

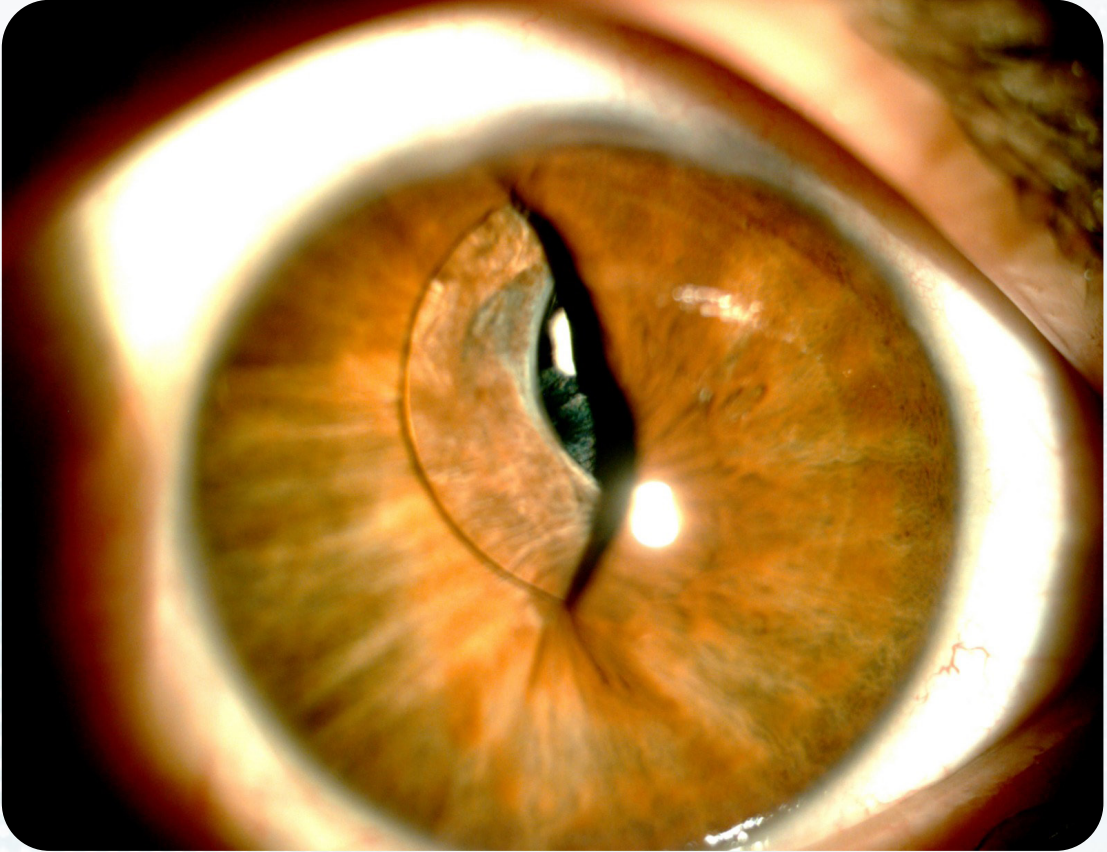
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Ethical Responsibilities and Policies

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Endothelial Safety After Phacoemulsification in Patients with Fuchs Dystrophy: Short Term Outcomes and Predictors of Corneal Edema

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Abstract

Objectives: To compare the clinical outcomes of phacoemulsification combined with intraocular lens implantation in patients with Fuchs endothelial corneal dystrophy (FECD) and individuals with healthy corneas.

Methods: This retrospective study included eyes that underwent phacoemulsification and intraocular lens (IOL) implantation between January 2021 and September 2022. Phacoemulsification was performed using a contemporary oscillatory ultrasound mode; device-logged energy and fluidics metrics were recorded. Best corrected visual acuity (BCVA) and specular microscopy (CEM-530™; Nidek) were evaluated preoperatively and at postoperative week 1, month 1, and month 3. Endothelial cell density (ECD) and central corneal thickness (CCT) were recorded. The primary outcome measures were post-operative BCVA, ECD, and CCT changes. The study included 32 eyes with FECD and 29 control eyes with healthy corneas.

Results: In both groups, mean BCVA improved significantly from 0.7 LogMAR preoperatively to 0.15 LogMAR at 1 month postoperatively ($p<0.001$). The endothelial cell loss at 3 months was significantly higher in the FECD group compared to controls (20.9% vs. 17.9%, $p=0.022$). Baseline ECD was 2065.5 cells/mm² in the FECD group and 2289.4 cells/mm² in the control group, decreasing to 1633.1 and 1878.9 cells/mm², respectively, at 3 months. CCT increased from 564.5 μ m to 584.1 μ m in the FECD group ($p=0.006$), and from 550.5 μ m to 557.7 μ m in the control group ($p=0.124$). No cases of postoperative corneal decompensation were observed.

Conclusion: Phacoemulsification yielded meaningful visual improvement in FECD eyes without early corneal decompensation. Endothelial loss was higher and CCT recovery slower than in controls, supporting energy-minimizing techniques and closer early follow-up in FECD.

Keywords: Fuchs endothelial corneal dystrophy, phacoemulsification, endothelial cell density, central corneal thickness, energy metrics

Introduction

Fuchs endothelial corneal dystrophy (FECD) is a bilateral, progressive disease characterized by focal excrescences of Descemet's membrane, or so-called guttata and endothelial cell loss (1). The prevalence of the disease ranges from 3.7 to 11.0% (2). It is seen in approximately 4% of individuals over the age of 40

(3). FECD ranks first or second among keratoplasty indications worldwide (4). The coexistence of cataract and FECD is a challenging situation for ophthalmic surgeons. In order to protect the corneal endothelium, careful surgery and the use of the latest technology are required. It is recommended to remove the cataract early before the nucleus becomes too hard (4). However, in eyes with FECD, phacoemulsification- intraocular lens

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(IOL) surgery carries the risk of corneal decompensation (5). Before surgery, patients should be informed about endothelial failure and the possible need for keratoplasty at some point in their lifetime (6). Presence of central guttata on biomicroscopy, anterior chamber depth, pupil size, corneal clarity and degree of nucleus hardness should also be considered (7). In a generally accepted rule, if the central corneal thickness (CCT) is over 640 μm , combined or sequential keratoplasty is recommended instead of cataract surgery alone (5,8). For each 10 μm increase in preoperative CCT, the risk of corneal decompensation increases 1.7 times (9). In addition, eyes with an endothelial cell density (ECD) under 1000 cells/ mm^2 , coefficient of variation (CV) >40 and hexagonality <50% may not tolerate cataract surgery (2,6).

In FECD, ophthalmologists have to work in a way that causes minimal damage to the corneal endothelium during surgery (7,9). Intra-operative measures known to protect the endothelium include the use of the soft-shell viscoelastic technique for dense cataracts, efficient cataract removal techniques like phaco-chop, use of oscillatory handpiece with high vacuum, low irrigation and surgery by an experienced surgeon (4,8). Previous clinical and experimental studies showed that using torsional phaco instead of longitudinal phaco during emulsification of the lens nucleus, reduces endothelial damage (10,11). Rather than comparing ultrasound modes, this study provides pragmatic, device-logged evidence on early safety in FECD versus normal corneas and explores preoperative CCT and intraoperative energy as predictors of early postoperative corneal status.

Methods

In this retrospective comparative cohort study; the clinical outcomes of 32 eyes with FECD and 29 control eyes (control group) with healthy corneal endothelium who underwent phacoemulsification-intraocular lens (Centurion-OZil) implantation surgery in our clinic between January 2021 and September 2022 were compared. The ethical approval of the study was obtained from the institutional Ethical Board (Date: 7.12.2023, Reference Number:2023/101). The study was conducted in accordance with the tenets of the Declaration of Helsinki and informed consent was obtained from all the patients. Best corrected visual acuity (BCVA), intraocular pressure (IOP) measurement with Goldmann applanation tonometer, slit-lamp biomicroscopy, dilated fundus examination and non-contact specular microscopy was performed before surgery and post-operative first day, first week, first month and third month visits. Nuclear hardness was graded with the Oxford system. Non-contact specular microscopy (CEM-530™, Nidek) was performed by a single experienced operator. Only high quality frames with sharp cell borders and ≥ 20 analyzable cells were accepted. When confluent

central guttae prevented reliable cell-border delineation, images were obtained from a paracentral annulus located 0.5-1.0 mm from the corneal apex, and the same locus was used at all follow-ups. Automated segmentation was reviewed and manually corrected when required. At each visit, three high quality frames were captured and averaged. To document the analyzable area, the number of endothelial cells included in the analysis was recorded. ECD, CV, hexagonality and CCT examined by specular microscopy were noted. Visual acuity was measured using a projected Snellen chart at 4 meters and converted to logarithm of the minimum angle of resolution (LogMAR) for analysis. Stage 1 and 2 FECD patients, according to the classification of Adamis, with central guttata were included in the study (12). Inclusion criteria were senile cataract without zonular weakness or pin-point pupilla due to severe pseudoexfoliation. The exclusion criteria were any other present or previous eye disorder than cataract, age under 40 years, CCT >650 μm , history of any ocular surgery or trauma, glaucoma and any intraoperative complication. Only one eye per patient was included in the analysis. Advanced FECD patients with stromal edema, scarring and drop outs from follow-up were also excluded. Nuclear hardness was graded from 1 to 4 according to the Oxford clinical cataract grading system (13).

The operations were performed by the same experienced surgeon (BY) with special care to keep the phacoemulsification tip pointed away from the endothelium. All surgical procedures were conducted under topical anesthesia using 0.5% proparacaine hydrochloride ophthalmic solution (Alcaine; Alcon Laboratories, Inc., Fort Worth, TX, USA). To preserve the depth of the anterior chamber, a dispersive ophthalmic viscoelastic agent (Viscoat, Alcon Laboratories), consisting of 3.0% sodium hyaluronate and 4.0% chondroitin sulfate, was administered following the formation of two corneal side ports positioned 90 degrees apart from the main incision using a 20-G paracentesis blade. Subsequently, capsulorhexis was carefully carried out. One of the divide&conquer, stop&chop or quick chop techniques was used according to Oxford nuclear grade (1-4). Torsional energy was used at 60-80% power for nucleus removal at Centurion System (Alcon) with the OZil handpiece and 0,9 mm 45° angled Kelman mini-flared tip. Typical setting for nucleus removal included; 450-500mmHg vacuum, 28cc/min aspiration rate and 80cm bottle height. In very hard cataracts, intelligent phaco (IP) mode of phacomachine was used to prevent the needle from clogging. Bimanual irrigation and aspiration were performed using dual I/A instruments to ensure efficient cortical cleanup. At the end of surgery, phaco parameters displayed as “metrics” on the device screen were recorded in the operative notes. Phacoemulsification metrics presented on the device interface at the conclusion of surgery were

documented as part of routine operative records and were accessed retrospectively for data analysis. These parameters were cumulative dissipated energy (CDE), total ultrasound time, torsional time, average torsional amplitude, average torsional amplitude in foot pedal position 3, total aspiration time, estimated fluid used and operation time. Main outcome measures were postoperative BCVA, ECD and CCT. Secondary outcomes were CV and hexagonality.

Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). The data obtained by taking the average of all measurements were recorded as mean±standard deviation (range). Normality and variance homogeneity were assessed using Shapiro-Wilk and Levene tests, respectively. Repeated measures ANOVA was used for multiple comparisons, and Paired t-test was used for pairwise comparisons. Independent t test was used for comparisons between groups. Relationships between dependent variables were analyzed by Pearson correlation analysis. A value of $p < 0.05$ was considered statistically significant.

Results

Fuchs group consisted of 32 eyes and control group 29 eyes. Fourteen (14/32, 43.8%) of the Fuchs group and 18 of the control group (18/29, 62.1%) were female. Mean age was 69.8 ± 9.6 (42-83) and 68.3 ± 8.1 (50-81) respectively ($p = 0.514$). Preoperative characteristics of both groups are shown in Table 1.

The number of endothelial cells available for analysis was significantly lower in the FECD group because confluent guttae reduced the analyzable area on specular microscopy. These black spots occupying some part of the analyzed area reduces the number of the cells analyzed. Due to the known nature of the disease, the endothelial count was low in the Fuchs group before surgery. The phacoemulsification parameters are summarized in Table 2. At baseline, the two groups were comparable with respect to age, sex, BCVA, intraocular pressure, central corneal thickness and nuclear hardness (all $p > 0.05$). Intraoperative metrics, including ultrasound time, average power, aspiration time, fluid usage, and cumulative dissipated energy (CDE), did not differ significantly between groups (all $p > 0.05$). These findings indicate

Table 1. Preoperative characteristics of the FECD and control groups.

Preoperative Parameter	FECD n=32 eyes	Control n=29 eyes	P
Best corrected visual acuity (LogMAR)	0.7 ± 0.2 (2.0-1.3)	0.7 ± 0.1 (2.0-0.4)	0.333
Intraocular pressure (mm/Hg)	15.8 ± 2.9 (10-21)	14.5 ± 3.5 (9-22)	0.125
Number of endothelial cells evaluated	63.9 ± 44.2 (20-170)	115.1 ± 41.3 (35-196)	0.000*
Endothelial cell density (cells/mm ²)	2065.5 ± 494.0 (826-2737)	2289.4 ± 331.8 (1574-2828)	0.044*
Coefficient of variation	30.9 ± 7.2 (18-56)	29.1 ± 4.0 (21-39)	0.247
Hexagonality (%)	67.0 ± 9.7 (38-88)	69.0 ± 4.6	0.323
Central corneal thickness (µm)	564.5 ± 41 (495-646)	550.5 ± 35.3 (502-634)	0.161

*, Independent samples t test. FECD: Fuchs endothelial corneal dystrophy.

Table 2. Metric parameters displayed by the phaco device at the end of surgery in both groups.

Phaco Parameter	FECD n=32 eyes	Control n=29 eyes	P*
Nucleus hardness ^a (1-4)	2.6 ± 0.6 (1-4)	2.5 ± 0.5 (2-3)	0.758
US total time (seconds)	115.2 ± 33.9 (28-177)	108.7 ± 44.1 (40-210)	0.521
CDE (percent-seconds)	14.6 ± 6.1 (5.0-30.7)	14.2 ± 7.3 (4.9-32.5)	0.792
Torsional time (seconds)	110.1 ± 34.6 (28-177)	103.4 ± 40.4 (40-190)	0.485
Average torsional amplitude (%)	31.8 ± 9.2 (20.7-61.5)	32.6 ± 10.8 (18.3-62.7)	0.752
Average torsional amplitude in pos3 (%)	29.6 ± 7.7 (14.9-48.4)	30.5 ± 7.9 (18.3-47.8)	0.657
Aspiration time (minutes)	6.1 ± 1.8 (4.1-12.4)	5.6 ± 1.5 (3.5-8.4)	0.230
Estimated fluid used (ml)	88.4 ± 34.6 (47-226)	79.8 ± 21.5 (46-120)	0.252
Operation time (minutes)	17.2 ± 4.7 (10-32)	17.9 ± 4.3 (12-29)	0.592

*, Independent samples t test, ^a, Oxford classification system, US: ultrasound, CDE: cumulative dissipated energy, pos: foot pedal position. FECD: Fuchs endothelial corneal dystrophy.

that surgical technique and energy exposure were similar in both cohorts.

Data from the first postoperative day were not analyzed because transient corneal edema precluded the acquisition of reliable specular microscopy in most cases. In both groups, statistically significant visual improvement was achieved compared to baseline at postoperative 1st week, 1st month and 3rd month visits ($p<0.001$). At postoperative 3 months, IOP showed a significant decrease in Fuchs group compared to preoperative value (15.8 to 14.5mmHg) ($p=0.025$). Whereas, in the control group, no significant change was observed in IOP compared to baseline in any visit. ($p=0.405$).

In both groups, the sharp decrease in ECD at first postoperative week slowed down in the following months 1 and 3 (Fig. 1).

In the Fuchs group, a significant endothelial cell loss was observed in all three postoperative exams compared to the preoperative ECD ($p=0.004$; $p=0.001$ and $p<0.001$ respectively) (Fig. 2).

Similarly, a significant endothelial loss was observed in the control group in all three visits compared to baseline ($p<0.001$) (Fig. 3).

However, the endothelial loss rate was higher in the Fuchs group compared to controls at the first and third months ($p=0.047$ and $p=0.022$ respectively).

While the increase in CV in the Fuchs group was not significant in the first week compared to preoperative value ($p=0.065$), it was significant at months 1 ($p=0.025$) and 3 ($p=0.005$). In the control group, while the increase in the 1st week was statistically significant ($p=0.005$), increases at months 1 ($p=0.154$) and 3 ($p=0.457$) were not significant. Although the postoperative hexagonality decreased in both groups compared to the preoperative level, that decrease was not statistically significant. In the Fuchs group, CCT showed a significant thickening compared to baseline in all three postoperative visits ($p<0.001$; $p=0.001$ and $p=0.006$). However, the significant thickening ($p<0.001$) observed in the control group at the 1st week, approached the baseline level at months 1 ($p=0.014$) and 3 ($p=0.124$).

Two most severe Fuchs patients who had a CCT or ECD out of generally accepted range were operated. One of them had a CCT>640 μm , and the other had an ECD<1000cells/ mm^2 . The first patient was an 81-year-old female with preoperative BCVA of 20/200, CCT of 646 μm and ECD of 1922 cells/ mm^2 . At the postoperative 1st month: BCVA improved to 20/40, CCT 661 μm and ECD was 1514 cells/ mm^2 . The second patient was a 71-year-old female with preoperative BCVA of 20/66, CCT of 591 μm and ECD of 826 cells/ mm^2 . At the postoperative 1st month: BCVA was 20/20, CCT; 596 μm and ECD was 1003 cells/ mm^2 .

Pearson correlation analysis showed month 3 CCT was significantly correlated with preoperative CCT in both

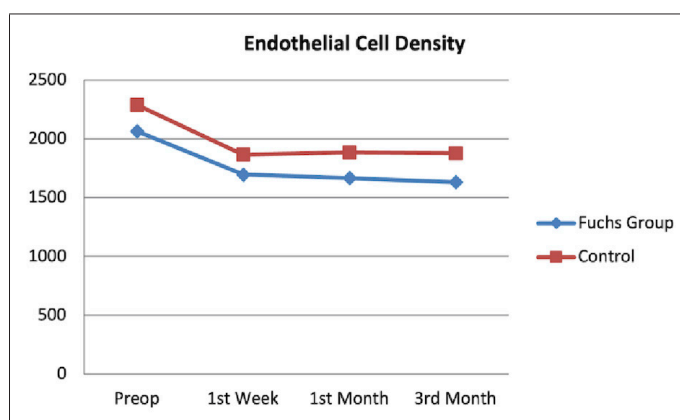


Figure 1. Changes in endothelial cell density of both groups during follow-up.

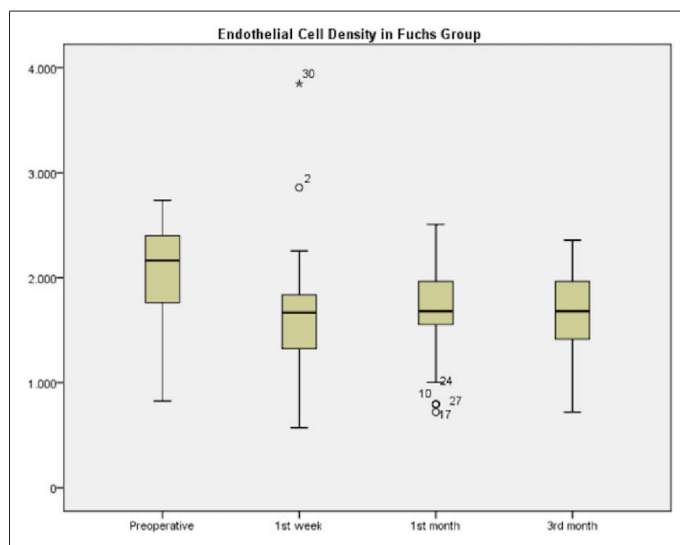


Figure 2. Changes in endothelial cell density after surgery in the FECD group.

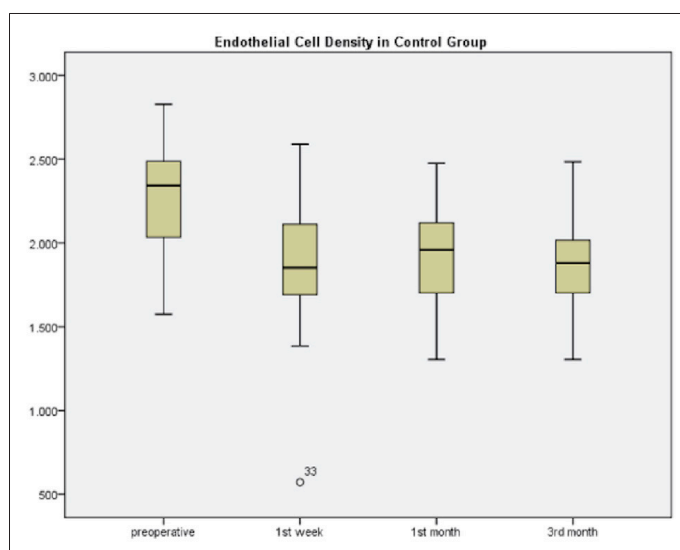


Figure 3. Changes in endothelial cell density after surgery in the control group.

groups ($p < 0.001$). While there was no correlation between the preop ECD and the 3rd month ECD in Fuchs group ($p = 0.212$), it was found to be correlated in controls ($p = 0.026$). A significant correlation was found between CDE and month 3 CCT in the Fuchs group ($p = 0.030$) but not in controls ($p = 0.552$). There was no significant correlation between preop CCT, ECD and 3rd month BCVA.

Discussion

In this case-control cohort, FECD eyes experienced larger early endothelial loss and thicker corneas after phacoemulsification compared with controls, while visual improvement was comparable between groups. As a natural outcome of cataract surgery, vision improved in both groups after surgery (5). The vision, gradually increased from preoperative level of 0.7 LogMAR to 0.22 at first week and 0.15 LogMAR at 1 month. This finding suggests that patients with Fuchs dystrophy can also gain vision, with torsional phacoemulsification, at a similar rate to normal patients. Kim et al. reported that vision gain, in eyes with FECD, was preserved up to the 2nd year following the phacoemulsification (1). IOP showed no significant elevation after surgery in both groups. Interestingly, a significant decrease in intraocular pressure was observed in the FECD group, whereas no such change was noted in controls. One possible explanation is that subclinical corneal edema present preoperatively in FECD eyes may have led to overestimation of intraocular pressure measurements. Following surgery, improvement in corneal clarity may have resulted in more accurate applanation readings. Therefore, this finding should be interpreted with caution, as it may reflect measurement related factors rather than a true physiological reduction in intraocular pressure. Our correlation analyses showed that preoperative CCT was significantly correlated with month 3 CCT in both groups. Therefore preoperative CCT may be considered as the most reliable parameter in estimating the surgical outcome and making the decision before surgery. By looking at the preoperative ECD, it is more likely to predict the outcome at the 3rd month in the control group but we can hardly rely on ECD in the Fuchs group.

Preoperative ECD was lower in the Fuchs group as expected. CV was a little high and hexagonality little low but these were not significantly different from the control eyes. As known, normal CV is < 30 and hexagonality > 60 . In patients with FECD, the cornea was slightly thicker than controls due to the edema, but this was not statistically significant either. However, endothelial function demonstrated by specular microscopy was significantly worse in the Fuchs group. Number of cells evaluated was running low in Fuchs dystrophy in all 3 visits due to excrescences in Descemet membrane. ECD decreased postoperatively in both groups due to surgical trauma. However, postoperative endothelial

loss was significantly higher in the Fuchs group at 1st and 3rd months when compared to control group. Endothelial loss rate at 1 month was 19.2% in Fuchs and 17.7% in control eyes. At 3 months, it was 20.9% and 17.9% respectively. However, in the Fuchs group, the mean ECD was 1633 cells/ mm^2 at 3 months, that was well above required for corneal transparency. Therefore, endothelial failure did not develop in any of our patients. In general, phacoemulsification has been shown to decrease endothelial cells by 8.5–16.0%. Factors such as a low endothelial cell count, the presence of stromal edema, guttata, and epithelial microcystic changes indicate a higher possibility for corneal decompensation after cataract surgery (5). Kim et al reported annual ECD loss rate after phacoemulsification 29.3% per year in patients with Fuchs' dystrophy and 19.4% in normal eyes (1). Our 3rd month endothelial loss rates are significantly less than these numbers in both Fuchs eyes and normal eyes. That favorable result may be due to our use of torsional phaco. Likewise, Doors et al reported that, corneal edema in eyes with FECD also resolved faster with torsional phaco compared to longitudinal phaco (9).

CCT, indicative of corneal edema, was significantly higher in Fuchs group compare to controls in all 3 postoperative visits. The insignificant difference in CCT between the two groups at the 1st week (17,8 μm); became significant at the 1st (26.1 μm) and 3rd months (26.4 μm). The reduction in edema in the Fuchs group was 27.7 μm between the 1st week and the 3rd month, while it was 36.3 μm in the control group. There was a mild corneal edema in the Fuchs group at the 1st postoperative week. Although, edema slowly decreased starting from the 1st month, that decrease was not as much as the control group. At the 3rd month; the mean CCT was still 584.1 μm indicating the residual edema. Whereas, in the control group, it was 557.7 μm which is closer to baseline value of 550.5 μm . Chou et al reported that CCT returns to baseline values 1 month after cataract surgery in eyes with FECD (5). However in the long run, corneal decompensation may occur due to the progression of Fuchs disease, especially in eyes with complications during surgery (4,9). In control group, CV increase, in other words, endothelial disorganization was only evident at the first week and the endothelium quickly recovered starting from the 1st month and returned to normal value of 30 at 3 months. Whereas, in the Fuchs group, endothelial disorganization continued at 3 months and the mean CV was 34.6, which is still high (2). Although some of these changes reached statistical significance, their magnitude was relatively limited and may not translate into clinically meaningful functional impairment. Therefore, these findings should be interpreted in the context of overall endothelial function rather than on the basis of statistical significance alone.

As known, in longitudinal phaco, the needle tip moves back and forth coring the nucleus and decreasing followability. In torsional phaco, the phaco tip oscillates around its axis, with side-to-side tip motion, to emulsify the lens (10). It shaves nuclear material effectively and decreases repulsion of nuclear material from the tip (4). Improved followability, provides fewer tiny nuclear particles moving in the anterior chamber and allows the use of a lower vacuum and flow rates during surgery. Torsional phaco delivers 20% less energy into the eye providing thermal safety and endothelial protection (11). CDE is the total energy dissipated at the wound site in foot position 3 involving the sum of torsional and longitudinal ultrasound energies (14). It has been reported that torsional phaco reduces CDE, provides less fluid use, shortens aspiration and surgical times (9,10). On the other hand, if the intelligent phaco (IP) mode is on, longitudinal power is activated in case of occlusion and it causes an increase in CDE (15). Experimental studies showed less free radical production in torsional phaco (10). Less endothelial loss (5.5%) was reported with torsional phaco compared to longitudinal phaco (6.5%) in non-FECD eyes at 2 months (11). Likewise, at 6-o'clock position, where the phaco needle tip points, both corneal thickness and CV values were found smaller in torsional group than longitudinal group at day 1. It might be a result of less repulsion opposite to the incision site (9). All these advantages of torsional mode are useful in eyes with FECD. Therefore, the use of transverse or torsional phaco modes are recommended in patients with FECD (6). However, according to our results of correlation analyzes; although safer, excessive use of torsional energy and high CDE affect the 3rd month CCT result in Fuchs patients. In other words, in eyes with Fuchs dystrophy, the endothelium is more fragile and more energy causes more pronounced edema. Whereas healthy eyes are more resistant to phaco energy. Little increases in CDE are well tolerated and do not cause significant corneal edema at month 3.

Our study has some limitations that should be addressed. First, the present study is retrospective in design and follow-up period is relatively short. Longer follow-up is needed to assess delayed decompensation. Single surgeon design and modest sample size limit precision and generalizability; findings should be viewed as exploratory. In addition, it would be better to compare the torsional phaco with the longitudinal phaco. However, given the torsional phaco has the advantages mentioned above, it would be unethical to operate on Fuchs patients with longitudinal mode. There are few studies on the use of torsional mode in eyes with FECD, therefore our study may be considered a contribution to the literature. Although the 3 month follow up is adequate to assess early postoperative safety, it may not fully capture delayed corneal decompensation, which can occur in the natural

course of FECD. Therefore, the absence of decompensation in our cohort should be interpreted with caution. Given the retrospective design and limited sample size, no a priori sample size calculation was performed. Therefore, the results should be interpreted as exploratory.

This study complements prior reports by providing comparative, real-world early outcomes in FECD vs normal corneas with device-logged metrics. Two practice-relevant observations merit emphasis. First; preoperative CCT was the most consistent predictor of 3-month CCT across both cohorts. Second, in FECD eyes greater intraoperative energy exposure -reflected by CDE- as associated with thicker 3-month CCT, underscoring heightened endothelial vulnerability and reinforcing the need of energy minimizing strategies.

Conclusion

In conclusion; although the endothelial loss is slightly higher and the corneal edema resolves a little later, patients with Fuchs dystrophy can achieve visual gains comparable to normal ones with torsional phacoemulsification. None of the patients developed corneal decompensation. Therefore, it may be preferable to use the torsional phaco in Fuchs endothelial dystrophy patients. Preoperative CCT is a reliable criterion on the prediction of the postoperative corneal edema. These findings support careful case selection and perioperative counseling in FECD undergoing cataract surgery, and justify closer early postoperative monitoring. Larger prospective studies with longer follow up are warranted.

Disclosures

Ethical approval: The ethical approval of the study was obtained from the institutional Ethical Board of Health Sciences University İzmir Bozkaya Hospital (Date: 7.12.2023, No: 2023/101)

Informed consent: Written informed consent was obtained from all individual participants included in the study.

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Repeatability and Reliability of Corneal Tomography in Keratoconus Patients with Corneal Allogenic Intrastromal Ring Segments

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Abstract

Objectives: To assess the repeatability and reliability of anterior and posterior corneal measurements in keratoconus patients who underwent corneal allogenic intrastromal ring segment (CAIRS) implantation using a Scheimpflug-based tomography system.

Methods: This prospective observational study included 42 eyes: 20 keratoconic eyes that had undergone CAIRS implantation and 22 healthy controls. All participants were imaged with the Pentacam HR (Oculus Optikgeräte GmbH, Germany). Each eye underwent three consecutive scans during a single session. Repeatability was evaluated using within-subject standard deviation (Sw), repeatability index (RI), and tolerance index (TI), and reliability was assessed using intraclass correlation coefficients (ICC). A TI>0.36 was considered indicative of reduced repeatability.

Results: Anterior corneal curvature parameters (K1 and K2) and pachymetric indices demonstrated excellent reliability (ICC>0.90) and acceptable repeatability (TI<0.36). In contrast, CAIRS-implanted eyes exhibited greater variability in Kmax, Kmean, anterior elevation, and several posterior corneal metrics, with TI values exceeding 0.36. Despite having high ICC values, posterior elevation showed the greatest variability. Pachymetry at the corneal vertex and the thinnest corneal thickness remained highly reproducible (TI 0.08 and 0.18, respectively), suggesting strong measurement accuracy.

Conclusion: The implantation of CAIRS alters the shape of the cornea and decreases the repeatability of several tomography-derived metrics, especially posterior corneal indices and Kmax. Although overall reliability remains high, clinicians should cautiously interpret small postoperative changes in monitoring these parameters. Pachymetric measurements maintain excellent precision and can be reliably used for postoperative follow-up and progression assessment after CAIRS surgery.

Keywords: Cornea ectasia, intrastromal ring implantation, cornea tomography

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Introduction

Keratoconus is a progressive, non-inflammatory corneal ectatic disorder characterized by stromal thinning, conical protrusion, and irregular astigmatism, typically beginning in adolescence or early adulthood. As the disease progresses, there is a notable decline in quality of life and visual impairment. In the early stages, rigid gas-permeable lenses and eyeglasses might be enough to correct vision, but in more advanced cases, surgery is frequently necessary. Over the past two decades, various surgical procedures have been developed to stabilize and improve the corneal architecture, including corneal cross-linking (CXL), intracorneal ring segment implantation (ICRS), and deep anterior lamellar keratoplasty (DALK).

Intrastromal ring segments are implantable arc-shaped devices that apply biomechanical force to the ectatic cornea in order to flatten and regularize the corneal form. While synthetic polymethyl methacrylate (PMMA) rings such as INTACS and Keraring are widely used, they are associated with complications such as extrusion, infection, or poor biocompatibility in some cases (1,2). Recently, corneal allogenic intrastromal ring segments (CAIRS) have emerged as a novel, biologically compatible alternative. CAIRS utilize human donor corneal tissue shaped into ring segments and implanted intrastromally to achieve similar geometric and biomechanical effects with potentially improved integration and fewer complications.

Studies have shown the excellent repeatability of measurements taken with the Pentacam HR (Oculus Optikgeräte GmbH, Wetzlar, Germany) in healthy eyes (3,4). On the other hand, decreased repeatability and reliability have been reported in patients with moderate to advanced keratoconus, suggesting that as the cornea diverges further from its normal anatomical configuration, measurements become increasingly unpredictable (5-10). Moreover, corneal stromal interventions, such as ICRS implantation, may further compromise the precision of corneal measurement parameters (11).

Several studies have assessed the visual and topographic outcomes of CAIRS; data on the repeatability and reliability of anterior and posterior corneal measurements in CAIRS-implanted eyes remain unknown. Accurate and reproducible corneal measurements are critical for both the clinical follow-up of ectatic diseases and the objective assessment of surgical efficacy. However, the presence of stromal implants may introduce measurement variability due to alterations in corneal thickness, curvature, and elevation. Furthermore, there are no studies addressing repeatability and reproducibility in CAIRS-implanted eyes. Therefore, the present study aims to evaluate the repeatability and reliability

of anterior and posterior corneal parameters in eyes with keratoconus that have undergone CAIRS implantation, using a Scheimpflug-based corneal tomography system.

Method

Study Design and Patient Selection

This prospective, observational study was conducted at the Istanbul Swiss Vision Clinic between August 2022 and July 2023. The study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of İstanbul Medipol University (Date: 11/03/2025, No: E-10840098-202.3.02-1941). Written informed consent was obtained from all participants prior to their involvement in the study. An a priori sample size calculation was performed before study initiation. Based on the expected effect size, significance level ($p=0.05$), and desired statistical power of 80%, the required sample size was determined to be adequate for the primary study outcomes.

Two groups were included: keratoconus patients who had undergone CAIRS implantation and healthy controls seeking refractive surgery. The keratoconus group consisted of 20 eyes that had undergone CAIRS implantation at least three months before study inclusion, allowing sufficient time for postoperative wound stabilization. Keratoconus diagnosis was based on characteristic slit-lamp findings—such as stromal thinning, Fleischer ring, and Vogt's striae—combined with tomographic patterns including asymmetric inferior steepening, abnormal elevation maps, and reduced central or paracentral pachymetry.

The control group who presented to the clinic requesting refractive surgery ($n=22$ healthy control group). These subjects had spherical equivalent myopia between -3.00 D and -6.00 D, with regular astigmatism up to -1.25 D. All controls exhibited normal corneal topography and tomography, as confirmed by a comprehensive ophthalmologic examination. All subjects in this group underwent a comprehensive ophthalmologic examination, including visual acuity testing, manifest and cycloplegic refraction, slit-lamp biomicroscopy, intraocular pressure measurement, fundus evaluation, and corneal imaging with Scheimpflug tomography. Patients in whom keratoconus or any other corneal pathology was suspected or detected were excluded.

For both groups, exclusion criteria were as follows: history of previous ocular surgery (except CAIRS in the keratoconus group), current or recent use (within 3 weeks) of rigid gas permeable or scleral contact lenses, presence of active or past ocular surface inflammation or infection (e.g., blepharitis, conjunctivitis, or keratitis), systemic diseases with known ocular involvement (e.g., autoimmune disease, diabetes mellitus), and poor compliance or inability to complete repeated imaging procedures. Only one eye from each participant was

included in the final analysis to avoid inter-eye correlation. Only one eye per subject was included; in bilateral cases, an eye was randomly selected using a computerized random number generator.

Surgical Technique

All surgeries were performed by the same surgeon (A.K.) under topical anesthesia (0.5% proparacaine; Alcaine, Alcon Laboratories, Inc., Fort Worth, TX). The visual axis was delineated using an ink-stained Sinskey hook beneath a Wave-Light EX500 biomicroscope (Alcon Laboratories, Inc.), with the initial Purkinje reflex serving as a reference point. After centralization using the reference point, docking was executed with an iFS 150 kHz Intralase femtosecond laser platform (Abbott Medical Optics Inc., CA), resulting in the formation of an intrastromal tunnel. The characteristics of the Istanbul nomogram established by our study group were utilized to construct the intrastromal circular tunnel (12). The tunnel was dissected through the incision site with a blunt-tipped semicircular dissector. Allograft rings (KeraNatural; Vision-Gift) were cut to an arc length of approximately 160 degrees using surgical scissors. The rings were then inserted into the tunnel using modified forceps and placed according to the cone localization. Suturing was not required in any of the cases. Topical moxifloxacin 0.5% (Vigamox, Alcon Laboratories) and dexamethasone 0.1% (Dexasine SE, Liba, Istanbul, Turkey) eye drops were administered, ending the surgery.

Measurement System and Procedure

All participants underwent corneal imaging using the Pentacam HR system, a non-contact rotating Scheimpflug camera that provides comprehensive anterior segment analysis, including pachymetry, corneal curvature, elevation, and densitometry.

All measurements were performed by a single experienced technician (initials: M.A.) to minimize inter-operator variability. Imaging sessions were scheduled between 9:00 a.m. and 12:00 p.m. to reduce the effect of diurnal variation in corneal parameters. Prior to each imaging session, participants were instructed to blink several times to ensure an even tear film distribution and were then positioned at the device. Proper alignment along the visual axis was confirmed by the system's automatic alignment function, and the subject was asked to fixate on the central green target light. When focus and alignment were optimal, the acquisition was initiated.

Each eye was scanned three times with a five-minute interval between each measurement to assess the repeatability of corneal parameters. Between scans, subjects were asked to recline slightly and reposition their heads to restore baseline positioning. Care was taken to ensure that the cornea was not exposed to ambient light or airflow that could

affect tear film quality during the intervals. If necessary, the Pentacam device was realigned before each scan.

The Pentacam HR uses a monochromatic blue light-emitting diode with a wavelength of 475 nm and acquires 25 images within 2 seconds, providing a three-dimensional model of the anterior segment. The system automatically assesses the quality of each scan and assigns a quality score. Only scans rated as "OK" by the system's quality control algorithm were accepted for analysis. Scans with poor quality were repeated until three acceptable measurements were obtained. All repeatability analyses were performed using all three consecutive scans. For patients with bilateral disease or eligibility, data from only one eye (selected at random) was included in the statistical evaluation.

The primary objective of this imaging protocol was to evaluate the repeatability and stability of corneal parameters rather than their absolute values. Therefore, all imaging steps were standardized to minimize external influences and maximize internal consistency across measurements.

Analyzed Parameters

To evaluate the repeatability and reliability of corneal measurements, we analyzed a series of anterior and posterior corneal surface parameters derived from three consecutive scans obtained during the same visit. From the anterior surface, flat keratometry (K1), steep keratometry (K2), mean keratometry (Kmean), maximum keratometry (Kmax), anterior corneal astigmatism, anterior elevation (measured at the thinnest point), thinnest corneal thickness (TCT), and pachymetry at the corneal vertex were included. Posterior surface analysis comprised flat (K1b), steep (K2b), and mean (Kmeanb) posterior keratometry values, posterior astigmatism, and posterior elevation at the thinnest point.

Statistical Analysis

All statistical analyses were performed using SPSS for Windows software (version 22.0, SPSS Inc., Chicago, IL, USA). The normality of data distribution was assessed using the Kolmogorov–Smirnov test.

This study followed the definitions of intrasession repeatability and intersession reproducibility according to the British Standards Institute and the International Organization for Standardization (13). Repeatability was defined as the degree of variation between repeated measurements obtained under the same conditions (e.g., same examiner and device). To evaluate the repeatability of anterior segment measurements, the following parameters were calculated: within-subject standard deviation (Sw) and the repeatability index (RI). The Sw quantifies the size of the measurement error, while the RI (also known as test–retest variability) represents the range within which 95% of the differences between two repeated measurements are expected to fall.

Table 1. Patients' demographics and clinical information

	CAIRS (n=20)	Healthy Control (n=22)	Total (n=42)	p
Sex (M/F)	13/7	4/18	17/25	P<0.05
Age	25.5±6.32	25.5±4.14	25.5±5.16	0.324
History of CXL treatment	6/20	-	-	-

The RI is calculated as $2.77 \times Sw$, and lower RI values indicate better repeatability. Repeatability was considered acceptable when the RI was smaller than the mean value of the respective parameter.

To enable comparison across parameters with different units of measurement (e.g., diopters, micrometers), a tolerance index (TI) was calculated using the formula: $TI = \log(rP/rC)$ where rP is the RI in the pathological (keratoconus) group, and rC is the RI in the control group. The TI is a scale-independent measure that reflects whether the repeatability of a given parameter significantly differs between two groups. Based on the sample size in this study, a TI value > 0.36 was considered to indicate a statistically significant difference in repeatability at the 5% level ($P < 0.05$), corresponding to non-overlapping confidence intervals.

Reliability was defined as the consistency of repeated measurements and assessed using the intraclass correlation coefficient (ICC). ICC is a variance-based measure that expresses the proportion of total variability attributed to differences between subjects, relative to the total variability (within and between subjects). ICC values approaching 1.0 indicate minimal within-subject variability and excellent reliability. According to commonly accepted criteria, ICC values < 0.50 indicate poor reliability; values between 0.50 and 0.75 suggest moderate reliability; values between 0.75 and 0.90 indicate good reliability; and values > 0.90 are considered to reflect excellent reliability.

Results

A total of 42 eyes were included in the analysis: 20 eyes in the CAIRS group and 22 eyes in the healthy control group. The demographic characteristics of the participants are summarized in Table 1. The two groups were comparable in

age, whereas sex distribution differed significantly between groups. Six eyes in the CAIRS group had a history of prior corneal cross-linking. Figure 1 shows representative preoperative and postoperative anterior segment optical coherence tomography (AS-OCT) images.

Repeatability and Reliability of Anterior Corneal Parameters

The anterior keratometric values (K1 and K2) exhibited excellent reliability in both groups ($ICC > 0.90$ for all), as shown in Table 2. Repeatability was acceptable for these parameters, with TI values were below 0.36, indicating no statistically significant decrease in repeatability in the CAIRS group compared with controls. In contrast, Kmean and Kmax exhibited reduced repeatability (TI of 0.43 and 0.42, respectively) exceeding the predefined significance threshold. Although ICC values for these parameters remained high (> 0.90), the wider repeatability interval suggests increased variability in CAIRS-implanted corneas relative to controls.

Anterior elevation measurements showed the lowest repeatability among anterior surface measurements, indicated by a TI of 0.69. Despite a high ICC in healthy eyes, CAIRS eyes showed greater measurement variability, presumably related to altered stromal curvature and postoperative surface irregularity.

The TCT and pachymetry at the corneal vertex exhibited excellent reliability ($ICC > 0.98$) and tight repeatability limits, with TI values of 0.08 and 0.18, respectively. These findings indicate that central pachymetry measurements remain highly stable and demonstrate excellent repeatability.

Repeatability and Reliability of Posterior Corneal Parameters

Posterior keratometry values (K1b, K2b, Kmeanb) demonstrated excellent reliability across all groups ($ICC > 0.95$),

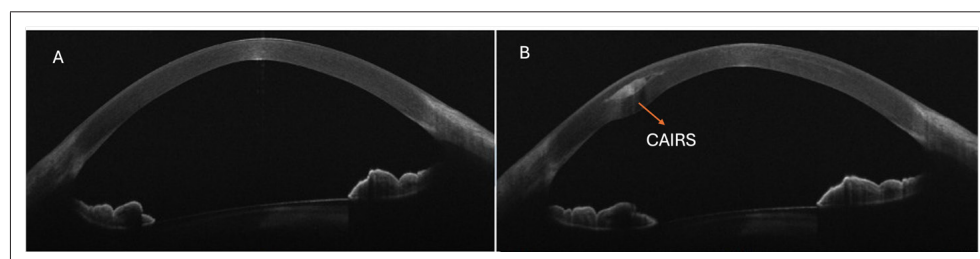


Figure 1. Preoperative and postoperative anterior segment optical coherence tomography (AS-OCT) images illustrating corneal changes following CAIRS implantation.

