos (Korlimbinis & Truscott, 2006). Interferons gamma (IFN- γ) stimulē IDO ekspresiju LEC, aktivizējot JAK–STAT1 ceļu, kas veicina kinurenīna, īpaši 3-HK, ražošanu. Šie metabolīti izraisa oksidatīvo stresu un apoptozi, kas var būt nozīmīgs mehānisms hroniskā iekaisuma saistītā kataraktas attīstībā (Mailankot & Nagaraj, 2010).

Fibroblastu augšanas faktors-2 (FGF2) ir svarīgs lēcas šķiedru šūnu diferenciācijai. Kinurenīns kavē FGF2 inducētu kristalīnu un MIP26 ekspresiju peles lēcas epitēlija šūnās, inhibējot Akt un ERK1/2 fosforilēšanos, taču ne FGF2 receptoru saistīšanos. Šie dati liecina, ka KYN var traucēt šķiedru šūnu diferenciāciju, bloķējot būtisko proteīnu ražošanu (Mailankot et al., 2010). Imūnhistoķīmiskās analīzes apstiprina kinurenīna aminotransferāžu (KAT I–III) ekspresiju lēcas ekstracelulārajā matricā jau kataraktas agrīnajā stadijā, norādot uz aktīvu kinurenīna ceļa iesaisti šūnu adaptācijas un deģenerācijas procesos (Rejda et al., 2013).

Šāda metabolisma dinamika akcentē kinurenīna ceļa nozīmi kataraktas patoģenēzē, un tā modulācija, piemēram, IDO inhibēšana vai KAT aktivitātes stimulācija, var nodarēt kā potenciāla terapeitiska pieeja. Turklāt ne tikai absolūtais NAD⁺ līmenis, bet arī tā biosintēzes ceļa kvalitāte un metabolītu profils ir būtiski faktori kataraktas attīstībā. Tāpēc stratēģija, kas apvieno NAD⁺ prekursoru, piemēram, nikotīnamīda ribozīda, papildināšanu ar IDO aktivitātes vai 3-HK veidošanās modulāciju, varētu piedāvāt jaunu, vielmaiņas balstītu pieeju kataraktas profilaksei un terapijai.

KAT aktivitāte kā biomarkieris un terapeitiskais mērķis

KAT ir būtisks enzīms triptofāna–kinurenīna metabolisma ceļā, kas katalizē KYN pārvēršanu par KYNA – metabolītu ar izteiktām neuroaizsargājošām, antioksidatīvām un fotoprotektīvām īpašībām. KYNA ir UV-A spektra (315–400 nm) absorbējošs savienojums, kas

spēj darboties kā fotosensibilizators, veidojot trīskāršo stāvokli ($^3\text{KNAH}^-$), kurš var reaģēt ar citām biomolekulām. KYNA ir konstatēta cilvēka acs lēcā koncentrācijā ap 1–2 $\mu\text{M}/\text{mg}$, un, pakļaujot UV starojumam, tā var piedalīties proteīnu oksidatīvās modifikēšanas procesos, potenciāli veicinot kataraktas attīstību (Morozova et al., 2023). UV starojuma ietekmē KYNA pāriet tripleta stāvoklī un inducē pašoksidāciju, veidojot reaktīvus radikāļus, kuri kovalenti piesaistās aminoskābēm, piemēram, triptofānam un tirozīnam. Šie rezultāti liecina, ka KYNA var veidot proteīnu modifikācijas dzīvos audos un potenciāli veicināt ar UV starojumu saistītus bojājumu mehānismus (Morozova et al., 2023). Cilvēka un žurku kataraktas modeļos novērota KYNA koncentrācijas paaugstināšanās un KAT I/II ekspresijas aktivācija atkarībā no kataraktas smaguma (Zarnowski et al., 2005; Zarnowski et al., 2007). KYNA ir paaugstināta multiplās sklerozes pacientu plazmā, kas liek secināt par tās iespējamu aizsargfunkciju pret ekscitotoksisku bojājumu (Hartai et al., 2005). Kinurenīna ceļa metabolīti – KYN, 3-HK un to glikozīdi – funkcionē kā endogēni UV filtri acs lēcā, absorbējot kaitīgo starojumu un nodrošinot fotoprotekciju, taču to vecuma laikā palielinātā saistība ar kristalīnu un potenciālā fotosensibilizējošā iedarbība var veicināt oksidatīvo bojājumu un kataraktas attīstību (Zarnowski et al., 2005).

KAT aktivitāte ir būtiska lēcas caurspīdīguma un strukturālās integritātes uzturēšanā, jo tā regulē līdzsvaru starp aizsargājošajiem un potenciāli toksiskajiem kinurenīna ceļa metabolītiem. Mūsu pētījuma dati norāda, ka KAT aktivitāte sasniedz augstāko līmeni kataraktas agrīnā stadijā (SPONCS 2), kad lēca vēl spēj aktīvi pretoties oksidatīvajam stresam un virzīt kinurenīna metabolismu aizsargājošā virzienā. Šī paaugstinātā aktivitāte, visticamāk, atspoguļo kompensējošu adaptācijas mehānismu, ar kuru šūnas cenšas neitralizēt UV starojuma inducēto ROS iedarbību un uzturēt redoksbalansu.

Tomēr, slimībai progresējot, mūsu dati norāda uz pakāpenisku KAT aktivitātes samazināšanos, īpaši SPONCS 4–5 stadijā. Šo regresīvo tendenci, iespējams, izraisa piridoksāla 5-fosfāta (B_6 vitamīna aktīvās formas) samazināšanās (Whittaker, 2016), kas nepieciešama KAT katalītiskajai darbībai, vai arī enzīma strukturālā bojāeja oksidatīvā stresa ietekmē (Francisqueti et al., 2017). Enzīmu funkciju var traucēt arī posttranslācijas modifikācijas, piemēram, nitrozilācija (Song et al., 2011) vai karbonilācija (Ortuño-Sahagún et al., 2014), kas zinātniskajā literatūrā tiek saistīta ar dažādu šūnu funkciju zudumu novecošanas laikā.

Šāda KAT aktivitātes disfunkcija noved pie KYNA sintēzes samazināšanās, līdz ar to samazinot fotoprotektīvo aizsardzību un palielinot iespēju, ka KYN tiek pārvirzīts uz alternatīviem ceļiem, piemēram, 3-HK vai kvinolīnskābes ražošanu. Abiem šiem metabolītiem ir prooksidatīva un proapoptotiska iedarbība, un tie spēj šķērssaistīt kristalīnus, destabilizējot to struktūru un veicinot opacitāti.

Interesanti, lai gan citi kinurenīna ceļa enzīmi, piemēram, kinurenīna monooksigenāze, šķiet mazāk mainīgi dažādās kataraktas stadijās, tieši KAT izrāda visizteiktāko aktivitātes gradientu. Tas norāda uz KAT īpašo jutīgumu pret mikrovides izmaiņām, padarot to par potenciālu indikatoru metaboliskajām pārmaiņām kataraktas progresijā.

Tādējādi KAT var tikt uzskatīts ne tikai par potenciālu biomarkieri, bet arī par mērķa punktu terapeitiskām iejaukšanās stratēģijām. Agrīnā slimības stadijā iespējams apsvērt piridoksāla 5-fosfāta papildināšanu vai KYNA analogus kā līdzekļus, kas pastiprina šūnas aizsardzību pret fotooksidatīvu bojājumu. Vēlīnākās stadijās būtu lietderīgi attīstīt pieejas, kas samazina 3-HK uzkrāšanos vai neitralizē to radītās sekas, piemēram, inhibējot kaspāzes aktivāciju vai veicinot kristalīnu stabilizāciju.

Metaboloma atšķirības pacientiem ar dažādām oftalmoloģijas patoloģijām

Izmaiņas pacientiem ar PEXS

Mūsu pētījuma rezultāti norāda, ka PEXS ir saistīts ar izteiktiem vielmaiņas traucējumiem, kas veicina šūnu bojāeju ferroptozes mehānismā – dzelzs atkarīgā, regulētā šūnu nāves formā, ko raksturo lipīdu peroksidācija un oksidatīvā stresa inducēta šūnu disfunkcija. (Chen et al., 2021). Identificētie metaboliskie profili, tostarp paaugstināts cisteīna un citrulīna līmenis, kā arī izmaiņas ubikvinona metabolismā, liecina par antioksidatīvās aizsardzības sistēmu vājināšanos, īpaši attiecībā uz glutamīna–cisteīna antiportera (sistēma Xc^-) funkcionalitātes traucējumiem (de Baat et al., 2023). Šie novērojumi uzsver, ka PEXS nav reducējams vienīgi uz priekšējā segmenta morfoloģiskām izmaiņām, bet drīzāk atspoguļo sistēmiskus šūnu vielmaiņas un redokslīdzsvara traucējumus, kas var būt būtiski slimības patoģenēzes dziļākai izpratnei un potenciāli jaunu terapijas stratēģiju izstrādei (Scharfenberg & Schlötzer-Schrehardt, 2012).

Šie atklājumi būtiski paplašina līdzšinējo izpratni par PEXS patofizioloģiju, piedāvājot konceptuāli jaunu skatījumu uz slimības izcelsmi – ne tikai kā lokālu fibrilārā materiāla uzkrāšanās procesu, bet arī kā sistēmiski regulētu vielmaiņas disfunkciju ar potenciāli destruktīvām sekām redzes funkcijai (Zenkel & Schlötzer-Schrehardt, 2014). Turklāt pētījumā identificētie metaboliskie biomarkieri, kas iesaistīti ferroptozes mehānismos un oksidatīvā stresa ceļos, var būt nozīmīgs pamats jaunu terapeitisku stratēģiju izstrādei. Mērķtiecīga šo metabolisma ceļu modulācija nākotnē varētu veicināt metabolomikā balstītas, personalizētas pieejas izstrādi PEXS pacientu ārstēšanā, potenciāli samazinot intraoperatīvo komplikāciju risku kataraktas ķirurģijas laikā.

Izmaiņas pacientiem ar glaukomu

Mūsu pētījums identificēja vairākus metabolītus, kas var būt iesaistīti glaukomas patoģenēzē. Glaukomas pacientu grupā tika konstatēta būtiska triptofāna, fenilalanīna, tirozīna, leicīna un glutamīna koncentrācijas palielināšanās, kas norāda uz traucējumiem aromātisko aminoskābju metabolismā (Lynch & Dudareva, 2020). Šīs izmaiņas varētu būt saistītas ar aromātisko aminoskābju hidroksilāžu aktivitātes samazināšanos, kuru darbība ir atkarīga no tetrahidrobiopterīna (BH₄) – būtiska kofaktora dažādos enzīmu procesos, tostarp slāpekļa oksīda (NO) sintēzē (Kim & Han, 2020). BH₄ deficīts var rasties oksidatīvā stresa apstākļos, kā arī nepietiekamas BH₄ biosintēzes, atjaunošanās traucējumu vai metilēntetrahidrofolāta reduktāzes gēna polimorfismu rezultātā (Raghubeer & Matsha, 2021). Šādi vielmaiņas traucējumi var veicināt intraokulārā spiediena palielināšanos NO biodisponibilitātes samazināšanās dēļ (Aliancy et al., 2017), kā arī sekmēt glaukomi raksturīgos neirodeģeneratīvos procesus (Lionaki et al., 2022).

Identificētie metaboliskie traucējumi norāda, ka glaukomas attīstībā būtiska loma varētu būt ne tikai paaugstinātam intraokulārajam spiedienam, bet arī sistēmiskiem šūnu metabolismu ietekmējošiem faktoriem, tostarp redokslīdzsvara traucējumiem un aminoskābju vielmaiņas disbalansam (Wang et al., 2021). Paaugstināts glutamīna un leicīna līmenis var liecināt par šūnu mēģinājumiem aktivēt neiroprotektīvus kompensācijas mehānismus, mazinot eksitotoksisko bojājumu ietekmi (Lotery, 2005). Šie dati papildina izpratni par glaukomu kā multifaktoriālu, vielmaiņas procesus modulētu neirodeģeneratīvu slimību, kur nozīmīga loma varētu būt arī biopterīna ceļa regulācijai (Eichwald et al., 2023). Tādējādi turpmāki pētījumi šajā jomā varētu veicināt jaunu metabolisma biomarkieru identifikāciju un pamatot antioksidantu vai metaboliski mērķētu terapiju izmantošanu glaukomas profilaksē un ārstēšanā.

Izmaiņas pacientiem ar cukura diabētu

Mūsu pētījumā tika identificētas būtiskas metaboliskas atšķirības intraokulārajā šķidrumā starp pacientiem ar un bez cukura diabēta, kuriem tika veikta kataraktas ekstrakcijas operācija. Diabēta pacientu grupā tika konstatēta ievērojami paaugstināta 3-HK, histamīna un oktanoilkarboksīta koncentrācija, kā arī samazināts putrescīna līmenis, kas kopumā liecina par traucētu triptofāna metabolismu, pastiprinātu oksidatīvo stresu un iespējamu iekaisuma aktivitāti acs priekšējā segmentā. Metabolisko ceļu bagātināšanas analīze īpaši uzsvēra kinurenīna ceļa aktivāciju, kas saskan ar pieaugošajiem pierādījumiem par šī ceļa iesaisti diabēta inducētajos oksidatīvajos un neirodeģeneratīvajos bojājumos (Kozielec & Urbanska, 2023).

Iegūtie rezultāti apstiprina, ka diabēta izraisītie patofizioloģiskie procesi acs priekšējā segmentā atspoguļojas arī metaboliskajā profilā, kas sniedz papildu pierādījumus par sistēmisku vielmaiņas disregulāciju šiem pacientiem (Dolar-Szczasny et al., 2024). Identificētie metabolīti

var kalpot kā potenciāli biomarkieri ar iespējamu diagnostisku vai prognostisku nozīmi, īpaši diabētiskās retinopātijas attīstības vai progresēšanas kontekstā (Ma et al., 2024). Tomēr, ņemot vērā korekciju par daudzkārtēju testēšanu un augstāku kļūdas līmeni, rezultāti interpretējami piesardzīgi un uzskatāmi par hipotēzes ģenerējošiem, kam nepieciešams apstiprinājums neatkarīgos kohortas pētījumos.

Secinājumi

1. Pacienti ar augstākas pakāpes lēcas cietību konstatējamas statistiski nozīmīgas intraokulārā šķidruma metaboloma atšķirības, īpaši antioksidantu sistēmās, aminoskābju metabolismā un kinurenīna ceļā. Šie rezultāti apstiprina hipotēzi par specifiska metabolītu profila klātbūtni atkarībā no kataraktas attīstības pakāpes.
2. Priekšējās kameras dziļums un tilpums mūsu pētījumā neuzrādīja statistiski nozīmīgu saistību ar lēcas cietības pakāpi, tādēļ hipotēze par lielāku ACD un ACV kā kataraktas progresijas paātrinātāju netika apstiprināta.
3. Pacienti ar PEXS identificētas gan izteiktas biometriskas, gan metaboliskas izmaiņas: samazināts ACD, ACV un acs garums, kā arī metaboloma profils, kas atspoguļo ferroptozes mehānismu aktivāciju un antioksidatīvās aizsardzības pavājināšanos. Šie rezultāti norāda, ka PEXS ir ne tikai strukturāla, bet arī sistēmiska vielmaiņas deregulācijas slimība.
4. Glaukomas pacientiem tika identificētas būtiskas metabolītiskās izmaiņas, tostarp triptofāna, fenilalanīna, tirozīna, leicīna un glutamīna pieaugums, kas norāda uz traucētu aromātisko aminoskābju metabolismu un iespējamu BH₄ deficītu. Tas papildina izpratni par glaukomu kā multifaktoriālu vielmaiņas un neurodeģeneratīvu slimību.
5. Cukura diabēta pacientiem konstatētas būtiskas intraokulārā šķidruma metaboloma izmaiņas, tostarp 3-HK, histamīna un oktanoilkarboksīta pieaugums un putrescīna samazinājums. Šīs izmaiņas atspoguļo kinurenīna ceļa aktivāciju, oksidatīvo stresu un iekaisuma procesus priekšējā segmentā un var kalpot par potenciāliem biomarkšiem diabētiski saistīto acu komplikāciju ārstēšanai.

Teorētiskās atziņas par kataraktas vielmaiņas mehānismiem

1. Novecošanās un redokslīdzsvara izmaiņas

Novecošanās gaitā organismā pakāpeniski rodas redokslīdzsvara traucējumi, jo ROS ražošana pārsniedz antioksidantu aizsardzības kapacitāti, kas veicina oksidatīvo stresu gan acs lēcā, gan citos audos.

2. Glutathiona loma kataraktas patoģenēzē

GSH sistēma lēcas epitelija šūnās ir primārais oksidatīvā stresa neitralizators. Samazinoties GSH rezervēm, lēcas proteīni kļūst jutīgāki pret lipīdu peroksidāciju un citām oksidatīvām modifikācijām, veicinot kristalīnu denaturāciju un lēcas opacitātes palielināšanos.

3. Taurīna aizsargfunkcija

Taurīns darbojas kā papildu antioksidants un osmoregulators, uzturot šūnu redokslīdzsvaru. Pietiekams taurīna līmenis palīdz optimizēt GSH izmantošanu aizsardzībā pret ROS un kavē agrīno kataraktas patoģenētisko mehānismu attīstību.

4. Kinurenīna ceļa aktivācija GSH deficīta apstākļos

GSH rezerves izsīkuma gadījumā šūnas aktivizē alternatīvus antioksidatīvus mehānismus, tostarp triptofāna metabolisma kinurenīna ceļu. Šajā ceļā paaugstināta IDO un KAT aktivitāte veicina KYNA ražošanu.

5. Toksisko starpproduktu – 3-HK – uzkrāšanās

Nepietiekama kofaktoru, piemēram, vitamīna B6, pieejamība ierobežo kinurenīna ceļa metabolītu pareizu pārveidi, izraisot prooksidatīvu un fototoksisku 3-HK akumulāciju. Šie toksiskie starpprodukti veicina proteīnu karbonilāciju, apoptozi un papildu ROS ražošanu, radot apburto loku, kas paātrina lēcas apduļķošanu.

6. Cilvēka lēcas caurspīdīguma saglabāšanas stratēģijas

Lai kavētu kataraktas progresiju, nepieciešama integrēta pieeja, kas ietver:

- GSH rezervju atjaunošanu (piemēram, GSH prekursoru papildināšanu),
- taurīna līmeņa uzturēšanu optimālā diapazonā,
- kinurenīna ceļa aktivitātes modulāciju, izmantojot IDO vai KAT inhibitorus, kā arī kofaktoru atjaunošanas terapiju.

Kataraktas patoģenēze ir cieši saistīta ar vielmaiņas un redoksbalansa disfunkcijām, kurās būtiskākais ir GSH deficīts un toksisko kinurenīna ceļa starpproduktu uzkrāšanās. Šie mehānismi ne tikai veicina oksidatīvo stresu un proteīnu agregāciju, bet arī ietekmē NAD^+ homeostāzi un traucē šūnu enerģijas metabolismu, īpaši anaerobos apstākļos lēcas kodolā. Mērķētas metabolisma terapijas izstrāde, kas vienlaikus atjauno antioksidatīvās rezerves sistēmas (piemēram, ar GSH un taurīna papildināšanu) un kavē toksisko starpproduktu veidošanos kinurenīna vai citu šūnas stresa ceļu aktivācijas laikā, varētu būt efektīvs līdzeklis kataraktas profilaksei un slimības progresēšanas palēnināšanai.

