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AT A GLANCE

2026 Issue 2 at a Glance:

Esteemed colleagues,

In the second issue of 2026, the Turkish Journal of Ophthalmology features one editorial, five original research articles, one review, four letters to the editor, and one response to the letter to the editor, all of which we hope you will find engaging and beneficial.

In their editorial titled "Functional or Dysfunctional Epiphora? A Reminder for Refined Terminology", Yazıcı and Altın Ekin emphasized that in cases of persistent epiphora and tear retention despite patent lacrimal irrigation and dacryocystography and otherwise normal ocular findings, the most frequently used terms "functional epiphora" and "functional nasolacrimal duct obstruction" lead to terminological confusion and inconsistency, and that using the term "dysfunctional epiphora" is more appropriate (See pages 72-73).

In the original research section, a retrospective study by Çelik Büyüktepe et al. evaluated the visual, refractive, keratometric, tomographic, and aberrometric outcomes of epithelial-island corneal cross-linking therapy in progressive keratoconus patients with thin corneas. The authors reported that no endothelial cell loss, endothelial dysfunction, prolonged corneal edema, or severe vision-threatening complications were observed in any of the cases, indicating that this approach may serve as a safe and effective treatment alternative (See pages 74-80).

In their study titled "Six-Month Outcomes of Combined Phacoemulsification and Kahook Dual Blade Excisional Goniotomy Surgery in Various Glaucoma Subtypes", Biberoğlu Çelik et al. found that this surgical approach significantly reduced both intraocular pressure (IOP) and the need for antiglaucoma medications in patients with early to moderate glaucoma, and noted that complication rates were also low (See pages 81-88).

In a study investigating the effect of accelerated epi-off corneal cross-linking on visual acuity and quality in adolescent patients with progressive keratoconus, Yıldırım Erdal and Kazancı concluded that this method is an effective treatment that facilitates visual improvement and the reduction of both total corneal and corneal epithelial higher-order aberrations (See pages 89-97).

Özdemir Yalçınsoy et al. compared the demographic characteristics, clinical findings, disease course, and visual outcomes of patients with syphilitic uveitis according to HIV-positive and -negative groups and determined that signs of intraocular inflammation were more frequent in patients with HIV co-infection. However, the presence of HIV co-infection did not impact final visual acuity or the rates of ocular complication development (See pages 98-109).

In their study titled "Evaluation of Changes in the Iridocorneal Angle and Anterior Segment Parameters Following Selective Laser Trabeculoplasty in Pseudoexfoliation Glaucoma", Yıldırım Erdal and Bayraktar examined the effects of this procedure on the iridocorneal angle, anterior chamber, and iris and evaluated the relationship between these structural changes and IOP reduction (See pages 110-118).

As the scope of artificial intelligence applications in medicine expands, interest in utilizing these technologies in ophthalmology is steadily growing. In the review section, Köseoğlu and Liu present the current landscape of large language model (LLM) research in ophthalmology through a bibliometric analysis. The authors emphasized that the vast majority of these studies focus on clinical decision support, predominantly for retinal applications, and are increasingly featured in top-tier Q1 journals. Furthermore, they highlighted a geographical imbalance in publications, noting that female researchers remain significantly underrepresented across all authorship categories (See pages 119-130).

In the letter to the editor section, Koçer and Aksoy present a case of chronic hypotony secondary to traumatic cyclodialysis, wherein a medically refractory IOP elevation developed following cyclodialysis repair and was successfully controlled via suture revision. Through this case, the authors highlight the importance of utilizing adjustable sutures in incisional cyclodialysis closure surgeries (See pages 131-134).

In another letter, Üçgül and Aktaş present the management of a case of cyclodialysis and persistent hypotony following gonioscopy-assisted transluminal trabeculotomy (GATT) and discuss the available treatment options (See pages 135-139).

Finally, Cintas et al. present the management of a rare case of *Enterobacter cloacae* keratitis, highlighting the predisposing roles of severe dry eye and topical corticosteroids, and briefly review previously reported cases to address the risk factors associated with this opportunistic infection (See pages 140-144).

We hope that the articles in the second issue of this year will make for interesting reading and provide guidance in your professional practice.

Respectfully on behalf of the Editorial Board,

Özlem Yıldırım, MD

Editorial

Functional or Dysfunctional Epiphora? A Reminder for Refined Terminology

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Persistent epiphora with objective tear retention, despite patent lacrimal irrigation and dacryocystography and otherwise normal ocular findings, represents a challenging clinical entity. A variety of terms have been used to describe this condition, including "functional obstruction," "functional epiphora," and "functional nasolacrimal (duct or drainage) obstruction." Although confusion and inconsistency in terminology have been addressed in several articles, a solution has yet to be achieved.[1,2,3,4,5]

Currently, "functional epiphora" and "functional nasolacrimal duct obstruction" are the most commonly used terms. In a 2012 editorial, Perry[5] proposed the term "dysfunctional epiphora," emphasizing the conceptual limitations inherent in the term "functional." Despite its compelling rationale, this proposal has had minimal impact on subsequent literature. A PubMed search from 2012 to 2025 identified 44 publications that use "functional epiphora" or "functional nasolacrimal (duct or drainage) obstruction" in the title or abstract, whereas no publications used the term "dysfunctional epiphora". Here, we aim to reintroduce the term "dysfunctional epiphora" and further refine its use.

Keywords: Epiphora, functional, dysfunctional, lacrimal, terminology

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Labeling epiphora as "functional" may be misleading, as it implies a normal and physiological process, despite the presence of a symptomatic abnormality. This terminology can complicate communication with patients and colleagues and may lead to the premature cessation of diagnostic and critical thinking processes. In contrast, "dysfunctional epiphora" acknowledges an underlying abnormality even when conventional tests fail to demonstrate a discrete obstruction.

Effective tear drainage requires both an anatomically patent outflow pathway and intact functional mechanisms that allow tears to enter and progress through the system, primarily the lacrimal pump. The phrase "dysfunctional epiphora" accurately reflects epiphora caused by impaired function and should be classified as a symptom-based category, similar to obstructive epiphora.

Dysfunctional epiphora may arise from a wide range of abnormalities. Epiphora associated with facial paralysis clearly illustrates the critical role of orbicularis muscle tone and blinking dynamics in both eyelid position and lacrimal pump function. Other common causes include ectropion, entropion, conjunctivochalasis, punctal apposition syndrome, inadequate globe-eyelid contact, and botulinum toxin injection.

In a subset of patients, no specific cause can be determined. For these cases, often labeled as "functional epiphora" in prior studies, the term "idiopathic dysfunctional epiphora" would be a more accurate description. A further subgroup consists of patients with persistent epiphora following dacryocystorhinostomy despite a patent drainage pathway. These cases may be classified as "postoperative dysfunctional epiphora". Adoption of this terminology may help eliminate confusion in scholarly and clinical communication.

Declarations

Authorship Contributions

Concept: B.Y., Design: B.Y., M.A.E., Data Collection or Processing: B.Y., M.A.E., Analysis or Interpretation: B.Y., M.A.E., Literature Search: B.Y., M.A.E., Writing: B.Y., M.A.E.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

Epithelial-Island Corneal Crosslinking in the Treatment of Progressive Keratoconus Patients with Thin Corneas: 2-Year Visual, Refractive, Keratometric, Tomographic, and Aberrometric Outcomes

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Abstract

Objectives: To evaluate the visual, refractive, tomographic, and aberrometric outcomes of epithelial-island corneal collagen crosslinking (CXL) treatment in halting progression in keratoconic eyes with thin corneas.

Materials and Methods: We retrospectively reviewed the charts of consecutive patients with advanced keratoconus who had a thinnest corneal thickness (TCT) of <380 µm as measured by anterior segment optic coherence tomography and underwent epithelial-island CXL. The procedure involved tomography-guided customized epithelial debridement, followed by corneal saturation with iso-osmolar and hypo-osmolar riboflavin solutions and ultraviolet-A irradiation (30 min, 3.0 mW/cm^2). Best spectacle-corrected distance visual acuity (CDVA), manifest refraction (MR), slit lamp biomicroscopy, corneal tomography, corneal aberrometry, and endothelial cell count (ECC) were evaluated before CXL and at postoperative months 12 and 24.

Results: The study included 10 eyes of 9 patients with a median age of 29.5 (range, 17-51) years. The median postoperative follow-up time was 24.0 (12.0-108.0) months. The median preoperative TCT was 324.0 (232.0-380.0) µm. Preoperatively, the median CDVA was 1.00 (0.70-1.80) logarithm of the minimum angle of resolution, MR spherical equivalent was -18.00 (-25.00 to -6.00) diopters (D), maximum keratometry value was 84.75 (59.80-99.00) D, vertical coma was -1.068 (-6.428 to 0.613) D, and ECC was 2568 (2021-2750) cells/mm^2. At postoperative year 1 and year 2, there were no statistically significant changes in any of these parameters (all p>0.05). No significant haze, endothelial cell loss, or any other clinically significant adverse event was encountered in any of the eyes.

Conclusion: Epithelial-island CXL seems to be an effective alternative treatment modality in halting progression in keratoconic eyes with thin corneas. Further studies with a longer follow-up and a larger sample size would help to establish the long-term safety and efficacy of this treatment modality.

Keywords: Corneal crosslinking, epithelial-island corneal crosslinking, customized epithelial debridement, keratoconus, thin cornea

Cite this article as: Çelik Büyüktepe T, Kılıç B, Uçakhan ÖÖ. Epithelial-Island Corneal Crosslinking in the Treatment of Progressive Keratoconus Patients with Thin Corneas: 2-Year Visual, Refractive, Keratometric, Tomographic, and Aberrometric Outcomes. Turk J Ophthalmol. 2026;56:74-80

This study was partially presented at the 50th European Contact Lens Society of Ophthalmologists (ECLSO) Congress (April 27, 2024, İstanbul, Türkiye).

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Introduction

Corneal collagen crosslinking (CXL) is the only proven effective treatment for halting the progression of ectasia in keratoconus.[1] Corneal CXL was introduced by Wollensak et al.[1] and involves application of iso-osmolar 0.1% riboflavin solution to de-epithelized corneal stroma for 30 minutes, followed by ultraviolet-A (UVA) irradiation (365 nm, 3 mW/cm^2) for another 30 minutes while iso-osmolar riboflavin application is continued. Known as the "Standard protocol" or "Dresden protocol", this is the most commonly used CXL protocol, and the safety and efficacy of this procedure have been demonstrated in *in vivo* and *in vitro* studies, as well as randomized clinical trials.[2,3] The

main limitation of the technique is the requirement of a corneal stromal thickness of at least 400 µm to protect the endothelial and deeper ocular structures from UVA exposure.[4] However, in many cases of advanced progressive keratectasia, minimal stromal thickness is below 400 µm. To overcome this limitation, several alternative approaches have been described, including the use of hypo-osmolar riboflavin,[5] reduced UVA exposure time (Sub400 protocol),[6] transepithelial CXL,[7] contact lens-assisted CXL,[8] lenticule-assisted CXL,[9] peripheral CXL,[10] and epithelial-island CXL.[11] However, the short- and long-term outcomes of these alternative protocols have not been fully elucidated.[12]

The aim of this study was to evaluate the visual, refractive, keratometric, tomographic, and aberrometric outcomes of epithelial-island CXL in patients with progressive keratoconus and thin corneas.

Materials and Methods

The study was approved by the Ankara University Faculty of Medicine, Human Research Ethics Committee (decision no: İ11-790-23, date: 21.12.2023) and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient or their legal guardian.

The charts of consecutive progressive keratoconus patients who underwent CXL were reviewed retrospectively. Those with thin corneas who underwent epithelial-island CXL using iso-osmolar riboflavin 0.1%/dextran 20% and hypo-osmolar riboflavin 0.1% solutions were included in the study. "Thin cornea" was defined as a thinnest corneal thickness (TCT) of <380 µm measured by preoperative anterior segment optical coherence tomography (AS-OCT). Exclusion criteria included the use of hydroxypropyl methylcellulose during the CXL procedure, a history of herpetic keratitis or other corneal disease, a history of autoimmune disease, and pregnancy or breastfeeding.

All patients were examined at baseline, at postoperative month 1, 3, and 6, and yearly thereafter. The following were recorded during each visit: uncorrected distance visual acuity, best spectacle-corrected distance visual acuity (CDVA), manifest refraction (MR), corneal tomography with pachymetry and aberrometry (Pentacam, Oculus GmbH, Wetzlar, Germany), AS-OCT (Visante, Carl Zeiss Meditec, Dublin, CA, USA), and endothelial cell count (ECC) on *in vivo* confocal microscopy (HRT II, Rostock Cornea Module, Heidelberg, Germany). Prior to CXL, patients discontinued rigid gas permeable contact lens wear for 4 weeks and soft contact lens wear for at least 2 weeks. Keratoconus progression was defined as an increase of at least 1 diopter (D) in maximum keratometry (Kmax) on consecutive corneal tomography measurements obtained during the postoperative follow-up period.

Surgical Technique

Corneal tomography measurements were reviewed immediately before surgery. On the pachymetric maps, displacement of the cone apex from the geometric center of the cornea was calculated in the x and y coordinates. Before the procedure, with the patient seated at the biomicroscope, the vertical and horizontal meridians of the cornea were marked with a Mendez marker, and the geometric center of the cornea was marked with a Sinskey hook.

The CXL procedure was performed under sterile conditions in an operating room, using the same protocol for all cases. After positioning the patient in the supine position, the surgical field was draped and topical anesthesia was applied (0.5% proparacaine hydrochloride; Alcaine, Alcon Laboratories, Texas, USA). Then, 10-12 consecutive ultrasound pachymetry measurements were obtained as close as possible to the marked geometric center of the cornea. The mean of the three thinnest readings was calculated. The cone apex location was identified by measuring the vertical and horizontal offsets previously determined from the corneal tomography pachymetric maps using a caliper. An 8- to 9-mm epithelial debridement was performed, preserving an epithelial island of approximately 3×3-mm over the cone apex. The cornea was then saturated with iso-osmolar riboflavin 0.1% in dextran 20% solution (MedioCross D, Peschke Meditrade GmbH, Germany) for 30 minutes. Corneal thickness was subsequently measured at the central cornea by ultrasound pachymetry, and the mean of the three thinnest readings was recorded. Hypo-osmolar riboflavin 0.1% solution (MedioCross H, Peschke Meditrade GmbH, Germany) was then instilled for an additional 30 minutes, after which the measurement was repeated. Once a stromal thickness of >400 µm was achieved, UVA irradiation was initiated (365 nm, 3.0 mW/cm^2; UV-X system, IROC AG, Switzerland). During the UVA phase, instillation of iso-osmolar riboflavin 0.1% in dextran 20% solution was continued. At the end of the procedure, a silicone hydrogel soft contact lens was placed (Air Optix Night & Day Aqua, Alcon Laboratories, Texas, USA).

Postoperatively, topical antibiotic drops (0.5% moxifloxacin, 4x1; Vigamox, Alcon Laboratories, Texas, USA) and artificial tears (1.4% polyvinyl alcohol + 0.6% povidone, 4x1; Novaqua single-dose eye drops, Deva Holding, İstanbul, Türkiye) were prescribed. Once complete re-epithelialization was confirmed at postoperative follow-up, the contact lens was removed and topical corticosteroid therapy was initiated (1% prednisolone acetate 4 times

daily; Pred Forte, Allergan, Dublin, Ireland), then tapered to discontinuation while monitoring for the development of corneal haze. All patients were warned not to rub their eyes and were advised to wear sunglasses.

Statistical Analysis

The data were described using frequency and percentage for categorical variables and as mean ± standard deviation (median; range) for numerical variables. Changes over time were assessed using the Wilcoxon signed-rank test or the Friedman test. Statistical analysis was performed using SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, ABD). A p value of <0.05 was considered statistically significant.

Results

Between March 2014 and March 2022, epithelial-island CXL was performed in 17 eyes of 16 patients. Ten eyes of 9 patients with at least 1 year of follow-up were included in the study.

The mean age was 34.2±14.2 (median, 29.5; range, 17-51) years. All cases were classified as stage 4 keratoconus according to the Amsler-Krumeich grading system.[13] Four patients had a history of atopy. Complete epithelial closure was achieved at a mean of 3.3±0.8 (median, 3; range, 2-4) days postoperatively. The mean follow-up time was 37.2±30.2 (median, 24.0; range, 12.0-108.0) months. Prolonged corneal edema or severe corneal haze were not observed in any case during the follow-up period.

In all cases, the cornea was sequentially treated with iso-osmolar riboflavin followed by hypo-osmolar riboflavin during the CXL procedure.

The mean preoperative TCT was 314.7±48.0 (median, 324.0; range, 232.0-380.0) μm and the Kmax was 82.8±10.8 (median, 84.8; range, 59.8-99.0) D. At postoperative year 1, TCT was 298.1±56.1 (median, 290.0; range, 218.0-386.0) μm and Kmax was 80.3±10.2 (median, 81.3; range, 58.8-99.2) D, demonstrating clinical stability (p=0.944 and p=0.196, respectively). No clinically significant progression was observed in CDVA, MR, tomographic indices, aberrometry values, or ECC values at postoperative year 1 (p>0.05) (Table 1).

Six patients (7 eyes) completed the 2-year postoperative follow-up. Clinical stability was maintained across all visual, refractive, keratometric, tomographic, and aberrometric parameters at the 2-year follow-up visit (all p>0.05) (Table 1).

In the postoperative period, 6 patients were fitted with scleral lenses, while 4 eyes of 3 patients were followed without lenses. None of the eyes required keratoplasty.

The 7 eyes of 7 patients followed for less than 1 year after epithelial-island CXL were lost to follow-up due to non-attendance of scheduled visits. In this group, the mean (median; range) follow-up time was 1.7±1.0 (1; 1-3) months and preoperative Kmax, TCT, and CDVA values were 86.2±11.5 (90.2; 68.8-97.8) D, 305.3±64.7 (269.0; 267.0-380.0) μm, and 1.40±1.40 (1.69; 1.70-1.00) logarithm of the minimum angle of resolution, respectively.