Table 2. Repeatability and reliability of anterior cornea topographic parameters

Parameters	Mean $\pm$ SD	Sw	RI	TI	ICC
K1 (D)					
CAIRS	43.49 $\pm$ 3.21	0.23	0.66	0.22	0.984
Healthy	43.42 $\pm$ 1.18	0.14	0.39		0.957
Total	43.45 $\pm$ 2.38	0.18	0.52		0.980
K2 (D)					
CAIRS	46.52 $\pm$ 3.21	2.37	6.59	0.12	0.975
Healthy	45.18 $\pm$ 1.52	1.79	4.98		0.925
Total	45.81 $\pm$ 2.53	2.07	5.74		0.967
Kmean (D)					
CAIRS	44.93 $\pm$ 3.18	0.24	0.68	0.43	0.986
Healthy	44.27 $\pm$ 1.18	0.09	0.25		0.985
Total	44.58 $\pm$ 2.35	0.16	0.46		0.986
Kmax (D)					
CAIRS	52.43 $\pm$ 5.66	0.77	2.13	0.42	0.923
Healthy	45.84 $\pm$ 1.44	0.29	0.80		0.958
Total	48.98 $\pm$ 5.19	0.52	1.44		0.948
Astigmatism (front) (D)					
CAIRS	3.03 $\pm$ 1.40	0.33	0.91	0.12	0.946
Healthy	1.76 $\pm$ 1.33	0.24	0.68		0.931
Total	2.36 $\pm$ 1.49	0.29	0.79		0.949
Elevation (front) (D)					
CAIRS	2.92 $\pm$ 11.5	2.91	8.06	0.69	0.869
Healthy	4.48 $\pm$ 3.4	0.58	1.62		0.961
Total	3.76 $\pm$ 8.20	1.69	4.69		0.876
TCT (μ m)					
CAIRS	475.9 $\pm$ 46.5	5.03	13.9	0.08	0.989
Healthy	514.9 $\pm$ 30.2	4.17	11.5		0.981
Total	496.8 $\pm$ 42.9	4.58	12.7		0.989
Pachymetry (vertex) (μ m)					
CAIRS	486.9 $\pm$ 48.9	2.82	7.83	0.18	0.994
Healthy	518.5 $\pm$ 31.1	2.32	5.09		0.994
Total	503.9 $\pm$ 42.9	2.57	6.46		0.995

SD: Standard deviation; Sw: Within-subject standard deviation; Ri: Repeatability index; ICC: Intraclass correlation coefficient; Ti: Tolerance index

as summarized in Table 3. However, repeatability appeared to be reduced in CAIRS-implanted eyes, and TI values for posterior keratometry remained above the critical threshold, suggesting increased variability that reached statistical significance (TI>0.36 for all parameters).

Posterior astigmatism demonstrated moderate-to-good reliability (ICC=0.856 in CAIRS eyes) with a TI of 0.81, suggesting a significant decrease in repeatability compared with controls. This indicates that posterior astigmatic readings are more prone to fluctuation in eyes having stromal implants.

Posterior elevation showed the highest measurement variability of all parameters studied. The TI value (0.66) exceeded the significance threshold, showing substantially reduced repeatability in the CAIRS group. Although ICC values remained high (>0.94), the increased Sw and RI values high-

light the sensitivity of posterior elevation measurements to structural alterations induced by CAIRS implantation.

Discussion

Accurate and repeatable corneal measurements are crucial for monitoring keratoconus progression and guiding treatment decisions, particularly in eyes that have undergone surgical interventions such as CAIRS implantation. This study assessed the repeatability of anterior and posterior segment characteristics in CAIRS-implanted keratoconus eyes and used the TI to allow scale-independent parameter comparison. Our findings highlight that while most anterior keratometric and pachymetric measurements showed acceptable repeatability in both groups, several posterior corneal parameters and sensitive indices, such as Kmax and elevation

Table 3. Repeatability and reliability of posterior cornea topographic parameters

Parameters	Mean $\pm$ SD	Sw	RI	TI	ICC
K1b (D)					
CAIRS	-6.45 $\pm$ 0.37	0.23	0.65	1.33	0.985
Healthy	-6.16 $\pm$ 0.25	0.03	0.03		0.984
Total	-6.29 $\pm$ 0.34	0.13	0.36		0.987
K2b (D)					
CAIRS	-7.43 $\pm$ 0.93	0.16	0.45	0.95	0.951
Healthy	-6.64 $\pm$ 0.27	0.02	0.05		0.992
Total	-7.02 $\pm$ 0.77	0.09	0.68		0.966
Kmeanb (D)					
CAIRS	-6.88 $\pm$ 0.47	0.22	0.62	1.79	0.988
Healthy	-6.39 $\pm$ 0.24	0.006	0.01		0.997
Total	-6.62 $\pm$ 0.44	0.11	0.30		0.992
Astigmatism (back) (μ m)					
CAIRS	0.98 $\pm$ 0.87	0.23	0.65	0.81	0.856
Healthy	0.48 $\pm$ 0.20	0.03	0.10		0.973
Total	0.72 $\pm$ 0.66	0.13	0.36		0.877
Elevation (back) (μ m)					
CAIRS	44.85 $\pm$ 41.61	6.97	19.3	0.66	0.965
Healthy	8.98 $\pm$ 5.53	1.52	4.22		0.945
Total	25.60 $\pm$ 33.5	4.12	11.41		0.974

SD: Standard deviation; Sw: Within-subject standard deviation; Ri: Repeatability index; ICC: Intraclass correlation coefficient; Ti: Tolerance index

maps, exhibited reduced measurement stability in the CAIRS group.

In the present study, anterior K1, K2, and anterior astigmatism had TI values ≤ 0.36 and, showed high measurement repeatability. However, while all anterior segment parameters demonstrated excellent reliability, the TI values for Kmean, Kmax, and anterior elevation were above the cut-off value of 0.36. Repeatability is affected not only by the intrinsic measurement variability of the device but also by the characteristics of the study population. The frequently used threshold of 1.0 diopter (D) in Kmax to define keratoconus progression—commonly applied as an inclusion criterion in cross-linking trials—was derived from a repeatability limit of 0.8 D reported by McAlinden et al. in a large cohort of healthy eyes examined with the Pentacam (14). In accordance with this, our study found a repeatability index (RI) of 0.80 D in the healthy control group. However, in the CAIRS group, the RI increased markedly to 2.13 D, exceeding the accepted TI threshold (>0.36). In a previous study, Montiel et al. investigated the intraobserver repeatability of a Scheimpflug camera in measuring corneal parameters in naive keratoconus eyes and eyes with ICRS implantation. They reported that the RI of anterior Kmax was 1.05 D, K1 was 0.54 D, K2 was 0.71 D, and anterior elevation was 6.19 μ m (11). In the present study, all parameters demonstrated lower repeatability than those reported by Montiel et al.

ICRS implantation is a localized stromal intervention, typically inducing limited biomechanical and structural alterations. In contrast, CAIRS implantation involves inserting an entire corneal graft devoid of epithelium and endothelium into the stromal pocket. This procedure likely induces more extensive structural remodeling of the host cornea compared to ICRS. Such additional alterations in stromal architecture may increase measurement variability, which could explain the higher-than-expected repeatability index observed in keratoconus patients who had undergone CAIRS implantation. On the other hand, Kmax values were automatically generated by the Pentacam HR software. Manual adjustment or relocation toward the central corneal zone was not performed. Therefore, localized effects related to CAIRS implantation may have contributed to increased Kmax variability. Considering all these factors, future longitudinal studies are warranted to establish clinically validated progression thresholds specifically in post-CAIRS eyes.

Corneal thickness measurements are critical for both longitudinal monitoring and determining eligibility for surgical interventions such as corneal cross-linking and ICRS implantation. In the present study, TCT and vertex pachymetry demonstrated excellent reliability (ICC > 0.90 in both groups). Previous studies have suggested that a reduction in corneal thickness of 2–5% or more than 30 μ m may indicate keratoconus progression (15–17). In the CAIRS-implanted

group, the RI values for TCT and vertex pachymetry were 13.9 μm and 7.83 μm , respectively, with TI values below the established cut-off ($\text{TI} < 0.36$). These findings indicate that, even after CAIRS implantation, TCT and vertex pachymetry can be measured with high precision, supporting their continued use for keratoconus progression monitoring and for biometric calculations, including intraocular lens power determination.

In the present study, posterior corneal parameters demonstrated excellent reliability ($\text{ICC} > 0.90$) in both the healthy control and CAIRS-implanted groups. However, none of the posterior parameters met the accepted TI cut-off value of 0.36, indicating that despite good overall reproducibility, the measurement variability was higher than the desired threshold for precise clinical monitoring. In a previous study conducted in normal eyes, the repeatability index was similar to that observed in the healthy control group of our study, supporting the validity of our baseline measurements (18). Although posterior corneal surface changes are not typically included in the definition of keratoconus progression for cross-linking eligibility, several studies have reported that in progressive keratoconus, alterations in the posterior corneal curvature and elevation can precede detectable changes in the anterior surface (19). The Global Consensus on Keratoconus Diagnosis and Management has also emphasized the diagnostic and prognostic value of posterior corneal assessment, highlighting its importance in both initial evaluation and follow-up (14). In our study, posterior parameters consistently demonstrated worse TI values than anterior parameters, particularly in the CAIRS-implanted group. This suggests that CAIRS implantation may disproportionately affect the stability of posterior corneal measurements, potentially due to altered posterior corneal biomechanics, changes in hydration patterns, or interface irregularities created by the surgical pocket. Such increased variability could reduce the reliability of posterior metrics for detecting subtle progression or for use in long-term follow-up, especially when precision is required for surgical decision-making or refractive planning.

This study suggests valuable insights but has several limitations that should be considered. Firstly, the single-center nature of this study and its relatively small sample size (20 CAIRS eyes and 22 controls) may limit the generalizability of our findings across broader populations and different clinical settings. Furthermore, a proportion of the CAIRS eyes had previously undergone CXL treatment, which may have affected corneal biomechanics and, consequently, measurement repeatability. Owing to the limited sample size, subgroup analyses could not be performed and warrant further investigation in future studies. Secondly, as a prospective observational study, it could not control for all potential

confounding variables and did not assess inter-visit reproducibility or long-term stability of measurements beyond the initial three-month post-operative period. A significant limitation is the reduced measurement repeatability observed for several critical corneal parameters in CAIRS-implanted eyes, particularly Kmax, Kmean, anterior elevation, and posterior corneal curvature and elevation values. Despite often demonstrating strong ICC, their TI values frequently exceeded acceptable thresholds. This discrepancy indicates that while these measurements may be statistically reliable in terms of rank order, their precision for individual patient monitoring and detecting subtle changes is compromised. This reduced precision is likely due to the structural alterations, potential biomechanical changes, and interface irregularities introduced by the allogenic ring segments within the corneal stroma. Thirdly, our findings are specific to the Pentacam HR system. Repeatability and reliability may differ when using other corneal tomography or topography devices with varying measurement principles. Lastly, repeatability may vary according to keratoconus severity, and previous studies have demonstrated reduced measurement precision in more advanced disease stages (8,20). Due to the limited sample size, subgroup analysis according to severity was not feasible and should be explored in larger future studies.

Conclusion

In summary, while CAIRS implantation offers a promising therapeutic option for keratoconus, clinicians should exercise caution when interpreting changes in sensitive parameters such as Kmax, Kmean, anterior elevation, and particularly posterior corneal measurements in these eyes, as their inherent measurement variability post-procedure may mask or falsely indicate subtle clinical changes. This study underscores the importance of understanding device-specific measurement limitations in altered corneas to ensure precise follow-up and optimized patient care.

Disclosures

Ethics Committee Approval: The Study was approved by the Institutional Ethics Committee of İstanbul Medipol University (Date: 11/03/2025, No: E-10840098-202.3.02-1941).

Informed Consent: Written informed consent was obtained from all participants prior to their involvement in the study.

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Acute Effects of Cigarette Smoking on Corneal Tomographic and Biometric Parameters: A Prospective Controlled Study

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Abstract

Objectives: To evaluate the acute effects of cigarette smoking on corneal tomography and ocular biometry.

Methods: This prospective, controlled study included 92 healthy volunteers (46 smokers and 46 non-smokers); only the right eye was analyzed. Baseline ophthalmological examination, corneal tomography and biometry were performed. Participants remained outdoors for 10 minutes under standardized conditions; smokers smoked one cigarette, whereas controls did not. Measurements were then repeated, and within-group changes and between-group differences in change (Δ) were analyzed.

Results: Baseline demographic, tomographic, and biometric measurements were similar between groups (all $p>0.05$). Within the smoking group, significant reductions were observed in corneal thickness at the pupil center, corneal vertex, and thinnest point ($p=0.011$, $p=0.012$, and $p=0.017$, respectively). Within the smoking group, anterior chamber depth also decreased from 3.08 ± 0.44 mm to 2.98 ± 0.52 mm ($p=0.034$); however, the between-group difference in Δ values was not statistically significant ($p=0.068$). In contrast, no significant changes were observed in anterior chamber volume, keratometric values, axial length, or emmetropia-targeted intraocular lens power calculated using the Barrett Universal II formula ($p>0.05$ for all). No significant changes were observed in any of the parameters examined in the control group. In the between-group comparison of Δ values, changes in pupil-center pachymetry and thinnest corneal thickness were significantly different ($p=0.002$ and $p=0.004$). Anterior 0–2 mm densitometry decreased in smokers, with a significant between-group difference in Δ ($p=0.029$).

Conclusion: Acute cigarette smoking was associated with measurable alterations in corneal thickness, anterior chamber depth and several corneal densitometry parameters. However, these changes did not significantly affect keratometric values, axial length, or intraocular lens power calculations. Recent cigarette smoking may affect anterior segment measurements, and recent cigarette smoking should be considered when interpreting measurements, especially in situations requiring sensitive corneal assessment.

Keywords: Anterior Eye Segment, anterior chamber, cigarette smoking, corneal pachymetry, corneal topography

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Introduction

Smoking is one of the most important public health problems worldwide, affecting more than one billion individuals (1). Cigarette smoke is a mixture that contains thousands of chemical constituents, many of which have toxic effects (2). Because it contains numerous pro-oxidant components, including free radicals, aldehydes, peroxides, epoxides, and nitrogen oxides, it can induce both short- and long-term effects through oxidative stress (3). In addition, the ocular surface remains in constant contact with environmental factors. For this reason, smoking may influence the eye through both systemic mechanisms and direct exposure to tobacco smoke.

Previous studies have explored the association between smoking and ocular surface health (4-8). Cigarette smoking has been reported to impair tear film stability and may contribute to dry eye disease development (4). The relationship between smoking and corneal endothelial cell density remains unclear, and studies have yielded conflicting results (5,6). Long-term smoking has been associated with decreased basal epithelial cell density, keratocyte density, endothelial cell density, and subbasal nerve fiber density (7). Smoking has also been associated with an increase in corneal immune cell density and morphological changes in the subbasal nerve plexus (8). However, most studies have focused on the chronic effects of smoking, while acute effects have been examined in fewer studies. Transient decreases in pupil diameter and superficial/deep foveal vascular density have been reported following acute cigarette smoking (9,10).

Corneal tomography and biometry are widely used in corneal evaluation and surgical planning (11,12). However, studies examining the effects of smoking on these measurements are limited. Identifying early changes after cigarette smoking is of clinical importance, particularly for corneal evaluation and refractive surgery planning. Therefore, investigating the early effects of smoking on these parameters may help fill a gap in the literature.

This study aimed to evaluate the short-term effects of smoking on corneal tomography and ocular biometric parameters. Specifically, pre- and post-smoking measurements were compared in the smoking group, and the magnitude of these changes was examined in comparison with a non-smoking control group.

Methods

This prospective controlled comparative study was carried out in the Department of Ophthalmology at Istanbul University, Istanbul Faculty of Medicine. The research protocol followed the principles of the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of Is-

tanbul University, Istanbul Faculty of Medicine (No: 03, Date: 06/02/2026). The study was registered at ClinicalTrials.gov (registration number: NCT07580040). Before enrollment, all participants provided written informed consent.

Ninety-two healthy volunteers were enrolled, including 46 current smokers and 46 individuals who had never smoked. To avoid inter-eye correlation, the right eye was prespecified as the study eye before statistical analysis, and only right-eye data were included. Participants in the smoking group had a smoking history of at least one pack per day for a minimum of one year. The inclusion criteria included an age range of 18 to 60 years and the absence of ocular pathology. Exclusion criteria comprised previous ocular surgery, ocular trauma, and any corneal or retinal pathology, clinically significant dry eye disease, or ocular surface disorder; contact lens use within the last two weeks; medication use that could affect pupillary dynamics or the ocular surface; systemic diseases such as diabetes mellitus or hypertension; a history of former smoking in the control group; and use of electronic cigarettes or other tobacco products for all participants.

Demographic data of all participants were recorded, and detailed ophthalmological examinations were performed. Visual acuity measurements including uncorrected distance visual acuity (UDVA) and best-corrected visual acuity (BCVA), were obtained at 6 m with a Snellen chart. Manifest spherical refraction, cylindrical refraction, and axis values were also recorded. Subsequently, tomographic and biometric measurements were performed on all participants using the Pentacam AXL system (Oculus, Wetzlar, Germany), which integrates Scheimpflug imaging with optical biometry. Measurements were performed using the device's AXL mode and the 25-image Scheimpflug 3D scan setting (default: 25 Images per second). To ensure consistency in measurements, all examinations were performed under the same lighting conditions by the same experienced technician. The quality of each scan was evaluated according to the device's quality criteria, and only measurements marked "QS: OK" were included in the analysis. Participants then remained outdoors for 10 minutes under standardized conditions without interacting with each other. During this period, participants in the smoking group smoked a single cigarette containing 0.8–1.0 mg of nicotine under standard conditions, while the control group was kept in similar outdoor conditions without exposure to cigarette smoke. During the study period, the mean ambient temperature was approximately 8.7°C and the mean relative humidity was 84%. Repeat measurements began about 5 minutes after completing the cigarette using the same device. To standardize the acute effect of smoking, baseline measurements were performed only in participants who had not smoked within the previous 8 hours. In addi-

tion, all procedures were performed within the same time window of the day to reduce the effect of diurnal variability.

In the topographic and biometric evaluation, anterior corneal keratometry values [K1 (flat meridian keratometry), K2 (steep meridian keratometry), and Kmax (maximum keratometry)], simulated keratometry values derived from the 15° ring (Sim-K1 and Sim-K2), and anterior corneal asphericity (Q value) were recorded. In the pachymetric evaluation, corneal thickness at the pupil center, corneal vertex (central corneal thickness - CCT), and thinnest point was measured. Corneal densitometry analysis was performed in the anterior, central, posterior, and total layers across the 0–2 mm, 2–6 mm, 6–10 mm, and 10–12 mm zones, and the total values. In addition, pupil center coordinates (x and y relative to the corneal vertex), corneal volume, anterior chamber volume, anterior chamber depth (ACD), white-to-white (WTW) distance, anterior chamber angle, pupil diameter, chord α , and chord μ values were recorded. Axial length (AL) was recorded. For biometric calculations, a standardized intraocular lens (IOL) model with a lens factor of 119.8 was selected, and the Barrett Universal II formula was applied using the Pentacam AXL IOL Calculator. The “IOL SEQ Emm” value, corresponding to the recommended IOL power (in diopters) for the emmetropia target, was recorded.

The primary outcome was the comparison of pre- to post-exposure changes (Δ values) in each parameter between the smoking and control groups. Secondary outcomes included within-group comparisons of pre- and post-exposure measurements and between-group comparisons of baseline values.

The sample size was calculated based on a previous study reporting changes in pupil diameter after acute cigarette smoking (9). In that study, the mesopic pupil diameter was reported as 6.42 ± 0.75 mm before smoking and 6.14 ± 0.75 mm after smoking, with a mean change of 0.26 ± 0.24 mm. Based on this change, the standardized effect size was calculated as 1.08. Using a two-tailed t-test for comparing the means of two independent groups in G*Power 3.1, it was

determined that at least 43 participants were required for each group at $\alpha=0.01$ and 99% power. Considering possible exclusions and missing data, it was planned to include 46 participants in each group.

Statistical Analysis

All statistical evaluations were carried out using IBM SPSS Statistics software version 29.0 (IBM Corp., Armonk, NY, USA). Distribution normality of continuous variables was examined with the Shapiro–Wilk test together with histogram-based visual assessment. For within-group before and after comparisons, normally distributed variables were analyzed using the paired t-test, whereas non-normally distributed data were evaluated with the Wilcoxon signed-rank test. Between-group differences were assessed using the independent t-test for normally distributed variables and the Mann–Whitney U test for non-normally distributed data. Categorical variables were compared using the chi-square test or, where appropriate, Fisher’s exact test. For the main between-group comparisons, mean differences were reported with 95% confidence intervals (CIs), and effect sizes were expressed as Hedges’ g. A p value of <0.05 was considered statistically significant.

Results

This study included 92 participants, consisting of 46 smokers and 46 non-smokers. The mean age was 32.0 ± 10.6 years; 44 (47.8%) were female and 48 (52.2%) were male. As shown in Table 1, there were no statistically significant differences between the groups in baseline demographic and clinical characteristics ($p>0.05$ for all). There were no significant differences between the groups in baseline corneal tomographic and biometric measurements ($p>0.05$ for all, Table 2). Axial length was 23.34 ± 0.78 mm in the smoking group and 23.42 ± 0.90 mm in the control group ($p=0.170$). Similarly, the emmetropia-targeted IOL SEQ Emm value calculated using the Barrett Universal II formula was 22.44 ± 1.87 D and 22.22 ± 2.99 D, respectively ($p=0.153$).

Table 1. Baseline demographic and clinical characteristics of the smoking and control groups

Parameter	Smoking Group (n=46)	Control Group (n=46)	p
Age (years)	32.6 ± 10.0	31.5 ± 11.3	0.627*
Sex (female/male)	20 (43.5%) / 26 (56.5%)	24 (52.2%) / 22 (47.8%)	0.404**
UCVA	0.67 ± 0.33	0.57 ± 0.46	0.228*
BCVA	1.07 ± 0.13	1.07 ± 0.16	0.100*
Manifest spher (D)	-0.29 ± 1.49	-0.90 ± 1.95	0.100*
Manifest cylinder (D)	-0.26 ± 0.39	-0.28 ± 0.38	0.794*
Manifest axis (°)	36.0 ± 54.4	35.6 ± 57.4	0.978*

UCVA: uncorrected visual acuity; BCVA: best-corrected visual acuity; D: diopter; *: Mann–Whitney U test; **: Chi-square test

Table 2. Comparison of baseline corneal tomographic and biometric measurements between the smoking and control groups

Parameter	Smoking Group (n=46)	Control Group (n=46)	p
K1 (D)	42.6±1.3	42.4±1.5	0.462*
K2 (D)	43.5±1.3	43.6±1.5	0.982*
Kmax (D)	44.1±1.3	43.9±1.4	0.833*
Sim-K1 (D)	42.8±1.6	42.4±1.6	0.487*
Sim-K2 (D)	43.6±1.3	43.6±1.5	0.824*
Q value	-0.33±0.17	-0.34±0.09	0.854**
Pachymetry at pupil center (μm)	541.9±32.3	549.6±25.4	0.204*
Pachymetry at corneal vertex (μm)	542.9±32.5	551.5±26.0	0.165*
Thinnest corneal thickness (μm)	537.9±32.2	545.7±25.2	0.198*
Pupil center X coordinate (mm)	-0.033±0.173	-0.104±0.251	0.874*
Pupil center Y coordinate (mm)	0.017±0.147	-0.005±0.199	0.542**
Corneal volume (mm ³)	59.5±3.7	60.3±3.3	0.221*
Anterior chamber volume (mm ³)	170.3±37.0	160.9±30.3	0.185*
ACD (mm)	3.08±0.44	3.00±0.34	0.348*
WTW (mm)	12.1±0.5	12.0±0.3	0.149*
ACA (°)	37.3±6.0	38.3±6.2	0.418*
Pupil diameter (mm)	2.99±0.62	3.14±0.68	0.277**
Chord α (mm)	0.41±0.13	0.44±0.11	0.347*
Chord μ (mm)	0.20±0.09	0.20±0.13	0.993**
AL (mm)	23.34±0.78	23.42±0.90	0.170**
IOL SEQ Emm (D)	22.44±1.87	22.22±2.99	0.153*

*: Independent-samples t test; **: Mann–Whitney U test; SD: standard deviation; K1: flat keratometry; K2: steep keratometry; Kmax: maximum keratometry; Sim-K1: simulated flat keratometry; Sim-K2: simulated steep keratometry; Q value: anterior corneal asphericity; Pupil center X coordinate: horizontal coordinate of the pupil center relative to the corneal vertex; Pupil center Y coordinate: vertical coordinate of the pupil center relative to the corneal vertex; ACD: anterior chamber depth; WTW: white-to-white distance; ACA: anterior chamber angle; AL: axial length; IOL SEQ Emm: intraocular lens spherical equivalent for emmetropia.

In the smoking group, significant decreases were observed in pachymetry at the pupil center, pachymetry at the corneal vertex, and thinnest corneal thickness after smoking ($p=0.011$, 0.012 , and 0.017 , respectively; Table 3). Additionally, anterior chamber depth decreased from 3.08 ± 0.44 mm to 2.98 ± 0.52 mm ($p=0.034$). No statistically significant change was detected in anterior chamber volume (170.3 ± 37.0 mm³ vs. 164.9 ± 36.4 mm³; $p=0.695$). No significant changes were detected in keratometric values—K1, K2, Kmax, Sim-K1, Sim-K2—or axial length (all $p>0.05$). Although anterior chamber depth decreased significantly, no significant change was observed in the emmetropia-targeted intraocular lens power calculated using the Barrett Universal II formula (22.44 ± 1.87 D vs. 22.35 ± 2.11 D; $p=0.752$). In the control group, no significant changes were observed in any of the parameters examined. In the between-group comparison of Δ values, the mean differences were -2.54 μm for pupil-center pachymetry (95% CI, -4.12 to -0.96 ; Hedges' $g=-0.66$; $p=0.002$)

and -2.50 μm for thinnest corneal thickness (95% CI, -4.17 to -0.83 ; Hedges' $g=-0.61$; $p=0.004$), whereas no significant differences were observed in the other tomographic and biometric parameters.

Baseline corneal densitometry values were similar between the smoking and control groups. In the corneal densitometry analysis, a significant decrease was observed in the anterior 0–2 mm zone in the smoking group after exposure, with values decreasing from 22.82 ± 2.48 to 22.43 ± 2.08 ($\Delta=-0.39\pm1.75$, $p=0.016$), whereas no significant change was detected in the control group ($p=0.082$, Table 4). Additionally, the magnitude of change in the anterior 0–2 mm zone differed significantly between the two groups ($p=0.029$). No significant within-group changes were found in the other anterior zones. In contrast, significant reductions in corneal densitometry were observed in the posterior layer of the control group within the 0–2 mm, 2–6 mm, and 6–10 mm annular zones ($p=0.037$, $p=0.019$, and $p=0.007$, respectively, Fig. 1).

Table 3. Within-group pre-post changes and between-group comparison of Δ values in corneal tomographic and biometric parameters

	Smoking Group (n=46)				Control Group (n=46)				
	Pre	Post	Δ	p	Pre	Post	Δ	p	p for Δ
K1 (D)	42.6±1.3	42.7±1.4	0.1±0.2	0.808*	42.4±1.5	42.5±1.5	0.1±0.3	0.099*	0.206***
K2 (D)	43.5±1.3	43.6±1.2	0.2±0.3	0.731*	43.6±1.5	43.6±1.5	0.1±0.2	0.066*	0.127***
Kmax (D)	44.1±1.3	44.0±1.3	-0.2±0.3	0.966**	43.9±1.4	44.1±1.5	0.1±0.1	0.320**	0.319****
Sim-K1 (D)	42.8±1.6	42.7±1.4	-0.1±1.2	0.284**	42.4±1.6	42.1±2.3	-0.3±2.4	0.515**	0.788****
Sim-K2 (D)	43.6±1.3	43.6±1.2	0.1±0.1	0.164*	43.6±1.5	43.6±1.6	0.1±0.2	0.067*	0.584***
Q value	-0.33±0.17	-0.32±0.16	0.01±0.21	0.816**	-0.34±0.09	-0.34±0.10	0.01±0.06	0.788**	0.631****
Pachy pupil center (μ m)	541.9±32.3	540.5±31.2	-1.4±3.6	0.011*	549.6±25.4	550.8±25.1	1.2±4.1	0.060*	0.002***
Pachy cornea vertex (μ m)	542.9±32.5	541.6±31.4	-1.3±3.4	0.012*	551.5±26.0	551.5±25.7	-0.2±3.9	0.970*	0.099***
Pachy thinnest (μ m)	537.9±32.2	536.3±31.7	-1.6±0.9	0.017*	545.7±25.2	546.6±24.8	0.9±3.7	0.104*	0.004***
X (mm)	-0.033±0.173	-0.104±0.174	-0.071±0.216	0.537*	-0.104±0.251	-0.018±0.188	0.077±0.078	0.603*	0.989***
Y (mm)	0.017±0.147	0.018±0.155	0.011±0.095	0.773**	-0.005±0.199	0.016±0.097	0.021±0.162	0.240**	0.474****
CV (mm ³)	59.5±3.7	59.5±3.1	0.1±1.6	0.721*	60.3±3.3	60.1±3.2	-0.2±1.2	0.232*	0.322***
ACV (mm ³)	170.3±37.0	164.9±36.4	-5.4±17.5	0.695**	160.9±30.3	162.3±31.1	1.4±4.9	0.068**	0.176****
ACD (mm)	3.08±0.44	2.98±0.52	-0.09±0.15	0.034**	3.00±0.34	2.98±0.34	-0.03±0.17	0.329**	0.068****
WTW (mm)	12.1±0.5	12.0±0.4	-0.1±0.3	0.309**	12.0±0.3	12.0±0.3	-0.1±0.1	0.652**	0.444****
ACA (°)	37.3±6.0	36.4±5.9	-0.8±3.9	0.082**	38.3±6.2	38.4±5.7	0.1±2.4	0.068**	0.142****
Pupil diameter (mm)	2.99±0.62	3.05±0.59	0.05±0.32	0.331*	3.14±0.68	3.13±0.72	-0.01±0.36	0.709*	0.326***
Chord α (mm)	0.41±0.13	0.42±0.13	0.01±0.08	0.872*	0.44±0.11	0.43±0.20	-0.01±0.17	0.326*	0.610***
Chord μ (mm)	0.20±0.09	0.21±0.11	0.01±0.06	0.841**	0.20±0.13	0.18±0.11	-0.05±0.09	0.152**	0.105****
AL (mm)	23.34±0.78	23.32±0.78	-0.02±0.01	0.328**	23.42±0.90	23.36±0.92	-0.06±0.30	0.149**	0.203****
IOL SEQ Emm (D)	22.44±1.87	22.35±2.11	-0.04±0.22	0.752*	22.22±2.99	22.35±3.30	0.06±0.26	0.117*	0.121***

Δ values represent post-exposure minus baseline values.; K1: flat keratometry; K2: steep keratometry; Kmax: maximum keratometry; Sim-K1: simulated flat keratometry; Sim-K2: simulated steep keratometry; Q value: anterior corneal asphericity; CV: corneal volume; ACV: anterior chamber volume; ACD: anterior chamber depth; WTW: white-to-white distance; ACA: anterior chamber angle; AL: axial length; IOL SEQ Emm: intraocular lens spherical equivalent for emmetropia. X and Y indicate the pupil center coordinates relative to the corneal vertex; *: Paired-samples t test; **: Wilcoxon signed-rank test; ***: Independent-samples t test ****: Mann-Whitney U test; Statistically significant p values (<0.05) are shown in bold.

Discussion

In this prospective controlled study, we showed that cigarette smoking was associated with small but significant acute changes in corneal pachymetric parameters. In addition, a significant decrease in anterior chamber depth was observed in the smoking group. However, this change did not result in a significant alteration in emmetropia-targeted intraocular lens power calculation. In corneal densitometry analysis, significant changes were observed in some zones after acute exposure, suggesting that the acute effect of smoking may affect not only corneal thickness but also measurements related to corneal optical properties. Overall, these findings

indicate that short-term cigarette smoking is associated with measurable changes in anterior segment measurements, but these changes do not significantly alter biometric calculations in the short term.

The non-smoking control group underwent the same outdoor conditions for the same duration, reducing potential confounding by the cold and humid environment. Low ambient temperature can reduce ocular surface temperature, thin the tear lipid layer, and shorten tear break-up time, thereby affecting anterior segment measurements (13). Although this design improved comparability between groups, environmental effects could not be completely excluded.

Table 4. Baseline and repeat-measurement corneal densitometry values and changes (Δ) by corneal layer and annular zone in the smoking and control groups

Region		Smoking Group (n=46)				Control Group (n=46)				p for Δ
Layer	Zone	Pre	Post	Δ	p	Pre	Post	Δ	p	
Anterior	0-2 mm	22.82±2.48	22.43±2.08	-0.39±1.75	0.016	22.81±1.79	22.87±1.51	0.07±1.24	0.082	0.029
	2-6 mm	19.84±2.22	19.64±1.86	-0.20±1.54	0.761	20.44±3.07	19.95±1.46	-0.49±2.37	0.296	0.490
	6-10 mm	19.54±5.70	19.34±5.88	-0.20±2.06	0.885	21.68±6.72	21.18±6.39	-0.50±1.89	0.172	0.472
	10-12 mm	24.50±7.15	23.86±6.97	-0.64±4.74	0.474	27.62±6.30	28.02±6.11	0.39±4.67	0.077	0.041
	Total	21.03±3.24	20.76±3.34	-0.26±1.90	0.852	22.44±3.82	21.99±4.07	-0.45±2.45	0.901	0.691
Central	0-2 mm	14.66±1.79	14.41±2.75	-0.25±2.21	0.690	14.49±1.17	15.57±1.57	1.09±1.95	0.712	0.297
	2-6 mm	12.82±1.69	12.90±1.77	0.07±0.47	0.362	13.29±3.28	12.77±1.56	-0.52±2.92	0.870	0.177
	6-10 mm	13.52±4.58	13.53±4.95	0.01±1.10	0.898	15.04±6.52	14.53±5.74	-0.51±1.56	0.049	0.067
	10-12 mm	16.81±4.99	16.60±5.01	-0.21±2.48	0.714	17.72±4.29	17.82±4.30	0.09±2.44	0.678	0.834
	Total	14.07±2.80	14.20±5.02	0.13±1.87	0.797	14.81±3.76	14.72±2.89	-0.09±1.47	0.935	0.315
Posterior	0-2 mm	9.10±2.65	9.23±2.96	0.13±1.13	0.375	8.75±1.68	8.45±1.92	-0.30±1.91	0.037	0.197
	2-6 mm	8.40±2.44	8.60±2.44	0.20±0.89	0.214	8.50±2.31	8.01±1.34	-0.49±1.59	0.019	0.012
	6-10 mm	10.33±4.86	10.47±5.13	0.14±0.93	0.149	10.81±4.11	10.40±3.70	-0.42±0.95	0.007	0.006
	10-12 mm	13.13±5.27	13.20±5.67	0.07±2.31	<0.001	13.75±4.36	13.72±4.23	-0.02±2.08	0.244	0.828
	Total	9.94±3.49	10.03±3.83	0.09±1.01	0.499	9.76±3.27	9.97±2.22	0.26±2.24	0.251	0.763
Total	0-2 mm	15.38±2.14	15.43±2.14	0.04±1.34	0.595	15.36±1.13	15.18±1.78	-0.22±1.64	0.057	0.086
	2-6 mm	13.71±1.81	13.68±1.19	-0.03±0.82	0.889	13.85±1.60	13.67±1.08	-0.18±0.95	0.128	0.409
	6-10 mm	14.27±5.01	14.45±5.25	0.18±1.87	0.487	16.30±6.33	15.51±5.06	-0.79±3.34	0.141	0.090
	10-12 mm	18.05±5.37	17.87±5.46	-0.19±3.13	0.986	19.70±4.60	20.23±4.41	0.53±3.09	0.134	0.271
	Total	15.09±3.04	14.92±3.31	-0.17±1.36	0.921	15.70±3.37	15.52±2.69	-0.18±2.10	0.788	0.972

Corneal densitometry values are expressed in grayscale units (GSU). Δ values represent post-exposure minus baseline values. For p values, the paired-samples t test was used for normally distributed within-group comparisons and the Wilcoxon signed-rank test for non-normally distributed within-group comparisons. For between-group comparisons of Δ values, the independent-samples t test was used for normally distributed data and the Mann-Whitney U test for non-normally distributed data. Statistically significant p values (<0.05) are shown in bold.

Previous studies have reported conflicting associations between smoking and corneal thickness, ranging from no significant difference to increased CCT with reduced corneal endothelial cell density (6,14,15). In our study, pachymetric measurements decreased after acute cigarette smoking, with significantly greater changes in pupil-center pachymetry and thinnest corneal thickness in the smoking group. Tear-film disruption and transient changes in corneal hydration are possible mechanisms for the observed pachymetric changes (8). However, because tear-film parameters and corneal endothelial measurements were not assessed, these mechanisms remain hypothetical. Nevertheless, the absolute magnitude of the pachymetric changes was small (approximately 1.3–1.6 μ m). Pentacam test-retest repeatability has been reported as 11.63 μ m for central corneal thickness and 12.57 μ m for thinnest corneal thickness in healthy eyes (16). Therefore, although statistically significant, these changes were below the expected repeatability limits and should be interpreted cautiously in terms of clinical relevance.

In our study, ACD decreased by 0.09 mm after smoking. This change exceeded the reported test-retest repeatability of approximately 0.07 mm for Pentacam ACD measurements in healthy eyes (16), suggesting that it may not be fully explained by measurement variability. However, the between-group comparison of Δ values was not statistically significant, and ACV remained unchanged. The decrease in ACD also did not affect the emmetropia-targeted IOL power calculation. This finding suggests that acute cigarette smoking may induce short-term changes in anterior segment measurements, although these changes may not reach a level sufficient to alter biometric outcomes. Indeed, a recent study evaluating chronic smokers also reported no significant difference between smokers and the control group in terms of ACD, ACV, and ACA, with more significant changes observed in pupillometry and ocular surface parameters (17). On the other hand, current literature shows that tear film instability can affect the accuracy of IOL power calcu-

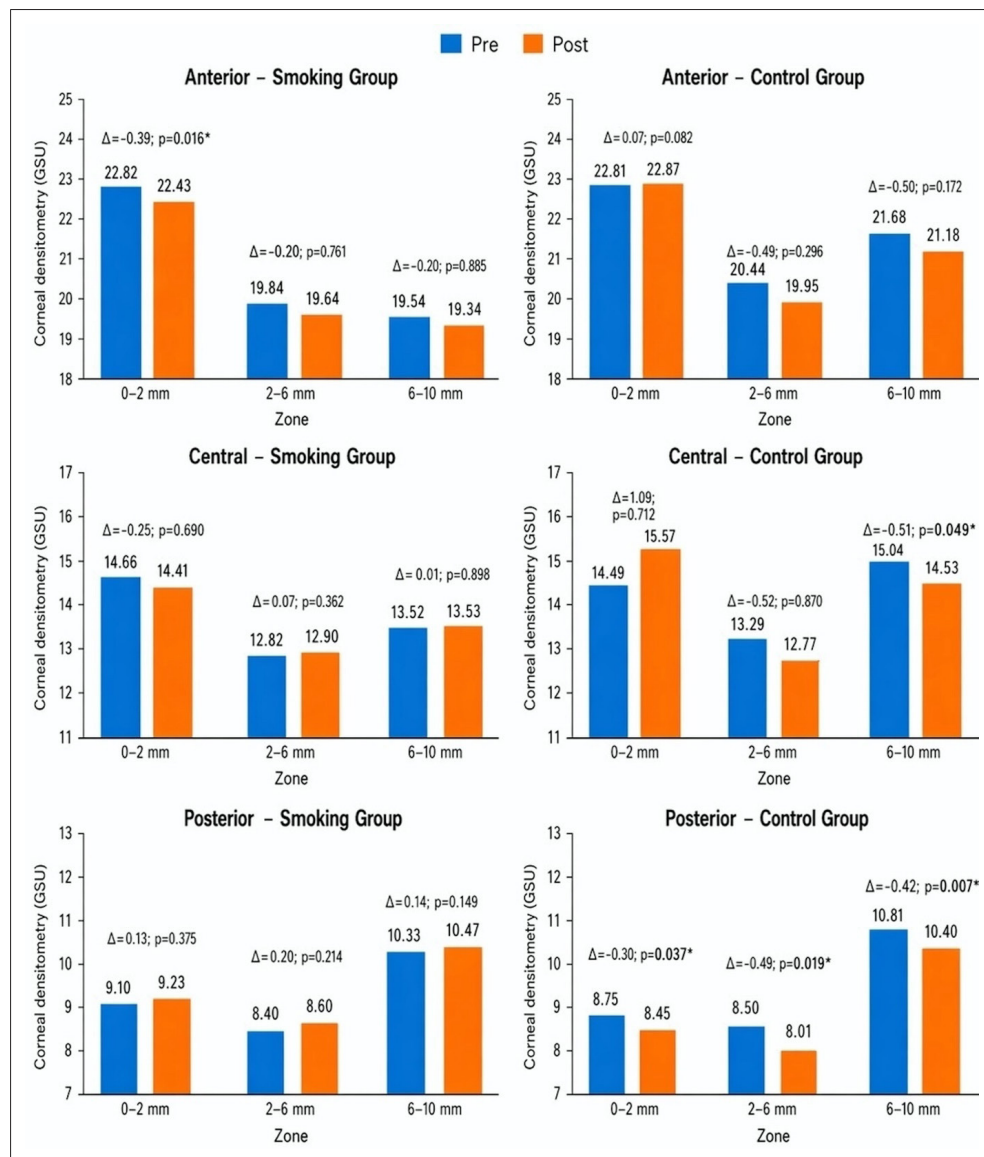


Figure 1. Baseline and repeat-measurement corneal densitometry values according to corneal layer, zone, and study group. Corneal densitometry measurements are presented for the anterior, central, and posterior layers in the 0–2 mm, 2–6 mm, and 6–10 mm zones in the smoking and control groups before and after exposure. Bars represent mean values in grayscale units (GSU). Δ indicates post-exposure minus baseline change.

lations, particularly by reducing keratometry repeatability (18,19). Therefore, although a statistically significant decrease in ACD was observed in our series, the lack of significant change in ACV, axial length, and keratometric values may explain why the IOL power calculation remained stable. Autonomic or hemodynamic changes and an accommodative response are possible mechanisms for the observed ACD reduction; however, these mechanisms were not directly assessed in our study (20).

The literature is not entirely consistent regarding pupillary findings. Some studies have reported a significant decrease in both photopic and mesopic pupil diameter after acute cig-

arette smoking (9,21). Bardak et al. (22) did not observe a significant change in pupil diameter but did observe a significant increase in objective accommodation. Although a slight increase in pupil diameter was observed in our study, this change was not statistically significant. Therefore, the effect of acute cigarette smoking on pupil size may vary according to measurement conditions and study characteristics.

Previous studies have found no significant differences in corneal densitometry between chronic smokers and controls, although smoking load may correlate with densitometry in the 6–10 mm zone and total cornea (23,24). Özcan (24) reported increased lens rather than corneal densitom-

etry in smokers. Consistent with these studies, baseline corneal densitometry values were similar between groups. After acute cigarette smoking, however, anterior 0–2 mm densitometry decreased in the smoking group, and the change differed significantly between groups. This may reflect a short-term change in measurements related to corneal transparency. Although Scheimpflug-based measurements can be affected by tear-film abnormalities (25), whether this contributed to the observed densitometry change cannot be determined because tear-film parameters were not assessed. However, significant changes in some posterior zones in the control group may be related to measurement variability and should be interpreted cautiously.

This study has several limitations. Its single-center design and modest sample size may limit generalizability. In addition, only short-term changes after acute cigarette smoking were evaluated, and the duration and cumulative effects of repeated smoking remain unknown. The absence of tear-film testing, corneal endothelial assessment by specular microscopy, and objective accommodation measurements was another limitation of the study. However, since this study primarily focused on the short-term effects of acute cigarette smoking on tomographic and biometric measurements, these analyses were not included in the study design. Since no adjustment was made for multiple comparisons, the isolated significant densitometry findings should be regarded as exploratory. Finally, although we attempted to control for environmental conditions by including a control group, environmental influences may not have been completely ruled out.