Priekšlikumi

Turpmākai attīstībai ieteicams vērst uzmanību uz dziļāku intraokulārā šķidruma metabolikas izpēti, integrējot plašākas metabolītu un lipīdu analīzes. Šāda multidisciplināra pieeja ļautu identificēt jaunus biomarkierus, kas saistīti ar kataraktas progresiju, īpaši agresīvākām vai straujāk progresējošām slimības formām. Metabolisko izmaiņu raksturošana varētu palīdzēt labāk saprast redoksbalansa traucējumus, kristalīnu agregācijas mehānismus un šūnu bojājuma attīstību dažādās kataraktas stadijās.

Īpaša uzmanība būtu jāpievērš kinurenīna ceļa un NAD⁺ metabolismam lēcas audos. Turpmākie pētījumi varētu fokusēties uz toksisko kinurenīna ceļa starpproduktu uzkrāšanās saistību ar kristalīnu strukturālajām izmaiņām, proteīnu agregāciju un šūnu nāves mehānismiem. Vienlaikus būtu nozīmīgi analizēt NAD⁺ pieejamību un tās saistību ar enerģētiskās homeostāzes saglabāšanu, ņemot vērā, ka NAD⁺ izsīkšana var sekmēt redoksbalansa zudumu un LEC uzņemību pret oksidatīviem bojājumiem.

Eksperimentālā līmenī nākotnes pētījumos būtu lietderīgi pārbaudīt metabolītiski mērķētu terapiju efektivitāti, piemēram, taurīna un GSH donoru kombinēto lietojumu, kā arī NAD⁺ prekursoru papildināšanu. Šādas terapijas stratēģijas potenciāli varētu kavēt kataraktas progresiju, atjaunojot antioksidatīvās rezervju sistēmas un ierobežojot toksisko starpproduktu uzkrāšanos. Turklāt būtu nozīmīgi izvērtēt šādu intervenciju efektivitāti dažādās kataraktas stadijās, lai noteiktu optimālu profilaktisku vai ārstniecisku pieeju.

Klīniskā līmenī perspektīvā ir integrēt intraokulārā šķidruma metabolītu profilus kā papildu biomarkierus agrīnai slimības diagnostikai un personalizētai ķirurģijas plānošanai. Īpaši nozīmīgi tas varētu būt pacientiem ar PEXS vai citiem priekšējā segmenta nestabilitātes riska faktoriem, kur savlaicīga riska stratifikācija var samazināt intraoperatīvo komplikāciju iespējamību. Vienlaikus precīzāka ACV un ACD novērtēšana un validētās aprēķinu formulas izmantošana sniedz iespēju paplašināt riska izvērtēšanas un ķirurģiskās taktikas plānošanas iespējas.

Turklāt iegūtie rezultāti un nākotnes pētījumi potenciāli sniedz plašāku ieguldījumu ne tikai oftalmoloģijā, bet arī citu proteīnu agregācijas slimību, piemēram, Alcheimera un Parkinsona slimības, izpratnē. Šīm slimībām raksturīgi līdzīgi pamatmehānismi – oksidatīvais stress, NAD⁺ izsīkšana, mitohondriju disfunkcija un proteīnu strukturālās izmaiņas. Multidisciplināra pieeja, kas apvieno metabolomiku, bioķīmiju un klīnisko praksi, var pavērt ceļu uz personalizētām un mērķētām stratēģijām kataraktas profilaksē un ārstēšanā, vienlaikus paplašinot izpratni par neirodeģeneratīvu un proteīnu agregācijas slimību, saistītu ar vecumu, mehānismiem.

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Ziņojumi un tēzes:

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 Cornea 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/Kynurenine 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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Pateicības

Ar patiesu cieņu un sirsnību vēlos izteikt pateicību visiem kolēģiem, kuri ar savu darbu, atbalstu un zināšanām palīdzēja šī pētījuma tapšanā. Vislielākais paldies ārstiem un medicīnas personālam, kas ar pacietību un profesionalitāti palīdzēja intraokulārā šķidruma paraugu iegūšanā, – bez jūsu precizitātes, rūpības un atsaucības šis pētījums nebūtu iespējams. Īpašu pateicību vēlos izteikt doc. Vanagam, dr. Jurjānei, dr. Markevičai un dr. Kursītei par aktīvu iesaisti acs priekšējās kameras šķidruma iegūšanā, rūpību biometrisku mērījumu veikšanā un dokumentēšanā, kā arī operācijas zāles medmāsām par nenovērtējamo atbalstu un ieguldīto darbu.

No sirds pateicos maniem darba vadītājiem prof. Laganovskai un doc. Vanagam, kā arī zinātniskajam konsultantam asoc. prof. Kļaviņam par viņu neatlaidību, nemainīgo ticību mūsu pētījuma mērķiem un nenovērtējamo atbalstu visa doktorantūras procesa laikā.

Īpaši pateicos dr. Lavrinovičai un dr. Rizzuto par ilgu un rūpīgu darbu biometrisku datu iegūšanā, kā arī par nenovērtējamu palīdzību zinātniskās literatūras apskatā – jūsu ieguldījums būtiski veicināja pētījuma kvalitāti un padziļināja analītisko un teorētisko pamatu.

Jūsu iedvesmojošais piemērs, vērtīgie padomi un nemainīgā ticība manām spējām sniedza spēku un motivāciju arī tajos brīžos, kad darbs šķita sarežģīts un izaicinājumiem pilns. Jūsu klātbūtne ne tikai vadīja akadēmisko procesu, bet arī stiprināja cilvēcīgi, par ko esmu patiesi pateicīgs.

Šī darba tapšana ir kopīgs sasniegums, kas balstās uz sadarbību, uzticēšanos un kopīgu vēlmi virzīt zinātni uz priekšu. Paldies jums visiem, kas bijāt līdzās šajā procesā.

Pielikumi

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Metabolomic Disparities in Intraocular Fluid Across Varied Stages of Cataract Progression: Implications for the Analysis of Cataract Development

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Abstract

Introduction: The lens's metabolic demands are met through a continuous circulation of aqueous humor, encompassing a spectrum of components such as organic and inorganic ions, carbohydrates, glutathione, urea, amino acids, proteins, oxygen, carbon dioxide, and water. Metabolomics is a pivotal tool, offering an initial insight into the complexities of integrated metabolism. In this investigative study, we systematically scrutinize the composition of intraocular fluid in individuals afflicted with cataracts.

Methods: The investigation involved a comprehensive analysis of aqueous humor samples from a cohort comprising 192 patients. These individuals were stratified by utilizing the SPONCS classification system, delineating distinct groups characterized by the hardness of cataracts. The analytical approach employed targeted quantitative metabolite analysis using HILIC-based liquid chromatography coupled with high-resolution mass spectrometric detection. The metabolomics data analysis was performed with MetaboAnalyst 5.0.

Results: The results of the enrichment analysis have facilitated the inference that the discerned disparities among groups arise from disruptions in taurine and hypotaurine metabolism, variations in tryptophan metabolism, and modifications in mitochondrial beta-oxidation of short-chain saturated fatty acids and pyrimidine metabolism.

Conclusion: A decline in taurine concentration precipitates diminished glutathione activity, prompting an elevated requirement for NAD⁺ and instigating tryptophan metabolism along the kynurenine pathway. Activation of this pathway is additionally prompted by interferon-gamma and UV radiation, leading to the induction of IDO. Concurrently, heightened mitochondrial beta-oxidation signifies a distinctive scenario in translocating fatty acids into the mitochondria, enhancing energy production.

Keywords: cataract, metabolomics, taurine, IDO, NAD⁺, tryptophan, mitochondrial beta-oxidation

Introduction

Approximately 95 million individuals across the globe are afflicted by cataracts.¹ The prevalence and absolute numerical count of individuals affected by blindness attributed

to cataracts persist at elevated levels, notwithstanding a decreasing trend in incidence observed across various geographical regions worldwide.² The exclusive remedial approach for cataracts is surgical intervention, making it one of the most prevalent surgical procedures globally.³ Comprehending the

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structural underpinnings of protein stability and interactions within the unimpaired ocular lens constitutes the pivotal path toward addressing the substantial medical and economic challenges of cataracts.⁴

The lens is an intricately structured, transparent optical syncytial tissue whose primary function is to converge incoming light onto the retinal surface. Its transparency is a consequence of the composition of its constituent fiber cells, which consist of densely concentrated proteins.⁵ A monolayer of epithelial cells is located in immediate proximity to the anterior lens capsule. These cells exhibit heightened metabolic activity and engage in the full spectrum of typical cellular functions, encompassing DNA, RNA, protein, and lipid biosynthesis. The mammalian lens is composed of three distinct categories of crystallin proteins, namely alpha (α), beta (β), and gamma (γ), each composed of several subunits.⁶

The lens is characterized by the absence of both vascularization and innervation. The lens has developed an internal ion circulation mechanism intricately linked to fluid motion, establishing an internal microcirculatory system. This adaptation compensates for the absence of vascularization within the lens.⁷ Consequently, the metabolic requirements of the lens are sustained through a continuous circulation of aqueous humor, which functions as a medium for eliminating metabolic waste products and transporting essential nutrients.⁸

The aqueous humor is produced by the ciliary epithelium through the active transport of solutes, primarily sodium chloride, from the stroma to the posterior chamber of the eye, with the passive movement of water accompanying this process.⁹ Aqueous humor formation involves three distinct mechanisms: diffusion, ultrafiltration, and active secretion.⁸ The energy needed for active transport is generated by the hydrolysis of adenosine triphosphate to adenosine diphosphate.¹⁰ This process is facilitated by the enzyme Na-K-ATPase, which is present in both pigmented and nonpigmented ciliary epithelial cells. Of notable pharmacological significance, Na-K-ATPase can be inhibited by various molecules, including cardiac glycosides, dinitrophenol, and acetazolamide.¹¹ The primary constituents of the aqueous humor include organic and inorganic ions, carbohydrates, *glutathione*, urea, *amino acids*, proteins, oxygen, carbon dioxide, and water.¹²

While metabolic diseases are frequently associated with their characteristic metabolites (such as diabetes with glucose and cardiovascular disease with cholesterol), it is essential to recognize that biochemical pathways do not operate in isolation; instead, they are interconnected and influence each other.¹³ Advancements in analytical technologies have reached a stage where most known endogenous metabolites can be quantified using one of several existing analytical platforms.¹⁴ These technologies are integral to the swiftly evolving field of metabolomics, offering researchers an initial glimpse into the intricacies of integrated metabolism and, consequently, the profound impact of integrated metabolism on human health. To elucidate deviations in the levels of specific metabolites from the normal range and, more significantly, to forecast how to modify inputs, such as diet, drugs, and lifestyle, to achieve a desired metabolic alteration, an in-depth understanding of the functionality of pathways and their associated reactions is imperative.¹⁵

Metabolomics leverages advanced analytical chemistry methodologies to facilitate the high-throughput characterization of metabolites from cells, organs, tissues, or biofluids.¹⁶ The rapid expansion of metabolomics research has spurred a

renewed fascination with metabolism and the pivotal roles that small-molecule metabolites assume in many biological processes. Consequently, conventional perspectives regarding metabolites, previously regarded as mere constituents of cellular structure or as cellular energy sources, are undergoing a profound transformation. Indeed, metabolites are increasingly recognized for their diverse and pivotal functions as signaling molecules, immune system regulators, endogenous toxins, and sensors responsive to environmental cues.¹⁷

Not only are alterations in metabolism observable but also the tools to interpret these changes within the context of specific metabolic pathways are readily available. This is primarily because understanding biochemical pathways has been a central research objective in the life sciences for well over a century.¹⁵

Methods

Study design

The investigation entailed the examination of aqueous humor specimens derived from a cohort comprising 192 patients who underwent cataract surgery at Pauls Stradins Clinical University Hospital. These patients were categorized into two groups based on the SPONCS¹⁸ classification system, which differentiated between individuals with hard and softer cataracts. Patients with softer cataracts were categorized within stages 1 to 3, encompassing subcapsular cataracts with a clear nucleus, mild hardness, and moderate hardness. In contrast, harder cataracts were classified within stages 4–5, including advanced hardness and hypermature/Morgagnian cataracts. According to this approach, the study groups were categorized into 130 cases with soft cataracts and 62 with hard cataracts. Among the chosen participants, 70 were men, while 122 were women. The average age of individuals diagnosed with cataracts was 73.7 years, with a standard deviation of ± 9.29 . The age range varied from a minimum of 50 years to a maximum of 94 years. It is noteworthy that patients with concomitant ocular pathologies, such as glaucoma, age-related macular degeneration, or diabetes, were not excluded from the study (Table 1).

TABLE 1. SUMMARY OF DEMOGRAPHICS AND OPHTHALMIC COMORBIDITIES AMONG PATIENTS INCLUDED IN THE STUDY

Variable	Soft (n = 130)	Hard (n = 62)	P value
Age, mean (SD)	73.7 $\pm$ 9.13	73.8 $\pm$ 9.70	0.935
Gender			0.293
Male	44 (22.9%)	26 (13.5%)	
Female	86 (44.8%)	36 (18.8%)	
Glaucoma			0.01
Present	37 (19.3%)	7 (3.6%)	
Absent	93 (48.4%)	55 (28.6%)	
Pseudocystfoliation syndrome			0.352
Present	57 (29.7%)	23 (12.0%)	
Absent	73 (38.0%)	39 (20.3%)	
Diabetes			0.573
Present	34 (17.7%)	14 (7.3%)	
Absent	96 (50.0%)	48 (25%)	

The *t*-test was used for comparing age distributions, while the chi-squared test was employed for analyzing associations among categorical variables.

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Before the commencement of the surgical procedure, a paracentesis was performed, followed by a biopsy of the aqueous humor employing a 27G needle. Depending on the quantity of available fluid, between 50 and 120 μL of aqueous humor were aspirated and subsequently transferred to Eppendorf tubes. These samples were then promptly frozen and transported to the Faculty of Materials Science and Applied Chemistry of Riga Technical University for storage and subsequent analysis.

The research conducted adhered to the Declaration of Helsinki. Notably, the study's ethical considerations underwent meticulous scrutiny and obtained approval from the Medical Ethics Committee of Rigas Stradins University, as indicated by decision number 2-PEK-4/307/2023. Furthermore, the study received the necessary approval from the Pauls Stradins Clinical University Hospital.

Metabolite analysis

Metabolites were extracted using a methanol-based extraction protocol. Around 10 μL of the aqueous humor sample was transferred to an empty Eppendorf tube and mixed with 80 μL methanol and 10 μL isotopically labeled internal standard. Each sample was vortexed for 15 s and then centrifuged for 10 min at 10,000 RPM. The supernatant was transferred into an HPLC glass vial.

Targeted quantitative metabolite analysis was conducted using HILIC-based liquid chromatography combined with mass spectrometric detection employing a Thermo Orbitrap Exploris 120 mass spectrometer. An ACQUITY UPLC BEH Amide 1.7 μm 2.1 $\times$ 100 mm analytical column (Waters) was employed for chromatographic separation. The gradient elution was carried out using 0.15% formic acid and 10 mM ammonium formate in water as mobile phase A and a solution of 0.15% formic acid and 10 mM ammonium formate in 85% acetonitrile as mobile phase B. The initial conditions were set to 100% in mobile phase B. After 6 min, a 0.1 min gradient (6.0–6.1 min) was started, and the mobile phase B level was reduced to 94.1%. From 6.1 to 10 min, mobile phase B was set to 82.4%, and from 10 to 12 min mobile phase B was set to 70.6%. The column was then equilibrated for 6 min at initial conditions. The total analysis time was 18 min. The mobile phase flow rate was 0.4 mL/min, the injection volume was 2 μL , and the column temperature was 40°C. For MS detection, an Orbitrap Exploris 120 (Thermo Fisher Scientific) mass spectrometer was used. The MS analysis was performed in ESI positive and ESI negative modes using full scan detection; the scan range was set from 50 to 600 m/z , and the mass resolution was set to 60,000. The ESI spray voltage was set to 3.5 kV in positive mode and 2.5 kV in negative mode; the gas heater temperature was set to 400°C; the capillary temperature was set to 350°C; the auxiliary gas flow rate was set to 12 arbitrary units; and the nebulizing gas flow rate was set to 50 arbitrary units. For quantitative analysis, seven-point calibration curves with internal standardization were used. Tracefinder 51.1 General Quan (Thermo Fisher Scientific) software was used for LC-MS data processing and quantification. Every reported metabolite was identified at level A¹⁹ by using an authentic standard compound previously mapped to the analytical system. Detailed information about metabolite identification (RT, m/z , HMDB IDs) is provided in the Supplementary Table S1.

Metabolite data analysis

The metabolomics data analysis was performed with MetaboAnalyst 5.0.²⁰ Data normalization was implemented to ensure that metabolites of different magnitudes were reasonably analyzed. Specifically, the metabolite levels with different ranges were normalized by the median with a log (base 10) transformation. The metabolite levels were scaled by mean-centering and divided by the square root of the standard deviation of each variable. The statistical analysis was conducted with the normalized concentrations of each metabolite. The two-group comparison data were analyzed by an unpaired *t*-test using parametric tests. A one-way analysis of variance (ANOVA) followed by a Tukey's comparison was used for statistical analysis. Enrichment analysis was applied based on SMPDB (the Small Molecule Pathway Database).

Results

The outcomes of the enrichment analysis have enabled us to infer that the observed distinctions among groups emanate from perturbations in taurine and hypotaurine metabolism, alterations in tryptophan metabolism, and mitochondrial β -oxidation of short-chain saturated fatty acids.

By employing a targeted metabolomics approach, more than 100 metabolites were measured, with 54 of these compounds identified in the aqueous humor samples shown in Figure 1A. Noteworthy constituents encompassed amino acids, organic acids, acylcarnitines, nucleotides, and glucose. A discernible disparity in metabolite profiles was noted between soft and hard cataracts. Amino acids within aqueous humor samples obtained from individuals with hard cataracts exhibited reduced levels compared with those observed in the soft cataract cohorts. Conversely, constituents of the carnitine family, particularly octanoyl-carnitine, demonstrated heightened concentrations, as shown in Figure 1B. Notably, amino-n-butyric acid displayed a notable increase in concentration in hard cataracts (5.08 μM) relative to soft cataracts (1.01 μM), yielding a fold change of 7.82 and a highly significant *p*-value ($P = 0.0003$). Similarly, kynurenine and members of the carnitine family shown in Figure 1C, including octanoylcarnitine and butyrylcarnitine, exhibited significant elevations in hard cataracts, with *P*-values of 0.0036 and 0.0066, respectively. The fold change for octanoylcarnitine was particularly pronounced at 29.21, indicative of a substantial metabolic alteration associated with cataract hardness. Although the fold change for tryptophan was modest (FC = 0.40), its levels still manifested a statistically significant difference ($P = 0.0456$), albeit with a smaller effect size.

Pathway enrichment analysis, a computational technique in molecular biology, was applied to discern the most significantly altered metabolic pathways. This method identifies biological functions overrepresented in a group of metabolites, surpassing what would be expected by chance alone. The subsequent ranking of these functions is based on their relevance within the analyzed metabolite set. The outcome of the pathway enrichment analysis unveiled notable impacts on taurine metabolism, fatty acid β -oxidation, and pyrimidine metabolism, as shown in Figure 1D.

