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Elevated Aqueous Humor Levels of RANTES, Eotaxin, and IP-10 in Fuchs Endothelial Corneal Dystrophy with Cataract: Evidence of Subclinical Inflammation

Carlos M. Ruiz[1]*, Javier L. Moreno[1], Alejandro F. Ortega[1]

[1]Department of Medical and Clinical Sciences, Complutense University of Madrid, Madrid, Spain.

Abstract

This investigation examined the spectrum of chemokines and growth factors present in the aqueous humor (AH) of eyes affected by Fuch's endothelial corneal dystrophy (FECD) together with cataracts, using individuals with cataracts alone as controls. In total, 52 AH samples were obtained prior to cataract extraction (26 from FECD + cataract eyes and 26 from cataract-only eyes). All participants were free of any clinically detectable ocular inflammation during sampling. Concentrations of MCP-1 (CCL2), MIP-1α (CCL3), MIP-1β (CCL4), RANTES (CCL5), eotaxin (CCL11), IP-10 (CXCL10), FGF basic, G-CSF, GM-CSF, PDGF-bb, and VEGF in AH were compared across groups, with measurements performed via the Bio-Plex 200 System (Bio-Rad). Among all analytes, RANTES, eotaxin, and IP-10 showed significantly higher AH levels in FECD + cataract samples relative to cataract controls ($p < 0.05$). These increases suggest heightened inflammatory activity in FECD + cataract eyes. Furthermore, the elevated presence of RANTES, eotaxin, and IP-10 may serve as early biomarkers indicating a risk of FECD in patients presenting with cataracts. Detecting increased biochemical marker levels in individuals not yet clinically diagnosed could justify closer follow-up of the fellow eye for possible FECD development.

Keywords: Cataract, Eotaxin, Fuch's endothelial corneal dystrophy, IP-10, RANTES, VEGF

Corresponding author: Carlos M. Ruiz
E-mail: carlos.ruiz@outlook.com

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Introduction

Fuch's endothelial corneal dystrophy (FECD) is a bilateral, progressive disorder of the corneal endothelium that occurs predominantly in women. This degenerative condition results in endothelial failure, leading to stromal and epithelial swelling and, eventually, to bullous keratopathy, which may culminate in vision loss. FECD exists in two variants: a rare early-onset form and a more prevalent late-onset form. The early form is inherited, becomes evident from infancy or childhood, and often reaches advanced severity between 10 and 20 years of age. The late-onset type typically arises after age 40 and is the form most commonly encountered. Although substantial progress has been made in understanding the genetic and molecular aspects of FECD, its precise pathogenic mechanisms remain uncertain [1, 2]. Globally, it is estimated that roughly 300 million individuals aged 30 and older exhibit FECD features [3].

FECD is frequently associated with an elevated likelihood of developing primary open-angle glaucoma or cataracts [2]. Cataracts involve loss of lens clarity and increased opacification and represent the leading cause of global blindness, affecting approximately 16 million people worldwide [4–6]. Cataractogenesis is primarily related to alterations, aggregation, and deposition of crystallins—the lens proteins responsible for maintaining transparency and refractive power. Age-related cataract is the most common

subtype, typically emerging after 50 years of age [7]. In addition to age and genetic predisposition, risk factors include ultraviolet exposure, diabetes, and long-term corticosteroid therapy [6]. FECD may also contribute to the likelihood of cataract formation.

The mechanisms driving cataract development in patients with FECD remain unresolved. Surgical extraction is the sole definitive management for cataracts; however, FECD eyes require particular perioperative measures to preserve endothelial integrity.

From a clinical standpoint, identifying predictors of FECD—especially during early disease stages—is valuable regardless of concurrent cataract status. If biochemical abnormalities are detected in an individual who has not yet been clinically diagnosed, this may justify more vigilant monitoring of the contralateral eye for early FECD changes. Cytokine profiling of aqueous humor may offer such predictive potential.

Altered cytokine patterns in AH have been documented in numerous ocular disorders, yet information regarding AH cytokine characteristics in FECD and/or cataracts remains limited.