Conclusion

In conclusion, the findings of this study suggest that acute cigarette smoking may lead to measurable changes in corneal pachymetric measurements, anterior chamber depth, and corneal densitometry measurements. However, the observed changes did not significantly affect biometric calculations, including intraocular lens power calculation. These results indicate that acute cigarette smoking may affect anterior segment measurements, but this effect did not appear to be clinically meaningful, at least in the short term. Nevertheless, recent smoking exposure should be considered when interpreting measurements, particularly in settings requiring sensitive corneal assessment and preoperative evaluation.

Disclosures

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of Istanbul University (No: 03, Date: 06/02/2026)

Informed Consent: Before enrollment, all participants provided written informed consent.

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Twenty Years of Anophthalmic Surgery in a Tertiary Referral Center: Etiologies, Surgical Trends, and Clinical Findings

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Abstract

Objectives: To evaluate the etiological causes, demographic characteristics, surgical procedures, implant features, complications, and additional surgical interventions in patients undergoing anophthalmic surgery over a 20-year period.

Methods: The records of patients who underwent evisceration, enucleation, sphere exchange, secondary sphere implantation, and anophthalmic socket reconstruction at our institution between 2003 and 2023 were reviewed. Etiologic and demographic data, surgical procedures, orbital implant diameter and material, postoperative complications, additional surgical procedures, and follow-up periods were recorded. Female patients were classified as group 1 and male patients as group 2, and both groups were subjected to comparative analysis.

Results: A total of 603 patients were divided into two groups: Group 1 (female, 32.2%) and Group 2 (male, 67.8%). The mean age at the time of surgery was comparable between the two groups ($p=0.830$). Trauma was the most common etiology, malignancy the least common. Evisceration was the most frequently performed procedure, and enucleation the least. The mean diameter of implanted spheres was significantly smaller in Group 1 ($p=0.001$). No significant difference in implant materials was observed ($p=0.590$). Conjunctival suture dehiscence and infection were the most common complications, showing similar profiles in both groups.

Conclusion: Trauma was the leading cause in both groups, with evisceration as the most frequently performed procedure. These procedures addressed the underlying ocular pathologies and contributed to orbital volume restoration when indicated.

Keywords: Anophthalmic Surgeries, anophthalmic socket reconstruction, enucleation, evisceration, sphere exchange, sphere implantation

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Introduction

Anophthalmic surgical procedures have long been performed for the palliative treatment of painful eyes that have lost vision or for therapeutic purposes in the presence of intraocular tumors. Evisceration is a surgical procedure in which the intraocular structures are entirely removed through an incision in the cornea or sclera, while the conjunctiva, sclera, extraocular muscles, and optic nerve are preserved. Enucleation is a surgical procedure in which the extraocular muscles and the optic nerve are disconnected from the globe, followed by the complete removal of the eyeball (1,2). The indications for anophthalmic surgery include trauma, advanced glaucoma, intraocular neoplasia, panophthalmos, a painful blind eye, phthisis bulbi, and cosmetic reasons. The etiologic factors that precipitate these surgical interventions exhibit variability contingent upon the level of economic and social development of the countries in question, as well as the age and gender of the affected individuals (3).

The reduction in the number of enucleation procedures performed over time, along with the shift in indications in favor of evisceration, can be attributed to significant medical and surgical advancements. Nevertheless, the most significant indication for enucleation that has remained constant is the presence of intraocular malignancies. Despite the introduction of new chemotherapeutic agents and radioactive plaque therapy, there has been no reduction in neoplasia-related cases (4). In the present era, evisceration surgery is the preferred procedure among ophthalmologists due to its numerous advantages. These include a shorter surgical time, a reduced incidence of complications when the globe is preserved, and superior cosmetic outcomes (5,6).

In cases where orbital implants are not placed during evisceration and enucleation surgery, secondary orbital implant surgery is performed to correct the volume deficiency and to provide a more effective prosthesis fit (7). Implants made of bioceramic and hydroxyapatite materials, which were widely used in the past, have expired over time, necessitating the need for replacement of these implants and causing problems such as volume deficiency in the anophthalmic socket and shallow fornices that may lead to prosthesis incompatibility. In the management of these complications, socket reconstruction with tissues such as dermal fat graft, buccal mucosa or hard palate graft is applied (8-10).

Based on 20 years of experience in a tertiary referral center in a developing country, we report the etiologic characteristics, surgical methods, complications, secondary surgical interventions, and follow-up results of patients undergoing anophthalmic surgery.

Methods

A retrospective review of the medical records of patients who underwent anophthalmic surgery at the department of

oculoplastic surgery of a tertiary eye hospital in Türkiye between 2003 and 2023 was conducted. The study protocol was approved by the Health Sciences University Ethic Committee (Date: 27.10.2023, No: 2023-286) and was conducted in accordance with the principles set forth in the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

A comprehensive record was kept of the demographic characteristics, etiologic causes, surgical methods, type and diameter of implant material used, complications encountered, additional surgeries and follow-up period. In instances where the etiologic factor was trauma, the age of exposure to the traumatic event was documented as the age of etiology. In the preoperative evaluation, orbital imaging was obtained by computed tomography (CT) or magnetic resonance imaging (MRI) to exclude the possibility of malignancy. The study population was divided into two groups: Group 1, comprising female patients, and Group 2, comprising male patients. For the secondary etiology-based analysis, patients who underwent primary globe-removal surgery, including evisceration and enucleation, were further categorized into trauma and non-trauma groups according to the underlying etiology. The surgical procedures performed on the patients were analyzed in five different categories: In cases where evisceration was indicated, this procedure was preferred for indications such as trauma, advanced glaucoma, painful blind eye, and panophthalmos. Conversely, enucleation was performed for intraocular tumors, irreparable globe rupture, and advanced phthisis bulbi. Secondary sphere implantation was performed in patients with adequate scleral reserve who had not been implanted during primary surgery, with the objective of correcting volume deficiency and improving cosmetic appearance. In cases diagnosed as sphere exposure, the removal and re-implantation of the sphere (sphere exchange) was performed if the anophthalmic socket was suitable. In instances where reimplantation of the sphere was not a viable option or in cases where complications such as volume deficiency, contracture of the socket, or prosthesis incompatibility due to deep superior sulcus were identified, socket reconstruction was undertaken using dermal fat or mucous membrane grafts. In all surgical procedures involving orbital implant placement, the implants were inserted without wrapping material. Intravenous cefazolin (1 g) and methylprednisolone (1 mg/kg) were administered perioperatively in the absence of any contraindication. In addition to postoperative topical corticosteroid-antibiotic treatment, oral antibiotic therapy (amoxicillin-clavulanic acid) and non-steroidal anti-inflammatory drugs (NSAIDs) were administered routinely. The temporary tarsorrhaphy suture was removed on the fifth postoperative day.

In the analyses, continuous variables were reported as the mean and standard deviation (SD), while categorical vari-

ables were reported as the frequency and percentage. The normality of the distribution of continuous variables was assessed using the Shapiro-Wilk test. The independent t-test and chi-square test were employed for the purpose of comparing parameters between groups. Comparisons were also performed between trauma and non-trauma groups among patients undergoing primary globe-removal surgery. The statistical analysis was conducted using the SPSS 26.0 software (IBM Corp., Armonk, NY, USA), and a p-value of less than 0.05 was considered statistically significant.

Results

A total of 603 patients were examined in the study, of whom 194 were included in Group 1 (32.2%) and 409 in Group 2 (67.8%). The mean age at the time of surgery was 38.46 ± 18.69 years in Group 1 and 38.80 ± 17.49 years in Group 2 ($p=0.830$). The mean follow-up duration was 31.50 ± 44.27 months for the overall cohort, 39.93 ± 48.75 months in Group 1, and 27.70 ± 41.60 months in Group 2. The follow-up duration was significantly longer in Group 1 ($p=0.007$). The demographic data of the groups are presented in Table 1 for reference.

In both groups, the most prevalent etiological factor was trauma, while the least common was malignancy. The most frequently performed surgical procedure was evisceration, while enucleation was the least common in both groups. A comparison of the etiologic causes and surgical procedures

between the groups is presented in Tables 2 and Table 3. The distribution of procedures performed according to etiologic cause is illustrated in Figure 1.

Among the 509 patients who underwent primary globe-removal surgery, 313 (61.5%) were included in the trauma group and 196 (38.5%) in the non-trauma group. Patients in the trauma group were significantly younger at the time of surgery than those in the non-trauma group. The proportion of male patients was significantly higher in the trauma group. The mean implant diameter was also significantly greater in the trauma group. In the trauma group, 301 patients underwent evisceration and 12 underwent enucleation, whereas in the non-trauma group, 184 patients underwent evisceration and 12 underwent enucleation. No significant difference was observed between the two groups in the distribution of evisceration and enucleation ($p=0.283$) or in the rate of early postoperative complications (5.8% vs. 5.6%, $p=1.000$). The findings of the trauma and non-trauma group comparison are presented in Table 4.

The mean diameter of the implanted sphere was 19.21 ± 2.36 mm in Group 1 and 20.01 ± 2.08 mm in Group 2. A statistical analysis revealed that the diameter of the sphere was smaller in Group 1 ($p=0.001$). In Group 1, the implanted sphere material was acrylic in 73 cases (37.6%) and hydroxyapatite in 48 cases (24.7%). In Group 2, the material was acrylic in 174 cases (42.5%), hydroxyapatite in 101 cases (24.7%), and bioceramic in two cases (0.7%). No significant difference was observed between the groups re-

Table 1. Baseline characteristics

	Group 1 (n=194)	Group 2 (n=409)	p
Age, years	38.46 ± 18.69	38.80 ± 17.49	0.830
Age at etiology, years	23.01 ± 22.57	23.51 ± 19.78	0.844
Side, right/left	100/94	203/206	0.661
Follow-up time, months	39.93 ± 48.75	27.70 ± 41.60	0.007*

*statistically significant

Table 2. Etiological causes

	Group 1 (n=194)	Group 2 (n=409)	p
Trauma	83 (42.8%)	230 (56.2%)	0.002*
Phthisis bulbi	37 (19.1%)	51 (12.5%)	0.032*
Glaucoma	23 (11.9%)	38 (9.3%)	0.329
Cosmetic Reasons	18 (9.3%)	28 (6.8%)	0.293
Endophthalmitis	13 (6.7%)	29 (7.1%)	0.861
Sphere Exposure	7 (3.6%)	23 (5.6%)	0.288
Anophthalmic Socket Contracture	10 (5.2%)	8 (2%)	0.031*
Malignancy	3 (1.5%)	2 (0.5%)	0.335

*statistically significant

Table 3. Comparison of the surgical procedures between the groups

	Group 1 (n=194)	Group 2 (n=409)	p
Evisceration	150 (77.3%)	335 (81.9%)	0.185
Enucleation	9 (4.6%)	15 (3.7%)	0.569
Secondary Sphere Implantation	12 (6.2%)	13 (3.2%)	0.084
Sphere Change	10 (5.2%)	29 (7.1%)	0.367
Socket Reconstruction	13 (6.7%)	17 (4.2%)	0.179

*statistically significant

garding the material used for the spheres ($p=0.590$). Seven cases (3.6%) exhibited sphere exposure in Group 1, while 23 cases (5.6%) demonstrated this outcome in Group 2. All patients in Group 1 underwent a sphere exchange due to sphere exposure, while four patients in Group 2 underwent a socket reconstruction with dermal fat grafting and 19 patients underwent a sphere exchange. The exposed implants

were composed of hydroxyapatite in 15 cases, bioceramic in 9 cases, and acrylic in 6 cases ($p=0.192$).

Two patients in Group 1, diagnosed with anophthalmic socket syndrome, underwent secondary sphere implantation for volume replacement. Eight patients in the same group underwent socket reconstruction with dermal fat grafts and mucous membrane grafts, including lip mucosa,

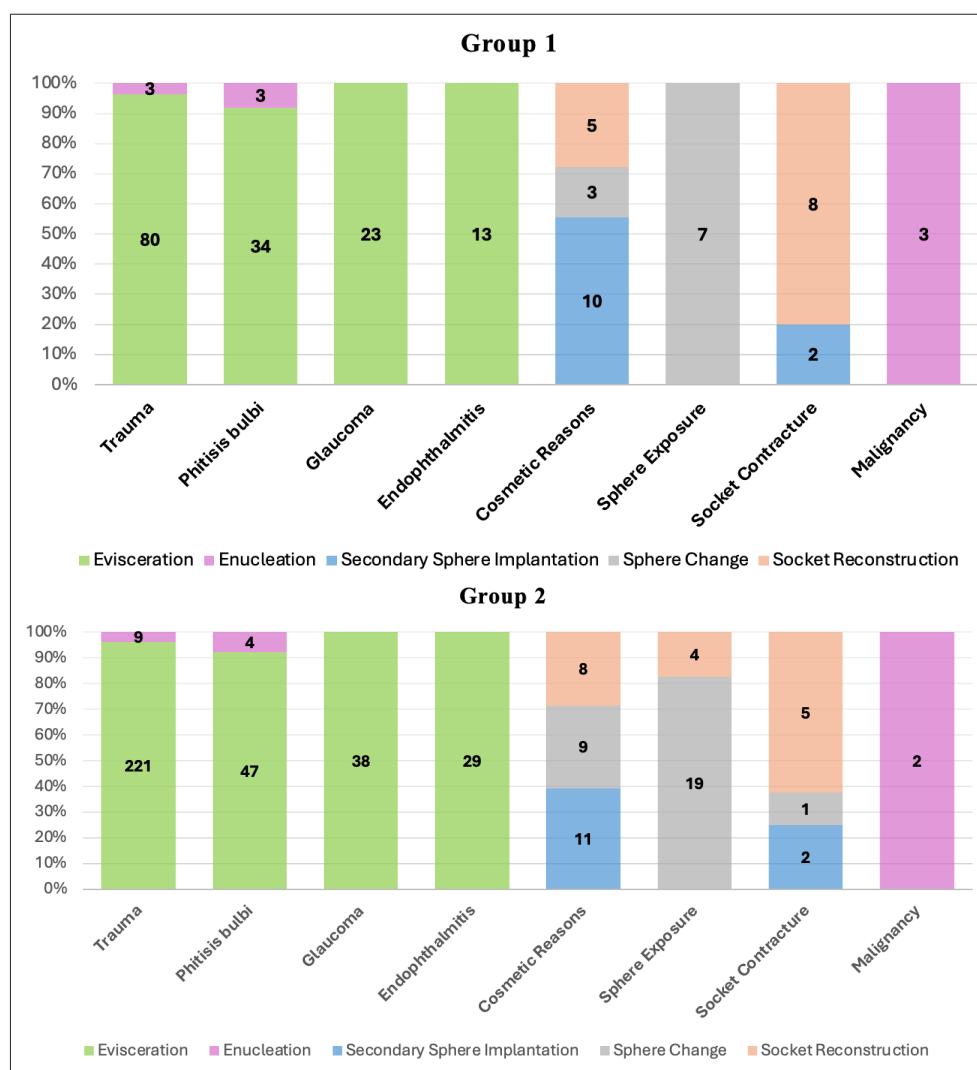
**Figure I.** Distribution of surgical procedures performed by etiologic cause.

Table 4. Comparison of trauma and non-trauma groups among patients undergoing primary globe-removal surgery

	Trauma group (n=313)	Non-trauma group (n=196)	p
Age at surgery, years	34.44±15.48	46.45±20.06	<0.001*
Male sex	230 (73.5%)	120 (61.2%)	0.004*
Implant diameter, mm	20.42±1.86	19.19±2.54	<0.001*
Early postoperative complication	18 (5.8%)	11 (5.6%)	1.000

*statistically significant

amniotic membrane, and cryopreserved umbilical amnion, when necessary. In Group 2, two patients underwent secondary sphere implantation, one patient underwent sphere exchange, and five patients underwent socket reconstruction with dermal fat graft and mucous membranes when necessary.

Early postoperative complications requiring parenteral therapy (broad-spectrum antibiotics/corticosteroids) and/or surgical intervention in Group 1, infection was observed in 2 cases, conjunctival suture dehiscence in 5 cases, and severe periorbital edema and pain in 3 cases. In Group 2, infection was observed in 2 cases, conjunctival suture dehiscence in 16 cases, periorbital diffuse hematoma in 1 case, and severe periorbital edema and pain in 4 cases.

Discussion

Although the frequency of anophthalmic surgeries has decreased in recent years, these surgeries are still successfully performed in cases where other treatment options have been exhausted. The indications for anophthalmic surgeries, the age at which they are performed, and the preferred methods vary in parallel with the level of societal development. As a reference center for a developing country, our objective was to present the largest case series in this field in our country by sharing our 20-year results.

Evisceration is the preferred surgical procedure over enucleation due to several advantages. It is a faster and easier procedure, causes less bleeding due to the preservation of the extraocular muscles and optic nerve, and offers better cosmetic results in the postoperative period due to better preservation of the orbital anatomy (11,12). In our study, evisceration was the more frequently utilized surgical method, with a rate of 77.3% in Group 1 and 81.9% in Group 2 over the 20-year period. The mean age of patients in both groups was comparable ($p=0.830$). While the mean age of patients undergoing evisceration is higher in developed countries, the procedure is performed at younger ages in developing countries (5,13). The most significant factor contributing to this discrepancy is the underlying etiology. In developed countries, evisceration is typically performed for indications such as postoperative endophthalmitis or the

presence of a painful and blind eye. In contrast, in developing countries, the most common indication is trauma (13,14).

Ocular trauma is a major source of morbidity leading to vision loss worldwide and is one of the most common reasons for anophthalmic surgery. Although most cases of eye injury result in significant recovery, severe trauma can lead to complete loss of visual potential. Anophthalmic surgeries can be applied to eyes that are irreparable after trauma, or they can be preferred in the late period in cases where the ocular architecture is disrupted, and vision is lost. In a study by Savar et al. 660 eyes with open globe trauma were examined and it was reported that evisceration or enucleation was performed in 55 cases. In the study, it was stated that the primary approach in open globe injuries was primary repair, but anophthalmic surgeries could be performed in cases where repair could not be performed (15). Our approach was similar; primary repair was performed in all patients who had no light perception but could undergo primary repair and anophthalmic surgeries were postponed to the next sessions. In our study, trauma was the most common indication for anophthalmic surgery in both men and women, consistent with the literature; however, the rate of exposure to trauma was significantly higher in men than in women (56.2% vs. 42.8%, $p=0.002$). This may be attributed to the higher rate of trauma exposure, especially in young men. Although evisceration was the most common procedure performed in trauma cases in both groups, enucleation was performed after trauma in 3 cases in Group 1 and 9 cases in Group 2.

In the secondary etiology-based analysis, patients in the trauma group were significantly younger and more frequently male, consistent with previous reports that severe ocular trauma predominantly affects younger men, particularly in occupational settings (16). The larger implant diameter in this group may partly reflect the higher proportion of male patients. However, the distribution of evisceration and enucleation and the rate of early postoperative complications were similar between the trauma and non-trauma groups.

Sympathetic ophthalmia is an autoimmune disease characterized by destructive, potentially blinding panuveitis in which the injured eye triggers inflammation in the other, intact eye. Although its pathophysiology is not fully under-

stood, it is thought to be an immune response to exposure of ocular tissues previously isolated from the immune system (17). Evisceration, along with some other intraocular procedures, has been shown to be a potential cause of sympathetic ophthalmia (12,18). In past years, surgeons have more often preferred enucleation to avoid the risk of sympathetic ophthalmia and to provide better pain control. However, studies have shown that evisceration is associated with a lower risk of sympathetic ophthalmia and is not inferior to enucleation in terms of pain control (3,19). Consistent with these findings, the frequency of enucleation has decreased over the years. Currently, the main indication for enucleation is the management of eyes with suspected or diagnosed malignancy. Enucleation is contraindicated in eyes with suspected or known intraocular malignancy (12,20). In our study, enucleation was performed in 4.6% in Group 1 and 3.7% in Group 2. The etiologic causes of these cases included trauma, physis bulbi, and malignancy.

In addition to providing adequate orbital volume, an ideal orbital implant should be biocompatible, have a low risk of exposure, be easily sterilized without disruption, provide sufficient mechanical strength for safe intraoperative manipulation, be cost effective, and support satisfactory mobility of the ocular prosthesis (21). Although orbital implants in integrated (hydroxyapatite (HA), porous polyethylene (PP), bioceramic composites) and non-integrated (polymethylmethacrylate (PMMA)/acrylic and silicone) forms have been used over the years, they unfortunately do not meet all the characteristics of the ideal orbital implant (22). Large implant size, failed surgical techniques such as inadequate sclerotomy, and infection have been cited as potential causes of implant exposure (12,23). Surgical techniques such as suturing the tenon and conjunctiva separately, using temporary tarsorrhaphy sutures, and suturing the muscles end-to-end in enucleation cases have been reported to reduce the risk of exposure (10,24). Although there is no clear consensus on the management of an extruded implant, small exposure areas can usually be monitored for spontaneous healing, whereas large exposure areas may require reconstruction or implant exchange using various flaps, grafts, or donor or synthetic materials (25-27). In our study, implant exposure was observed in 7 (3.6%) patients in Group 1 and 23 (5.6%) patients in Group 2. Sphere exchange was performed in 19 patients in Group 2, while 4 patients underwent socket reconstruction with dermal fat graft. There was no significant difference between the implant materials with exposure.

Regardless of the etiology or surgical method, eye loss results in facial deformity due to the loss of an organ. This can lead to both functional and psychological problems (28). The main goals of anophthalmic orbital surgery include preservation of orbital volume to provide acceptable

facial symmetry, creation of a satisfactory eyelid contour, and availability of a removable ocular prosthesis (10). Various factors such as trauma, previous surgery, radiation exposure, and smoking are considered to be the major risk factors for the development of anophthalmic socket contracture (29,30). Previous studies have suggested algorithms such as dermal fat grafting for volume replacement, superiostal implants for sulcus deformity, fat transfer or filling options (10). Depending on the severity of the contracture, gradually growing conformers are preferred in mild cases, while in more advanced cases it may be possible to use an ocular prosthesis by reconstructing the fornices with amniotic membrane, cryopreserved umbilical amnion, and oral mucosa grafts (31,32). In our study, the mean diameter of the implanted spheres was significantly smaller in female patients ($p=0.001$), which may reflect anatomical differences in orbital dimensions between sexes. Female patients also exhibited a significantly higher rate of anophthalmic socket contracture ($p=0.031$). Although relatively lower volume replacement with smaller implants might theoretically contribute to volume deficiency and subsequent socket changes, a direct association between implant size and socket contracture could not be established in this retrospective study. Moreover, socket contracture is multifactorial and may be influenced by the underlying etiology, previous surgical procedures, infection, and tissue scarring. The longer follow-up duration in female patients may also have increased the likelihood of detecting this complication. Therefore, the relationship between smaller implant diameter and the higher contracture rate should be interpreted cautiously. In both groups, larger spheres were placed, or dermal fat grafting was performed in patients with ocular prosthesis incompatibility due to volume deficiency or contracture. Mucous membranes were used to enlarge the fornices and acceptable facial symmetry and ocular prosthesis fit was achieved in all cases.

Data on early postoperative complications vary in the literature. In a study by Kase C. et al. 20.66% complications were reported in patients who underwent evisceration and 36% of these complications were conjunctival dehiscence (33). One patient who developed orbital cellulitis was treated with intravenous antibiotics, while local infections were treated with oral antibiotics (33). In a study in which antibiotics were not used after evisceration and enucleation surgery, the authors aimed to determine the rate of wound infection and stated that the routine use of perioperative intravenous and postoperative oral antibiotics to prevent wound infection is not indicated. Instead, they advocated an individualized approach and recommended the use of antibiotics when necessary (34). In our study, the rate of early postoperative complications was 5.1% in Group 1 and 5.5%

in Group 2. Conjunctival dehiscence was observed in 5 cases in Group 1 and 16 cases in Group 2. Extensive wound infection was observed in 2 cases in both groups. All of these patients were hospitalized and treated with intravenous antibiotics/corticosteroids, and additional surgical intervention was performed when necessary. Patients with milder complaints such as infection, edema, and pain were followed on an outpatient basis with topical and oral treatment.

Although our study is the largest case series reported in our country, it has several limitations. Besides its retrospective design, one of the major limitations is the lack of data on long-term complications. We attribute this to the fact that we are a referral center that accepts patients from all over the country. Most of our patients consult their local physicians for long-term follow-up after surgery. Also, the unequal distribution of implant materials and the small sample sizes in some material subgroups limited the statistical power to detect differences in implant exposure rates.

Conclusion

In conclusion, according to our data, as one of the referral centers in a developing country, evisceration is the most common method of anophthalmic surgery and trauma is the most common cause of eye loss in both women and men. These findings emphasize that trauma is a preventable cause of eye loss and the importance of raising awareness of the measures to be taken against this condition.

Disclosures

Ethics approval and consent to participate

The study protocol was approved by the Health Sciences University Ethic Committee (Date: 27.10.2023, No: 2023-286).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

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The Clinical Characteristics of Eyelid Tumors: A Three-Year Retrospective Study at A Tertiary Eye Hospital

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Abstract

Objectives: Eyelid tumors are neoplasms commonly diagnosed in routine ophthalmology practices. Some malignant tumors may mimic benign lesions and inflammatory conditions, which can lead to delayed diagnosis and treatment. The study aimed to identify the clinical characteristics of eyelid tumors at a tertiary eye hospital by analyzing retrospective data from a 3-year observational study.

Methods: A descriptive retrospective study was carried out on 1295 patients diagnosed with eyelid tumors between January 2022 and December 2024. All patients with eyelid tumors who underwent histopathological examination were included. Eyelid tumor characteristics, surgical procedures, and histopathological characteristics were collected.

Results: The study comprised 837 (65%) female patients and 458 (35%) male patients. A total of 922 benign lesions (71%) and 373 malignant neoplasms (29%) were identified. Among the benign lesions, the most prevalent types were nevus (26%), epidermoid cyst (15%), and dermoid cyst (12%). The most common malignant neoplasms were basal cell carcinoma (35%), sebaceous gland carcinoma (25%), and malignant lymphoma (19%). Most benign lesions were managed with excision and direct closure of the eyelid defect (47%), and malignant neoplasms were excised with reconstruction (57%).

Conclusion: This study found majority of eyelid tumors were benign, with a higher number of female patients compared to males. Intradermal nevus was the most common benign eyelid lesion, while basal cell carcinoma was the most prevalent malignant neoplasm. The surgical technique of eyelid tumor excision followed by histopathological examination can provide excellent cosmetic and functional results.

Keywords: Benign lesion, eyelid tumor, malignant neoplasm

Introduction

Eyelid tumors are the most common neoplasms encountered in ophthalmology practice, encompassing various types of benign and malignant tumors (1,2). These lesions represent 15% of facial tumors and 5-10% of all skin tumors (3,4). The highest incidence of eyelid tumors is in the population aged

over 60 years. The challenging clinical diagnosis often results in delayed treatment and potentially devastating outcomes (5-7).

Benign and malignant tumors can arise from various layers of the eyelid. Lesions can originate from the skin, connective tissue, glandular tissue, blood vessels, nerves, or muscles around the eyelid (3,8). Previous research found that

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benign lesions account for 70-75% of all eyelid lesions (9–11). While the majority of lesions are benign, the incidence of malignant tumors remains a significant clinical concern, for approximately 25-30% (6,12). However, regional variations significantly influence tumor prevalence. A study conducted in Singapore showed an incidence of sebaceous gland carcinoma at 8.7%. Studies in India and Japan found basal cell carcinoma was 29.8% and 32.6%, respectively, while squamous cell carcinoma was 28.1% and 13.5% (4,9,13).

Although most eyelid tumors can be diagnosed based on clinical presentation, some require confirmation with histopathological examination results (6,14). In a study by Silverman et al., a 2.3% risk of clinical misdiagnosis was reported in differentiating benign from malignant eyelid lesions (5). Previous studies reported a 1.4% risk of inconsistency between clinical diagnosis and histopathology results in cases of chalazion with basal cell carcinoma (1.1%) and sebaceous gland carcinoma (0.3%) (8,15).

Some malignant tumors can mimic benign lesions and inflammatory conditions, which can lead to delayed diagnosis and difficulty in appropriate management (16,17). If histopathology results confirm malignancy, complete tissue removal is necessary, and the tissue margins must be free of tumor cells. Accurate clinical diagnosis paired with histopathology examination is essential for successful functional and cosmetic management (10,18).

Therefore, the purpose of this study was to identify the clinical characteristics of eyelid tumors in patients at a tertiary eye hospital, so that it can provide a framework for optimizing the diagnosis and management of eyelid tumors.

Methods

A descriptive observational study with a retrospective approach was conducted at a tertiary eye hospital. Total sampling was applied and data were collected using electronic medical records of patients diagnosed with eyelid tumors between January 2022 and December 2024. This study was reviewed and approved by the institutional ethical committee of RS Mata Cicendo (Date: 13/01/2025, No: DP.04.03/D. XXIV.16/635/2025) and conducted in accordance with the Declaration of Helsinki guideline.

The inclusion criteria of this study were all patients with eyelid tumors who underwent surgery and histopathological examination. The exclusion criteria were patients who did not have complete medical record data and histopathological results.

The recorded data from each sample includes demographic characteristics and eyelid tumor characteristics. Demographic data covers age, gender, and area of residence. The age was recorded at the time of initial presentation. The area of residence was classified into inside and outside Java

to assess potential environmental exposure. Eyelid tumor characteristics include lesion location, laterality, tumor size, management procedure, and histopathological examination results. The location of tumors was divided into the upper or lower eyelid, canthus, and multiple locations. The tumor size was measured by the largest diameter using a surgical caliper. Tumor size is categorized into two groups: <10 mm and ≥10 mm. The management procedure is defined as the surgical technique employed, which includes excision with direct closure or reconstruction, extirpation, incisional biopsy, and exenteration. The clinical diagnosis made before the surgical procedure was recorded. The definitive diagnosis of the eyelid tumor was established through histopathological examination. This histopathological finding was compared to the initial clinical diagnosis to determine the rate of concordance. All tissue specimens were fixed in 10% buffered formalin, processed, and stained with Hematoxylin and Eosin. The slides were reviewed by an anatomical pathologist at our center and classified into benign lesions and malignant neoplasms.

The data were analyzed descriptively using IBM SPSS Statistics version 26 software (SPSS Inc., Chicago, IL, USA). Categorical data is presented in frequency (n) and percentage (%), while numerical data is presented in mean and standard deviation. The distribution of numerical data was assessed using Kolmogorov-Smirnov normality test.

Results

The retrospective study analyzed 1295 patients diagnosed with either benign or malignant eyelid tumors between January 2022 and December 2024. The demographic characteristics of eyelid tumor patients who underwent histopathological examination in this study are presented in Table 1. The mean age for benign tumor patients was 37.25 years, while malignant tumor patients was 53.27 years. The majority of patients with benign lesions were female patients, accounting for 609 patients (66%). The malignant neoplasm group showed the same pattern, with 228 female patients making up the majority (61%).

The clinical characteristics of eyelid tumors are demonstrated in Table 2. The upper eyelid was most frequently affected, seen in 673 patients (52%). Specifically, for benign lesions, 535 cases (58%) occurred on the upper eyelid. In contrast, malignant neoplasms showed an equal distribution between the upper and lower eyelids, with 138 patients (37%) for each location. In this study, Basal Cell Carcinoma (BCC) was the most prevalent malignant lesion at 35%, followed by Sebaceous Gland Carcinoma (SGC) at 25%. The most common size of benign lesion was <10 mm, observed in 489 patients (53%), while 433 patients (47%) had tumors with a size of ≥10 mm. Conversely, the majority of malignant

Table 1. Demographic characteristics of eyelid tumor patients at a tertiary eye hospital between January 2022 and December 2024

Characteristics	Eyelid Tumor Group	
	Benign Tumor (n=922) (%)	Malignant Tumor (n=373) (%)
Age, mean $\pm$ SD (years)	37.25 $\pm$ 21.45	53.27 $\pm$ 19.51
Age, n (%)		
<19 years	221 (24)	19 (5)
19–50 years	452 (49)	116 (31)
>50 years	249 (27)	238 (64)
Gender, n (%)		
Male	313 (34)	145 (39)
Female	609 (66)	228 (61)
Place of Residence, n (%)		
West Java	728 (79)	228 (61)
Java Island (except West Java)	184 (20)	96 (26)
Outside Java	10 (1)	49 (13)

SD: Standard Deviation

neoplasms were ≥ 10 mm, affecting 242 patients (65%), while only 131 patients (35%) had tumors <10 mm. The tumor size is crucial as it influences the surgical technique and the defect closure method. The goal is to ensure the surgical margins are free of tumor tissue while simultaneously preserving the function and aesthetics of the eyelid.

The operative management of eyelid tumors depends on the location, size, and type of the tumor. Table 2 presents the types of surgical procedures performed for benign and malignant eyelid tumor cases. The most frequently performed surgical procedure was excisional with direct closure, carried out on 433 patients (47%). This was followed by extirpation in 396 patients (43%), incisional in 55 patients (6%), and excision with reconstruction in 38 patients (4%).

The most frequently performed surgical technique in malignant neoplasms was excision with reconstruction, accounting for 232 patients (62%). This was followed by excision with direct closure in 60 patients (16%), incisional biopsy in 49 patients (13%), and exenteration (due to intraorbital infiltration) in 32 patients (9%). For cases involving systemic involvement, most malignant cases were consulted with other departments, such as Oncology and Radiotherapy.

Based on the histopathological examination results, benign lesions were found in 922 patients (71%), while malignant neoplasms were present in 373 patients (29%), as seen in Table 3. The concordance rate is 96% for eyelid tumors, with 1243 out of 1295 showing similar clinical diagnosis and

Table 2. Clinical characteristics of eyelid tumors at a tertiary eye hospital between January 2022 and December 2024

Characteristics	Eyelid Tumor Group	
	Benign Tumor (n=922) (%)	Malignant Tumor (n=373) (%)
Location, n (%)		
Upper eyelid	535 (58)	138 (37)
Lower eyelid	277 (30)	138 (37)
Canthus	64 (7)	56 (15)
Multiple	46 (5)	41 (11)
Laterality, n (%)		
Right	396 (43)	216 (58)
Left	498 (54)	149 (40)
Bilateral	28 (3)	8 (2)
Tumor Size, n (%)		
<10 mm	489 (53)	131 (35)
≥ 10 mm	433 (47)	242 (65)
Surgical Technique		
Excision with direct closure	433 (47)	60 (16)
Excision with reconstruction	38 (4)	232 (62)
Extirpation	396 (43)	0 (0)
Incisional biopsy	55 (6)	49 (13)
Exenteration	0 (0)	32 (9)

histopathological findings. Only 4% of the histopathological findings deviated from the initial clinical diagnosis. In the benign eyelid lesion group, the most frequently identified case was intradermal nevus in 240 patients (26%). The most common type of malignant neoplasm was basal cell carcinoma in 130 patients (35%).

Discussion

This study found a higher incidence of benign eyelid lesions compared to malignant neoplasm, which aligns with research by Kadir et al. and Mohan et al., who also reported a similar prevalence of benign eyelid lesions over malignant ones (3,4). The majority of patients with benign eyelid tumors were aged between 19–50 years, whereas malignant eyelid tumors were more frequently observed in patients over 50 years old. The higher incidence of malignant tumors in the elderly in this study is consistent with findings by Caglar et al. and Kaliki et al., who stated that the most common age range for malignant eyelid tumors is in the older age group (8,10). This might be attributed to prolonged exposure to causative agents or a failure in Deoxyribonucleic Acid (DNA) surveil-

Table 3. Histopathological characteristics of eyelid tumors at a tertiary eye hospital between January 2022 and December 2024

Pathological Anatomy Result	Count (n=1295)	Percentage (%)
Benign	922	
Nevus	240	26
Epidermoid cyst	138	15
Dermoid cyst	110	12
Verruca vulgaris	73	8
Pilomatrixoma	46	5
Seborrheic keratosis	37	4
Molluscum contagiosum	28	3
Others	248	27
Malignant Tumors	373	
Basal cell carcinoma	130	35
Sebaceous gland carcinoma	93	25
Lymphoma	71	19
Squamous cell carcinoma	41	11
Adenoid cystic carcinoma	11	3
Malignant melanoma	7	2
Metastatic tumor	7	2
Others	13	3

lance mechanisms leading to the development of malignant eyelid tumors (8). Ultraviolet (UV) radiation exposure is a crucial factor in the development of skin malignancies (3,4). Radiation penetrates the skin, inducing the formation of carcinogenic components, causing DNA damage, and suppressing local immunity. This is further supported by previous studies such as those by Ho et al. and Goncu et al., who demonstrated the role of DNA damage in the development of eyelid tumors (6,9).

In this study, the data revealed that the majority of eyelid tumor patients were female, for both benign and malignant tumors. This finding is consistent with studies by Paul et al., Hui et al., and Supartoto et al., which showed a similar result where females were more affected than males (53% versus 47%) (12,19,20). This differs from the studies by Caglar et al. and Silverman et al., where males were found to be more numerous than females (58% versus 42%) (5,8). This difference might be related to higher sunscreen usage by women in developed countries compared to women in developing countries (12,20).

In this study, the upper eyelid was the most frequently affected area compared to the lower eyelid in the benign group, while an equal distribution was seen in the malignant group. Prior studies revealed comparable results for the benign group and varying results in the malignant group (14,21).

This aligns with the study conducted by Fazil et al., which identified that benign lesions are typically found in the upper eyelid. Conversely, the malignant lesions showed a predilection for the lower eyelid, with the notable exception of SGC (22). This study found SGC as the second most frequent malignant lesion, resulting in an equal distribution of eyelid lesions among the malignant group.

The most common benign eyelid tumor found in this study was intradermal nevus, which is similar to results from an African study by Bagheri et al. that also identified nevus as the most common benign palpebral lesion (18). This differs from Fazil et al. which found xanthelasma as the most common benign lesion (22). BCC was the most common histopathological type of malignant eyelid tumor found in this study. These aligns with the findings of Han et al. in Taiwan, which reported BCC in 62.2% of cases. Other studies conducted in the United States and Australia reported the incidence of BCC was 92.5% and 88.8%, respectively. This study found SGC in 25% of malignant lesions, which aligns with epidemiological trends across Asia. Several factors contribute to a high prevalence of SGC in the Asian cohort include ethnic predisposition, environmental factors of UV exposure, and an aging population. These differences in incidence rates indicate geographical and demographic variations across different countries (14,17,19).

Based on the research findings, the concordance rate between clinical diagnosis and histopathological examination results was 96% (1243 out of 1295 eyelid tumor patients), with 4% having histopathological results differing from the clinical diagnosis. This is similar to the study by Silverman et al., which reported a 2.3% risk of clinical misdiagnosis in differentiating benign from malignant eyelid lesions (5). Caglar et al. reported a 1.4% risk of inconsistency between clinical diagnosis and histopathology results in chalazion cases with basal cell carcinoma (1.1%) and sebaceous gland carcinoma (0.3%) (8). However, a study by Deprez et al. in Belgium, with a sample size of 5504 cases, found a misdiagnosis risk of 20% in basal cell carcinoma cases that turned out to be nevus on histopathology, especially in nevus cases infiltrating the dermis or subcutaneous tissue which clinically appeared as malignant lesions. Clinical presentation in early-stage lesions may mimic benign conditions like chalazia or chronic blepharitis, which contributes to misdiagnosis (23). In contrast to this study, which was conducted in a tertiary referral center in Indonesia, patients often present with advanced-stage disease. The combination of advanced clinical presentation and high-volume patients significantly reduces the likelihood of clinical misdiagnosis. Therefore, it is recommended to perform a biopsy first to confirm the diagnosis.

The management of eyelid tumors is determined by their clinical characteristics, size, and signs of tumor infiltration.

In this study, for benign tumors, the majority underwent excision followed by direct closure of the eyelid defect, while for malignant tumors, reconstruction was performed. This is consistent with the findings of Hui et al., Wahyudi et al., and Supartoto et al., who stated that the primary management for eyelid tumors is surgical excision with direct closure, accounting for 47.2% of cases (12,13,20).

Generally, benign lesions can be managed with incisional or excisional biopsy. Most symptomatic benign lesions can be safely and easily excised, with precautions taken to avoid damage to vital ocular and adnexal structures (12,20). In cases of suspected malignant eyelid tumors, the primary surgical option is excision with adequate clear margins to minimize recurrence, metastasis, and mortality. However, this study found 9% of exenteration rate in malignant lesions. The contributing factors include late-stage presentation which may lead to orbital invasion, and socioeconomic barriers to early care in a developing country, causing diagnosis delay. The surgical technique of eyelid tumor excision followed by immediate closure during surgery can provide excellent cosmetic and functional results. The limitation of this study was no final data after patients had local or systemic adjuvant therapy such as radiotherapy or chemotherapy.

Conclusion

Most eyelid tumor patients who sought treatment at a tertiary eye hospital were over 50 years old, with a higher number of female patients compared to males. Intra dermal nevus was the most common type of benign eyelid tumor found, while basal cell carcinoma was the most prevalent malignant eyelid tumor, with the most frequent predilection for the upper eyelid. The most common surgical technique performed in benign lesions was excisional surgery with direct closure, whereas the malignant neoplasm was managed with tumor excision followed by reconstruction.

In cases of suspected malignant eyelid neoplasms, especially basal cell carcinoma, it is advisable to perform a biopsy to differentiate it from nevus before definitive surgery to improve patient outcomes. For cases of benign inflammatory lesions, patients should be informed about the risk of malignancy, particularly sebaceous gland carcinoma, to increase patient vigilance. Medical record keeping should be done in detail to obtain more complete data, and community outreach and education are necessary regarding the importance of early detection and optimal management for every case of eyelid tumor.

Disclosure

Ethics Committee Approval: This study was reviewed and approved by the institutional ethical committee of RS Mata Cicendo (Date: 13/01/2025, No: DP.04.03/D.XXIV.16/635/2025)

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List of abbreviations: DNA–Deoxyribonucleic Acid; SD–Standard of Deviation; UV–Ultraviolet.

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Surgical Outcomes of Pediatric Blepharoptosis

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Abstract

Objectives: The results of ptosis surgery and revision surgery performed in blepharoptosis of different etiologies in the paediatric age group were evaluated.

Methods: The 78 eyes of 66 patients followed up at our clinic between 2020 and 2024 were retrospectively examined. The patient's age, gender, etiology, preoperative and postoperative Best Corrected Visual Acuity (BCVA), levator function, Margin Reflex Distance-I (MRD-I), surgical techniques and revisions performed, amount of lagophthalmos, Bell's phenomenon, strabismus and amblyopia status were evaluated.

Results: The mean age of the patients was 9.05 ± 4.18 years, and the follow-up period was 21.19 ± 12.90 months. The etiology of ptosis was congenital myogenic in 49 (74.4%) patients, congenital neurogenic in 13 (19.6%) patients, and acquired in 4 (6%) patients. Strabismus was detected in 12 patients (18%), and amblyopia was detected in 35 eyes (44.9%). The most frequently used surgical techniques were frontal suspension with silicone (30.8%), müller muscle conjunctival resection (28.2%), and levator surgery (25.6%). Revision surgery was performed in 29 eyes (37.2%). The preoperative MRD-I (0.72 ± 1.26 mm) showed a significant increase at 6 months postoperatively (2.20 ± 1.42 mm) ($p < 0.001$). A positive correlation was found between final BCVA and preoperative BCVA ($r = 0.579$, $p < 0.001$). A low to moderate significant correlation was found between postoperative lagophthalmos and punctate staining ($r = 0.308$, $p = 0.012$). Lagophthalmos was more pronounced in the silicone sling group.

Conclusion: In pediatric ptosis surgery, a high rate of functional and aesthetic success is achieved through the selection of surgery appropriate to the etiology and careful postoperative follow-up.

Keywords: Blepharoptosis surgeries, Eyelid symmetry, Lagophthalmos, Margin reflex distance, Pediatric blepharoptosis

Introduction

Pediatric blepharoptosis is a clinically important condition that may adversely affect both visual development and psychosocial well-being in childhood. Depending on the severity of eyelid drooping, children may develop amblyopia, abnormal head posture, refractive abnormalities, and strabismus, making early recognition and appropriate management essential (1–3).

Pediatric ptosis may be congenital or acquired and may arise from myogenic, neurogenic, mechanical, or aponeurotic

causes. Management is individualized according to the underlying etiology, levator muscle function, degree of ptosis, ocular findings, and the risk of visual impairment. Surgical intervention is indicated to restore visual function, improve eyelid symmetry, and reduce long-term functional and aesthetic consequences (2,3).