Table 1. Comparison of preoperative and postoperative visual, refractive, keratometric, tomographic, and aberrometric values in patients who underwent epithelial-island corneal crosslinking

	Preoperative (n=10)	1 year (n=10)	2 years (n=7)	p
CDVA (logMAR)	0.99±0.37 (1.00; 0.70-1.80)	0.95±0.33 (1.00; 0.70-1.60)	0.79±0.29 (1.00; 0.40-1.00)	0.051
MRcyl (D)	-5.14±2.04 (-6.00; -8.00 to -2.00)	-4.69±2.25 (-5.50; -8.00 to -2.00)	-4.90±2.56 (-6.00; -8.00 to -2.00)	1.000
MRSE (D)	-15.86±7.72 (-18.00; -25.00 to -6.00)	-16.86±6.79 (-21.00; -25.50 to -6.00)	-14.21±6.93 (-15.00; -21.25 to -6.00)	0.392
K1 (D)	66.37±7.63 (66.25; 49.40-75.60)	67.21±7.81 (67.95; 49.00-77.50)	64.36±7.88 (65.60; 49.40-73.40)	0.957
K2 (D)	69.28±7.83 (70.25; 50.80-77.90)	70.59±7.54 (70.70; 50.70-79.60)	67.07±8.64 (68.70; 49.60-75.80)	0.075
TCT (μm)	314.67±47.99 (324.00; 232-380)	298.08±56.07 (290.00; 218-386)	330.33±66.16 (317.50; 244-434)	0.960
CCT (μm)	404.56±52.65 (395.00; 346-503)	379.38±67.59 (360.00; 289-492)	419.50±84.16 (372.00; 358-544)	0.440
Kmax (D)	82.84±10.84 (84.75; 59.80-99.00)	80.32±10.20 (81.25; 58.80-99.20)	74.48±8.66 (77.45; 58.30-81.70)	0.443

Table 1. Continued				
	Preoperative (n=10)	**1 year (n=10)**	**2 years (n=7)**	**p**
ISV	163.00±39.68 (160.00; 120-230)	170.71±39.91 (170.50; 111-226)	159.71±35.66 (162.00; 114-220)	0.108
IVA	0.91±0.35 (0.93; -0.25 to 1.55)	0.83±0.32 (0.86; 0.33-1.39)	0.91±0.22 (0.98; 0.55-1.17)	0.270
KI	1.37±0.18 (1.37; 1.17-1.72)	1.38±0.15 (1.34; 1.14-1.65)	1.37±0.09 (1.36; 1.21-1.46)	0.673
CKI	1.19±0.08 (1.18; 1.07-1.34)	1.18±0.11 (1.16; 1.00-1.40)	1.15±0.08 (1.12; 1.06-1.27)	0.172
Rmin	4.12±0.62 (3.98; 3.41-5.64)	4.29±0.59 (4.16; 3.40-5.74)	4.45±0.68 (4.26; 3.58-5.79)	0.065
IHA	45.70±0.62 (3.98; 3.41-5.64)	35.69±20.40 (34.60; 6.10-69.60)	33.69±21.11 (26.40; 0.40-82.30)	0.682
IHD	0.199±0.132 (0.158; 0.048-0.483)	0.186±0.117 (0.179; 0.043-0.438)	0.194±0.065 (0.189; 0.136-0.315)	0.308
Vertical coma	-1.723±2.106 (-1.068; -6.428 to 0.613)	-1.122±1.946 (-0.199; -5.210 to 1.796)	-1.255±0.981 (-1.216; -2.457 to -0.073)	0.552
Horizontal coma	-0.537±2.307 (-0.887; -3.625 to 2.568)	-0.251±2.098 (-0.376; -4.021 to 2.950)	-0.309±2.589 (-1.269; -3.833 to 2.481)	0.825
ECC (cells/mm^2)	2453.0±407.6 (2568; 2021-2750)	2405.0±219.42 (2510; 2261-2621)	2418.25±249.15 (2498; 2209-2523)	0.957

Values are presented as mean ± standard deviation (median; range). P values were calculated using Friedman two-way analysis of variance by ranks for dependent samples. CDVA: Corrected distance visual acuity, logMAR: Logarithm of the minimum angle of resolution, MRcyl: Manifest refraction cylinder, MRSE: Manifest refraction spherical equivalent, K1: Flat keratometry, K2: Steep keratometry, TCT: Thinnest corneal thickness, CCT: Central corneal thickness, Kmax: Maximum keratometry, ISV: Index of surface variance, IVA: Index of vertical asymmetry, KI: Keratoconus index, CKI: Central keratoconus index, Rmin: Minimum sagittal curvature, IHA: Index of height asymmetry, IHD: Index of height decentration, ECC: Endothelial cell count

Discussion

In our study, epithelial-island CXL provided clinical stabilization of visual, refractive, keratometric, tomographic, and aberrometric parameters over a 2-year follow-up period in patients with progressive keratoconus and thin corneas. No significant endothelial cell loss, endothelial dysfunction, prolonged corneal edema or any other clinically significant adverse event was encountered in any eye.

In the standard Dresden protocol, UVA surface irradiation at 3 mW/cm^2 induces crosslinking within the anterior 300 µm of the corneal stroma.[14] *In vitro* studies have established a UVA cytotoxicity threshold of 0.36 mW/cm^2 for corneal endothelial cells,[15] and a minimum stromal thickness of 400 µm prior to UVA irradiation has been emphasized as a prerequisite for the safe application of the standard protocol. Although corneal thickness in early and moderate keratoconus typically ranges from 410 to 470 µm,[16] this safety threshold cannot be met in advanced keratoconus, where standard UVA doses carry a risk of endothelial injury. Kymionis et al.[17] reported endothelial cell loss in thin corneas (<400 µm) treated with the standard CXL protocol. Alternative CXL protocols have been described for keratoconus cases with thin corneas.[12] The use of hypo-osmolar riboflavin was found to be safe in corneas with a stromal thickness greater than 330-345 µm,[5,18] with long-term effectiveness comparable to that of the standard Dresden protocol.[18] In contrast, transepithelial CXL has been shown to be less effective than the standard Dresden protocol. Reduced UVA exposure time as in the Sub400 protocol,[6] contact lens-assisted CXL,[8] lenticule-assisted CXL,[9] peripheral CXL,[10] and epithelial-island CXL[11] have emerged as promising alternatives for thin corneas. However, their long-term efficacy and safety profiles have not yet been fully established.

Epithelial-island CXL is an alternative CXL protocol specifically designed for thin and ultra-thin corneas. It can be used alone or in combination with hypo-osmolar riboflavin. In this technique, individualized epithelial debridement is performed prior to riboflavin application to preserve the epithelium overlying the cone apex. The aim is to provide approximately 50 µm of additional barrier over

the corneal endothelium in this region before UVA exposure in order to prevent endothelial cytotoxicity. One study employing this technique reported reduced postoperative pain and faster epithelial healing.[19] It is thought that the preserved epithelial border acts as a refractive surface, directing UVA irradiation toward the mid-stromal layers,[20] while the debrided peripheral epithelial zones facilitate riboflavin penetration beneath the island.[21]

The epithelial-island CXL technique was first described by Kymionis et al.[11] They performed epithelial-island CXL using iso-osmolar riboflavin solution in 2 eyes of 2 patients, one with keratoconus and one with iatrogenic ectasia, with TCT values of 380 and 375 μm.[11] At postoperative month 9, topographic measurements were reported to be stable, with no deterioration in endothelial cell density or morphology.[11] Subsequently, Mazzotta and Ramovecchi[20] performed epithelial-island CXL in 10 eyes with keratoconus (mean TCT: 384 μm; range 368-391 μm), preserving a 3.25-mm diameter epithelial island over the cone apex during keratectomy. However, they used both iso-osmolar and hypo-osmolar riboflavin solutions. Clinical stabilization of visual acuity, keratometry, pachymetry, coma aberrations, and ECC was reported at postoperative year 1.[20] The authors suggested that epithelial-island CXL may offer a safer and more effective treatment option for thin corneas compared to transepithelial CXL.[20] Using a similar protocol, Omar et al.[21] reported clinical stability in visual acuity, mean keratometry, and Kmax in 30 eyes with keratoconus (preoperative mean TCT: 377 μm) over a 1-year follow-up period. AS-OCT assessment of the demarcation line revealed a more superficial but clearly identifiable line (at 216 μm and 300 μm) in the region overlying the preserved epithelial island. Although greater visual and keratometric improvement was reported compared to previous studies, a 2.6% ECC loss was observed and attributed to the exclusive use of iso-osmolar riboflavin. The authors proposed that the addition of hypo-osmolar riboflavin and preservation of a larger epithelial island over the cone apex may provide additional protection against endothelial cytotoxicity.[21] In contrast, Seyyar et al.[19] treated 40 keratoconus eyes with epithelial-island CXL using only iso-osmolar riboflavin and preserving a mean 2-mm diameter epithelial island, and reported refractive and keratometric improvement and stable ECC at postoperative year 1. However, a key distinction in that study was that the mean preoperative TCT was 413 μm (range, 341-528 μm), which may explain why iso-osmolar riboflavin alone was sufficient to ensure endothelial safety.

As evidenced by the available data, epithelial-island CXL has been applied to halt progression in a limited number of eyes with progressive keratoconus and thin corneas and has consistently been reported as a promising and reliable method. However, variability in surgical protocols and the small number of cases remain the most important limiting factors in the existing literature, including the present study. In our study, the epithelial-island CXL using a sequential iso-osmolar and hypo-osmolar riboflavin protocol halted progression and stabilized visual, refractive, and keratometric values over 2 years of follow-up in eyes with thin corneas. No procedure-related decrease in ECC was observed. Significant visual improvement was achieved with scleral lens fitting in 6 of 10 eyes. These findings demonstrate that in advanced keratoconus, progression can be halted with epithelial-island CXL and visual acuity can subsequently be improved through a less invasive approach such as scleral lens fitting, thereby avoiding the need for keratoplasty. Indeed, the anatomical and visual outcomes of lamellar or penetrating keratoplasty may be suboptimal in eyes with advanced keratoconus and no central corneal scarring. Given that keratoconus predominantly affects young individuals, it is important to recognize that eyes undergoing keratoplasty at an early age are at risk of developing long-term complications that can adversely affect visual prognosis, such as endothelial cell loss, stromal opacification, and graft failure. Moreover, post-keratoplasty irregular astigmatism may hinder adequate visual recovery, and achieving satisfactory lens tolerance and visual acuity with contact or scleral lenses in these eyes may prove challenging. Therefore, in advanced keratoconus without central scarring, the therapeutic goal should be to arrest progression while maximally preserving the native corneal tissue, thereby enabling effective visual rehabilitation with contact or scleral lenses.

Study Limitations

The main limitations of our study are its retrospective design and small sample size. Given the multiple parameters analyzed, the absence of statistically significant differences does not preclude the possibility of type II error. Furthermore, the limited sample size reduces the generalizability of our findings. However, the frequent corneal scarring and need for keratoplasty in advanced keratoconus limit the available sample size, as reported in other studies. In addition, there is currently no standardized method for determining the epithelial island to be preserved during debridement. Although we used methods employed in earlier studies, there remains the possibility of measurement errors or inaccuracies in cone

apex identification. Nevertheless, preserving a 3x3-mm epithelial island can mitigate the risk of error. Patient attrition during the follow-up period also introduces a potential risk of selection bias. In clinical practice, it is known that patients with a more stable disease course are just as likely to skip follow-ups as those who develop complications. Therefore, it is not possible to determine with certainty whether the cases with truncated or longer follow-up were clinically more stable, and the results should be interpreted with this limitation in mind. Nevertheless, our study has the longest follow-up after epithelial-island CXL treatment in the published literature. In the cohort followed for 2 years, no significant decline in ECC was observed, and *in vivo* confocal microscopy revealed no evidence of endothelial cytotoxicity.

Conclusion

In conclusion, epithelial-island CXL appears to be a safe and effective treatment option for progressive keratoconus in eyes with thin corneas. Controlled studies with larger sample sizes and extended follow-up periods are needed to confirm the safety and efficacy of this technique.

Ethics

Ethics Committee Approval: The study was approved by the Ankara University Faculty of Medicine, Human Research Ethics Committee (decision no: İ11-790-23, date: 21.12.2023) and the study was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from each patient or their legal guardian.

Declarations

Authorship Contributions

Surgical and Medical Practices: Ö.Ö.U., Concept: Ö.Ö.U., Design: Ö.Ö.U., T.Ç.B., Data Collection or Processing: T.Ç.B., B.K., Analysis or Interpretation: T.Ç.B., Literature Search: T.Ç.B., Writing: T.Ç.B., Ö.Ö.U.

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Original Article

Six-Month Outcomes of Combined Phacoemulsification and Kahook Dual Blade Excisional Goniotomy Surgery in Various Glaucoma Subtypes

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Abstract

Objectives: To evaluate the efficacy and safety of the Kahook Dual Blade (KDB) excisional goniotomy procedure combined with phacoemulsification in patients with primary open-angle glaucoma (POAG), pseudoexfoliation glaucoma (PEXG), and primary angle-closure glaucoma (PACG).

Materials and Methods: This retrospective study included 25 eyes of 25 patients (13 males, 12 females) who underwent combined phacoemulsification and KDB excisional goniotomy for early- to moderate-stage glaucoma. Pre- and postoperative intraocular pressure (IOP), number of antiglaucoma medications, and best-corrected visual acuity (BCVA) were evaluated. Postoperative complications and surgical success rates were analyzed during a 6-month follow-up period. Surgical success was defined as a ≥20% reduction in IOP from baseline and IOP <18 mmHg, with or without medication.

Results: The patients' mean age was 67.0±11.9 years; 36% had POAG, 36% PEXG, and 28% PACG. The mean preoperative IOP was 22.7±6.0 mmHg, which significantly decreased to 12.8±2.2 mmHg at 6 months ($p<0.05$). The median number of medications decreased from 2 preoperatively to 0 postoperatively ($p<0.05$). There were no significant differences in 6-month IOP values ($p=0.96$) or IOP reduction rates ($p=0.61$) among glaucoma subtypes. BCVA improved from 0.5±0.4 to 0.1±0.1 logarithm of the minimum angle of resolution ($p=0.001$). The most common complications were transient hyphema (12%) and corneal edema (20%), all of which resolved with conservative/topical treatment. One patient required trabeculectomy at month 3, and 3 patients demonstrated less than 20% IOP reduction. The surgical success rate at month 6 was 84%.

Conclusion: The KDB procedure combined with cataract surgery provided significant reductions in both IOP and the need for IOP-lowering medications at 6 months of follow-up in patients with early and moderate POAG, PACG, and PEXG, while maintaining a very low rate of complications.

Keywords: Kahook Dual Blade goniotomy, combined KDB surgery, glaucoma, minimally invasive glaucoma surgery

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Introduction

Glaucoma is a progressive optic neuropathy characterized by retinal ganglion cell loss. The single most important and modifiable risk factor is elevated intraocular pressure (IOP). Glaucoma is the leading cause of irreversible yet preventable blindness worldwide.[1] The advent of minimally invasive glaucoma surgery (MIGS) has substantially expanded the available options in glaucoma surgery. MIGS procedures are advantageous in that they can be performed in the early stages of disease, potentially deferring the need for more invasive surgeries.[2,3]

Additional advantages are its low risk of complications, short operative time, and faster postoperative recovery.[3]

MIGS procedures are generally classified into three groups based on whether the aqueous outflow is directed into Schlemm's canal, the supraciliary space, or the subconjunctival space. The Kahook Dual Blade (KDB; New World Medical Inc. Rancho Cucamonga, CA, USA) is a bleb-free MIGS device designed to enhance conventional outflow by facilitating aqueous drainage through Schlemm's canal. The trabecular meshwork and inner wall of Schlemm's canal are the main sites of resistance to aqueous humor outflow. Trabeculotomy procedures aim to eliminate this resistance.[4] In contrast to ab externo approaches, KDB goniotomy is an ab interno trabeculotomy procedure. Ab interno methods do not scar the conjunctiva or sclera, thereby avoiding additional complications when trabeculectomy is required.[5]

KDB excisional goniotomy performed in combination with phacoemulsification was reported to yield greater IOP reduction than either procedure alone.[6,7] Reported IOP reductions after KDB surgery have ranged from 11% to 36%. Significant reductions in glaucoma medication burden have also been reported, with the proportion of patients requiring medical therapy decreasing from 92% to 15%. These findings provide compelling evidence supporting the efficacy of KDB surgery in the management of glaucoma.[8,9] The present study aimed to evaluate the surgical outcomes of KDB excisional goniotomy combined with phacoemulsification cataract surgery in patients with glaucoma.

Materials and Methods

The medical records of patients with early or moderate glaucoma who underwent combined KDB excisional goniotomy and cataract surgery in the glaucoma unit of our center between January 2020 and April 2024 were reviewed retrospectively. None of the patients included in the study had a history of prior glaucoma surgery. Data collected included glaucoma subtype, best-corrected visual acuity (BCVA), IOP, anterior segment findings, cup-to-disc (C/D) ratio, pre- and postoperative antiglaucoma medications, and postoperative complications. Surgical success was defined as an IOP reduction of more than 20% from the preoperative value and an IOP of less than 18 mmHg at the 6-month postoperative examination, with or without antiglaucoma medication. Surgical failure was defined as an IOP reduction of less than 20%, IOP ≥18 mmHg, or the need for additional glaucoma surgery. Glaucoma severity was staged according to the mean deviation (MD) on Humphrey visual field testing as mild (MD ≥-6.0 dB), moderate (-6.0> MD ≥-12.0 dB), and advanced (MD <-12.0 dB).

