



Subclinical corneal endothelial alterations in Familial Mediterranean Fever patients during clinical remission

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Abstract

Purpose Although ocular involvement in Familial Mediterranean Fever (FMF) has been described, the corneal endothelium has not been systematically evaluated in these patients. This study aimed to compare corneal endothelial and anterior segment parameters between FMF patients in clinical remission and healthy controls, and to explore whether these parameters differ according to MEFV M694V genotype.

Methods In this prospective, observational case–control study, 90 genetically confirmed FMF patients in clinical remission and 60 age- and sex-matched healthy controls were evaluated. Only the right eye of each participant was analyzed. Corneal endothelial parameters were assessed by non-contact specular microscopy, and corneal structural parameters by Scheimpflug-based tomography. Measured parameters included endothelial cell density (ECD), central corneal thickness (CCT), coefficient of variation of cell area (CV), and percentage of hexagonal cells (HEX). MEFV mutation analysis was performed by Sanger sequencing.

Results Compared with controls, FMF patients showed a lower ECD (median 2154.5 vs. 2348 cells/mm², $p < 0.001$; approximately 8.2% lower), a higher CCT (556.5 vs. 543 μm , $p < 0.001$), a higher CV (42 vs. 39.5, $p = 0.003$), and a lower HEX (44.5% vs. 48%, $p < 0.001$). Intraocular pressure was modestly higher (18 vs. 15 mmHg, $p < 0.001$) and the iridocorneal angle was narrower (42° vs. 47°, $p < 0.001$) in the FMF group, with both groups remaining within normal physiological ranges. Within the FMF group, patients homozygous for M694V ($n = 14$) showed a higher mean CCT (540.93 ± 39.14 vs. 510.93 ± 36.21 μm , $p = 0.020$) and a lower median ECD (2071 vs. 2218.5 cells/mm², $p = 0.006$) than heterozygotes ($n = 29$). In an exploratory multivariable logistic regression within this subgroup, CCT and ECD were jointly associated with M694V homozygous versus heterozygous status (correct classification 69.8%).

Conclusion FMF patients in clinical remission show measurable differences in corneal endothelial parameters compared with healthy controls, and these differences appear more pronounced in M694V homozygous patients. Because the study is cross-sectional, it is not possible to conclude that these parameters reflect ongoing disease activity; prospective, longitudinal studies are needed to determine whether corneal endothelial assessment has a role in the ophthalmologic follow-up of patients with FMF.

Key messages

What is known

- FMF is a systemic autoinflammatory disease that can affect various ocular structures.
- Corneal endothelial changes have been reported in several systemic inflammatory conditions.

What is new

- Subclinical corneal endothelial alterations are present in FMF patients even during clinical remission.
- Specular microscopy may serve as a non-invasive tool for detecting subclinical ocular involvement in FMF.

Keywords Familial Mediterranean Fever · Corneal endothelium · Endothelial cell density · Specular microscopy · MEFV mutations · Autoinflammatory disease

Extended author information available on the last page of the article

Introduction

Familial Mediterranean Fever (FMF) is the most prevalent monogenic autoinflammatory disease worldwide, affecting several million individuals and characterized by recurrent febrile attacks with serositis [1, 2]. Although ocular involvement in FMF has been documented, the existing literature has focused predominantly on retinal vascular changes and optic nerve pathologies, and systematic assessment of the cornea — in particular the corneal endothelium — has received comparatively little attention [3, 4]. A recent comprehensive review of ocular manifestations in monogenic and polygenic autoinflammatory diseases explicitly highlights this gap, noting that anterior segment involvement has not been systematically investigated in these conditions [4].

FMF is caused by mutations in the MEFV gene, which encodes pyrin, a key regulator of inflammasome activation. MEFV variants, and particularly M694V, are associated with enhanced pyrin inflammasome activity and increased production of IL-1 β , which is considered a central cytokine in the pathogenesis of FMF [2]. Ongoing low-grade inflammatory activity has been reported even during clinically quiescent periods, especially in patients homozygous for M694V [5, 6]. Whether this persistent inflammatory state is accompanied by subclinical changes in specific target tissues, including the corneal endothelium, is not well characterized.

The corneal endothelium is a single-cell layer with very limited regenerative capacity, and its functional integrity is essential for maintaining corneal transparency. In vitro studies have shown that IL-1 β can affect corneal endothelial cells through NF- κ B and AP-1 signaling pathways [7], and more broadly influence corneal cellular responses [8, 9]. Although these experimental observations cannot be directly extrapolated to the in vivo setting, they provide a biological rationale for assessing corneal endothelial morphology in diseases characterized by chronic IL-1 β -related inflammation, such as FMF.

Modern imaging technologies, including non-contact specular microscopy and Scheimpflug-based corneal tomography, allow non-invasive, high-resolution quantitative assessment of corneal endothelial and anterior segment parameters [10, 11]. These tools offer an opportunity to evaluate whether measurable corneal differences exist between FMF patients in remission and healthy controls, and whether such differences are related to MEFV genotype.

The primary aim of this study was to compare corneal endothelial and anterior segment parameters between FMF patients in clinical remission and age- and sex-matched healthy controls. As a secondary aim, we explored whether these parameters differed between patients homozygous and heterozygous for the M694V mutation.

Materials and methods

Study design and population

This prospective, observational case-control study was conducted at a tertiary academic medical center following approval by the institutional ethics committee (Protocol Number: [2024/116]). The study was designed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

Between June 2024 and March 2025, adult patients (aged 18–65 years) with genetically confirmed subclinical FMF, diagnosed based on the Tel-Hashomer criteria and verified by comprehensive molecular genetic testing for pathogenic MEFV mutations, were prospectively recruited from Rheumatology and Internal Medicine departments. Age- and sex-matched healthy controls were selected from hospital personnel and community volunteers undergoing routine health screenings, following a rigorous evaluation to exclude subclinical inflammatory conditions.