One hit (taurine) out of 14 compounds was identified in the context of taurine and hypotaurine metabolism. For mitochondrial β -oxidation of short-chain saturated fatty acids, two hits (carnitine and octanoylcarnitine) were detected out of

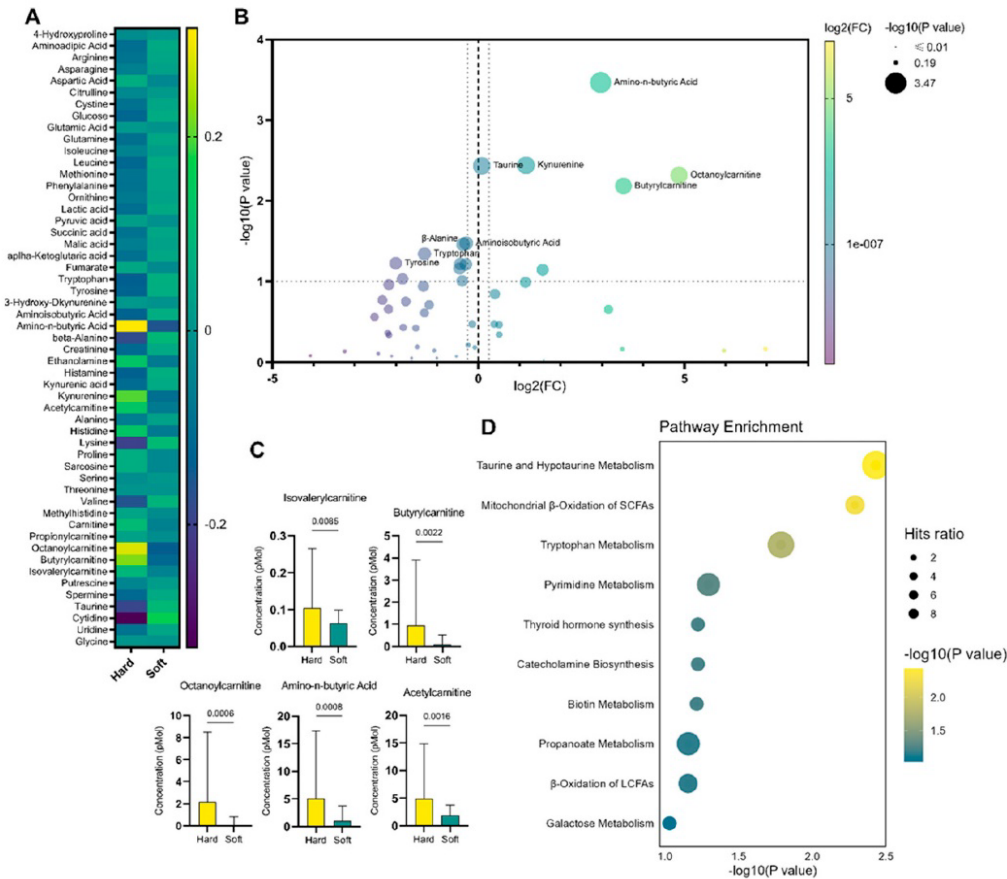


FIG. 1. Metabolomic analysis of differences between aqueous humor samples from soft and hard cataracts. **(A)** Heatmap depicting the relative changes of all quantified metabolites. **(B)** Volcano plots showing fold changes (FC) and p -values between hard and soft cataracts. The cutoff values for FC were 1.2 and -1.2, for a p -value of 0.05. **(C)** Metabolite concentrations of the most significantly changed metabolites in the hard and soft cataract groups. **(D)** In pathway enrichment analysis, the hit ratio is computed by dividing observed hits by expected hits.

27 total compounds. Five hits shown in Figure 2A were identified out of 59 compounds in tryptophan metabolism. These results further contribute to understanding the nuanced alterations in metabolic pathways associated with the observed distinctions between hard and soft cataracts.

In the tryptophan metabolism pathway, an oxoglutaric acid gains an amino group from kynurenine to form a glutamic acid,

as shown in Figure 2B. The lower level of kynurenine may result in a lower level of glutamic acid in the soft cataract group.

Discussion

Osmolytes constitute a category of low-molecular-weight organic compounds that notably influence the characteristics

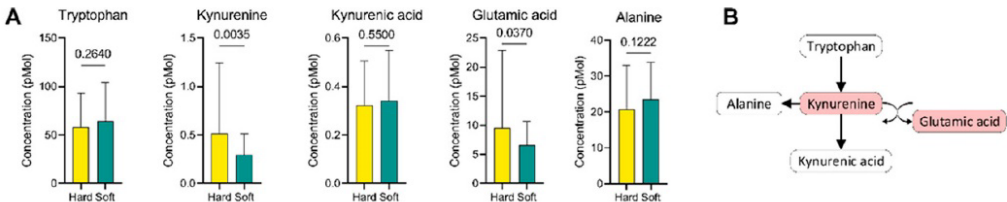


FIG. 2. Tryptophan metabolism pathway alteration. **(A)** The concentrations of metabolites involved in tryptophan metabolism in hard and soft cataract aqueous humor samples. **(B)** Metabolites that were detected from the tryptophan metabolism pathway. Kynurenine and glutamic acid are significantly downregulated in the soft cataract group.

of biological fluids. This class of organic molecules is crucial in modulating osmotic pressure and upholding cellular homeostasis across diverse organisms, particularly in response to environmental stressors.²¹ Osmolytes also play a role in impeding the accumulation of reactive oxygen species (ROS), mitigating DNA and RNA damage, and inhibiting transcription processes. Numerous osmolytes, including sugars, amino acids, and polyols, enhance protein stability by facilitating their compaction into native structures. This mechanism rescues defective proteins, averting intracellular toxicity.²²

Taurine, a pivotal organic osmolyte within mammalian cells, undergoes notable dynamics in response to osmotic cell swelling.²³ Specifically, there is an augmentation in taurine release facilitated through a volume-sensitive taurine efflux pathway, concomitant with a reduction in active taurine uptake mediated by the taurine-specific transporter TauT. The intricacies of cellular signaling cascades, the profile of second messengers, the activation patterns of specific transporters, and the subsequent temporal dynamics governing the readjustment of osmolyte content and cellular volume exhibit considerable variability across distinct cell types.²⁴

Taurine manifests diverse physiological functions, encompassing conjugation with bile acids, osmoregulation, antioxidant, facilitation of neuronal development, and membrane stabilization.²⁵ The antioxidative efficacy of taurine hinges on its ability to mitigate mitochondrial oxidative stress.²⁶ When examining the clinical complications associated with diabetes, a nexus becomes apparent between perturbed taurine metabolism and the onset of cellular dysfunctions. These dysfunctions contribute significantly to the clinical complications observed in diabetes.²⁷

Numerous investigations have been conducted to elucidate the beneficial ramifications of taurine supplementation and its facilitation of intricate physiological processes. Taurine is observed to exert a stimulatory effect on both protein synthesis and the proliferation of C₂C₁₂ myoblast cells, a phenomenon mediated through the PI3K-ARID4B-mTOR pathway. This delineation provides a nuanced comprehension of the regulatory mechanisms by which taurine modulates anabolic processes within muscle cells.²⁸ Taurine demonstrates inhibitory effects on methamphetamine-induced autophagic processes by activating mTOR. In the context of METH-induced damage to PC12 cells, taurine protects against ROS production, apoptosis, and autophagy. This protective effect is, at least in part, mediated through the mTOR signaling pathway.²⁹ The attenuation of acrylamide-induced apoptosis *in vivo* by taurine through a PI3K/AKT-dependent pathway offers novel insights into the molecular mechanisms underlying taurine was observed to diminish phosphorylation levels of ERK1/2 without affecting the phosphorylation of adenosine monophosphate-activated protein kinase or ribosomal protein S6 kinase associated with the MTORC1 pathway. These findings imply that taurine may facilitate the nuclear translocation of transcription factor EB through ERK1/2 activation, thereby expediting the autophagic process.³⁰

The central significance of glutathione (GSH) within the crystalline lens is underscored by its pivotal role as an antioxidant, protecting against the oxidation of lens proteins.³¹ Noteworthy is the observed progressive reduction in GSH levels within normal lenses as age advances, diminishing from approximately 5 μmol per gram of lens to 3 μmol per gram of lens.³² The lens epithelium and outer cortex are believed to

play a crucial role in furnishing the predominant share of lens GSH through *de novo* synthesis, facilitated by a continuous influx of constituent amino acids from the aqueous humor. GSH is a tripeptide composed of cysteine, glutamate, and glycine.³³ In addition, extracellular GSH recycling from the gamma-glutamyl cycle contributes to this GSH pool. However, under impaired *de novo* synthesis conditions, such as in the aging human lens with reduced GSH levels, compensatory mechanisms come into play, indicating the lens's capacity to uptake GSH from the adjacent ocular tissues.³⁴ A deficiency in GSH elicits an AMPK (AMP-activated protein kinase)-independent induction of autophagy in germ cells, functioning as an adaptive stress response.³⁵ The depletion of GSH initiates a cascade of events that may ultimately culminate in cellular demise.³⁶ Taurine facilitates the uptake of GSH in lens epithelial cells.³⁷

Age-related nuclear cataract is associated with a decline in GSH levels, specifically within the central region of the lens.³⁸ Taurine, a vital antioxidant in lens tissue, experiences a reduction in concentration as individuals age, notwithstanding its initial abundance in lenses during early life. The depletion of GSH and the dietary supplementation of taurine emerge as potentially significant factors in impeding the progression of cataract formation.³⁹ Epidemiological data indicate an association between elevated levels of taurine and a reduced incidence of specific types of cataracts.⁴⁰ Mechanistically, taurine demonstrates a multifaceted impact on cellular processes, including the reduction of cellular senescence, protection against telomerase deficiency, suppression of mitochondrial dysfunction, mitigation of DNA damage, and attenuating inflammation. Consequently, taurine deficiency is posited as a potential contributor to the aging process, as its reversal has been shown to extend the health span of worms, rodents, and primates.⁴¹

The detoxification of free radicals necessitates reduced GSH, a process contingent upon the availability of nicotinamide adenine dinucleotide phosphate (NADPH).⁴² Substantially diminished nicotinamide adenine dinucleotide (NAD⁺) is concurrent with aging. Augmenting NAD⁺ levels has been demonstrated to enhance health and lifespan in various animal models. The biosynthesis of NAD⁺ emerges as a prospective target for the prevention and treatment of age-associated diseases.⁴³ NAD⁺ is an indispensable cofactor in numerous enzyme-catalyzed reactions, encompassing alcohol, lactate, and amino acid metabolism. In addition, NAD⁺ is pivotal as an electron transporter, driving oxidative phosphorylation and facilitating ATP production.⁴⁴ The traditional function of NAD⁺ involves serving as a coenzyme that catalyzes cellular redox reactions, transitioning into its reduced form, NADH. This pivotal role manifests in fundamental metabolic processes, including glycolysis, fatty acid beta-oxidation, and the tricarboxylic acid cycle.⁴⁵ NAD kinase facilitates the phosphorylation of NAD⁺ to generate NADPH, employing adenosine triphosphate as the phosphoryl donor.⁴⁶

There is a growing consensus that the levels of NAD⁺ experience a decline at the cellular, tissue/organ, and organismal levels throughout aging. This reduction in NAD⁺ levels influences the activities of enzymes that consume NAD⁺, contributing to a diverse array of age-associated pathophysiologicals.⁴⁷

As the aging process ensues and concentrations of NAD⁺ decline, there is an increased activation of *de novo* synthesis. NAD⁺ can be synthesized *de novo* through two primary pathways: the kynurenine pathway, starting from L-tryptophan, and the Preiss-Handler pathway, which utilizes vitamin precursors,

such as nicotinic acid.⁴⁸ De novo NAD⁺ synthesis is correlated with elevated levels of kynurenine.⁴⁹ Inhibition of kynurenine pathway metabolism may jeopardize cell viability, NAD-dependent SIRT1 activity, and central nervous system function.⁵⁰ NAD⁺ concentrations in rat-derived astrocytes can be regenerated through the utilization of nicotinic acid, nicotinamide, or quinolinic acid after NAD⁺ depletion induced by hydrogen peroxide.⁵¹

The accumulation of kynurenine with age has been observed in various organs and tissues. Increased levels of kynurenine relative to tryptophan are correlated with frailty and heightened age-related mortality. Moreover, the kynurenine pathway is implicated in age-associated diseases, including inflammation, neurodegeneration, and immunosenescence.⁵² The kynurenine pathway is involved in acute and chronic skin damage induced by ultraviolet radiation.⁵³ Elevated levels of kynurenine and neopterin have been associated with more advanced cataracts.⁵⁴ Reduced levels of tryptophan and kynurenine have been identified in the plasma of individuals with Parkinson's disease.⁵⁵ The heightened levels of kynurenine noted during the aging process may play a role in the observed bone fragility among older people.⁵²

Interferon-gamma (IFN- γ) and UV (ultraviolet) radiation stimulate the expression of indoleamine 2,3-dioxygenase (IDO), an enzyme crucial in the catabolism of tryptophan, by releasing various cytokines, including interleukin 1. IDO converts tryptophan and other indole derivatives into kynurenine.⁵⁶ The Kynurenine-Tryptophan (Kyn/Trp) ratio serves as an index for assessing the activity of IDO.⁵⁷ IDO-mediated catabolism of tryptophan not only inhibits the immunoregulatory kinases, mTOR, and PKC- θ , but also induces autophagy.⁵⁸

Dysregulated tryptophan catabolism and subsequent depletion of NAD⁺ contribute to increased fatty acid oxidation by IFN- γ in coronary endothelial cells.⁵⁹ IDO contributes to cellular survival and proliferation by augmenting free fatty acid oxidation, supplying the necessary energy for these processes.⁶⁰ Anoxia, followed by subsequent reoxygenation, induces the upregulation of IDO. Consequently, increased IDO activity culminates in tryptophan depletion and triggers the activation of the GCN2 (general control nonderepressible 2) kinase pathway.⁶¹ GCN2 functions as a molecular sensor in T cells, enabling them to detect and respond to the conditions established by IDO.⁶² Amino acids and insulin collaboratively influence translation processes by activating mTOR, AMPK, and GCN2 transduction pathways.⁶³

Acylcarnitines are emerging as a pivotal group of biomolecules in metabolomics, given the distinctive acylcarnitine profiles observed in a growing spectrum of diseases and nutritional conditions.⁶⁴ Long-chain acylcarnitines play dual roles, functioning as transporters in oxidative catabolism and as modulators of various physiological and pathophysiological processes. Their involvement extends to crucial aspects such as cardiac electrophysiology, insulin signaling, cellular stress responses, and regulating inflammatory pathways.⁶⁵

The most significant metabolites are those from the carnitine family involved in carnitine metabolism. Octanoylcarnitine, butyrylcarnitine, propionylcarnitine, amino-n-butyric acid, and isovalerylcarnitine are all upregulated in hard cataracts, indicating a different transportation situation of fatty acids into the mitochondria for energy production. The lens of the eye is avascular; energy requirements are primarily met through anaerobic glycolysis.⁶⁶ Elevated levels of octanoyl-carnitine have been

observed to be increased in patients' plasma with pseudoxifoliation syndrome.⁶⁷ In patients with age-related macular degeneration, there is an observed enrichment in the metabolic pathway associated with the oxidation of branched-chain fatty acids and the synthesis of carnitine.⁶⁸ At the same time, carnitine has antioxidant properties, and any disruption in its metabolism may affect the lens's ability to defend against oxidative damage.⁶⁹ This may also play a role in the cataract process. The regulation of ROS will become fragile and sensitive due to the anaerobic environment. Such regulation is also easily destroyed in the case of abnormal fatty acid oxidation.⁷⁰

Conclusion

While investigations into intraocular fluid metabolomics are still in their nascent stages, it is evident that they hold the promise of providing valuable insights into cataract progression. Our study provides evidence of specific metabolic distinctions in aqueous humor samples from soft and hard cataracts. We identified the significant role of taurine and hypotaurine metabolism, tryptophan metabolism, and mitochondrial beta-oxidation of short-chain saturated fatty acids in the development of cataracts. Considering these findings, the primary objective of intervention should center on taurine supplementation, aiming to impede the advancement of the disease. Although a definitive method for reversing the effects of cataracts remains elusive, arresting the disease's progression promises to enable individuals to lead lives with their natural lenses intact. Considering the progression of the disease, additional supplementation with NAD⁺ precursors should be contemplated for patients aiming to arrest its advancement. This could lower an increased tryptophan metabolism through the kynurenine pathway. Furthermore, the activation of this pathway is prompted by interferon-gamma and UV radiation, resulting in the induction of IDO. A reduced energy demand would diminish the heightened mitochondrial beta-oxidation, which signifies a distinctive process in the translocation of fatty acids into the mitochondria, ultimately contributing to the augmentation of the energy production process. Such an attenuation would halt the progression of this sequence of events, ultimately preventing the culmination of mTOR inhibition and the activation of the Sir2 pathway. Commercially available and ready-to-use eye drops, formulated with taurine and NAD⁺ precursors, provide a convenient option for individuals seeking to incorporate these beneficial compounds for ocular health.

We clearly demonstrated that aqueous humor analysis is an emerging method for unraveling the processes within the eye's anterior chamber. This approach extends beyond cataracts, potentially enhancing our understanding of disease progression in conditions such as glaucoma, pseudoxifoliation, endothelial dystrophies, and numerous others. The findings of this study lay the foundation for a more efficient pharmacological target for preventing and treating cataracts. The potential of metabolomics to leverage the accumulated knowledge of biochemistry toward achieving personalized and preventive healthcare is undeniably profound.

Authors' Contributions

A.Z.: Conceptualization (equal), Formal analysis (equal), Investigation (equal), Methodology (equal), Project administration (equal), Data collection (equal), and Writing—review

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& editing (equal). J.V.: Conceptualization (equal), Data collection (equal), Formal analysis (equal), Investigation (equal), and Review & editing (equal). K.K.: Formal analysis (equal), Investigation (equal), Data collection (equal), Resources (equal), and Review & editing (equal). J.F.: Data collection (equal), Formal analysis (equal), and Review & editing (equal). G.L.: Conceptualization (equal), Formal analysis (equal), Investigation (equal), Methodology (equal), Project administration (equal), Data collection (equal), Resources (equal), and Review & editing (equal).

Data Availability Statement

We acknowledge and appreciate the *Journal of Ocular Pharmacology and Therapeutics*' commitment to promoting data sharing and transparency in research. The data supporting the results presented in our article have been deposited in an appropriate repository. A comprehensive data accessibility statement, along with the corresponding repository link, is provided to facilitate access and verification of the findings. This ensures compliance with the *Journal of Ocular Pharmacology and Therapeutics*' guidelines, and we encourage readers and fellow researchers to utilize and explore the available data for a deeper understanding of the study outcomes.

Author Disclosure Statement

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Supplementary Material

Supplementary Table S1

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Redefined Formula for Anterior Chamber Volume Calculation: Quantitative Analysis of Biometric Parameters Across Ocular Pathologies

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Purpose: This study evaluates the discrepancies between ACV measurements obtained from the Heidelberg Anterior and Zeiss IOLMaster 700 and investigates the significance of ACV and other ocular biometry parameters.