All surgeries were performed under sedation by two surgeons experienced in glaucoma surgery. In all cases, KDB excisional goniotomy was performed immediately after standard phacoemulsification surgery. Following standard phacoemulsification and in-the-bag intraocular lens implantation, intracameral carbachol (MioStat®, Alcon Laboratories Inc., Fort Worth, TX, USA) was applied to achieve intraoperative miosis. To optimize visualization of the nasal angle, the patient's head was rotated 30° nasally and the operating microscope was tilted 45° temporally. The anterior chamber was filled with dispersive viscoelastic (Viscoat®, Alcon Laboratories Inc., Fort Worth, TX, USA) through the temporal side port. The angle structures were visualized by direct gonioscopy using a single-mirror Swan-Jacob goniolens (Ocular Instruments Inc., Bellevue, WA, USA). In patients with open-angle glaucoma, the KDB tip was introduced into Schlemm's canal and advanced approximately 3 to 4 clock-hours clockwise and counterclockwise along the nasal angle to excise a total of approximately 8 clock-hours of trabecular meshwork. In patients with primary angle-closure glaucoma (PACG), goniosynechialysis was performed before excisional goniotomy. The sharp tip of the KDB was engaged at the peripheral iris and gentle, controlled force was applied centrally along the iris plane to release peripheral anterior synechiae (PAS) and expose the underlying trabecular meshwork for goniotomy. KDB excisional goniotomy was then performed along the exposed trabecular meshwork. At the end of the procedure, the viscoelastic material was carefully aspirated from the anterior chamber and intracameral cefuroxime (Aprokam®, Laboratoires Théa, Clermont-Ferrand, France) was administered.

To mitigate the risk of early postoperative IOP elevation attributable to residual ophthalmic viscosurgical material, all patients received oral acetazolamide (Diazomid®, Deva Holding A.Ş., İstanbul, Türkiye) at postoperative 2 and 4 hours. Postoperative topical therapy consisted of nepafenac 0.3% (Apfecto®, World Medicine, İstanbul, Türkiye) once daily, a fixed-combination containing moxifloxacin 0.5% and dexamethasone 0.1% (Moxidexa®, Abdi İbrahim İlaç, İstanbul, Türkiye) 4 times daily, and artificial tears containing sodium hyaluronate (Hyonat®, Vem İlaç, İstanbul, Türkiye) 4 times daily, all prescribed for 1 month. In patients with an IOP exceeding the target level at 12 hours postoperatively, additional antiglaucoma therapy was initiated. A postoperative IOP spike was defined as an increase of >10 mmHg over preoperative IOP at the 1-week postoperative follow-up.

Given the retrospective nature of the study, individual informed consent was not required. Ethics committee approval was obtained from the Marmara University Faculty of Medicine (protocol code: 09.2025.25-0294; decision date: 18.04.2025) and the study was carried out in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

All statistical analyses were performed using IBM SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean ± standard deviation or median, and categorical variables as frequency and percentage. The normality of data distribution was assessed using the Shapiro-Wilk test. Preoperative and postoperative values were compared using the paired-samples t-test for normally distributed data and the Wilcoxon signed-rank test for non-normally distributed data. Variables reported as medians, such as medication count, were analyzed using appropriate non-parametric tests. Differences among the three glaucoma subgroups were assessed using one-way analysis of variance (ANOVA) for normally distributed variables and the Kruskal-Wallis test for non-normally distributed data. The durability of surgical success was assessed using Kaplan-Meier survival analysis. Between-group comparisons were performed using the log-rank test. A p value of <0.05 was regarded as statistically significant in all analyses.

Results

Twenty-five eyes of 25 patients (13 male, 12 female) who underwent KDB excisional goniotomy combined with phacoemulsification were included in the study. Of the included eyes, 71.4% were right eyes. The mean patient age was 67.0±11.9 years. Glaucoma subtype was primary open-angle glaucoma (POAG) in 36.0%, PACG in 28.0%, and pseudoexfoliation glaucoma (PEXG) in the remaining 36.0% of patients. All patients were using IOP-lowering drugs before the surgery. The mean BCVA was 0.5±0.4 logarithm of the minimum angle of resolution at baseline and improved to 0.1±0.1 at 6 months postoperatively (p=0.001). The mean preoperative IOP was 22.7±6.0 mmHg and the median C/D ratio was 0.7 (range, 0.6-0.9) (Table 1).

Postoperative complications included hyphema in 3 patients, corneal edema in 5 patients, IOP spike in 2 patients, cyclodialysis cleft in 1 patient, and vitreomacular traction in 1 patient (Table 2). All complications occurred in the early postoperative period. Corneal edema observed on postoperative day 1 resolved completely with standard postoperative topical therapy during follow-up. The patient who developed an intraoperative cyclodialysis cleft did not develop persistent hypotony during follow-up and did not require surgical intervention. The patient who developed vitreomacular traction at postoperative month 1 showed no functional or anatomical progression in regular follow-up examinations. Patients with hyphema noted on postoperative day 1 were managed conservatively with head elevation and reduced activity.

The mean IOP was 14.3±4.9 mmHg on postoperative day 1, 14.3±4.6 mmHg at week 1, 13.9±4.4 mmHg at 1 month, 13.6±3.6 mmHg at month 3, and 12.8±2.2 mmHg at month 6 (Table 2). The percentage IOP reduction across all patients was 33.3%, 33.9%, 33.7%, 35.9%, and 39.9% at day 1, week 1, month 1, month 3, and month 6, respectively (all p<0.01) (Table 3). The IOP reduction at month 6 was statistically significant within each glaucoma subgroup (POAG p=0.008, PEXG p=0.011, and PACG p=0.018) (Table 3).

Table 1. General characteristics of the patients

Eyes, n		**25**
Age (years), mean ± SD [range]		67.0±11.9 [41-85]
Sex, n (%)	Male	13 (52.0)
	Female	12 (48.0)
Laterality, n (%)	Right	14 (56.0)
	Left	11 (44.0)
Preoperative C/D ratio, median [95% CI]		0.7 [0.6-0.9]
Preoperative BCVA (logMAR)		0.5±0.4
Postoperative BCVA (logMAR)		0.1±0.1
Glaucoma subtype, n (%)	POAG	9 (36.0)
	PACG	7 (28.0)
	PEXG	9 (36.0)

SD: Standard deviation, C/D: Cup/disc, CI: Confidence interval, BCVA: Best-corrected visual acuity, logMAR: Logarithm of the minimum angle of resolution, POAG: Primary open-angle glaucoma, PACG: Primary angle-closure glaucoma, PEXG: Pseudoexfoliation glaucoma

Table 2. Frequency of postoperative complications

Complication	**n (%)**
Corneal edema	5 (20.0)
Transient hyphema	3 (12.0)
Intraocular pressure spike	2 (8.0)
Cyclodialysis cleft	1 (4.0)
Vitreomacular traction	1 (4.0)

Table 3. Mean intraocular pressure (IOP) values and percent change in IOP from baseline (%ΔIOP) at various time points in the overall cohort and by glaucoma subtype

Glaucoma subtype	Preop	Day 1 (%ΔIOP) p value	Week 1 (%ΔIOP) p value	Month 1 (%ΔIOP) p value	Month 3 (%ΔIOP) p value	Month 6 (%ΔIOP) p value
All patients	22.7±6.0 [12-40]	14.3±4.9 [7-25] (33.3%) **<0.001**	14.3±4.6 [9-32] (33.9%) **<0.001**	13.9±4.4 [8-30] (33.7%) **<0.001**	13.6±3.6 [9-27] (35.9%) **<0.001**	12.8±2.2 [9-17] (39.9%) **<0.001**
POAG	22.9±5.6 [17-34]	14.3±3.4 [10-19] (34.2%) **0.011**	15.1±3.5 [12-23] (29.3%) **0.021**	14.8±2.2 [10-18] (32.2%) **0.008**	13.4±1.9 [11-17] (38.1%) **0.012**	13.9±1.5 [12-16] (35.4%) **0.008**
PEXG	21.0±4.9 [12-27]	17.0±6.0 [7-25] (17.2%) 0.097	15.0±7.1 [9-32] (29.0%) 0.106	13.2±6.6 [8-30] (31.2%) 0.086	12.2±2.8 [9-18] (38.0%) **0.013**	11.7±2.5 [9-17] (40.7%) **0.011**
PACG	24.9±7.8 [17-42]	10.9±2.5 [7-15] (53.0%) **0.018**	12.6±1.6 [10-15] (45.5%) **0.018**	13.7±3.1 [9-19] (39.1%) **0.028**	15.4±5.4 [12-27] (30.2%) 0.075	12.9±2.0 [10-15] (44.5%) **0.018**

Data are presented as mean ± standard deviation [range]. Comparisons were made using Wilcoxon signed-rank test according to preoperative value. Bold values indicate statistical significance (p<0.05). POAG: Primary open-angle glaucoma, PEXG: Pseudoexfoliation glaucoma, PACG: Primary angle-closure glaucoma

At 6 months postoperatively, the mean IOP had decreased from 22.7±6.0 mmHg preoperatively to 12.8±2.2 mmHg, representing a mean reduction of 9.9 mmHg (39.9%). Analysis by glaucoma subtype showed that the mean IOP decreased from 22.9±5.6 mmHg to 13.9±1.5 mmHg in the POAG group, from 21.0±4.9 mmHg to 11.7±2.5 mmHg in the PEXG group, and from 24.9±7.8 mmHg to 12.9±2.0 mmHg in the PACG group (Table 2). The IOP reduction from baseline to month 6 was statistically significant in all groups (p<0.05) (Figure 1). However, the degree of IOP reduction did not differ significantly among the three groups (p=0.61). There was also no statistically significant difference in absolute IOP values between the glaucoma subgroups at 6 months (p=0.96).

The median number of antiglaucoma medications decreased from 2 preoperatively to 0 at the final postoperative visit (p<0.01). The mean number of antiglaucoma medications decreased from 3.24±1.01 preoperatively to 1.00±1.23 postoperatively, representing a 69.9% reduction.

One patient required trabeculectomy at month 3, and 3 patients achieved less than 20% IOP reduction from baseline. The overall surgical success rate at 6 months was 84.0%. Kaplan-Meier survival analysis demonstrated no statistically significant difference in the probability of sustained surgical success between the three glaucoma subtypes (log-rank test, p=0.773) (Figure 2).

Discussion

This study aimed to evaluate the effectiveness and safety of combined KDB excisional goniotomy and cataract surgery using clinical data. The KDB is a single-use ophthalmic blade developed specifically for ab interno excisional goniotomy. Several studies have reported on the early outcomes of KDB excisional goniotomy combined with cataract surgery.[7,10] In the present series, we retrospectively analyzed the 6-month outcomes of KDB excisional goniotomy combined with phacoemulsification.

In a multicenter study by Bravetti et al.[11] involving 40 eyes with severe or refractory open-angle glaucoma who underwent standalone or combined KDB goniotomy, surgical success was defined as an IOP reduction of at least 20% from baseline at 12 months with fewer medications than preoperatively. Mean IOP decreased from 18.1±5.0 mmHg at baseline to 14.8±3.7 mmHg at 12 months (18.2% reduction), and the mean number of medications was reduced by 32.0%.[11] A multicenter study of 71 patients with various glaucoma subtypes who underwent combined KDB and phacoemulsification reported a mean IOP decrease from 17.4 mmHg to 12.8 mmHg, with a significant reduction in antiglaucoma medication use.[7] A separate prospective study involving 51 patients demonstrated a 26.2% IOP reduction and 50% reduction in medication count.[10] Mechleb et al.[12] reported a 24.9% IOP reduction from baseline and a surgical success rate of 82.1%. In our cohort,

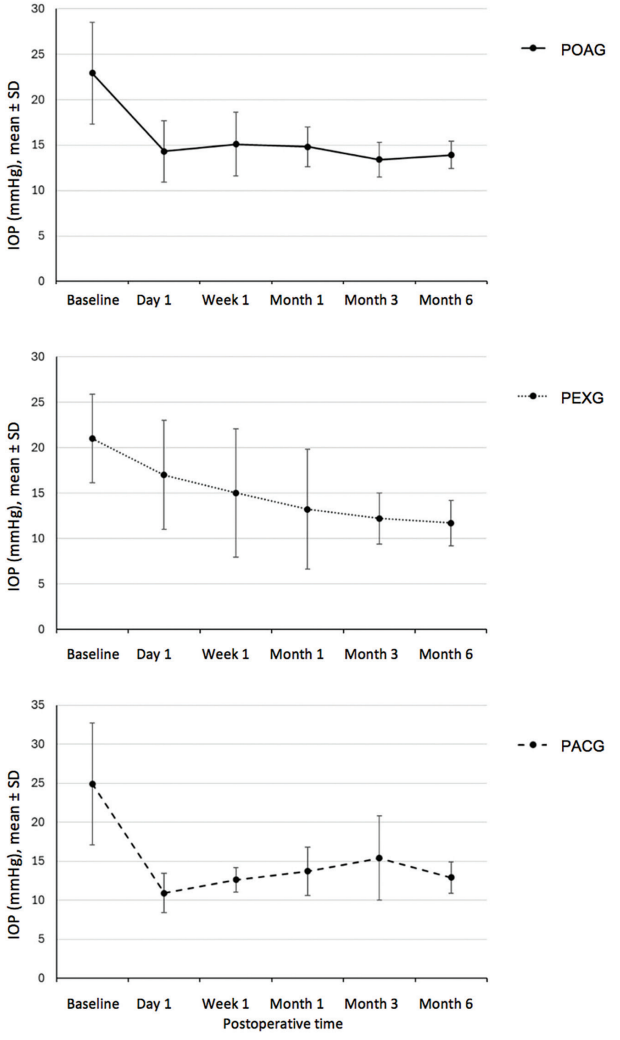

Figure 1. Changes in mean intraocular pressure (IOP ± standard deviation) over a 6-month follow-up period across different glaucoma subtypes
IOP: Intraocular pressure, POAG: Primary open-angle glaucoma, PEXG: Pseudoexfoliation glaucoma, PACG: Primary angle-closure glaucoma, SD: Standard deviation

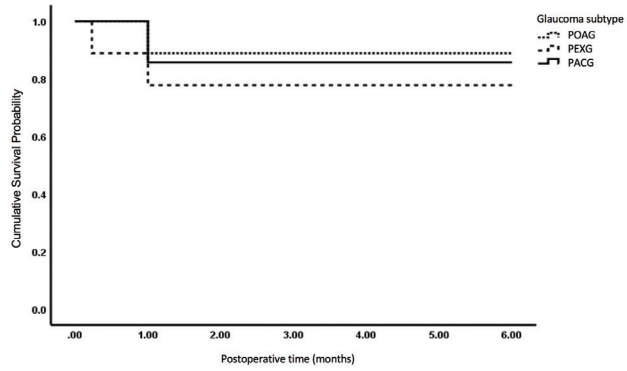

Figure 2. Kaplan-Meier survival analysis of surgical success over a 6-month follow-up period across different glaucoma subtypes
POAG: Primary open-angle glaucoma; PEXG: Pseudoexfoliation glaucoma, PACG: Primary angle-closure glaucoma

combined surgery yielded a mean absolute IOP reduction of 10 mmHg at 6-month follow-up, corresponding to a 39.9% decrease. In the literature, the mean IOP reduction following standalone KDB goniotomy has been reported as approximately 4 mmHg; the greater reduction observed in our series is likely attributable to the additive IOP-lowering effect of concurrent phacoemulsification.[7,10,12] In a study evaluating standalone KDB in 53 eyes of 42 patients with a mean baseline IOP of 23.5 mmHg, Berdahl et al.[8] reported mean IOP reductions ranging from 29.8% to 43.8% over a 6-month follow-up period, comparable to the reduction observed in our combined series. In our study, one patient required additional surgery and 3 patients failed to achieve at least 20% IOP reduction, yielding an overall surgical success rate of 84% for combined KDB. This is consistent with the 74.1%, 82.1%, and 86% success rates at postoperative 6 months reported in the literature.[6,12,13]

Non-adherence to medical therapy is a major problem that can arise in the long-term management of glaucoma. KDB excisional goniotomy helps address this challenge by reducing the patient's dependence on topical antiglaucoma medications.[3] The mean reduction in the medication count in our cohort (69.9%) was greater than the 46-50% reductions reported at 6 months in comparable studies.[10,12]

Reductions in both IOP and medication burden have been demonstrated in eyes with PEXG and POAG following KDB goniotomy.[14] In a study of 132 eyes, Pratte et al.[15] reported a 15.3% reduction in IOP (from 17.6±4.6 to 14.9±3.2 mmHg) and a 45% reduction in medication count (from 2±1.2 to 1.1±1.2) at 6 months postoperatively, noting that patients using more medications at baseline may derive greater benefit from combined surgery. Sieck et al.[6] reported a 12-month surgical success rate of 71.8% in 165 eyes undergoing combined KDB and phacoemulsification, with the mean IOP decreasing from 16.7 to 13.8 mmHg and a significant reduction in antiglaucoma medication use. The 39.9% IOP reduction observed at 6 months in our study is consistent with the literature. Our success

rate also seems comparable to those of other studies. One study conducted in China reported a 100% success rate at 6 months.[16] Bravetti et al.[11] emphasized that the efficacy of KDB excisional goniotomy tended to decrease over time based on their 12-month follow-up data, and Pratte et al.[15] reported differing success rates at 6 and 12 months, underscoring the importance of extended follow-up in evaluating the durability of surgical outcomes. In this context, the Kaplan-Meier analysis in our study complements the existing literature by demonstrating that combined surgery provides comparable and sustained surgical success across different glaucoma subtypes during the first 6 months, independent of early postoperative IOP fluctuations.