This study therefore assessed selected chemokines, primarily from the CC (β) family—MCP-1/CCL2, MIP-1α/CCL3, MIP-1β/CCL4, RANTES/CCL5, IP-10/CXCL10, and the eosinophil-directed chemotactic factor eotaxin/CCL11—along with growth factors including VEGF, FGF basic, G-CSF, and PDGF-bb. These molecules have roles in the pathophysiology of various ocular conditions, such as age-related macular degeneration, glaucoma, proliferative retinopathies, neovascular processes, and uveitis [8–10]. Based on this, we proposed that they may also contribute to FECD development. Consequently, the goal of this research was to characterize chemokine and growth-factor profiles in the AH of individuals with FECD and cataracts compared with cataract-only controls.

Results and Discussion

Table 1 provides an overview of the ophthalmic measurements that showed statistical relevance, together with the associated p-values for comparisons between the study cohorts. The ratio of women to men did not differ meaningfully between groups (p = 0.09). Age distributions were likewise comparable. Median visual acuity reached 0.180 (range 0.0200–1.000**)**, and median intraocular pressure measured 15.00 mmHg (range 11.00–20.00).

Table 1. Summary of ophthalmic variables demonstrating statistical significance.

Variable	FECD + Cataract Group	Cataract Only (Control) Group	p-value
	Median (Min – Max)	Median (Min – Max)	
Best-corrected visual acuity (decimal)	0.10 (0.02 – 0.60)	0.40 (0.02 – 1.00)	0.001
Endothelial cell density (cells/mm²)	1282.00 (886.0 – 1395.00)	2452.00 (1908.00 – 3331.00)	0.01
Cylinder (D)	−1.28 (−18.10 – −0.46)	−0.56 (−4.09 – 0.00)	0.001
Cylinder axis (degrees)	118.00 (10.00 – 179.00)	32.00 (0.00 – 177.00)	0.03

Visus—visual performance index; ECD—endothelial cell count; CYL—astigmatic cylinder derived from keratometric curvature values (Δk, axis); AXIS—orientation of the keratometric cylinder.

The median spherical refraction was 1.00 D (spanning −14.00 to 7.00). Cylindrical refractive error showed a median of −0.75 D (interval −4.00 to 0.00), while the median cylinder axis was 70.0° (range 0.00–179.00). Endothelial cell density displayed a median of 2404.0 cells/mm², varying from 886.00 to 3331.00. For keratometry, the flat K1 value had a median reading of 43.89 D (range 29.51–59.80) with an axis of 75.0° (range 0.00–179.00). The steep K2 median equaled 44.54 D (range 15.68–65.70) and its axis median was 92.0° (range 90.00–174.00). The cylindrical power median measured −0.80 D (extending from −18.1 to 0.00).

Figures 1–3 depict the concentrations of RANTES, eotaxin, and IP-10. **Table 2** lists all chemokines analyzed. Mean aqueous humor values for RANTES, eotaxin, and IP-10 were markedly higher in the FECD + cataract group relative to the cataract/control cohort (p = 0.04, 0.001, 0.01). In contrast, MIP-1α, MCP-1, and MIP-1β showed no meaningful differences **(Table 2)**.

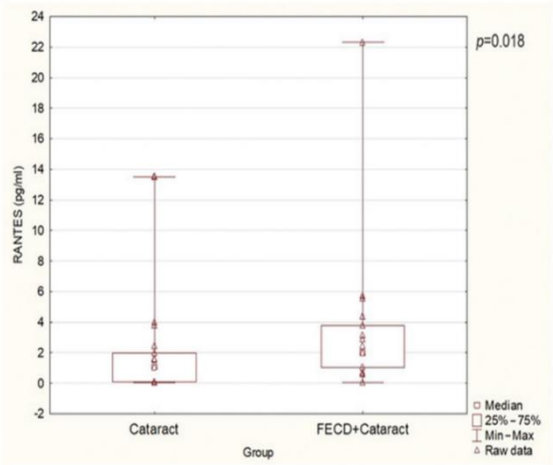

Figure 1. Aqueous humor RANTES (CCL5) levels (p = 0.018).