Sample size determination

Statistical power analysis was performed using G*Power 3.1.9.7 software (Heinrich Heine University Düsseldorf, Germany), based on preliminary data from pilot studies assessing corneal endothelial parameters in inflammatory conditions. Assuming an α error of 0.05, 80% power, and a moderate-to-large effect size (Cohen's $d=0.6$) for intergroup differences in endothelial cell density (ECD), a minimum of 45 participants per group was required. To accommodate potential dropouts (estimated at 15%) and ensure sufficient power for subgroup analyses and multivariate modeling, the initial recruitment targets were 80 FMF patients and 60 healthy controls. The lower control group target was chosen considering the practical challenges of recruiting healthy volunteers and cost-effectiveness. Ultimately, 90 FMF patients and 60 controls completed the study protocol. A post-hoc power analysis confirmed >85% power to detect clinically meaningful differences in primary endothelial parameters.

Inclusion criteria

FMF Group: Adults aged 18–65 years with genetically confirmed subclinical FMF based on Tel-Hashomer criteria [12]; documented pathogenic MEFV gene mutations; stable colchicine therapy (≥ 1.0 mg/day) for at least 6 months; clinical remission as defined by absence of acute attacks

for ≥ 3 months per EULAR recommendations; and normal ophthalmic examination apart from $\leq \pm 3.00$ diopters spherical equivalent refractive error [13].

Control Group: Healthy adults aged 18–65 years without a history of autoinflammatory diseases; normal inflammatory biomarkers (C-reactive protein < 3.0 mg/L, erythrocyte sedimentation rate within age-adjusted reference ranges); absence of systemic inflammatory disorders based on comprehensive history and laboratory evaluation; and no infections in the past 6 months.

Exclusion criteria

History of ocular trauma or surgery; systemic diseases affecting corneal physiology (e.g., diabetes mellitus, connective tissue disorders, thyroid dysfunction); ocular pathologies (e.g., glaucoma, uveitis, corneal dystrophies, keratoconus with > 2.0 diopters of irregular astigmatism); contact lens use within the last 4 weeks; use of systemic medications known to affect the cornea (e.g., corticosteroids, chloroquine derivatives, amiodarone); refractive error $> \pm 3.00$ diopters spherical equivalent; acute FMF flare within the past 3 months; pregnancy or lactation; or inability to maintain stable fixation for reliable imaging. All participants underwent Scheimpflug-based corneal tomography (Sirius, CSO, Florence, Italy) prior to enrollment. For each eye, the system's built-in keratoconus screening indices (SCORE and Kvf) were reviewed, and any case flagged as keratoconus or keratoconus-suspect was excluded, irrespective of the magnitude of irregular astigmatism. Accordingly, no participant in either group carried a diagnosis of keratoconus or forme fruste keratoconus.

Molecular genetic analysis

MEFV gene analysis was conducted in the molecular genetics laboratory of the study center. Genomic DNA was extracted from EDTA-anticoagulated venous blood samples using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). All coding exons of the MEFV gene (exons 1–10), along with exon–intron boundary regions, were analyzed using the Sanger sequencing method. Primer design was performed in accordance with protocols previously described in the literature [14]. Both common FMF mutations (M694V, M694I, M680I, V726A, E148Q) and rare variants were systematically screened. Pathogenicity of the variants was assessed based on the American College of Medical Genetics (ACMG) guidelines [15].

Clinical and laboratory evaluation

Comprehensive medical histories were obtained using standardized case report forms, including demographic

characteristics, FMF phenotype classification, disease duration, previous attack frequency and severity, current colchicine dosage and treatment duration, medication adherence (assessed by the Morisky-8 scale), and comorbidity profiles. Disease activity was evaluated using the validated Pras scoring system, and attack patterns over the previous 6 months were systematically documented [16].

Laboratory data—including complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and serum amyloid A levels—were recorded during attack-free periods. An attack-free period was defined as a minimum of 3 months without clinical symptoms and normalization of acute phase reactants, in line with inclusion criteria. Subclinical inflammation was defined as elevation of any acute phase reactant (hsCRP > 3.0 mg/L, ESR above age-adjusted reference, or serum amyloid A > 10 mg/L) during this period.

To minimize circadian variation, fasting venous blood samples were collected between 08:00 and 10:00 following a 12-h overnight fast. Inflammatory biomarkers were analyzed using standardized automated platforms: high-sensitivity CRP (hsCRP) was measured by turbidimetric immunoassay (coefficient of variation $< 5\%$), ESR by the Westergren method, serum amyloid A by nephelometric assay, and fibrinogen by the Clauss method. All analyses were performed within 2 h of sample collection in the hospital's accredited clinical laboratory.

Ophthalmologic examination protocol

All ophthalmologic evaluations were performed by a single experienced ophthalmologist (F.S.), who was blinded to the participants' group assignments and clinical status. For all analyses, only the right eye of each participant was included. This approach was adopted a priori to ensure statistical independence between observations, as including both eyes from the same individual would violate the assumption of independent observations in standard statistical models. To minimize circadian variation, examinations were conducted between 09:00 and 12:00 under standardized environmental conditions (temperature 21 ± 1 °C, relative humidity 45–55%, ambient light < 50 lx) and in a fixed sequence.

Comprehensive ocular evaluation

Best-corrected visual acuity (BCVA) was measured monocularly at a distance of 4 m using ETDRS charts (Precision Vision, LaSalle, IL) in accordance with standard illumination (85 cd/m^2), following full refractive correction. Results were converted into Snellen equivalents for analysis. Intraocular pressure (IOP) was measured using Goldmann applanation tonometry following topical anesthesia with 0.5%

proparacaine hydrochloride, and the mean of three consecutive readings was used for analysis. Anterior segment examination was performed via slit-lamp biomicroscopy (Haag-Streit BQ 900, Switzerland) to assess corneal clarity, anterior chamber depth, and iris configuration. Fundus examination was conducted after adequate pupil dilation with 1% tropicamide using a non-contact 90D lens under slit-lamp biomicroscopy.