Although glaucoma subtypes have varying pathophysiological mechanisms, reduction of trabecular meshwork resistance, which is the primary mechanism of action of the KDB, is a common therapeutic target across all glaucoma forms. The EAGLE trial demonstrated that phacoemulsification in patients with early angle-closure glaucoma resulted in significantly greater IOP reduction and better quality of life compared with laser peripheral iridotomy alone.[17,18] Combined KDB surgery with phacoemulsification has been reported to be safe and effective in patients with PACG. This approach lowers IOP through a dual mechanism: lens extraction widens the anterior chamber angle, while goniotomy directly reduces trabecular resistance.[19,20] PAS permanently occlude the angle and chronically damage the underlying trabecular meshwork. Therefore, releasing the trabecular meshwork with goniosynechialysis alone often results in a dysfunctional outflow pathway.[21] In the combined procedure, the anatomical block is relieved by lens extraction, PAS are disrupted by goniosynechialysis, and the residual outflow resistance is addressed by KDB excisional goniotomy, which creates a functional bypass from the damaged trabecular meshwork into Schlemm's canal.[21] Studies have shown that KDB combined with phacoemulsification achieves significant reductions in both IOP and medication burden.[19,20] Combined cataract surgery, goniosynechialysis, and KDB excisional goniotomy in angle-closure glaucoma have been reported to reduce IOP by approximately 38-49% and decrease medication use by approximately 90-98% at 6-12 months.[20,21] The pronounced IOP reduction observed in our PACG cases suggests that the angle-widening effects of lens extraction and goniosynechialysis act synergistically with the trabecular-level mechanism of KDB excisional goniotomy. Consistent with the literature, these results support combined surgery as a safe and effective option for the treatment of PACG.

Several studies have demonstrated that combined KDB with cataract surgery has a favorable postoperative complication profile.[7,13,15] In cases where the IOP-lowering effect of KDB goniotomy decreases over time and additional surgical intervention is required, the preserved conjunctival integrity enables subsequent filtration surgery without compromise. As KDB goniotomy does not involve conjunctival incisions, future procedures are more likely to be successful. The combination of KDB with cataract surgery offers other additional benefits, particularly with respect to long-term glaucoma management. Given that trabeculectomy is known to accelerate cataract formation, performing concurrent cataract extraction at the time of KDB goniotomy preempts this complication in patients who may later require filtration surgery. Conversely, performing cataract surgery after filtration surgery risks compromising bleb function through increased postoperative inflammation and conjunctival scarring. Therefore, combining KDB with cataract surgery not only provides immediate IOP reduction but also preserves the surgical landscape for future interventions, optimizing conditions for subsequent glaucoma management. This approach highlights the value of strategic surgical sequencing in glaucoma management, securing both near-term efficacy and long-term therapeutic flexibility.

Early postoperative hyphema may occur due to blood reflux through Schlemm's canal during goniotomy. It is relatively common, typically developing within the first postoperative week, and is usually self-limiting.[10] The prevalence of transient hyphema in our series (21.4%) is consistent with the 35.1% and 39.4% rates reported in comparable studies.[7,13] Transient IOP spikes occurred in 14.3% of patients, also consistent with rates reported in the literature.[7,10] IOP spikes were managed successfully with topical antiglaucoma therapy, and hyphema resolved in all affected eyes with conservative observation. Cyclodialysis cleft is a rare complication following KDB goniotomy and has been reported in association with persistent hypotony.[22,23] Hypotony did not occur in any of our patients.

Study Limitations

Limitations of this study include its retrospective design, which precluded randomization, the inclusion of heterogeneous glaucoma subtypes within a single cohort, and the small sample size. Nevertheless, the available data provide promising early-stage evidence supporting the feasibility and safety of KDB excisional goniotomy across different glaucoma subtypes.

Conclusion

Combined KDB excisional goniotomy and phacoemulsification provided significant reductions in IOP and antiglaucoma medication use at 6 months in patients with early to moderate glaucoma, with a low rate of complications. KDB excisional goniotomy appears to be a promising and safe treatment option for both angle-closure glaucoma and various forms of open-angle glaucoma.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Marmara University Faculty of Medicine (protocol code: 09.2025.25-0294; decision date: 18.04.2025) and the study was carried out in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Given the retrospective nature of the study, individual informed consent was not required.

Declarations

Authorship Contributions

Surgical and Medical Practices: M.E., E.B.Ç., Concept: E.B.Ç., M.E., Ö.Ş., Design: E.B.Ç., M.E., Ö.Ş., Data Collection or Processing: E.B.Ç., H.H., Analysis or Interpretation: E.B.Ç., M.E., Ö.Ş., H.H., Literature Search: E.B.Ç., M.E., Writing: E.B.Ç.

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Original Article

Effect of Accelerated Epi-Off Crosslinking on Optical Quality, Corneal Aberrations, and Epithelial Wavefront During Adolescence

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Abstract

Objectives: To examine the effect of accelerated epi-off crosslinking (A-CXL) on visual acuity and quality in adolescent patients with progressive keratoconus.

Materials and Methods: The study included 109 eyes of 109 patients (mean age 16.24±2.55 years). MS-39 anterior segment optical coherence tomography images from before A-CXL and 1 month, 6 months, and 12 months after A-CXL were analyzed. Corneal tomographic parameters, total corneal aberrations, corneal epithelial aberrations, and optical quality indicators such as modulation transfer function (MTF) and Strehl ratio of the point spread function (PSF) were recorded.

Results: A significant improvement in corrected distance visual acuity was observed at 6 and 12 months after A-CXL (0.23±0.10 and 0.22±0.10 logarithm of the minimum angle of resolution [logMAR]) compared to the pre-A-CXL value (0.30±0.12 logMAR) ($p<0.001$ for both). MTF-5 and MTF-15 values were significantly higher at 12 months after A-CXL compared to before A-CXL ($p<0.001$). However, almost all MTF and PSF values were significantly lower at 1 month after A-CXL than at the other visits ($p<0.05$). Significant improvements were seen in root mean square higher-order aberrations (RMS-HOAs), vertical coma, and vertical trefoil values at 12 months after A-CXL compared to before A-CXL. A significant improvement was also detected in corneal epithelial aberrations, specifically in the vertical coma value. The change in corrected distance visual acuity at 12 months after A-CXL was significantly correlated with changes in keratometry values, with total corneal RMS-HOAs, vertical coma, and vertical trefoil, and with corneal epithelial RMS-HOAs (all $p<0.05$).

Conclusion: Besides total corneal aberrations, corneal epithelial aberrations may also influence the improvement of visual acuity and quality after A-CXL.

Keywords: Accelerated epi-off crosslinking, corneal aberration, corneal epithelial wavefront, modulation transfer function, point spread function

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Introduction

Keratoconus is the most common form of corneal ectasia, a serious condition that causes progressive thinning and steepening of the cornea, leading to deterioration of the corneal refractive surface.[1] The progressive decline in visual acuity and quality associated with the disease poses a major visual health concern, especially in adolescents. Individuals diagnosed before age 18 are often identified at a later stage and tend to experience more progression than those diagnosed in adulthood.[1,2] Therefore, early diagnosis and treatment are essential.

Corneal crosslinking (CXL) is the leading treatment for stopping keratoconus progression, with proven safety and effectiveness.[1] CXL treatment involves saturating the corneal stroma with the photosensitizer riboflavin, which reacts with ultraviolet A (UVA, 315-400 nm) to increase corneal stromal rigidity. While some studies have demonstrated the importance of improved anterior curvature parameters for visual recovery after CXL, others have highlighted the role of reduced higher-order aberrations (HOAs).[3,4,5,6] Indicators of impaired visual quality in patients with keratoconus include corneal HOAs and optical quality indices such as the modulation transfer function (MTF) and point spread

function (PSF). Optical quality indicators are affected by the severity and progression of keratoconus.[7,8] The few available studies on changes in optical quality indicators following CXL have reported inconsistent findings.[3,9,10]

Anterior segment optical coherence tomography (AS-OCT) is a current imaging technique that enables assessment of the corneal layers. Epithelial wavefront analysis using the MS-39, which combines Placido disk technology with AS-OCT, is a recent development that has not yet gained sufficient coverage in the literature. Ning et al.[11] reported that epithelial aberrations were significantly higher in patients with keratoconus compared with a healthy control group. Studies analyzing changes in optical power due to epithelial remodeling after keratorefractive surgery have highlighted the importance and reproducibility of the epithelial wavefront.[12,13] Previous studies have also shown that epithelial remodeling occurs after CXL.[14,15] However, to our knowledge, no research has been conducted to examine the impact of corneal epithelial aberrations on the level and quality of vision, which can change after CXL.

This study aimed to investigate the effects of accelerated CXL (A-CXL) performed during adolescence on visual quality by analyzing changes in and relationships between optical quality, corneal aberrations, and corneal epithelial aberrations.

Materials and Methods

This retrospective study was conducted in the cornea unit within the ophthalmology department of a tertiary referral hospital. The study protocol was approved by a University of Health Sciences Türkiye, Ankara Etlik City Hospital Ethics Committee (decision no: AEŞH-BADEK1-2025-289, date: 27.08.2025) in accordance with the Declaration of Helsinki.

Patient Selection

The study included adolescent patients who were referred to the cornea and contact lens unit for keratoconus, were diagnosed with progressive keratoconus during follow-up, and were subsequently treated with A-CXL. A total of 109 eyes from 109 patients were included in this study. One eye of each patient who underwent bilateral A-CXL treatment was randomly selected.

Patients with a ≥1 diopter (D) increase in the maximum keratometry (Kmax) value, ≥1 D increase in corneal astigmatism, and ≥25 μm decrease in the thinnest corneal thickness at 1-year follow-up were classified as having progressive keratoconus.[1,16] Additionally, all patients under 18 years of age were considered to have progressive keratoconus because they were identified as having a very high risk of progression at the time of diagnosis.[2,17]

Inclusion criteria were as follows: patients under 20 years of age who were treated with A-CXL for progressive keratoconus and who had regular follow-up measurements at 1, 6, and 12 months after A-CXL. An important reason for selecting patients aged <20 years is that studies comparing adults and pediatric patients in the literature have shown that improvements in corrected distance visual acuity (CDVA) and anterior curvature parameters are more pronounced in the pediatric group.[16,18] Exclusion criteria were as follows: patients who developed keratitis, sterile corneal infiltrates, or greater than grade 2 haze after A-CXL; patients with preexisting corneal opacities such as sequelae of hydrops, apical scars, or sequelae of keratitis; patients with ocular surface diseases; patients who were pregnant or breastfeeding; and patients who wore contact lenses during the 1-year follow-up before or after A-CXL.

CDVA values measured with spectacle lenses using the Early Treatment Diabetic Retinopathy Study logarithm of the minimum angle of resolution (logMAR) chart were recorded retrospectively from the patients' digital records from before A-CXL and at 1, 6, and 12 months after A-CXL treatment.

Surgical Procedure

A total of 87 of 109 patients received topical anesthesia, while the remaining 22 received general anesthesia. After an 8-mm debridement of the corneal epithelium, a riboflavin solution containing 0.1% riboflavin and 1.1% hydroxypropyl methylcellulose was applied every 2 minutes for 20 minutes (MedioCROSS® M, Glaukos Company). Using a crosslinking device (CRS-X®, YURATEK), 370 nm UVA light was directed at the intersection of the target beams at the corneal apex for 10 minutes at an intensity of 9 mW/cm^2 (5.4 J/cm^2). UVA radiation was maintained while applying riboflavin drops every minute. The procedure was completed with cold irrigation and placement of a bandage contact lens. Postoperative management consisted of 0.5% moxifloxacin drops (Moxai, Abdi İbrahim İlaç San. ve Tic. A.Ş., İstanbul, Türkiye), 0.5% loteprednol etabonate drops (Lotemax, Bausch & Lomb Inc., Tampa, FL, USA) and artificial tears.

MS-39 Combined Placido Disk and High-Resolution AS-OCT

The MS-39 AS-OCT (software Phoenix version 4.1.1.5; CSO, Firenze, Italy) combines a Placido disk with a spectral domain (SD)-OCT system. The device uses an infrared superluminescent diode source emitting at 850 nm to acquire slices over a 16-mm diameter with an axial resolution of 3.6 μm. The SD-OCT scan consisted of 1024 A-scans and 25 B-scans across 16-mm sections, each captured in approximately 1 s. In our study, all AS-OCT images were acquired in the "12 × 5 @ 10 mm" mode by an experienced technician due to its higher resolution. Kmax,

flat keratometry (Kflat), steep keratometry (Ksteep), average keratometry (Kavg) values, thinnest pachymetry, minimum and maximum epithelial thicknesses (ET) in the central 6-mm zone, along with maximum anterior and posterior elevation values and anterior astigmatism measurements in the 6-mm and 3-mm zones, were obtained from pre-A-CXL and 1-month, 6-month, and 12-month post-A-CXL images.

Total corneal aberrations, PSF, MTF, and corneal epithelial aberrations were calculated by selecting a 4.5-mm virtual pupil diameter, centered on the corneal vertex. The PSF value is expressed as the Strehl ratio (SR), which is the ratio between the peak intensity of the PSF of the optical system under study and the peak intensity of a flat wavefront that passes through the same pupil. MTF values were expressed at different spatial frequencies (5, 10, 15, and 20 cpd).

The MS-39 software automatically converts the anterior and posterior corneal elevation profiles into corneal wavefront data based on Zernike polynomials up to a seventh-order expansion. Total corneal aberrations and HOAs were recorded as root mean square (RMS) values. Documented third- and fourth-order HOAs derived from the Zernike polynomials included vertical trefoil (Z_3^{-3}), vertical coma (Z_3^{-1}), horizontal coma (Z_3^{1}), oblique trefoil (Z_3^{3}), and spherical aberration (Z_4^{0}). Corneal epithelial aberrations, specifically epithelial wavefront errors, were calculated using virtually refracted rays via the MS-39 software. The epithelial optical wavefront was simulated by modeling the interaction of light with the epithelial layer and its interfaces, including the air-tear film interface and the epithelium-stroma interface. A collimated beam of light with a specific diameter was virtually projected onto the epithelium, deflected according to the corneal curvature, and finally influenced by the Bowman layer curvature. For corneal epithelial aberrations, total aberrations and HOAs were similarly recorded as RMS values, including the same third- and fourth-order aberrations mentioned above for the total cornea.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA). We used the Kolmogorov-Smirnov test to evaluate the normality of quantitative variables. Repeated measures from the same individuals were compared using the repeated-measures one-way analysis of variance (ANOVA) with Bonferroni multiple comparison tests for normally distributed data and with the Friedman test followed by the Wilcoxon test with Bonferroni correction for non-normally distributed data. Pearson's or Spearman's correlation coefficients were employed to analyze the relationships between variables, depending on data normality. Statistical significance was defined as a p value less than 0.05.

Results

This study evaluated 109 eyes of 109 patients, including 46 females and 63 males. The average age was 16.24±2.55 years (range, 11-20 years). The patients' mean CDVA values were 0.30±0.12 logMAR before A-CXL, 0.29±0.12 logMAR at 1 month after CXL, 0.23±0.10 logMAR at 6 months after CXL, and 0.22±0.10 logMAR at 12 months after CXL. Significant improvements were observed at 6 and 12 months compared to pre-CXL values ($p<0.001$ for both) (Table 1).

Following A-CXL, substantial flattening was observed in Kmax ($p<0.001$) and Ksteep ($p=0.004$) values at 12 months after the procedure compared to before A-CXL and at 1 and 6 months post-procedure. Significant flattening was also observed in Kavg values at 12 months after A-CXL compared to pre-treatment ($p=0.020$). The minimum ET in the central 6-mm zone was significantly thicker at 6 and 12 months post-A-CXL compared to before A-CXL ($p=0.037$). The maximum ET in the central 6-mm zone was significantly thicker at 1 month post-A-CXL compared to before and at 6 and 12 months post-A-CXL ($p=0.002$). The difference between the maximum and minimum ET in the central 6-mm zone was significantly lower at 6 and 12 months post-A-CXL compared to before and at 1 month post-A-CXL ($p<0.001$). Anterior elevation decreased significantly at 6 and 12 months post-A-CXL compared to pre-treatment ($p<0.001$). Additionally, corneal astigmatism within the central 3-mm zone decreased significantly at 12 months after A-CXL compared to pre-treatment and 1 month post-treatment values ($p=0.003$ and $p<0.001$, respectively). No significant changes were observed in Kflat, thinnest pachymetry, posterior elevation, or corneal astigmatism values ($p>0.05$) (Table 1).

When we examined optical quality markers, SR-PSF was significantly lower at 1 month than at 6 and 12 months after A-CXL ($p=0.006$ and $p<0.001$, respectively). The MTF-5 value at 12 months after A-CXL was significantly higher than that before and at 1 month after A-CXL ($p=0.033$ and $p=0.001$, respectively). MTF-10 and MTF-20 values were significantly lower at 1 month than at 12 months after A-CXL (both $p=0.001$). The MTF-15 value at 12 months after A-CXL was significantly higher than that before and at 1 and 6 months after A-CXL ($p=0.022$, $p=0.004$, and $p=0.005$, respectively). However, no significant differences were observed in the SR-PSF, MTF-10, and MTF-20 values at 12 months post-A-CXL compared to baseline ($p>0.05$) (Table 2).

Total corneal aberrations showed significant decreases in RMS-HOAs and vertical coma at 6 and 12 months

after A-CXL compared to pre-A-CXL levels (p=0.034 and p<0.001 for RMS-HOA; p=0.006 and p<0.001 for vertical coma, respectively). Vertical trefoil showed significant improvement at 12 months after A-CXL compared to pre-A-CXL levels (p=0.017). No significant differences were observed in horizontal coma, oblique trefoil, or spherical aberration values (p>0.05) (Table 3).

Regarding corneal epithelial aberrations, only the vertical coma value improved at 1, 6, and 12 months after A-CXL compared to before A-CXL (p=0.004, p=0.038, and p=0.003, respectively). No significant differences were observed in other corneal epithelial aberrations (p>0.05) (Table 3).

The change in the difference between maximum and minimum ET in the central 6-mm zone from baseline to 12 months after A-CXL was significantly correlated with the changes in corneal epithelial RMS-HOAs (r=0.423, p<0.001) and vertical coma (r=-0.252, p=0.008) at 12 months after A-CXL (Figure 1).