Patients and Methods: To investigate intraocular fluid circulation, a robust formula was developed for ACV measurement using the Zeiss IOLMaster 700. A pilot study was conducted to validate this formula, which relied on WTW, CCT, and ACD. The formula used was $ACV = (RAC)^2 \times (CCD) \times 1.51$. ACV measurements showed a median of 155.38 (IQR = 131.15–180.06) for the Heidelberg Anterior and 144.11 mm³ (IQR = 125.62–159.81) for the Zeiss IOLMaster 700. The intraclass correlation coefficient (ICC) for ACV was 0.908, indicating excellent agreement between devices.

Results: Intraocular fluid volume was significantly lower in eyes with PEXS compared to those without. Eyes with PEX had an ACV of 133 ± 28.3 mm³ versus 142 ± 30.7 mm³ in non-PEX eyes, a statistically significant difference ($t(196) = -2.09$, $p = 0.038$, $d = -0.301$). Significant differences were also observed in ACD and AL between PEX and non-PEX eyes, with PEX eyes showing reduced measurements.

Conclusion: Our findings reveal that age-related changes in ACD and ACV are significant, with the redefined formula showing excellent agreement with AS-OCT methods. Eyes with PEX exhibit reduced ACD, ACV, and AL measurements. Additionally, an accessible method for ACV measurement, not relying on Pentacam or AS-OCT, would be valuable, particularly in developing countries, to facilitate broader clinical research.

Plain Language Summary: Our study examines the differences in measuring aqueous humor volume in the eye using two devices, the Heidelberg Anterior and the Zeiss IOLMaster 700. Aqueous humor is the clear fluid in the front part of the eye, which circulates at a rate of 1.0% to 1.5% per minute. We refined a formula to calculate the volume of this fluid using the Zeiss IOLMaster 700, based on specific eye measurements. We found that the volume measurements from both devices were very similar, showing a strong agreement. The study also discovered that eyes with pseudoexfoliation syndrome (PEXS), a condition affecting the eye, had significantly lower fluid volume compared to eyes without the condition. This was also true for other eye measurements like anterior chamber depth (ACD) and axial length (AL). These findings are important because they show that simpler and more accessible methods for measuring fluid volume in the eye can be used effectively, especially in developing countries where advanced equipment may not be available. The study highlights the changes in eye measurements with age and how the new formula aligns well with existing methods. Overall, eyes with PEX show reduced measurements in various eye parameters.

Keywords: anterior chamber volume, pseudoexfoliation, IOL power calculation, Heidelberg Anterior, performance measures

Introduction

Aqueous humor is a transparent, watery fluid that occupies the anterior and posterior chambers of the eye.¹ It serves to nourish the avascular structures, such as the lens and cornea, and is critical in maintaining intraocular pressure.² This

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fluid is produced by the ciliary body's pigmented and non-pigmented epithelium, circulates through the pupil into the anterior chamber, and is predominantly drained via the trabecular meshwork and Schlemm's canal, with a smaller fraction exiting through the uveoscleral outflow pathway.³ Aqueous humor formation involves three primary mechanisms: diffusion, ultrafiltration, and active secretion.⁴

Several pathologies relate to aqueous humor dynamics, including glaucoma,⁵ ocular hypertension,⁶ hypotony,⁷ uveitis,⁸ angle-closure glaucoma,⁹ pseudoexfoliation syndrome,¹⁰ and neovascular glaucoma.¹¹ Aqueous humor dynamics are measured through techniques such as tonometry, gonioscopy, pachymetry, aqueous humor outflow facility measurement, aqueous humor production rate estimation, and imaging modalities like optical coherence tomography (OCT) and ultrasound biomicroscopy.¹²

The turnover rate of aqueous humor within the anterior chamber is estimated to range from 1.0% to 1.5% per minute, corresponding to a measured flow rate of $2.4 \pm 0.6 \text{ mm}^3/\text{min}$, thereby inferring an anterior chamber volume (ACV) of approximately 160 to 240 mm^3 .¹³ The production and drainage rates of aqueous humor are not routinely measured in clinical practice due to their limited diagnostic utility.¹⁴ Significant nocturnal changes in aqueous humor dynamics in healthy mature humans include reductions in aqueous flow, outflow facility, and possibly uveoscleral outflow.¹⁵

Numerous methodologies have been proposed for calculating the ACV based on the dimensions obtained from photographically recorded optical sections of the eye.^{16–21} Although most of these methods were developed approximately 50 years ago, the advent of modern ophthalmological equipment necessitates a more straightforward approach to calculating the ACV.

Aqueous humor circulates from the posterior to the anterior segment of the eye, with its production and drainage extensively studied, though its volume has not been as thoroughly examined. While the ACV has not been directly linked to other ocular pathologies, the study of its metabolomics and composition can provide valuable insights into the various mechanisms operating within the eye.²²

In our study, we evaluated the discrepancies between measurements obtained from the Heidelberg Anterior (Heidelberg Engineering, Germany) and the Zeiss IOLMaster 700 (Carl Zeiss AG, Germany). We also refined a formula for calculating intraocular fluid volume and conducted a pilot study to validate this formula. Additionally, we compared measurement differences between a control group and a cataract group. Subsequently, we investigated the significance of ACV and various ocular biometry parameters in relation to a spectrum of ocular comorbidities.

Materials and Methods

To thoroughly investigate intraocular fluid circulation in the eye, it was essential to develop a robust formula to aid our research. Although our hospital is equipped with a Heidelberg Anterior²³ anterior segment OCT imaging device, utilizing this machine for ACV calculations would be time-consuming and ultimately impractical. Therefore, we opted to use the Zeiss IOLMaster 700²⁴ for this analysis.

All data for our study were collected using the Zeiss IOLMaster 700, as it was already integrated into the routine examination process for patients undergoing cataract surgery who consented to participate in the study. Consequently, we first needed to establish a reliable method for obtaining ACV measurements using this machine, ensuring accurate and efficient data collection for our research.

During our endeavors, we conducted a pilot study to assess the sufficiency of our formula for analyzing ACV in the eye. This preliminary study included 30 participants, comprising both cataract patients and a younger control group. The study comprised 18 patients in the cataract group and 12 in the control group. The mean age of the cataract group was 73.3 years (± 8.22), ranging from 57 to 88 years. In contrast, the control group had a mean age of 32.2 years (± 7.73), with ages ranging from 26 to 48 years. The objective was to determine if we could develop a reliable formula for ACV measurement using only white-to-white corneal diameter (WTW), central corneal thickness (CCT), and anterior chamber depth (ACD). The ACD, measured using the Heidelberg Anterior AS-OCT device, was defined as the distance from the central anterior corneal epithelium to the anterior surface of the crystalline lens capsule.²⁵

To estimate the ACV using Zeiss IOLMaster 700 ocular biometry parameters, we conducted an extensive literature review to identify an appropriate formula. Our investigation included articles from the 1970s and 1980s that described

various optical methods for measuring ACV. We employed the empirical formula initially developed by Max Heim in 1941²⁶ and later utilized by Tomlinson et al in 1974²⁷ and Johnson et al²⁸ to address our research needs.

Central to our study, the ACV was computed using the following parameters:

- The radius of the anterior chamber (RAC) was established based on the WTW distance.
- The central chamber depth (CCD) was derived from the disparity between the ACD and the CCT.

The WTW distance represents the horizontal measurement across the cornea from one limbus to the other, effectively measuring the diameter of the anterior chamber. This measurement is typically acquired using devices such as the Zeiss IOLMaster 700. Given that the WTW distance corresponds to the diameter, dividing it by two yields the RAC. The radius, being half of the diameter, is crucial for subsequent calculations involving volume. The CCD is determined by subtracting the CCT from the ACD.

This relationship was formalized in the formula:

$$\begin{aligned} \text{ACV} &= (\text{RAC})^2 \times (\text{CCD}) \times 1.51 \\ &\text{or} \\ \text{ACV} &= ((\text{WTW}/2)^2) \times (\text{ACD} - \text{CCT}) \times 1.51 \end{aligned}$$

This formula is derived from the correlation between ACV and ACD, which has been demonstrated to explain approximately 85% of the variation in ACV across multiple studies employing OCT for volume estimation.^{29,30} ACV can be effectively quantified using both Pentacam (Oculus Optikgeräte GmbH, Germany) and anterior segment optical coherence tomography (AS-OCT), as demonstrated by their reliability. Nonetheless, the lack of substantial agreement between these measurements precludes their interchangeability.³¹

The intraclass correlation coefficient (ICC) was calculated using a two-way mixed effects model to evaluate the consistency and reliability of the measurements obtained from the two devices. This approach is widely recognized for assessing agreement between different raters or instruments.^{32,33} The specific model employed for the ICC calculation was “inter-rater reliability, two-way mixed effects, single rater, absolute agreement.” This methodologically aligns with the guidelines provided by Koo and Li,³² which recommend appropriate methods for ICC calculation in inter-rater reliability studies.

We conducted a comparative analysis of the measurements obtained using the Heidelberg Anterior device against the volumes calculated from the Zeiss IOLMaster 700 data, employing the specified formula as outlined earlier. Descriptive statistics, including the median and interquartile range (IQR), were computed for each parameter as assessed by both raters. These statistics provide a detailed summary of the central tendency and dispersion, ensuring a comprehensive depiction of the measurement data.³⁴

To compare the distributions of the measurements from the Heidelberg Anterior and the Zeiss IOLMaster 700, we employed the Mann–Whitney *U*-test. This non-parametric test is appropriate for comparing two independent groups, especially when the data do not follow a normal distribution.³⁵ The threshold for statistical significance was set at a *p*-value of < 0.05. This threshold was used to determine whether the results were statistically significant in our analysis.³⁶ Additionally, Levene’s test was performed to assess the homogeneity of variances between the measurements from both devices, ensuring the assumption of equal variances was met. Evaluating the homogeneity of variances is critical for validating many statistical analyses, as it enhances the reliability of subsequent comparative analyses.³⁷ This assessment was crucial in validating our methodology and ensuring the accuracy and reliability of ACV measurements in our research. The measurements are shown in Table 1.

For the WTW measurements, the Heidelberg Anterior device reported a median of 11.60 mm (IQR = 11.33–11.88), whereas the Zeiss IOL Master reported a median of 11.80 mm (IQR = 11.53–12.08). The ICC for WTW was 0.808, with a 95% confidence interval ranging from 0.63 to 0.90, indicating moderate agreement between the two devices. The Mann–Whitney *U*-test indicated a significant difference between the devices (*p* = 0.0056), while Levene’s test confirmed the homogeneity of variances (*p* = 0.103).

Table 1 Comparison of Ocular Biometry Parameters Between Heidelberg Anterior and Zeiss IOLMaster 700

Parameter	Median (IQR) – Heidelberg Anterior	Median (IQR) – Zeiss IOLMaster 700	ICC	95% CI	p-value	Rater reliability
WTW	11.60 (11.33–11.88)	11.80 (11.53–12.08)	0.700	[0.17, 0.92]	0.008	Moderate Agreement
CCT	0.53 (0.52–0.55)	0.54 (0.52–0.55)	0.951	[0.82, 0.99]	<0.001	Excellent Agreement
ACD	3.25 (2.97–3.43)	3.21 (2.97–3.43)	0.988	[0.95, 1.0]	<0.001	Excellent Agreement
ACV	155.38 (131.15–180.06)	144.11 (125.62–159.81)	0.902	[0.66, 0.97]	<0.001	Excellent Agreement

Note: The table presents the results of various statistical tests and descriptive analyses for four parameters: WTW, CCT, ACD, and ACV. The key metrics include the median and interquartile range (IQR) of measurements by both devices (Heidelberg Anterior and Zeiss IOL Master), the ICC with 95% confidence intervals, the p-values indicating the significance of the ICC, and the rater reliability assessment. The table illustrates the consistency and agreement between the two devices, highlighting moderate to excellent agreement across the parameters.

For CCT measurements, the Heidelberg Anterior device reported a median of 0.53 mm (IQR = 0.52–0.55) and the Zeiss IOLMaster 700 reported a median of 0.54 mm (IQR = 0.52–0.55). The ICC for CCT was notably high at 0.961, with a 95% confidence interval from 0.92 to 0.98, indicating excellent agreement. Neither the Mann–Whitney *U*-test ($p = 0.267$) nor Levene’s test ($p = 0.588$) revealed significant differences between the measurements.

For ACD measurements, the Heidelberg Anterior device reported a median of 3.25 mm (IQR = 3.00–3.50), while the Zeiss IOLMaster 700 reported a median of 3.21 mm (IQR = 2.97–3.43). The ICC for ACD was 0.991, with a 95% confidence interval from 0.98 to 1.00, indicating excellent agreement between the devices. Neither the Mann–Whitney *U*-test ($p = 0.355$) nor Levene’s test ($p = 0.939$) indicated significant differences between the measurements.

ACV measurements showed a median of 155.38 mm³ (IQR = 131.15–180.06) for the Heidelberg Anterior and 144.11 mm³ (IQR = 125.62–159.81) for the Zeiss IOLMaster 700, with the latter calculated using the formula. The ICC for ACV was 0.908, with a 95% confidence interval from 0.82 to 0.96, suggesting excellent agreement between the devices. The Mann–Whitney *U*-test revealed a statistically significant difference between the measurements ($p = 0.0519$), indicating divergent assessments between the two devices. However, Levene’s test did not detect significant variance ($p = 0.216$), indicating consistency in the spread of measurements across the two groups.

In our analysis, we examined the cohorts and identified distinctions between the younger cohort and the cataract cohort. Statistically significant differences in measurements between groups were found for the ACV Formula, WTW Anterior, ACD Anterior, and ACD IOLMaster. These results indicate a clear trend of decreasing ACD with advancing age, corroborating findings reported in existing literature.³⁸

The differences in ACV should also be observed in the ACV Anterior and ACV Formula groups. These differences can be attributed to the WTW measurement’s ability to differentiate between various diagnostic machines.³⁹ The observed variations are shown in Table 2.

The main investigation involved examining ACV, WTW, ACD, and AL in patients undergoing cataract surgery at Pauls Stradins Clinical University Hospital. Among the chosen participants, 72 were men, while 126 were women.

Table 2 The Measurements Were Compared Between the Heidelberg Anterior and the Zeiss IOLMaster 700, as Well as Between the Cataract and Control Groups

	Cataract (n = 18)	Control (n = 12)	p-value	Effect Size
ACV Anterior, median (SD)	150 ± 35.2	185 ± 28.5	0.095	0.370
ACV Formula, median (SD)	133 ± 26.5	157 ± 22.4	0.015	0.528
WTW Anterior, median (SD)	11.5 ± 0.353	11.8 ± 0.317	0.019	0.509
WTW IOL master, median (SD)	11.9 ± 0.268	11.9 ± 0.357	0.492	0.153
ACD Anterior, median (SD)	3.09 ± 0.459	3.63 ± 0.273	0.010	0.569
ACD IOL master, median (SD)	3.01 ± 0.455	3.56 ± 0.276	0.010	0.565
CCT Anterior, median (SD)	536 ± 16.6	531 ± 32.4	0.340	0.213
CCT IOL master, median (SD)	543 ± 19.0	536 ± 38.8	0.421	0.181

Note: The Mann–Whitney *U*-test was employed to assess differences between the groups. Bold font indicates p-values less than 0.05, representing statistically significant results.

Furthermore, the SPONCS⁴⁰ system was utilized to classify the hardness of cataracts. Demographics and ocular pathologies are shown in Table 3.

Results

A comprehensive analysis displaying patient concurrent pathologies and their statistical relevance to ACV, WTW, ACD, and AL is shown in Table 4.

The volume of intraocular fluid differed significantly between groups with and without pseudoexfoliation (PEX). Eyes with PEX had a significantly lower ACV ($133 \pm 28.3 \text{ mm}^3$) compared to eyes without PEX ($142 \pm 30.7 \text{ mm}^3$), with

Table 3 Summary of Demographics and Ophthalmic Co-Morbidities Among Patients Included in the Study

	Male (n = 72)	Female (n = 126)	p-value
Age, mean (SD)	72.0±9.49	74.3±9.44	0.092
ACV, mean (SD)	140 ± 32.3	138 ± 28.6	0.587
WTW, median (SD)	12.0 ± 0.387	11.8 ± 0.399	<0.001
ACD, median (SD)	3.15 ± 0.518	3.14 ± 0.466	0.457
AL, median (SD)	23.9 ± 1.39	23.3 ± 1.34	0.027
Cataract hardness (SPONCS)			0.527
1 (Subcapsular with clear nucleus)	2 (1.0%)	1 (0.5%)	
2 (Mild hardness)	21 (10.6%)	45 (22.7%)	
3 (Moderate hardness)	24 (12.1%)	44 (22.2%)	
4 (Advanced hardness)	7 (3.5%)	14 (7.1%)	
5 (Hypermaturation/Morganian)	18 (9.1%)	22 (11.1%)	
Glaucoma			0.822
Present	17 (8.6%)	28 (14.1%)	
Absent	55 (27.8%)	98 (49.5%)	
Pseudoexfoliation syndrome			0.183
Present	35 (17.7%)	49 (24.7%)	
Absent	37 (18.7%)	77 (38.9%)	
Diabetes			0.098
Present	12 (6.1%)	34 (17.2%)	
Absent	60 (30.3%)	92 (46.5%)	

Note: The t-test and Mann-Whitney U-test was used to compare distributions of age, volume, WTW, ACD, and AL, while the chi-squared test was employed to analyze associations among categorical variables.

Table 4 The ACV, WTW, ACD, and AL, Along with Their Statistical Significance in Relation to Ocular Comorbidities

	p-value			
	ACV	WTW	ACD	AL
Cataract hardness (SPONCS)	0.720	0.929	0.631	0.910
Glaucoma	0.461	0.267	0.393	0.801
Pseudoexfoliation syndrome	0.038	0.711	0.016	0.046
Diabetes	0.712	0.841	0.502	0.166

Note: The t-test and one-way ANOVA were used to compare parametric ACV data, while the Mann-Whitney test and Kruskal-Wallis test were employed to analyze non-parametric WTW, ACD, and AL data. Bold font indicates p-values less than 0.05, representing statistically significant results.

a statistically significant difference of -8.94 mm^3 , 95% CI $[-17.4, -0.518]$, $t(196) = -2.09$, $p = 0.038$, $d = -0.301$. There was also a significant difference in ACD between eyes with PEX (median = 3.00 mm, IQR = 2.71–3.32 mm) and without PEX (median = 3.17 mm, IQR = 2.90–3.45 mm), $U = 3824$, $p = 0.016$, $r = 0.201$. There was also a significant difference in AL between eyes with PEX (median = 23.4 mm, IQR = 22.8–24.0 mm) and without PEX (median = 23.6 mm, IQR = 22.9–24.6 mm), $U = 3784$, $p = 0.046$, $r = 0.169$.

Discussion

Although the measurement of ACV has not yet become standard clinical practice, it holds significant potential for addressing various ocular issues. It can aid in glaucoma diagnosis and management, cataract surgery planning, refractive surgery, assessment of ocular health, and research and development.