Corneal imaging

Scheimpflug-based corneal tomography

Comprehensive corneal analysis was conducted using the Sirius imaging system (CSO, Florence, Italy), which combines a rotating Scheimpflug camera with Placido disk-based corneal topography. The system captures 25 radial cross-sectional images with 35,632 elevation points. Parameters assessed included anterior and posterior keratometry (K1, K2, Kmean), corneal astigmatism magnitude and axis, symmetry indices (SAI, SRI), elevation maps relative to the best-fit sphere, and pachymetric thickness maps within the central 9-mm zone. Quality control required a signal strength > 8.0 and absence of motion artifacts. The device was calibrated monthly according to the manufacturer's protocol.

Specular microscopy analysis

Corneal endothelial morphometry was assessed using a non-contact specular microscope (Tomey EM-4000, Tomey Corporation, Nagoya, Japan) equipped with automated image analysis software. The device uses a 470 nm LED light source and provides $\times 200$ magnification with a 0.16 mm² sampling area. Five consecutive high-quality images were captured from the central corneal region, and automated cell border detection was manually corrected when necessary. Only images with > 75% analyzable endothelial area and well-defined cell borders were included.

Morphometric parameters analyzed included: endothelial cell density (ECD, cells/mm²), mean cell area (MCA, μm^2), standard deviation of cell area (SD), coefficient of variation ($\text{CV} = \text{SD}/\text{MCA} \times 100$) indicating pleomorphism, percentage of hexagonal cells (HEX, %) reflecting polymegathism, minimum and maximum cell areas (CA-min, CA-max), and central corneal thickness (CCT, μm) measured at the corneal apex.

Statistical analysis

All analyses were conducted using IBM SPSS Statistics software (version 29.0; IBM Corp., Armonk, NY, USA).

Data quality control, outlier analysis, and missing data evaluation were systematically performed. As the proportion of missing data was < 5%, a complete case analysis approach was adopted. The distribution characteristics of continuous variables were assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Descriptive statistics for normally distributed variables were reported as mean $\pm$ standard deviation, while non-normally distributed variables were presented as median (Q1–Q3). Categorical variables were expressed as frequency and percentage [n (%)].

For intergroup comparisons, the independent samples t-test was used for normally distributed continuous variables, and the Mann–Whitney U test was applied for non-normally distributed variables. Pearson's chi-square test or Fisher's exact test was used for categorical variables, as appropriate. To correct for multiple comparisons, the Holm–Bonferroni method (a modified version of the Bonferroni correction) was applied. Non-parametric correlations between variables were assessed using Spearman's correlation coefficient, and the strength of associations was interpreted according to Cohen's classification (weak: 0.1–0.3, moderate: 0.3–0.5, strong: > 0.5).

The relationship between the M694V polymorphism and the CCT and ECD parameters was evaluated using univariate and multivariate logistic regression analyses. In the multivariate model, potential confounding variables (age, sex, BMI, disease duration) were adjusted for. Model fit was assessed using the Hosmer–Lemeshow test, and discriminatory power was evaluated using the area under the receiver operating characteristic curve (AUC). Effect sizes were reported using Cohen's d , η^2 , or Cramer's V , as appropriate.

A p -value < 0.05 was considered statistically significant, and effect sizes were interpreted as small (0.2), medium (0.5), or large (0.8). All statistical results were reported in accordance with the STROBE guidelines.

Reliability and quality assurance

Measurement reproducibility was assessed through intra-observer reproducibility analysis with repeated examinations performed at 7-day intervals in 25 randomly selected participants. Inter-observer reliability was evaluated using measurements performed by two independent, masked examiners in 20 participants. Reliability coefficients were calculated using intraclass correlation coefficients (ICC) with 95% confidence intervals, and $\text{ICC} > 0.80$ was considered excellent agreement. The obtained ICC values were: 0.94 (95% CI: 0.89–0.97) for ECD and 0.92 (95% CI: 0.86–0.96) for CCT.

Calibration verification for all devices was performed monthly using manufacturer-provided standards. Data quality was maintained through real-time range controls, logical consistency validation, and inconsistency resolution protocols with double data entry.

Ethical considerations

The study protocol received approval from the Institutional Ethics Committee (Protocol: [2024/116], Date: [23/05/2024]). All participants provided written informed consent following detailed explanation of study procedures, potential risks, and data processing protocols. The study was conducted without any external funding or commercial sponsorship, eliminating potential conflicts of interest.

Results

Demographic and genetic characteristics

The study included 90 FMF patients and 60 healthy controls. There were no significant differences between groups regarding age (31.28 ± 10.32 vs 32.17 ± 9.43 years, $p=0.866$) and gender distribution (67.4% vs 53.3% female, $p=0.054$). Genetic analysis revealed that 26.8% of patients carried homozygous mutations and 73.2% carried heterozygous mutations. M694V mutation showed 16.3% homozygous and 33.7% heterozygous positivity (Tables 1 and 2).

Primary corneal endothelial outcomes

The FMF group showed significant alterations in corneal endothelial morphology compared with controls (Table 3). Endothelial cell density was significantly reduced in FMF patients (2154.5 vs. 2348 cells/mm², $p<0.001$), corresponding to an approximately 8.2% lower ECD than in the control group. Central corneal thickness was increased by 13.5 μ m (556.5 vs. 543 μ m, $p<0.001$). The coefficient of variation in cell area was higher (42 vs. 39.5 , $p=0.003$) and the hexagonality index was lower (44.5% vs. 48% , $p<0.001$) in the FMF group. Mean cell area (391.5 vs. 371 μ m², $p<0.001$) and maximum cell area (996 vs. 819.5 μ m², $p<0.001$) were also higher in FMF patients.