The change in CDVA at 12 months after A-CXL compared to baseline was significantly correlated with the changes in Kmax (r=0.640, p<0.001), Kflat (r=0.566, p<0.001), Ksteep (r=0.670, p<0.001), Kavg (r=0.637, p<0.001), and corneal astigmatism within the central 3-mm zone (r=0.457, p<0.001). Change in CDVA was also significantly correlated with changes in total corneal RMS-HOAs (r=0.606, p<0.001), vertical coma (r=0.506, p<0.001), and vertical trefoil (r=-0.541, p<0.001) values. Among the corneal epithelial aberration changes, only the RMS-HOA value was significantly correlated (r=0.224, p=0.019). The changes in optical quality indicators SR-PSF, MTF-5, MTF-10, MTF-15, and MTF-20 from baseline to 12 months after A-CXL were not significantly correlated with the change in CDVA (p>0.05) (Table 4).

Table 1. Changes in corrected distance visual acuity and topographic and tomographic data after accelerated corneal crosslinking (A-CXL)

	Before A-CXL	1 month after A-CXL	6 months after A-CXL	12 months after A-CXL	p
CDVA (logMAR)	0.30±0.11[a]	0.30±0.12[a]	0.23±0.10[b]	0.22±0.10[c]	**<0.001**
Kmax (D)	53.79±5.82[a, b]	53.73±5.08[a]	52.95±4.57[b]	52.38±4.49[c]	**<0.001**
Kflat (D)	44.96±2.76	45.05±2.65	44.76±2.44	44.73±2.50	0.064
Ksteep (D)	48.94±3.74[a, b]	49.01±3.66[a]	48.67±3.45[b]	48.49±3.29[c]	**0.004**
Kavg (D)	46.87±3.06[a, b]	46.90±2.95[a]	46.61±2.75[b, c]	46.51±2.72[c]	**0.020**
Thinnest pachymetry (µm)	453.38±35.42	449.53±36.37	449.13±36.89	451.02±39.17	0.058
Min. ET (µm)	42.79±5.56[a]	43.42±5.39[a, b]	43.77±5.07[b]	43.84±6.15[b]	**0.037**
Max. ET (µm)	62.53±4.43[a]	64.70±7.61[b]	62.88±5.61[a]	62.34±5.46[a]	**0.002**
Max.-min. ET (µm)	19.74±0.70[a]	21.28±0.81[b]	18.57±0.61[c]	18.21±0.61[c]	**<0.001**
Anterior elevation	26.32±14.42[a]	24.58±13.89[a]	22.42±12.95[b]	20.62±12.56[c]	**<0.001**
Posterior elevation	40.59±17.86	40.74±21.47	39.45±19.33	38.74±18.93	0.099
Corneal astigmatism (3 mm) (D)	4.24±2.30[a]	4.22±2.25[a]	3.93±2.11[a,b]	3.80±2.00[b]	**<0.001**
Corneal astigmatism (6 mm) (D)	3.19±1.66	3.14±1.60	3.01±1.53	2.99±1.53	0.055

Different lowercase letters indicate statistically different groups. CDVA: Corrected distance visual acuity (with spectacle lenses), logMAR: Logarithm of the minimum angle of resolution, K: Keratometry value, D: Diopters, Kmax: Maximum keratometry, Kflat: Flat keratometry, Ksteep: Steep keratometry, Kavg: Average keratometry, ET: Epithelial thickness, Min.: Minimum, Max.: Maximum

Table 2. Changes in the Strehl ratio of the point spread function (SR-PSF) and the modular transfer function (MTF) after accelerated corneal crosslinking (A-CXL)

	Before A-CXL	1 month after A-CXL	6 months after A-CXL	12 months after A-CXL	p*
SR-PSF	0.077±0.06[a, b]	0.071±0.04[a]	0.079±0.05[b]	0.080±0.05[b]	**<0.001**
MTF-5 (cpd)	0.229±0.20[a, b]	0.217±0.18[a]	0.243±0.20[b, c]	0.256±0.21[c]	**<0.001**
MTF-10 (cpd)	0.122±0.13[a, b]	0.104±0.11[a]	0.118±0.12[a, b]	0.135±0.13[b]	**0.003**
MTF-15 (cpd)	0.075±0.09[a]	0.072±0.07[a]	0.073±0.08[a]	0.083±0.08[b]	**0.001**
MTF-20 (cpd)	0.063±0.07[a, b]	0.052±0.07[a]	0.060±0.07[a, b]	0.068±0.08[b]	**0.001**

*Friedman test. Different lowercase letters indicate statistically different groups. cpd: Cycles per degree

Table 3. Changes in total corneal aberrations and corneal epithelial aberrations after accelerated corneal crosslinking (A-CXL)					
	Before A-CXL	**1 month after A-CXL**	**6 months after A-CXL**	**12 months after A-CXL**	**p**
Total corneal aberrations					
RMS-HOAs (μm)	1.41±0.93[a]	1.38±0.74[a]	1.26±0.67[b]	1.17±0.64[c]	**<0.001**
Vertical coma (μm)	1.05±0.77[a]	0.99±0.70[a]	0.92±0.64[b]	0.85±0.60[c]	**<0.001**
Horizontal coma (μm)	0.03±0.40	0.01±0.40	0.03±0.36	0.01±0.34	0.861*
Vertical trefoil (μm)	-0.48±0.38[a]	-0.46±0.38[a, b]	-0.43±0.35[a, b]	-0.41±0.32[b]	**0.009**
Oblique trefoil (μm)	0.00±0.44	-0.006±0.37	0.00±0.35	0.025±0.19	0.746*
Spherical aberration (μm)	0.046±0.25	0.058±0.23	0.027±0.21	0.025±0.19	0.200*
Corneal epithelial aberrations					
Total aberrations-RMS (μm)	1.22±0.54	1.28±0.60	1.23±0.54	1.20±0.50	0.370
RMS-HOAs (μm)	0.78±0.39	0.85±0.46	0.79±0.39	0.77±0.36	0.207
Vertical coma (μm)	-0.38±0.36[a]	-0.30±0.38[b]	-0.32±0.39[b]	-0.29±0.38[b]	**<0.001**
Horizontal coma (μm)	0.02±0.34	0.02±0.29	-0.03±0.27	-0.02±0.31	0.537
Vertical trefoil (μm)	0.10±0.17	0.09±0.24	0.12±0.19	0.14±0.19	0.067
Oblique trefoil (μm)	0.01±0.19	0.02±0.26	0.01±0.20	-0.01±0.19	0.700
Spherical aberration (μm)	-0.10±0.21	-0.07±0.26	-0.09±0.20	-0.08±0.21	0.398
*Friedman test. Different lowercase letters indicate statistically different groups. RMS-HOAs: Root mean square higher-order aberrations					

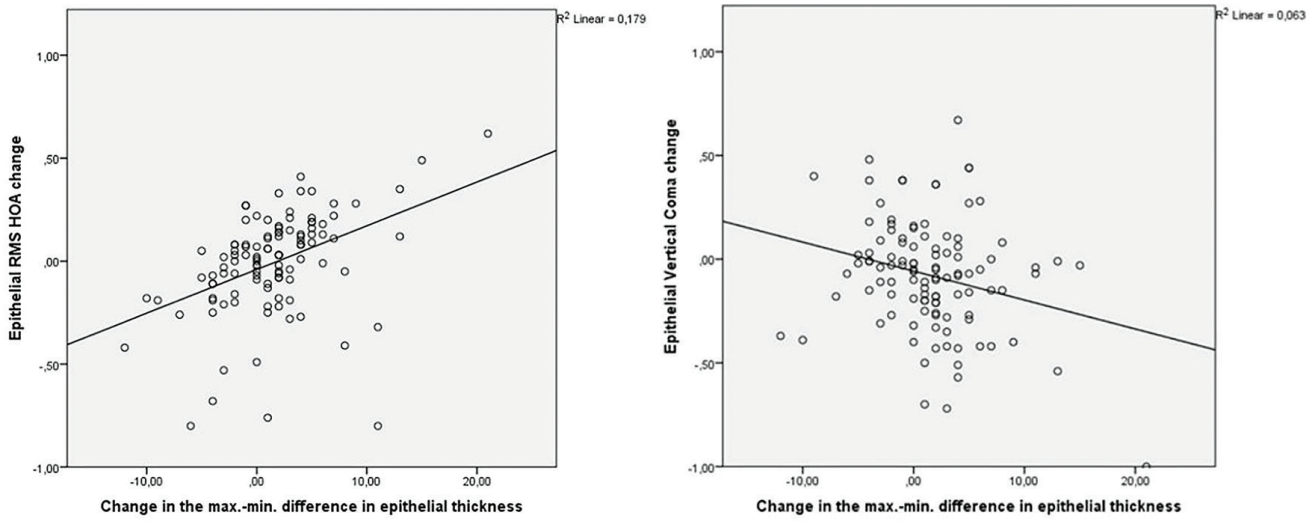

Figure 1. Correlations between the change in the difference of maximum and minimum corneal epithelial thicknesses in the central 6-mm zone from baseline to 12 months after A-CXL and the change in corneal epithelial RMS-HOA and vertical coma aberration from baseline to 12 months after A-CXL

A-CXL: Accelerated corneal crosslinking, RMS-HOA: Root mean square higher-order aberrations, max.: Maximum, min.: Minimum

Table 4. Correlations between change in corrected visual distance acuity at 12 months after accelerated corneal crosslinking (A-CXL) vs. baseline and changes in corneal topometric parameters, Strehl ratio of the point spread function, modular transfer function, and total and epithelial corneal aberrations

Change at 12 months after A-CXL	Change in CDVA at 12 months after A-CXL	
	r	p
Age (years)	-0.130	0.177
Kmax (D)	0.640	**<0.001**
Kflat (D)	0.566	**<0.001**
Ksteep (D)	0.670	**<0.001**
Kavg (D)	0.637	**<0.001**
Corneal astigmatism (3 mm) (D)	0.457	**<0.001**
SR-PSF	0.022	0.817*
MTF-5 (cpd)	-0.055	0.573*
MTF-10 (cpd)	-0.067	0.487*
MTF-15 (cpd)	0.005	0.955*
MTF-20 (cpd)	-0.054	0.580*
RMS-HOAs (µm)	0.606	**<0.001**
Vertical coma (µm)	0.506	**<0.001**
Vertical trefoil (µm)	-0.541	**<0.001**
Epithelial RMS-HOAs (µm)	0.224	0.019
Epithelial vertical coma (µm)	-0.152	0.116
Epithelial vertical trefoil (µm)	0.102	0.291

*Spearman correlation analysis. CDVA: Corrected distance visual acuity, D: Diopters, Kmax: Maximum keratometry, Kflat: Flat keratometry, Ksteep: Steep keratometry, Kavg: Average keratometry, SR-PSF: Strehl ratio of the point spread function, MTF: Modulation transfer function, RMS-HOAs: Root mean square higher-order aberrations, r: Correlation coefficient

Discussion

Many studies have investigated the impact of corneal CXL treatment on visual quality and function employing various parameters, including CDVA, corneal and ocular aberrations, optical quality indicators, and contrast sensitivity.[3,9,10,19,20,21] To our knowledge, our study is the first to evaluate corneal epithelial aberrations following A-CXL. Consistent with many studies in the literature, we observed significant improvements in CDVA, the anterior curvature parameters Kmax, Ksteep, and Kavg, corneal astigmatism in the central 3-mm area, and anterior elevation from baseline to 12 months after A-CXL.[1,16,20,22,23,24] This may be related to remodeling of the anterior cornea caused by A-CXL through the reorganization of stromal collagen lamellae.[1,25]

Most studies evaluating corneal aberration changes after CXL have found significant reductions in third- and fourth-order aberrations, such as vertical coma, spherical aberration, vertical trefoil, and secondary astigmatism. While some studies have argued that reductions in HOAs after CXL are associated with visual improvement, others have found no such association.[3,6,19,20,23,26] In the 5-year follow-up results after standard CXL, Taşçı et al.[27] found an improvement in visual acuity and a decrease in HOAs, but no change in vertical coma as found in our study. Together with RMS-HOAs, we observed significant reduction in vertical coma and vertical trefoil values at 12 months post-A-CXL compared to baseline levels. Moreover, we determined that this improvement correlated significantly with the improvement in CDVA. The reduction in aberrations after CXL is primarily a result of the anterior corneal reshaping induced by A-CXL. This creates a smoother optical surface and explains the linear relationship between decreased aberrations and improved CDVA.

While aberrations play a crucial role in assessing visual quality, they are insufficient on their own. Optical quality indicators, such as the PSF and MTF, are used to describe how an image is formed at the fovea and the relationship between the image and the object. The MTF is an objective reflection of vision under different contrast conditions. The SR-PSF represents the ratio of the light intensity at the fovea in an eye with aberration (scattering) to that of a perfect optical system with no scatter. Previous studies have

emphasized the importance of optical quality indicators in distinguishing eyes with keratoconus from those of healthy eyes and in assessing the severity and progression of keratoconus.[7,8] However, there are very few publications on how optical quality indices change after CXL. Uysal et al.[3] found no significant difference in MTF and SR-PSF values when they compared 111 patients before and 12 months after CXL using a standard protocol. Similarly, Kaya Ergen et al.[10] found no significant change in SR-PSF values from baseline to 12 months after transepithelial CXL in 110 eyes. Ozdas et al.[9] found a significant improvement in SR-PSF values after A-CXL in a 3-year follow-up of 110 patients.

In our study, we observed a worsening in almost all SR-PSF and MTF values at 1 month after A-CXL, whereas we found a significant improvement in MTF-5 and MTF-15 values at 12 months after A-CXL compared to baseline. This deterioration in optical quality indicators at 1 month after A-CXL may have resulted from early subclinical haze during the healing period due to incomplete stromal healing.[9,28] The improvement we achieved in MTF-5 and MTF-15 values compared to other studies may be due to our lower mean age and the fact that we worked with adolescent patients (11-20), which allowed us to observe the effectiveness of A-CXL differently. Similarly, studies comparing the effects of CXL in pediatric and adult groups have reported that the improvements in CDVA and changes in anterior curvature were more pronounced in the pediatric group.[16,18] This indicates that CXL is more effective in this group.

However, we observed no significant correlation between the changes in optical quality indicators from baseline to 12 months post-A-CXL and the change in CDVA. This may be because the limited change in visual acuity was insufficient to correlate with the change in optical quality indicators. Indeed, a study conducted in 20 eyes of 16 patients treated using the Cretan protocol (a procedure that includes CXL and limited refractive correction) demonstrated greater improvements in PSF and MTF values, as well as in CDVA.[28]

The ability to examine corneal layers in detail with AS-OCT has made ET maps an important tool in the clinical practice of both refractive surgery and the diagnosis and treatment of corneal ectasia. Epithelial remodeling can cause undercorrection, particularly in refractive surgery. This highlights the importance of epithelial optical power. Epithelial wavefront analysis, a novel technology, allows for better examination of the effects of epithelial optical power and epithelial remodeling. Indeed, some studies have suggested that epithelial remodeling after CXL results in a more uniform corneal optical surface.[14,15]

In our study, total epithelial aberrations did not change significantly, but among the epithelial HOAs, we observed a significant improvement in the vertical coma values 12 months after A-CXL compared to baseline. This result in particular indicates that the vertical coma value, which is often the corneal aberrometric result of the inferotemporal displacement of the cone in keratoconus, is similarly reflected in the epithelium. Indeed, studies have shown that the epithelial layers in patients with keratoconus are thinner, particularly in the inferotemporal and inferior regions, compared to those in healthy controls, and this correlates with posterior elevation on the steepest keratometry readings.[29,30] Furthermore, differences between the maximum and minimum ET, an indicator of epithelial uniformity, have been reported to be more pronounced in keratoconic patients.[30,31] Lautert et al.[15] demonstrated that this difference decreased after CXL, indicating that epithelial remodeling resulted in a more uniform epithelium. In our study, we also observed that the differences between the maximum and minimum ET decreased after A-CXL.

The improvement in the epithelial vertical coma value observed in our study, as well as our finding that the improvement in CDVA was correlated with the change in epithelial RMS-HOAs, may indicate that A-CXL provides a more uniform structure to the epithelial layer, resulting in a more regular refractive surface in the epithelium, thus improving the optical power. Furthermore, the correlation we found between the changes in corneal epithelial RMS-HOAs and vertical coma and the changes in the difference between maximum and minimum ET in the central 6-mm zone may indicate that epithelial remodeling plays a role in the change of the corneal epithelial wavefront after A-CXL.

Study Limitations

Our study has some important limitations. First, we examined only corneal and corneal epithelial aberrations and did not evaluate whole-eye ocular aberrations. Indeed, a significant portion of corneal aberrations is neutralized by internal aberrations. Another important limitation is the one-year follow-up period. With longer follow-up periods, the effects of A-CXL on total corneal and corneal epithelial aberrations, as well as optical quality indicators, can be assessed more clearly.

Conclusion

In conclusion, A-CXL is an effective treatment for adolescent patients with progressive keratoconus, playing a significant role in improving vision and reducing total corneal and corneal epithelial HOAs. The association between visual improvement after A-CXL and the reduction in total corneal and corneal epithelial aberrations may be a consequence of anterior corneal remodeling after A-CXL. Longitudinal studies with longer follow-up periods could

contribute to a clearer understanding of the effects of CXL on optical quality indicators as well as total and epithelial corneal aberrations.

Ethics

Ethics Committee Approval: The study protocol was approved by a University of Health Sciences Türkiye, Ankara Etlik City Hospital Ethics Committee (decision no: AEŞH-BADEK1-2025-289, date: 27.08.2025) in accordance with the Declaration of Helsinki.

Informed Consent: Retrospective study.