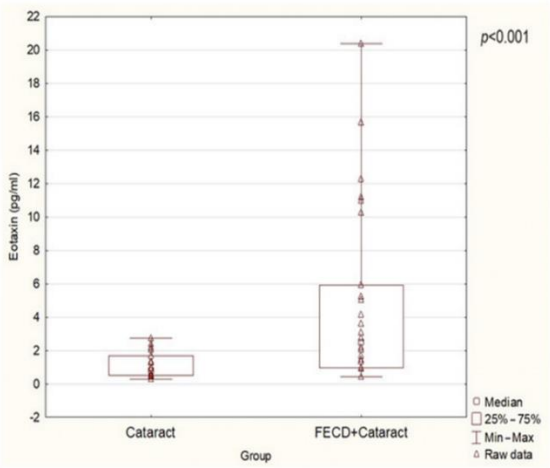

Figure 2. Aqueous humor eotaxin (CCL11) levels (p = 0.001).

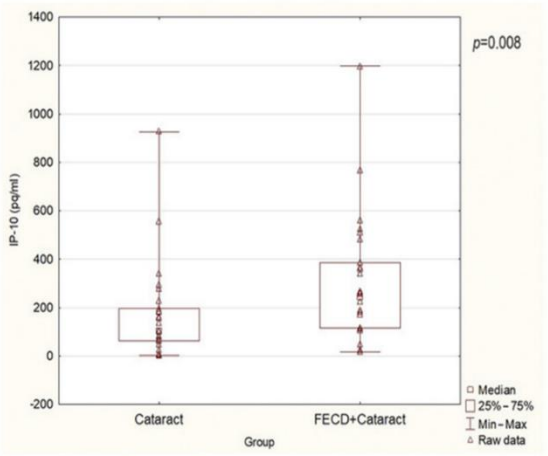

Figure 3. Aqueous humor IP-10 (CXCL10) levels (p = 0.008).

Table 2. Concentrations of chemokines detected in aqueous humor samples.

Cytokine/Chemokine [pg/mL]	FECD + Cataract (n=26)	Cataract only (Control, n=26)	p-value
	Median (Min – Max)	Median (Min – Max)	
MCP-1 (CCL2)	462.36 (60.37 – 6239.71)	301.26 (0.30 – 4025.51)	0.284
MIP-1α (CCL3)	0.52 (0.08 – 4.41)	0.52 (0.01 – 16.69)	0.545
MIP-1β (CCL4)	6.85 (2.09 – 130.06)	5.22 (0.28 – 359.61)	0.558
RANTES (CCL5)	1.98 (0.03 – 22.32)	1.04 (0.04 – 13.51)	0.018
Eotaxin (CCL11)	2.46 (0.42 – 20.37)	0.77 (0.27 – 2.74)	<0.001
IP-10 (CXCL10)	239.99 (16.73 – 1197.18)	100.98 (1.40 – 925.68)	0.008
IFN-γ	4.00 (0.97 – 15.31)	2.66 (0.13 – 15.08)	0.220

MCP-1 (CCL2)—monocyte chemotactic protein-1; MIP-1α (CCL3)—macrophage inflammatory protein-1α; MIP-1β (CCL4)—macrophage inflammatory protein-1β; RANTES (CCL5)—regulated on activation, normal T-cell expressed and secreted; eotaxin (CCL11)—eosinophil-selective chemotactic agent; IP-10 (CXCL10)—IFN-γ-inducible protein-10; IFN-γ—interferon-gamma.

Table 3 summarizes the aqueous humor levels of the analyzed growth factors. None of the five molecules (FGF-basic, GM-CSF, PDGF-BB, G-CSF, VEGF) showed statistically reliable variation between the two cohorts.

Table 3. Growth factor concentrations in aqueous humor.

Growth Factor	FECD + Cataract (n=26)	Cataract only (Control, n=26)	p-value
	Median (Min – Max)	Median (Min – Max)	
FGF basic	5.87 (3.52 – 651.72)	5.87 (0.72 – 13.69)	0.940
G-CSF	6.60 (0.41 – 76.99)	1.44 (0.07 – 124.56)	0.090
GM-CSF	0.28 (0.17 – 1.91)	0.29 (0.02 – 1.18)	0.620
PDGF-BB	4.71 (2.79 – 42.27)	4.71 (4.19 – 11.00)	0.590
VEGF	15.62 (3.34 – 132.84)	7.25 (0.24 – 40.77)	0.260

FGF basic—fibroblast growth factor-2; G-CSF—granulocyte colony-stimulating factor; GM-CSF—granulocyte-macrophage colony-stimulating factor; PDGF-BB—platelet-derived growth factor BB; VEGF—vascular endothelial growth factor.