A considerable body of research has explored the ACV across various ocular pathologies. Eyes with an ACV of 100 mm^3 or less may be classified as having a high risk for the development of acute angle-closure glaucoma.⁴¹ The ACV increased significantly at 1 day, 1 week, and 1 month following cataract surgery.⁴² While there was no observed change in ACV, a notable reduction in ACD was found following myopic LASIK in young patients.⁴³ Corneas with increased thickness might correlate with reduced aqueous production and diminished uveoscleral outflow.⁴³ Biometric differences between Caucasian and Chinese adults include larger ACVs.⁴⁴ Reduced anterior chamber area and ACV were found to be independently associated with narrow angles, even following adjustment for established ocular biometric parameters such as ACD and AL.⁴⁵ Greater ACV was found to be associated with decreased deformation altitude values and increasing age while exhibiting higher stiffness parameters and intraocular pressure values.³⁰

In our study, the most pronounced differences were observed within the groups affected by PEX. The literature reveals a lack of consensus concerning the biometric characteristics of the anterior segment in eyes affected by PEXS. A population-based cross-sectional cohort study has shown that PEXS is correlated with advanced age, reduced AL, and a diminished ACD.⁴⁶ A study demonstrated that the anterior chamber of the eye is significantly shallower in patients with PEX syndrome compared to the control group.⁴⁷ Research has indicated that eyes with PEX syndrome and cataracts exhibit significantly reduced ACD and increased lens thickness compared to eyes with cataracts alone.⁴⁷ The reduced ACD observed in patients with PEX syndrome is believed to result from the forward displacement of the lens, which is attributed to lens thickening and the weakening of the lens zonules.⁴⁸ The fragility of the zonular apparatus significantly contributes to the elevated incidence of phacodonesis, lens dislocation, and vitreous complications encountered during extracapsular cataract surgery in eyes with PEXS.⁴⁹

However, according to the findings from the Reykjavik Eye Study, PEX did not exhibit a correlation with CCT, ACD, lens thickness, nuclear lens opacifications, or optic disc morphology when analyzed within a multivariate model.⁵⁰ Duran et al observed no significant differences in ACD when comparing eyes with PEX to their fellow eyes or to control eyes.⁵¹

There are only a few studies that have investigated the association between PEX and the axial length of the eye. Topouzis et al found that individuals with incident PEX had a statistically significantly shorter axial length compared to those who had not developed PEX.⁵² Topouzis's findings propose that shorter axial length might contribute to the onset of PEX, which may explain the association observed with a shallow anterior chamber in the Beijing Eye Study 2011 by You Q. et al.⁴⁶

The evidence concerning differences in ACV between eyes with PEX and those without is inconclusive. Mohamed-Noriega et al reported that the ACV, measured using the Pentacam, exhibited negligible differences between the control group (mean $\pm$ SD: $109.6 \pm 25.6 \text{ mm}^3$) and the group affected by PEXS (mean $\pm$ SD: $113.363 \pm 24.79 \text{ mm}^3$).⁵³ Doganay et al employed the Pentacam-Scheimpflug imaging system to assess anterior segment parameters in patients with PEXS, pseudoexfoliative glaucoma (PEXG), and a control group. Their findings revealed no significant differences in mean values of ACV, anterior chamber angle width, CCT, pupil diameter, or corneal volume at 3.0 mm, 5.0 mm, and 7.0 mm among the three groups.⁵⁴ According to Gharagozloo et al, ACV was markedly decreased in both affected and unaffected eyes of individuals with unilateral PEXS compared to control eyes.⁵⁵ The Duran et al study revealed no significant differences in ACD, ACV, iridocorneal angle, or keratometry values when comparing eyes with PEX to either fellow eyes or control eyes.⁵¹ Omura et al observed that eyes positive for PEXS exhibited a diminished ACV in comparison to PEX-negative eyes.⁵⁶ Studies have demonstrated that patients with PEXG experience a more pronounced reduction in intraocular pressure following cataract surgery compared to control groups.⁵⁷

During this study, we hypothesized that glaucoma would be the ocular comorbidity most strongly associated with ACV. However, this hypothesis was not supported by our findings. Lens thickness is an important parameter that can influence ACV and may have implications for conditions such as glaucoma. Increased lens thickness was significantly associated with advancing age, male sex, greater body height, elevated body mass index, hyperopic refractive error, thicker central corneal measurements, reduced anterior chamber depth, and the presence of nuclear cataracts.⁵⁸ However, in our study, lens thickness was not measured due to the exclusion of patients with severe lens opacities, which cannot be accurately assessed using optical interferometry. While this limitation restricts our ability to explore the relationship between lens thickness and ACV, future studies that include lens thickness measurements would provide valuable insights into how lens thickness may correlate with ACV and its role in ocular health. However, in both POAG patients and individuals without the condition, no meaningful relationship was observed between IOP and ACD, nor between IOP and lens thickness.⁵⁹ Eyes with angle-closure glaucoma or occludable angles exhibit noticeably shorter AL, shallower ACD, and thicker lenses when compared to those in the normal group.⁶⁰ Glaucoma is defined as a group of disorders characterized by the degeneration of ganglion cells resulting from axonal damage at the lamina cribrosa of the optic nerve. In essence, glaucoma is a diagnosis of exclusion when the etiology of the optic nerve damage remains unidentified.⁶¹ Lowering IOP does not fully address the underlying mechanisms of neurodegeneration. Therefore, there is a significant need for pharmacologic approaches that can protect against glaucomatous neurodegeneration independently of IOP.⁶²

There have been studies linking glaucoma to ACV. The IOP/ACV ratio may serve as a novel diagnostic parameter for predicting the likelihood of success in prostaglandin analogue treatment.⁶³ ACV is a robust and precise predictor of the outcomes of primary angle closure disease.⁶⁴

Emerging research on the intraocular fluid metabolome shows promise in elucidating integrated biological mechanisms within the anterior segment of the eye and advancing treatment strategies for ocular diseases. Variations in intraocular fluid composition among cataract patients^{65,66} and individuals with PEX⁶⁷ have been documented in existing literature. Future investigations could harness data from liquid chromatography-mass spectrometry machines and consider ACV as a potential alternative for concentration calculations in these studies. The product of a substance's concentration within a fluid and the volume of that fluid determines the total mass or amount of the substance, a critical factor in assessing its overall presence within the fluid.

An accessible and cost-effective method for measuring ACV that does not rely on advanced equipment such as the Pentacam or AS-OCT would be highly beneficial, particularly in developing countries where access to such technology may be limited. With the availability of ocular biometry, it could significantly enhance clinical research on ACV by enabling broader and more comprehensive studies.

Conclusion

Our study evaluated the discrepancies between ACV measurements obtained from the Heidelberg Anterior and Zeiss IOLMaster 700. ACV measurements showed a median of 155.38 mm³ (IQR = 131.15–180.06) for the Heidelberg Anterior and 144.11 mm³ (IQR = 125.62–159.81) for the Zeiss IOLMaster 700, with the latter calculated using the formula. The ICC for ACV was 0.908 (95% CI: 0.82–0.96), indicating excellent agreement between the devices. While the Mann–Whitney *U*-test revealed a statistically significant difference ($p = 0.0519$), Levene's test showed no significant variance ($p = 0.216$), suggesting consistency in the spread of measurements across both devices. We also refined a formula for calculating intraocular fluid volume, which demonstrated excellent agreement with AS-OCT methods. Additionally, our investigation highlighted the significance of ACV and other ocular biometry parameters in relation to ocular comorbidities, revealing that both ACD and ACV exhibit age-related changes. Notably, eyes affected by PEXS showed reduced ACD, ACV, and AL measurements. This is the first study to validate our redefined formula, which could enable broader clinical research, particularly in settings with limited access to advanced imaging technologies. While ACV remains underexplored, its potential applications in ophthalmology merit further investigation.

Abbreviations

OCT, optical coherence tomography; ACV, anterior chamber volume; WTW, white-to-white corneal diameter; CCT, central corneal thickness; ACD, anterior chamber depth; RAC, radius of the anterior chamber; CCD, central chamber depth; AS-OCT, anterior segment optical coherence tomography; ICC, intraclass correlation coefficient; IQR, interquartile range; PEX, pseudoexfoliation; PEXS, pseudoexfoliation syndrome; PEXG, pseudoexfoliative glaucoma; IOP, intraocular pressure.

Data Sharing Statement

All data generated or analyzed during this study are presented within this article. Additional information is available upon request by contacting the corresponding author.

Ethics Approval and Informed Consent

The research adhered to the ethical principles delineated in the Declaration of Helsinki. Stringent ethical scrutiny was applied to the study's considerations, resulting in approval from the Medical Ethics Committee of Rigas Stradins University, denoted by decision number 2-PEK-4/307/2023. Furthermore, the requisite approval was obtained from the Pauls Stradins Clinical University Hospital. Patients provided written informed consent to participate in the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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The Role of IDO Activity in Cataract Progression: Correlation to Age and Cataract Severity

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ABSTRACT

Purpose: Cataract is a prevalent, progressive lens disorder characterized by gradual opacity, often related to aging. Oxidative stress, ultraviolet radiation, and inflammation contribute to lens damage and protein modifications. Indoleamine 2,3-dioxygenase plays a critical role in tryptophan metabolism, with kynurenines implicated in various diseases. This study aimed to assess IDO activity in cataract patients by analyzing IDO activity in aqueous humor.

Methods: The study included 170 cataract surgery patients (60 males, 110 females; mean age 73.9 ± 9.43 years). Cataract severity was categorized using the SPONCS system: SPONCS 1 (1.8%), SPONCS 2 (30.6%), SPONCS 3 (35.3%), SPONCS 4 (11.8%), and SPONCS 5 (20.6%). Aqueous humor samples (50–120 µL) were collected *via* paracentesis and analyzed using HILIC liquid chromatography with mass spectrometry. Target metabolite quantification was performed using internal standards and calibration curves.

Results: Significant differences in IDO activity were observed across SPONCS groups ($X^2(4) = 12.0$, $p = .018$, $\eta^2 = 0.0707$), particularly between SPONCS 2 and SPONCS 5 ($p = .013$). Age differences across SPONCS groups were also significant ($p < .001$). Males had lower tryptophan levels than females ($p = .027$). Correlations were found between SPONCS and IDO activity ($r_s = -0.255$, $p < .001$), SPONCS and kynurenine ($r_s = 0.196$, $p = .011$), and kynurenic acid with kynurenine ($r_s = 0.355$, $p < .001$).

Conclusion: Patients with SPONCS 2 cataract exhibit increased susceptibility to elevated IDO activity and heightened kynurenine production. IDO serves as a more reliable prognostic marker for cataract progression than chronological age. Furthermore, IDO activity may be associated with reduced glutathione levels in human lens epithelial cells, suggesting a potential link between the enzyme and oxidative stress within the lens.

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Introduction

Cataract is an extremely common and chronic, progressive disorder of the lens characterized by gradual opacification and yellowing over time, commonly associated with aging. The natural aging process and oxidative stress are frequently associated with it.¹ Epidemiological data indicate that individuals with early-onset cataracts or those undergoing cataract surgery at a younger age may experience reduced life expectancy.² This raises critical questions regarding whether cataracts are primarily a consequence of aging or if they are more closely related to oxidative stress or inflammatory processes. A significant portion of the cataractogenous alterations are either induced or exacerbated by oxidative stress, ultraviolet radiation, osmotic imbalances, and other forms of cellular damage.³ Epidemiological studies have independently linked these environmental factors to an increased risk of cataract formation.⁴ For lens crystallins, these biochemical modifications involve processes such as proteolysis, enhanced formation of disulfide bridges, racemization of aspartic acid

residues, deamidation of asparagine and glutamine residues, as well as phosphorylation, carbamylation, and nonenzymatic glycosylation.⁵ These modifications result in increased protein insolubility, contributing to lens opacification.

Indoleamine 2,3-dioxygenase (IDO) is an enzyme responsible for extrahepatic tryptophan (Trp) conversion to kynurenine (Kyn). It is expressed in various organs, while tryptophan-2,3-dioxygenase (TDO) is mainly expressed in the liver and accounts for 95% of Trp catabolism. IDO is a heme-containing dioxygenase.⁶ IDO activation is predominantly driven by interferon- γ (IFN- γ) and select cytokines, whereas its function is inhibited by nitric oxide.⁷ IDO serves as both a predictive biomarker and a therapeutic target for immune-mediated diseases. IDO appears to play critical roles in processes such as infection, inflammation, and T-cell-mediated immune responses. The Kynurenine-to-Tryptophan ratio (Kyn/Trp ratio) ratio serves as an index for assessing the activity of IDO.⁸ The use of this ratio is valid in *in vitro* studies, including those involving cell cultures or isolated organs. However, it is important to

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note that *in vivo* plasma IDO activity may be more closely associated with TDO activity.⁹

IDO is believed to be the primary enzyme, and possibly the rate-limiting step, in the biosynthetic pathway of UV filters.¹⁰ The activation of IDO leads to an increased production of kynurenines. These Kyn metabolites are further metabolized into various compounds, including picolinic acid, quinolinic acid, xanthurenic acid, and kynurenic acid. These metabolites play significant roles in neuroinflammatory diseases.¹¹ Kynurenines are associated with various diseases, including coronary heart disease, chronic renal failure, and neurodegenerative disorders like Alzheimer's,¹² Parkinson's,¹³ and Huntington's¹⁴ diseases. They are also linked to rheumatoid arthritis and collagen-induced arthritis in experimental models.¹⁵ Elevated Kyn levels, due to IDO activation, contribute to inflammation, immune dysregulation, and protein modifications, which may exacerbate these conditions. In the human lens, IDO activity is predominantly localized in the lens epithelium.¹⁶ Several kynurenines are also present within the lens, functioning as UV filters and believed to protect the retina from UV-induced damage. However, these compounds are susceptible to oxidation and deamination, processes that can result in modifications to lens proteins.¹⁷ Kynurenines can also harm lens proteins if glutathione (GSH) levels are insufficient to prevent their interaction with those proteins.¹⁸ IDO activity has been observed in lenses from individuals aged 26–80 years. It has been proposed that the yellowing of the lens during cataractogenesis is associated with IDO activity and that inhibition of IDO might serve as a preventive measure against this process.¹⁹

In this study, we examined the aqueous humor of cataract patients to assess IDO activity, employing the Kyn/Trp ratio as a biomarker for IDO activity. We correlated IDO activity, Trp, Kyn, and kynurenic acid to patients age, gender, and cataract severity. Our aim is to enhance the understanding of the biochemical processes underlying cataract progression.

Materials and methods

Study group

The study involved analyzing aqueous humor samples from 170 patients who underwent cataract surgery at Pauls Stradins Clinical University Hospital. Of these, 60 were male and 110 were female. The mean age of the cohort was 73.9 years, with a standard deviation of ± 9.43 years, ranging from 50 to 94 years. The severity of cataracts was classified using the SPONCS classification system,²⁰ which stratifies cataracts into progressively increasing levels of severity based on nuclear opalescence and coloration. The SPONCS scale includes SPONCS 1, SPONCS 2, SPONCS 2+, SPONCS 3, SPONCS 3+, SPONCS 4, SPONCS 4+, and SPONCS 5. For the purposes of this study, patients were grouped into five distinct categories: SPONCS 1 was classified as Group 1, SPONCS 2 (including SPONCS 2 and SPONCS 2+) as Group 2, SPONCS 3 (including SPONCS 3 and SPONCS 3+) as Group 3, SPONCS 4 (including SPONCS 4 and

SPONCS 4+) as Group 4, and SPONCS 5 as Group 5. Based on this classification, the patient distribution was as follows: Group 1 (SPONCS 1, 1.8%), Group 2 (SPONCS 2, 30.6%), Group 3 (SPONCS 3, 35.3%), Group 4 (SPONCS 4, 11.8%), and Group 5 (SPONCS 5, 20.6%). A limitation of the study is that the presence and severity of age-related macular degeneration were not systematically documented prior to the procedure, preventing analysis of their potential impact on IDO activity. Additionally, while comorbid conditions such as diabetes, glaucoma, and pseudoexfoliation were included in the cohort, our analysis did not identify any statistically significant association between these conditions and IDO activity. However, due to the sample size and potential for residual confounding, these findings should be interpreted with caution.

Prior to the commencement of the surgical procedure, paracentesis was performed, during which a 27 G needle was employed to obtain a biopsy of the aqueous humor. Volumes of aqueous humor ranging from 50 to 120 μ L were aspirated, depending on the availability of fluid, and subsequently transferred into Eppendorf tubes. The collected samples were immediately frozen and transported to the Faculty of Materials Science and Applied Chemistry at Riga Technical University for further analytical processing and archival storage.

The ethical approval for this study was obtained from the Medical Ethics Committee of Riga Stradins University, as documented in decision number 2-PEK-4/307/2023. Approval and support were also provided by the Pauls Stradins Clinical University Hospital. All participants provided written informed consent prior to their involvement in the study. The research was conducted in strict adherence to the principles outlined in the Declaration of Helsinki.

LC-MS based metabolite analysis

Metabolites were extracted using a methanol-based extraction protocol. 10 μ L of the aqueous humor sample were transferred to an empty Eppendorf tube and mixed with 80 μ L methanol and 10 μ L isotopically labeled internal standards. Each sample was vortexed for 15 s and then centrifuged for 10 min at 10,000 RPM. The supernatant was transferred into an HPLC glass vial.

Targeted quantitative metabolite analysis was conducted using HILIC-based liquid chromatography combined with mass spectrometric detection employing a Thermo Orbitrap Exploris 120 mass spectrometer. An ACQUITY UPLC BEH Amide 1.7 μ m 2.1 $\times$ 100 mm analytical column (Waters) was employed for chromatographic separation. The gradient elution was carried out using 0.15% formic acid and 10 mM ammonium formate in water as mobile phase A and a solution of 0.15% formic acid and 10 mM ammonium formate in 85% acetonitrile as mobile phase B. The initial conditions were set to 100% in mobile phase B. After 6 min, a 0.1 min gradient (6.0–6.1 min) was started, and the mobile phase B level was reduced to 94.1%. From 6.1 to 10 min, mobile phase B was set to 82.4%, and from 10 to 12 min, mobile phase B was set to 70.6%. The column was then equilibrated for 6 min at the initial conditions. The total analysis time was 18 min.

The mobile phase flow rate was 0.4 mL/min, the injection volume was 2 µL, and the column temperature was 40°C. For MS detection, an Orbitrap Exploris 120 (Thermo Fisher Scientific) mass spectrometer was used. The MS analysis was performed in ESI positive and ESI negative modes using full scan detection; the scan range was set from 50 to 600 m/z, and the mass resolution was set to 60,000. The ESI spray voltage was set to 3.5 kV in positive mode and 2.5 kV in negative mode; the gas heater temperature was set to 400°C; the capillary temperature was set to 350°C; the auxiliary gas flow rate was set to 12 arbitrary units; and the nebulizing gas flow rate was set to 50 arbitrary units. For quantitative analysis, seven-point calibration curves with internal standardization were used. Tracefinder 51.1 General Quan (Thermo Fisher Scientific) software was used for LC-MS data processing and quantification. Every reported metabolite was identified at level A²¹ by using an authentic standard compound previously mapped to the analytical system. Detailed information about metabolite identification (RT, m/z, HMDB IDs) is provided in the [Supplementary Table S1](#).

Statistics

Correlations between variables were assessed using Spearman's rank-order correlation, which is particularly appropriate for data that may not adhere to a normal distribution. The Shapiro-Wilk test was employed to determine whether the data conformed to a normal distribution. For normally distributed data, such as age, a one-way ANOVA was conducted. In cases where data were not normally distributed, the Mann-Whitney U test was used to evaluate statistical differences between groups with two variables. For comparisons involving multiple groups, where normality and homogeneity of variance assumptions were violated—such as in the analysis of IDO activity, kynurenic acid, Kyn, and Trp—the Kruskal-Wallis test was applied. All statistical analyses were conducted using the Jamovi software platform. Data tables and visualizations were generated using Microsoft Excel.