Declarations

Authorship Contributions

Surgical and Medical Practices: B.D.Y.E., B.K., Concept: B.D.Y.E., B.K., Design: B.D.Y.E., B.K., Data Collection or Processing: B.D.Y.E., B.K., Analysis or Interpretation: B.D.Y.E., Literature Search: B.D.Y.E., B.K., Writing: B.D.Y.E., B.K.

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Original Article

Syphilitic Uveitis in HIV-Positive and -Negative Patients: A Multicenter Cohort Study

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Abstract

Objectives: To evaluate the clinical manifestations and visual outcomes of patients with syphilitic uveitis, and to compare these features based on human immunodeficiency virus (HIV) infection status.

Materials and Methods: The records of patients diagnosed with syphilitic uveitis between 2014 and 2024 were analyzed retrospectively. Demographics, history, ocular examination findings, syphilis and HIV serology, lumbar puncture test, treatment approaches, and best-corrected visual acuity (BCVA) results of all patients were documented.

Results: A total of 51 eyes of 33 patients were included in the study. Twenty-seven patients (82%) were male, with a mean age of 44 years (range, 21-69). HIV co-infection was present in 39% of the patients (all male). Prior to presentation, 9 patients (27%) had received an incorrect diagnosis or inappropriate treatment. The most common form of syphilitic uveitis was panuveitis (63%), followed by posterior uveitis (31%). Anterior segment inflammation and optic nerve involvement were observed at higher rates in patients with HIV co-infection ($p<0.05$). All patients received systemic penicillin therapy, and 51% received systemic corticosteroids. Visual acuity improved significantly after treatment in all patients ($p<0.01$). HIV co-infection status was not associated with age, laterality, lumbar puncture findings, the development of ocular complications, or baseline and final BCVA outcomes ($p>0.05$).

Conclusion: Syphilitic uveitis is an important clinical entity due to its broad spectrum of ocular manifestations. In this study, severe intraocular inflammatory findings, including panuveitis and optic nerve involvement, were more frequently observed in patients with HIV co-infection. However, HIV co-infection did not influence final visual acuity or the rate of ocular complication development.

Keywords: Syphilis, ocular syphilis, syphilitic uveitis, treatment, HIV

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Introduction

Syphilis is a sexually transmitted infection caused by the bacterium *Treponema pallidum* that can cause systemic and ocular involvement.[1] Since the beginning of the twentieth century, syphilis has undergone a resurgence and remains a significant public health concern worldwide.[1,2,3,4] Co-infection with human immunodeficiency virus (HIV) is common among patients with syphilis due to their common routes of transmission. If left untreated, syphilis progresses through various stages: primary, secondary, latent, and tertiary.[1] Ocular involvement of syphilis is uncommon and usually presents as syphilitic uveitis.[1,3] Syphilitic uveitis can occur at any stage of syphilis. Epidemiological studies have demonstrated that syphilitic uveitis accounts for a small proportion (<3%) of all uveitis cases.[5] This rate varies

regionally, reported in the literature as 1.4% in Japan,[6] 2.5% in France,[4] and 6.08% in Brazil.[7] According to a national registry report, syphilitic uveitis accounts for 0.1% of all uveitis in our country.[8] However, the rising incidence of syphilis in recent years has been accompanied by a parallel increase in syphilitic uveitis cases, both in Türkiye and globally.

Ocular involvement in syphilitic uveitis can present with a variety of anterior and posterior segment manifestations, including scleritis, anterior uveitis, retinitis, choroiditis, retinal vasculitis, optic neuritis, and panuveitis.[1,3,9] Although advances in ocular imaging have enabled the identification of the distinctive features of syphilitic uveitis, including acute syphilitic posterior placoid chorioretinitis (ASPPC), confluent retinochoroiditis, and superficial retinal precipitations, the condition can still mimic a wide spectrum of ocular inflammatory and infectious diseases.[9,10,11] This is why syphilis is called the "Great Imitator." This frequently results in misdiagnosis and delayed initiation of appropriate treatment.[9,12]

Given the increasing frequency of ocular syphilis and HIV co-infection, studies in recent years have aimed to investigate how HIV status affects the presentation, treatment response, and prognosis of syphilitic uveitis.[13,14,15,16,17,18,19] Although some studies suggest that HIV-positive patients present with more severe disease than those who are HIV-negative, the findings in the literature remain conflicting.[13,14,15,16,17] Despite these discrepancies, most studies show that both groups generally have comparable visual prognoses.[14,15,16,17] This multicenter study aimed to comparatively assess the demographic characteristics, clinical findings, disease course, and visual outcomes of patients with syphilitic uveitis according to HIV co-infection status.

Materials and Methods

This was a retrospective, multicenter medical record review of patients diagnosed with syphilitic uveitis between January 2014 and March 2024. Four ophthalmology departments from different tertiary referral centers across Türkiye participated in the study. The study was conducted in accordance with the principles of the Declaration of Helsinki. Ankara Training and Research Hospital Ethics Committee approval was obtained prior to study initiation (decision no: 95/2024, approval date: 17.04.2024, protocol number: E-24-95). Given the retrospective nature of the study, individual informed consent was not obtained.

Study Population and Data Collection

The diagnosis of ocular syphilis was established by uveitis specialists at each center based on clinical history, ocular examination and multimodal imaging findings, and positive syphilis serology. Treponemal tests used in the serological diagnosis of syphilis included fluorescent treponemal antibody absorption test, *Treponema pallidum* hemagglutination test, and enzyme immunoassay test. Non-treponemal tests included the Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin tests. The serological testing algorithms used for the diagnosis of syphilis varied between centers and within centers over time.[1,11]

In addition to syphilis serology, complete blood count, biochemical parameters, acute-phase reactants (erythrocyte sedimentation rate and C-reactive protein), and enzyme-linked immunosorbent assay results for hepatitis viruses and HIV were reviewed for all patients. If performed on clinical grounds, additional laboratory investigations to exclude alternative causes of uveitis were also noted. In patients who underwent lumbar puncture (LP), the results of cerebrospinal fluid (CSF) analysis (non-treponemal testing [VDRL], cell count, and total protein) were recorded. CSF examination via LP is recommended for ocular syphilis patients presenting with neurological symptoms or signs.[2] Conversely, CSF examination is not imperative in patients without neurological findings who have ocular symptoms consistent with ocular syphilis (e.g., uveitis, optic neuritis, neuroretinitis) and confirmatory syphilis serological results.[2] Nevertheless, there are some advocates for routine LP in all patients with ocular syphilis. In the present study, LP was performed by the departments of neurology or infectious diseases. Syphilis staging was determined on the basis of clinical symptoms, serological findings, and examination results.

Demographic data, presenting complaints, history of syphilis and HIV infection, HIV status, and sexual history were retrieved from medical records. Best-corrected visual acuity (BCVA, assessed by Snellen chart), intraocular pressure (measured by non-contact tonometry), slit-lamp biomicroscopy findings, and fundus examination results at the time of admission were documented. When available, optical coherence tomography (OCT), fundus autofluorescence imaging, and fundus fluorescein angiography (FFA) results were also reviewed. All visual acuity data were converted to logarithm of the minimum angle of resolution (logMAR) for analysis. Assessment of ocular inflammation was performed according to the Standardization of Uveitis Nomenclature Working Group criteria.[20] Additionally, posterior segment involvement patterns described in the literature as distinctive of syphilitic uveitis (ASPPC, superficial retinal precipitations, confluent retinochoroiditis, and punctate inner retinitis) were specifically evaluated.[10,11] Treatment data, including the route of administration, dose, and

duration of systemic antibiotics and corticosteroids, were recorded and analyzed. Data regarding periocular and intravitreal injections administered as local therapy were also noted.

Patients with a prior history of misdiagnosis before referral were identified, and details of any systemic or periocular corticosteroid therapy administered were recorded. The clinical characteristics of the patients were evaluated according to HIV co-infection status. Sex, age, clinical features, and laboratory findings were compared between the HIV-negative and HIV-positive patient groups. The BCVA measured at the final post-treatment visit was defined as final BCVA for each patient.

Statistical Analysis

The data were analyzed using IBM SPSS Statistics version 22.0 (IBM, Armonk, NY, USA). Descriptive statistics were presented as mean, standard deviation, median, frequency, and percentage. Categorical variables were compared using chi-square test and Fisher's exact test. Continuous variables were compared using the Mann-Whitney U test or Student's t-test for independent samples and the Wilcoxon signed-rank test for paired samples. A p value <0.05 was considered statistically significant.

Results

Demographic and Clinical Characteristics

We initially identified 38 patients diagnosed with ocular syphilis. Of these, 5 patients (13.2%) with indeterminate HIV status were excluded from the analysis. A total of 51 eyes of 33 patients were included in the study. Thirteen patients (39.4%) were HIV-positive and 20 patients (60.6%) were HIV-negative. Twenty-seven patients (81.8%) were male. The mean age at admission was 43.8±11.9 years (range: 21-69 years). The mean follow-up duration was 9.2±5.9 months (range: 3-26 months). Sexual history data were available for only 13 patients (39.4%). Of these, 8 (24.2%) were heterosexual men with a history of multiple sexual partners, and 5 (15.2%) reported a history of male-to-male sexual contact. The most frequent presenting complaints were reduced visual acuity (22 patients, 66.6%), blurred vision (7 patients, 21.2%), and ocular redness (4 patients, 12.1%). None of the patients had a prior history of syphilis diagnosis or treatment. HIV co-infection was identified in 13 of 33 patients (39.4%), of whom 8 (24.2%) had a pre-existing diagnosis of HIV infection. The remaining 20 patients (60.6%) tested negative for HIV. CD4+ T-cell count data were unavailable for HIV-positive patients. No additional co-infections were identified other than HIV.

Syphilis stage was determinable in 16 patients (48.4%). Secondary syphilis was most common (9 patients, 27.2%), followed by latent (5 patients, 15.2%) and tertiary (2 patients, 6.1%) disease. At presentation, dermatological manifestations (maculopapular rash or genital ulcer) were evident in 11 patients (33.3%) (Figure 1). Four patients (12.1%) reported neurological symptoms at presentation: headache in 2 patients (6.1%), balance disorder in 1 patient (3.0%), and speech disorder in 1 patient (3.0%). However, neurological examination findings were normal in all patients. LP was performed in 12 patients (36.3%). CSF analysis revealed a positive VDRL in 4 patients (12.1%), pleocytosis in 5 patients (15.1%), and elevated protein in 5 patients (15.1%). The demographic and laboratory characteristics of the study population are summarized in Table 1.

Ocular Findings and Treatment

Bilateral ocular involvement was present in 18 patients (54.5%). At presentation, the median logMAR BCVA was 0.70 (range: 0-2.5) and the mean intraocular pressure was 13.1±0.8 mmHg (range: 10-21 mmHg). Panuveitis was the most common clinical presentation of syphilitic uveitis (32 eyes, 62.7%). This was followed by posterior uveitis (16 eyes, 31.4%), intermediate uveitis (2 eyes, 3.9%), and isolated anterior uveitis (1 eye, 1.9%). The most common anterior segment inflammatory findings at admission included anterior chamber cells (28 eyes, 54.9%) and keratic precipitates (19 eyes, 37.3%). The most frequent posterior segment inflammatory findings were vitreous cells (36 eyes, 70.6%) and retinochoroiditis (33 eyes, 64.7%) (Table 2). Regarding the distinctive posterior segment features of syphilitic uveitis, the most common patterns were ASPPC (14 eyes, 27.5%) (Figure 2), confluent retinochoroiditis (8 eyes, 15.7%), superficial retinal precipitations (8 eyes, 15.7%) (Figure 3), and punctate inner retinitis (3 eyes, 5.9%). Syphilitic multifocal chorioretinitis (2 eyes, 3.9%) presented as bilateral acute posterior multifocal placoid pigment epitheliopathy in one patient (Figure 4). Concomitant macular edema was present in 7 eyes (13.7%).

On FFA, the most prevalent findings were optic disc hyperfluorescence secondary to disc leakage (27 eyes, 52.9%), late-phase hyperfluorescence corresponding to areas of retinochoroiditis (21 eyes, 41.2%), and hyperfluorescence attributable to vascular leakage (12 eyes, 23.5%). On OCT, the most common finding was disruption of the outer retinal layers and disorganization of the retinal pigment epithelium (15 eyes, 29.4%), followed by macular edema (7 eyes, 13.7%), punctate hyperreflective lesions in the inner retinal layers (3 eyes, 5.9%), subretinal fluid (2 eyes, 3.9%), and placoid hyperreflective lesions in the outer nuclear layer (2 eyes, 3.9%). The imaging findings are

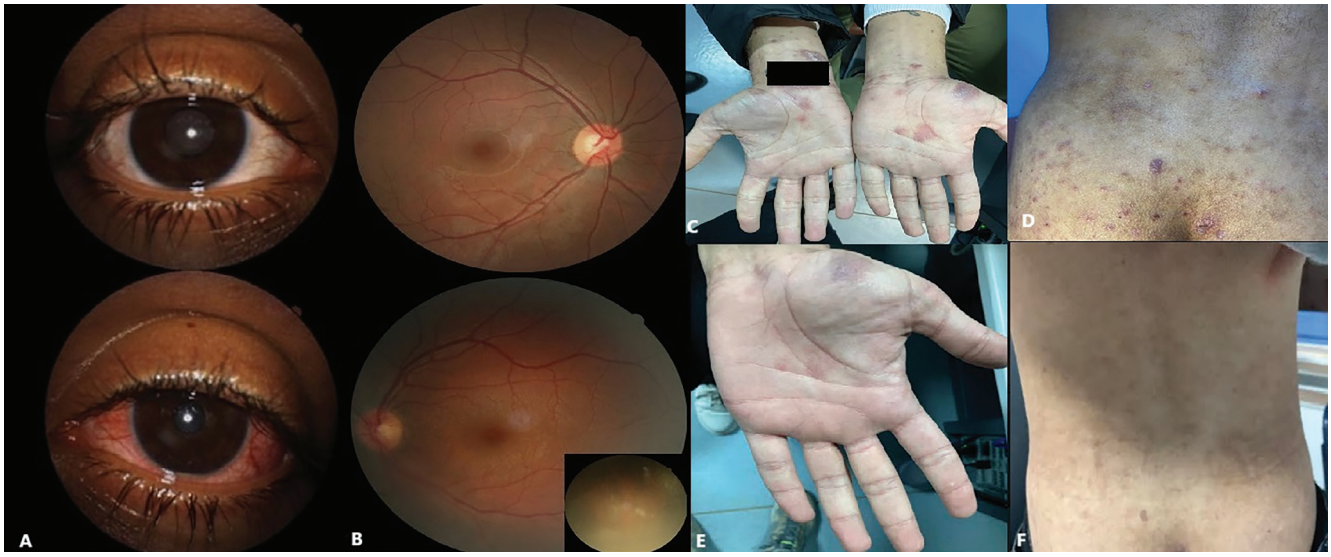

Figure 1. A 25-year-old man had been misdiagnosed with psoriasis for one month on the basis of dermatological findings. He was referred to the ophthalmology department for panuveitis in the left eye. A) The anterior segment of the right eye was quiet (upper), while the left eye showed ciliary injection, anterior chamber cells, and non-granulomatous keratic precipitates (lower). B) Color fundus photography shows a normal right fundus (upper) and vitreous haze with inferotemporal retinitis foci in the left eye (lower). C, D) Clinical photographs show a diffuse maculopapular rash involving the palms and entire body surface. Syphilis serology and human immunodeficiency virus testing were both positive. Following systemic antibiotic and topical corticosteroid therapy, both the cutaneous (E, F) and ocular findings regressed

Table 1. Demographic and clinical characteristics of patients with syphilitic uveitis (n=33 patients)	
Age (years)	
Mean ± SD Median	43.8±11.9 44.0
Sex, n (%)	
Female Male	6 (18.2) 27 (81.8)
Laterality, n (%)	
Unilateral Bilateral	15 (45.5) 18 (44.5)
Syphilis serology tests, n (%)	
Positive TPHA and VDRL Positive FTA-ABS and VDRL Positive TPHA and RPR Positive EIA and TPHA, negative VDRL	10 (30.3) 15 (45.5) 5 (15.2) 3 (9.0)
HIV co-infection, n (%)	
Positive HIV test Negative HIV test	13 (39.4) 20 (60.6)
Lumbar puncture, n (%)	12 (36.4)
Positive VDRL Pleocytosis Elevated protein	4 (12.1) 5 (15.2) 5 (15.2)

SD: Standard deviation, TPHA: *Treponema pallidum* hemagglutination assay, VDRL: Venereal Disease Research Laboratory test, FTA-ABS: Fluorescent treponemal antibody absorption, RPR: Rapid plasma reagin test, EIA: Enzyme immunoassay, HIV: Human immunodeficiency virus

reported in grouped categories due to the heterogeneous clinical presentations.