Secondary anterior segment parameters

Intraocular pressure was higher in the FMF group than in controls (18 vs. 15 mmHg, $p<0.001$), and the iridocorneal angle was narrower (42° vs. 47° , $p<0.001$). Both groups remained within the normal physiological range for IOP.

Exploratory biometric and keratometric findings

Keratometric values (K1: 43.45 vs. 43.03 D, $p=0.003$; Kmean: 43.8 vs. 43.21 D, $p<0.001$) and apex curvature (44.68 vs. 44.12 D, $p<0.001$) were higher in the FMF group. Horizontal visible iris diameter was larger in the FMF group (12.05 vs. 11.68 mm, $p<0.001$). Anterior and

posterior corneal surface asymmetry indices differed significantly between groups (both $p<0.001$), and corneal volume was higher in the FMF group (57.4 vs. 48 mm³, $p<0.001$).

Correlation analyses

A weak negative correlation was found between disease activity index and keratometric cylinder ($r=-0.240$, $p=0.023$). BMI showed negative correlations with anterior depth ($r=-0.210$, $p=0.047$) and ECD ($r=-0.226$, $p=0.033$), and positive correlation with mean cell area ($r=0.224$, $p=0.033$). Disease duration was positively correlated with corneal volume ($r=0.210$, $p=0.047$) and CA-MAX ($r=0.380$, $p<0.001$), and negatively correlated with hexagonality ($r=-0.210$, $p=0.047$). Detailed correlation results are presented in Tables 4 and 5.

M694V genotype analysis

Within the FMF group, we compared CCT and ECD between M694V homozygous ($n=14$) and heterozygous ($n=29$) patients. Homozygous patients showed higher central corneal thickness (540.93 ± 39.14 vs. 510.93 ± 36.21 μ m; $p=0.020$) and lower endothelial cell density (median 2071 vs. 2218.5 cells/mm²; $p=0.006$) than heterozygous patients (Table 6). In logistic regression with homozygous status as the dependent variable, higher CCT was associated with homozygous status on univariate analysis (OR 1.023 per 1 μ m; 95% CI 1.002–1.045; $p=0.029$), and higher ECD was inversely associated with homozygous status (OR 0.898 per 100 cells/mm²; 95% CI 0.821–0.982; $p=0.019$). In a multivariable model including both parameters and adjusting for age, sex, BMI, and disease duration, both associations were retained: CCT OR 1.033 per 1 μ m (95% CI 1.008–1.058; $p=0.009$) and ECD OR 0.918 per 100 cells/mm² (95% CI 0.856–0.985; $p=0.017$). The multivariable model correctly classified 69.8% of cases (Table 7). These results describe differences between genotype-defined subgroups rather than indicating that corneal parameters predict MEFV genotype in a clinically useful sense.

Discussion

Although FMF is traditionally considered an attack-based disease that is clinically quiescent between flares, accumulating evidence suggests that low-grade inflammatory activity may persist during symptom-free periods [5]. In this context, our study documents measurable differences in corneal endothelial parameters between FMF patients in clinical remission and healthy controls, including an approximately 8.2% lower endothelial cell density,

Table 1 Clinical and demographic characteristics of the FMF group

	<i>n</i> = 90	
Gender		
Female	60 (67.4)	
Male	30 (32.6)	
Age	31.28 ± 10.32	29 (16—59)
BMI	23.79 ± 3.67	23.1 (17.7—38.6)
Duration of Disease (Year)	10.97 ± 8.63	10 (1—37)
Cigarette	66 /24	
Alcohol		
Education Status		
Primary School	9 (10)	
Middle School	7 (7.8)	
High School	37 (41.1)	
University	37 (41.1)	
Marital Status		
Single	45 (50)	
Widow	6 (6.7)	
Married	39 (43.3)	
Parents Related		
No	74 (82.2)	
Yes	16 (17.8)	
FMF in The Family		
No	32 (35.6)	
Yes	58 (64.4)	
Age at First Attack	17.08 ± 13.08	15 (1—55)
Age at Diagnosis	22.53 ± 12.95	21 (2—58)
Time Delay in Diagnosis (Years)	6.42 ± 9.16	2.5 (0—37)
International Severity Scoring for FMF	4.14 ± 1.11	4 (2—8)
Autoinflammatory Disease (FMF) Activity Index	5.48 ± 1.84	5 (3—12)
Attack Trigger Factor*		
No	4 (4.4)	
Cold	44 (48.9)	
Stress	51 (56.7)	
Fatigue	16 (17.8)	
Hunger	2 (2.2)	
Overeating	10 (11.1)	
Mens	19 (21.1)	
Heavy Exercise	5 (5.6)	
Standing	15 (16.7)	
Other	1 (1.1)	
Biologic		
No	83 (92.2)	
Anakinra	4 (4.4)	
Canakinumab	3 (3.3)	
FMF International Severity Level		
≤ 2	2 (2.2)	
3–5	79 (87.8)	
≥ 6	9 (10)	
Attack in the Last 6 Months		
0	6 (6.7)	
1	13 (14.4)	
2	26 (28.9)	
3	18 (20)	
4	18 (20)	
5	2 (2.2)	
6	6 (6.7)	

Table 1 (continued)