Although the group differences were not statistically validated, G-CSF and VEGF exhibited higher median values in the FECD + cataract eyes (6.60 vs. 1.44 for G-CSF; 15.62 vs. 7.25 for VEGF) when compared with the cataract/control group.

The visual system possesses a distinct immunological environment shaped by the eye's structural layout, functional characteristics, and specialized components that maintain ocular stability. These anatomical and physiological features give rise to barriers responsible for sustaining immune privilege. The aqueous humor (AH),

which supports the cornea and lens, contains molecules with anti-inflammatory and immunomodulatory activity and additionally clears metabolic waste while delivering essential nutrients [11, 12]. When exposed to various stimuli—such as environmental insults, surgical intervention, or coexisting illnesses—pro-inflammatory mediators may enter the AH, potentially promoting ocular pathology.

Because cataract and FECD frequently occur together in clinical settings, and because this coexistence complicates surgical planning, we sought to identify biological indicators that might distinguish cataract patients with underlying FECD from those with cataracts alone. Ideally, such indicators could be applied pre-operatively to guide endothelial-preserving surgical strategies. Given current progress in ocular immunology, we concentrated on chemokines and growth-related signaling molecules.

Chemokines—recognized since the 1990s—participate in numerous regulatory and immune-driven processes, including intracellular signaling, defense responses, leukocyte recruitment, adhesion molecule activation, immune cell differentiation, programmed cell death, vascular formation, and developmental pathways. They are also implicated in inflammatory, autoimmune, and proliferative disorders [13]. Similar to other cytokine families, changes in their concentrations during disease make them useful as potential prognostic, diagnostic, or therapeutic biomarkers. The CC (beta) subset contains a wide array of chemokines with varied functions, including MCP-1, MIP-1α, MIP-1β, RANTES, and eotaxin—all of which we measured. These factors act as chemoattractants, guiding motile cells toward higher extracellular gradients of the signal [14]. Their synthesis is tightly regulated and can be stimulated by hypoxia, microbial products, oxidative injury, thrombin, and pro-inflammatory cytokines such as TNF-α, IL-1, IFN-γ, and IL-6 [15].

A considerable body of literature links CC chemokines to allergic conditions, HIV-1 infection, rheumatoid arthritis, multiple sclerosis, transplant rejection, and asthma [15, 16]. Despite this, only limited research has explored the involvement of chemotactic molecules in ocular conditions, including dry eye disease [17], macular degeneration [18], keratoconus [19], and FECD [20]. These studies examined cytokine and chemokine concentrations in fluids such as serum, tears, and AH, demonstrating their relevance to ocular inflammatory processes.

In our work, the chemokines whose AH levels differed significantly between FECD + cataract eyes and cataract-only eyes were eotaxin, IP-10, and RANTES. Eotaxin, known for its strong attraction of eosinophils, is associated with disorders such as atopic dermatitis, allergic rhinitis, airway inflammation, and parasitic infections [15]. IP-10, part of the CXC chemokine family, promotes recruitment of monocytes, NK cells, and T lymphocytes, and affects adhesion molecule expression. It contributes to diseases including rheumatoid arthritis, multiple sclerosis, transplant rejection, and asthma [15]. RANTES attracts monocytes, T-helper cells, and eosinophils, triggers histamine release from basophils, and activates eosinophils; it is also implicated in allergic, infectious, and autoimmune disorders [15]. MCP-1 showed an upward trend in FECD + cataract eyes, though the increase did not meet statistical significance. MCP-1 is a chemoattractant for monocytes and basophils and is elevated in several systemic diseases, including atherosclerosis, psoriatic and rheumatoid arthritis, multiple sclerosis, allergic disease, and asthma [21].

It is important to note that all measurements were taken from eyes that had not undergone corneal transplantation and before cataract extraction, as some authors have reported increased cytokine activity only after surgery [22, 23]. The substantially elevated concentrations of RANTES, eotaxin, and IP-10—along with the modest increase in MCP-1—suggest that FECD eyes may experience enhanced inflammatory signaling. Because these molecules can attract immune cells into the AH, they may contribute to both the worsening of FECD-related endothelial changes and the acceleration of cataract progression. The alterations observed here also imply that FECD may disturb the eye's normal immune-privileged state. The upstream mechanisms driving increased AH levels of RANTES, eotaxin, and IP-10 remain unclear. While NF-κB is a well-known regulator of inflammatory chemokine expression [24, 25], the selective upregulation identified in our data does not fully align with the broad inflammatory profile typically associated with NF-κB activation.