All patients received intravenous (18-24 MU crystallized penicillin G; Kristapen, Deva İlaç, İstanbul, Türkiye) or intravenous and intramuscular (2.4 MU benzathine penicillin G; Deposilin, Ulagay İlaç, İstanbul, Türkiye) antibiotic therapy. None of the patients required alternative antibiotic therapy. Seventeen patients (51.5%) with severe posterior uveitis or optic nerve involvement received adjunctive oral corticosteroids (0.5 mg/kg/day; Prednol, Mustafa Nevzat İlaç, İstanbul, Türkiye), initiated 24 to 48 hours after the commencement of systemic antibiotic therapy. Four eyes (7.8%) received posterior sub-Tenon triamcinolone acetonide injections (Kenacort-A, Deva İlaç, Istanbul, Türkiye) for macular edema. One of these eyes (1.9%) subsequently required an intravitreal dexamethasone implant (Ozurdex, AbbVie, Chicago, IL, USA) for refractory macular edema. Treatment details and durations are summarized in Table 2. The most frequent post-treatment ocular complications were optic atrophy (6 eyes, 11.7%), cataract (3 eyes, 5.9%), retinal detachment (3 eyes, 5.9%), and atrophic maculopathy (3 eyes, 5.9%). Recurrence was not observed in any of the patients. The median final BCVA was 0.10 (range: 0-2.5) logMAR, representing a significant improvement from the presenting BCVA (Table 2). No statistically significant difference in median final BCVA was observed between

Table 2. Ocular involvement findings and treatment approaches (n=51 eyes)	
Anterior segment inflammatory findings, n eyes (%)	
Anterior chamber cell (≥1+)	28 (54.9)
Keratic precipitates	19 (37.3)
Granulomatous	3 (5.9)
Non-granulomatous	16 (31.4)
Hypopyon	3 (5.9)
Iris nodules	0 (0)
Posterior synechiae	9 (17.6)
Posterior segment inflammatory findings, n eyes (%)	
Vitreous cells (≥1+)	36 (70.6)
Optic nerve involvement	30 (58.8)
Retinochoroiditis	33 (64.7)
Retinal vasculitis	13 (25.5)
Macular edema	7 (13.7)
Exudative RD	5 (9.8)
Systemic treatment, n patients, (%)	
IV and IV + IM penicillin G	33 (100)
Duration of antibiotic treatment (days), median (range)	21 (14-21)
Oral corticosteroid	17 (51.5)
Oral corticosteroid duration (days), median (range)	14.0 (7-60)
Local treatment, n eyes (%)	
Posterior sub-Tenon triamcinolone acetonide	4 (7.8)
Intravitreal dexamethasone implant	1 (1.9)
logMAR BCVA, median (range)	
Presenting	0.70 (0-2.5)
Final	0.10 (0-2.5)
p value	<0.001*

Statistically significant at p<0.05, *Wilcoxon signed ranks test, n: number, RD: Retinal detachment, IV: Intravenous, IM: Intramuscular, logMAR: Logarithm of the minimum angle of resolution, BCVA: Best-corrected visual acuity

patients who received systemic corticosteroids (0.10; range: 0-1.5) and those who did not (0.10; range: 0-2.5) (p=0.681).

Prior to the diagnosis of ocular syphilis, 9 patients (27.2%) had been misdiagnosed at other centers as having optic neuritis (4 patients, 12.1%), non-infectious posterior uveitis (1 patient, 3.0%), psoriasis (3 patients, 9.1%), or vitreous hemorrhage (1 patient, 3.0%). Seven of these patients (77.7%) had received corticosteroids, without systemic antibiotic therapy. Four patients (44.4%) had received intravenous pulse corticosteroid, 1 patient (11.1%) received oral corticosteroid, and 1 patient (11.1%) received subconjunctival corticosteroid injections in both eyes. All of these patients had been referred to a tertiary center owing to progressive worsening of ocular symptoms and visual acuity. Notably, syphilis serology had not been conducted for any of the misdiagnosed patients. Among the misdiagnosed patients, 4 (44.4%) were HIV-positive and 5 (55.6%) were HIV-negative. Following confirmation of ocular syphilis, all prior corticosteroid therapies were discontinued and systemic antibiotic treatment was promptly initiated. The median logMAR BCVA at presentation was significantly worse in patients who had been initially misdiagnosed (1.60; range: 0.1-2.5) compared to patients without a prior misdiagnosis (0.40; range: 0-2.5) (p=0.002). Despite appropriate treatment, the final median logMAR BCVA was significantly worse in the initially misdiagnosed group (0.40; range: 0-2.5) than in patients diagnosed correctly at first presentation (0.07; range: 0-1.51) (p=0.048).

Clinical Characteristics According to HIV Co-infection Status

Of the 33 ocular syphilis patients with known HIV status, 13 (39.4%) were HIV-positive and 20 (60.6%) were HIV-negative. There was no statistically significant difference in median age between HIV-positive and HIV-negative patients (p=0.06). Regarding sex distribution, all of the HIV-positive patients were male (p=0.032). The laterality of ocular involvement did not differ according to HIV status (p=0.515). Demographic characteristics, laterality of ocular involvement, IOP values, and syphilis staging stratified by HIV co-infection status are summarized in Table 3.

In both groups, panuveitis and posterior uveitis were the most common anatomical patterns; however, the rate of panuveitis was significantly higher among HIV-positive patients (p=0.002). Anterior segment inflammatory findings (anterior chamber cells, keratic precipitates, and posterior synechiae) were more frequent in HIV-positive patients (all p<0.01). The prevalence of optic nerve involvement was significantly higher among HIV-positive patients than HIV-negative patients (p=0.035). The rates of the distinctive posterior segment findings of syphilitic uveitis according to HIV co-infection status are presented in Table 4. ASPPC, confluent retinochoroiditis, and superficial retinal precipitations were more common among HIV-negative patients, but these differences did not reach statistical significance (all p>0.05). There were no significant differences in LP findings between HIV-positive and HIV-negative patients (p=0.208). Median logMAR BCVA values at presentation and at the final visit did not differ statistically between HIV-positive and HIV-negative patients (p>0.05 for all). Patients with and without HIV co-infection developed at least one ocular complication at comparable rates (p=0.673). No clinical findings suggestive of immune reconstitution inflammatory syndrome-associated uveitis were identified in the HIV-positive patients. Clinical characteristics, ocular findings, and presenting and final BCVA values stratified by HIV co-infection status are presented and compared between the groups in Table 4.

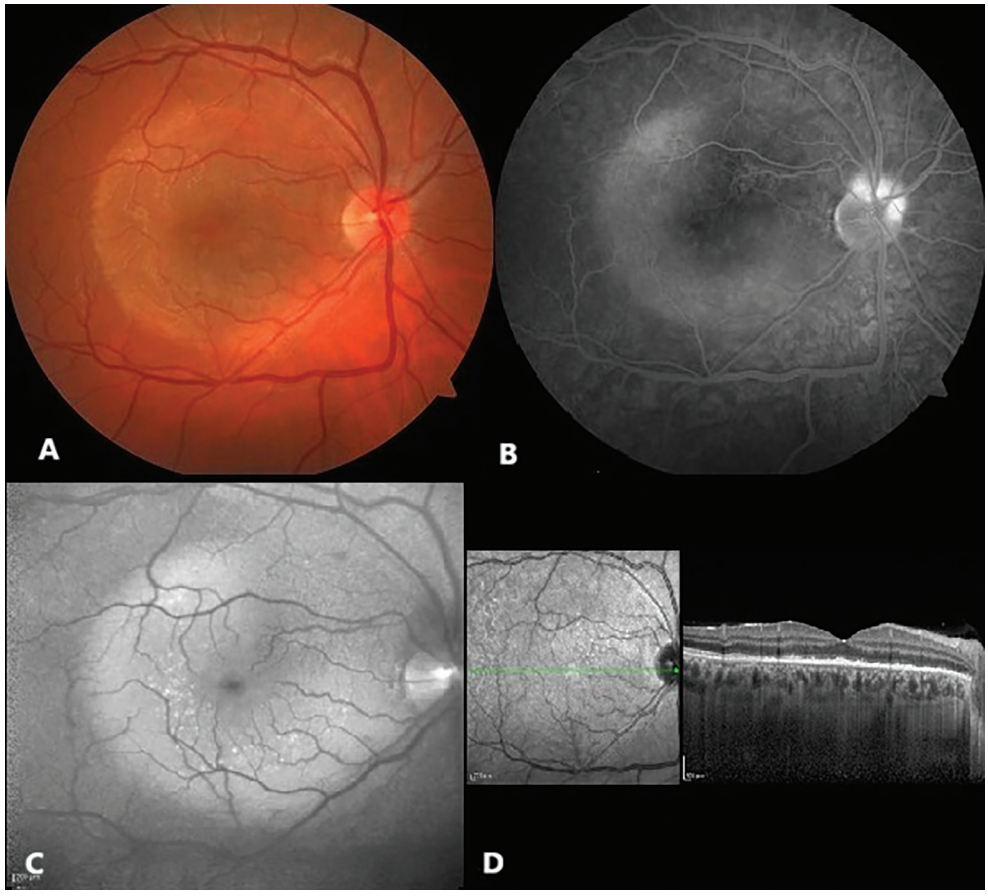

Figure 2. Color fundus photograph (A) demonstrates a large, yellowish, circular syphilitic posterior placoid chorioretinitis (ASPPC) lesion in the macula. Fundus fluorescein angiography (B) shows hyperfluorescence in the lesion area and late-phase optic disc hyperfluorescence. Fundus autofluorescence imaging (C) reveals punctate hyperautofluorescence within the ASPPC lesion. Optical coherence tomography (D) demonstrates irregular hyperreflectivity at the photoreceptor-retinal pigment epithelium junction, with segmental disruption of the ellipsoid zone and outer limiting membrane

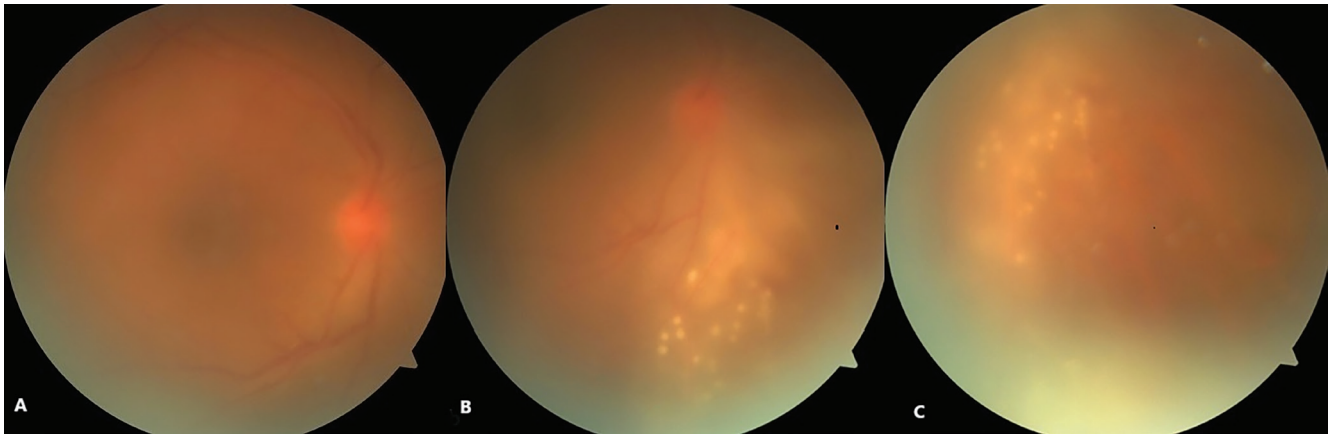

Figure 3. Color fundus photographs of a patient with syphilitic posterior uveitis. A) There is marked vitreous inflammation with vitreous haze and cells, as well as optic disc hyperemia. B) A ground-glass appearing confluent retinochoroiditis lesion is evident inferior to the optic disc. C) In addition to the area of retinochoroiditis, numerous small, round, cream-white superficial preretinal precipitations are observed

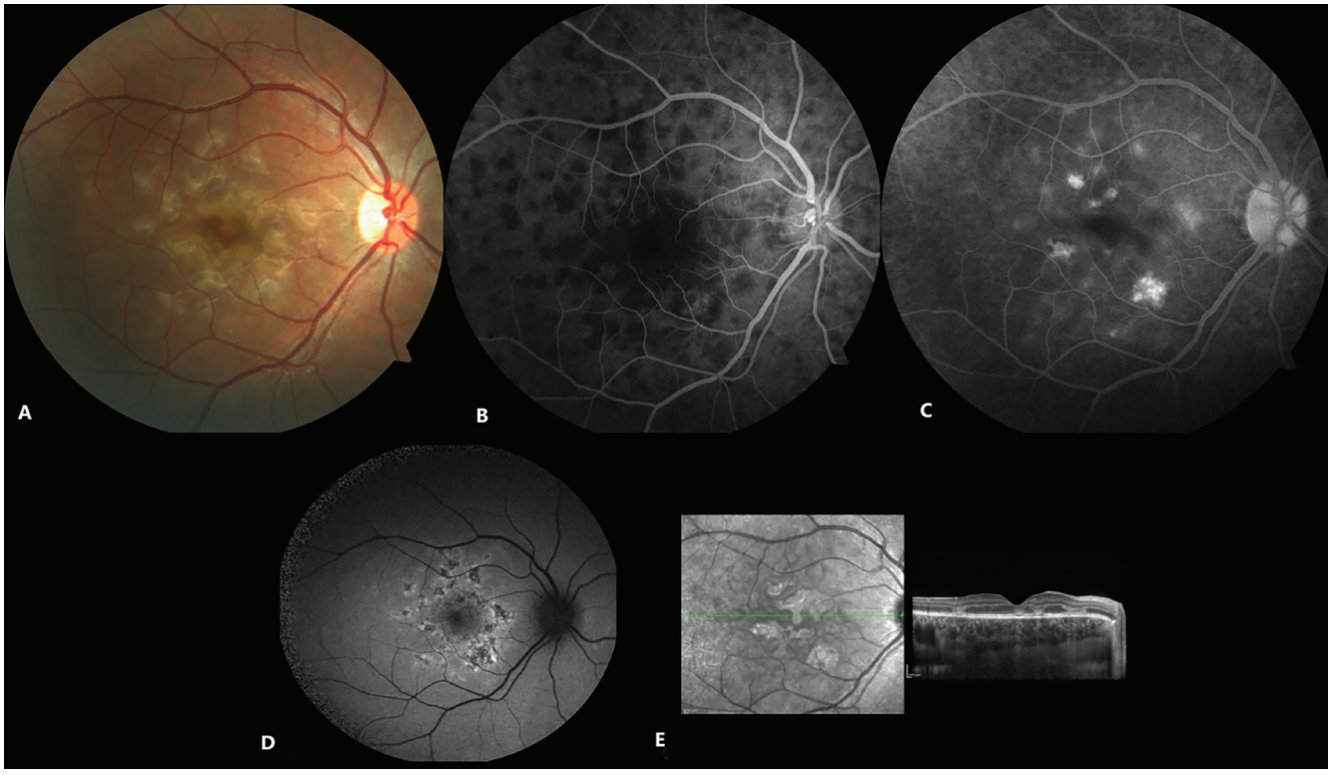

Figure 4. Features mimicking acute posterior multifocal placoid pigment epitheliopathy. Color fundus photograph (A) shows multifocal white lesions in the macula. Fundus fluorescein angiography reveals multiple hypofluorescent spots at the posterior pole in the early phase (B) and hyperfluorescence and optic disc hyperfluorescence in placoid lesions in the late phase (C). On fundus autofluorescence imaging (D), the lesions show central hypoautofluorescence surrounded by hyperautofluorescence. Optical coherence tomography (E) demonstrates disruption of the outer retinal layers with prominent focal hyperreflective lesions in the outer nuclear layer

Table 3. Demographic and clinical characteristics by HIV co-infection status

	HIV-positive (13 patients, 21 eyes)	HIV-negative (20 patients, 30 eyes)	p value
Age (years), median (range)	37 (23-59)	43 (21-64)	0.125¶
Sex, n (%) Female Male	 0 (0) 13 (100)	 6 (30) 14 (70)	0.032*
Laterality, n (%) Unilateral Bilateral	 5 (38.5) 8 (62.2)	 10 (50) 10 (50)	0.515*
IOP (mmHg), median (range)	15 (10-20)	15 (10-21)	0.513¶
Syphilis stage, n (%) Secondary Tertiary Latent	 6 (46.1) 0 (0) 0 (0)	 3 (15) 2 (10) 5 (5)	0.061*

Statistical significance at p<0.05, *chi-square test or Fisher's exact test, ¶Mann-Whitney U or Student's t-test, HIV: Human immunodeficiency virus, IOP: Intraocular pressure

Table 4. Ocular involvement characteristics according to HIV co-infection status			
	HIV-positive (13 patients, 21 eyes)	**HIV-negative (20 patients, 30 eyes)**	**p value**
Uveitis by anatomical classification, n (%)			
Isolated anterior uveitis	0 (0)	1 (3.3)	
Intermediate uveitis	0 (0)	2 (6.7)	
Posterior uveitis	2 (9.5)	14 (46.7)	0.002*
Panuveitis	19 (90.5)	13 (43.3)	
Anterior segment inflammatory findings, n (%)			
Anterior chamber cells (≥1+)	18 (85.7)	10 (33.3)	<0.001*
Keratic precipitates	14 (66.7)	5 (16.7)	<0.001*
Hypopyon	2 (9.5)	1 (3.3)	0.561*
Posterior synechiae	8 (38.1)	1 (3.3)	0.002*
Posterior segment inflammatory findings, n (%)			
Vitreous cells (≥1+)	18 (85.7)	18 (60)	0.064*
Optic nerve involvement	16 (76.2)	14 (46.7)	0.035*
Retinochoroiditis	15 (71.4)	18 (60)	0.401*
Retinal vasculitis	6 (28.6)	7 (23.3)	0.750*
Macular edema	2 (9.5)	5 (16.7)	0.685*
Exudative RD	1 (4.8)	4 (13.3)	0.391*
Distinguishing posterior segment findings, n (%)			
ASPPC	5 (23.8)	9 (30.0)	0.610*
Confluent retinochoroiditis	3 (14.3)	5 (16.7)	1.000*
Syphilitic multifocal chorioretinitis	0 (0)	2 (6.7)	0.506*
Superficial retinal precipitations	3 (14.3)	5 (16.7)	1.000*
Punctate inner retinitis	2 (9.5)	1 (3.3)	0.561*
Lumbar puncture, n (%)			
Yes	4 (30.8)	8 (40)	0.719*
No	9 (69.2)	12 (60)	
At least 1 positive LP finding	4 (30.8)	4 (20)	0.208*
logMAR BCVA, median (range)			
Presenting	1.00 (0-2.5)	0.40 (0-2.5)	0.332¶
Final	0.10 (0-1.5)	0.10 (0-2.5)	0.960¶
p value	<0.001ϕ	<0.001ϕ	
Any ocular complication, n (%)	6 (28.6)	7 (23.3)	0.673*