	<i>n</i> =90
10	1 (1.1)
Diabet	
No	90 (100)
Amyloidosis	
No	89 (98.9)
vYes	1 (1.1)
CKD	
No	90 (100)
Hypertension	
No	90 (100)
Hyperlidemia	
No	77 (85.6)
Yes	13 (14.4)
Fever	
No	19 (21.1)
Yes	71 (78.9)
Abdominal pain	
No	19 (21.1)
Yes	71 (78.9)
Pleuretic Pain	
No	55 (61.1)
Yes	35 (38.9)
Chest Pain	
No	59 (65.6)
Yes	31 (34.4)
Arthritis	
No	71 (78.9)
Yes	19 (21.1)
Arthralgia	
No	40 (44.4)
Yes	50 (55.6)
Skin Rash	
No	73 (81.1)
Yes	17 (18.9)
Diarrhea	
No	46 (51.1)
Yes	44 (48.9)
Nausea	
No	33 (36.7)
Yes	57 (63.3)
Muscle Pain	
No	51 (56.7)
Yes	39 (43.3)
Constipation	
No	65 (72.2)
Yes	25 (27.8)
Kolşin Dozu	
2*1	25 (27.8)
2*2	9 (10)
3*1	56 (62.2)
Side Effect	
No	90 (100)

Mean±s. deviation, median (min.—max.), *n* (%)*BMI* Body Mass Index; *FMF* Familial Mediterranean Fever; *CKD* Chronic Kidney Disease

Table 2 Distribution of gene analysis results of the FMF group

	Homozygote	Heterozygote
Gene Analysis *		
M694V	14 (16.3)	29 (33.7)
M680I	2 (2.3)	15 (17.4)
F479L	1 (1.2)	-
A761H	-	3 (3.5)
R314R	1 (1.2)	-
R202Q	-	5 (5.8)
V726A	5 (5.8)	2 (2.3)
G148G	-	11 (12.8)
E148G	-	2 (2.3)
A202G	-	1 (1.2)
P369S	-	5 (5.8)
R408Q	-	2 (2.3)
E148Q	-	5 (5.8)
Total	22 (26.8)	80 (93)

*Multiple response, n (%)

a 13.5 μm greater central corneal thickness, and a modest increase in intraocular pressure. These findings are consistent with the possibility that subclinical processes related to the underlying inflammatory state of FMF are detectable at the level of the corneal endothelium, and they suggest that the anterior segment deserves more systematic attention in ophthalmologic evaluation of these patients.

Corneal endothelial differences in FMF: potential biological context

The reductions in endothelial cell density ($\sim 8.2\%$) and hexagonality index ($\sim 7.3\%$) observed in this cohort are consistent with the pattern of endothelial alteration reported in experimental models of IL-1 β exposure, in which IL-1 β has been shown to affect corneal endothelial cells via NF- κB and AP-1 signaling [7]. While the present study did not measure IL-1 β and cannot establish a mechanistic link in vivo, prior in vitro work [7–9] provides a plausible biological framework for the endothelial differences observed here. In the context of the limited regenerative capacity of the corneal endothelium [17], any chronic pro-inflammatory exposure may be expected to contribute, over time, to accelerated deviation from the normal physiological endothelial cell loss rate of approximately 0.6% per year [18]; our cross-sectional findings are compatible with, but do not by themselves demonstrate, such a process in FMF.

The 13.5 μm greater central corneal thickness observed in the FMF group may reflect subtle alterations in endothelial pump-barrier function, as described in the physiology of the corneal endothelium [19]. However, because corneal thickness was not accompanied by clinical evidence of decompensation — no patient in our cohort had corneal edema, bullous changes, or a history of endothelial failure — this

Table 3 Examination of right eye measurements according to groups

	Control Group (n=60)	FMF Group (n=90)	Test ist	p ^m
SE	-0.25 (-7—1)	-0.25 (-13—1.5)	-0.024	0.981
AL	23.76 (22.78—24.74)	23.54 (22.96—24.24)	-0.781	0.435
CCT	543 (519—579)	556.5 (481—658)	-3.809	<0.001
IOP	15 (13—18)	18 (15—21)	-11.292	<0.001
AD	3.11 (2.93—3.28)	3.12 (2.88—3.41)	-0.412	0.680
ACD	3.34 (3.09—3.84)	3.29 (2.96—3.89)	-2.934	0.643
LT	3.52 (3.32—3.99)	3.56 (3.26—3.94)	-1.515	0.212
WTW	12.14 (11.55—12.76)	12.13 (11.52—12.88)	-0.980	0.327
ECD	2348 (2199—2590)	2154.5 (1243—2941)	-5.731	<0.001
NUM	234 (159—293)	233.5 (67—302)	-0.026	0.979
AVG	371 (359—378)	391.5 (340—805)	-6.037	<0.001
SD	154 (122—375)	157 (109—375)	-0.808	0.419
CV	39.5 (26—57)	42 (37—49)	-2.940	0.003
CA-MAX	819.5 (689—932)	996 (673—2677)	-8.525	<0.001
CA-MIN	98.5 (82—128)	97.5 (4—213)	-0.531	0.595
6A	48 (43—52)	44.5 (23—62)	-4.722	<0.001
CORNEAL VOLUME	48 (43—52)	57.4 (49—72.7)	-11.423	<0.001
K1	43.03 (41.42—44.02)	43.45 (40.36—47.18)	-2.923	0.003
K2	43.23 (41.99—44.12)	43.46 (40.47—46.64)	-1.336	0.181
K AVG	43.21 (41.99—44.12)	43.8 (40.53—47.54)	-3.640	<0.001
K CYL	-0.73 (-3.09—0.1)	-0.71 (-3.09—0.1)	-0.127	0.899
HVID	11.68 (11.11—12.89)	12.05 (11.1—12.88)	-4.976	<0.001
APEX	44.12 (43.02—53.34)	44.68 (43.87—54.23)	-4.842	<0.001
CURVATURE	-1.56 (-1.61—1.44)	0.11 (0—0.75)	-11.628	<0.001
ASYM F	-0.24 (-0.27—0.19)	0.03 (0—1.06)	-11.672	<0.001
IRIDOCORNEAL ANGLE	47 (40—52)	42 (25—55)	-4.859	<0.001

m: Mann Whitney U test, median (min.—max.)