Other investigations have similarly linked fluctuations in these cytokines to ocular disease. Haozhe *et al*. showed that eotaxin and CXCL10 concentrations in tears decreased in meibomian gland dysfunction–related dry eye after light-based treatments, corresponding with reduced inflammation [17]. Miyagawa *et al*. found that tear eotaxin-2 may serve as a marker for severe allergic conjunctival disorders [26]. Mo *et al*., examining serum cytokines in various stages of age-related macular degeneration, proposed that eotaxin and IP-10 might function as early indicators of disease activity. They further suggested that maintaining a balance between IP-10 and eotaxin could influence neovascular dynamics in AMD [18].

Shoji *et al*. demonstrated that both mRNA expression and protein concentrations of eotaxin-family molecules on the ocular surface function as essential indicators for studying eosinophilic inflammation and assessing antiallergic therapy outcomes in vernal keratoconjunctivitis (VKC) patients [27]. Matthaei and colleagues analyzed epithelial–mesenchymal-transition (EMT)–associated cytokines (TGF-β1, TGF-β2, TGF-β3, MCP-1, bFGF, TNF-α, and

IL-1β) in the AH of phakic FECD (FECDph) and pseudophakic FECD (FECDpsph) eyes compared with cataract controls. As FECDph eyes did not show protein-level deviations relative to cataract subjects, the authors inferred that these cytokines were unlikely to be central drivers of FECD. Conversely, increased TGF-β1, TGF-β2, and MCP-1 in FECDpsph eyes indicated that cataract surgery may induce long-term intraocular changes, with altered cytokines potentially contributing to postoperative corneal deterioration [22]. In addition, De Roo *et al*. reported rises in MCP-1 and IL-8 following cataract extraction and suggested that TGF-β signaling may have relevance to FECD pathology [23]. Their interpretations differ from ours, as those studies attribute cytokine elevation primarily to surgical disruption (either cataract surgery or corneal transplantation), whereas our cohort consisted exclusively of early-stage FECD patients who had never undergone ocular surgery. Thus, higher chemokine levels in FECD + cataract eyes relative to cataract-only eyes in our data imply that these biomarkers might reflect disease-related changes rather than postoperative consequences.

Beyond chemokines, our research also assessed several growth factors in AH from FECD and/or cataract eyes. VEGF and G-CSF showed a strong upward tendency in the FECD + cataract group compared with cataract-only subjects, though without reaching statistical significance. Meanwhile, FGF-basic, GM-CSF, and PDGF-bb did not differ between groups. Other studies have documented growth-factor disturbances in ocular pathology. Fischenko *et al*. observed that GM-CSF (together with MCP-1 and MIP-1β) was markedly increased in FECD eyes relative to healthy controls and proposed that loss of immune privilege in FECD promotes persistent local inflammation leading to stromal remodeling and fibrosis [20]. Differences between that study and ours likely reflect distinct disease stages; our participants had early FECD, while theirs had more advanced disease.

Wang and Tao reported that VEGF and bFGF concentrations in AH from Fuchs uveitis syndrome (FUS) were significantly higher than in age-matched cataract eyes, accompanied by elevated IL-6 and IL-8; these changes correlated with increased severity of posterior subcapsular cataract [28]. Their findings support an inflammatory component in early cataract development in FUS. The divergence from our results is expected, as their work focused on Fuchs uveitis syndrome, whereas our investigation targeted Fuchs endothelial dystrophy.

In our dataset, median VEGF concentrations increased by over 100% in FECD + cataract eyes relative to cataract controls. While variability prevented statistical significance, this pattern may indicate increased capillary permeability, potentially promoting FECD-related pathology through inflammation, edema, and enhanced immune-cell entry. VEGF exerts strong proliferative and anti-apoptotic effects on endothelial cells, while also driving permeability, migration, and extracellular-matrix remodeling. Through these mechanisms, VEGF regulates physiologic and pathologic angiogenesis. Immune activation and inflammatory stimuli enhance the expression of VEGF and its receptors. As a potent mitogen and chemoattractant for endothelial cells, VEGF accelerates neovascular growth and heightens vascular permeability [29].