Several surgical techniques are currently used in pediatric ptosis management. Levator resection or advancement is generally preferred in patients with adequate levator function, while frontalis suspension is usually the preferred option in cases with poor levator function (1,4). Müller mus-

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cle-conjunctival resection (MMCR) has also emerged as an effective option in selected patients with mild-to-moderate ptosis, good levator function, and a positive phenylephrine response (5). Despite the availability of these techniques, pediatric ptosis surgery remains challenging because of heterogeneous etiologies, examination difficulties in children, surgery under general anesthesia, and the risk of postoperative complications or revision procedures.

Although numerous studies have reported outcomes of individual surgical techniques, real-world comparative data evaluating different surgical approaches, revision requirements, and postoperative functional outcomes in a heterogeneous pediatric ptosis population remain limited.

Therefore, the aim of this study was to evaluate the surgical outcomes, postoperative complications, and revision requirements in pediatric patients who underwent different ptosis correction procedures at a tertiary oculoplastic referral center, with particular emphasis on MRD-I improvement, eyelid symmetry, amblyopia, and ocular surface outcomes.

Methods

Between 2020 and 2024, 78 eyelid files of 66 patients followed up and treated at the Oculoplastic Surgery Clinic were retrospectively screened and included in the study. The ethics of the study were approved by the Istanbul Education and Research Hospital Non-Interventional Clinical Research Ethics Committee (Date: 25.07.2025, No: 197). Written informed consent was obtained from all patients undergoing surgery in accordance with the World Medical Association's Declaration of Helsinki.

The patient's detailed medical history, personal history and family history were recorded. Best-corrected visual acuity (BCVA), detailed anterior and posterior segment biomicroscopic examinations, strabismus examination, eye movements, periorbital area and eyelids were evaluated in detail. Preoperative and postoperative photographs of the patients were taken and recorded at 1 week, 1 month, 3 months, and 6 months postoperatively, with a red dot placed on the glabella as a 10 x 10 mm reference point. Informed consent was obtained from each patient who underwent surgery for the surgery and for the use of the photographs.

Patient's age, gender, ptosis etiology, preoperative and postoperative BCVA, amblyopia status, presence of strabismus, preoperative levator function, preoperative and postoperative 1 week, 1 month, 3 months, and 6 months MRD-I, type of ptosis surgery performed, follow-up periods, symmetry between both eyelids, Bell phenomenon assessment, preoperative and postoperative 1 week, 1 month, 3 months, and 6 months lagophthalmos, corneal punctate condition and corneal staining, follow-up periods, development of postoperative complications, whether revision sur-

gery was required, and if revision surgery was performed, which surgery was performed were recorded and evaluated. Surgeon-related variables, including years of residency or specialist practice, subspecialty training, annual or cumulative pediatric ptosis case volume, and surgeon-specific surgical outcomes, were not systematically recorded in the institutional database and therefore could not be included in the analysis.

The study included patients with ptosis under the age of 18 who attended regular follow-up appointments (at least 6 months of follow-up).

Statistical Analysis

Analyses were performed using IBM SPSS (Statistical Package for the Social Sciences) version 26.0 (IBM Corporation, Armonk, NY, USA). Descriptive statistics were presented as mean $\pm$ standard deviation, minimum–maximum values, or frequency (%), as appropriate. Normality of continuous variables was assessed using the Shapiro-Wilk Test. For repeated non-parametric comparisons, the Friedman test was used, followed by Bonferroni-corrected Wilcoxon signed-rank tests for pairwise analyses. Associations between continuous variables were evaluated using Spearman correlation analysis. Comparisons between amblyopic and non-amblyopic groups were performed using the Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate. A *p* value <0.05 was considered statistically significant.

Results

The mean age of pediatric blepharoptosis patients was 9.05 ± 4.18 years (minimum 1–maximum 17 years). The study included 78 eyes of 66 patients (24 girls, 42 boys). 12 patients underwent surgery due to bilateral ptosis. The follow-up period was determined to be 21.19 ± 12.90 months on average. The preoperative levator function mean was 8.13 ± 4.84 (Table 1). Regarding ptosis etiology, 49 patients (74.2%) had congenital myogenic ptosis, 13 patients (19.7%) had congenital neurogenic ptosis, and 4 patients (6.1%) had acquired ptosis. Because only four patients had acquired ptosis, the acquired subgroup was not further analyzed according to specific etiological causes. Additionally, blepharophimosis syndrome was identified in two patients in the congenital myogenic group, Marcus Gunn jaw-winking syndrome in four patients in the congenital neurogenic group, and chronic progressive external ophthalmoplegia in two patients in the congenital neurogenic group. Positive family history was present in 8 patients (12%). Strabismus was detected in 12 patients (18%), and strabismus surgery was performed on 9 (13%) of these 12 patients prior to ptosis surgery. The Bell phenomenon in patients was positive in 53

Table 1. Sociodemographic and etiological characteristics of patients

	Number	Percentage (%)
Gender		
Girl	24	36.4
Boy	42	63.6
Side		
Right upper eyelid	42	53.8
Left upper eyelid	36	46.2
Etiology of Ptosis		
Congenital Myogenic	49	74.2
Congenital Neurogenic	13	19.7
Acquired	4	6.1
Bell Phenomenon		
Positive	53	67.9
Weakly Positive	20	25.6
Negative	5	6.4
Average Age	9.05±4.18 year (1-17 years)	
Follow Up	21.19±12.90 months	
Preoperative Levator Function	8.13±4.84 mm	

eyes (67.9 %), weakly positive in 20 (25.6%), and negative in 5 (6.4%). In patients with weak positive and negative Bell's phenomenon, the eyelid level was adjusted to a limited extent during surgery, and efforts were made to minimise the risk of postoperative lagophthalmos (Table 1).

Amblyopia was detected in 35 eyes (44.9%). A subgroup analysis comparing amblyopic and non-amblyopic eyes showed that mean preoperative MRD-I was numerically lower in the amblyopic group than in the non-amblyopic group (0.42 ± 1.49

vs. 0.95 ± 0.99 mm); however, this difference did not reach statistical significance ($p=0.076$, Mann-Whitney U test). The relatively large variability and overlapping distributions of MRD-I values, particularly in the amblyopic group, should be considered when interpreting this finding. No statistically significant differences were observed in age (8.09 ± 4.21 vs. 9.84 ± 4.03 years, $p=0.067$), sex distribution ($p=0.239$), time elapsed since the first operation (20.42 ± 21.79 vs. 29.00 ± 42.10 months, $p=0.251$), or ptosis etiology ($p=0.061$). However, strabismus was significantly more frequent in amblyopic patients compared with non-amblyopic patients (31.4% vs 7.0%, $p=0.007$) (Table 2).

When surgical methods are examined; 22 eyes underwent MMCR (28.2%) (Fig. 1), 20 eyes underwent levator surgery (25.6%) (Fig. 2), 24 eyes underwent frontal suspension with silicone (30.8%) (Fig. 3), 7 (9.0%) eyes underwent maximum levator resection, 4 (5.1%) underwent levator disinsertion + frontal suspension, and 1 (1.3%) underwent frontal suspension removal + maximum levator resection. The initial surgery for 3 patients was performed at an external centre. As the initial surgery for these patients was not performed at our clinic, they were not included in the revision group. Revision was performed on 29 (37.2%) eyelids, and it was determined that 5 of these patients underwent revision surgery for the second time. It was determined that all patients undergoing revision surgery were operated on due to ptosis associated with insufficient correction in the initial surgery. Among the eyes requiring revision, levator-based surgery was the most frequent initial procedure, and all revisions were performed because of residual or recurrent ptosis resulting from insufficient initial correction. However, because the study was retrospective and the revision subgroups were small and clinically heterogeneous, the reasons for the higher repre-

Table 2. Comparison of demographic and clinical characteristics between amblyopic and non-amblyopic eyes

	Amblyopic eyes (n=35)	Non-amblyopic eyes (n=43)	p*
Gender			
Girl	16 (45.7%)	13 (30.2%)	0.239
Boy	19 (54.3%)	30 (69.8%)	
Age (years)	8.09 ± 4.21 (3-16 years)	9.84 ± 4.03 (1-17 years)	0.067
Preoperative MRD-I (mm)	0.42 ± 1.49 (-4-+2 mm)	0.95 ± 0.99 (-1-+2 mm)	0.076
Time elapsed between the first operation (months)	20.42 ± 21.79 (1-72 months)	29 ± 42.10 (1-118 months)	0.251
Strabismus frequency			0.007
Yes	11 (31.4%)	3 (7.0%)	
No	24 (68.6%)	40 (93.0%)	
Etiology			
Congenital	35 (100%)	38 (88.4%)	0.061
Acquired		5 (11.6%)	

p* values were calculated using the Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate. Data are presented as mean±standard deviation or n (%). MRD-I: Margin Reflex Distance-I

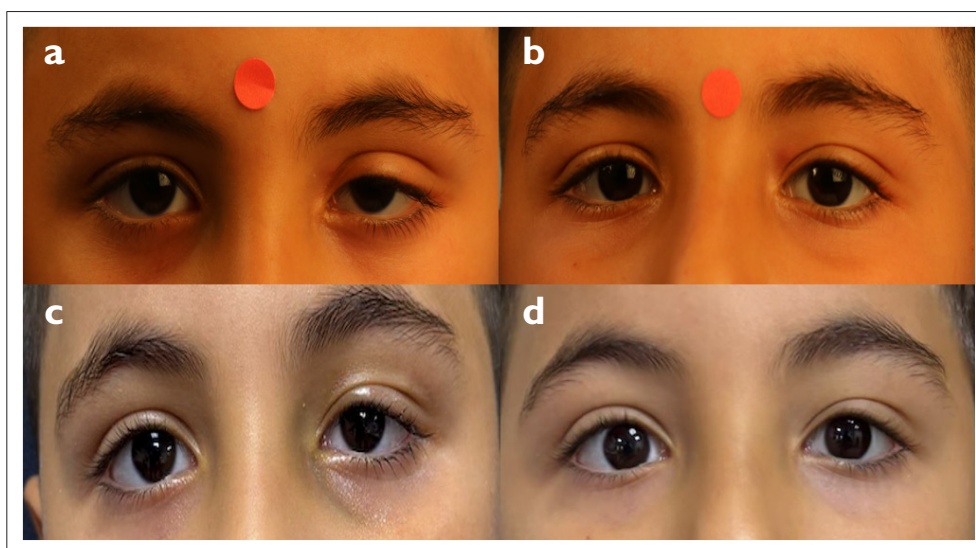


Figure 1. Surgical outcome of müller muscle conjunctival resection. **a)** 10 years old boy, left ptosis, preoperative, **b)** After left 2,5% Phenylephrine HCl, **c)** After left 9 mm MMCR, at 1 month, **d)** After left 9 mm MMCR, at 3 months (Taken with a C and D mobile phone).

MMCR: Müller Muscle Conjunctival Resection, HCl: Hydrochloride

sensation of levator-based procedures among revised eyes could not be formally determined. As revision surgery, levator revision was performed in 11 eyes (14.1%), re-frontal suspension with silicone in 7 eyes (9%), maximum levator surgery in 6 eyes (7.7%), and frontal suspension tightening in 5 eyes (6.4%) (Table 3). Five patients underwent revision within the first 15 days and were therefore grouped as early revision surgery. Four of these 5 patients underwent levator surgery revision. One patient who underwent revision had surgery on both eyelids, and one patient who had surgery on both eyelids had surgery on one eyelid. At postoperative

month 6, mean lagophthalmos was highest in the silicone frontalis suspension group (0.74 ± 1.04 mm), followed by levator surgery (0.69 ± 0.60 mm) and MMCR (0.28 ± 0.52 mm); however, this difference did not reach statistical significance ($p > 0.05$).

Preoperative MRD-I (0.72 ± 1.26 mm) differed significantly from postoperative values at 1 week (1.81 ± 1.24 mm), 1 month (2.07 ± 1.31 mm), 3 months (1.91 ± 1.36 mm), and 6 months (2.20 ± 1.42 mm). A statistically significant difference was found between MRD-I ($p < 0.001$). Further analyses to determine the source of the difference revealed statistical-

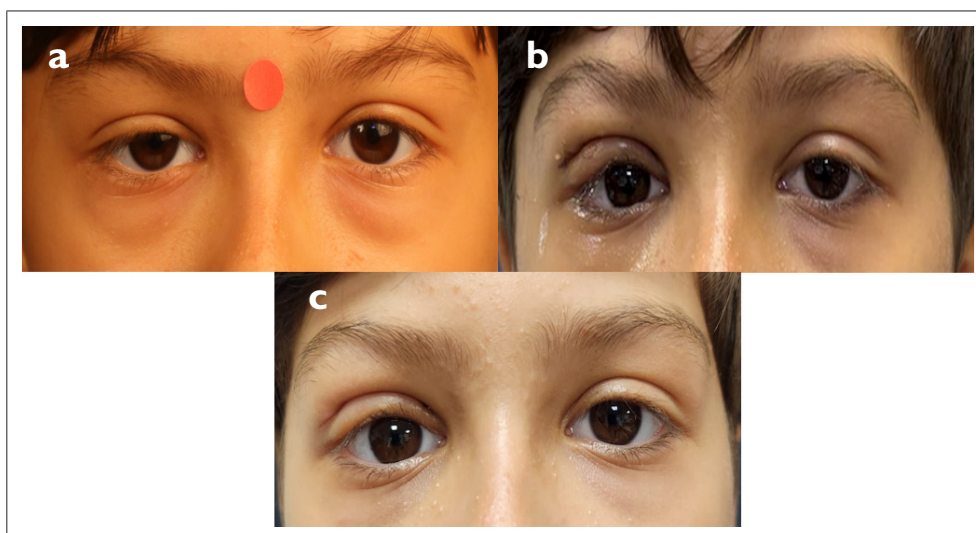


Figure 2. Surgical outcome of levator resection. **a)** 9 years old, boy, right ptosis, preoperative, **b)** After right levator resection, at 1 month, **c)** After right levator resection, at 3 months (Taken with a B and C mobile phone).

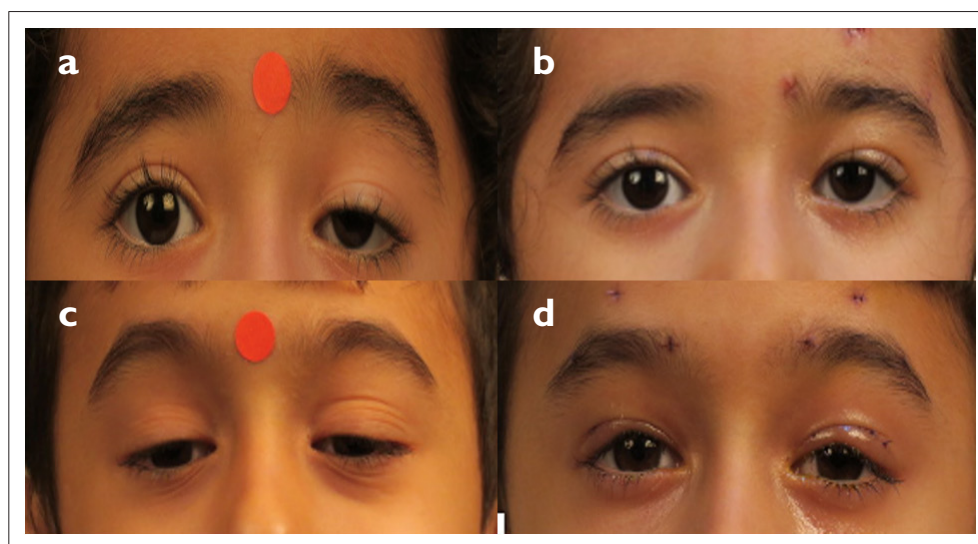


Figure 3. Surgical outcome of frontal suspension with silicone. **a)** 11 years old girl, left ptosis, **b)** After left frontal suspension with silicone, at 3 months, **c)** 10 years old boy, bilateral ptosis, **d)** After bilateral frontal suspension with silicone, at 1 week (Taken with a B and D mobile phone).

ly significant differences between preoperative MRD-I and postoperative 1 week, 1 month, 3 months, and 6 months MRD-I (each $p < 0.001$) (Table 4).

A moderately positive statistically significant correlation was found between the latest BCVA and BCVA levels ($r = 0.579$, $p < 0.001$). A low to moderate positive statistically significant correlation was found between preoperative lagophthalmos and preoperative corneal staining levels ($r = 0.367$, $p < 0.001$). A positive, low to moderate statistically significant correlation was found between preoperative

lagophthalmos and preoperative punctate staining levels ($r = 0.304$, $p < 0.008$). A positive, low to moderate statistically significant correlation was found between postoperative 3. month lagophthalmos and postoperative punctate staining levels ($r = 0.308$, $p < 0.012$).

Discussion

Pediatric ptosis presents a heterogeneous picture with various etiological causes and clinical findings. Nemet et al. (6) reported that systemic and ophthalmic conditions associated with paediatric ptosis cover a wide spectrum and are mostly diagnosed after the age of 5. This finding is consistent with the mean age and etiological distribution in our study. Similarly, in a 5 year study by Pavone et al. (7) to identify the most common causes of ptosis and possible treatment methods, myogenic and neurogenic ptosis were reported to be the most common causes, mostly congenital and with a positive family history in 10% of cases. In a large case series of 268 children with acquired blepharoptosis, Rasiah et al. (8) reported infantile haemangioma and trauma as the most common identifiable causes, while no definitive diagnosis could be established in a substantial proportion of cases. In contrast, our cohort predominantly comprised patients with congenital ptosis, and only four patients had acquired ptosis. Therefore, a direct comparison of the distribution of acquired ptosis etiologies between the two studies was not possible. Nevertheless, these findings highlight the broad etiological spectrum of pediatric blepharoptosis and the importance of a detailed clinical history and examination in determining the underlying cause. The choice of surgical technique is influenced by levator function, disease severity,

Table 3. Surgical Methods and Revision Surgeries in Patients

Surgical Method	Number	Percentage (%)
Frontal Suspension with Silicone	24	30.8
MMCR	22	28.2
Levator Surgery	20	25.6
Maximum Levator Resection	7	9.0
Levator Disinsertion + Frontal Suspension	4	5.1
Removal of the Frontal Suspension + Maximum Levator Resection	1	1.3
Revision Surgery		
Levator Revision	11	14.1
Re-frontal Suspension	7	9.0
Maximum Levator Resection	6	7.7
Frontal Suspension Tightening	5	6.4
2. Revision Surgery	5	

MMCR: Müller Muscle Conjunctival Resection

Table 4. Relationship between Preoperative and Postoperative (1 week, 1 month, 3 months, 6 months) MRD-I

PREOP. MRD-I (mm) mean±SD	POSTOP. 1 WEEK MRD-I (mm) mean±SD	POSTOP. 1 MONTH MRD-I (mm) mean±SD	POSTOP. 3 MONTHS MRD-I (mm) mean±SD	POSTOP. 6 MONTHS MRD-I (mm) mean±SD	P
0.72±1.26	1.81±1.24	2.07±1.31	1.91±1.36	2.20±1.42	<0.001
* Friedman Test					
MRD-I: Margin Reflex Distance-I, Preop: Preoperative, Postop: Postoperative, SD: Standard Deviation					

patient characteristics, and the surgeon's clinical judgment and experience. Revision or additional surgery may be required in a proportion of pediatric ptosis cases, particularly in patients with severe ptosis, poor levator function, or surgery performed at a very young age; however, the likelihood of reoperation varies according to the surgical technique, suspension material, and patient characteristics (9). After blepharoptosis surgery, there may be undercorrection, overcorrection, loss of the eyelid crease with sagging skin, and eyelid contour abnormalities. Surgical intervention is often indicated in children with drooping eyelids. Surgery can be performed at an early age to maximise visual potential and help ensure normal development.

Amblyopia is a significant visual development disorder in pediatric patients with ptosis and is a condition that requires careful consideration in the management of children with ptosis. In our subgroup analysis, no significant association was found between amblyopia and preoperative MRD-I, age at surgery, or ptosis etiology, whereas strabismus was significantly more common in amblyopic patients. Although the mean preoperative MRD-I was lower in amblyopic eyes than in non-amblyopic eyes, the difference did not reach statistical significance. This finding should be interpreted cautiously because MRD-I values showed considerable variability, particularly in the amblyopic group, and the distributions of the two groups overlapped substantially. The greater variability, together with the subgroup sample sizes, may have reduced the statistical power to detect a modest between-group difference. Therefore, the p value of 0.076 should not be interpreted as evidence that preoperative eyelid height is unrelated to amblyopia, but rather as an inconclusive finding that requires confirmation in larger, adequately powered cohorts. However, the literature suggests that this relationship has a complex structure. In a study conducted on patients with uncomplicated congenital ptosis, the incidence of amblyopia was reported as 20%, and it was demonstrated that ptosis directly caused amblyopia in some cases (10). Similarly, Merriam et al. (11) observed an increase in astigmatism and the development of associated amblyopia in the postoperative period in children who underwent surgery for congenital ptosis. In a retrospective study by Gazzola et al. (12), ear-

ly surgical intervention was reported to significantly reduce the amblyopia rate (from 34% to 8%). Furthermore, it has been reported that torticollis associated with ptosis and the accompanying developmental motor delay rapidly improved after surgery (13). In our study, amblyopia was detected in 35 (44.9%) eyes. According to the literature, our high amblyopia rate can be explained by the late referral of patients to our clinic. These data indicate that in children with ptosis, factors such as accompanying strabismus, refractive error, and ocular position, not just eyelid position, may play a role in the development of amblyopia, and that early intervention is critical in this regard.

Lagophthalmos is common after surgery (up to 40%), but symptomatic dry eye is rare and usually resolves with appropriate treatment (14). The degree of lagophthalmos can be estimated using intraoperative formulas, taking into account preoperative eyelid measurements and levator function (15). In our study, the positive correlation between the degrees of lagophthalmos and corneal staining indicates the need for attention to the ocular surface after surgery. In the study by Jeong et al. (14), no significant correlation was observed between postoperative eyelid healing and lagophthalmos, indicating that surgical outcomes are influenced by multiple factors. Surgical treatment in our series involved the selection of surgery appropriate to preoperative assessments, with levator surgery, MMCR and frontal suspension methods being commonly used; similarly, the literature shows that these methods are preferred. Gazzola et al. detailed the rates of levator resection and frontal suspension surgery and the complication rates; they reported that frontal suspension carries a higher risk of complications than levator resection, with a success rate of 75%, a complication rate of 15%, and ptosis due to minor correction of 21.5% (12). Skaat et al. (16) reported a success rate of over 80% and good cosmetic results in ptosis surgery performed on 162 pediatric patients, with more postoperative asymmetry seen in unilateral cases. Wu et al. (17) also reported a surgical success rate of 84.5% after levator resection. Various surgical options are available to correct ptosis in childhood. When comparing the surgical outcomes mentioned with our study, postoperative MRD-I success, symmetry success in both eyelids, and revision rates

were found to be similar to the literature. In our study, when compared according to surgical methods, it was found that levator surgery was performed more frequently, and complications associated with silicone frontal suspension were more common as long-term complications.

Although frontalis suspension remains the conventional surgical option in patients with poor levator function, recent evidence suggests that maximal levator resection may be a viable alternative in selected cases. A recent network meta-analysis comparing surgical techniques for congenital moderate-to-severe blepharoptosis reported favorable efficacy and safety outcomes for levator-based approaches in appropriately selected patients. Similarly, recent studies have demonstrated encouraging results with maximal levator resection even in severe congenital ptosis with poor Bell's phenomenon (18,19).

From a surgical perspective, MMCR stands out as an effective and reliable option, particularly in patients who respond positively to the phenylephrine test and have good levator function (6). A recent comprehensive review further supports the safety and effectiveness of MMCR in appropriately selected ptosis patients (5). The low complication rate due to its minimally invasive nature is also an advantage of this method. Levator resection is preferred in patients with unilateral congenital ptosis due to its high surgical success rates (17); however, complications such as insufficient or excessive correction and loss of the eyelid crease may occur with this method. In the present series, levator-based procedures were the most frequently represented initial operations among eyes requiring revision, and the indication for revision was residual or recurrent ptosis due to insufficient correction. Several factors may have contributed to this finding. Levator surgery was used in a clinically heterogeneous group with varying degrees of ptosis and levator function, and the relationship between the extent of levator resection and postoperative eyelid elevation may be variable in congenital levator dysgenesis. Furthermore, because all pediatric procedures were performed under general anesthesia, dynamic intraoperative assessment of eyelid height and symmetry was not possible. Nevertheless, no formal risk-factor analysis according to the initial surgical procedure was performed; therefore, this finding should not be interpreted as evidence that levator surgery independently carries a higher revision risk. It may also reflect case selection, disease severity, surgeon-related variability, and the tertiary referral nature of our cohort. Frontal suspension is used in cases of poor levator function or severe ptosis, but higher complication and revision surgery rates have been reported compared to levator resection (12). Although frontalis suspension is preferred in cases of poor levator function, the higher risk of complications should be considered. Kim et al. (20) emphasized that levator function is decisive in terms of the amount of eyelid elevation during surgery and postoperative

outcomes, and that adjusting eyelid height is difficult in cases operated under general anaesthesia. In our study, the revision rate was observed to be 37.2%, which is higher than the revision rates reported in the literature. The relatively high revision rate in our series may reflect the nature of our tertiary referral training center, where more complex and severe cases are concentrated, together with variability related to surgeon experience and the technical difficulty of achieving ideal eyelid height under general anesthesia in pediatric patients. To increase the success rate in pediatric ptosis surgeries, it is important to carefully evaluate parameters such as surgical technique selection, patient age, levator function, and phenylephrine test. Surgeon-related factors may potentially influence procedure selection and postoperative outcomes in technically demanding pediatric ptosis surgery. However, the present study did not record years of surgical practice, duration of residency or specialist experience, subspecialty training, or the annual and cumulative number of pediatric ptosis procedures performed by each surgeon. Therefore, the association between surgeon experience or procedural volume and surgical success or revision risk could not be examined, and no conclusion regarding an independent surgeon-experience effect can be drawn from our data.

This study has several limitations. First, its retrospective design may introduce selection bias. Second, the heterogeneity of ptosis etiologies and surgical techniques limits direct comparison between groups. Third, inclusion of both unilateral and bilateral eyes may introduce inter-eye dependency. Fourth, surgeries were performed in a pediatric population under general anesthesia, where intraoperative eyelid height adjustment is inherently challenging. Fifth, the number of revised eyes was insufficient for a reliable procedure-specific risk-factor analysis; therefore, the higher representation of levator-based procedures among revision cases may reflect case selection and clinical severity rather than an independent effect of the surgical technique. Finally, surgeon-related variables—including years of practice, training level, subspecialty experience, and pediatric ptosis case volume—were not systematically recorded; therefore, their potential effects on procedure selection, revision rates, and postoperative outcomes could not be evaluated. In addition, the amblyopia subgroup analysis may have had limited statistical power to detect modest differences in preoperative MRD-I because of the relatively small subgroup sizes and the considerable variability in MRD-I measurements, particularly among amblyopic eyes.

Conclusion

Surgical success in the treatment of pediatric ptosis is closely related to the surgeon's experience, correct patient selection, and the choice of an appropriate technique. In our study, MMCR stood out with high success and low compli-

cation rates in cases selected with appropriate indications. Levator surgery is a strong option in cases with good levator function, but the risk of lagophthalmos should be considered. Frontal suspension surgery is usually the first choice in cases with poor levator function, but it has been found to have a higher revision rate.

In children with ptosis, the phenylephrine test, levator function assessment and ocular surface preservation should be considered during the surgical planning process; furthermore, amblyopia and aesthetic outcomes should be closely monitored postoperatively.

In ptosis surgeries performed in the pediatric age group, difficulties in optimally adjusting the eyelid height under general anaesthesia and ocular surface complications associated with lagophthalmos that may develop in the postoperative period constitute significant limitations. However, in the large patient series included in our study, satisfactory functional and anatomical success was achieved despite these potential risks.

Disclosures

Ethics Committee Approval: The ethics of the study were approved by the Istanbul Education and Research Hospital Non-Interventional Clinical Research Ethics Committee (Date: 25.07.2025, No: 197).

Informed Consent: Written informed consent was obtained from all patients undergoing surgery in accordance with the World Medical Association's Declaration of Helsinki

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Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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OCT Assessment of Deep Optic Nerve Head, Subfoveal Choroidal Thickness, and Retinal Layers in Unilateral Anisometropic Amblyopia

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Abstract

Objectives: To evaluate retinal layers, subfoveal choroidal thickness, and optic nerve head parameters in adults with unilateral anisometropic amblyopia using optical coherence tomography.

Methods: This comparative cross-sectional study included 41 adults with unilateral anisometropic amblyopia and 35 healthy controls. Optical coherence tomography measurements were obtained from amblyopic eyes, fellow eyes, and control eyes. Retinal analysis included the nerve fiber layer, inner plexiform layer, outer plexiform layer, inner segment/outer segment (IS/OS) junction, retinal pigment epithelium, and subfoveal choroidal thickness. Peripapillary retinal nerve fiber layer, ganglion cell complex, mean macular thickness, Bruch's membrane opening, Bruch's membrane opening-minimum rim width, and lamina cribrosa-related parameters were also assessed. Comparisons were performed using linear mixed-effects models, with Bonferroni correction for post hoc analyses.

Results: After adjustment for age, significant between-group differences were mainly limited to the IS/OS parameter, mean macular thickness, and selected lamina cribrosa measurements. IS/OS was significantly higher in amblyopic eyes than in control eyes (172.55 ± 42.50 vs 151.26 ± 26.14 ; overall $p=0.029$, adjusted $p=0.029$), whereas mean macular thickness was lower in amblyopic eyes (246.00 ± 20.90 vs 261.99 ± 14.67 ; overall $p=0.015$, adjusted $p=0.016$). Temporal lamina cribrosa curve value ($p=0.005$), superior lamina cribrosa depth ($p=0.016$), temporal lamina cribrosa depth ($p=0.017$), and temporal lamina cribrosa width ($p=0.005$) also differed significantly after age adjustment. Retinal nerve fiber layer, ganglion cell complex, Bruch's membrane opening, Bruch's membrane opening-minimum rim width, subfoveal choroidal thickness, and lamina cribrosa curvature index showed no significant differences.

Conclusion: In adults with unilateral anisometropic amblyopia, structural changes after age adjustment were subtle and region-specific rather than diffuse. The main differences involved the IS/OS parameter, mean macular thickness, and selected lamina cribrosa-related measurements, while other retinal, choroidal, and optic nerve head parameters were largely similar across groups.

Keywords: Amblyopia, anisometropia, optical coherence tomography, retinal layers, choroid, lamina cribrosa

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Introduction

Amblyopia is a developmental visual disorder characterized by reduced best-corrected visual acuity that cannot be fully explained by an overt structural abnormality of the eye. Although it has traditionally been regarded primarily as a consequence of abnormal visual cortical development, this does not exclude the possibility that subtle retinal and optic nerve head changes may also accompany the disease (1).

Recent OCT studies in amblyopia have mainly focused on macular thickness, peripapillary retinal nerve fiber layer (RNFL), ganglion cell complex (GCC), and choroidal thickness. However, the published findings have been inconsistent. Some studies have reported thicker choroid or altered retinal measurements in amblyopic eyes, whereas others have found no significant differences in RNFL, GCC, or central macular measurements between amblyopic, fellow, and control eyes (2–4).

A segmental, layer-by-layer retinal analysis may provide a more informative structural profile than global retinal thickness measurements alone. Earlier segmentation-based studies suggested that amblyopia may not affect the retina uniformly and that any structural differences may be limited to selected retinal layers rather than the entire macular profile. This may help explain why studies based only on total macular thickness have produced conflicting results (2).

Interest has also expanded beyond the neurosensory retina to deeper optic nerve head structures, particularly the lamina cribrosa. OCT-derived parameters such as Bruch's membrane opening (BMO) and BMO-minimum rim width (BMO-MRW) provide anatomically grounded measurements of the optic nerve head and neuroretinal rim, whereas lamina cribrosa depth (LCD), lamina cribrosa curve value (LCC), and lamina cribrosa curvature index (LCCI) offer additional information about the structural configuration and posterior bowing of the lamina cribrosa (5).

This issue is particularly relevant in adults with unilateral anisometropic amblyopia, where structural OCT findings remain less clearly defined than functional visual outcomes. Most previous studies have concentrated on retinal or peripapillary measurements, whereas deep optic nerve head biomarkers have been evaluated much less frequently. A combined assessment of segmental retinal layers, subfoveal choroidal thickness, RNFL, GCC, mean macular thickness, BMO, BMO-MRW, LCD, LCC, and LCCI may therefore help clarify whether unilateral anisometropic amblyopia in adulthood is associated with diffuse structural alterations or with more selective changes involving specific retinal and lamina cribrosa-related parameters (1–5).

Therefore, the aim of the present study was to perform a segmental analysis of retinal layers and to evaluate subfo-

veal choroidal thickness, RNFL, GCC, mean macular thickness, and lamina cribrosa-related parameters including BMO, BMO-MRW, LCD, LCC, and LCCI in adults with unilateral anisometropic amblyopia, and to compare amblyopic eyes, fellow eyes, and healthy control eyes using OCT.

Methods

Study design and participants

This single-center comparative cross-sectional study included 41 adults with unilateral anisometropic amblyopia and 35 healthy controls. Written informed consent was obtained from all participants before enrollment, and the study protocol was approved by the local ethics committee (approval no. 2025/214). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Amblyopia was defined as best-corrected visual acuity ranging from 20/32 to 20/400 in the eye with lower vision, or an interocular difference of at least two Snellen lines, with best-corrected visual acuity of 20/25 or better in the fellow eye. Anisometropia was defined as a spherical equivalent refractive difference greater than 1.5 diopters between the two eyes. Only previously untreated patients with unilateral anisometropic amblyopia were included in the amblyopia group.

Participants with strabismic, mixed, or deprivation amblyopia, organic ocular disease, previous ocular surgery, hereditary or acquired optic nerve or optic disc pathology, visual acuity worse than 20/400 associated with poor fixation, neurologic disease, or insufficient cooperation for reliable OCT imaging were excluded. Healthy control subjects had best-corrected visual acuity of 20/25 or better in both eyes, no significant anisometropia, no history of amblyopia treatment or ocular surgery, no neurologic disease, and no clinically detectable ocular pathology on slit-lamp biomicroscopy or fundus examination.

In the amblyopia group, eyes were classified as amblyopic eyes and fellow eyes according to the clinically affected side. In the control group, both eyes were included in the analysis when eligible.

Ophthalmic examination

All participants underwent a complete ophthalmic examination, including best-corrected visual acuity assessment, slit-lamp biomicroscopy, intraocular pressure measurement, cycloplegic refraction, axial length measurement and dilated fundus examination. Demographic and clinical characteristics were recorded for all participants. Spherical equivalent values were recorded for amblyopic and fellow eyes, and control participants had no clinically relevant refractive error, with refractive values within -0.50 to +0.50 diopters. Axial length values were within the normal range in both groups.

OCT acquisition protocol

All optical coherence tomography examinations were performed using the same Nidek OCT device under standardized conditions. To minimize possible diurnal variation, all measurements were obtained between 09:00 and 11:00 a.m. Only scans with adequate centration, clear segmentation boundaries, and acceptable image quality were included. Each measurement was performed three times, and the mean of the three measurements was used for statistical analysis. Only scans with a signal strength of ≥ 8 were considered acceptable and included in the study.

Retinal, choroidal, and peripapillary measurements

Segmental retinal layer analysis included the nerve fiber layer (NFL), inner plexiform layer (IPL), outer plexiform layer (OPL), inner segment/outer segment (IS/OS) junction, and retinal pigment epithelium (RPE). The IS/OS parameter was considered an OCT-derived reflectivity-based signal characteristic rather than a direct histological measurement of a discrete retinal structure. Subfoveal choroidal thickness was measured as the perpendicular distance between the outer border of the retinal pigment epithelium/Bruch's membrane complex and the inner scleral border at the foveal center. Peripapillary retinal nerve fiber layer thickness and ganglion cell complex measurements were obtained using the device's standard acquisition protocol and built-in segmentation software.

Deep optic nerve head and lamina cribrosa measurements

Deep optic nerve head analysis included Bruch's membrane opening (BMO), Bruch's membrane opening-minimum rim width (BMO-MRW), lamina cribrosa depth (LCD), lamina cribrosa curve value (LCC), lamina cribrosa width, and lamina cribrosa curvature index (LCCI) (Fig. 1; Fig. 2).

BMO was defined as the termination points of Bruch's membrane at the optic nerve head and served as the anatomical reference for rim-based measurements. BMO-MRW was defined as the minimum distance between the BMO and the internal limiting membrane and was used as an anatomically based measure of the neuroretinal rim (Fig. 2).

Lamina cribrosa measurements were obtained from enhanced-depth optic nerve head B-scan images centered on the optic disc. The anterior lamina cribrosa surface was identified on each scan, and measurements were performed only when the relevant borders could be clearly visualized. A reference line was drawn by connecting the two BMO points. LCD was defined as the perpendicular distance from this reference line to the anterior lamina cribrosa surface. Lamina cribrosa width was defined as the distance between the two points used as the lateral limits of the measured lamina segment. LCC was defined as the maximum perpendicular distance from the reference line connecting the two width endpoints to the most posterior point of the anterior



Figure 1. Optic disc imaging plan. The optic disc center was used as the reference point, and the radial scan directions are indicated by green lines. The red arrow shows the horizontal reference axis.

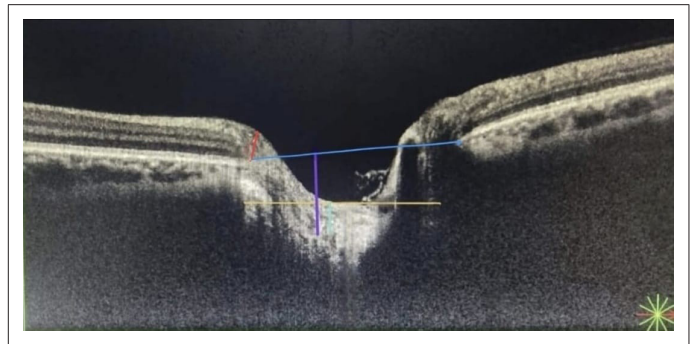


Figure 2. OCT assessment of deep optic disc excavation. The B-scan image demonstrates deep optic disc excavation, with the colored lines indicating the reference measurements used for structural evaluation. Red Line; BMO minimum rim width (BMO-MRW), Blue Line; Bruch's membrane opening (BMO), Yellow Line; Width, Purple Line; Lamina cribrosa depth (LCD), Green Line; Lamina cribrosa curve depth (LCC).

or lamina cribrosa surface. LCCI was calculated as the ratio of LCC to lamina cribrosa width multiplied by 100. Higher LCCI values indicated greater posterior bowing of the lamina cribrosa (Fig. 2).

For quadrant-based analyses, measurements were recorded separately in the nasal, inferior, superior, and temporal sectors according to the scan orientation used for optic nerve head imaging. Repeated measurements were averaged to reduce random measurement variability. Manual choroidal and lamina cribrosa measurements were performed by a single examiner masked to whether the image belonged to an amblyopic eye, fellow eye, or control eye.

Statistical analysis

All statistical analyses were performed at the eye level. Because the dataset included paired observations from the

same individual, namely amblyopic and fellow eyes in the amblyopia group and, when eligible, both eyes in the control group, linear mixed-effects models were used to account for within-subject inter-eye correlation. In these models, group (amblyopic eye, fellow eye, and control eye) was entered as a fixed effect, and subject was included as a random effect. Age adjustment was applied to all OCT-derived parameters because of the baseline age difference between the amblyopia and control groups. Axial length and spherical equivalent were also evaluated as potential biometric and refractive confounders. Axial length values were within the normal range and did not differ meaningfully between the amblyopia and control groups; spherical equivalent was recorded for amblyopic and fellow eyes, while controls had minimal refractive error. Separate models were constructed for each OCT-derived parameter. When the overall group effect was significant, Bonferroni-adjusted post hoc pairwise comparisons were performed. Bonferroni correction was applied to these post hoc pairwise comparisons and was not used as a global correction across all exploratory OCT-derived parameters. Continuous variables are presented as mean±standard deviation, and a two-sided *p* value <0.05 was considered statistically significant.

Results

A total of 41 adults with unilateral anisometropic amblyopia and 35 healthy controls were included in the study. The mean age was 35.73±10.29 years in the amblyopia group and 43.71±12.41 years in the control group. In the amblyopia group, eyes were categorized as amblyopic eyes and fellow eyes, whereas eligible eyes from healthy participants were analyzed as control eyes. The mean spherical equivalent was -0.74±2.39 diopters in amblyopic eyes and -0.65±1.54 diopters in fellow eyes. In the control group, refractive error was minimal, with values within -0.50 to +0.50 diopters. Mean

axial length was 23.52±0.69 mm in the amblyopia group and 23.59±0.84 mm in the control group, indicating no meaningful biometric imbalance between the groups.

In the age-adjusted linear mixed-effects analysis, most retinal and peripapillary parameters, including NFL, IPL/INL, OPL/ONL, RPE, subfoveal choroidal thickness, RNFL quadrant measurements, and GCC values, did not differ significantly among the groups. However, the IS/OS-related OCT band parameter remained significantly different after adjustment for age (overall *p*=0.0293). Post hoc Bonferroni analysis showed that IS/OS values were significantly higher in amblyopic eyes than in control eyes (adjusted *p*=0.0292). Mean macular thickness also remained significantly different among the groups after age adjustment (overall *p*=0.0150), and the significant pairwise difference was confined to amblyopic versus control eyes (adjusted *p*=0.0163) (Tables 1; Table 2).

Regarding optic nerve head parameters, no significant between-group differences were detected for BMO or BMO-MRW measurements after age adjustment (Table 3). In contrast, several lamina cribrosa-related parameters remained significantly different. Temporal LCC showed a significant overall group effect (*p*=0.0051), with significant post hoc differences between fellow and control eyes (adjusted *p*=0.0292) and between amblyopic and control eyes (adjusted *p*=0.0105). Superior LCD also remained significantly different among the groups (overall *p*=0.0164), with amblyopic eyes showing greater values than control eyes (adjusted *p*=0.0095). Similarly, temporal LCD remained significantly different after age adjustment (overall *p*=0.0169), and amblyopic eyes demonstrated greater values than control eyes (adjusted *p*=0.0135). Temporal lamina cribrosa width also differed significantly among the groups (overall *p*=0.0049), with a significant reduction in fellow eyes compared with control eyes (adjusted *p*=0.0061). By contrast, LCCI values

Table 1. Outer retinal and choroidal parameters in amblyopic, fellow, and control eyes

Parameter	Amblyopic eyes	Fellow eyes	Control eyes	Age-adjusted overall <i>p</i> value	Significant post hoc comparison
RPE	243.05±46.29	239.93±33.48	232.61±24.13	NS	—
IS/OS	172.55±42.50	161.55±33.95	151.26±26.14	0.0293	Amblyopic vs control (adjusted <i>p</i> =0.0292)
OPL/ONL	64.58±48.98	55.95±36.94	49.90±32.70	NS	—
IPL/INL	37.38±23.80	33.52±19.44	30.30±14.64	NS	—
NFL	58.95±19.47	52.67±16.50	53.71±22.98	NS	—
Subfoveal choroidal thickness	220.34±82.83	208.12±55.11	219.26±54.14	NS	—

Data are presented as mean±SD. Comparisons were performed using age-adjusted linear mixed-effects models. Bonferroni correction was applied for post hoc pairwise comparisons when the overall group effect was significant. Abbreviations: INL, inner nuclear layer; IPL, inner plexiform layer; IS/OS, inner segment/outer segment; NFL, nerve fiber layer; ONL, outer nuclear layer; OPL, outer plexiform layer; RPE, retinal pigment epithelium; SD, standard deviation.

Table 2. Peripapillary RNFL, ganglion cell complex, and mean macular thickness measurements

Parameter	Amblyopic eyes	Fellow eyes	Control eyes	Age-adjusted overall p value	Significant post hoc comparison
RNFL superior	128.09±67.13	126.15±17.84	135.94±37.93	NS	—
RNFL inferior	135.29±59.57	133.41±20.80	140.51±33.16	NS	—
RNFL nasal	98.50±134.61	84.68±41.81	78.31±23.16	NS	—
RNFL temporal	70.88±14.70	71.65±21.32	72.49±17.70	NS	—
GCC superior	93.61±11.89	97.06±8.05	96.63±10.19	NS	—
GCC inferior	96.30±11.98	97.15±9.08	98.31±9.51	NS	—
Mean macular thickness	246.00±20.90	252.30±21.11	261.99±14.67	0.0150	Amblyopic vs control (adj p=0.0163)

Data are presented as mean±SD. Comparisons were performed using age-adjusted linear mixed-effects models. Bonferroni correction was applied for post hoc pairwise comparisons when the overall group effect was significant. Abbreviations: GCC, ganglion cell complex; RNFL, retinal nerve fiber layer; SD, standard deviation.

did not differ significantly among the groups in any quadrant after age adjustment (Table 4).