Results

Our results revealed significant statistical differences in the IDO activity across SPONCS groups ($X^2(4) = 12.0$, $p = .018$, $\mathcal{E}^2 = 0.0707$). Specifically, the median IDO activity values were as follows: SPONCS 1 (median = 143, IQR = 119.6–387), SPONCS 2 (median = 265, IQR = 158.1–367), SPONCS 3 (median = 188, IQR = 137.1–289), SPONCS 4 (median = 197,

IQR = 108.9–261), and SPONCS 5 (median = 157, IQR = 84–226). Post hoc analysis indicated a statistically significant difference in the IDO activity between SPONCS 2 and SPONCS 5 ($p = .013$), while no other significant differences were observed between the groups.

Age differed significantly between the SPONCS groups ($X^2(4) = 14.3$, $p = .006$, $\mathcal{E}^2 = 0.0847$): SPONCS 1 (median = 59.0, IQR = 56.0–59.5), SPONCS 2 (median = 73.0, IQR = 65–79), SPONCS 3 (median = 77.5, IQR = 74.0–81.0), SPONCS 4 (median = 75.0, IQR = 62.8–82.0), and SPONCS 5 (median = 73.0, IQR = 65.0–81.5). Post hoc analysis revealed statistically significant differences in age between SPONCS 1 and SPONCS 3 ($p = .047$), SPONCS 1 and SPONCS 5 ($p = .049$), and SPONCS 2 and SPONCS 3 ($p = .039$). No other pairwise comparisons showed statistically significant differences.

There were statistically significant differences between Trp levels between males (median = 51.6, IQR = 28.3–66.7) and females (median = 61.0, IQR = 39.9–80.4), $U = 2623$, $p = .027$, $r = 0.205$. No other statistical tests achieved statistical significance.

A statistically significant small negative correlation was observed between SPONCS and IDO activity ($r_s = -0.255$, $n = 170$, $p < .001$). Additionally, a statistically significant small positive correlation was found between SPONCS and kynurenic levels ($r_s = 0.196$, $n = 170$, $p = .011$). A weak yet significant positive correlation was also identified between IDO activity and kynurenic acid ($r_s = 0.245$, $n = 168$, $p = 0.001$). Furthermore, a statistically significant medium positive correlation was detected between kynurenic acid and kynurenine ($r_s = 0.355$, $n = 168$, $p < .001$). A medium positive correlation was found between tryptophan and kynurenic acid ($r_s = 0.563$, $n = 166$, $p < .001$). We found a statistically significant small negative correlation between gender and Trp ratio ($r_s = -0.170$, $n = 168$, $p < .027$). None of the measured markers showed any correlation with the patient's age. All correlations are shown in [Table 1](#).

Correlations were observed between Trp, Kyn, and IDO activity; however, these were not reported, as IDO activity is inherently derived from the relationship between Trp and Kyn concentrations. Scatter plots of significant correlations are shown in [Figure 1](#).

Mann-Whitney U tests showed no statistically significant difference in IDO activity between patients with and without glaucoma ($p = .964$), pseudoexfoliation ($p = .921$), or diabetes ($p = .587$). Gender was also not significantly associated with IDO activity ($p = .187$).

Table 1. Heatmap displaying the correlation matrix of the analyzed metabolites, highlighting their relationships with age, SPONCS, and gender.

	SPONCS	<i>p</i> value	Tryptophan	<i>p</i> value	Kynurenic acid	<i>p</i> value	Kynurenine	<i>p</i> value	IDO	<i>p</i> value
Tryptophan	–0.071	.355	—		—		—		—	
Kynurenic acid	–0.075	.335	0.563	<.001	—		—		—	
Kynurenine	0.196	.011	0.362	<.001	0.355	<.001	—		—	
IDO	–0.255	<.001	0.632	<.001*	0.245	.001	–0.424	<.001*	—	
Age	0.122	.114	–0.046	.555	0.071	.362	0.098	.204	–0.103	.183
Gender	–0.075	.332	0.17	.027	0.106	.17	0.101	.189	0.102	.187

Spearman correlations were used to analyze the data with all corresponding *p*-values displayed. Statistically significant *p*-values are highlighted in bold. *P*-values marked with an asterisk (*) represent the correlation between IDO and kynurenine or tryptophan. However, since IDO is a calculated ratio of these two metabolites, these correlations were not considered statistically significant.

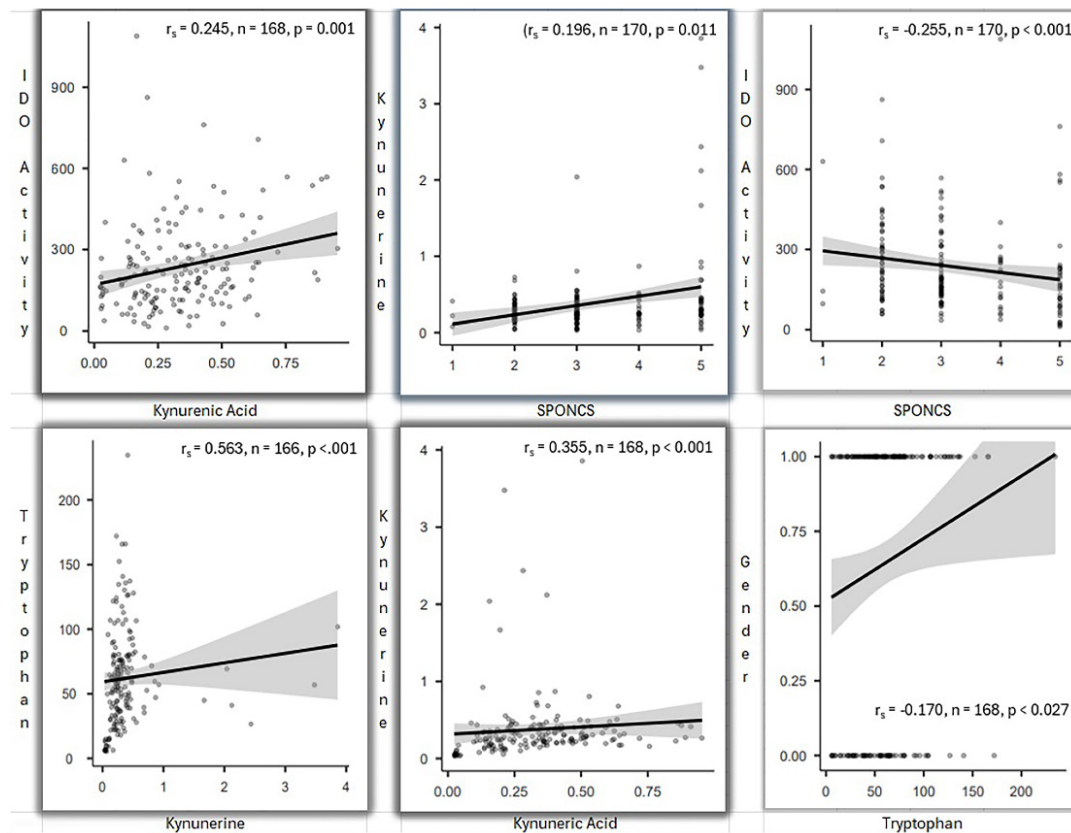


Figure 1. Scatter plot analysis of statistically significant correlations through visual representation.

Discussion

In our prior research, we investigated the metabolic changes associated with cataract progression, with a particular emphasis on the role of nicotinamide adenine dinucleotide (NAD⁺) production in Trp metabolism to convert oxidized GSH to its reduced form.²² In that study, we explored the role of GSH depletion and its downstream effects on metabolic pathways, including kynurenine metabolism and mitochondrial function. The depletion of GSH leads to increased reliance on NAD⁺ and activation of the kynurenine pathway, processes that we observed to be dysregulated in cataract patients. This prior work has been instrumental in framing the metabolic changes observed in the present study, and we hope it provides a foundation for future research focused on oxidative stress markers and their link to metabolic disruptions in cataractogenesis. In the present discussion, we will shift our focus to the impact of IDO activity and Kyn metabolites on cataract progression and our findings in this context.

In our study, the highest IDO activity, as measured by IDO activity, was observed in patients with SPONCS 2 lens hardness. These patients exhibit elevated IDO activity and are more susceptible to progressive yellowing of the lens.

Elevated IDO activity may be a compensatory response to oxidative stress and inflammation occurring in the lens. Enhancing GSH levels within the lens is recommended for these patients to mitigate the progression of cataracts. We also observed a decline in IDO activity as lens hardness increased. The underlying mechanisms behind this reduction are not fully understood, but it may be linked to the apoptosis of lens epithelial cells during the later stages of cataract progression. As the cataract matures and lens hardness increases, a decrease in viable epithelial cells could lead to a reduction in IDO expression. Previous studies have reported that IDO activation exerts a protective effect on corneal endothelial cells.²³ Our results suggest that IDO activity in the lens may similarly be involved in cellular defense mechanisms during cataract formation. Notably, kynurenine levels increased with the progression of cataract hardness and protein aggregation, suggesting a role in driving the morphological changes associated with cataract development. This observation aligns with previous findings, where elevated levels of kynurenine and neopterin have been identified in more advanced stages of cataracts.²⁴

IFN- γ has been implicated in the induction of apoptosis in lens epithelial cells and the subsequent development of cataracts. It is suggested that the formation of kynurenine

through IDO-mediated pathways may contribute to cataractogenesis in the context of chronic inflammation.²⁵ Murine corneal endothelial cells (MCECs) exhibit a consistent, low-level expression of IDO under baseline conditions. Upon exposure to UV-B radiation, there is a dose-dependent upregulation of IDO expression. This UV-B irradiation also induces elevated levels of apoptosis and caspase-3 activity in MCECs. However, the addition of Kyn or the overexpression of IDO in these cells significantly attenuates apoptosis following UV-B exposure.²³ Caspase-3 is a cysteine-aspartate protease responsible for cleaving specific cellular substrates, playing a key role in the execution phase of programmed cell death.²⁶ Caspase-3 plays a dual role by inhibiting reactive oxygen species (ROS) production and being essential for the efficient execution of apoptosis.²⁷ While caspase-3 is primarily linked to apoptosis, there is some evidence suggesting that under certain conditions, it may play a role in pyroptosis as well, though pyroptosis is more commonly associated with caspase-1 activation.²⁸

The cornea and lens are the two most significant tissues responsible for the absorption of UV radiation within the eye. Ascorbic acid present in the aqueous humor plays a critical role in absorbing UVR and offers antioxidant protection against UV-induced damage to the lens surface.²⁹ With aging, structural changes in lens proteins and the progressive yellowing of the lens diminish its ability to transmit UV wavelengths. This age-related reduction in UV transmission is thought to provide enhanced protection to tissues beyond the lens during adulthood.³⁰ UV radiation is known to generate ROS, such as hydroxyl, peroxy, and superoxide radicals, which induce photodamage to protein residues, including Trp, tyrosine, methionine, and cysteine. This oxidative damage is a key factor in the pathogenesis of cataractogenesis, with excited-state tryptophan playing a critical role in the photodamage reaction.³¹ Age-related lens coloration and fluorescence likely result from the covalent binding of UV filters, such as kynurenine, to crystallins, driven by the formation of reactive α,β -ketoalkenes. GSH effectively inhibits this process by intercepting reactive intermediates, while ascorbate has little impact and NADH provides protection through both reduction of intermediates and competition for binding sites on crystallins.³² While GSH concentration in the lens has been shown to decrease with age, this decline is associated with increased oxidative stress and the accumulation of damaged proteins, both of which contribute to cataract formation.³³ The reduction in GSH levels impairs the lens's ability to neutralize ROS, leading to further oxidative damage. Recent findings suggest that IDO1 activity suppresses ferroptosis by the cystine/glutamate antiporter system X_c⁻.³⁴

Kyn metabolites are primarily present in the lens to protect it from oxidative damage induced by constant exposure to UV light. These metabolites can be categorized into two groups: the primary group, which includes kynurenine, 3-hydroxykynurenine (3OHKG), and 3-hydroxykynurenine O- β -d-glucoside, and the secondary group, which comprises 4-(2-aminophenyl)-4-oxobutanoic acid and glutathionyl-

kynurenine. Notably, the metabolites in the secondary group are more effective as photosensitizers. The ratio of these primary and secondary filters in the human lens declines with age, resulting in a reduced efficiency of secondary UV filters, thereby increasing susceptibility to UV-induced damage.³⁵ The conversion of kyn to 3OHKG could be implicated in cataract progression.³⁶ 3OHKG triggers apoptosis in human lens epithelial cells.³⁷ Previous studies have shown that xanthurenic acid can induce apoptosis-like cell death in human lens epithelial cells, involving mitochondrial damage and DNA fragmentation at high concentrations.³⁸ However, it is important to note that xanthurenic acid and related apoptotic markers were not assessed in the present study.

Our findings revealed elevated levels of kynurenic acid in patients with higher levels of IDO activity. This could possibly suggest that other kynurenines are likely elevated. These results point to a potential therapeutic strategy: reducing kynurenine metabolites could help mitigate the pathological changes associated with cataract progression. Targeting the kynurenine pathway may therefore offer a novel approach for delaying or preventing cataract development.

Although GSH and its oxidized form were not measured in the present study, previous research has suggested that oxidative stress and redox imbalance may influence IDO activity.³⁹ While this connection remains to be directly validated in the lens, exploring the relationship between GSH status and IDO activity may offer useful insights in future studies. Therapeutic strategies aimed at enhancing antioxidant defenses, such as GSH supplementation, have been proposed in the context of cataract prevention but require further investigation.⁴⁰ In selenite-induced cataract models, the Tephrosia purpurea extracts significantly reduced malondialdehyde levels and prevented the depletion of reduced glutathione.⁴¹ This suggests that targeting oxidative stress, in conjunction with reducing kynurenine metabolites, may provide a dual therapeutic approach to slow cataract development and improve lens clarity. It seems plausible that giving taurine supplementation might benefit patients experiencing symptoms linked to Trp metabolite accumulation.⁴²

Our findings demonstrate a clear association between cataract progression and IDO activity. While age has been identified as a contributing factor to lens hardness, it is plausible that aging may result in decreased levels of GSH, necessitating alternative mechanisms for lens protection against UV light. Age may not be the sole determinant of cataract progression; rather, the extent of IDO activity could play a more critical role.

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Data availability statement

All data generated or analyzed during this study are presented within this article. Additional information is available upon request by contacting the corresponding author.

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Article

Assessment of Kynurenine Pathway Enzyme Activity in Ocular Diseases: Associations with Cataract, Diabetes, Glaucoma, and Pseudoexfoliation Syndrome

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Abstract

Purpose: To investigate the role of the kynurenine pathway (KP) in ocular diseases by evaluating the activity of key enzymes—kynurenine aminotransferase (KAT) and kynurenine monooxygenase (KMO)—and the 3-hydroxykynurenine to kynurenic acid (3-HK/KYNA) ratio in relation to cataract severity, diabetes, glaucoma, and pseudoexfoliation syndrome (PEXS). **Methods:** Tryptophan metabolite levels were measured in patients undergoing cataract surgery and stratified by SPONCS grading and comorbid conditions. KAT and KMO activities were estimated using metabolite ratios (KYNA/KYN and 3-HK/KYN, respectively). Statistical analyses included Kruskal–Wallis tests with post hoc comparisons and Mann–Whitney U tests. **Results:** KAT activity declined significantly with increasing SPONCS grade ($p = 0.014$), suggesting a progressive loss of KYNA production and antioxidative capacity in advanced cataracts. Diabetic patients exhibited higher KMO activity ($p = 0.039$) and elevated 3-HK/KYNA ratios ($p = 0.013$), indicating a metabolic shift toward oxidative stress and neurotoxicity. Similarly, glaucoma patients had significantly increased KMO activity ($p = 0.032$), consistent with enhanced 3-HK-mediated retinal ganglion cell damage. In contrast, PEXS showed no significant alterations in KP markers. **Conclusions:** The kynurenine pathway is differentially modulated in ocular diseases. A decline in KAT activity correlates with cataract severity, while upregulation of KMO is prominent in diabetes and glaucoma, revealing disease-specific metabolic dysregulation. Targeting KMO to reduce toxic metabolite accumulation or enhancing KYNA synthesis may offer novel therapeutic avenues. These findings also support the potential of KP metabolites as biomarkers for disease monitoring and progression.

Keywords: kynurenine pathway; cataract; glaucoma; diabetes; kynurenine aminotransferase; kynurenine monooxygenase; 3-Hydroxykynurenine; kynurenic acid; oxidative stress; ocular metabolism



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1. Introduction

The kynurenine pathway (KP) is the principal route of tryptophan catabolism, generating metabolites that serve as UV filters in the lens, modulators of neurotransmission in the retina, and mediators of redox balance throughout the eye [1]. This pathway generates various metabolites, such as kynurenine (KYN), kynurenic acid (KYNA), and 3-hydroxykynurenine (3-HK), which have been implicated in both protective and harmful

roles in various physiological and pathological processes [2]. Kynurenines such as 3-HK absorb ultraviolet light but can undergo oxidative transformation to form protein-bound adducts, contributing to lens opacification and cataractogenesis [3,4]. Elevated levels of KP metabolites, such as KYN and 3-HK, have been observed in the lenses of patients with cataracts. These metabolites can modify lens proteins, leading to oxidative stress and cross-linking of α -crystallins, which are critical for maintaining lens transparency [5].

Kynurenine aminotransferases (KATs) direct flux toward KYNA, a broad-spectrum antagonist of excitatory amino acid receptors with documented neuroprotective and antioxidant effects [6,7]. In retinal models, elevated KYNA levels—whether via KAT activity or Kynurenine 3-monooxygenase (KMO) inhibition—mitigate ischemia/reperfusion injury and protect retinal ganglion cells from excitotoxic death [8]. KMO catalyzes the conversion of KYN to 3-HK, a neurotoxic precursor of quinolinic acid and reactive oxygen species [9]. Dysregulated KMO activity and subsequent 3-HK accumulation have been implicated in both diabetic cataract formation and glaucomatous retinal damage, linking metabolic flux through this branch to ocular oxidative stress [10].