SE Spherical equivalent; AL Axial length; CCT Central corneal thickness; AD Aqueous depth; ACD Anterior chamber depth; LT Lens thickness; WTW White-to-white corneal diameter; ECD Endothelial cell density; NUM Number of cells; AVG Average cell area; CAmx Maximum cell area; CAmin Minimum cell area; SD Standard deviation; CV Coefficient of variation in cell area. 6 A: the percentage of hexagonal endothelial cells, K1 Keratometry flat; K2 Keratometry steep; K AVG Keratometry average; K CYL Keratometry cylindric; HVID Horizontal visible iris diameter Distributional normality was assessed by the Shapiro–Wilk test; all variables were non-normally distributed and accordingly analyzed by Mann–Whitney U test

Table 4 Investigation of the relationship between FMF activity index and right eye measurements in a patient group

	International severity scoring for FMF		Autoinflam-matory disease (FMF) activity index		N
	r	p	r	p	
SE	0.060	0.577	-0.060	0.572	90
AL	0.033	0.760	-0.027	0.801	90
CCT	0.089	0.404	-0.116	0.276	90
AD	0.176	0.098	0.005	0.966	90
ACD	0.084	0.433	0.076	0.477	90
LT	-0.015	0.889	0.057	0.596	90
WTW	0.054	0.615	0.030	0.777	90
ECD	0.032	0.766	-0.073	0.496	90
NUM	0.111	0.296	-0.010	0.924	90
AVG	-0.032	0.768	0.070	0.509	90
SD	-0.031	0.775	0.008	0.937	90
CV	-0.044	0.681	-0.052	0.628	90
CA-MAX	-0.059	0.579	-0.109	0.305	90
CA-MIN	0.095	0.372	0.076	0.479	90
6A	-0.069	0.515	-0.042	0.695	90
CORNEAL VOLUME	-0.092	0.388	-0.068	0.523	90
K1	0.025	0.815	0.061	0.566	90
K2	0.017	0.871	0.031	0.775	90
K AVG	0.013	0.906	0.110	0.304	90
K CYL	-0.081	0.447	-0.240	0.023	90
HVID	0.034	0.750	0.048	0.654	90
APEX CURVATURE	0.080	0.451	0.190	0.073	90
CURVATURE ASYM F	0.035	0.742	0.074	0.487	90
CURVATURE ASYM B	-0.108	0.310	0.129	0.227	90
IRIDOCORNEAL ANGLE	0.094	0.377	-0.005	0.966	90

r: Spearman's rho correlation coefficient

finding is best interpreted as a subclinical quantitative difference rather than as direct evidence of pump dysfunction.

Ocular findings associated with FMF in the existing literature have been reported in a limited manner, predominantly focusing on retinal vascular changes and optic neuritis [3, 4]. The 2024 update by Fonollosa and colleagues highlights that anterior segment involvement in autoinflammatory diseases has not been systematically investigated [4]. Van Gorp and colleagues have shown that the pyrin inflammasome pathway, which is centrally implicated in FMF pathogenesis, contributes to systemic IL-1 β elevation, although the organ-specific consequences of this elevation remain incompletely characterized [1]. A clinical case series by Yazici and colleagues further illustrates that ocular involvement in FMF has been reported primarily in the context of uveitis and its complications, rather than as primary corneal or anterior segment pathology [20]. Our observations add to this literature by describing quantitative differences in corneal endothelial parameters between FMF patients and controls, and support the case for including anterior segment assessment in future studies of ocular involvement in FMF.

Within the FMF group, patients homozygous for M694V showed greater central corneal thickness and lower endothelial cell density than heterozygotes in our cohort. This is biologically plausible, as different MEFV variants have been reported to differ in their functional impact on caspase-1 activation and downstream IL-1 β production [2], and M694V homozygosity has been associated with a higher inflammatory burden and more severe clinical phenotypes in FMF [5]. It should be emphasized, however, that our data describe differences between genotype-defined subgroups rather than establishing that corneal parameters predict genotype or mutation severity. Given the relatively small number of homozygous patients ($n=14$), these genotype-related observations should be regarded as preliminary and require confirmation in larger, independent cohorts. It should be emphasized that several biometric and keratometric parameters — including K1, K2, Kmean, apex curvature, and horizontal visible iris diameter — reached statistical significance but with absolute differences (~ 0.4 – 0.6 D for keratometric values and ~ 0.37 mm for HVID) that do not exceed established clinical action thresholds. These parameters are therefore interpreted as exploratory, hypothesis-generating findings and are not considered clinically actionable in their own right. In contrast, the primary endothelial outcomes of this study (ECD, CCT, CV, and HEX) demonstrated differences of clinically meaningful magnitude. An 8.2% reduction in ECD is notable in light of evidence that chronic inflammatory conditions can accelerate the normal physiological endothelial cell loss rate of 0.6% per year [18], and losses exceeding 5% have been proposed as a threshold of clinical concern in the context of chronic ocular disease.

Clinical implications and future perspectives

An exploratory observation of this study is that the FMF group showed a modestly higher intraocular pressure (approximately 3 mmHg) and a narrower iridocorneal angle (approximately 5°) compared with controls. Both groups remained within the normal physiological range for IOP, and the cross-sectional design of the study does not allow any causal inference regarding glaucoma risk. These findings should therefore be interpreted as observations rather than as evidence of an established increase in angle-closure glaucoma risk in FMF. Whether these anterior segment differences have prognostic significance — and whether FMF patients would benefit from structured anterior segment screening over time — can only be addressed by prospective longitudinal studies. No specific prophylactic intervention can be recommended on the basis of the present data.