Overall, after adjustment for age and consideration of refractive and biometric characteristics, the between-group differences were mainly confined to the IS/OS-related OCT band parameter, mean macular thickness, and selected lamina cribrosa measurements, particularly in the temporal sector. By contrast, the previously observed RNFL-related differences were no longer significant after age adjustment.

Discussion

In the present study, we performed a comprehensive OCT-based evaluation of segmental retinal layers, subfoveal choroidal thickness, RNFL, GCC, mean macular thickness, and deep optic nerve head/lamina cribrosa parameters in adults with unilateral anisometropic amblyopia. The overall pattern of our findings indicates that unilateral anisometropic amblyopia in adulthood is associated with selective rather than

diffuse OCT-derived differences. Among the retinal layer measurements, only the IS/OS-related OCT band parameter differed significantly, with higher values in amblyopic eyes than in control eyes. In addition, mean macular thickness showed significant intergroup differences, whereas RNFL and GCC measurements were broadly comparable after age adjustment. At the level of the deep optic nerve head, BMO, BMO-MRW, and LCCI were broadly similar across groups, while selected quadrant-specific differences were observed in LCC, LCD, and width, particularly in the superior and temporal sectors. Taken together, these findings suggest that OCT-derived differences in adult unilateral anisometropic amblyopia, when present, are subtle, regional, and not uniformly distributed across all retinal and optic nerve head metrics (3,6).

Our retinal layer analysis supports the view that amblyopia may involve localized OCT-derived retinal differences rather than generalized retinal thickening or thinning. In our cohort,

Table 3. Bruch's membrane opening and minimum rim width measurements

Parameter	Amblyopic eyes	Fellow eyes	Control eyes	Age-adjusted overall p value	Significant post hoc comparison
Nasal BMO	1578.72±241.51	1543.68±174.46	1617.30±164.25	NS	—
Inferior BMO	1728.02±230.50	1757.70±201.85	1831.23±196.32	NS	—
Superior BMO	1835.17±222.20	1871.73±243.21	1864.31±193.34	NS	—
Temporal BMO	1737.07±229.33	1726.54±219.87	1784.43±194.94	NS	—
Nasal BMO-MRW	348.35±121.34	378.15±120.12	361.17±112.88	NS	—
Inferior BMO-MRW	327.88±132.47	367.15±149.13	365.26±130.22	NS	—
Superior BMO-MRW	333.07±137.72	349.85±121.80	353.49±108.74	NS	—
Temporal BMO-MRW	342.34±108.27	344.95±109.76	375.17±109.52	NS	—

Data are presented as mean±SD. Comparisons were performed using age-adjusted linear mixed-effects models. Abbreviations: BMO, Bruch's membrane opening; BMO-MRW, Bruch's membrane opening-minimum rim width; SD, standard deviation.

Table 4. Lamina cribrosa-related measurements

Parameter	Amblyopic eyes	Fellow eyes	Control eyes	Age-adjusted overall p value	Significant post hoc comparison
Nasal LCC	376.23±98.17	387.90±120.28	414.69±97.67	NS	—
Inferior LCC	407.63±112.40	387.85±119.70	425.64±97.77	NS	—
Superior LCC	386.17±119.31	387.27±105.59	401.49±93.91	NS	—
Temporal LCC	359.34±103.03	334.07±91.03	403.51±107.72	0.0051	Fellow vs control (adjusted p=0.0292); amblyopic vs control (adjusted p=0.0105)
Nasal LCD	270.12±97.98	269.37±115.60	230.51±90.05	NS	—
Inferior LCD	220.39±114.84	213.95±86.28	201.56±76.15	NS	—
Superior LCD	290.68±129.73	241.56±111.94	211.31±99.98	0.0164	Amblyopic vs control (adjusted p=0.0095)
Temporal LCD	300.90±131.01	251.32±106.98	216.73±100.21	0.0169	Amblyopic vs control (adjusted p=0.0135)
Nasal width	1431.05±241.38	1438.27±227.49	1537.41±176.16	NS	—
Inferior width	1527.83±242.74	1546.20±209.33	1598.21±154.24	NS	—
Superior width	1617.22±214.98	1640.73±241.78	1651.69±159.24	NS	—
Temporal width	1530.29±212.74	1494.02±227.53	1629.69±203.47	0.0049	Fellow vs control (adjusted p=0.0061)
Nasal LCCI	26.70±7.69	27.70±9.24	27.27±7.07	NS	—
Inferior LCCI	25.89±9.45	26.27±11.86	26.91±9.26	NS	—
Superior LCCI	26.04±8.92	27.51±10.41	29.04±11.13	NS	—
Temporal LCCI	25.37±8.45	27.25±9.57	27.54±6.76	NS	—

Data are presented as mean±SD. Comparisons were performed using age-adjusted linear mixed-effects models. Bonferroni correction was applied for post hoc pairwise comparisons when the overall group effect was significant. Abbreviations: LCC, lamina cribrosa curve value; LCCI, lamina cribrosa curvature index; LCD, lamina cribrosa depth; SD, standard deviation.

NFL, IPL/INL, OPL/ONL, and RPE were comparable among amblyopic, fellow, and control eyes, whereas the IS/OS-related OCT band parameter differed significantly. This pattern is broadly consistent with earlier segmentation-based studies suggesting that retinal changes in amblyopia, if present, tend to be layer-specific rather than generalized across the retina. Szigeti et al. (6), for example, reported only limited macular segmentation differences after accounting for potential confounders, rather than evidence of a uniform structural abnormality. Likewise, Al-Haddad et al. (1) described qualitative macular ultrastructural differences in amblyopic eyes, including attenuation or absence of the foveal IS/OS bulge together with a shallower foveal pit. Although our study did not reproduce those exact morphologic findings, the broader implication is similar in that the outer retinal OCT signal may be more informative than global thickness measurements alone in adult amblyopia.

At the same time, the IS/OS result should be interpreted cautiously. On OCT, the IS/OS-related hyperreflective

band is commonly used as a surrogate of photoreceptor integrity, but its apparent thickness or prominence does not represent a true histological structure. It may be influenced by scan quality, segmentation behavior, foveal contour, reflectivity characteristics, and device-specific definitions. For that reason, the higher IS/OS value observed in amblyopic eyes is better interpreted as a reflectivity-based surrogate or OCT-derived signal characteristic rather than as direct proof of photoreceptor injury, remodeling, or a definite structural photoreceptor alteration. This conservative interpretation is consistent with the broader OCT literature in amblyopia, which has remained heterogeneous across age groups, imaging devices, and amblyopia subtypes (3,6,7).

Subfoveal choroidal thickness did not differ significantly among groups in our study. This finding contrasts with some adult anisometropic amblyopia studies, particularly the study by Kantarci et al., which reported thicker subfoveal, nasal, and temporal choroid in amblyopic eyes, but it is in agreement with other adult series reporting no clear difference in

subfoveal choroidal thickness between amblyopic and fellow eyes (2,4,8,9). One plausible explanation is clinical heterogeneity. Choroidal thickness is influenced by age, refractive profile, axial length, and probably amblyopia subtype, so differences in inclusion criteria can materially affect the result. In the present cohort, axial length was within the normal range and showed very similar mean values in the amblyopia and control groups, which reduces but does not completely eliminate the possibility of biometric confounding. Our data therefore add to the evidence that choroidal involvement is not a universal structural feature of adult amblyopia and may depend strongly on the characteristics of the sampled population (2,4,8,10).

RNFL measurements did not remain significantly different among the groups after adjustment for age. This finding is broadly in line with previous studies reporting no consistent diffuse peripapillary RNFL abnormality in amblyopia, including Kantarci et al., Yakar et al., and Repka et al. A meta-analysis by Li et al. also suggested that retinal findings in unilateral amblyopia are variable and do not support a consistent diffuse RNFL abnormality. Taken together, these data and our results argue against a robust peripapillary RNFL abnormality in adult unilateral anisometropic amblyopia (7,8,11,12).

Another notable finding was that mean macular thickness was lower in both amblyopic and fellow eyes than in control eyes, whereas GCC did not differ significantly among groups. This combination is of interest because it suggests that any macular structural signal in adult amblyopia may not be driven primarily by ganglion cell complex changes. Preserved GCC measurements in adult anisometropic amblyopia have also been reported previously, including in the study by Celik et al. In contrast, the literature on central or mean macular thickness has remained mixed, with some studies reporting thicker or altered macular morphology and others showing no meaningful difference (1,2,4,7,12). The fact that both amblyopic and fellow eyes showed lower mean macular thickness in our study may indicate that the relevant structural phenotype, at least in some adults with amblyopia, is not restricted entirely to the clinically amblyopic eye. The observation that both amblyopic and fellow eyes differed from control eyes is particularly important because it raises the possibility of a bilateral developmental effect rather than a purely monocular consequence of reduced visual acuity. From a neurodevelopmental perspective, anisometropic amblyopia is driven primarily by abnormal binocular visual experience and cortical processing; however, abnormal visual input during development may also be accompanied by subtle bilateral retinal or optic nerve head characteristics. Alternatively, these bilateral findings may reflect shared individual-level refractive or biometric factors within affected subjects rather than amblyopia-specific retinal remodeling.

The similar axial length values between the amblyopia and control groups make a major axial-length imbalance less likely, but the potential influence of spherical equivalent and other biometric variables should still be considered. In this regard, the findings of Chen et al. are particularly relevant, as some apparent OCT differences may lose significance after adjustment for axial length and refractive error (4,13).

One of the strengths of the present study is the inclusion of deep optic nerve head measurements, an area that has been only rarely investigated in adult amblyopia. BMO and BMO-MRW were similar among amblyopic, fellow, and control eyes in all quadrants. This is an important negative finding because BMO-MRW is considered an anatomically grounded measure of the neuroretinal rim, and a previous adult anisometropic amblyopia study specifically examining BMO-MRW and RNFL also found no significant structural difference between amblyopic and fellow eyes (5). Our results extend that observation by showing that even when healthy control eyes are included and inter-eye correlation is handled with eye-level modeling, BMO and BMO-MRW remain largely preserved (5,14).

The lamina cribrosa-related findings are more nuanced. Although temporal LCC, superior LCD, temporal LCD, and temporal width showed significant regional differences, LCCI did not differ significantly in any quadrant after age adjustment. At first glance, this may appear inconsistent, but it is biologically plausible that individual geometric components of the deep optic nerve head may vary without necessarily producing a parallel difference in a derived curvature-based index. In other words, localized changes in depth or span do not inevitably translate into a measurable shift in overall curvature index. It is also noteworthy that some differences, particularly temporal LCC and temporal lamina cribrosa width, involved not only amblyopic eyes but also fellow eyes compared with control eyes. This pattern again supports a possible bilateral developmental or subject-level structural phenotype, although it cannot distinguish between cortical-developmental mechanisms, retinal/optic nerve head developmental characteristics, and shared refractive or biometric influences. Against that background, our findings should be regarded as exploratory evidence of subtle regional geometric differences rather than definitive proof of lamina cribrosa remodeling in adult anisometropic amblyopia (3,5).

This point is important in the broader context of the amblyopia OCT literature. Most OCT studies in amblyopia have focused on retinal, macular, RNFL, GCC, or choroidal measurements, and direct comparison with earlier amblyopia series is therefore limited. Even so, the present results suggest that if amblyopia is associated with optic nerve head structural differences in adulthood, those differences are

more likely to be regional, geometry-specific, and potentially bilateral rather than gross and diffuse. This interpretation also matches the overall pattern of our study, in which significant findings clustered in selected parameters rather than across the entire OCT profile (3,6).

Several limitations should be acknowledged. First, the sample size was moderate, particularly after the analyses were separated by quadrant, which may have limited the power to detect smaller between-group effects. Second, some measurements, especially subfoveal choroidal thickness and deep optic nerve head parameters, were obtained manually, although this was mitigated by averaging three measurements per parameter and restricting analyses to scans with signal strength of at least 8. Third, although axial length values were available, were within the normal range, and were similar between the amblyopia and control groups, axial length remains an important determinant of choroidal thickness, macular thickness, RNFL measurements, and lamina cribrosa-related parameters. Therefore, residual biometric confounding cannot be completely excluded. Similarly, spherical equivalent was available in the amblyopia group and controls had minimal refractive error, but refractive status may still influence OCT-derived measurements and should be incorporated more extensively in larger future studies. Given the modest sample size and the large number of OCT-derived parameters analyzed separately, the models were intentionally kept parsimonious, and age was prioritized as the primary covariate because it represented the most evident baseline imbalance between the study groups. Bonferroni correction was applied to post hoc pairwise comparisons after a significant overall group effect, but not as a global correction across all exploratory OCT parameters; therefore, the lamina cribrosa-related findings should be interpreted cautiously. An additional limitation is the age imbalance between groups, with controls being older than participants with amblyopia. Given the known influence of age on several OCT-derived retinal, choroidal, and optic nerve head parameters, residual confounding cannot be excluded despite age adjustment. Finally, the cross-sectional design precludes any inference about developmental sequence or causality. These issues should be considered when interpreting both the positive and negative findings.

Conclusion

In conclusion, adults with unilateral anisometropic amblyopia showed selective OCT-derived differences involving the IS/OS-related OCT band parameter, mean macular thickness, and selected regional lamina cribrosa measurements, while RNFL, GCC, BMO, BMO-MRW, and LCCI were largely comparable among groups. The involvement of

some fellow-eye parameters may indicate a bilateral developmental or subject-level structural phenotype rather than a strictly monocular effect. However, the findings should be interpreted cautiously because OCT-derived outer retinal signals are device- and segmentation-dependent and because refractive and biometric variables may influence several of the measured parameters. Larger prospective studies incorporating detailed axial length and refractive adjustment are needed to clarify the structural significance of these findings.

Disclosures

Ethics Committee Approval: This study was approved by the Yalova University Ethics Committee (Date: 04.06. 2025 , No: 2025/214).

Informed Consent: Written informed consents were obtained from all patients.

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A Clinical Study of Retinal Nerve Fibre Layer and Ganglion Cell Layer changes in patients with Migraine at a Tertiary Care Hospital

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Abstract

Objectives: This study aimed to assess and compare retinal nerve fibre layer (RNFL) and ganglion cell layer (GCL) thickness in migraine patients versus controls and to analyze differences between chronic and episodic migraine.

Methods: A cross-sectional, case-control study was conducted from June 2022 to December 2023. A total of 100 migraine patients (33 chronic, 67 episodic) and 102 controls underwent detailed ocular evaluation using OCT. RNFL and GCL parameters were compared between cases and controls using an independent t-test. Paired t-tests assessed differences between chronic and episodic migraine, as well as between the right and left eyes.

Results: Photophobia (90%) and ocular pain (85%) were the most common symptoms. Migraine patients showed a significant reduction in average (106 μ m), superior (129 μ m), and nasal (80 μ m) RNFL thickness compared to controls. Chronic migraine patients exhibited significant thinning in the temporal (67 μ m) and nasal (72 μ m) RNFL quadrants and superotemporal (67 μ m) and superonasal (70 μ m) GCL quadrants in the right eye. Episodic migraine patients had reduced superotemporal GCL thickness (71 μ m) in the left eye.

Conclusion: The retinal nerve fibre layer (RNFL) and ganglion cell layer (GCL) thickness is reduced in chronic and episodic type of migraine patients. Hence, ophthalmologists should consider the potential impact of migraine headaches on the thickness of RNFL and GCL.

Keywords: Migraine, optical coherence tomography, retinal nerve fibre layer thickness, ganglion cell layer thickness

Introduction

Migraine is a common primary headache disorder typically characterised by recurrent episodes of unilateral, throbbing head pain, often accompanied by nausea, photophobia and, in some patients, visual or sensory aura. These attacks usually last from 4 to 72 hours and are classified as episodic when they occur on fewer than 15 days per month and chronic when they occur on 15 or more days per month for more than three months.

Two principal theories have been proposed to explain the pathophysiology of migraine. The vascular theory suggests that intracranial vasoconstriction causing transient cerebral ischemia is followed by vasodilation, which contributes to aura and headache. In contrast, the neurovascular theory posits that migraine is primarily a neurogenic process, with cortical and brainstem neuronal dysfunction leading to secondary alterations in cerebral perfusion (1).

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Neuroimaging and electrophysiological studies have reported structural and functional changes in the occipital cortex and other brain regions in patients with recurrent migraine, suggesting that repeated attacks may be associated with cumulative neural alterations over time (2).

Because the eye and brain are anatomically and functionally connected via the optic nerve, there has been growing interest in whether migraine-related central changes are accompanied by subtle structural changes in the retina. Optical coherence tomography (OCT) allows high-resolution, non-invasive measurement of the retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL), which reflect the axons and cell bodies of retinal ganglion cells, respectively (3). Several studies have reported reduced RNFL and GCL thickness in some groups of migraine patients, particularly those with frequent or long-standing disease, raising the possibility of a neurodegenerative component or shared microvascular vulnerability. However, the exact mechanisms linking migraine and retinal structural changes remain uncertain, and OCT findings have not been consistent across all studies (3).

On this background, we hypothesised that migraine patients may show subtle alterations in RNFL and GCL thickness compared with healthy individuals, and that patients with chronic migraine might exhibit more pronounced changes than those with episodic migraine due to higher attack frequency. The aim of this study was therefore to use spectral-domain OCT (SD-OCT) to assess RNFL and GCL thickness in patients with migraine compared with matched controls, and to explore differences between chronic and episodic migraine.

Methods

Study Design and Setting

We conducted a cross-sectional, observational case-control study at a tertiary care hospital in Bangalore, India, from June 2022 to December 2023. The study protocol was approved by the institutional review board on 22 September 2022 (No: MSRMC/EC/PG-97/07-2022), and all procedures adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants in their vernacular language before enrolment.

Participants

Patients aged 18–60 years with a diagnosis of episodic or chronic migraine according to the International Classification of Headache Disorders, 3rd edition (ICHD-3), and under follow-up with the Neurology department, were eligible for inclusion (4). Patients were referred to the Ophthalmology department for detailed ocular evaluation and OCT imaging. Age- and sex-matched controls without a history of migraine or other primary headache disorders were recruited

from individuals attending the hospital for routine eye examination.

We excluded participants with evidence of glaucomatous optic nerve head changes (cup–disc ratio >0.5) or intraocular pressure >20 mmHg, as these conditions can independently affect RNFL thickness. Individuals with systemic diseases such as hypertension, diabetes mellitus, or neurological disorders including Parkinson's disease and Alzheimer's disease were also excluded. Ocular conditions that could influence RNFL or GCL measurements, such as optic atrophy, retinal detachment or other significant retinal pathology, were additional exclusion criteria. Pregnant individuals were not enrolled.

Clinical Assessment

For all migraine patients, a detailed history was obtained, including duration of illness and frequency of attacks per month; based on this information, cases were classified as episodic or chronic migraine according to ICHD-3 criteria. Associated symptoms such as photophobia, visual aura, scintillating scotoma and curtain-like visual disturbance were recorded, along with whether these symptoms subsided with treatment. Neuroimaging with computed tomography (CT) or magnetic resonance imaging (MRI) was performed in most cases to rule out secondary causes of headache and to document presence of white matter lesions.

All cases and controls underwent a comprehensive ophthalmic examination. Best-corrected visual acuity (BCVA) was assessed using standard refraction techniques. Anterior segment evaluation was performed with slit-lamp biomicroscopy, and fundus examination was conducted by indirect ophthalmoscopy with a +90 D lens. Intraocular pressure was measured using Goldmann applanation tonometry.

OCT Imaging

Spectral-domain OCT (SD-OCT) was used to obtain three-dimensional scans of both eyes in all participants. Average RNFL thickness and quadrant-specific RNFL thickness (superior, inferior, nasal, temporal) were recorded for each eye. For the GCL, thickness values were obtained in pre-defined macular sectors, including superior, superotemporal, superonasal, inferior, inferotemporal and inferonasal quadrants. Scans with a signal strength <6 were considered to be of poor quality and were excluded from analysis.

Sample Size

The sample size was calculated based on data from a previous study by Gipponi et al., which reported mean RNFL thickness of 111.27 μm (standard deviation [SD] 9.77) in controls and 107.64 μm (SD 8.49) in migraine cases. Assuming a 95% confidence level, 80% power and these mean and SD values, the minimum required sample size was estimated as 100 subjects in each group. We therefore aimed to recruit at least 100 migraine patients and 100 controls.

Statistical Analysis

Data were analysed using SPSS for Windows, Version 16.0 (SPSS Inc., Chicago, IL, USA). Qualitative variables, such as sex, were expressed as frequencies and percentages, and quantitative variables, including age and OCT parameters (RNFL and GCL thickness), were presented as mean $\pm$ SD. An independent Student's t-test was used to compare RNFL and GCL parameters between migraine cases and controls. A paired t-test was employed to compare right and left eyes within the migraine group and to assess differences between chronic and episodic migraine. An independent t-test was also used to compare OCT parameters between male and female patients. A p-value <0.05 was considered statistically significant.

Results

Study Population

A total of 202 participants were included, comprising 100 migraine patients (200 eyes) and 102 controls (204 eyes). The mean age of the study population was 34.58 ± 8.56 years (range 18–56 years), with most individuals (49.5%) falling in the 28–38-year age group (Table 1). Among the migraine cases, 17 (17%) were male and 83 (83%) were female; in the control group, 25 (24.5%) were male and 77 (75.5%) were female, and the two groups were comparable in age and sex distribution.

Of the 100 migraine patients, 33 (33%) had chronic migraine and 67 (67%) had episodic migraine. Photophobia was the most common associated symptom, reported by 90% of patients, followed by ocular pain in 85%. Only five patients reported visual aura; among these, two experienced

scintillating scotoma and three reported a curtain-like visual disturbance. BCVA was 6/6 in both eyes for all cases and controls, and no anterior or posterior segment pathology was identified on clinical examination. Neuroimaging identified white matter lesions in 2 of 100 migraine patients; other causes for such lesions were excluded from these individuals.

RNFL Thickness: Migraine vs Controls

Comparison of OCT RNFL parameters between migraine cases and controls showed a statistically significant reduction in several measures in the right eye of migraine patients. Specifically, average RNFL thickness (mean 106 μm), superior quadrant thickness (mean 129 μm) and nasal quadrant thickness (mean 80 μm) were all significantly lower in the right eyes of migraine patients compared with controls ($p=0.01$, $p=0.01$ and $p=0.03$, respectively). No statistically significant differences in RNFL thickness were observed in the left eye between cases and controls. (Table 2)

GCL Thickness: Migraine vs Controls

When GCL parameters were compared between cases and controls, there was no statistically significant difference in any quadrant in either eye. Mean GCL thickness values in all sectors of the right and left eyes were broadly similar between migraine patients and controls, and p-values were >0.05 across all comparisons. (Table 3)

Subgroup Analysis: Chronic vs Episodic Migraine

In the subgroup analysis, we compared RNFL and GCL thickness between chronic and episodic migraine patients. For the GCL, patients with chronic migraine demonstrated a significant reduction in superotemporal (mean 67 μm) and superonasal (mean 70.7 μm) quadrants of the right eye compared with episodic migraine patients ($p<0.05$ for both) (Fig. 1). Conversely, in the left eye, episodic migraine patients showed a significant reduction in superotemporal GCL thickness (mean 79.7 μm vs 71.1 μm , $p=0.01$) compared with chronic migraine patients (Fig. 2). This pattern resulted in an inconclusive picture with respect to laterality.

For RNFL parameters, chronic migraine patients had significantly reduced temporal (mean 67.2 μm) and nasal (mean 78.2 μm) quadrant thickness in the right eye compared with

Table 1. Age distribution

Age (years)	Number of patients
18- 28	47 (23%)
28-38	100 (49.5%)
38-48	38 (18.8%)
48-56	17 (8.41%)

Table 2. Comparison of Retinal Nerve Fibre Layer (RNFL) thickness in cases and controls

Variable	Right eye			P	Left eye			P
	Case Mean	+/- SD	Control Mean+/-SD		Case Mean+/-SD	Control Mean+/-SD		
OCT RNFL average thickness	106.2 +/- 10.5		111.7+/- 12	0.01	100.41+/- 15.35		99.77+/- 19.56	0.79
OCT RNFL Superior	129.7+/- 1.68		135.65+/- 2.137	0.01	127.81+/- 22.64		120.54+/- 32.31	0.06
OCT RNFL Inferior	131.15 +/- 25.25		127.38 +/- 20.64	0.24	129.96+/- 21.82		133.35+/- 30.85	0.36
OCT RNFL Temporal	71.23 +/- 1.85		68.05 +/- 14.06	0.17	71.12+/- 14.87		67.32+/- 14.93	0.067
OCT RNFL Nasal	86.74 +/- 21.84		90.83 +/- 17.77	0.03	76.01+/- 17.56		80.18+/- 24.75	0.17

Table 3. Ganglion Cell Layer (GCL) thickness of cases and controls

Variable	Right eye		P	Left eye		P
	Case Mean +/- SD	Control Mean +/- SD		Case Mean +/- SD	Control Mean +/- SD	
OCT GCL superior	70.73 +/- 10.01	74.26 +/- 16.52	0.07	70.94 +/- 6.25	74.00 +/- 18.39	0.11
OCT GCL Superior temporal	70.24 +/- 7.93	71.43 +/- 14.03	0.46	73.50 +/- 15.65	73.55 +/- 19.81	0.98
OCT GCL Superior nasal	74.95 +/- 12.99	77.14 +/- 14.79	0.26	73.70 +/- 5.96	74.60 +/- 17.14	0.62
OCT GCL Inferior	68.94 +/- 9.86	71.17 +/- 14.23	0.19	67.89 +/- 6.83	71.53 +/- 17.86	0.58
OCT GCL Inferior temporal	71.17 +/- 14.23	72.85 +/- 7.93	0.42	71.44 +/- 9.21	72.20 +/- 16.93	0.69
OCT GCL inferior nasal	74.56 +/- 19.93	74.06 +/- 10.01	0.12	73.24 +/- 6.23	75.97 +/- 16.48	0.12

episodic migraine patients ($p < 0.01$ for both). No significant differences in average, superior or inferior RNFL thickness were observed between chronic and episodic migraine in either eye. (Fig. 3)

The GCL and RNFL thickness of the two types of migraine patients are presented (Tables 4; Table 5)

Discussion

In this cross-sectional case-control study, we evaluated RNFL and GCL thickness in 100 migraine patients and 102 controls using SD-OCT. We found a significant reduction in average, superior and nasal RNFL thickness in the right eyes of migraine patients compared with controls, whereas left-eye RNFL and overall GCL thickness did not differ significantly between groups. In subgroup analyses, chronic migraine patients showed thinning of temporal and nasal

RNFL quadrants and superotemporal and superonasal GCL quadrants in the right eye compared with episodic migraine, while episodic migraine patients had reduced superotemporal GCL thickness in the left eye, yielding an inconclusive picture regarding laterality.

According to the Global Burden of Disease (GBD) 2019 data, migraine is more common in females, particularly women of child-bearing age (15–49 years), among whom annual prevalence rates range between 21% and 28% (5). In our case-control cohort, migraine was similarly more prevalent in females (83%), and the mean age was 34 years, with most patients in the 28–38-year group, consistent with previous epidemiological studies (6,7). Chronic migraine accounts for a smaller proportion of all migraine cases; population-based data indicate 1-year prevalences of episodic migraine of 17.1% in women and 5.6% in men, compared with 1.3% and

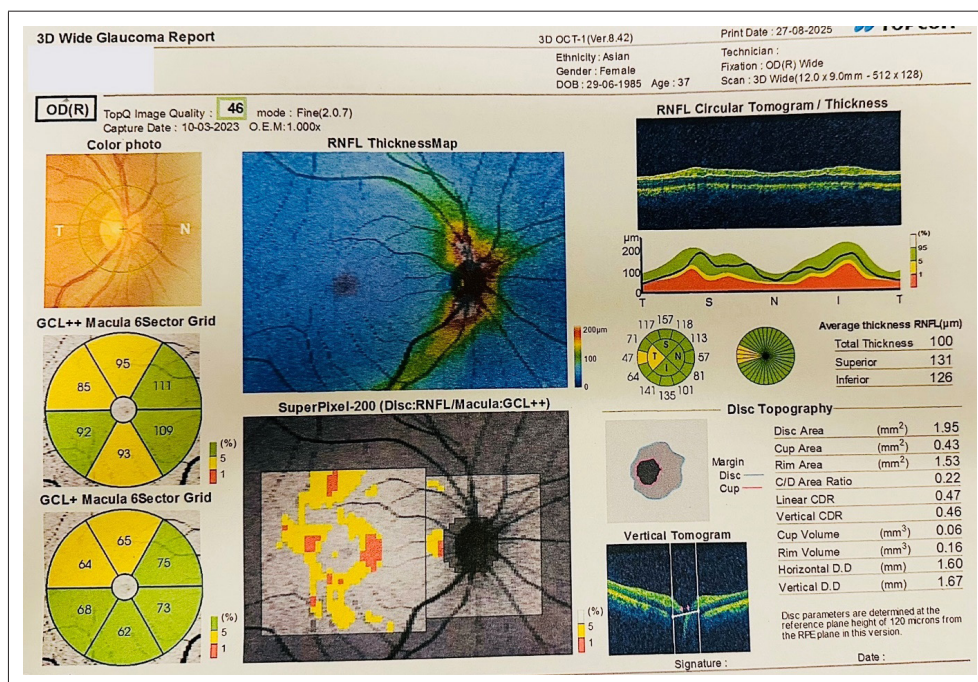


Figure 1. Right eye OCT GCL report of case number 47 with chronic migraine showing a reduction in thickness in the superior and superotemporal quadrant.

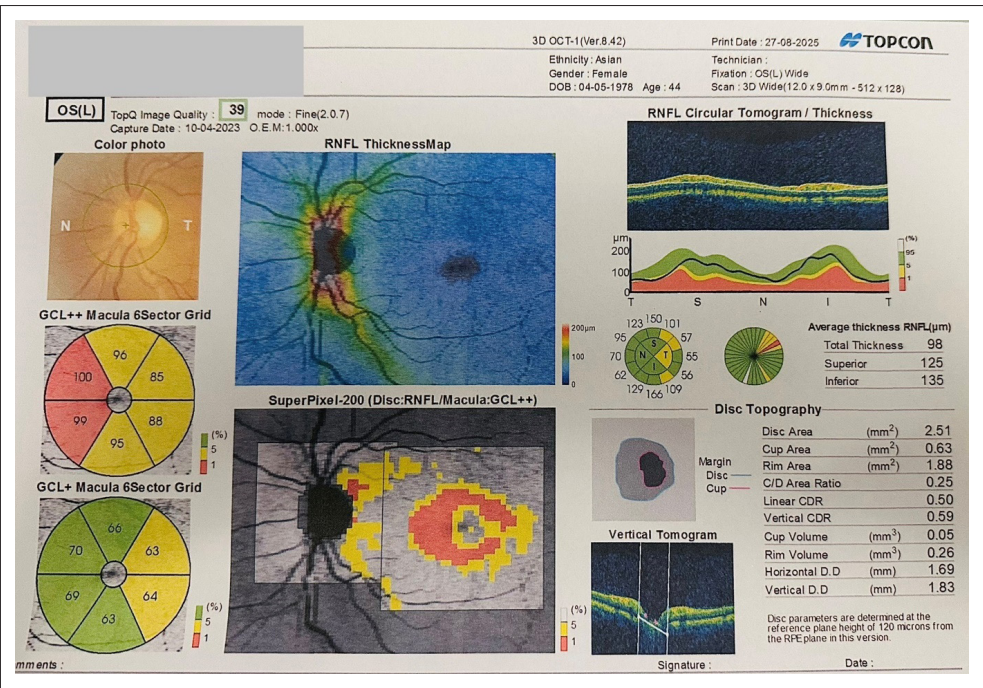


Figure 2. Left eye OCT GCL report case number 39 with episodic migraine patient showing a reduction in thickness in the temporal quadrant.

0.5% for chronic migraine, respectively (8). In line with these figures, episodic migraine was more frequent than chronic migraine in our sample (67% vs 33%).

Photophobia and ocular pain were the most common associated symptoms in our patients (90% and 85%, respectively), a pattern that agrees with prior reports (5,6). Visu-

al aura was relatively uncommon; only five patients experienced aura, whereas some studies (for example, Go Lee et al. and Costa et al.) have described visual aura in up to 90% of their migraine cohorts (6,7). Among the few patients with aura in our study, curtain-like phenomena and scintillating scotoma were observed, which differs from other series

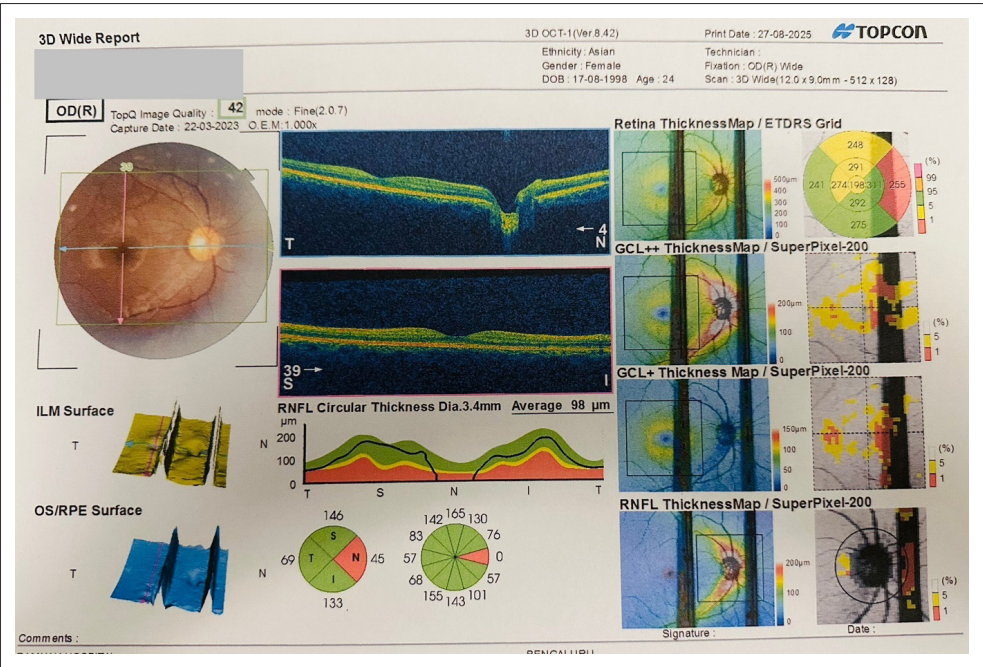


Figure 3. Right eye OCT RNFL report of case number 42 with chronic migraine showing reduced thickness in the nasal quadrant.

Table 4. Ganglion Cell Layer (GCL) thickness of chronic and episodic migraine patients

Variable	Right eye		P	Left eye		P
	Chronic Mean +/- SD	Episodic Mean +/- SD		Chronic Mean +/- SD	Episodic Mean +/- SD	
OCT GCL superior	68.75 +/- 9.13	71.50 +/- 10.29	0.22	70.36 +/- 6.22	71.17 +/- 6.29	0.56
OCT GCL Superior temporal	67.50 +/- 6.64	71.31 +/- 8.17	0.03	79.71 +/- 26.60	71.08 +/- 7.17	0.01
OCT GCL Superior nasal	70.71 +/- 8.00	76.60 +/- 14.18	0.04	73.21 +/- 6.58	73.89 +/- 5.74	0.61
OCT GCL Inferior	67.43 +/- 4.01	69.53 +/- 11.32	0.34	69.64 +/- 4.77	67.21 +/- 7.39	0.11
OCT GCL Inferior temporal	72.79 +/- 5.29	72.88 +/- 8.78	0.96	72.14 +/- 5.08	71.17 +/- 10.41	0.64
OCT GCL inferior nasal	72.71 +/- 6.42	74.58 +/- 11.09	0.41	74.11 +/- 7.54	72.90 +/- 5.68	0.39

Table 5. Comparison of Retinal Nerve Fibre Layer (RNFL) thickness between chronic and episodic migraine patients

Variable	Right eye		P	Left eye		P
	Chronic Mean +/- SD	Episodic Mean +/- SD		Chronic Mean +/- SD	Episodic Mean +/- SD	
OCT RNFL average thickness	106.07 +/- 10.72	106.28 +/- 10.55	0.9	98 +/- 16.66	101.35 +/- 14.82	0.33
OCT RNFL Superior	128.11 +/- 16.75	130.44 +/- 16.95	0.5	120.96 +/- 26.09	130.99 +/- 20.37	0.06
OCT RNFL Inferior	136.89 +/- 17.97	128.92 +/- 27.35	0.1	129.79 +/- 21	130.03 +/- 22	0.96
OCT RNFL Temporal	67.18 +/- 27.9	81.04 +/- 11.08	0.01	74.04 +/- 6.22	69.9 +/- 6.30	0.22
OCT RNFL Nasal	78.21 +/- 11.08	90.06 +/- 24.11	0.01	72.39 +/- 9.8	77.42 +/- 19.6	0.21

where scintillating scotoma and blurry vision were more frequently reported (9,10). Because only five patients had aura, our study was underpowered to analyse RNFL and GCL changes specifically in migraine with aura.

Previous OCT studies have reported that migraine, especially migraine with aura, may be associated with thinning of RNFL and GCL compared with controls (11,12). Labib et al. and Kanar et al. found greater reductions in RNFL and GCL thickness in patients with aura than in those without aura, which has been attributed to repeated episodes of cerebral hypoperfusion in the posterior cerebral circulation during attacks (11,12). In our study, the number of aura patients was too small to permit a separate analysis, and our overall case-control comparison did not show a significant difference in GCL thickness between migraine and controls. Our findings therefore suggest that, in an unselected migraine population with predominantly non-aura migraine, GCL changes may be subtle or absent, whereas RNFL changes may be more readily detectable.

Ischemic changes in the central nervous system of migraine patients can present as white matter hyperintensities (WMHs) on MRI (13). These lesions are not specific to migraine and may also be related to hypertension, stroke and other vascular conditions (13). In our cohort, only two patients had WMHs after other causes had been excluded, and we could not establish a correlation between WMHs and RNFL or GCL thickness due to the very small numbers. This is consistent with studies that have not found a clear association between WMHs and retinal structural changes in

migraine (13). Thus, while both WMHs and retinal thinning may reflect microvascular or neurovascular involvement, our data do not support a direct one-to-one relationship.

Yuan et al. have reported rare cases of retinal ischemic changes, such as cotton wool spots, in migraine patients (14). However, in our study and in most published series, clinical fundus examination did not reveal obvious structural retinal abnormalities (14). This underscores the value of OCT for detecting subtle changes in RNFL and GCL thickness when conventional ophthalmoscopy appears normal. In our cohort, OCT revealed a significant decrease in average RNFL thickness (mean 106 μ m) in the right eye of migraine patients compared with controls, along with significant thinning in the superior (mean 129 μ m) and nasal (mean 80 μ m) quadrants of the right eye. Similar superior quadrant thinning has been demonstrated by Gipponi et al. and Kirbas et al. in migraine patients compared with healthy controls (15,16) İlke Bahçeci et al. reported reduced RNFL thickness in the nasal quadrant in migraine, which is consistent with our nasal quadrant finding (17). Martinez et al. described significant RNFL thinning confined to the temporal quadrant, indicating that different quadrants may be preferentially affected in different cohorts (18,19). Taken together, these studies and our results suggest that migraine-related RNFL changes can involve various quadrants and do not follow a single stereotyped pattern, unlike glaucoma, where inferior quadrant thinning is often considered a hallmark diagnostic feature (16-19).

In our case–control analysis, we did not find significant GCL differences between migraine patients and controls, whereas in the chronic versus episodic subgroup analysis we observed GCL thinning in the superotemporal and superonasal quadrants of the right eye in chronic migraine and superotemporal GCL thinning in the left eye in episodic migraine. The unilateral and partially discordant nature of these findings makes their biological significance uncertain. One proposed explanation for retinal structural changes in migraine is that repeated attacks, particularly in chronic migraine, may lead to cumulative neurovascular stress and subtle axonal or neuronal loss over time (11,12). However, the retinal ganglion cells and their axons measured by OCT are distinct from cortical neurons, and our cross-sectional design cannot establish a direct causal pathway from cerebral hypoperfusion to retinal thinning (1–3,11–13). Moreover, we did not systematically record the side of hemicranial headache, so we cannot determine whether the right-eye-predominant RNFL thinning in our data corresponds to the clinically more symptomatic side. As a result, the side-specific differences observed in this study should be regarded as exploratory and interpreted with caution.

Migraine and glaucoma share several proposed pathophysiological mechanisms, including vascular dysregulation and reduced ocular blood flow, and both conditions have been associated with RNFL thinning (11–13). In glaucoma, decreased perfusion of the optic nerve head and peripapillary retina can cause ischemic damage to the GCL and RNFL, and it has been suggested that recurrent vasospastic events in migraine might exacerbate such damage in susceptible individuals (11–13). To isolate migraine-related changes in our study, we excluded patients with systemic comorbidities such as diabetes and hypertension and ocular comorbidities such as glaucoma. Nevertheless, our findings highlight that when ophthalmologists encounter RNFL thinning in relatively young patients, particularly in the fifth decade, it may be important to enquire about a history of migraine before attributing the changes solely to glaucoma. The possible coexistence of both conditions should also be considered, as this may lead to more pronounced RNFL loss.

Limitations

Our study has several limitations. We did not document headache laterality, which prevented us from correlating ipsilateral or contralateral retinal changes with the clinically more affected side, thereby limiting interpretation of unilateral OCT findings. A standardised severity or disability score for migraine was not used, so we could not examine dose–response relationships between attack burden and retinal thickness. The small number of patients with aura precluded meaningful comparison between migraine with and without aura, despite evidence that aura may be associated

with more pronounced retinal thinning (11,12). The low frequency of WMHs also prevented any robust analysis of their relationship with OCT parameters (13). The number of patients with MRI-detected white matter lesions was very low, precluding robust analysis of any association with OCT parameters. Although we carefully excluded systemic and ocular comorbidities that might affect RNFL or GCL thickness, unmeasured confounders and inter-individual variability in retinal anatomy cannot be completely ruled out. Finally, the cross-sectional design means we cannot determine whether the observed RNFL and GCL changes represent stable traits or progressive alterations over time. Longitudinal studies with detailed phenotyping, including headache laterality and severity, as well as repeated OCT measurements, are needed to clarify the temporal evolution and clinical implications of retinal changes in migraine.

Conclusion

In this SD-OCT-based case–control study, migraine patients demonstrated modest, quadrant-specific reductions in RNFL thickness in the right eye compared with healthy controls, while overall GCL thickness did not differ significantly between groups. Within the migraine cohort, chronic migraine was associated with more pronounced RNFL and GCL thinning in selected quadrants of the right eye than episodic migraine, although laterality patterns were inconsistent and should be interpreted cautiously. These findings suggest that recurrent migraine may be associated with subtle structural differences in the retina, particularly in patients with chronic disease, but the underlying mechanisms and clinical significance remain to be fully elucidated. Larger, longitudinal studies that incorporate detailed clinical phenotyping, headache laterality and functional visual assessments are needed to clarify whether these OCT changes reflect progressive neurovascular or neurodegenerative processes in migraine.

Disclosures

Ethics Committee Approval: This study was approved by the Ramaiah Medical College Ethics Committee (Date: 22/07/2022, No: MSRMC/EC/PG-97/07-2022).

Informed Consent: Written informed consent was obtained from all participants in their vernacular language before enrolment.

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Outcomes and Safety of Femtosecond Laser-Assisted Phacovitrectomy Using 25-Gauge Pars Plana Vitrectomy

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Abstract

Objectives: To evaluate the safety, visual outcomes, and complication profile of femtosecond laser-assisted cataract surgery (FLACS) combined with 25-gauge pars plana vitrectomy (PPV) in patients with concurrent cataract and vitreoretinal disease.

Methods: This retrospective study included 57 eyes of 57 patients who underwent FLACS with a standardized 4.8-mm capsulotomy followed by 25-gauge PPV at a tertiary referral center in Istanbul, Türkiye, between August 2020 and May 2025. Data collected included intraoperative events, postoperative best-corrected visual acuity (BCVA, Snellen converted to logMAR for analysis), intraocular pressure (IOP), and complication rates over a mean follow-up of 15.8±1.8 months.