Nuclear cataract severity is objectively quantified by the Simplified Pre-Operative Nuclear Classification Score (SPONCS), a reproducible grading system strongly correlated with lens density and intraoperative outcomes [11]. Despite growing interest in KP metabolites as biomarkers, no study has yet mapped KAT and KMO activities across SPONCS grades to elucidate how flux through each branch relates to cataract severity. In systemic disease, diabetes mellitus hyperactivates indoleamine 2,3-dioxygenase (IDO) and downstream KP enzymes, driving KMO flux and oxidative stress in both lens and retinal tissues [12]. Recent work demonstrated progressive increases in aqueous humor IDO activity correlating with cataract severity (SPONCS 2 vs. SPONCS 5, $p = 0.013$), suggesting kynurenine pathway activation contributes to oxidative stress in lens epithelial cells during cataractogenesis [13]. In diabetic patients, the accumulation of KYN and its metabolites in the aqueous humor and lenses is significantly higher compared to non-diabetic individuals. This accumulation is associated with oxidative damage and advanced glycation end-product (AGE) formation, which accelerates cataract progression [14]. Glaucoma is characterized by progressive retinal ganglion cell loss and optic nerve degeneration [15]. Its pathogenesis involves oxidative damage and excitotoxicity to retinal ganglion cells, processes that may be exacerbated by an imbalance between KAT and KMO-mediated metabolites [16]. Studies have shown that the levels of KYN and its derivatives, such as KYNA, are significantly altered in the aqueous humor of glaucoma patients. These changes are associated with mitochondrial dysfunction and oxidative stress, which contribute to retinal ganglion cell (RGC) death [17]. KP imbalance exacerbates retinal neurodegeneration: preclinical studies show that optic nerve injury or NMDA-induced RGC death triggers downregulation of KAT isoforms and transient KMO upregulation, leading to elevated 3-HK and depleted KYNA [1]. In a murine model of hereditary glaucoma, reduced levels of tryptophan and KP metabolites, such as KYNA and KYN, were observed in the retina. This suggests that imbalances in the KP may play a role in the progression of glaucoma [18]. Conversely, pseudoexfoliation syndrome (PEXS) is characterized by extracellular matrix abnormalities and oxidative stress, but its relationship to KP enzyme activity has not been clearly defined [19]. While PEXS has long been associated with oxidative stress, recent metabolomic evidence reveals a potential link to ferroptosis [20].

Our study aims to evaluate the relationship between KP enzyme activities and key ocular phenotypes by correlating KAT and KMO activities measured indirectly via KYNA/KYN and 3-HK/KYN ratios with nuclear cataract severity as graded by SPONCS and determining how these activities differ in patients with diabetes, glaucoma, and PEXS. We also assess the 3-HK/KYNA ratio as an index of the balance between the neurotoxic

(KMO-driven) and neuroprotective (KAT-driven) branches of the pathway. By linking enzymatic flux through each branch of the pathway to clinical measures of disease, we seek to clarify the contribution of KP dysregulation to ocular pathology and identify potential targets for therapeutic intervention.

2. Materials and Methods

2.1. Study Group

This cross-sectional investigation examined aqueous humor specimens obtained from 101 individuals undergoing cataract surgery at Pauls Stradiņš Clinical University Hospital. The cohort comprised 32 male and 69 female participants, with a mean age of 74.7 years (± 9.06 SD) and an age range of 50–94 years. Cataract severity was evaluated using the SPONCS classification system, which hierarchically categorizes nuclear opalescence and coloration across eight incremental stages (SPONCS 1 to 5, with intermediate “+” designations). Patients were categorized by their SPONCS classification levels. The study included 34 patients (33.7%) with SPONCS 2/2+, 33 patients (32.7%) with SPONCS 3/3+, 12 patients (11.9%) with SPONCS 4/4+, and 22 patients (21.8%) with SPONCS 5. Patients with the mildest classification (SPONCS 1) were not included in the study.

The study included participants with age-related macular degeneration. However, since baseline AMD status was not systematically recorded prior to surgery, this represents an important limitation in our data collection that may affect the interpretation of results. Although AMD patients were present in the cohort, the absence of standardized phenotyping (e.g., AREDs classification, OCT/angiography) precluded subgroup analysis. We posit that serum KP metabolites—reflecting systemic inflammation—may better correlate with AMD progression than aqueous humor, given its posterior segment locus. Future studies should prioritize serum KP profiling in dedicated AMD cohorts. The distribution of ocular comorbidities and their relationships within the study cohort are detailed in Tables 1–4.

Table 1. Comparison of age, sex, and ocular comorbidities across SPONCS severity groups.

	SPONCS 2/2+ (n = 34)	SPONCS 3/3+ (n = 33)	SPONCS 4/4+ (n = 12)	SPONCS 5 (n = 22)	<i>p</i> -Value
Age, mean (SD)	72.1 $\pm$ 9.95	78.2 $\pm$ 6.39	77.5 $\pm$ 8.36	71.0 $\pm$ 9.76	0.021
Gender					0.205
Male	10 (9.9%)	8 (7.9%)	3 (3.0%)	11 (10.9%)	
Female	24 (14.1%)	25 (24.8%)	9 (8.9%)	11 (10.9%)	
Glaucoma					0.256
Present	6 (5.9%)	10 (9.9%)	2 (14.1%)	2 (2.0%)	
Absent	28 (27.7%)	23 (22.8%)	10 (9.9%)	20 (19.8%)	
Pseudoexfoliation syndrome					0.011
Present	9 (8.9%)	22 (21.8%)	5 (10.9%)	11 (10.9%)	
Absent	25 (24.8%)	11 (10.9%)	7 (6.9%)	11 (10.9%)	
Diabetes					0.796
Present	9 (8.9%)	11 (10.9%)	5 (5.0%)	7 (6.9%)	
Absent	25 (24.8%)	22 (21.8%)	7 (6.9%)	15 (14.9%)	

Age distributions were compared using one-way ANOVA, while categorical variables were analyzed with chi-square tests. Bold *p*-values denote statistically significant differences ($p < 0.05$).

Table 2. Association between glaucoma status and patient demographics, cataract severity, diabetes, and pseudoexfoliation syndrome.

	Glaucoma (n = 20)	No Glaucoma (n = 81)	p-Value
Age, mean (SD)	74.2 ± 7.80	74.9 ± 9.38	0.771
Gender			0.857
Male	6 (5.9%)	26 (33.9%)	
Female	14 (13.9%)	55 (54.5%)	
Cataract severity			0.256
SPONCS 2/2+	6 (5.9%)	28 (27.7%)	
SPONCS 3/3+	10 (9.9%)	23 (22.8%)	
SPONCS 4/4+	2 (2.0%)	10 (9.9%)	
SPONCS 5	2 (2.0%)	20 (19.8%)	
Pseudoexfoliation syndrome			0.065
Present	13 (12.9%)	34 (33.7%)	
Absent	7 (6.9%)	47 (46.5%)	
Diabetes			0.857
Present	6 (5.9%)	26 (25.7%)	
Absent	14 (13.9%)	55 (54.5%)	

Continuous variables were compared using independent *t*-tests, while categorical variables were analyzed with chi-square tests.

Table 3. Association between pseudoexfoliation syndrome status and patient demographics, cataract severity, diabetes, and glaucoma.

	PEXS (n = 47)	No PEXS (n = 54)	p-Value
Age, mean (SD)	77.7 ± 7.78	72.1 ± 9.33	0.001
Gender			0.634
Male	16 (15.8%)	16 (15.8%)	
Female	31 (30.78%)	38 (37.6%)	
Cataract severity			0.011
SPONCS 2/2+	9 (8.9%)	25 (24.8%)	
SPONCS 3/3+	22 (21.8%)	11 (10.9%)	
SPONCS 4/4+	5 (5.0%)	7 (6.9%)	
SPONCS 5	11 (10.9%)	11 (10.9%)	
Glaucoma			0.065
Present	13 (12.9%)	7 (6.9%)	
Absent	34 (33.7%)	47 (46.5%)	
Diabetes			0.417
Present	13 (12.9%)	19 (18.8%)	
Absent	34 (33.7%)	35 (34.7%)	

Continuous variables were compared using independent *t*-tests, while categorical variables were analyzed with chi-square tests. Bold *p*-values denote statistically significant differences (*p* < 0.05).

Table 4. Association between diabetes status and patient demographics, cataract severity, pseudoexfoliation syndrome, and glaucoma.

	Diabetes (n = 32)	No Diabetes (n = 69)	p-Value
Age, mean (SD)	75.0 ± 8.84	74.6 ± 9.11	0.823
Gender			0.057
Male	6 (5.9%)	26 (25.7%)	
Female	26 (25.7%)	43 (42.6%)	
Cataract severity			0.796
SPONCS 2/2+	9 (8.9%)	25 (24.8%)	
SPONCS 3/3+	11 (10.9%)	22 (21.8%)	
SPONCS 4/4+	5 (5.0%)	7 (6.9%)	

Table 4. Cont.

	Diabetes (n = 32)	No Diabetes (n = 69)	p-Value
SPONCS 5	7 (6.9%)	15 (14.9%)	0.857
Glaucoma			
Present	6 (5.9%)	14 (13.9%)	0.417
Absent	26 (25.7%)	55 (54.5%)	
PEXS			0.417
Present	13 (12.9%)	34 (33.7%)	
Absent	19 (18.8%)	35 (34.7%)	

Continuous variables were compared using independent *t*-tests, while categorical variables were analyzed with chi-square tests.

Prior to surgery, aqueous humor samples were collected via paracentesis using a 27-gauge needle. Depending on availability, between 50 and 120 µL of fluid was carefully aspirated and transferred into sterile Eppendorf tubes. The samples were initially frozen at −18 °C on-site and transported the same day in insulated iceboxes to the Faculty of Materials Science and Applied Chemistry at Riga Technical University. There, they underwent further analysis and were stored long-term at −80 °C to preserve sample integrity.

Ethical oversight was provided by the Riga Stradiņš University Medical Ethics Committee (Approval No. 2-PEK-4/307/2023, dated 21 March 2023), with operational approval granted by Pauls Stradiņš Clinical University Hospital. All participants provided written informed consent, and the study was conducted in full compliance with the ethical principles outlined in the Declaration of Helsinki.

2.2. LC-MS-Based Metabolite Analysis

Aqueous humor metabolites were isolated via methanol-based extraction. Briefly, 10 µL of each sample was aliquoted into Eppendorf tubes and combined with 80 µL methanol and 10 µL isotope-labeled internal standards. The mixture was vortex-mixed for 15 s, followed by centrifugation (10,000 RPM, 10 min) to pellet insoluble debris. The clarified supernatant was collected and transferred to HPLC vials for downstream analysis.

Quantitative metabolite profiling was performed using hydrophilic interaction liquid chromatography (HILIC) coupled to a high-resolution Orbitrap Exploris 120 mass spectrometer (Thermo Fisher Scientific, Waltham, MA, USA). Chromatographic separation was achieved on an ACQUITY UPLC BEH Amide column (2.1 × 100 mm, 1.7 µm; Waters, Milford, MA, USA) maintained at 40 °C. The mobile phase comprised (A) 0.15% formic acid and 10 mM ammonium formate in water and (B) 0.15% formic acid and 10 mM ammonium formate in 85% acetonitrile. A stepwise gradient was applied as follows: initial conditions at 100% B (0–6.0 min), followed by a rapid reduction to 94.1% B (6.0–6.1 min), a gradual decline to 82.4% B (6.1–10.0 min), and a final decrease to 70.6% B (10.0–12.0 min). The column was re-equilibrated at 100% B for 6 min, yielding a total run time of 18 min. The flow rate was fixed at 0.4 mL/min, with an injection volume of 2 µL.

Electrospray ionization was conducted in both positive and negative modes, with spray voltages set to 3.5 kV (positive) and 2.5 kV (negative). Full-scan MS data were acquired across a mass range of 50–600 *m/z* at a resolution of 60,000. Operational parameters included a capillary temperature of 350 °C, auxiliary gas flow rate of 12 arbitrary units, nebulizer gas flow rate of 50 arbitrary units, and heater temperature of 400 °C. Quantitation relied on seven-point calibration curves with internal standardization, processed using TraceFinder 5.1.1 software (Thermo Fisher Scientific).

Metabolites were unequivocally confirmed at identification level A [21] by matching retention times (RT) and accurate *m/z* values (<5 ppm error) to authenticated reference standards analyzed under identical conditions.

2.3. Enzyme Identification

KAT activity was estimated indirectly by calculating the ratio of KYNA to KYN. The KYNA/KYN ratio is widely used as a surrogate for net KAT activity in biological samples [22,23]. While this ratio provides a useful index of net transamination activity directed toward KYNA formation, it does not fully represent the intrinsic catalytic properties of the KAT enzymes. Specifically, the KYNA/KYN ratio is influenced by factors such as the availability of the cofactor pyridoxal 5'-phosphate, the presence and concentration of the necessary 2-oxoacid cosubstrate, and the relative activities of competing metabolic pathways (e.g., the metabolism of 3-HK to xanthurenic acid) [24,25]. Moreover, it does not provide kinetic parameters such as $V_{\max}$ and K_m , which are critical for a comprehensive characterization of enzyme function. Therefore, while changes in this ratio reflect alterations in net KYNA production, they do not completely capture the full scope of KAT enzymatic activity.

KMO activity was estimated indirectly by calculating the ratio of 3-HK to KYN. The 3-HK/KYN ratio serves as a practical index of KMO-mediated hydroxylation of KYN to 3-HK [26]. While this ratio serves as a practical indicator of net KMO activity, it does not fully represent the intrinsic kinetic properties of the enzyme, which can be influenced by cofactor availability, competing metabolic pathways, and the downstream metabolism of 3-HK. KMO relies on NADPH and FAD; fluctuations in cellular redox status can decouple the ratio from true enzyme capacity [27]. Thus, although useful for relative comparisons under our experimental conditions, the 3-HK/KYN ratio represents an indirect measure of KMO activity.

In our study, we also calculated the ratio of 3-HK to KYNA as an index of the balance between the neurotoxic and neuroprotective arms of the KP. Reflects the balance between neurotoxic (KMO) and neuroprotective (KAT) branches [28]. Although this ratio serves as a useful biomarker, reflecting the relative flux through KMO compared to KAT-mediated reactions, it should be interpreted with caution. The 3-HK/KYNA ratio is affected by the availability of substrates, cofactors, and the activity of competing metabolic routes, and therefore, it provides an indirect measure of enzymatic control rather than a direct kinetic assessment of KMO or KAT activity.

Using metabolite ratios such as KYNA/KYN for KAT activity and 3-HK/KYN for KMO activity is a common indirect approach that offers practical insights into pathway flux but does not substitute for direct kinetic characterization. These ratios are influenced by cofactor (e.g., pyridoxal-5'-phosphate, NADPH/FAD) availability, cosubstrate concentrations, and competing metabolic branches (e.g., xanthurenic or quinolinic acid formation).

2.4. Statistics

Normality of the data distribution was assessed using the Shapiro–Wilk test. For data that did not conform to a normal distribution, non-parametric statistical methods were employed. Specifically, the Mann–Whitney U test was used to compare differences between two independent groups. For comparisons involving more than two groups, a non-parametric one-way ANOVA (Kruskal–Wallis test) was applied. All statistical analyses were performed using the Jamovi 2.6.25. software platform. Data tables were prepared in Microsoft Excel. Notably, metabolite concentrations obtained via MS-LC were analyzed as raw values without normalization.

3. Results

In our study, KAT activity was different between groups [$X^2(3) = 10.63$, $p = 0.014$, $\epsilon^2 = 0.1063$]. Specifically, the median KAT activities were as follows: SPONCS 2/2+—1.598 (IQR: 0.974–2.47), SPONCS 3/3+—1.273 (IQR: 0.776–1.93), SPONCS 4/4+—1.192

(IQR: 0.726–1.62), and SPONCS 5—0.738 (IQR: 0.231–1.50). Post hoc analysis revealed that the largest difference was between SPONCS 2 and SPONCS 5 ($p = 0.017$). In contrast, neither KMO activity nor the 3-HK/KYNA ratio differed among the cataract groups. The observed decrease in KAT activity from SPONCS 2 to SPONCS 5 reveals a shift in the KP away from the production of KYNA, a neuroprotective metabolite. This shift could contribute to increased oxidative stress and neurotoxicity, potentially exacerbating cataract severity.

When comparing patients with and without diabetes, we found that KMO activity was increased more in diabetic patients (median = 0.765, IQR = 0.498–1.095) than in non-diabetic patients (median = 0.545, IQR = 0.364–0.802); this was supported by a Mann–Whitney U test ($U = 820$, $p = 0.039$, $r = 0.257$). Moreover, the 3-HK/KYNA ratio was elevated in diabetic patients (median = 0.668, IQR = 0.306–1.215) compared to those without diabetes (median = 0.401, IQR = 0.401–0.717; $U = 764$, $p = 0.013$, $r = 0.308$). KAT activity, however, did not show significant differences in relation to diabetes status. Elevated KMO activity and a higher 3-HK/KYNA ratio in diabetic patients indicate a metabolic shift toward the production of 3-HK, a metabolite associated with oxidative stress and neurotoxicity. This alteration may contribute to the development of diabetic cataracts and other ocular complications associated with diabetes.

For patients with glaucoma, KMO activity was elevated (median = 0.819, IQR = 0.601–1.085) compared to non-glaucoma patients (median = 0.526, IQR = 0.368–0.824; $U = 558$, $p = 0.032$, $r = 0.3111$), while no statistically significant differences were observed for KAT activity or the 3-HK/KYNA ratio between the glaucoma groups. The increased KMO activity observed in glaucoma patients suggests enhanced production of neurotoxic metabolites like 3-HK, which could contribute to RGC damage and optic nerve degeneration characteristic of glaucoma.

Lastly, in the group with PEXS, none of the measured values (KAT activity, KMO activity, or the 3-HK/KYNA ratio) reached statistical significance. The lack of changes in KAT and KMO activities or the 3-HK/KYNA ratio in PEXS patients implies that the KP may not be directly involved in the pathogenesis of PEXS. This aligns with studies indicating that PEX is associated with other mechanisms, such as oxidative stress and extracellular matrix abnormalities.

Overall, while the KYNA/KYN ratio (for estimating KAT activity) and the 3-HK/KYNA ratio (for assessing the balance between the neurotoxic and neuroprotective branches of the pathway) provide valuable indirect measures, our findings indicate that alterations are mainly observed in KMO activity in specific subgroups (i.e., diabetes and glaucoma) and in KAT activity across SPONCS severity levels. These indices should be interpreted within the context of the limitations inherent to indirect biochemical assays.

4. Discussion

4.1. Cataract

Progressive diminution of KAT activity from SPONCS grade 2 through grade 5 cataracts implies a stage-dependent reprogramming of lens tryptophan metabolism that parallels disease progression. In the earliest stage (SPONCS 2), elevated KAT activity may represent an intrinsic antioxidative mechanism [29]: by transaminating KYN to KYNA, KAT enzymes reduce ROS accumulation and slow protein aggregation. As cataract severity advances, the observed, stepwise attenuation of KAT activity likely reflects cumulative oxidative insult and progressive depletion of essential cofactors—most notably pyridoxal phosphate—or direct oxidative inactivation of the enzyme complex. By SPONCS 5, this decline in KAT function not only impairs KYNA-mediated photoprotection but also shunts KYN metabolism toward neurotoxic intermediates, such as 3-HK and quinolinic acid,

which have been implicated in crystallin cross-linking and exacerbation of lens opacity in cataracts [30]. Moreover, reduced KAT activity may exacerbate NAD^+ depletion [31,32], undermining lens cellular repair processes and redox equilibrium.

Despite the progressive decrease in KAT activity, KMO activity and the systemic 3-HK/KYNA ratio remain ostensibly unaltered across SPONCS grades, suggesting either stringent regulatory control of these enzymatic branches or enhanced catabolism of their metabolites. This differential vulnerability underscores the pivotal role of KAT in maintaining lens transparency, whereas broader modulation of the KP may necessitate complementary interventions targeting multiple enzymatic nodes.