The measurable differences in corneal endothelial parameters observed in this cohort raise the possibility that such parameters could be explored as candidate indicators of

Table 5 Investigation of the relationship between some demographic characteristics and right eye measurements in a case group

	Age		BMI		Disease duration		Age of first attack		Age at diagnosis		Delay in diagnosis		N
	r	p	r	p	r	p	r	p	r	p	r	p	
SE-R	0.142	0.182	-0.071	0.504	-0.050	0.640	-0.006	0.954	0.118	0.267	0.083	0.434	90
AL-R	0.057	0.596	-0.133	0.213	-0.143	0.180	0.106	0.320	0.098	0.360	0.013	0.905	90
CCT-R	-0.110	0.302	0.018	0.864	0.053	0.620	-0.068	0.527	-0.117	0.273	-0.010	0.928	90
AD-R	-0.189	0.075	-0.210	0.047	0.026	0.804	-0.043	0.690	-0.098	0.359	0.019	0.862	90
ACD-R	0.059	0.580	0.001	0.991	0.000	0.997	-0.026	0.806	-0.014	0.896	-0.034	0.751	90
LT-R	0.092	0.387	0.038	0.724	-0.063	0.555	-0.066	0.538	-0.109	0.307	-0.156	0.141	90
WTW-R	0.068	0.521	-0.134	0.206	-0.104	0.329	0.004	0.971	-0.024	0.823	-0.058	0.590	90
ECD-R	-0.124	0.243	-0.226	0.033	-0.179	0.090	-0.022	0.835	0.060	0.577	0.114	0.287	90
NUM-R	-0.080	0.452	-0.167	0.115	-0.104	0.330	0.017	0.873	0.130	0.221	0.186	0.079	90
AVG-R	0.125	0.240	0.224	0.033	0.172	0.106	0.023	0.829	-0.063	0.555	-0.117	0.274	90
SD-R	0.015	0.885	0.166	0.117	0.228	0.030	0.071	0.506	-0.011	0.919	-0.126	0.237	90
CV-R	-0.101	0.345	0.066	0.540	0.207	0.051	0.075	0.484	0.003	0.980	-0.085	0.424	90
CA-MAX -R	0.136	0.200	0.001	0.992	0.380	<0.001	0.069	0.520	0.153	0.149	0.043	0.688	90
CA-MIN-R	0.069	0.520	0.107	0.317	-0.018	0.867	0.031	0.771	-0.015	0.888	-0.242	0.021	90
6A-R	0.069	0.520	-0.126	0.236	-0.210	0.047	0.053	0.618	0.077	0.470	0.078	0.468	90
CORNEAL VOLUME-R	-0.077	0.469	0.064	0.548	0.210	0.047	0.022	0.836	0.005	0.965	-0.016	0.881	90
K1 -R	0.292	0.005	0.008	0.943	-0.151	0.156	0.148	0.164	0.048	0.652	-0.006	0.952	90
K2-R	0.251	0.017	0.023	0.829	-0.150	0.158	0.170	0.110	0.081	0.445	0.025	0.817	90
K AVG-R	0.261	0.013	0.013	0.900	-0.136	0.202	0.147	0.168	0.047	0.659	0.018	0.866	90
K CYL-R	0.229	0.030	0.079	0.458	-0.014	0.894	0.019	0.860	0.000	0.998	0.125	0.239	90
HVID-R	-0.309	0.003	0.011	0.916	-0.233	0.027	-0.063	0.552	-0.101	0.342	-0.129	0.225	90
APEX CURVATURE -R	0.024	0.824	-0.060	0.572	-0.213	0.044	0.199	0.060	0.177	0.095	-0.107	0.317	90
CURVATURE ASYM -F-R	-0.146	0.169	0.081	0.446	-0.033	0.761	0.029	0.785	-0.012	0.912	-0.046	0.670	90
CURVATURE ASYM -B-R	0.089	0.405	-0.055	0.605	-0.054	0.613	0.080	0.456	0.040	0.705	-0.125	0.241	90
IRIDOCORNEAL ANGLE-R	-0.273	0.009	-0.022	0.835	-0.174	0.101	0.043	0.685	-0.085	0.425	-0.009	0.935	90

r: Spearman's rho correlation coefficient

Table 6 Investigation of the relationship between patients carrying the M694V gene and eye measurements

	M694V Gene Group		Test ist	<i>p</i>
	M694V Homozygote (<i>n</i> = 14)	M694V Heterozygote (<i>n</i> = 29)		
SE	-0.7 ± 1.18	-0.4 ± 0.94	-0.900	0.373 ^t
AL	23.54 (23.09—24.15)	23.86 (22.96—24.16)	-0.117	0.907 ^m
CCT	540.93 ± 39.14	510.93 ± 36.21	-2.411	0.020^t
AD	3.1 ± 0.11	3.13 ± 0.12	-0.630	0.532 ^t
ACD	3.48 (3.08—3.87)	3.28 (2.96—3.64)	-1.154	0.249 ^m
LT	3.57 (3.48—3.94)	3.55 (3.26—3.92)	-0.883	0.377 ^m
WTW	12.21 (11.76—12.78)	11.98 (11.52—12.78)	-1.182	0.237 ^m
ECD	2071 (1243—2519)	2218.5 (2133—2848)	-0.181	0.006^m
NUM	237.5 (134—266)	249 (67—287)	-2.308	0.121 ^m
AVG	397.5 (351—469)	389 (343—805)	-0.272	0.785 ^m
SD	162.5 (122—217)	158 (112—375)	-0.117	0.907 ^m
CV	40.21 ± 6.14	40.48 ± 6.24	-0.133	0.895 ^t
CA-MAX	963.5 (673—1194)	1061 (768—2677)	-1.296	0.195 ^m
CA-MIN	104.5 (4—136)	93 (75—213)	-1.701	0.089 ^m
6A	41.57 ± 8.78	43.86 ± 8.81	-0.800	0.428 ^t
CORNEAL VOLUME	56.18 ± 2.72	57.96 ± 4.71	-1.309	0.198 ^t
K1	43.83 ± 1.55	43.6 ± 1.55	0.459	0.648 ^t
K2	43.84 ± 1.71	43.6 ± 1.48	0.462	0.646 ^t
K AVG	44.38 ± 1.63	44.02 ± 1.58	0.697	0.490 ^t
K CYL	-0.97 ± 0.54	-0.84 ± 0.45	-0.864	0.393 ^t
HVID	12.08 ± 0.37	12 ± 0.39	0.655	0.516 ^t
APEX	44.65 (43.89—54.23)	44.62 (43.87—45.38)	-0.285	0.775 ^m
CURVATURE ASYM F	0.18 (0—0.53)	0.08 (0—0.63)	-0.599	0.549 ^m
CURVATURE ASYM B	0.01 (0—0.83)	0.01 (0—0.88)	-0.260	0.795 ^m
IRIDOCOR- NEAL ANGLE	39.93 ± 6.81	42.03 ± 5.94	-1.039	0.305 ^t