Results: Mean BCVA significantly improved from 0.68±0.34 logMAR preoperatively to 0.28±0.14 logMAR at 1 month, 0.19±0.11 logMAR at 3 months, and 0.15±0.14 logMAR at the final visit (all p<0.001). All eyes achieved meaningful visual recovery with stable and well-centered intraocular lenses and attached retinas. On postoperative day 1, post-hoc pairwise analysis revealed a significantly lower IOP in the air tamponade group compared with the SF6 and BSS groups (MD=-4.24, p<0.001); no significant IOP differences were found between groups at week 1, month 1, or month 3. Intraoperative complications included loss of cone suction (n=2, 3.5%) and incomplete capsulorhexis (n=2, 3.5%). Miosis occurred in 6 eyes (10.5%), and sclerotomy leakage requiring suturing in 7 eyes (12.3%).

Conclusion: Combined FLACS and 25-gauge PPV is a safe and effective option for the management of coexisting cataract and vitreoretinal pathologies. The procedure provides favorable anatomical and visual outcomes with a low incidence of intraoperative and postoperative complications, supporting its use in appropriately selected patients. Prospective controlled studies are warranted to confirm these findings.

Keywords: Cataract extraction, femtosecond laser-assisted cataract surgery, pars plana vitrectomy, phacovitrectomy, retinal diseases, vitrectomy

Introduction

The femtosecond laser is among the most significant technological innovations in modern ophthalmic surgery. Its application in cataract extraction was first described by Bali et al. in a small series of patients with coexisting cataract

and retinal pathologies undergoing combined femtosecond laser-assisted cataract surgery and sutureless 25-gauge pars plana vitrectomy (PPV) (1,2). Their encouraging results supported the feasibility of this technique and highlighted its potential advantages in phacovitrectomy.

Key Messages: Femtosecond laser-assisted cataract surgery combined with 25-gauge pars plana vitrectomy is a safe and effective surgical procedure with minimal technical difficulties in various vitreoretinal pathologies when careful, suitable case selection is conducted.

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In the past decade, combined femtosecond laser-assisted phacoemulsification and vitrectomy has gained increasing acceptance for the management of patients with concurrent cataract and vitreoretinal disease (3,4). The rationale stems from the high prevalence of cataract in patients requiring PPV and the benefits of addressing both anterior and posterior segment pathologies in a single surgical setting (5–8). Several studies have demonstrated favorable outcomes with this approach, reporting improvements in visual acuity and surgical efficiency while maintaining acceptable complication rates (9–14). In cataract surgery, femtosecond laser technology provides reproducible and precisely sized anterior capsulotomies, enhanced capsular stability, and optimized intraocular lens (IOL) centration, thereby minimizing postoperative tilt or decentration (15–18). These advantages are especially relevant in eyes undergoing vitrectomy, where zonular weakness or capsular instability can compromise IOL positioning. Recent studies confirmed that FLACS in vitrectomized eyes or in combined phacovitrectomy cases results in improved capsulotomy quality, reduced intraoperative complications, and favorable long-term refractive stability (19,20).

Despite these advantages, robust evidence from larger patient cohorts remains limited. Although previous studies have reported outcomes of femtosecond laser-assisted phacovitrectomy, most involved small case series or heterogeneous cohorts (9,10,12–14,20). To our knowledge, the present investigation represents the largest single-surgeon cohort from Turkey, providing valuable evidence on the feasibility and safety of FLACS combined with 25-gauge PPV. Our study contributes practical insights such as the routine use of manual corneal incisions, delayed intraocular lens implantation, and consistent capsulotomy diameter, which may improve IOL stability and surgical outcomes. The present retrospective study aims to evaluate the safety, visual outcomes, and complication profile of femtosecond laser-assisted cataract surgery (FLACS) combined with 25-gauge PPV in patients with coexisting cataract and vitreoretinal pathology, thereby contributing further clinical data to the growing literature on femtophacovitrectomy.

Methods

The medical records of patients who underwent combined femtosecond laser-assisted cataract surgery (FLACS) and 25-gauge pars plana vitrectomy (PPV) at our Hospital, Istanbul, Türkiye, between August 2020 and May 2025 were retrospectively reviewed. Institutional Review Board approval was obtained (Date: 31/10/2025, No: 2025/425), and all patients provided informed consent after receiving detailed information regarding the procedure. The study adhered to the tenets of the Declaration of Helsinki. All surgeries were performed by a single experienced vitreoretinal surgeon.

Demographic and clinical data, including age, sex, laterality, systemic comorbidities (e.g., diabetes mellitus and hypertension when present), lens status (phakic/pseudophakic), medical and ophthalmologic history, and pre- and postoperative best-corrected visual acuity (BCVA) and intraocular pressure (IOP) were collected. Cataract severity was graded preoperatively at the slit lamp according to the Lens Opacities Classification System III (LOCS III) (nuclear opalescence and nuclear color). For eyes with retinal detachment, preoperative characteristics were recorded, including etiology (rhegmatogenous vs tractional), macular status (macula-on vs macula-off), and extent of detachment (quadrants involved) based on clinical examination and available imaging.

Surgical Technique

Under topical anesthesia (proparacaine hydrochloride 0.5%), a femtosecond laser system (LENSAR Cataract Laser with Augmented Reality™, LENSAR Inc., Orlando, FL, USA) was used to create a standardized 4.8-mm anterior capsulotomy and to fragment the crystalline lens. No corneal incisions were created during this step. Subsequently, cataract extraction and vitrectomy were performed in a separate operating room. Peribulbar anesthesia (2% lidocaine hydrochloride) was administered.

Manual 2.2-mm clear corneal incisions were made in the superior temporal or superior nasal quadrant. The anterior chamber was filled with a viscoelastic agent. The capsulotomy was completed using forceps, followed by hydrodissection and phacoemulsification of the nucleus. Cortical remnants were aspirated, and capsule polishing was performed on both anterior and posterior surfaces (Centurion Vision System, Alcon Laboratories Inc., Fort Worth, TX, USA). No corneal wound hydration or suturing was applied.

A standard 25-gauge transconjunctival vitrectomy was performed using the EVA system (Dutch Ophthalmic Research Center, Zuidland, Netherlands) under a wide-angle viewing system (Resight, Carl Zeiss Meditec AG, Jena, Germany). Trocars were placed 3.5 mm posterior to the limbus at a 45° transconjunctival angle. After core vitrectomy, posterior hyaloid detachment was induced, if attached, using 500 mmHg suction above the optic disc. For peripheral vitreous shaving, scleral indentation and chandelier illumination were employed.

In cases of epiretinal membrane or macular hole, membrane blue dye was injected onto the macula with irrigation pressure reduced to 15 mmHg. The dye was removed after 30 seconds by passive aspiration, and epiretinal/internal limiting membranes were peeled. In retinal detachment cases, perfluorocarbon liquid was used to flatten the retina, followed by endolaser photocoagulation. At the end of surgery, a one-piece monofocal IOL was implanted into the capsular bag. After viscoelastic removal, the anterior chamber was

stabilized, and tamponade was applied with SF₆ gas in cases of macular hole or retinal detachment, air tamponade in selected cases, or balanced salt solution (BSS) in eyes with epiretinal membrane. The 4.8-mm capsulotomy diameter was standardized across all tamponade groups to ensure complete anterior capsule coverage of the IOL optic, thereby minimizing the risk of IOL decentration; a consideration of particular importance in gas-tamponade cases where buoyant forces can displace the IOL posteriorly.

All trocars were removed at the end of the procedure, and sclerotomy sites were checked for leakage. In eyes with persistent leakage, 8-0 sutures were placed. Intracameral antibiotics were administered before closure.

Postoperative Care

Patients with gas tamponade were observed for two hours postoperatively and instructed to avoid supine positioning for three days. Topical moxifloxacin 0.5% (Vigamox, Alcon, Fort Worth, TX, USA) and prednisolone acetate 1% (Pred Forte, Allergan, Irvine, CA, USA) were prescribed five times daily for one week. Antibiotic drops were discontinued after one week, while steroids were tapered over three weeks (3×/day). Antiglaucoma drops were added when IOP exceeded 21 mmHg on two consecutive measurements or when a single measurement exceeded 30 mmHg. Follow-up examinations included refraction, BCVA, IOP measurement, slit-lamp biomicroscopy, dilated fundus examination, and SD-OCT imaging. Sutures, when present, were removed during the first postoperative week under topical anesthesia.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used for demographic and clinical variables. Pre- and postoperative BCVA values (logMAR) were compared. As BCVA differences were not normally distributed, the Wilcoxon signed-rank test was applied. A *p*-value <0.05 was considered statistically significant. Effect sizes (*r*) for Wilcoxon signed-rank tests were calculated as $Z/\sqrt{N}$ to quantify the magnitude of changes, with values of 0.1, 0.3, and 0.5 considered small, medium, and large, respectively. Postoperative IOP values were compared across the three tamponade groups (SF₆ gas, air, and BSS) using the Kruskal-Wallis test, with post-hoc pairwise comparisons performed using the Mann-Whitney U test where applicable. A *p*-value <0.05 was considered statistically significant.

Results

Descriptive characteristics, diagnoses, and ophthalmologic data of the patients are summarized in Table 1. The mean age of 57 patients (32 females [56.1%], 25 males [43.9%]) was 63.6±6.6 years (range, 52–78) at the time of surgery. A

total of 30 left eyes (52.7%) and 27 right eyes (47.3%) were included. The mean postoperative follow-up was 15.8±1.8 months (range, 6–24).

The mean BCVA (logMAR ± SD), which was 0.68±0.34 preoperatively, improved to 0.28±0.14, 0.19±0.11, and 0.15±0.14 logMAR at 1, 3, and the final visit postoperatively, respectively (Table 1). The Wilcoxon signed-rank test indicated statistically significant differences between preoperative and postoperative BCVA at 1 month (*p*<0.05), 3 months (*p*<0.05), and final follow-up ($Z=-5.39$, *p* ≤ 0.001, *r*=0.71). All patients (100%, *n*=57) demonstrated improvement in logMAR BCVA. The corresponding effect size was *r*=0.71, representing a large effect according to Cohen's criteria, thereby confirming the clinical relevance of the observed visual improvement.

Preoperative mean IOP was 15.48±3.22 mmHg (range, 12–22). Postoperative IOP was 18.29±2.17 mmHg (range, 8–26) on day 1, 15.46±4.38 mmHg (range, 12–25) at week 1, 14.24±3.02 mmHg (range, 11–21) at week 2, 15.48±2.62 mmHg (range, 12–20) at month 1, and 15.97±1.78 mmHg (range, 13–21) at month 6. When comparing the three tamponade groups (SF₆ gas, air, and BSS), no statistically significant overall difference in postoperative IOP was found across groups at postoperative week 1 (*p*=0.71), month 1 (*p*=0.33), or month 3 (*p*=0.35). However, post-hoc pairwise comparison at postoperative day 1 revealed a significantly lower IOP in the air tamponade group compared with the other groups (*MD*=−4.24, *p*<0.001). In the BSS group, mean IOP was 16.3±7.9 mmHg on postoperative day 1 and 15.5±4.9 mmHg at postoperative week 1.

When stratified by diagnosis, mean postoperative BCVA improved significantly in all groups. Eyes with epiretinal membrane improved from 0.48±0.21 to 0.13±0.09 logMAR, macular hole cases from 1.03±0.26 to 0.24±0.12 logMAR, retinal detachment from 0.91±0.32 to 0.28±0.14 logMAR, and vitreous hemorrhage from 1.08±0.25 to 0.11±0.08 logMAR (all *p*<0.05). Differences in baseline BCVA between diagnostic groups reflected variations in underlying pathology and surgical indication; for example, some epiretinal membrane cases underwent surgery primarily for symptomatic metamorphopsia and OCT-confirmed traction despite relatively preserved Snellen acuity.

The summary of demographic characteristics, diagnosis, and outcomes of patients is given in Table 2. During femtosecond laser application, loss of cone suction occurred in two patients (3.5%), and there was an incomplete capsulotomy/capsulorhexis in two patients (3.5%). As a result of femtosecond laser application, six patients developed miosis (10.5%). An 8/0 suture was applied to seven patients (12.3%) with continued leakage from the sclerotomy. Postoperatively, twelve patients developed subconjunctival hemorrhage

Table 1. Patients' demographic and ophthalmologic data

Patient No	Age	Eye (R/L)	Sex	Diagnosis	Pre-op BCVA (logMAR)	Post-op BCVA (logMAR)	Follow-up (months)
1	64	L	F	MH	1.3	0.5	16
2	67	L	F	ERM	0.7	0.2	18
3	58	R	F	MH	1.0	0.4	14
4	54	R	M	VH	1.0	0.1	7
5	52	R	F	RD	1.0	0.0	18
6	77	L	M	ERM	0.4	0.1	16
7	60	R	M	RD	0.7	0.1	12
8	75	L	F	ERM	0.5	0.2	12
9	62	R	F	MH	1.0	0.3	20
10	60	R	M	ERM	0.2	0.0	12
11	59	L	M	MH	0.7	0.2	22
12	72	R	F	ERM	0.4	0.1	18
13	60	L	F	VH	1.0	0.0	12
14	57	L	F	RD	1.3	0.2	14
15	62	L	M	ERM	0.2	0.0	8
16	64	R	F	ERM	0.3	0.1	14
17	65	R	M	RD	0.7	0.2	16
18	78	L	M	ERM	0.3	0.1	18
19	63	L	F	VH	0.7	0.1	12
20	65	R	F	MH	1.0	0.4	20
21	62	L	M	ERM	0.2	0.0	14
22	68	R	F	ERM	0.3	0.0	16
23	55	R	F	RD	1.0	0.1	24
24	72	R	M	ERM	0.3	0.1	18
25	66	L	M	ERM	0.3	0.0	14
26	56	L	F	RD	0.4	0.0	22
27	71	L	F	ERM	0.5	0.3	19
28	60	R	F	VH	1.3	0.1	14
29	59	L	M	RD	0.5	0.1	20
30	66	L	F	MH	1.0	0.4	14
31	61	R	M	MH	0.7	0.3	16
32	70	L	F	ERM	0.5	0.1	19
33	68	L	M	MH	1.3	0.7	16
34	53	R	M	VH	1.0	0.0	24
35	66	R	F	ERM	0.3	0.1	14
36	71	L	F	ERM	0.5	0.2	12
37	54	L	F	VH	1.0	0.1	12
38	66	R	M	ERM	0.2	0.0	16
39	63	L	F	ERM	0.4	0.1	14
40	67	R	M	RD	0.8	0.2	18
41	58	L	F	MH	1.0	0.3	16
42	72	R	F	ERM	0.5	0.2	12
43	64	R	M	VH	0.9	0.1	24

Table 1. Continued

Patient No	Age	Eye (R/L)	Sex	Diagnosis	Pre-op BCVA (logMAR)	Post-op BCVA (logMAR)	Follow-up (months)
44	70	L	M	ERM	0.3	0.0	14
45	62	R	F	MH	1.1	0.4	20
46	56	L	M	RD	0.7	0.1	16
47	68	R	F	ERM	0.4	0.1	18
48	61	L	M	VH	1.0	0.0	12
49	74	R	F	ERM	0.3	0.1	14
50	59	L	M	MH	0.9	0.2	22
51	66	R	F	RD	1.0	0.1	12
52	55	L	M	ERM	0.2	0.0	16
53	73	R	F	ERM	0.5	0.2	12
54	60	L	M	VH	1.1	0.1	18
55	65	R	F	MH	1.0	0.3	14
56	57	L	M	RD	0.8	0.2	12
57	69	R	F	ERM	0.4	0.1	16

L: Left; R: Right; F: Female; M: Male; ERM: Epiretinal membrane; VH: Vitreous hemorrhage; RD: Retinal detachment; MH: Macular hole; BCVA: Best corrected visual acuity

(21.1%) and fifteen patients developed posterior capsular opacification (26.3%). Cystoid macular edema occurred in four eyes (7.0%), and retinal detachment occurred in one eye (1.8%). No cases of endophthalmitis or intraocular lens dislocation were observed. All patients had clear corneas, well-centered and stable IOLs, and attached retinas at final follow-up.

Discussion

Combined phacovitrectomy has become an increasingly adopted approach for eyes with concomitant visually significant cataract and vitreoretinal pathology, as it enables single-session rehabilitation and avoids the challenges of cataract progression following pars plana vitrectomy (5,7,8). In this study, femtosecond laser–assisted cataract surgery (FLACS) combined with 25-gauge pars plana vitrectomy (PPV) resulted in significant and clinically meaningful improvements in visual acuity across all diagnostic subgroups, with a low rate of serious intraoperative and postoperative complications.

A principal advantage of FLACS in combined surgery is the ability to create a consistently sized, circular, and well-centered capsulotomy (15,17,18). We intentionally used a 4.8-mm capsulotomy to promote complete anterior capsule overlap of the intraocular lens (IOL) optic. This consideration is particularly relevant in cases in which gas or air tamponade is used (e.g., macular hole and many retinal detachment cases), where the postoperative buoyant force and altered anterior–posterior segment dynamics may predispose to IOL displacement (21–23). In our series, no cases of

IOL decentration, tilt, or dislocation were observed during follow-up, supporting the stability of this strategy in the setting of combined vitreoretinal surgery. Nevertheless, we acknowledge that objective refractive outcomes (e.g., spherical equivalent, astigmatism) were not uniformly available in this retrospective dataset; future prospective studies should incorporate standardized refraction and imaging-based centration metrics.

Our cohort included epiretinal membrane, macular hole, retinal detachment, and vitreous hemorrhage, reflecting real-world indications for combined surgery (6,8,24). As expected, the magnitude of postoperative visual improvement varied by diagnosis. Eyes with vitreous hemorrhage demonstrated marked gain due to removal of media opacity and clearance of vitreous pathology, whereas macular hole eyes, despite significant improvement, may show relatively limited recovery because final acuity depends on foveal restoration. In epiretinal membrane, surgery may be indicated due to symptomatic metamorphopsia and OCT-confirmed traction even when baseline Snellen acuity is relatively preserved; therefore, heterogeneity in baseline BCVA among subgroups is clinically plausible and consistent with contemporary surgical decision-making.

Early postoperative IOP behavior is clinically important after combined procedures, particularly in tamponade cases. In our study, IOP was transiently higher in the early postoperative period overall, and subgroup analysis across the three tamponade groups (SF6 gas, air, and BSS) demonstrated no significant overall difference in IOP at postoperative week

Table 2. Demographic characteristics, diagnosis, outcomes of patients, and complications

Characteristics	Values
No. of Patients	57
Sex (M/F)	25/32
Mean Age (years) $\pm$ SD	63.6 $\pm$ 6.6
Eye (Left/Right)	30/27
Pre-surgery diagnostic	
Epiretinal membrane (ERM)	25
Macular hole (MH)	12
Retinal detachment (RD)	13
Vitreous hemorrhage (VH)	7
Pre-op BCVA (LogMar) (mean $\pm$ SD)	0.68 $\pm$ 0.34
Post-op BCVA (LogMar) (mean $\pm$ SD)	0.15 $\pm$ 0.14
Post-op follow-up (months)	15.8 $\pm$ 1.8
Type of femtolaser	Lensar
Type of vitrectomy	dorc
Intraocular tamponade	
BSS	25
Gas (SF ₆)	22
Air	10
Endolaser	16
Suture for sclerotomy	7 (12.3%)
Miosis	6 (10.5%)
Subconjunctival hemorrhage	12 (21.1%)
Posterior capsular opacification	15 (26.3%)
Cystoid macular edema	4 (7.0%)
Retinal detachment (postop)	1 (1.8%)
Endophthalmitis	0
IOL dislocation	0

BCVA: Best corrected visual acuity; F: Female; M: Male; BSS: Balanced salt solution

1, month 1, or month 3 ($p=0.71$, 0.33 , and 0.35 , respectively); however, post-hoc pairwise comparison at postoperative day 1 revealed a significantly lower IOP in the air tamponade group compared with the other groups ($MD=-4.24$, $p<0.001$) while no significant differences were detected at 7 days, 1 month, or 3 months. These findings are consistent with the known early IOP effects of tamponade choice and underscore the importance of close IOP monitoring during the first postoperative week.

In terms of wound integrity, sclerotomy leakage requiring suturing occurred in 12.3% of eyes. This rate is within the range reported for 25-gauge PPV in routine clinical practice (12,13) and may reflect factors such as case complexity, surgical duration, ocular rigidity, and individual wound architecture rather than an FLACS-specific effect. Importantly, no

endophthalmitis was observed, and all eyes had attached retinas and stable IOL position at final follow-up.

The observed intraoperative events related to FLACS, such as suction loss and incomplete capsulotomy, were infrequent. Intraoperative miosis occurred in a minority of cases and is a recognized phenomenon associated with femtosecond laser application, likely mediated by prostaglandin release (1,12); this may require additional pharmacologic pupil expansion or mechanical strategies during surgery. These potential disadvantages should be weighed against the benefits of capsulotomy precision and lens fragmentation (25,26). Additional disadvantages of FLACS in combined phacovitrectomy include increased cost, longer procedural time, and the need for coordination between laser and operating room workflows; these considerations may influence adoption in resource-limited settings.

Several limitations of this study warrant acknowledgment. First, the absence of a concurrent manual phacovitrectomy comparison group prevents definitive conclusions regarding the superiority of FLACS over conventional phacoemulsification in the setting of combined vitreoretinal surgery; our findings can only be contextualized against outcomes reported in prior series of conventional combined phacovitrectomy (6–8,21,23,24), where differences in patient populations, surgical technique, tamponade selection, and follow-up duration limit direct comparison. Second, the retrospective design introduces inherent selection bias and precludes standardized data collection across all variables. Third, the cohort is diagnostically heterogeneous, comprising epiretinal membrane, macular hole, retinal detachment, and vitreous hemorrhage, which limits the generalizability of pooled visual acuity outcomes to any single pathology and contributes to the wide range of preoperative BCVA values observed. Fourth, standardized postoperative refractive data (spherical equivalent, cylinder, and biometric prediction error) were not uniformly available in this retrospective dataset, precluding formal evaluation of refractive predictability. Future prospective studies with a concurrent control group, stratified analysis by diagnosis, and standardized refractive outcome reporting are needed to more definitively establish the role of FLACS in combined phacovitrectomy. Despite these limitations, our results support that FLACS combined with 25-gauge PPV is a safe and effective approach, with favorable visual and anatomical outcomes across common vitreoretinal indications.

Conclusion

Femtosecond laser-assisted cataract surgery combined with 25-gauge pars plana vitrectomy provides high anatomical success and significant visual improvement in eyes with concurrent cataract and vitreoretinal disease. The procedure

demonstrated a low rate of intraoperative and postoperative complications, supporting its role as a safe and effective option in appropriately selected patients.

Disclosures

Ethics Committee Approval: This study was approved by the Bezmialem University Ethics Committee (Date: 31/10/2025, No: 2025/425).

Informed Consent: All patients provided informed consent after receiving detailed information regarding the procedure.

Conflict of Interest: The authors report no conflicts of interest

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Effect of Internal Limiting Membrane Peeling on Macular and Optic Disc Vascular Density Following Epiretinal Membrane Surgery

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Abstract

Objectives: To investigate the effect of internal limiting membrane peeling on vascular density of macula and optic disc in idiopathic epiretinal membrane surgery.

Methods: Thirty-six eyes of 36 patients who underwent combined phacoemulsification with intraocular lens implantation followed by pars plana vitrectomy and epiretinal membrane (ERM) removal were prospectively included in this study. Based on the intraoperative status of the internal limiting membrane (ILM) after ERM removal, the eyes were classified into two groups: The ILM-peeled group (n=22) and the ILM-unpeeled group (n=14). Vascular density of superficial capillary plexus, deep capillary plexus, optic nerve head and radial peripapillary capillary plexus were obtained by optical coherence tomography angiography before and up to 3 months after surgery.

Results: After surgery, superficial capillary plexus fovea vascular density and foveal thickness decreased significantly in the internal limiting membrane unpeeled group. ($p=0.016$; $p=0.048$ respectively). There was no significant change in superficial capillary plexus paravofea ($p=0.257$), deep capillary plexus fovea ($p=0.569$), deep capillary plexus parafovea ($p=0.457$), optic nerve head ($p=0.545$) and radial peripapillary capillary plexus ($p=0.975$) vascular density comparison between groups.

Conclusion: Internal limiting membrane peeling has no significant effect on deep capillary plexus and the optic disc vascular density, but can reduce vascular density in the superficial capillary plexus after idiopathic epiretinal membrane peeling surgery.

Keywords: Internal limiting membrane, epiretinal membrane surgery, optical coherence tomography angiography, macula vascular density, optic disc vascular density

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Introduction

Epiretinal membrane (ERM) has been termed 'preretinal macular fibrosis' or 'surface wrinkling retinopathy' in the past due to the fundus appearance resulting from contraction. It is characterized by fibrocellular proliferation on the inner retinal surface, leading to retinal distortion, macular thickening, and progressive visual impairment (1).

Pars plana vitrectomy with membrane peeling remains the standard surgical treatment for symptomatic cases, providing functional and anatomical improvement in most patients. However, the role of internal limiting membrane (ILM) peeling in ERM surgery remains controversial. While some surgeons advocate routine ILM peeling to reduce ERM recurrence and facilitate complete removal of residual tractional components, others argue that additional ILM manipulation may induce unnecessary trauma to Müller cell footplates and inner retinal layers, potentially affecting retinal function. The ILM is firmly attached to Müller cell footplates, and mechanical stress during peeling may result in Müller cell injury, potentially affecting retinal architecture and microvascular integrity (2). In addition, ILM removal may alter the biomechanical properties of the retina and lead to retinal displacement, particularly changes in the position and configuration of the foveal region (3). Alterations in retinal nerve fiber layer thickness, including transient postoperative thickening followed by subsequent thinning, have also been reported after ILM peeling and are thought to reflect Müller cell dysfunction and inner retinal remodeling (4). Consequently, whether ILM peeling provides additional microstructural or functional benefit beyond ERM removal alone is still debated in the literature.

Optical coherence tomography angiography (OCT-A), a non-invasive method with erythrocyte motion detection technology, can evaluate retinal microvasculature segmentally and quantitatively using a novel algorithm. These properties, make it a very suitable method for evaluating the effect of ERM on retinal microvasculature (5). Although previous OCT-A studies have evaluated vascular changes after ERM surgery, the specific contribution of ILM peeling to macular and optic disc microvascular remodeling remains unclear. Therefore, we aimed to evaluate the effects of ILM peeling on macular and optic disc microvascular parameters using OCT-A.

Methods

This prospective, nonrandomized, interventional study was approved by the clinical research ethics committee of Kahramanmaraş Sütçü İmam University Faculty of Medicine (Ethics committee date: 16.10.2019, decision number: 2019/18/10, approval number: 312. It was not prospectively registered in

a clinical trial registry). Written informed consent in accordance with the Declaration of Helsinki was obtained from all participants. Thirty-six eyes of 36 patients who underwent pars plana vitrectomy (PPV) by a single surgeon for symptomatic idiopathic ERM were evaluated.

Participants

Only idiopathic ERMs were included in the study. ERM was secondary to other ocular diseases or previous intraocular surgery; patients using chronic ocular drugs or with optic disc pathology were excluded. Epiretinal membranes were graded according to the optical coherence tomography-based Govetto classification. Only patients with stage 2 or stage 3 idiopathic ERM were included in the study. Other exclusion criteria were severe media opacity, undetectable foveal localization due to severe contraction. OCT-A images were reviewed before analysis regarding image quality, acquisition artifacts, and segmentation accuracy. Scans with a signal strength index below 50% and cases with significant segmentation errors that could affect vascular density measurements were excluded. Vascular density parameters were obtained from the automated segmentation analysis provided by the OCT-A device software. OCT-A was performed after a complete ophthalmologic examination at preoperative and 1st week, 1st month, and 3rd month after surgery. Best-corrected visual acuity (BCVA) was recorded using the Snellen chart as part of routine clinical evaluation. Since visual acuity was not a study outcome Snellen values were not converted to logMAR.

Optical Coherence Tomography Angiography Protocol

Angiographic images were obtained with OCT-A (RTVue; Optovue Inc. Fremont, CA, USA). Superficial capillary plexus (SCP), deep capillary plexus (DCP), Optic nerve head (ONH), Radial peripapillary capillary plexus (RPCP), and retinal thickness were automatically segmented by the software. Fovea-centered (6x6 mm angio-retina) image was obtained for macular angioanalysis. Macular angioanalysis and retinal thickness data were automatically calculated from the fovea-centered Early Treatment Diabetic Retinopathy Study (ETDRS) grid (3mm diameter, central 1 mm fovea, peripheral 2 mm parafovea) (Fig. 1A). Vascular density (VD) was quantified by the percentage of vascular area in the selected area. The image (4.5x 4.5 mm angio-disc) was obtained for optic disc angioanalysis. Optic disc data were calculated from an automatically determined ring 750 μ m wider than the edges of the optical disc (Fig. 1B). The percentage of vascular area in this 750 μ m-thick elliptical ring corresponding to the peripapillary region was quantified as peripapillary VD.

Surgical Technique

All participants underwent phacoemulsification and intraocular lens implantation with the Centurion-Vision System

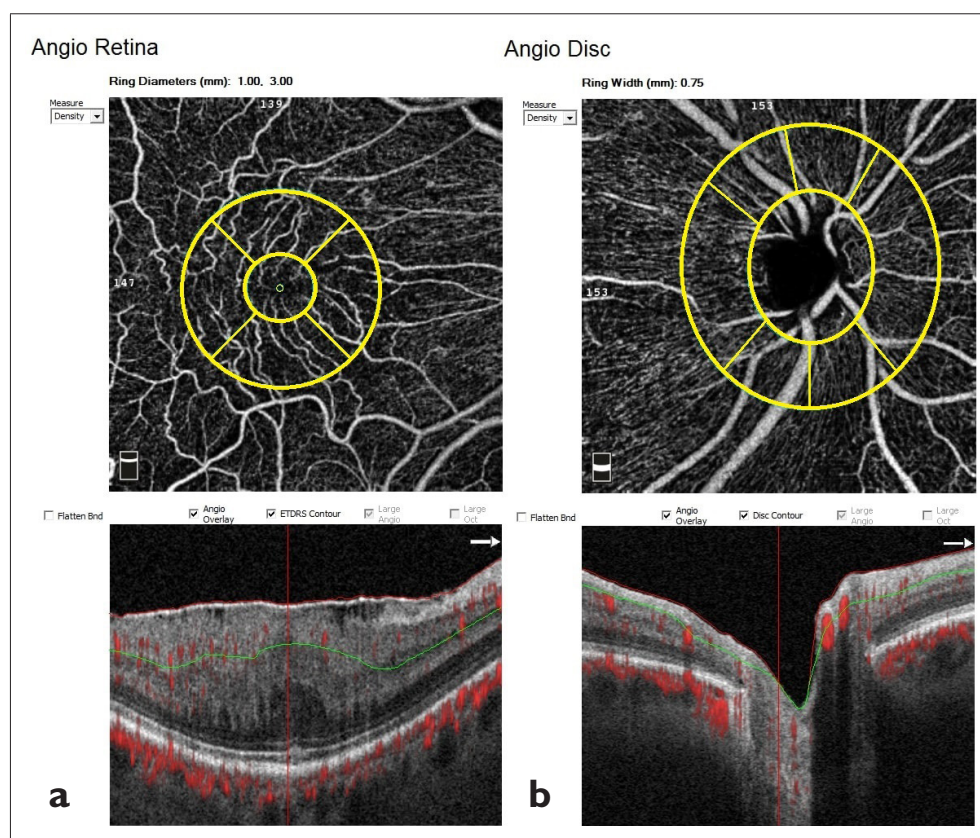


Figure 1. Automatic measurement of macula and optic disc vascular density with optic coherence tomography angiography. **(a)** Macular angioanalysis and retinal thickness data were automatically calculated from the fovea-centered Early Treatment Diabetic Retinopathy Study (ETDRS) grid (3mm diameter; central 1 mm fovea, peripheral 2 mm parafovea). Vascular density was quantified by the percentage of vascular area in the selected area. **(b)** Optic disc data were calculated from an automatically determined ring 750 μ m wider than the edges of the optical disc. The percentage of vascular area in this 750 μ m-thick elliptical ring corresponding to the peripapillary region was quantified as peripapillary vascular density.

(Alcon Laboratories, Inc. Texas, USA) device. Surgery continued with a 3-port 23-gauge transconjunctival sutureless PPV with an EVA phaco-vitrectomy system (DORC, The Netherlands) device. The ERM and ILM were stained with Mebrane-Blue-Dual (DORC, The Netherlands) dye and were peeled with 23-Gauge Eckardt end-gripping intraocular microforceps (DORC, The Netherlands).

After ERM removal, the integrity of the underlying ILM was routinely assessed under staining with Membrane Blue Dual. Eyes were categorized according to whether the ILM remained intact (14 patients) or was removed together with the ERM. Cases with uncertain ILM status were excluded. If the ILM was peeled, ILM peeling was performed in a standardized manner with an intended diameter of approximately 1500 μ m centered on the fovea (22 patients). The surgery was completed without the use of buffering material.

Primary outcomes were the change in retinal microvascular parameters measured by OCT-A, particularly vessel density changes in the SCP and DCP and in optic disc after

surgery. Other OCT and OCT-A parameters have been considered secondary outcomes.

Statistical Analysis

Statistical analysis was performed with SPSS software version 20.0 (SPSS Inc, Chicago, USA). Continuous variables are shown as mean $\pm$ standard deviation (SD), (minimum-maximum), and numbers for categorical variables. Pearson Chi-square test was used for categorical variables and the independent sample T-test was used for continuous variables in comparison of demographic data. The normal distribution of repeated measurements was checked with the Shapiro-Wilk test and the kurtosis and skewness values.

Repeated measurements within the ILM peeled or ILM unpeeled group were analyzed with repeated analysis of variance ANOVA. Pairwise comparisons were presented with Bonferroni correction. Although p values of repeated analysis of variance ANOVA are presented as standard in the tables, only values that reached statistical significance were

shown for pairwise comparisons. The differences between the first measurement and the last measurement of ILM peeled and ILM unpeeled groups were compared with an independent sample t-test. Analysis of differences was used to compare ILM peeled and ILM unpeeled groups. P value <0.05 was considered statistically significant.

Results

There was no statistically significant difference between the groups in terms of age and gender (Table 1).

Macular angioanalysis is shown in Table 2. SCP and DCP fovea VD were not significantly changed in the ILM peeled group ($p=0.989$; $p=0.095$ respectively). In the ILM unpeeled group, SCP fovea VD decreased significantly in the postoperative 3rd month compared to preoperative ($p=0.025$). This significant decrease in subgroup analysis was also significant when comparing between groups ($p=0.016$). Although parafovea VD showed a transient decrease in subgroup analysis at 1 week in the ILM peeled group, both SCP and DCP parafovea VD changes were not significant in comparison between groups ($p=0.257$; $p=0.457$, respectively).

Retinal thickness parameters are shown in Table 3. Foveal thickness did not change significantly in the ILM peeled group ($p=0.331$). In the ILM unpeeled group, foveal thickness reduced significantly in the postoperative 3rd month compared to the preoperative level ($p=0.012$). This significant reduction in pairwise subgroup analysis was also significant in comparison between groups ($p=0.048$). Parafoveal thickness was significantly reduced in both groups at 3 months postoperatively, ILM peeled ($p=0.050$) and unpeeled ($p=0.030$). However, the reduction levels were similar in both groups ($p=0.968$).

Inner retinal thickness did not change significantly in the ILM unpeeled group ($p=0.230$). In the ILM peeled group, inner retinal thickness increased in the 1st week and then progressively thinned, in the postoperative 3rd month compared to preoperative thickness ($p=0.001$). However, this

significant thinning in the subgroup analysis was not significant in comparison between groups ($p=0.419$).

Optic disc angioanalysis is shown in Table 4. Peripapillary VD showed a similar course in both groups, decreasing in the first week and then increasing again. Although this decrease in the 1st week could reach significant levels in the ILM peeled group, no significant difference was found between the preoperative and postoperative 3rd month in pairwise subgroup analysis. VD changes were not significant in comparison between groups in ONH ($p=0.545$) and RPCP ($p=0.975$).

BCVA increased significantly in both groups at 3 months postoperatively, ILM peeled ($p=0.006$) and unpeeled ($p=0.042$). However, the level of increase in BCVA was not significant in the comparison between groups ($p=0.768$) (Table 5).

Discussion

Centripetal contraction of the ERM drags vascular structures topographically toward the fovea (6-12). Although ERM peeling should theoretically shift vascularity from the fovea to the periphery, topographic change is not the only parameter affecting vascular density. There are functional changes such as recanalization and improvement in vascular tortuosity and occlusions with the relaxation of centripetal contraction (12,13). Another parameter that will affect the change in the OCT-A parameter is the ERM grade (8). For these reasons, OCT-A studies report conflicting results.

Chen et al. (10) reported the expansion of the foveal avascular zone (FAZ), a decrease in fovea VD, and an increase in parafovea VD in SCP and DCP after ERM peeling. The author explained these results of vascular density normalization by the relaxation of centripetal traction. However, there are also different OCT-A studies indicating that there is no significant change in total retinal perfusion, fovea VD, or FAZ after ERM peeling (11,14-16). Some authors associate centripetal contraction that persists after ERM removal with ILM peeling (6,16,17). Although these mentioned studies did not have an ILM unpeeling group, they can provide insight into ILM peeling. In our study, foveaVD and parafoveaVD did not change in the ILM peeling group. This may reflect the balancing of the centrifugal effect caused by ERM peeling with the centripetal effect caused by ILM peeling.

When OCT-A studies comparing ILM peeling and unpeeling groups in ERM surgery were reviewed; Ericcek et al. (18) reported that there was no significant change in FAZ, flow, and Parafoveal VD after surgery in both groups. The authors suggested that the effect of surgery on microvascular structures was limited. In the study of Muller et al. (19), the results regarding the macular microvasculature demonstrated no difference with peeling of the ILM. Another sim-

Table 1. Demographic characteristics of study groups

	ILM peeled (n=22)	ILM Unpeeled (n=14)	P
Age, year mean±SD (min-max)	66.8±7.1 (50-76)	71.5±7.1 (61-89)	0.063*
Gender n (%)			
Male	14 (63.6)	10 (71.4)	0.727**
Female	8 (36.4)	4 (28.6)	

All data are presented as the means ± SD, (min-max). SD: standard deviation
Min: minimum Max: maximum ILM: internal limiting membrane. * Independent sample T-test ** Pearson Chi-square test.

Table 2. Macular angioanalysis

	Preoperative	Postoperative			p		
		1. Week	1. Month	3. Month	Within Group (a)	Pairwise Subgroup (b)	Between Groups (c)
SCP Fovea VD (%)							
ILM Peeled	35.79±6.08 (20.84-44.54)	37.30±4.87 (29.38-44.74)	36.93±5.18 (28.64-46.57)	37.91±5.87 (25.78-46.77)	0.989		0.016
ILM Unpeeled	38.90±6.53 (28.54-54.72)	33.77±5.12 (26.96-43.41)	32.31±6.28 (26.72-48.40)	30.61±4.87 (23.65-40.00)	0.008	(preop-1.week) 0.040 (preop-1.month) 0.031 (preop-3.month) 0.025	
DCP Fovea VD (%)							
ILM Peeled	34.17±8.87 (15.85-48.79)	40.17±6.33 (30.27-51.26)	35.93±7.32 (16.10-48.84)	34.97±7.66 (18.67-46.91)	0.095		0.569
ILM Unpeeled	30.16±11.21 (7.60-48.30)	29.83±8.37 (12.59-40.79)	30.40±5.87 (19.65-39.75)	30.47±6.66 (21.33-43.41)	0.695		
SCP Parafovea VD (%)							
ILM Peeled	44.13±3.84 (37.77-53.81)	42.76±3.04 (36.12-46.84)	44.13±4.76 (35.12-52.65)	45.53±4.99 (34.01-52.52)	0.002	(preop-1.week) 0.030 (1.week-3.month) <0.001	0.257
ILM Unpeeled	41.80±6.01 (33.49-52.62)	42.62±4.95 (35.09-46.16)	44.46±4.86 (35.35-51.48)	44.58±7.55 (31.67-55.65)	0.109		
DCP Parafovea VD (%)							
ILM Peeled	50.49±4.54 (39.16-58.29)	48.19±5.15 (40.27-57.32)	50.42±4.93 (42.07-60.52)	52.01±5.53 (41.82-60.07)	<0.001	(preop-1.week) 0.026 (1.week-1.month) 0.011 (1.week-3.month) 0.009	0.457
ILM Unpeeled	45.65±7.06 (30.27-56.91)	46.56±7.05 (35.49-57.83)	48.48±6.55 (37.74-56.24)	50.18±5.27 (43.45-61.88)	0.419		

All data are presented as the means ± SD, (min-max). SD: standart deviation Min: minimum, Max: maximum, SCP: superficial capillary plexus, DCP: deep capillary plexus, ILM: internal limiting membrane, VD: vascular density, Preop: preoperative. (a) General linear model analysis of repeated measures (ANOVA) within each study group. (b) In pairwise comparison of subgroups, only values with p<0.05 are shown in subgroup analysis. (c) Comparison of the difference between the first measurement and the last measurement between ILM peeled and ILM unpeeled groups with independent sample t-test.

ilar study revealed that the retinal vascular tortuosity index and fovea VD after ERM surgery were similar in eyes with and without ILM peeling, and the authors suggested that ILM peeling had no additional effect on microvascular traction (20). Contrary to these studies, Kumagai et al. (3) demonstrated the centripetal movement caused by ILM peeling by comparing OCT-A with and without ILM peeling. They explained the centripetal movement that occurs after ILM peeling by the structural change in Müller cells that stretch the fovea centrifugally. We observed both SCP fovea VD and the foveal thickness significantly decreased in the ILM unpeeled group in our study, reflecting the centrifugal movement and foveal pit remodeling. In the study of Gabriel et al. (21) the change in FAZ and parafoveal VD was greater in the ILM unpeeled group than in the ILM peeled group. The authors emphasized that microvascular remodeling was more pronounced in the ILM unpeeled group. Similar to this study, although significant microvascular changes were observed in

the ILM unpeeled group we did not observe any significant microvascular changes in the ILM peeled group when compared to the preoperative and postoperative 3rd month. Li et al. (22) reported in their study on diabetic ERMs that ILM peeling delayed the improvement in DCP vascular parameters. However, we did not observe any significant change in DCP in either the ILM peeled or ILM unpeeled groups. On the contrary, there was a significant change in SCP in our study. The different results may be related to our participants having idiopathic ERM not diabetic.

In the subgroup analysis of the ILM peeled group, the inner retinal thickness tended to increase at week 1, but significant thinning was observed at the 3rd-month measurement. In the ILM unpeeled group, no change was observed in the inner retinal thickness over time. As it is known, the earliest change in the retina caused by ILM peeling is retinal nerve fiber layer (RNFL) edema. Edema can be detected as early as 1 week and completely regresses within 3 months (23,24).

Table 3. Comparison of retinal thickness within groups, subgroups, and between groups

	Preoperative	Postoperative			p		
		1. Week	1. Month	3. Month	Within Group (a)	Pairwise Subgroup (b)	Between Groups (c)
Fovea thickness (µm)							
ILM Peeled	422±86 (297-614)	412±56 (315-527)	411±49 (334-500)	394±58 (323-498)	0.331		0.048
ILM Unpeeled	437±85 (309-594)	379±82 (280-503)	358±77 (251-506)	348±88 (189-501)	0.001	(preop-1.week) 0.009 (preop-1.month) 0.003 (preop-3.month) 0.012 (1.month-3.month) 0.047	
Parafovea thickness (µm)							
ILM Peeled	398±56 (336-543)	385±28 (343-457)	374±24 (337-429)	360±32 (304-413)	0.011	(preop-3.month) 0.050 (1.week-3.month) 0.036 (1.month-3.month) 0.018	0.968
ILM Unpeeled	402±58 (321-537)	374±53 (301-492)	367±49 (288-453)	365±45 (281-455)	0.014	(preop-1.week) 0.011 (preop-1.month) 0.010 (preop-3.month) 0.030	
Inner retinal thickness (µm)							
ILM Peeled	153±10 (135-167)	160±10 (143-173)	147±13 (121-167)	137±19 (98-166)	<0.001	(preop-1.month) 0.018 (preop-3.month) 0.001 (1.week-1.month) 0.006 (1.week-3.month) 0.030 (1.month-3.month) 0.030	0.419
ILM Unpeeled	151±18 (105-172)	149±19 (105-171)	140±19 (106-166)	141±20 (99-166)	0.230		

All data are presented as the means ± SD, (min-max). SD: standart deviation Min: minimum, Max: maximum, µm: mikrometer, ILM: internal limiting membrane Preop: preoperative. **(a)** General linear model analysis of repeated measures within each study group. **(b)** In pairwise comparison of subgroups, only values with p<0.05 are shown in subgroup analysis. **(c)** Comparison of the difference between the first measurement and the last measurement between ILM peeled and ILM unpeeled groups with independent sample t-test.