Study limitations

Although novel, our findings require confirmation in larger cohorts. FECD's rarity limited recruitment in this pilot investigation; thus, multi-center research is recommended to establish reliable biomarkers.

Materials and Methods

The study was conducted from 2021 to 2023 in alignment with the Declaration of Helsinki. Ethical approval was granted by the Bioethical Committee of the Medical University of Silesia (PCN/CBN/0022/KB1/84/21; 15 June 2021). Participants were informed of all potential risks, and written consent for inclusion and publication was secured. To minimize bias, all samples were anonymized. Patient information was handled in compliance with GDPR regulations.

Study design and participants

The clinical procedures were performed in the Department of Ophthalmology, while laboratory analyses took place in the Department of Microbiology and Immunology at the Medical University of Silesia in Katowice, Poland. A total of 52 subjects were enrolled (32 women, 20 men; age 71.77 ± 7.59 years), with no significant group-to-group demographic differences ($p > 0.05$). Inclusion criteria consisted of FECD diagnosis **(Figure 4)**, cataract diagnosis **(Figure 5)**, age above 18, and written consent for study participation and publication. Exclusion criteria were pregnancy, malignancy, ocular trauma, glaucoma, uveal inflammatory diseases, systemic steroid therapy, and absence of informed consent.

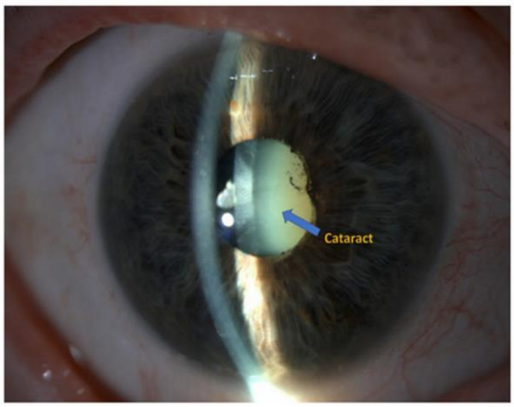

Figure 4. Cataract [Department of Ophthalmology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland].

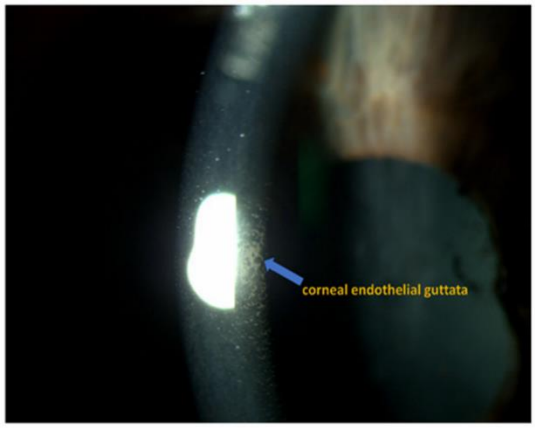

Figure 5. Endothelial layer in FECD [Department of Ophthalmology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland].

Two cohorts were established for the investigation: the FECD + Cataract group (n = 26) and the Cataract/control group (n = 26). The Bioethics Committee did not authorize sampling of aqueous humor from healthy individuals; therefore, cataract patients had to be used as the reference population. As a result, the inclusion of healthy subjects as controls was not possible. FECD was diagnosed based on a full ophthalmic assessment in accordance with recognized clinical guidelines [30, 31]. Before cataract extraction, each participant underwent imaging to document disease severity. These examinations comprised OCT scanning with SS CASIA and SD REVO OCT devices, as well as slit-lamp evaluation supported by photographic imaging. The sequence of the study procedure is summarized in **Figure 6**.