t: Independent samples t-test, m: Mann–Whitney U test. Values are presented as mean ± SD for normally distributed variables (analyzed by t-test) and as median (min–max) for non-normally distributed variables (analyzed by Mann–Whitney U test). Distributional normality was assessed by the Shapiro–Wilk test. Abbreviations as in Table 3

ocular involvement in FMF. Doughty and colleagues' standardization studies support the use of modern corneal imaging technologies as reproducible clinical endpoints [10, 11], and the high intra- and inter-observer reliability coefficients obtained in our study (ICC > 0.90) indicate that these measurements can be acquired consistently. Acar and colleagues

Table 7 Logistic regression analysis of CCT and ECD in relation to M694V homozygous versus heterozygous status

	Univariate		Multivariate	
	OR (%95 CI)	<i>p</i>	OR (%95 CI)	<i>p</i>
CCT	1.023 (1.002—1.045)	0.029	1.033 (1.008—1.058)	0.009
ECD	0.898 (0.821—0.982)	0.019	0.918 (0.856—0.985)	0.017

OR Odds ratio; CI Confidence interval; CCT Central corneal thickness; ECD Endothelial cell density. Dependent variable: M694V homozygous status (= 1) vs M694V heterozygous status (= 0). CCT is reported per 1 µm increment; ECD is reported per 100 cells/mm² increment. The multivariable model was adjusted for age, sex, body-mass index, and disease duration. 95% confidence intervals were derived from Wald standard errors. Overall correct classification: 69.8%

previously reported that cytokine responses in FMF are heterogeneous and that conventional acute-phase reactants may not fully capture ongoing inflammatory activity [6]; against this background, corneal endothelial parameters may warrant further investigation as complementary, organ-level readouts. However, whether these parameters actually track disease activity over time cannot be established from a cross-sectional design, and prospective longitudinal studies will be required to determine whether they have any role as monitoring biomarkers.

From a clinical perspective, our findings suggest that ophthalmologic evaluation may be a useful complement to standard rheumatologic follow-up in FMF, particularly in patients with genotypes associated with higher inflammatory burden. Whether structured anterior segment and endothelial assessment should be incorporated into routine FMF follow-up — and whether such an approach would add prognostic value beyond existing EULAR management recommendations [13] — remains to be determined in larger multicenter and longitudinal studies. At this stage, our data support the value of collaborative evaluation between rheumatology and ophthalmology in selected patients, rather than a redefinition of current management algorithms.

Study limitations

The cross-sectional design limits our evaluation of temporal dynamics of corneal changes. Planning long-term cohort studies is necessary to characterize progression rates and intervention response patterns. The absence of comprehensive posterior segment evaluation limits the assessment of FMF's total ocular burden. A further limitation is that intraocular pressure was measured by Goldmann applanation tonometry without correction for central corneal thickness; given the 13.5 µm greater mean CCT in the FMF group, a small component of the observed IOP difference may be attributable to this methodological factor. Applying commonly cited CCT–IOP correction estimates (approximately 0.5 mmHg per 10 µm [10]), the estimated CCT-adjusted intergroup IOP difference

remains in the same direction but is reduced to approximately 2.3 mmHg, reinforcing our interpretation that this difference, while statistically detectable, is of modest clinical magnitude. A further, methodologically important limitation is that IL-1 β was not measured, either in serum or in ocular fluids. Accordingly, although the experimental literature provides a plausible biological framework for linking chronic IL-1 β elevation to corneal endothelial alterations, our study cannot directly test this association in vivo and describes only between-group phenotypic differences. Prospective studies that incorporate serum IL-1 β measurement — and, where ethically justified (for example, in patients undergoing intraocular surgery for another indication), aqueous humour sampling — will be required to evaluate whether circulating or intraocular IL-1 β levels correlate with the corneal findings reported here.

Future research could also examine whether colchicine pharmacokinetics or other patient-level factors modify corneal endothelial findings in FMF, although such questions are beyond the scope of the present cross-sectional analysis.

Conclusion

In this cross-sectional study, FMF patients in clinical remission showed measurable differences in corneal endothelial parameters compared with healthy controls, including reduced endothelial cell density, increased central corneal thickness, greater pleomorphism, and lower hexagonality. Within the FMF group, M694V homozygous patients showed more pronounced differences than heterozygotes. These findings suggest that the anterior segment, and the corneal endothelium in particular, warrants more systematic attention in the ophthalmologic evaluation of patients with FMF. The cross-sectional nature of our data does not allow causal or prognostic inferences; whether corneal endothelial parameters can serve as useful indicators of ocular involvement or disease activity in FMF should be addressed in prospective, longitudinal, and ideally multicenter studies.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics committee approval The study was approved by the Recep Tayyip Erdogan University School of Medicine Ethics Committee (Ethics Committee Approval Number: 2024/116) and/or publication of this article.

Consent to participate All participants provided written informed consent prior to their inclusion in the study. Participants were informed about the purpose, procedures, potential risks, and benefits of the study, and their right to withdraw at any time without consequences.

Clinical trial number Not applicable.

Competing interests The authors declare no competing interests.

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