Following the resolution of edema, thinning can be observed in the inner retina (24,25). Although it could not reach a significant level between groups, our inner retinal thickness result in subgroup analysis is consistent with the literature.

To the best of our knowledge, there are not OCT-A studies in the literature comparing the optic disc VD parameters of eyes with and without ILM peeling in patients with ERM. Kumagai et al. studied papilla-foveal distance and FAZ with OCT-A but not VD. After ILM peeling, the fovea is displaced towards the optic disc in their study (3). Yoon et al. (26) peeled the ERM and ILM in all cases. The authors suggested that ILM peeling caused microvascular damage starting from the inferior sector in the peripapillary VD. Contrary to this study change in vascular parameters of the optic disc was temporary in our study. Peripapillary VD of ONH and RPCP decreased in both groups at week 1. Although this decrease reached a significant level in the ILM peeled group, the parameters increased again to the baseline level, thus there was

no significant difference between the first and the last measurement in both groups. As a result of the effects of some factors affecting optic discs, such as mechanical trauma caused by intraocular fluid movement or vitreous detachment during surgery, dyes used in visualization, or surgical inflammation; transient diffuse peripapillary RNFL edema develops in the early postoperative period (23). The similar course in both groups in our study suggests that the reduction in optic disc parameters at week 1 may be related to factors induced by surgery as mentioned above, rather than ILM peeling.

Lee and Kim showed that foveal contour formation was more frequent and the fovea was thinner in the eyes without ILM peeling. Visual results were similar in eyes with and without ILM peeling in their study (27). Supporting this we observed a thinner fovea in the ILM unpeeled group and we attributed this to centripetal motion. Also similarly the increase in BCVA did not affect ILM peeling in our study. Özdek et al. (28) showed that the improvement in foveal

Table 4. Optic disc angioanalysis

	Preoperative	Postoperative			p		
		1. Week	1. Month	3. Month			
ONH Peripapillary VD (%)							
ILM Peeled	57.71±4.17 (48.93-64.04)	51.96±4.88 (39.36-58.48)	54.76±4.20 (44.94-62.33)	56.39±4.13 (44.26-63.89)	<0.001	(preop-1.week) 0.015 (1.week-1.month) 0.012 (1.week-3.month) 0.001	0.545
ILM Unpeeled	53.56±6.13 (37.01-60.67)	51.90±6.65 (36.27-60.81)	54.49±4.70 (47.50-60.63)	55.51±4.89 (43.81-62.03)	0.115		
RPCP Peripapillary VD (%)							
ILM Peeled	58.30±5.18 (43.04-66.82)	52.46±6.57 (34.36-64.02)	54.65±5.32 (40.53-60.65)	56.60±6.20 (39.27-64.57)	<0.001	(preop-1.week) <0.001 (preop-1.month) 0.017 (1.week-1.month) 0.008 (1.week-3.month) 0.001 (1.month-3.month) 0.019	0.975
ILM Unpeeled	54.25±7.18 (32.87-61.95)	50.98±7.11 (32.90-59.08)	54.16±4.76 (43.10-60.80)	55.93±4.71 (43.33-60.03)	0.079		

All data are presented as the means ± SD, min-max). SD: standart deviation Min: minimum, Max: maximum, ONH: optic nerve head RPCP: radial peripapillary capillary plexus ILM: internal limiting membrane VD: vascular density Preop: preoperative. **(a)** General linear model analysis of repeated measures within each study group. **(b)** In pairwise comparison of subgroups, only values with $p < 0.05$ are shown in subgroup analysis. **(c)** Comparison of the difference between the first measurement and the last measurement between ILM peeled and ILM unpeeled groups with independent sample t-test.

Table 5. Comparison of visual acuity within groups, subgroups, and between groups

		Postoperative			p		
	Preoperative	1. Week	1. Month	3. Month	Within Group (a)	Pairwise Subgroup (b)	Between Groups (c)
BCVA, Snellen							
ILM Peeled	0.29±0.10 (0.10-0.50)	0.29±0.14 (0.10-0.70)	0.34±0.15 (0.05-0.60)	0.44±0.21 (0.05-0.80)	<0.001	(preop-1.month) 0.045 (preop-3.month) 0.002 (1.week-3month) 0.008	0.976
ILM Unpeeled	0.21±0.10 (0.05-0.40)	0.22±0.12 (0.05-0.4)	0.30±0.15 (0.05-0.60)	0.38±0.19 (0.05-0.70)	0.001	(preop-3.month) 0.030	

All data are presented as the means ± SD, (min-max). SD: standart deviation Min: minimum, Max: maximum, BCVA: best corrected visual acuity ILM: internal limiting membrane VD: vascular density Preop: preoperative **(a)** General linear model analysis of repeated measures within each study group. **(b)** In pairwise comparison of subgroups, only values with $p < 0.05$ are shown in subgroup analysis. **(c)** Comparison of the difference between the first measurement and the last measurement between ILM peeled and ILM nonpeeled groups with independent sample t-test.

anatomy and the decrease in foveal thickness were slower in eyes with ILM peeling in the first postoperative year, but there was no significant difference in foveal thickness and anatomy between eyes with and without ILM peeling at the end of 2 years. Although our follow-up period was 3 months, the main outcome measure in our study was vascular parameters, and the decrease in foveal thickness is only supported to explain the centrifugal movement after ILM preservation.

Our study have some limitations. An important limitation of this study is the non-randomized allocation of

groups. Since ILM peeling status was determined intraoperatively according to the presence or absence of spontaneous ILM separation after ERM removal, the groups may differ regarding underlying ERM biological characteristics. Eyes with spontaneous ILM separation may have stronger ERM-ILM adhesion, which could independently affect postoperative retinal microvascular parameters. Therefore, the observed findings should be interpreted cautiously, as differences between groups may reflect both the effects of ILM peeling and intrinsic biological differences in ERM character-

istics. Although ERM grading was performed according to the Govetto classification, the relatively small sample size prevented subgroup analysis according to ERM stage. Future studies with larger populations may further clarify whether the effects of ILM peeling on retinal microvascular remodeling differ according to ERM severity. Our follow-up period was 3 months. There is a study suggesting that recanalization continues for up to one year (13). Although our 3-month follow-up period was sufficient to evaluate early postoperative microvascular changes, longer follow-up may be required to assess the complete course of retinal vascular remodeling and anatomical displacement after ERM surgery. Future studies with longer observation periods are needed to clarify the long-term influence of ILM peeling on retinal microvascular changes. There is also a study that shows functional and anatomical recovery are similar in the long term, as mentioned above (28). The relatively small sample size is an important limitation of this study. Although the prospective design and standardized surgical approach strengthen the findings, the study may have limited power to detect small differences between groups. Therefore, non-significant between-group findings should be interpreted cautiously and do not necessarily exclude the possibility of clinically relevant differences. However, the number of OCT-A studies comparing eyes with and without ILM peeling in the treatment of ERM is very few (3,18-22). Among these studies, our study is the second with the largest sample size and the only study that evaluated optic disc VD and macular VD parameters together in the same eye. OCT-A vascular density measurements should be interpreted with caution, as they represent the proportion of detectable vascular signals within a defined area rather than direct measurements of blood flow, retinal perfusion, or oxygen delivery. Therefore, changes in vascular density observed in our study may reflect alterations in retinal vascular architecture or detectable flow signals rather than absolute changes in retinal circulation. Another limitation of this study is that all patients underwent combined phacoemulsification and intraocular lens implantation before vitrectomy. Cataract surgery itself may influence retinal thickness measurements, retinal perfusion parameters, and OCT-A image quality. Since a vitrectomy-only control group was not included, the individual contributions of cataract surgery, ERM removal, and ILM peeling to postoperative structural and vascular changes cannot be completely separated. Therefore, our findings should be interpreted as reflecting the combined effects of these surgical interventions rather than the isolated effect of ILM peeling. Given the exploratory nature of several secondary analyses and the number of evaluated OCT and OCT-A parameters, the possibility of type I error due to multiple comparisons should be considered when interpreting the results.

Conclusion

In conclusion, our results suggest that ILM peeling may influence SCP vascular remodeling after ERM removal by counterbalancing the tractional effects associated with ERM peeling. No statistically significant effect of ILM peeling on DCP or optic disc vascular density was detected within the 3-month follow-up period. Larger studies with longer follow-up are required to better elucidate the long-term effects of ILM peeling on retinal microvascular remodeling.

Disclosures

Ethics Committee Approval: This study was approved by the clinical research ethics committee of Kahramanmaraş Sütçü İmam University Faculty of Medicine (Date: 16.10.2019, No: 2019/18/10, clinical trial registration number: 312).

Informed Consent: Written informed consent in accordance with the Declaration of Helsinki was obtained from all participants.

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Clinical Manifestations of a Hereditary Vitreoretinopathy with Wagner Phenotype in a Multigenerational Turkish Family

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Abstract

Objectives: To report long-term clinical manifestations and genetic findings of a hereditary vitreoretinopathy exhibiting phenotypical characteristics of Wagner Syndrome in a multigenerational Turkish family originating from the same district in Central Anatolia.

Methods: Data from detailed medical histories and ophthalmological examinations were evaluated. Family pedigree was constructed. PCR and sequence analysis were performed to assess splice sites of introns 7 and 8 of the VCAN gene associated with Wagner syndrome.

Results: Thirty family members were examined, and 21 affected individuals were followed for 2–18 years. Cohort included 12 females and 9 males, with a mean age of 31 ± 19 years (4–71), mean spherical equivalent of -3.87 ± 5.03 diopters. Sixteen patients (76%) were myopic (≤ -0.50 D). Rhegmatogenous retinal detachment (RD) was presenting diagnosis in seven patients (33%). Hollow vitreous cavity with fibrous bands was detected in nine individuals (43%). Peripheral retinal pathology included multiple breaks in 16/21 (76%), snail-track degeneration in 3/21 (14%), lattice degeneration in 5/21 (24%), white without pressure in 2/21 (9.5%). One 20-year-old male with bilateral RD also had an optic nerve head astrocytoma. Mean age at onset was 21.6 ± 13.5 years (4–50). Earliest RD occurred at age 10, retinal breaks with attached retina were identified at age 8. Youngest patient (age 4) exhibited high axial myopia and vitreous bands. Laser prophylaxis was effective in 10 patients, although one later developed RD. Three patients (14%) developed phthisis, seven (33%) underwent cataract surgery, and four (19%) had glaucoma. Sequence analysis revealed no mutations in VCAN intron 7 or 8 splice sites.

Conclusion: This study presents a Turkish family with hereditary vitreoretinopathy exhibiting phenotypical characteristics of Wagner Syndrome. Although genetic analysis was inconclusive, detailed presentation of long-term clinical manifestations may provide valuable information about hereditary vitreoretinopathies and emphasize the importance of early and regular follow-up and prophylactic treatment for prevention of RD.

Keywords: Wagner syndrome, vitreoretinal degeneration, hereditary vitreoretinopathy, retinal detachment, VCAN

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Introduction

Hereditary vitreoretinopathies represent a diverse group of inherited disorders affecting the retina and vitreous. They are characterized by vitreous abnormalities alongside peripheral retinal changes and vascular alterations. These disorders are associated with an increased risk of retinal detachment and early-onset cataract. Clinically, hereditary vitreoretinopathies may present with visual impairment of varying severity, and early recognition is essential for appropriate monitoring, genetic counseling, and timely management of complications such as retinal detachment.

Wagner syndrome is a hereditary vitreoretinopathy associated with progressive retinal dysfunction. It was first described in 1938 in a Swiss family, as a hereditary hyaloid degeneration with autosomal inheritance (1). The initial clinical presentations of this syndrome are syneresis, optically empty vitreous cavity and preretinal avascular membranes (vitreous veils) which may occur in childhood or adolescence. Other pathological changes include sheathing of vessels, mild to severe myopia, cataract and atrophy of the choroid and retina. With aging, these findings usually increase and progress, leading to severe decrease in visual acuity (2-4).

Wagner Syndrome only involves the eye and does not have extraocular manifestations. It is related with mutations in *VCAN* gene in chromosome 5q (formerly named *CSPG2*) which encodes a versican protein, having a critical role in human vitreous structure (4).

This study aims to report the long-term clinical findings and molecular analysis of a hereditary vitreoretinopathy ex-

hibiting Wagner phenotype in a multigenerational Turkish family with origins from the same area in central Anatolia.

Methods

Thirty members of the family had complete ophthalmological examination including refraction, distance visual acuity, intraocular pressure and detailed fundus examination. Clinical data from 46 family members were collected from medical records. Systemic abnormalities were also questioned. The onset of disease, ocular findings and severity of the pathology were evaluated. A family pedigree was constructed based on detailed medical records and ophthalmological examinations (Fig. 1). Photo documentation with color fundus photography and spectral domain optical coherence tomography (HRA + OCT Spectralis, Heidelberg Engineering, Heidelberg, Germany) were performed where necessary.

Genomic DNA was extracted from blood samples of index case and her family members according to standard procedures. PCR was used to check splice sites of intron 7 and 8 of the *VCAN* gene and mutations were investigated by sequence analysis.

To check splice sites of intron 7 and 8 of the *VCAN* gene PCR was performed with the use of following primer pairs; 5'-TGTTCAATTATCTGTCCTTGGG-3' and 5'-TTCCAGGATCATTCTTGCAG-3' which produced a 724 bp PCR product to analyze intron 6/exon 7 acceptor site; 5'-TATTTGAAAAGCCCCAAAGCC-3' and 5'-GCAAAACGATTTTAGCCGTC-3' which produced a 869 bp PCR product to analyze exon 7/intron 7 donor site; 5'-CACAAAGATGAATTCCTGCAC-3' and 5'-AAAACATCAGGCTCACCACC-3' which

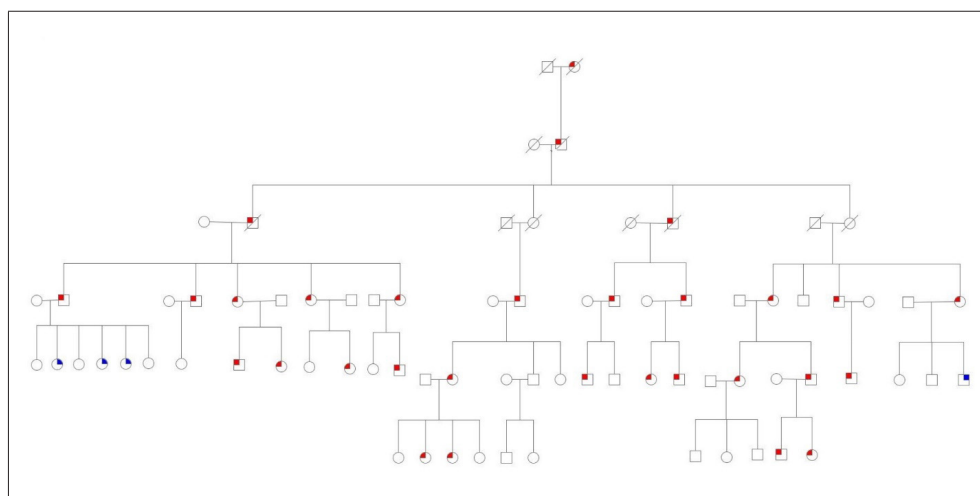


Figure 1. Pedigree of the Turkish family with hereditary vitreoretinopathy showing Wagner phenotype. Family consisted of 76 individuals of whom 34 were affected. Squares represent males and circles represent females; diagonal lines indicate deceased individuals. Red-filled symbols denote family members with retinal pathology at first diagnosis, while blue-filled symbols indicate individuals with initial diagnosis of myopia exceeding -10.00 diopters. The pattern observed is consistent with autosomal dominant inheritance across five generations.

produced a 825bp PCR product to analyze intron 7/exon 8 acceptor site and 5'-TCAAGTTTCTGGAGAAGCAATC-'3 and 5'-CATCCATCAATGGGAGGG-'3 which produced a 854 bp PCR product to analyze exon 8/intron 8 donor site. Primers were designed using the program PRIMER3 PLUS. PCR products were analyzed by electrophoresis on a 2% agarose gel. Mutations were investigated by ABI 310 Sequence Analyzer.

Ethics committee approval was not obtained for this retrospective study; institutional permission for the use of patient data was granted by Yeditepe University Faculty of Medicine, Department of Ophthalmology (01/10/2025). All patients or their legal guardians provided informed consent, and the study adhered to the principles of the Declaration of Helsinki.

Statistical Analysis

Descriptive statistical methods were used to summarize the clinical data, including mean, standard deviation, range and proportions where appropriate. No statistical software was used.

Results

All family members (76 individuals) came from Reşadiye, a small district of Tokat city in central Anatolia, with ancestors originating from Karaman, Konya. Thirty members of the family were examined; among these, 21 patients were found to be affected. This group, which consisted of 12 females and 9 males, were followed up for 2-18 years. Mean age of the group was 31 ± 19 years (range 4-71). Mean spherical equivalent of refractive error was -3.87 ± 5.03 diopters (D) (range +1.00D, -20.0D); 16 patients (76%) were myopic (≤ -0.50 D) while 5 (24%) were emmetropic or had mild hypermetropia. The initial diagnosis was rhegmatogenous retinal detachment (RD) in 7 patients (33%). Hollow vitreous cavity with bands were seen in 9 patients (43%). Peripheral retinal pathologies such as multiple breaks 16/21 (76%), snail track degeneration 3/21 (14%), lattice degeneration 5/21 (24%), white without pressure 2/21 (9.5%) were detected. A 20-year-old male patient with bilateral vitrectomy had astrocytoma of the optic nerve head in one eye (Fig. 2-5). Mean age of onset of disease was 21.6 ± 13.5 years (range, 4-50). Earliest occurrence of RD was at 10 years of age (1 patient) while retinal breaks with attached retina were detected as early as 8 years of age (4 patients). Youngest patient of the family was a 4-year-old boy with high axial myopia and vitreous bands. Laser prophylaxis was successful in 10 patients except for one patient who developed RD in one eye 2 years after photocoagulation. Three (14%) patients had phthisis bulbi in one eye due to unsuccessful RD surgery, 7 (33%) patients had cataract surgery and 4 (19%) had glaucoma. The fellow eye of one patient with phthisis bulbi had undergone retinal detachment

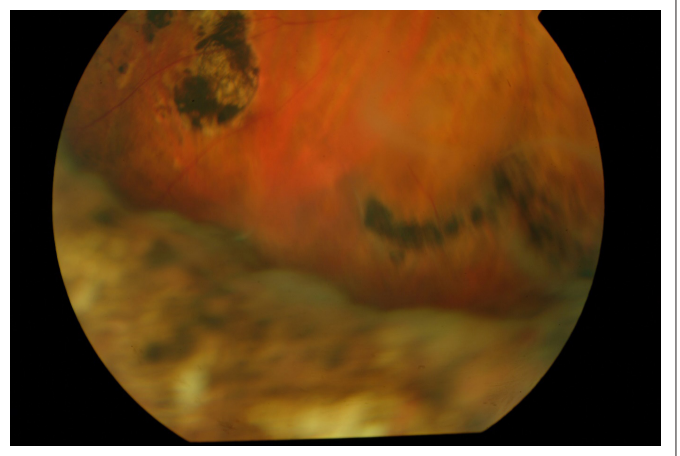


Figure 2. 62-year-old female patient with bilateral retinal detachment who underwent bilateral scleral buckling and cataract surgery, later developing open-angle glaucoma. Final best-corrected visual acuities were 0.7 in the right eye and 0.4 in the left eye.

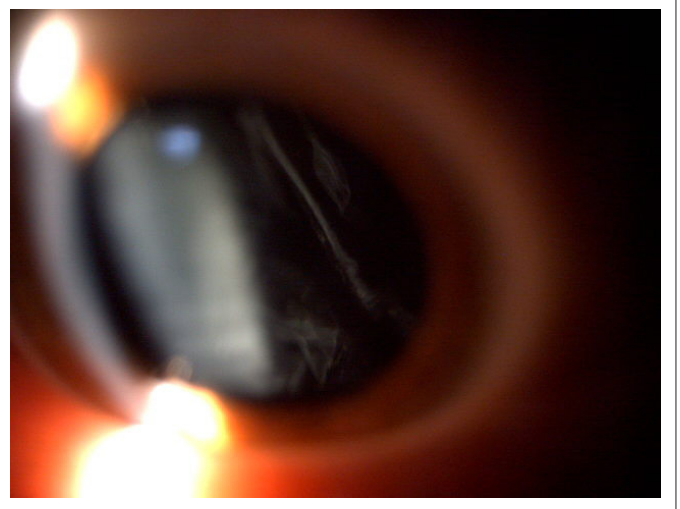


Figure 3. Hollow vitreous cavity with fibrous bands in a 37-year-old male patient. During a 15-year follow-up period, the patient underwent laser photocoagulation, scleral buckling surgery, and subsequently pars plana vitrectomy with silicone oil tamponade.

surgery with an encircling Arruga suture (Fig. 6). In 9 out of 30 family members who were examined, no pathological ocular finding was diagnosed at the time of examination.

Systemic abnormalities including orofacial and skeletal abnormalities associated with other inherited vitreoretinal diseases were not present in any of the family members.

Sequence analysis revealed no mutation in the splice sites of intron 7 and 8 of the VCAN gene in proband's genomic DNA.

Discussion

In our patient group, we found the classical clinical features of Wagner Syndrome: A hollow vitreous cavity with bands,

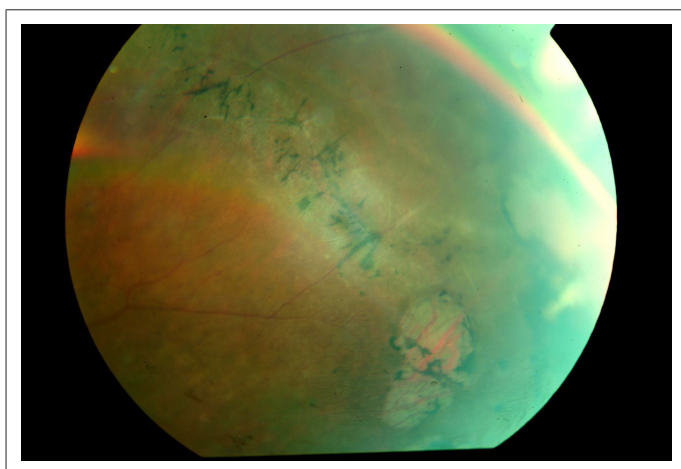


Figure 4. 44-year-old female patient with lattice degeneration who underwent scleral buckling surgery in both eyes, vitrectomy in the left eye, cataract surgery in both eyes and subsequently developed secondary glaucoma.

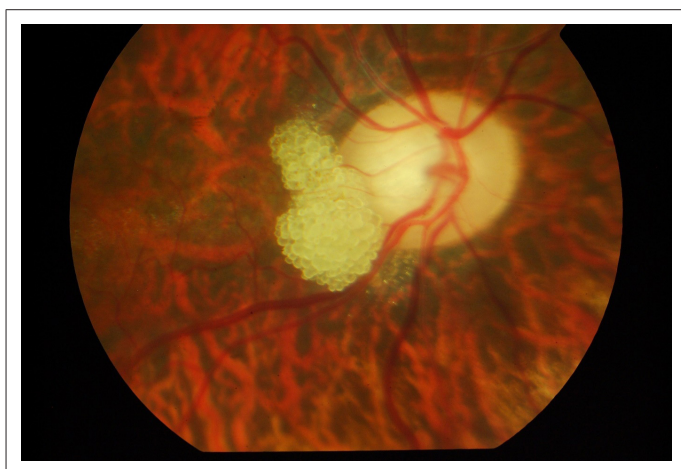


Figure 5. Right eye of a 17-year-old male patient with retinal astrocytoma. Best-corrected visual acuity was 0.16. The patient had previously undergone bilateral vitrectomy at 15 years of age.

peripheral retinal pathologies including typical and/or atypical lattice with pigmentation, moderate myopia, initial diagnosis of rhegmatogenous RD, open angle glaucoma and cataract. Pathological retinal changes predisposing to rhegmatogenous RD were observed in almost all patients, with varying degrees of severity, which showed an age-related increase in some patients, though not consistently across all cases. Additionally, 20-year-old male patient with bilateral vitrectomy had astrocytoma of the optic nerve head in one eye.

Retinal detachment is a major cause of vision loss in individuals with Wagner syndrome. In 50% of the cases, vitreous degeneration may be accompanied by RD, which occurs frequently in childhood and adolescence (4-7). Because Wagner syndrome is rare, evidence guiding optimal management of retinal detachment in these patients remains limited. Araujo

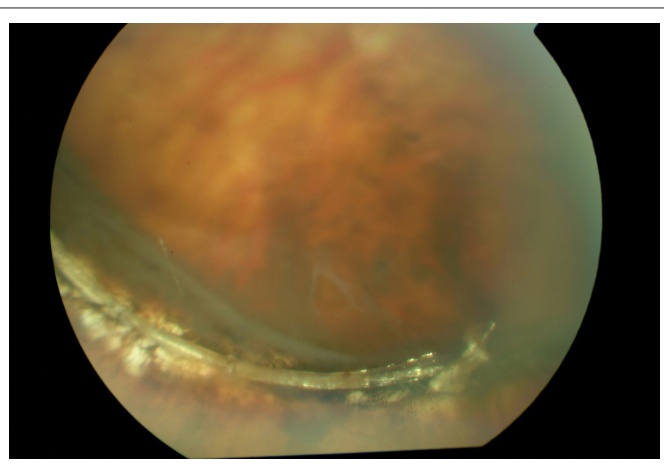


Figure 6. Left eye of an 84-year-old patient with retinal detachment. Surgery was performed using an Arruga encircling suture in 1969. Post-operative visual acuity was 0.2.

et al reported clinical findings in a Portuguese family with Wagner Syndrome (8). In their patient group, visual acuity was lower in those with previous RD (no light perception to 3/10). The prevalence of RD among the family members was high and occurred at young ages (5 cases, 4 of which occurred between 5 to 15 years of age). Three were successfully treated by scleral buckling and one by vitrectomy. Prophylactic scleral buckling was performed in four patients due to abnormal peripheral vitreoretinal adhesions with peripheral retinal traction.

A recent case report of a 9-year-old patient with Wagner syndrome, suggested that prophylactic encircling band and retinopexy might be effective in stabilizing vitreoretinal traction and potentially preventing retinal detachment in high-risk individuals (9).

Szeligowski et al. reported a familial case series with a heterozygous VCAN exon 8 deletion and highlighted the challenges of retinal detachment surgery due to strong vitreoretinal adhesions, which are associated with a high risk of recurrent RD. The authors emphasized the need for improved strategies to manage traction and prevent vision loss (10).

In our series, there were seven patients with RD; one of them developed RD in one eye 2 years after photocoagulation. Three patients had phthisis bulbi in one eye due to unsuccessful RD surgery. These case reports, together with our findings, highlight the importance of screening all family members starting from early ages. This is essential for identifying individuals at risk of retinal detachment (RD) or those with asymptomatic detachments, enabling timely prevention and treatment.

Wagner Syndrome is caused by mutation of the VCAN gene in chromosome 5q (previously known as CSPG2) which encodes the large extracellular matrix proteoglycan versican – a major component of the vitreous. Wagner syndrome has

been associated with mutations in the splice sites of intron 7 and 8 of the *VCAN* gene. In our study, sequence analysis of these regions revealed no detectable mutations. Whole exons of *VCAN* and some other genes including *FZD4*, *LRP5*, *NDP*, and *TSPAN12* genes should be alternatively sequenced, since autosomal dominant exudative vitreoretinopathy is known to be associated with these genes (11–14).

The main limitation of our study is that, due to technical constraints, comprehensive genetic analysis could not be performed. Only the splice-site regions of introns 7 and 8 of the *VCAN* gene were analyzed, and no mutations were detected. The retrospective design and descriptive nature of the study represent further limitations. Nevertheless, this study presents a large case series of hereditary vitreoretinopathy with Wagner phenotype consisting of individuals originating from the same region of Türkiye.

Conclusion

In conclusion, this study summarizes the clinical and molecular findings in a large family with distinctive vitreoretinal pathologies, consistent with Wagner syndrome phenotype. Despite the lack of genetic characterization, this case series emphasizes the importance of early and regular ophthalmic examinations of all family members including asymptomatic ones, to prevent sight loss in hereditary vitreoretinopathy.

Disclosures

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R.B.K., O.Y.K., I.B.S.; Data Collection and/or Processing – R.B.K., A.K., E.G., M.O.; Analysis and/or Interpretation – R.B.K., O.Y.K., I.B.S.; Literature Search – R.B.K., N.M.Y., E.G., I.B.S.; Writing – R.B.K., O.Y.K., I.B.S.; Critical Reviews – R.B.K., O.Y.K., A.K., M.O.

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Molecular Diagnostic Yield and Genotype-Phenotype Spectrum of Inherited Eye Diseases in a Tertiary Health Center in Türkiye

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Abstract

Objectives: To describe ophthalmic phenotypes prompting genetic testing and to calculate the molecular diagnostic yield retrospectively in a real-world tertiary health center cohort.

Methods: This retrospective observational study employed a phenotype-first review of archived clinical genetic testing records. Unique individuals with documented ocular manifestations were identified and deduplicated using demographic and phenotype consistency rather than laboratory patient number alone. Patients were assigned one primary molecular outcome: Phenotype-concordant pathogenic or likely pathogenic diagnosis, candidate/variant of uncertain significance/partial finding, unresolved, or secondary/non-diagnostic pathogenic or likely pathogenic finding. Variants of uncertain significance, single pathogenic alleles for recessive disorders, and unphased biallelic variants were not counted as definitive diagnoses.

Results: Among 33 unique individuals, phenotype-concordant molecular diagnoses were established in 18.2% (6/33), while candidate, variant of uncertain significance, or partial findings were more frequent at 54.5% (18/33). Diagnoses involved *REEP6*, *TYR*, *PTEN*, *BRPF1*, and *CACNA1F*. An additional patient with albinism carried two heterozygous *TYR* pathogenic or likely pathogenic variants, but phase was not established; confirmation in trans would increase the yield to 21.2%. Excluding a *CACNA1F* case with a nonspecific archived phenotype reduced the yield to 15.2%.

Conclusion: The conservative molecular diagnostic yield was 18.2%, with candidate and partial findings substantially outnumbering definitive diagnoses. This gap underscores the importance of phenotype concordance, inheritance-aware interpretation, and segregation analysis in real-world ophthalmic genetics, where unresolved cases represent a reanalysis cohort rather than a diagnostic dead end.

Keywords: Ophthalmic Genetics, genetic testing, molecular diagnostic yield, genotype-phenotype correlation, inherited eye diseases, albinism, inherited retinal disease

Introduction

Clinical utility of genetic testing relies on identifying causative etiology rather than isolated variant detection. Establishing an etiologic molecular diagnosis transforms raw genomic variation into actionable clinical insights, enabling subtype-directed therapeutics, recurrence risk estimation, and

predictive family cascade testing (1,2). Conversely, reporting uncontextualized variants or uncertain findings without established causality introduces ambiguity and risks inappropriate interventions (3,4). Molecular diagnostic yield (MDY) refers to the proportion of tested individuals in whom a genetic finding is sufficient to establish a clinically meaningful diagnosis (5). This distinction matters because sequencing

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often identifies variants that are uncertain or do not fully explain the observed phenotype (6,7). In inherited retinal disease, a case is usually considered solved when the detected variant or variants are pathogenic or likely pathogenic, match the reported phenotype, and fit the expected inheritance pattern (2,8) although studies vary in both the criteria used and the stringency with which those criteria are applied (9,10). MDY therefore reflects not only how often testing provides a definitive diagnosis, but also how many patients remain unresolved and may benefit from reanalysis, broader testing, or further gene discovery (1).

Inherited eye diseases are genetically and phenotypically heterogeneous: Similar ocular phenotypes may result from variants in different genes, whereas variants in the same gene may cause either isolated ocular disease or multisystem syndromes (11,12). Ocular findings may also precede systemic manifestations and provide an early clue to an underlying syndromic disorder (13). However, the same ocular phenotype often maps to multiple genes and the same gene to variable ocular and systemic presentations, limiting phenotype-only prediction (14,15). Establishing a molecular diagnosis can therefore distinguish phenotypically overlapping disorders (2,16), refine or confirm the clinical diagnosis, clarify inheritance and recurrence risks, guide genetic counselling (17), and prompt surveillance for extraocular manifestations that may not yet be clinically apparent. Molecular diagnosis is also increasingly relevant to treatment, as eligibility for clinical trials and gene- or mechanism-directed therapies may depend on identification of the causative gene or variant (1).

Despite these benefits, molecular diagnostic yield varies considerably across inherited retinal disease (IRD) cohorts according to phenotype definition, cohort ascertainment, sequencing approach, variant interpretation framework, ancestry, and the criteria used to define a molecularly solved case (1,9). In a systematic review and meta-analysis of panel-based IRD studies including 23,324 patients, pooled diagnostic yield was 57.0% in studies with IRD-related enrollment and 61.7% in studies with strict IRD enrollment (10). In a prospective single-centre cohort of 1,000 patients with inherited eye disease undergoing genome sequencing, a definite genetic diagnosis was established in 57.4%, while 16.7% had unresolved VUS findings in known IRD/ION genes (8). Thus, even with contemporary genomic testing, a substantial proportion of patients remain without a definitive molecular diagnosis (8,10).

A broad sequencing report may contain a pathogenic or likely pathogenic (P/LP) variant that is incidental to the presenting ocular phenotype, a single P/LP allele in a recessive disease gene, or one or more variants of uncertain significance (VUS) (8). American College of Medical Genetics and Genomics (ACMG)/Association for Molecular Pathology

(AMP) standards emphasize standardized variant terminology and evidence-based classification, including segregation and inheritance evidence (3). Consequently, variant detection should not automatically be equated with a phenotype-concordant molecular diagnosis (2,18,19).

We therefore evaluated a regional clinical genetics cohort retrospectively using a phenotype-first, patient-level adjudication strategy. Our objectives were to describe the ophthalmic spectrum that prompted genetic evaluation, determine a conservative phenotype- and inheritance-concordant molecular diagnostic yield, quantify candidate/VUS and secondary findings, and identify borderline cases in which segregation or improved ophthalmic phenotyping could alter molecular resolution.

Methods

Study Design and Setting

This retrospective observational cohort study reviewed archived clinical genetic testing records from Adiyaman University Faculty of Medicine Department of Medical Genetics, Adiyaman, Türkiye, during 7 March 2022–17 March 2025.

Ethics Committee Approval

The study was approved by the Adiyaman University School of Medicine Ethics Committee for Non-Interventional Clinical Research on May 6, 2026 (approval no. 2026/4-41) and conducted according to Declaration of Helsinki. The manuscript was prepared in accordance with the STROBE reporting guideline.

Cohort Identification

Patients were eligible when the referral indication or clinical description explicitly documented an ocular, visual, or periocular manifestation. Eligible findings included retinal dystrophy/retinitis pigmentosa, optic neuropathy/optic atrophy, cataract/lens disorder, microphthalmia, albinism/photophobia, nystagmus, strabismus, refractive error, ptosis, proptosis/orbital findings, visual impairment, and multisystem presentations containing an explicit ophthalmic feature. False-positive text matches, non-ophthalmic uses of similar terms, and family-history-only ocular findings without a proband ocular phenotype were excluded.

Patient-Level Deduplication

The unit of analysis was the unique individual, not the test row, accession, or laboratory patient number. Some individuals received different patient numbers during sequential testing. Records were therefore consolidated using name, date of birth, sex, and clinical phenotype/identity consistency. All molecular tests belonging to the same individual were reviewed together before assigning a final patient-level outcome.

Genetic Testing and Variant Interpretation

Testing reflected the clinically ordered next-generation sequencing panels, exonic profiling, and sequential gene panels documented in the archived reports. Variant nomenclature, transcript, protein consequence, zygosity, and laboratory classification were transcribed when directly retrievable. Missing molecular fields were not inferred. Laboratory classifications were interpreted in the context of ACMG/AMP terminology (3).

Molecular Adjudication and Primary Outcome

Each patient was assigned one primary outcome. Category A required a P/LP variant or genotype compatible with both the presenting phenotype and expected inheritance. Category B comprised phenotype-relevant VUS, candidate variants, single P/LP alleles for recessive disorders, unresolved phase, or other partial molecular explanations. Category C comprised appropriately tested patients without an explanatory finding. Category D comprised patients whose P/LP finding was secondary, incidental, carrier-related, or otherwise unrelated to the presenting ophthalmic phenotype and who did not have a stronger phenotype-relevant candidate category. Secondary findings were recorded separately and were never added to the diagnostic numerator. The primary diagnostic yield was category A divided by all unique individuals in the primary cohort.

Sensitivity Analysis

Two clinically motivated sensitivity analyses were prespecified during adjudication. First, an albinism case with two heterozygous *TYR* P/LP variants was modeled as diagnosed if segregation established that the variants were in trans. Second, a hemizygous *CACNA1F* likely pathogenic case was removed from the numerator in a strict phenotype analysis because the archived ophthalmic description was limited to eye deviation. *CACNA1F*-associated disease can include myopia and nystagmus and encompasses overlapping retinal phenotypes, supporting biological plausibility while also underscoring the need for precise ophthalmic phenotyping (20,21).

Statistical Analysis

Data were analyzed using Microsoft Excel for Microsoft 365 Enterprise, Version 2608 (Microsoft Corporation, Redmond, WA, USA). Data were summarized descriptively as counts and percentages. Because the study objective was descriptive and the cohort was small and clinically heterogeneous, no inferential comparisons between phenotype subgroups were prespecified. Diagnostic yield was calculated using the unique patient as the denominator. Sensitivity analyses were performed by recalculating the diagnostic numerator and yield under the prespecified *TYR* phase and strict *CACNA1F* phenotype scenarios.

Results

Cohort and Molecular Outcomes

Thirty-three unique individuals met the primary ophthalmic inclusion criteria after patient-level deduplication. Presentations included retinal dystrophy/retinitis pigmentosa, optic nerve disease, albinism, microphthalmia, congenital cataract/visual impairment, nystagmus, myopia, ptosis, proptosis, photophobia, and syndromic strabismus. Neurodevelopmental, neuromuscular, endocrine, craniofacial, and connective-tissue features were common in the syndromic subgroup.

Six of 33 individuals had a phenotype- and inheritance-concordant molecular diagnosis, corresponding to a conservative diagnostic yield of 18.2%. Eighteen (54.5%) had candidate/VUS/partial findings, six (18.2%) remained unresolved, and three (9.1%) had only secondary/non-diagnostic P/LP findings (Table 1).

Phenotype-Concordant Diagnoses

The primary diagnoses involved *REEP6*, *TYR*, *PTEN*, *BRPF1*, and *CACNA1F* (Table 2). A homozygous pathogenic *REEP6* splice variant was concordant with retinitis pigmentosa. A pathogenic *TYR* variant was concordant with albinism. Two patients with syndromic neurodevelopmental presentations including strabismus carried *PTEN* variants. A heterozygous truncating *BRPF1* likely pathogenic variant was considered explanatory in a patient with epilepsy, learning difficulty, and strabismus. A hemizygous *CACNA1F* likely pathogenic variant was retained as diagnostic in the primary analysis, with the phenotyping caveat addressed by sensitivity analysis.

Candidate, Partial, and Secondary Findings

The largest group comprised 18 patients with candidate/VUS/partial findings. Examples included a heterozygous pathogenic *PCARE* variant without a second confirmed pathogenic allele in a patient with retinitis pigmentosa and a heterozygous likely pathogenic *GNAT2* frameshift in a patient with nystagmus and visual loss, insufficient by itself for a recessive *GNAT2*-related diagnosis. This distinction parallels larger inherited-eye-disease studies in which unconfirmed biallelism and single heterozygous P/LP alleles in recessive genes constitute a substantial fraction of unresolved case.

Table 1. Patient-level molecular outcomes in the primary ophthalmic cohort

Molecular outcome	n	%
Phenotype-concordant molecular diagnosis	6	18.2
Candidate/VUS/partial	18	54.5
Unresolved	6	18.2
Secondary/non-diagnostic P/LP only	3	9.1
Total	33	100.0

P/LP: pathogenic/likely pathogenic; VUS: variant of uncertain significance.

Table 2. Phenotype-concordant molecular diagnoses

Phenotype	Gene	Principal variant	Classification / interpretation
Retinitis pigmentosa	<i>REEP6</i>	c.209+1G>A, homozygous	Pathogenic; Diagnostic
Albinism	<i>TYR</i>	c.715C>T	Pathogenic; Diagnostic
Strabismus, macrocephaly, developmental delay	<i>PTEN</i>	NM_000314.8:c.413A>G (p.Tyr138Cys), heterozygous	P/LP in source record; Diagnostic
Right-eye strabismus, autism/nonverbal phenotype	<i>PTEN</i>	NM_000314.8:c.1177del (p.Asp393MetfsTer23), heterozygous	Likely pathogenic; Diagnostic
Strabismus, epilepsy, learning difficulty	<i>BRPF1</i>	NM_001003694.2:c.1773G>A (p.Trp591Ter), heterozygous	Likely pathogenic; Diagnostic
Eye deviation, hypotonia, developmental delay	<i>CACNA1F</i>	NM_001256789.3:c.1717G>T (p.Gly573Cys), hemizygous	Likely pathogenic; Diagnostic in primary analysis†

†Retained in the primary analysis; excluded in strict phenotype sensitivity analysis because the archived ocular phenotype was nonspecific.

Table 3. Diagnostic-yield sensitivity analyses

Analysis	Diagnosed/total	Yield
Primary conservative analysis	6/33	18.2%
If additional <i>TYR</i> variants are confirmed in trans	7/33	21.2%
Strict phenotype analysis excluding <i>CACNA1F</i> case	5/33	15.2%

One patient with albinism carried *TYR* NM_000372.5:c.1264C>T (p.Arg422Trp), heterozygous pathogenic, and *TYR* c.1339T>A (p.Tyr447Asn), heterozygous likely pathogenic. Because phase was not established in the archived report, the patient was classified as partial rather than definitively diagnosed. Several other patients carried P/LP findings considered unrelated to their presenting ophthalmic phenotype; these findings were recorded but excluded from the diagnostic numerator.

Sensitivity Analyses

The primary diagnostic yield was 18.2% (6/33). If the two *TYR* P/LP variants in the additional albinism case are confirmed in trans, the yield would be 21.2% (7/33). Excluding the *CACNA1F* case under a strict ophthalmic-phenotype criterion yielded 15.2% (5/33) (Table 3).

Discussion

In this retrospective cohort from a regional, tertiary health center medical genetics service, a conservative molecular diagnostic yield of 18.2% was observed when the diagnostic numerator was restricted to phenotype- and inheritance-concordant findings. This yield is lower than most published IRD-focused sequencing cohorts, where reported yields commonly fall in the 50–75% range, but that difference is expected given the present study's broader real-world referral base,

inclusion of non-retinal and syndromic ophthalmic presentations, archived sequential testing pathways, and deliberately stringent case-adjudication rules (9,22). Published data show that yields differ markedly even within inherited eye disease, from relatively low rates in microphthalmia-anophthalmia-coloboma to much higher rates in congenital cataract and selected retinal subgroups, underscoring that pooled comparisons can be misleading when case mix differs (5,23,24). In addition, the present dataset derived from archived clinical reports generated across evolving eras of testing, and retrospective series spanning older sequencing approaches tend to underrepresent structural, copy-number, deep intronic, noncoding, and technically challenging variants that are more reliably detected by contemporary panel, exome, and especially genome sequencing, as well as by modern reanalysis pipelines (6,8,25,26).

A second major finding was the predominance of partial or inconclusive results. More than half of the cohort fell into the candidate/VUS/partial category, whereas only six patients had no explanatory or potentially explanatory variant. This pattern is consistent with contemporary inherited-eye-disease studies, in which unresolved cases often reflect incomplete molecular resolution—such as VUS, unconfirmed bi-allelicism, unresolved phase, or variants requiring functional validation—rather than complete absence of a molecular signal. Broader testing may also detect pathogenic variants, carrier states, or other reportable findings unrelated to the presenting ocular phenotype (8,27–30). Thus, the high proportion of category B cases should not be viewed simply as testing failure, but as the gap between variant detection and a fully adjudicated molecular diagnosis, underscoring the value of standardized ACMG-based interpretation and close clinician–laboratory correlation (3,5,7,31).