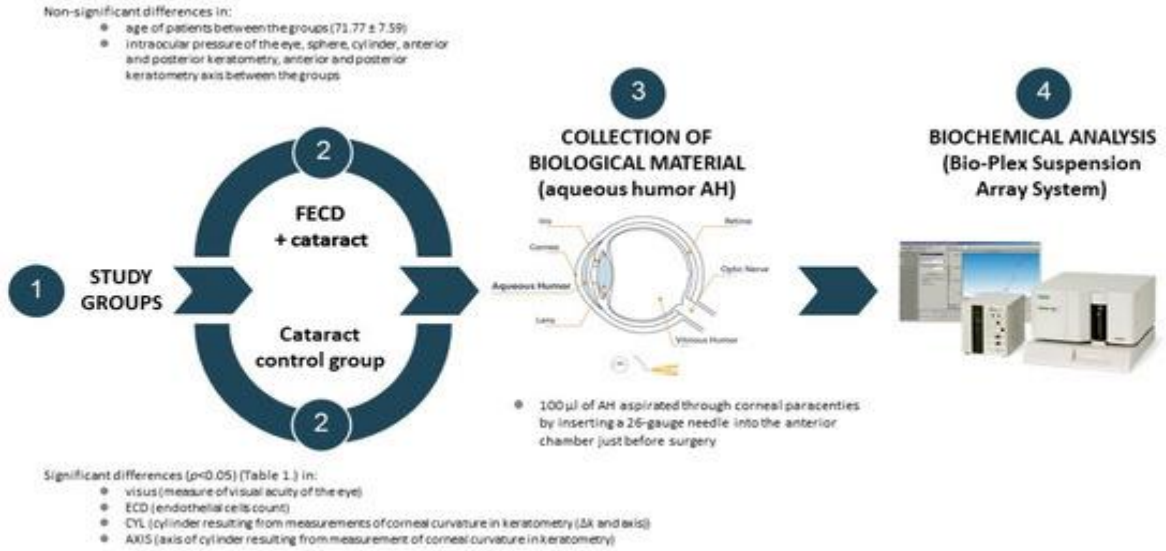

Figure 6. Overview of the study protocol, including group classification, sample acquisition, and analytic workflow.

Sample collection

For aqueous humor (AH) retrieval, the periocular area was disinfected, and approximately 100 µL of AH was obtained through a corneal paracentesis using a 26-gauge needle inserted into the anterior chamber immediately prior to surgery. All specimens were placed in sterile containers and frozen at −82 °C until laboratory processing. The sampling procedure neither compromised the cataract operation nor introduced additional complications.

Biochemical assessment

Laboratory analyses were performed in a blinded manner by trained personnel at the Department of Microbiology and Immunology, Silesian Medical University in Zabrze, following established laboratory standards. Cytokine measurements were conducted using the Bio-Plex 200 platform (Bio-Rad) together with the Bio-Plex Pro Human Cytokine 27-Plex panel (#M500KCAF0Y). The method employs bead-based fluorescent microspheres licensed from Luminex Corporation (Austin, TX, USA). Each AH sample contributed 30 µL to the assay. Calibration curves produced from kit standards were used to determine the concentration of each analyte. The lowest detectable limits were as follows: MCP-1 0.2 pg/mL, MIP-1α 0.05 pg/mL, MIP-1β 0.05 pg/mL, RANTES 0.02 pg/mL, eotaxin 0.1 pg/mL, IP-10 1.0 pg/mL, IFN-γ 0.1 pg/mL, FGF basic 0.5 pg/mL, G-CSF 0.05 pg/mL, GM-CSF 0.02 pg/mL, PDGF-bb 2.0 pg/mL, and VEGF 0.5 pg/mL.

Statistical analysis

All statistical computations were carried out using Statistica v. 13.3 (Tibco, Palo Alto, CA, USA). Distribution patterns of the measured variables were

checked with the Shapiro–Wilks test. For non-normally distributed data, the Mann–Whitney U test was applied; normally distributed variables such as age were examined with the t-test. Differences in sex distribution between the two groups were analyzed using the Chi-squared test. Statistical significance was defined as $p < 0.05$.

Conclusion

The study demonstrated that aqueous humor from patients with FECD combined with cataract displayed elevated concentrations of RANTES, eotaxin, and IP-10 when compared with cataract-only subjects. These chemotactic factors may be implicated in FECD onset and could potentially serve as markers distinguishing FECD from cataract. Detecting increased levels of these biochemical indicators in an eye without clinical FECD may warrant more vigilant monitoring of the contralateral eye for early disease development.

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Conflict of interest: None

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Ethics statement: The study was approved by the Bioethical Committee of the Medical University of Silesia, reference number PCN/CBN/0022/KB1/84/21 (15 June 2021), and was conducted in accordance with the Declaration of Helsinki.
Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

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