Given the modest effect size observed ($\epsilon^2 = 0.1063$), it is probable that additional variables—such as genetic polymorphisms, ultraviolet light exposure, or metabolic comorbidities—contribute to interindividual disparities in KAT activity. Accordingly, future investigations should incorporate targeted metabolomic analyses of aqueous humor or ex vivo lens tissue to substantiate these findings. From a translational perspective, early-stage (SPONCS 2/2+) lenses may benefit from pharmacologic strategies aimed at preserving KAT cofactor availability (for example, vitamin B₆ supplementation), whereas advanced-stage cataracts might require adjunctive therapies to scavenge 3-HK-derived radicals or replenish NAD^+ pools, thereby restoring redox homeostasis and decelerating opacification.

4.2. Diabetes

Our study reveals significant dysregulation of the KP marked by elevated KMO activity and an increased 3-HK/KYNA ratio. These alterations suggest a diabetes-induced metabolic shift favoring 3-HK production. This shift may enhance local oxidative stress within the eye, potentially contributing to the pathogenesis of diabetic ocular complications [33].

Chronic hyperglycemia is known to induce oxidative stress and inflammation—factors that can upregulate KMO expression via pathways involving NF- κ B [34] or HIF-1 α [35]. Increased KMO activity accelerates the conversion of KYN to 3-HK and downstream toxic metabolites such as quinolinic acid. This could lead to direct damage of ocular structures through mechanisms including protein glycation—whereby 3-HK reacts with lens crystallins to form AGEs [36] and mitochondrial dysfunction via the generation of ROS, both of which contribute to lens opacification and retinal injury.

The elevated 3-HK/KYNA ratio observed in diabetic patients highlights an imbalance between the neurotoxic and neuroprotective branches of the KP [37]. While KAT activity appears preserved, KYNA levels may be reduced due to increased consumption as an antioxidant or degradation under hyperglycemic oxidative stress. This selective disruption of the KMO-dependent arm of the KP is consistent with prior studies indicating tissue-specific metabolic alterations in diabetic conditions [38].

These alterations have functional consequences. In cataracts, 3-HK-driven AGE formation likely accelerates lens clouding, while in diabetic retinopathy, increased ROS and pro-inflammatory signaling linked to 3-HK may compromise the blood–retinal barrier and promote diabetic retinopathy via VEGF activation [39]. In patients with comorbid glaucoma, heightened KMO activity may synergize with glaucomatous damage by exacerbating RGC loss through oxidative and excitotoxic mechanisms [40].

These findings underscore the need for further mechanistic and clinical investigations. Future research should focus on quantifying downstream metabolites (e.g., quinolinic acid, NAD^+), assessing KMO transcriptional regulation in diabetic ocular tissues, and evaluating the prognostic value of KP biomarkers in tracking disease progression. Additionally, therapeutic strategies targeting this pathway—such as KMO inhibitors, KYNA analogs, or antioxidant adjuvants—warrant exploration for their potential to mitigate diabetes-associated ocular disease.

4.3. Glaucoma

The marked elevation of KMO activity in glaucoma patients ($p = 0.032$) points to a disease-associated shift in tryptophan metabolism toward the production of neurotoxic metabolites. By catalyzing the conversion of KYN into 3-HK. Elevated activity of KMO may exacerbate glutamate-induced excitotoxicity and promote the generation of ROS, thereby contributing to RGCs degeneration, accelerating optic nerve injury beyond what intraocular pressure alone would predict [41]. The observed increase in KMO activity and the elevated 3-HK/KYNA ratio in patients with glaucoma indicate a potential involvement of KP dysregulation in promoting fibrotic remodeling of the trabecular meshwork. Notably, 3-HK is a pro-oxidant metabolite known to stimulate the release of TGF- β 1 and enhance collagen deposition in trabecular meshwork cells, processes that may contribute to ECM stiffening [42]. These findings implicate the KP in both neurodegenerative and fibrotic mechanisms underlying glaucoma pathophysiology and highlight its components as promising therapeutic targets for modulating disease progression.

Despite the rise in KMO activity, the 3-HK/KYNA ratio remains stable, implying compensatory regulation that could mask imbalances within the retina or optic nerve head. Small, cross-sectional patient cohorts raise concerns about statistical power and the potential for false positives. Many glaucoma patients are on intraocular pressure-lowering medications that can independently influence metabolic pathways, introducing confounding factors that complicate causal inference.

Pro-inflammatory cytokines [43] (TNF- α , IL-6, IFN- γ) and chronic hypoxia [44] from reduced ocular perfusion remain plausible upstream drivers of KMO upregulation. Similarly, although small-molecule KMO inhibitors (such as CHDI-340246) have shown promise in Huntington's models [45], their ocular bioavailability, safety profile, and efficacy in rodent models of ocular hypertension remain untested.

To bridge these gaps, future work should (1) quantify KMO activity and downstream metabolites directly in ocular fluids or post-mortem retina, (2) expand and diversify patient cohorts with rigorous adjustment for multiple comparisons, (3) employ longitudinal designs linking baseline KMO levels to rates of visual field loss and RNFL thinning, and (4) evaluate KMO inhibitors—alone and in combination with NMDA antagonists (e.g., memantine) and antioxidants (e.g., N-acetylcysteine)—in glaucoma-relevant animal models. Such studies will be essential to determine whether targeting the KP can deliver meaningful neuroprotection in glaucoma. Modulating the KP to reduce neurotoxic metabolites and enhance neuroprotective ones, such as KYNA, may provide a therapeutic strategy for glaucoma. Additionally, targeting enzymes like IDO and KMO could help restore balance to the KP and mitigate oxidative stress [1,46].

4.4. Pseudoexfoliation Syndrome

PEXS exhibited no significant changes in KP metrics, including KAT activity, KMO activity, and the 3-HK/KYNA ratio. This preservation of pathway balance reveals that KYN metabolism is not a central driver of PEXS pathogenesis. Instead, PEXS appears to be mediated by non-metabolic mechanisms, primarily involving structural abnormalities in the extracellular matrix (ECM) and localized oxidative stress [47].

PEXS is characterized by the deposition of fibrillar material in ocular tissues, a process closely linked to genetic variants in LOXL1 [48] and dysregulation of TGF- β signaling [49].

The maintained 3-HK/KYNA ratio further supports the notion that compensatory mechanisms may preserve pathway homeostasis in PEXS. Balanced expression of both KAT and KMO, or reduced systemic inflammation compared to other ocular diseases, may prevent the skewing of tryptophan metabolism toward either oxidative or neuroprotective arms.

5. Conclusions

Our study demonstrates that specific kynurenine pathway (KP) disruptions drive distinct ocular pathologies: cataract progression shows a significant decline in KAT activity (KYNA/KYN ratio decreasing with SPONCS grade, $p = 0.014$), while glaucoma and diabetes exhibit elevated KMO activity (increased 3-HK/KYN ratios, $p = 0.032$ and $p = 0.039$, respectively) and neurotoxic 3-HK/KYNA imbalance ($p = 0.013$), with comorbid cases showing amplified effects. In contrast, PEXS displays no KP alterations, confirming the pathway's disease-specific involvement. Future studies should explore correlations between serum and aqueous humor KP metabolite levels to establish minimally invasive biomarkers for ocular pathology monitoring and therapeutic response assessment.

These insights open new avenues for therapeutic intervention. Modulating key enzymes—such as inhibiting KMO to reduce 3-HK toxicity or augmenting KYNA production to enhance neuroprotection—could represent a promising strategy to mitigate vision-threatening complications in at-risk populations. Furthermore, KYN metabolites may serve as accessible biomarkers in the aqueous humor for early diagnosis, disease monitoring, and therapeutic response assessment. Future research should aim to validate these targets in longitudinal clinical cohorts and explore the utility of kynurenine-modulating agents in preclinical and clinical settings.

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Data Availability Statement: The data used to support the findings of this study are available from the corresponding author upon reasonable request.

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Abbreviations

The following abbreviations are used in this manuscript:

KP	Kynurenine pathway
3-HK	3-hydroxykynurenine
KAT	Kynurenine aminotransferase
KYNA	Kynurenic acid
KMO	Kynurenine 3-monooxygenase
NMDA	<i>N</i> -methyl-D-aspartate
IDO	Indoleamine 2,3-dioxygenase
PEXS	Pseudoexfoliation syndrome
AGE	Advanced glycation end-product
ECM	Extracellular matrix

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Pētījuma / pētnieciskā darba nosaukums:

Acs priekšējās kameras dziļuma, intraokulārā šķidruma un perifēro asiņu metaboloma lēcas cietības prognozēšanā kataraktas pacientiem

Pētījumu ētikas komitejas sēdes datums:

23.02.2023.

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Izskatot augstāk minētā pētījuma pieteikuma materiālus, t.sk., protokolu, ir redzams, ka pētījuma mērķi – noteikt lēcas kameras dziļuma, intraokulārā šķidruma tilpuma, kā arī intraokulārā šķidruma un perifēro asiņu metaboloma atšķirības kataraktas pacientiem ar atšķirīgu lēcas brieduma pakāpi, ir paredzēti sasniegt, iesaistot pacientus, bez kāda papildus apdraudējuma veselībai, drošībai un dzīvībai, kļūstot pētījumā (asins un citu audu paraugu ņemšanu un izdarot atbilstošas analīzes, pārbaudes, mērījumus), veicot iegūto datu apstrādi un analīzi, kā arī publicējot iegūtos rezultātus. Personu (pacientu) informēta brīvprātīga piekrišana piedalīties, iegūto personu datu apstrāde un aizsardzība, to pielietošana, glabāšana, anonimitāte un konfidencialitāte ir nodrošināta. Līdz ar to pieteikums atbilst pētījuma ētikas prasībām.

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Komitejas priekšsēdētājs Jānis Vētra

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Projekta nosaukums un Nr. **			

PĒTĪJUMA ZINĀTNISKAIS VADĪTĀJS*

Vārds, uzvārds	Profesore Guna Laganovska (Rīgas Stradiņa universitāte, Paula Stradiņa klīniskā universitātes slimnīca) Docents Juris Vanags (Rīgas Stradiņa universitāte, Paula Stradiņa klīniskā universitātes slimnīca)
Zinātniskā vadītāja paraksts, datums	VSIA „Paula Stradiņa klīniskā universitātes slimnīca” Oftalmoloģijas klīnika Vadītājs ārsts oftalmologs Guna Laganovska 002462-10611 Oftalmologs Juris Vanags P.k. 161280-11902

PĒTĪJUMA NOSAUKUMS

Acs priekšējās kameras dziļuma, tilpuma un intraokulārā šķidruma metaboloma saistība ar lēcas cietību kataraktas pacientiem.

PĒTĪJUMA NORISES VIETA

Klīnika/centrs/nodaļa	Rīgas Stradiņa Universitātes Oftalmoloģijas katedrā un Paula Stradiņa klīniskās universitātes slimnīcas Acu slimību nodaļa.
Klīnikas vadītāja saskaņojums par pētījuma veikšanu : paraksts, datums	VSIA „Paula Stradiņa klīniskā universitātes slimnīca” Oftalmoloģijas klīnika Vadītājs ārsts oftalmologs Guna Laganovska 002462-10611

NORISES LAIKS

Pētījuma norises laiks, norādot sākuma un beigu datumu	01.09.2022. 31.07.2026.
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NEPIECIEŠAMĀS PACIENTU DATU APJOMS**IZMANTOJAMĀS PACIENTU SLIMĪBAS VĒSTURES**

Pētījumā paredzēts izmantot ≤ 300 ☐ $\geq 300^{**}$ ☐ nav paredzēts izmantot vēstures ☒

CITA MEDICĪNISKĀ DOKUMENTĀCIJA UN /VAI DATI

Ir paredzēts izmantot ☒ Veids _____ nav paredzēts izmantot ☐

APTAUJAS, ANKETĒŠANA

Ir paredzēts ☐ nav paredzēts ☒

Piezīmes: Slimības vēsturu diagnožu kodi (SSK-10) vai Slimības vēsturu numuri ja zināmi, cita informācija

Darbs pēc tā pabeigšanas un aizstāvēšanas nododams Zinātniskajā institūtā Jā ☐ Nē ☒

* Šo sadaļu aizpilda studenti, maģistranti un doktoranti

** Šo sadaļu aizpilda, ja pētījums tiek veikts kādas programmas, projekta, granta, starptautiska finansējuma ietvaros

** ja paredzēts izmantot vairāk kā 300 Slimības vēstures, iesniegumam nepieciešams pievienot rakstisku pamatojumu

Slimnīcas atļauja: 11.10.2022.

Zin-1-006 versija 03

/iesniedzēja paraksts, atslēdzums/
 VSIA „Paula Stradiņa klīniskā universitātes slimnīca”
 Zinātniskā institūta
 Zinātnes nodaļas vadītājs
 Pēteris Ersts
 Oftalmologs
 Artūrs Zemītis
 P.k. 161280-13116



/Pacienta vārds, uzvārds/

Personas kods

						-					
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Nodala

Slimības vēstures Nr.

- ✓ manu veselības stāvokli, tai skaitā slimības diagnozi un būtību;
- ✓ ārstēšanas (izmeklēšanas, ķirurģiskas operācijas, procedūras, medicīniskas manipulācijas) mērķi, nepieciešamību, paredzamo apjomu, norisi un izmantojamajām metodēm;
- ✓ ārstniecības riskiem un iespējamajām komplikācijām, sagaidāmajiem rezultātiem un rehabilitācijas plānu;
- ✓ alternatīviem ārstniecības veidiem, ieskaitot neārstēšanas riskus;
- ✓ kā arī atbildes uz visiem mani interesējošiem jautājumiem.

Informāciju pacientam skat. otrajā pusē.

Esmu informēta/s par tiesībām un iespēju atteikties no ārstniecībā izmantojamās metodes, neatsakoties no ārstniecības kopumā, atsaukt doto piekrišanu, parakstot rakstveida atteikumu.

PIEKRĪTU

- ☐ operācijas/izmeklējuma/manipulācijas/
ārstniecības metodes veikšanai
/vajadzīgo pasvītrot/

/apjomu un veidu ieraksta ārstējošais ārsts, ārsta paraksts,
vārds, uzvārds, datums, laiks /

- ☐
- anestēzijai/analģēzijai

/veidu ieraksta anesteziologs, ārsta paraksts, vārds,
uzvārds, datums, laiks /

- ☐
- asins komponentu transfūzijai

/ieraksta ārstējošais ārsts, ārsta paraksts, vārds, uzvārds,
datums, laiks /

Pacients vai pacienta likumiskais pārstāvis

/vārds, uzvārds, paraksts, datums, laiks/**

Arst-005 versija 03

****Informēto piekrišanu dod un paraksta pacients vai, norādot tiesisko pamatu un ievērojot pacienta iepriekš izteikto gribu attiecībā uz ārstniecību:**

- pacienta pilnvarotā persona, ja pacients ir informējis ārstniecības iestādi par pilnvarojumu un tas ietver tiesības piekrist ārstniecībai vai tās metodēm, saņemot informāciju par pacienta veselības stāvokli;
- pacienta laulātais, bet, ja tāda nav- pilngadīgie un rīcīspējīgie radnieki šādā secībā: pacienta bērni, vecāki, brālis vai māsa, vecvecāki, mazbērni, ja pacients sava veselības stāvokļa vai vecuma dēļ pats nespēj pieņemt lēmumu par ārstniecību;
- likumiskais pārstāvis, ja pacients atrodas aizbildnībā vai aizgādībā.

Informācija pacientam

ĶIRURĢISKĀ ACU OPERĀCIJA UN IETEIKUMI PACIENTAM PĒC KATARAKTAS OPERĀCIJAS

- HIV testam piekrītu
- Atļauju izmantot savas slimības datus klīniskam pētījumam

Iespējamās komplikācijas:

- ✓ vietējās anestēzijas un nepieciešamības gadījumā vispārējās anestēzijas komplikācijas – sāpes, medikamentu nepanesamība, vēnu iekaisums, zobu bojājums;
- ✓ asiņošana;
- ✓ brūces sadzīšanas traucējumi – pietūkums, iekaisums, rētainas deformācijas, sepse;
- ✓ acs, tās apkārtnējo audu un nervu bojājums: hematoma, iekaisums, redzes traucējumi, dubultošanās, asaru atteces traucējumi;
- ✓ redzes pazemināšanās pēc operācijas, līdz pat iespējamam redzes zudumam;
- ✓ sekundāras glaukomas attīstīšanās;
- ✓ acs subatrofijas attīstīšanās;
- ✓ acs zaudējums;
- ✓ citu orgānu un sistēmu slimību paasinājumi un akūti stāvokļi;
- ✓ psihiskas izmaiņas;
- ✓ letāls iznākums

Ieteikumi pacientam pēc kataraktas operācijas:

- Pirmās 6 nedēļas pēc operācijas nedrīkst gulēt uz operētās acs ķermeņa puses, strauji noliekties un ilgstoši atrasties ar noliektu ķermeņa augšdaļu (piem., uzkopjot telpas, izmantot slotu, nevis noliekties pie grīdas).
- Nedrīkst lietot grūti sakožamu, cietu pārtiku vai pārtikas produktus (jāizvairās no riekstu, burkānu, cepumu u.c. cietu produktu lietošanas).
- Izvairīties no saaukstēšanās gadījumiem (pirmās 3-4 nedēļas ārpus telpām acs jāpārsien, pēc tam jālieto aizsargbrilles, istabā pārsējs nav vajadzīgs). Izvairīties no ķermeņa atdzišanas vai izmirkšanas.
- Nav ieteicams lasīt, sasprindzināt redzi, taču televizoru var skatīties. Spilgtas gaismas gadījumā lietot aizsargbrilles.
- Aci nedrīkst berzēt, jāizvairās no svešķermeņu un gružu iekļūšanas acī (piem., gatavojot virtuvē, strādājot dārzā, atrodoties vējainā vietā – lietot aizsargbrilles).
- Izvairīties no ūdens, ziepju iekļūšanas acīs. Dušā ejot, pirmajās 3 nedēļās aci vajag pārsiet, lai acī neiekļūtu ūdens.
- Acu pilieni jālieto 6-8 nedēļas pēc operācijas:
 - pirmajās dienās – katru stundu;
 - otrajā nedēļā - 4 reizes,
 - trešajā – ceturtajā nedēļā 2-3 reizes;
 - pēc tam, atkarībā no vajadzības.
 Pie graušanas sajūtas, acī iesmērēt ziedi.
- Neskaidrību gadījumā, konsultēties ar savu ārstējošo vai ģimenes ārstu.

PIEKRĪTU

Pacients vai pacienta likumiskais pārstāvis

_____/vārds, uzvārds, paraksts, datums, laiks/**

Arst-005 versija 02

****Informēto piekrišanu dod un paraksta pacients vai, norādot tiesisko pamatu un ievērojot pacienta iepriekš izteikto gribu attiecībā uz ārstniecību:**
 - pacienta pilnvarotā persona, ja pacients ir informējis ārstniecības iestādi par pilnvarojumu un tas ietver tiesības piekrist ārstniecībai vai tās metodei, sagremt informāciju par pacienta veselības stāvokli;
 - pacienta laulātais, bet, ja tāda nav- pilngadīgie un rīcībspējīgie radnieki šādā secībā: pacienta bērni, vecāki, brālis vai māsa, vecvecāki, mazbērni, ja pacients savā veselības stāvokļa vai vecuma dēļ pats nespēj pieņemt lēmumu par ārstniecību;
 - likumiekie nūretāvie, ja pacients arrosas aizbildnībā vai aizsūdnībā