Several cases illustrate this challenge. Single heterozygous P/LP variants in recessive disease genes are a common source

of partial or unresolved diagnoses after broad sequencing, particularly when phase is unknown or the second allele remains unconfirmed (8,28,32). The *TYR* case is especially informative: Confirmation that the two heterozygous variants are in trans would convert a partial finding into a solved recessive diagnosis, underscoring the value of segregation analysis or phase-resolving long-read approaches when family testing is unavailable (26,30). The solved cases also support requiring phenotype concordance in addition to laboratory pathogenicity. The homozygous *REEP6* splice variant was strongly consistent with RP, whereas the *CACNA1F* case remained more tentative because *CACNA1F*-related disease spans overlapping retinal phenotypes and limited archived phenotyping constrained confident adjudication (20,21). More broadly, molecular testing can refine or revise both diagnosis and inheritance models in heterogeneous retinal disease, so excluding secondary or phenotype-discordant P/LP findings from the diagnostic numerator avoids inflating yield.

Several limitations should be acknowledged. The cohort was small, clinically heterogeneous, retrospectively assembled, and evaluated through a nonuniform testing pathway, which reflects real-world practice but limits precision and comparability with prospective or standardized single-platform studies. Archived reports were incomplete in some cases, molecular fields were not inferred, and meaningful subgroup analyses were therefore not possible. In addition, some currently partial cases may ultimately be resolved through segregation testing, VUS reclassification, or broader reanalysis, as demonstrated in reinvestigation studies (33).

Molecular diagnostic yield in routine regional medical genetics practice may be lower than that reported in highly selected inherited retinal disease cohorts, while unresolved and partially informative findings remain common. This difference likely reflects not only sequencing technology, but also patient selection, phenotype concordance, inheritance-aware interpretation, and the rigor of patient-level adjudication. Importantly, an inconclusive result is not necessarily a final diagnostic endpoint, as segregation analysis, variant reclassification, periodic reanalysis, and advances in genomic testing may resolve a proportion of cases over time. Real-world MDY should therefore be viewed as a dynamic measure shaped by both current interpretive limitations and the potential for future diagnostic resolution.

Disclosures

Ethics Committee Approval: The study was approved by the Adiyaman University School of Medicine Ethics Committee for Non-Interventional Clinical Research (Date: 06/05/2026, No: 2026/4-41).

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A Rare Homozygous Synonymous Variant in the *ECM1* Gene in a Lipoid Proteinosis Patient

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Abstract

Lipoid proteinosis (LP) is a rare autosomal recessive disorder resulting from mutations in the *ECM1* gene and characterized by mucocutaneous thickening and deposition of hyaline material. We present a 10-year-old male with hoarseness, moniliform blepharosis, oral mucosal nodules, and cutaneous lesions. Histopathology showed PAS-positive hyaline material deposition. Genetic analysis by next-generation sequencing identified a homozygous synonymous variation, *ECM1* c.879G>A (p.Ser293=), which has not been previously reported in a homozygous form. Segregation analysis showed heterozygosity in both parents. In accordance with ACMG guidelines, the variant meets criteria PS4, PM2, PM3, PP3, and PP4, supporting its reclassification as pathogenic. This case highlights the diagnostic value of combining clinical, histological, and genomic data, especially in the evaluation of variations of uncertain significance. Genotyping in patients clinically and histopathologically compatible with LP is crucial to inform disease management and enhance understanding of its genetic background.

Keywords: *ECM1* gene, lipoid proteinosis, moniliform blepharosis, next-generation sequencing, Urbach-Wiethe disease

Introduction

Lipoid Proteinosis (LP) is a rare autosomal recessive disorder characterized by thickening and scarring of the mucosal tissue (1). It is usually caused by mutations in the *ECM1* gene, located on chromosome 1q21. The protein, Extracellular Matrix Protein-1, encoded by the *ECM1* gene, plays a fundamental role in maintaining the structural composition

of the dermis, binding to perlecan, fibulin, and matrix metalloproteinase-9 (1). To date, the amount of known pathogenic variants in the *ECM1* gene causing LP remains limited. The disease mainly affects the eyelids, oral mucosa and upper respiratory tract, and presents with moniliform blepharosis, hoarseness and oral mucosa nodules (2,3). It may also affect the central nervous system, causing neuropsychiatric disorders and intracranial calcifications (4). Diagnostic tools

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include showing dermal hyaline material deposits in histopathology samples, and genetic screening of the *ECM1* gene. In this study, we describe the clinical characteristics of a young male patient, along with his homozygous variant of *ECM1* gene that has never been exhibited in homozygous state in a patient or populational data before, contributing to the variant's evidence of pathogenicity.

Case Report

A 10-year-old Caucasian male patient presented to a tertiary referral hospital with a history of hoarseness and characteris-

tic eyelid changes since infancy. Despite multiple treatments, his symptoms had not improved. Best-corrected visual acuity was 20/20 in both eyes. Slit-lamp examination revealed moniliform blepharosis and perifollicular telangiectasia along the lid margins (Fig. 1a, 1b, 1c, 1d). Intraocular pressure and fundus examination were unremarkable. Given the presence of moniliform blepharosis, oral mucosal nodules, thickened lingual frenulum (Fig. 1e, 1f), and longstanding hoarseness, LP was clinically suspected, and the patient was referred to the Ear, Nose and Throat (ENT) department for further evaluation. Laryngoscopic examination confirmed the presence of

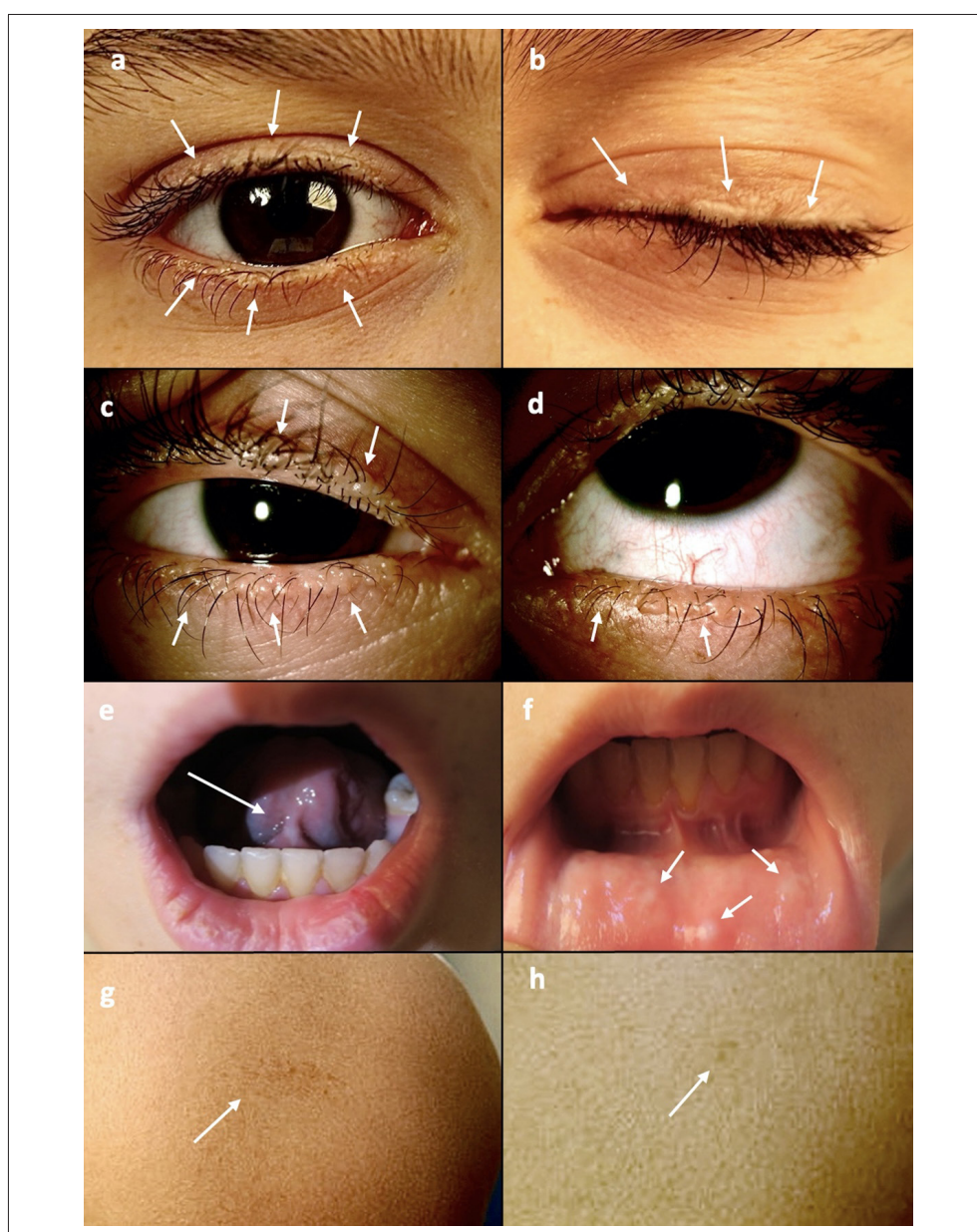


Figure 1. Moniliform blepharosis involving the upper and lower eyelid margins of both eyes (arrows) (a–d). Thickening of the lingual frenulum due to hyaline material deposition (arrow) (e) and nodular lesions in the oral mucosa (arrows) (f). Hyperpigmented skin lesions on the back (arrows) (g, h).

vocal cord nodules. Neurological examination findings were within normal limits and cranial computed tomography (CT) revealed no lesions characteristic of LP. During follow-up, hyperpigmented skin lesions occurred on his shoulders and back (Fig. 1g, 1h). Family history was reviewed, and no consanguinity was reported. To confirm the clinical diagnosis and exclude phenotypically similar conditions, histopathological examination and genetic testing were planned. An incisional biopsy of the eyelid and conjunctiva revealed PAS-positive hyalinized material in the pathology specimen (Fig. 2). Subsequently, genetic testing was performed to confirm the diagnosis. Analysis of genomic DNA extracted from peripheral blood samples of the patient and his parents was performed using Next-Generation Sequencing (NGS) on the Illumina

NextSeq 500 platform (Illumina Inc., San Diego, CA, USA). The analysis revealed a homozygous synonymous variant, c.879G>A (p.Ser293=), in the 7th exon of the *ECM1* gene (NM_004425). Segregation analysis of the patient's parents was performed by NGS and revealed that both were heterozygous carriers of this variant. The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent for publication was obtained from the patient's legal guardians. In line with the institutional policy for single-patient case reports, formal ethical approval was waived. Histopathological and genetic confirmation facilitated the discontinuation of previously administered treatments for presumed blepharitis and established a definitive molecular diagnosis. These findings supported a

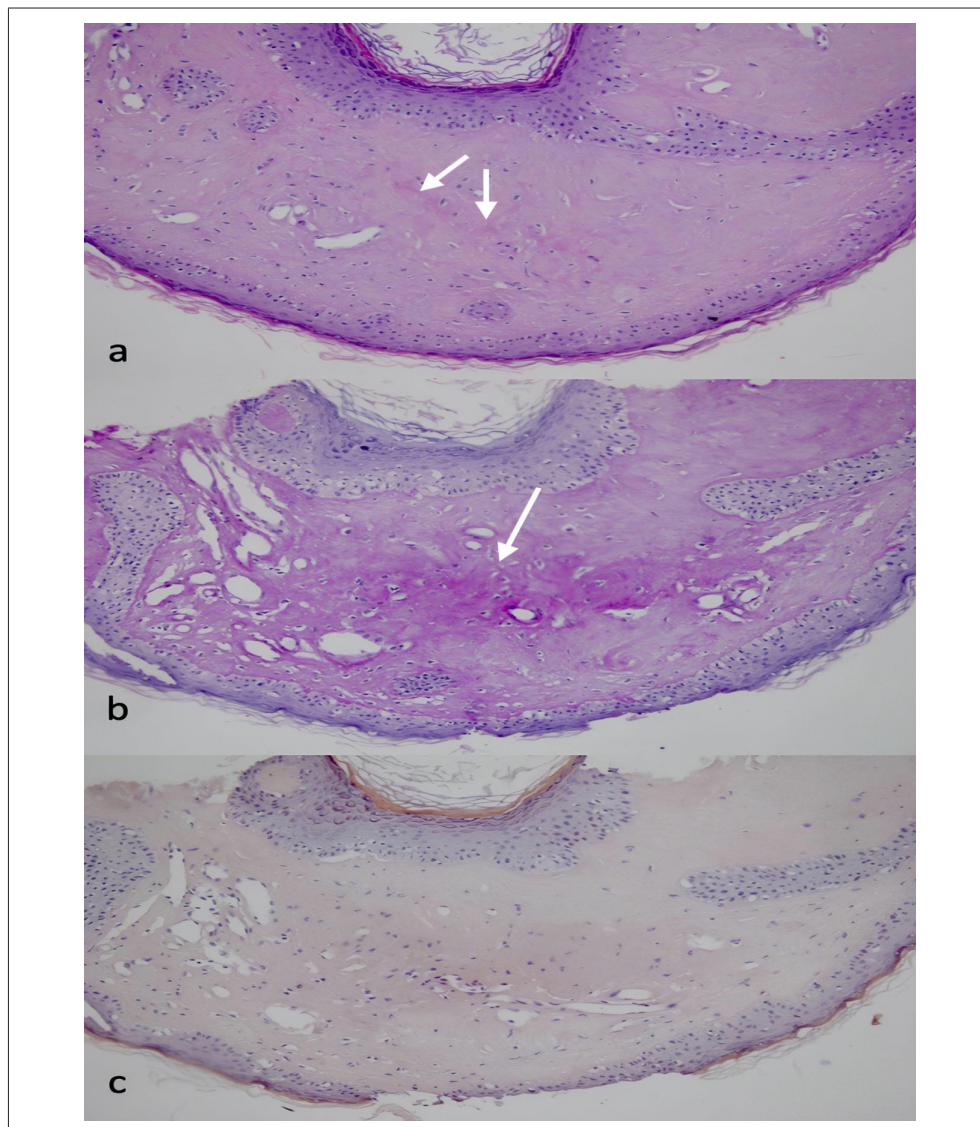


Figure 2. Histopathological examination of a biopsy taken from a moniliform eyelid lesion. Deposition of eosinophilic hyaline material on hematoxylin and eosin staining (arrows) (a). PAS positive hyaline material deposition (arrow) (b). Congo red negative staining consistent with hyaline deposition (c).

more focused multidisciplinary management approach, including targeted otolaryngological follow-up for vocal cord involvement. In addition, confirmation of the diagnosis and identification of parental carrier status enabled appropriate genetic counseling and the implementation of a structured long-term follow-up strategy, while avoiding unnecessary treatments and repeated diagnostic procedures.

Discussion

Urbach-Wiethe disease or LP is an autosomal recessive disorder characterized by the accumulation of hyaline material in the mucosa, usually presents as early-childhood hoarseness due to vocal cord nodules, although the age of onset and clinical presentation may vary (5–7).

Moniliform blepharosis, which can be confused with blepharitis, is a valuable finding (5). The patient had moniliform blepharosis of the eyelids and had used various medications with a misdiagnosis of blepharitis. He also had a history of hoarseness since childhood, similar to previous studies (2,5). This shows that LP should be considered in the differential diagnosis of the patients with hoarseness and persistent yellow-white bead-like papules such as blepharitis on the eyelid. The occurrence of cutaneous lesions during follow-up highlights the importance of performing comprehensive systemic evaluations at each visit in patients with LP.

The differential diagnosis should also include other conditions that may present with eyelid or mucocutaneous lesions. Eyelid or cutaneous amyloidosis may cause waxy infiltrative lesions, but typically lacks the characteristic beaded eyelid margin appearance and the combination of early-onset hoarseness and mucosal involvement seen in LP. Histopathologically, amyloidosis is characterized by extracellular amyloid deposits that are Congo red positive with apple-green birefringence under polarized light, in contrast to the PAS-positive hyaline material deposition observed in LP (8). Xanthomatous lesions may present as yellowish plaques or papules; however, they are typically associated with lipid metabolism disorders or systemic xanthomatous conditions such as hyperlipidemia or xanthoma disseminatum. These lesions commonly involve the periorbital region, particularly the medial canthus, and lack the characteristic beaded eyelid margin appearance seen in moniliform blepharosis. Histopathologically, they are characterized by the accumulation of lipid-laden foam cells within the dermis, further distinguishing them from LP (9). Verrucous or keratotic lesions and selected mucocutaneous storage disorders may also enter the differential diagnosis; however, they generally demonstrate distinct systemic associations and histopathological features.

Neuropsychiatric disorders such as migraine and epilepsy may be associated with LP (10). Detection of intracranial calcifications through imaging is an important diagnostic clue.

Bean-shaped calcifications in the amygdala are very valuable for the diagnosis (10). The patient did not have any neuropsychiatric disease and no pathological findings on cranial CT. This may be explained by the patient's relatively young age.

In LP, histopathological confirmation and genetic testing play a pivotal role in establishing a definitive diagnosis, particularly when clinical findings may overlap with other infiltrative or mucocutaneous disorders. In our patient, these investigations were essential to corroborate the clinical suspicion and provide molecular evidence supporting the diagnosis. Although the parents denied consanguinity, both were identified to be heterozygous carriers of the same pathogenic variant. This finding raises the possibility of either unrecognized distant consanguinity or, alternatively, a founder effect for this variant in the Turkish population. Given that LP presents with highly characteristic clinical features and is often diagnosed based on ophthalmological findings alone, genetic confirmation may be underutilized in regions where access to molecular testing has historically been limited. Consequently, founder variants causing LP may remain underrecognized in such populations. In the NGS analysis of our patient, a synonymous variant, *ECM1* c.879G>A (p.Ser293=), was detected in a homozygous state. The variant was previously classified as a variant of uncertain significance (VUS) in multiple variant databases; however, based on a thorough literature review, the homozygous state in our patient, and the results of segregation analysis, we reclassified this variant as *pathogenic* according to ACMG guidelines (11).

Synonymous variants, though preserving the amino acid sequence, can still influence the functions of the gene by alterations to the splicing mechanism. Further research on such variants which seem to be clinically relevant is required to better understand the underlying mechanisms of pathogenicity. Although the variant of the patient was observed to be a variant of unknown significance in multiple variant information services, the clinical and the histopathological diagnosis of the patient both confirm the diagnosis of LP, the disease has only been associated to loss-of-function changes in the *ECM1* gene. Our patient's variant, c.879G>A (p.Ser293=), appears to introduce an "AG" sequence which might establish a new acceptor site for the splicing event of the exons and introns of the *ECM1* gene. Therefore, we hypothesize the variant, c.879G>A, likely to be disease-causing and possibly interfering with alternative splicing of the gene as Delta scores from SpliceAI network also predict acceptor gain for this variant in pre-mRNA sequence (12).

Based on the homozygous occurrence of this variant in our patient and previously published in vitro RNA analyses (13), the variant fulfills the ACMG criteria PS4, PM2, PM3, PP3, and PP4. These correspond to: a significantly increased prevalence in affected individuals compared with controls (PS4); absence or extremely low frequency in population

databases such as the Exome Sequencing Project, 1000 Genomes Project, or ExAC (PM2); detection in trans with a pathogenic variant for recessive disorders (PM3); multiple lines of computational evidence supporting a deleterious effect (PP3); and a phenotype highly specific for a single-gene disease (PP4). Collectively, these findings support classification of the variant as *pathogenic*.

Although the patient was homozygous for the *ECM1* c.879G>A variant, which is consistent with the autosomal recessive inheritance pattern of LP, segregation analysis was performed to confirm parental carrier status. This approach strengthened the interpretation of this previously uncertain variant and excluded possibilities such as uniparental disomy or technical artifacts, thereby enhancing the robustness of the molecular diagnosis and genetic counseling. This case underscores the clinical relevance of integrating histopathological and genetic evaluation in patients with suspected LP, as even synonymous *ECM1* variants may have pathogenic consequences.

Genotyping in patients clinically and histopathologically compatible with LP is crucial for understanding the disease course and its genetic background. In particular, elucidating such challenging variants requires the combined use of multiple variant databases and a thorough review of the literature to ensure accurate classification. These integrative diagnostic approaches not only help clarify the molecular mechanisms underlying LP but also enhance patient care through precise genetic counseling and targeted management strategies. Clinically, persistent eyelid lesions resembling blepharitis, particularly when accompanied by early-onset hoarseness, should prompt suspicion of LP. Early recognition of this characteristic clinical constellation can prevent misdiagnosis, avoid unnecessary treatments, and facilitate timely histopathological and genetic evaluation. In addition, this case underscores that synonymous *ECM1* variants, often considered benign, may have pathogenic effects and should be interpreted cautiously in clinically compatible cases.

Disclosures

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: Written informed consents were obtained from patient and his family.

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Cidofovir-Induced Bilateral Uveitis, Hypotony and Choroidal Effusion: A Case Report

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Abstract

Cidofovir is an antiviral agent used in the treatment of viral infections but is associated with ocular toxicities. We report a case of a 71-year-old immunocompromised woman who developed bilateral anterior uveitis, marked hypotony, and choroidal effusion following intravenous cidofovir treatment for refractory herpes simplex virus type 2 infection. Ophthalmic examination and multimodal imaging, including optical coherence tomography and ocular ultrasonography, confirmed bilateral choroidal folds and effusion. Extensive systemic evaluation excluded infectious, inflammatory, and autoimmune etiologies. The close temporal relationship between cidofovir administration and symptom onset supported a diagnosis of cidofovir-induced ocular toxicity. Discontinuation of cidofovir and initiation of intensive topical corticosteroid therapy resulted in clinical improvement. This case highlights the importance of early recognition of cidofovir-related ocular adverse effects and the need for close ophthalmic monitoring during therapy.

Keywords: Cidofovir, uveitis, hypotony, choroidal effusion

Introduction

Cidofovir is a nucleotide analog that inhibits the viral DNA synthesis by competitive inhibition of viral DNA polymerase (1). It has been widely used in the treatment of cytomegalovirus (CMV) retinitis and other refractory viral infections in immunocompromised patients (2,3). Although effective, both intravenous and intravitreal administration of cidofovir have been associated with anterior uveitis, unilateral or bilateral, which may be accompanied by hypotony (4,5). These complications are believed to result from direct drug toxicity, disruption of the blood–retinal barrier, and damage to the ciliary body (6,7).

Cidofovir is also associated with an incidence of hypotony of up to 22%, which may be complicated by maculopathy and choroidal effusion (5). While most cases of cidofovir-as-

sociated uveitis can be managed with topical corticosteroids and cycloplegic agents without discontinuation of therapy, severe or persistent inflammation and hypotony may necessitate cessation of the drug (5). Although isolated cases of cidofovir-related uveitis or hypotony have been described, the simultaneous occurrence of bilateral uveitis, marked hypotony, and choroidal effusion with intravenous cidofovir, except for a report of recurrence with intravenous cidofovir (8), has not been previously reported. Herein, we present a case of cidofovir-induced bilateral uveitis complicated by hypotony and choroidal effusion, highlighting its clinical course, imaging findings, management, and outcome, and emphasizing the importance of close ophthalmic monitoring in patients receiving cidofovir therapy.

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Case Report

A 71-year-old woman was referred to our ophthalmology department from the infectious diseases clinic with complaints of decreased vision and ocular redness in both eyes. Her medical history was significant for T-cell lymphoma, diagnosed in 2022. In March 2025, she was hospitalized due to facial rash and pain. A biopsy obtained from the facial lesion confirmed herpes simplex virus type 2 (HSV-2) infection, and she was treated with ganciclovir, valacyclovir, and foscarnet.

At presentation to our clinic, dermatological examination revealed active rashes involving the frontal and glabellar regions of the face. Best-corrected visual acuity, measured using the Snellen chart, was 4/20 in the right eye and 8/20 in the left eye. Slit-lamp examination of the anterior segment demonstrated Descemet's membrane folds, extensive posterior synechiae, and +2 anterior chamber cells in both eyes. Mild conjunctival hyperemia was present bilaterally. Intraocular pressure was 6 mmHg in the right eye and 8 mmHg in the left eye.

Dilated fundus examination revealed choroidal effusion involving the superior, temporal, and nasal quadrants in both eyes. The macula and optic discs appeared preserved. Retinal folds were observed in the posterior pole (Fig. 1). Optical coherence tomography clearly demonstrated bilateral choroidal folds (Fig. 2). Ocular ultrasonography further confirmed the presence of bilateral choroidal effusion (Fig. 3).

Systemic oral corticosteroid therapy was considered; however, due to the patient's history of cytomegalovirus and HSV infections, the infectious diseases team advised against systemic steroid use. To investigate alternative etiologies, consultations with the rheumatology and pulmonology departments were obtained, both of which revealed no underlying systemic inflammatory or pulmonary pathology that could explain the ocular findings.

Further evaluation of the patient's medication history revealed that she had previously received three doses of intravenous cidofovir for refractory HSV-2 infection. The first dose had been administered 30 days before presentation, the second 25 days before, and the third 10 days before. Based on the temporal relationship between cidofovir administration and the onset of bilateral anterior uveitis, hypotony, and choroidal effusion, these findings were attributed to cidofovir-induced ocular toxicity.

Discontinuation of cidofovir therapy was recommended. The patient was started on hourly topical prednisolone acetate eye drops. One week after this treatment, the signs of anterior uveitis completely resolved. However, no significant improvement in hypotonia and choroidal effusion findings was observed during the patient's three-month follow-up. Due to the patient's discontinuation of follow-up, changes in long-term findings could not be observed. The patient consented to the publication of clinical information and images on the condition of anonymity.

Discussion

This report presents a rare case of cidofovir-induced bilateral ocular involvement characterized by the simultaneous occurrence of uveitis, hypotony and choroidal effusion. The close temporal association between cidofovir administration and symptom onset, together with the exclusion of alternative etiologies, strongly supports a diagnosis of cidofovir-induced ocular toxicity. Although a recurrence of bilateral uveitis and hypotony following intravenous cidofovir therapy has previously been reported (8), to our knowledge, the primary occurrence of this combination of bilateral findings associated with intravenous cidofovir has not been described.

The mechanism of cidofovir-induced uveitis is thought to be direct drug toxicity resulting from cumulative accumula-

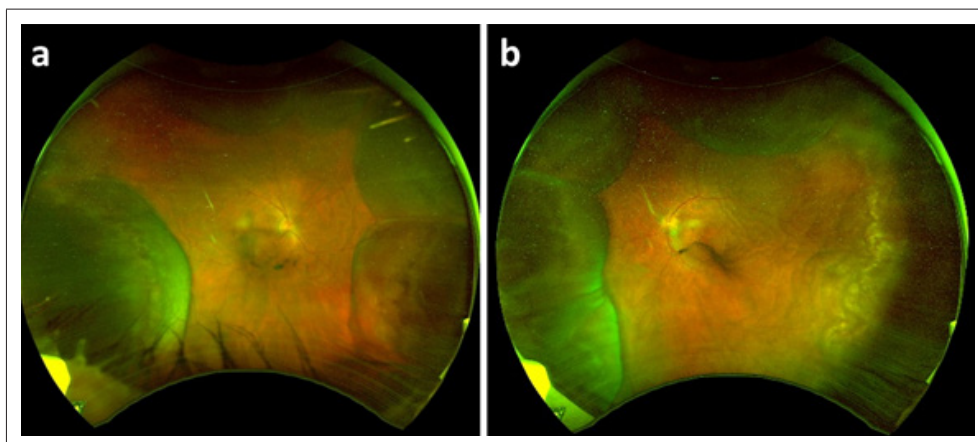


Figure 1. Fundus photographs of the right (a) and left (b) eyes. Choroidal effusion is observed in the superior, nasal, and temporal quadrants of both eyes. The macula and optic disc appear preserved. Retinal folds are noted in the posterior pole.

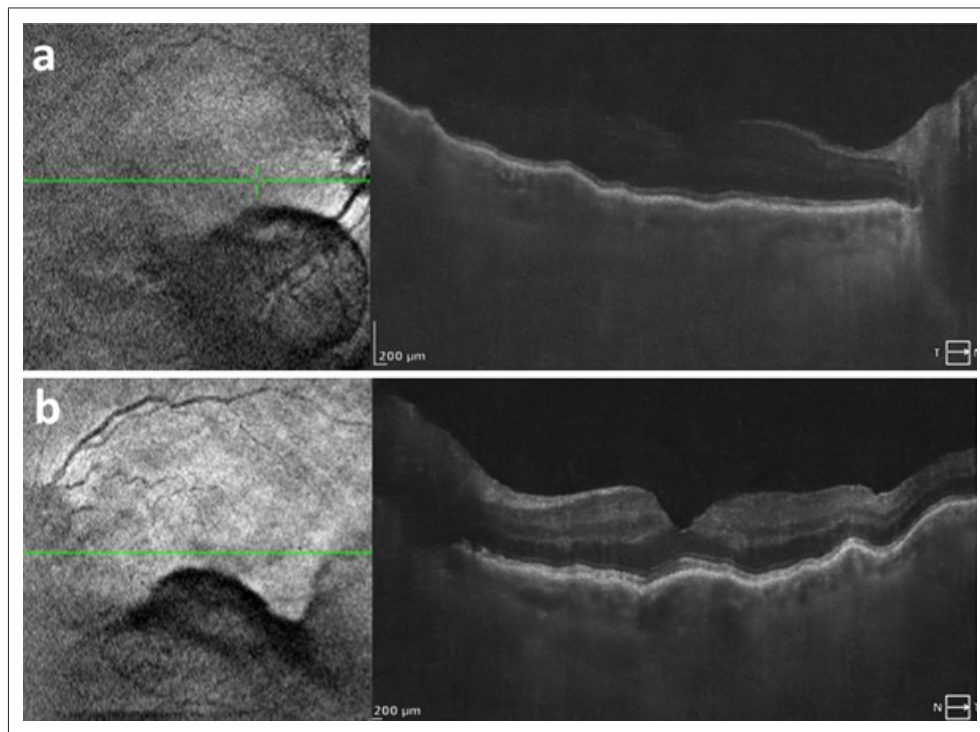


Figure 2. Optical coherence tomography scans of the right (a) and left (b) eyes. Foveal cross-sectional images demonstrate choroidal folds in both eyes.

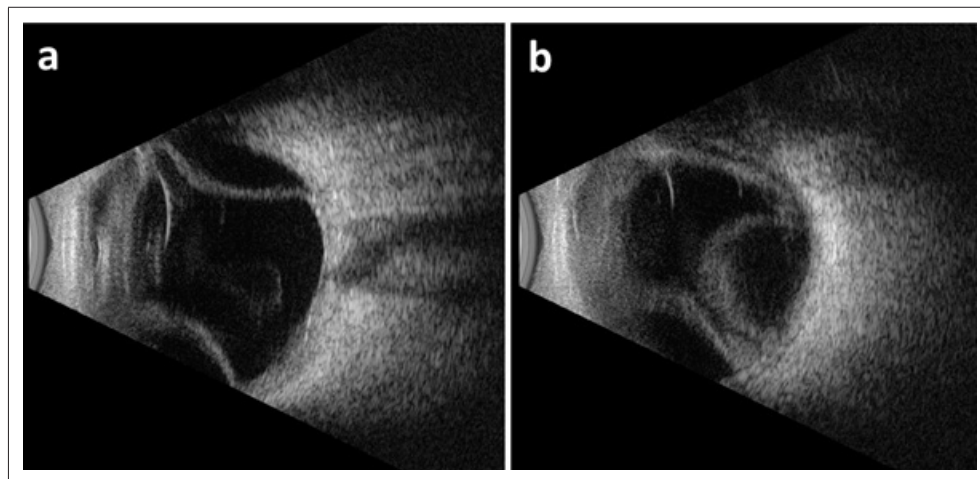


Figure 3. Ocular ultrasonography images of the right (a) and left (b) eyes. Findings consistent with choroidal effusion are observed in both eyes.

tion of the agent and the disruption of blood-retinal barrier; and the hypotony is attributed to drug-related damage to ciliary body and atrophy of the ciliary body, leading to reduced aqueous humor production (6,7). Cidofovir-associated hypotony may further be complicated by maculopathy and choroidal effusion (5). The bilateral and symmetric presentation observed in our patient is consistent with a systemic toxic effect rather than a localized inflammatory process.

In differential diagnosis, infectious etiologies, paraneoplastic causes, systemic or autoimmune diseases, and mas-

querade syndromes must be carefully considered. In the present case, the absence of active intraocular infection, lack of supportive systemic findings, and negative rheumatologic and pulmonary evaluations by corresponding specialists made these diagnoses unlikely. Furthermore, the close temporal relationship between cidofovir exposure and symptom development favored a drug-induced etiology.

Although the management of cidofovir-induced uveitis does not necessitate discontinuation of the agent and topical corticosteroids combined with cycloplegic agents are generally suf-

ficient, cidofovir should be ceased in case severe uncontrolled uveitis or persistent severe hypotony (5). Probenecid has also been reported to reduce the risk of cidofovir-induced uveitis by inhibiting intraocular secretion of the agent through competitive inhibition (9). In this case, concomitant oral probenecid prophylaxis was administered with cidofovir. The development of uveitis despite appropriate oral probenecid prophylaxis may be partially explained by increased systemic exposure related to cumulative dosing and potential alterations in renal clearance. In the present case, systemic corticosteroid therapy was avoided due to the patient's history of recurrent viral infections. Discontinuation of cidofovir and initiation of intensive topical corticosteroid therapy were deemed appropriate.

Conclusion

Cidofovir may cause severe bilateral ocular toxicity, including uveitis, hypotony, and choroidal effusion, even after a limited number of intravenous doses. This case highlights the importance of considering cidofovir-induced ocular adverse effects in the differential diagnosis of bilateral uveitis with hypotony, particularly in immunocompromised patients. Early recognition, prompt discontinuation of the agent, and appropriate topical anti-inflammatory treatment are essential to prevent irreversible visual morbidity. Close interdisciplinary collaboration and routine ophthalmic monitoring should be considered for patients receiving cidofovir therapy.

Disclosures

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: The authors certify that they have obtained all appropriate patient consent forms. The patient consented to the reporting of clinical information and images on the condition of anonymity.

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Histopathologically Proven Tarsal Lacrimal Gland Choristoma

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Abstract

Ectopic lacrimal glands, also known as lacrimal gland choristomas, are seen in various areas of the eyes and are characterized by their placement outside of their typical anatomical position. While tarsal lacrimal gland choristomas are uncommon, the bulbar conjunctiva and limbal area have been identified as the most frequent sites.

Herein, we report a 32-year-old female with a mass on the left lower eyelid conjunctiva that is histopathologically proved to be a lacrimal gland choristoma.

Keywords: Ectopic lacrimal gland, conjunctiva, lacrimal gland choristoma, choristoma, mass, tumor, orbit

Introduction

The secretory lacrimal apparatus consists of the main lacrimal gland located in the orbital lacrimal fossa, the palpebral lobe of the lacrimal gland located temporal to the superior fornix and two accessory glands (Krause and Wolfring glands) (1).

Ectopic lacrimal gland (lacrimal gland choristoma / choristomatous lacrimal gland) is defined as the localization of lacrimal gland out of its normal anatomical position and is referred to as simple or complex choristoma. While simple choristoma is considered an isolated mass, complex choristoma is found in combination with other tissue types (1,2).

In this case report, a patient presenting with a mass on the left lower eyelid conjunctiva histopathologically proved to be a simple choristoma is presented.

Case Report

A 32-year-old otherwise healthy woman admitted to out-patient clinic after noticing a mass formation on the left lower

eyelid 1 month earlier. Upon ophthalmologic examination a mass demonstrating both vascularized and cystic structures located in the left lower palpebral conjunctiva, adjacent to medial canthus was detected (Fig. 1a, b). Visual acuity was 1.0 bilaterally (according to Snellen chart) and anterior segment examination and dilated fundus examination were otherwise normal. Preoperative imaging was not performed because the lesion was a small (3 × 2 mm), well-circumscribed superficial mass confined to the palpebral conjunctiva. Given its extremely small size, it would also have been highly challenging to detect or adequately characterize even with high resolution computed tomography. In such cases, imaging is generally not required, and excisional biopsy is considered both diagnostic and therapeutic.

Total excision of the mass under local anesthesia was performed. Specifically, a complete excisional biopsy of the mass on the lower palpebral conjunctiva was carried out with clear margins. The lesion was carefully dissected from

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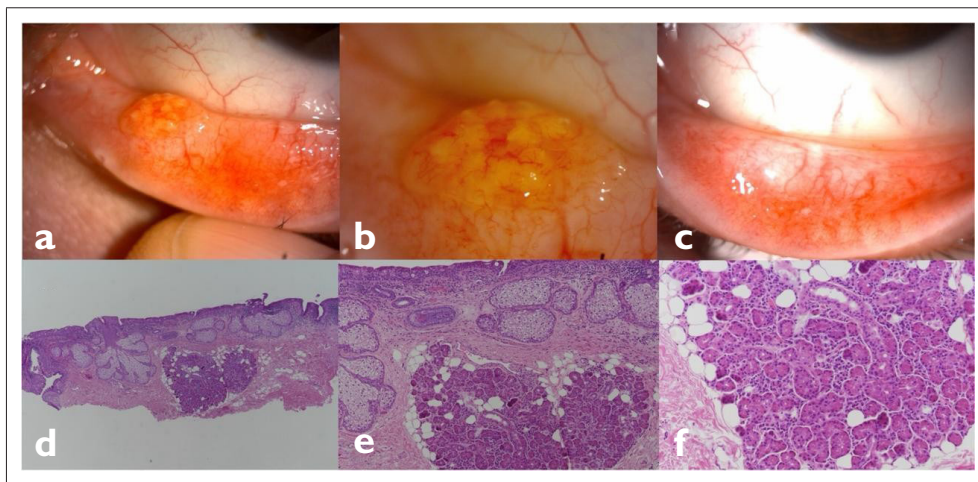


Figure 1. (a, b) An amelanotic mass containing glandular like cyts and vascular structures in the inferior tarsal conjunctiva, (c) Post-operative 3rd week appearance of the patient, (d) A lacrimal gland structure under the conjunctival epithelium. (H&E x40), (e) A lacrimal gland structure under the conjunctival epithelium. (H&E x100), (f) Lacrimal gland ducts and acini (H&E x200).

the surrounding conjunctival tissue, leaving no residual tissue behind. The surgical site was left to heal by secondary intention without the application of any grafts. Histopathologic examination of the excision material revealed lacrimal gland acinar and ductal structures in a focus in the tunica propria under the conjunctival epithelium upon Hematoxylin and Eosin (H&E) staining (Fig. 1c, d, e). Because the morphological features were entirely benign and no abnormal or malignant structures were observed, additional special staining was not deemed necessary. The result was compatible with ectopic lacrimal gland.

After excision, preservative-free artificial tears (Hyonat, VEM, Türkiye) 6x1, loteprednol etobonate (Dolte, Abdi Ibrahim, Türkiye) and eye drops containing tobramycin (Tobrased, Bilim, Türkiye) 4x1 were initiated. Postoperative follow-up at the first month was uneventful, with the wound healing completely without complications (Fig. 1f).

Discussion

The lacrimal gland begins to form with proliferation of epithelial cells in the fornix of the upper external conjunctiva in the 6th-8th weeks of gestation (3). Embryonic development of the gland is based on branching morphogenesis in the form of lobules consisting of acini, intralobular, interlobular, and excretory ducts because it has a tubulo-acinar branching structure similar to a grape cluster. The development of the gland depends on the chemical signaling interaction between the surface ectoderm and the surrounding mesenchyme. Localized abnormal expression of this signaling interaction causes deviations in morphogenesis and ends up with lacrimal gland choristomas (4). During embryogenesis, ectopic lacrimal gland tissue occurs as a result of abnormal accu-

mulation of supratemporal embryonic conjunctival epithelial cells that will differentiate into lacrimal gland tissue (1), invagination into the anterior orbital soft tissue and migration into deep tissues (5).

Ectopic lacrimal glands are present at birth or in early infancy in most individuals (1,5-8) and a minor male preponderance is seen according to the literature. Although there is no definitive epidemiological data specifically on the prevalence in adult age, a systematic review published in 2020 examined 180 cases of ectopic lacrimal gland tissue reported between 1946 and 2018. In this study, the mean age at diagnosis was reported as 21 years (1).

Although ectopic lacrimal gland can be found in many parts of the eye, the most common sites have been defined as bulbar conjunctiva and limbal region (2,6). Tarsal lacrimal gland choristomas are not often encountered (6). Orbital involvement, especially intraocular lacrimal gland formation is rarely observed (2). In the differential diagnosis of ectopic lacrimal glands other amelanotic conjunctival masses, including dermoid, dermolipoma, hemangioma, amelanotic malignant melanoma, conjunctival intraepithelial neoplasia and squamous cell carcinoma are included (7).

Dermoids are seen as well-circumscribed oval, yellow-white masses arising from the bulbar conjunctiva, often involving the bulbar conjunctiva or corneoscleral limbus (7,8). Dermalipomas are usually pale yellow, soft, fluctuant and fusiform masses lying under the palpebral lobe of the lacrimal gland (8). Hemangiomas are frequently observed as intertwined, slightly dilated blood vessels on the bulbar conjunctiva (7). Amelanotic malignant melanomas are seen as flesh-colored, elongated mass on the limbal, bulbar, palpebral conjunctiva or fornix, whereas conjunctival intraep-

ithelial neoplasia is seen as a sessile or minimally elevated lesion on the limbus and less frequently on the fornix or tarsal conjunctiva. Conjunctival squamous cell carcinoma is clinically similar to conjunctival intraepithelial neoplasia but may be larger and more elongated than intraepithelial neoplasia (7,8).

Although the diagnosis and treatment of orbital and intraocular choristomas, which are more rare, are quite difficult, they can severely affect visual function and have complications that may lead to enucleation of the eye (4). Therefore, recognition and early intervention of intraocular choristomal masses is also very important. Although computed tomography and magnetic resonance imaging findings are useful in the differential diagnosis of ectopic lacrimal tissue from other intraocular tumors, the rarity of ectopic lacrimal tissue in these regions is responsible for the frequent misdiagnosis of neoplasm (9). Retinoblastoma, ocular lymphoma, medulloepithelioma, uveal amelanotic nevus, choroidal hemangioma, choroidal osteoma and uveal leiomyoma should be kept in mind in the differential diagnosis of intraocular masses (9,10). To make a differential diagnosis, histopathologic confirmation is required (10).

Proptosis, glaucoma, or a mass on the bulbar conjunctiva are possible presenting complaints, depending on where the ectopic lacrimal gland is located (11). The most common presentation symptom of patients with lacrimal gland choristoma is proptosis (1,10), whereas ectopic glands located in the eyelids are most commonly presented with mass formation (1). In addition to epiphora secondary to fistula opening (1,11), ectopic lacrimal glands located in the lacrimal sac and nasal mucosa may also present with epiphora. Inflammation of the ectopic lacrimal gland may cause stasis of secretions, leading to growth of the ectopic tissue mass, and may also be responsible for patients developing symptoms in time (1). Due to a significant inflammatory response, an ectopic lacrimal gland can even result in bone damage (10).

On rare occasions, pleomorphic adenoma or adenocarcinoma may emerge from these abnormal glands (11). They must be taken into consideration as a differential diagnosis in cases with an abnormal clinical course since they can mimic dacryocystitis or lacrimal duct stenosis (12). The clinical and histologic characteristics emphasize the value of a multifaceted strategy to treating these individuals, which includes comparing the mass's anatomical and histologic characteristics with the clinical symptoms to determine the accurate diagnosis (13).

The management of conjunctival tumors differs depending on the presumed diagnosis and the size and extent of the lesion (8). While local excision is preferred as the main treatment modality in ectopic lacrimal glands, the clinical management of these choristomas and their effects on visual

acuity are defined depending on the location of the choristoma (1,4). Epibulbar conjunctival lesions and choristomas in the eyelids can be easily excised without serious impairment in visual function and usually appear as solitary masses that can be easily managed (4). However, the presence of complications such as the risk of tumor dissemination, glaucoma, amblyopia and poor prognosis in visual acuity in intraocular lacrimal choristomas might require harder treatments and surgeries even enucleation (14). In addition, ectopic lacrimal glands can undergo neoplastic transformation like normal lacrimal glands and there is a risk of recurrence after incomplete excision (1).

Conclusion

As a result, although the most common age of detection of lacrimal gland choristomas is in infancy (9), it should be kept in mind especially in the differential diagnosis of amelanotic conjunctival masses even in adults.

Disclosures

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: The authors confirm that written informed consent was obtained from the patient for the publication of this case report, including any related clinical data and images, in accordance with Declaration of Helsinki

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Conflict of Interest: The authors declare that there are no conflicts of interest related to the publication of this case report.

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