Statistical significance at p<0.05, *chi-square test or Fisher's exact test, ¶Mann-Whitney U or Student's t-test, ϕWilcoxon signed-rank test, HIV: Human immunodeficiency virus, RD: Retinal detachment, ASPPC: Acute syphilitic posterior placoid chorioretinitis, LP: Lumbar puncture, LogMAR: Logarithm of the minimum angle of resolution, BCVA: Best-corrected visual acuity

Discussion

This is the first multicenter study in Türkiye to evaluate the clinical features of syphilitic uveitis. Furthermore, the study provides a comparative analysis of the demographic and clinical profiles of syphilitic uveitis in HIV-positive and HIV-negative patients. Although syphilis can affect any ocular structure, uveitis is the most common ophthalmic manifestation.[11] Over the past decade, numerous published studies have substantially advanced our understanding of the clinical and multimodal imaging characteristics of syphilitic uveitis.[13,14,15,16,21,22,23]

Ocular syphilis predominantly affects men, with male patients comprising up to 90% of cases in recent series.[13,14,21] Key contributing risk factors include multiple sexual partners, unprotected sex, HIV co-infection, and the increasing prevalence of male-to-male sexual contact.[1,3,15,21] In a large ocular syphilis series by Vadboncoeur et al.,[13] HIV co-infection was detected in 32% of patients, all of whom were male, and 63% of those patients had a history of male-to-male sexual contact. Consistent with the literature,[13,14,15,21] the majority of patients in our study (82%) were male and HIV co-infection was detected in 39% of the patients, all of whom were men. Additionally, over one-third of the

patients reported a history of multiple sexual partners or male-to-male sexual contact. Ocular syphilis typically presents in the fourth and fifth decades of life; the mean age at presentation was 44 years in our cohort, consistent with previously published data.[3,10,13,16,24] Although previous studies have reported a younger mean age among HIV-positive patients with ocular syphilis compared to their HIV-negative counterparts,[13,23] no significant age difference was found between the two groups in the present study. Ocular involvement in syphilis is often bilateral, although unilateral presentation may also occur, as observed in our cohort. HIV co-infection in syphilis patients does not appear to influence the laterality of ocular involvement, and our results support this observation.[3,13,15,17,25]

Ocular syphilis most commonly manifests during the secondary and tertiary stages of the disease. However, ocular manifestations may arise at any stage and can occasionally represent the initial or sole presenting feature of syphilis in the absence of systemic findings.[1,9] In our study, syphilitic uveitis was most commonly identified in the secondary stage, with no significant difference in disease staging according to HIV co-infection status. In ocular syphilis patients presenting with uveitis, optic neuritis, or neuroretinitis in the absence of neurological signs and with confirmatory serology, routine pre-treatment CSF examination is not currently recommended.[2] However, approaches may vary according to the individual patient in clinical practice. Vadboncoeur et al.[13] identified at least one abnormality in 71% of patients who underwent CSF analysis, including positive VDRL (22%), pleocytosis (44%), and elevated protein (60%). In the present study, CSF analysis was performed in 36% of patients, and at least one abnormal finding was detected in 66% of those examined.

Syphilitic uveitis most commonly presents as posterior uveitis and panuveitis.[14,15,16,17] Ly et al.[14] reported posterior uveitis as the most prevalent form of syphilitic uveitis, and intermediate uveitis as the rarest presentation. In a more recently published series, panuveitis was the predominant presentation, whereas isolated anterior uveitis was the least common form.[26] Consistent with the literature, panuveitis was the most frequent presentation in our series, while intermediate uveitis and isolated anterior uveitis were rare. Common posterior segment manifestations of syphilitic uveitis include chorioretinitis, optic disc inflammation, necrotizing retinitis, and retinal vasculitis.[25,26] ASPPC has been described as a rare but distinctive posterior segment finding of syphilis.[10,18] In the present study, ASPPC was identified in 27% of the patients but was not significantly associated with HIV co-infection status. Hoogewoud et al.[25] reported a higher frequency of panuveitis among HIV-positive patients, along with more pronounced inflammatory signs such as vitreous haze, anterior chamber cells, flare, and posterior synechiae. Similarly, in addition to a higher rate of panuveitis, anterior segment inflammatory signs were significantly more prevalent among HIV-positive patients in the present study. Optic nerve involvement is a serious sign of posterior segment inflammation that has been reported with greater frequently in ocular syphilis patients with HIV co-infection.[15,19,26] Ahmed et al.[26] reported higher rates of diffuse necrotizing retinitis and optic nerve involvement in syphilitic uveitis patients with HIV co-infection. Additionally, marked ocular inflammation has been documented in syphilitic uveitis patients with HIV-coinfection, despite low CD4+ T-cell counts.[26,27] In our series, HIV-positive patients exhibited a higher burden of inflammatory findings, including optic nerve involvement and more pronounced anterior segment and vitreous inflammation. Although the retrospective study design precluded a formal analysis of the relationship between CD4+ T-cell counts and inflammatory burden, the current findings suggest that HIV co-infection may be associated with a more pronounced inflammatory phenotype in ocular syphilis.

According to the 2021 Sexually Transmitted Infections Treatment Guidelines published by the United States Centers for Disease Control and Prevention, the treatment protocol for syphilitic uveitis is equivalent to that of neurosyphilis. The recommended regimen is intravenous aqueous crystallized penicillin G at 18-24 MU for 10-14 days. Alternatively, 2.4 MU penicillin G procaine can be administered intramuscularly with concomitant oral probenecid for 10-14 days.[28] All patients in our cohort received penicillin G therapy, with treatment durations ranging from 14 to 21 days. As the recommended duration for neurosyphilis treatment is shorter than that for latent syphilis, some clinicians opted to extend therapy by an additional week. Systemic corticosteroids may be administered adjunctively, particularly in cases of ocular syphilis with severe posterior uveitis or optic nerve involvement.[11,14,16] Corticosteroids are also employed to mitigate the Jarisch-Herxheimer reaction, an acute febrile hypersensitivity response that can develop within the first 24-48 hours of initiating antibiotic therapy for syphilis.[11,16]

Bollemeijer et al.[16] reported a statistically significant improvement in visual acuity in patients with syphilitic uveitis who received periorbital or systemic corticosteroids in combination with antibiotic therapy. In contrast, Moradi et al.[15] found no significant difference in ocular complications or visual impairment among ocular syphilis patients treated with immunosuppressive therapy, including oral corticosteroids and immunomodulators. In our study, systemic corticosteroids were administered to approximately half of the patients (51%), and visual

outcomes were comparable between those who did and did not receive corticosteroid therapy. Furthermore, posterior sub-Tenon and intravitreal corticosteroid injections proved effective in the treatment of patients with macular edema (7.8%).

The majority of published studies report significant visual improvement following treatment in patients with ocular syphilis.[13,14,17,23] Our findings are consistent with the literature, demonstrating significant improvement in final BCVA compared to baseline across the entire cohort and within both the HIV-positive and HIV-negative subgroups. Mathew and Smit[23] reported that HIV status did not influence final visual acuity in patients with ocular syphilis, 92% of whom exhibited visual improvement. Furtado et al.[3] similarly reported no difference in rates of visual loss according to HIV status. Ly et al.[14] and Vadboncoeur et al.[13] also reported no significant difference in presenting or final visual outcomes in patients with HIV co-infection. In the present study, post-treatment final BCVA was similar in HIV-positive and HIV-negative patients.

Syphilis responds favorably to appropriate antibiotic therapy, with inflammatory signs typically resolving promptly after treatment.[1,15,16] Serious ocular complications of syphilitic uveitis are generally uncommon. The most frequently reported complications in the literature include macular edema, epiretinal membrane, macular scarring, glaucoma, and optic atrophy.[14,15,25,26] Hoogewoud et al.[25] reported that complication rates did not differ significantly between HIV-positive and HIV-negative patients with ocular syphilis. In our study, optic atrophy and cataract were the most frequently observed complications, and no significant association was identified between HIV co-infection status and the development of complications.

A report by the International Ocular Syphilis Working Group assessing current ophthalmological practices in syphilitic uveitis identified failure to request serological testing (30%) and initial misdiagnosis (21%) as the leading contributors to diagnostic delay.[12] Furthermore, various studies have demonstrated that patients with syphilitic uveitis who experience diagnostic or therapeutic delays present with worse visual acuity and have a poorer visual prognosis.[16,25] As the "Great Imitator," syphilis can manifest with a broad spectrum of clinical findings, rendering its recognition challenging and frequently resulting in misdiagnosis.[1,12] In our cohort, 27% of patients were misdiagnosed at initial presentation, primarily because syphilis serological tests had not been conducted. Both presenting and post-treatment BCVA were significantly worse in patients with prior misdiagnosis compared with those without. Moreover, the majority of misdiagnosed patients had been treated with systemic corticosteroids without concurrent antibiotic therapy. These findings once again underscore the importance of maintaining clinical suspicion and routine syphilis serological testing in all patients presenting with intraocular inflammation of undetermined etiology.[9,12,29] As with other forms of infectious uveitis, clinicians should bear in mind that corticosteroid use in the absence of antibiotic coverage may exacerbate syphilitic uveitis.[16,30]

Study Limitations

The main limitation of this study is the relatively small sample size, which limits the statistical analysis. Other limitations include the retrospective study design and variability in data collection protocols across participating centers. Due to the retrospective nature of the study, CD4+ T-cell count data were not available for HIV-positive patients, which precluded an assessment of the relationship between immune status and ocular findings. Future prospective, larger-scale studies employing standardized data collection protocols would be valuable in further characterizing this disease entity.

Conclusion

Panuveitis and posterior uveitis represent the most common anatomical patterns of syphilitic uveitis. Panuveitis was more prevalent in HIV-positive patients, who also demonstrated a higher burden of intraocular inflammatory signs, including anterior segment inflammation and optic nerve involvement. However, the presence of HIV co-infection did not impact final BCVA or the rate of ocular complication development. Misdiagnosis of syphilitic uveitis remains an important problem because of its wide range of clinical manifestations. Therefore, clinical suspicion and syphilis serology testing are essential for timely diagnosis of the disease. Systemic antibiotic therapy is effective for the treatment of ocular syphilis. However, the use of systemic corticosteroids had no benefit in terms of visual prognosis in our cohort. With proper diagnosis and treatment, syphilitic uveitis is a readily treatable condition with potential for visual recovery, irrespective of HIV serostatus.

Ethics

Ethics Committee Approval: Ankara Training and Research Hospital Ethics Committee approval was obtained prior to study initiation (decision no: 95/2024, approval date: 17.04.2024, protocol number: E-24-95).

Informed Consent: Given the retrospective nature of the study, individual informed consent was not obtained.

Declarations

Authorship Contributions

Surgical and Medical Practices: K.Ö.Y., M.O., M.İ.T., H.E-Ö., S.Ö., N.Z.K., B.T., P.Ç.Ö., Concept: K.Ö.Y., M.O., M.İ.T., Design: K.Ö.Y., M.O., M.İ.T., Data Collection or Processing: K.Ö.Y., M.O., M.İ.T., H.E-Ö., S.Ö., N.Z.K., B.T., P.Ç.Ö., Analysis or Interpretation: K.Ö.Y., M.O., M.İ.T., H.E-Ö., S.Ö., N.Z.K., B.T., P.Ç.Ö., Literature Search: K.Ö.Y., M.O., Writing: K.Ö.Y.

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Original Article

Evaluation of Changes in the Iridocorneal Angle and Anterior Segment Parameters Following Selective Laser Trabeculoplasty in Pseudoexfoliation Glaucoma

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Abstract

Objectives: To investigate the effects of selective laser trabeculoplasty (SLT) on the iridocorneal angle, anterior chamber, and iris in patients with pseudoexfoliation glaucoma (PEXG) and to evaluate the relationship between these structural changes and intraocular pressure (IOP) reduction.

Materials and Methods: Thirty-two eyes of 32 PEXG patients were included in the study. Anterior segment optical coherence tomography (AS-OCT) images were obtained using the MS-39 combined Placido disk/AS-OCT system (Phoenix version 4.1.1.5) before SLT and at 1 week and 1 month after SLT. Anterior chamber angle (ACA), angle opening distance at 250 μm, 500 μm, and 750 μm (AOD250, AOD500, and AOD750), and trabecular-iris space area at 250 μm, 500 μm, and 750 μm (TISA250, TISA500, and TISA750) were measured from these images. In addition, iris thickness was assessed at 1000 μm, 2000 μm, and 3000 μm from the pupillary margin.

Results: The mean IOP decreased significantly from 23.47±3.56 mmHg at baseline to 17.81±2.62 mmHg at 1 week and 16.12±2.57 mmHg at 1 month after SLT ($p<0.001$). At both 1 week and 1 month after SLT, temporal and nasal ACA values were significantly greater compared to baseline (all $p<0.05$). At 1 month, significant increases were observed in all temporal AOD and TISA values, as well as in the nasal AOD, TISA500, and TISA750 values (all $p<0.05$). No significant change in iris thickness was observed ($p>0.05$). Changes in IOP showed no significant correlation with baseline visual field parameters, baseline peripapillary retinal nerve fiber layer thickness, ACA, AOD, or TISA values (all $p>0.05$).

Conclusion: In patients with PEXG, SLT effectively reduces IOP and leads to widening of iridocorneal angle parameters. However, the absence of a correlation between changes in angle parameters and IOP reduction strengthens the notion that the primary effect of SLT is related to cellular and biochemical mechanisms rather than a purely mechanical widening of the angle.

Keywords: Intraocular pressure, iridocorneal angle, anterior segment optical coherence tomography, pseudoexfoliation glaucoma, selective laser trabeculoplasty

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Introduction

Pseudoexfoliation glaucoma (PEXG), which develops due to the accumulation of pseudoexfoliation material at the iridocorneal angle, is the most common form of secondary open-angle glaucoma.[1,2] PEXG is characterized by more irregular diurnal intraocular pressure (IOP) fluctuations and more rapid long-term disease progression compared to primary open-angle glaucoma (POAG).[3,4] As in most forms of glaucoma, the main goal in the treatment of PEXG is the reduction of IOP, which is the only modifiable risk factor.[5] Therefore, it is essential to achieve and maintain target IOP levels through close follow-up and appropriate treatment in these patients. Accordingly, medical therapy and laser procedures are among the first-line treatment options for IOP reduction.

In recent years, selective laser trabeculoplasty (SLT) has become an important option in the treatment of POAG and secondary open-angle glaucomas.[6,7,8] SLT lowers IOP by targeting the trabecular meshwork in the iridocorneal angle, thereby increasing trabecular aqueous humour outflow.[4,6,7] In this procedure, a Q-switched, frequency-doubled 532-nm neodymium-doped yttrium aluminium garnet (Nd:YAG) laser selectively targets melanin-containing pigmented cells in the trabecular meshwork, thereby minimizing collateral tissue damage.[4,8] The selective photothermolysis mechanism of SLT avoids thermal damage and triggers biochemical and cellular responses such as cytokine release, macrophage activation, and extracellular matrix remodeling, resulting in enhanced trabecular meshwork permeability and consequently reducing IOP.[9] Previous studies have shown that SLT effectively lowers IOP, reduces the need for multiple topical antiglaucoma medications, and reduces the need for surgical intervention in patients with PEXG.[4,7,10]

Anterior segment optical coherence tomography (AS-OCT) is a reliable and reproducible imaging method that enables detailed visualization of anterior segment anatomy and related pathologies.[11,12] AS-OCT offers significant advantages in the evaluation of the iridocorneal angle in glaucoma, as it is a non-contact, highly reproducible, operator-independent method that provides objective and quantitative measurements.[11,13] Previous studies have reported significant changes in angle parameters on AS-OCT after laser iridoplasty,[14,15] Nd:YAG laser iridotomy,[16,17] and Nd:YAG capsulotomy.[18,19] Furthermore, only a limited number of studies have investigated the changes in anterior chamber and iris structures following SLT in glaucoma patients.[20] However, to the best of our knowledge, there are no studies specifically evaluating the effects of SLT on iridocorneal angle and anterior segment findings in patients with PEXG.

The aim of this study was to examine the changes in iridocorneal angle parameters and the anterior chamber and iris structures following SLT in patients with PEXG, and to evaluate the possible relationship between these changes and post-procedural IOP reduction.

Materials and Methods

This single-center, prospective, observational study was conducted at the glaucoma clinic of a tertiary referral hospital and included 32 eyes of 32 patients diagnosed with PEXG. The study was carried out in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by the University of Health Sciences Türkiye, Ankara Etlik City Hospital Ethics Committee (decision no: AEŞH-EK-2025-224, date: 3/9/2025). Written informed consent was obtained from all participants prior to enrollment.

Patient Selection

Thirty-two eyes of 32 patients diagnosed with early-to-intermediate stage PEXG who were scheduled for primary SLT or were already receiving prostaglandin analog (PGA) therapy and planned to undergo adjunctive SLT were enrolled. The Hodapp-Parrish-Anderson criteria were used for staging early and intermediate PEXG.[21] Accordingly, the early stage was defined as a mean deviation (MD) value better than -6 dB, fewer than 25% of points on the pattern deviation plot depressed below the 5% level, fewer than 15% of points depressed below the 1% level, and no point within the central 5° with a sensitivity less than 15 dB. The intermediate stage was defined as MD between -6 dB and -12 dB, fewer than 50% of points on the pattern deviation plot depressed below the 5% level, fewer than 25% of points depressed below the 1% level, no point within the central 5° with a sensitivity below 0 dB, and only one hemifield containing a point with sensitivity below 15 dB.[21] In patients with bilateral SLT indication, the right eye was selected for inclusion. Exclusion criteria were defined as follows:

- Age ≤40 years,
- Iris anomalies that can cause iris deformity (iris coloboma, synechiae, iris atrophy, sphincter rupture, or history of ocular trauma),
- History of prior laser treatment or intraocular surgery involving iridocorneal angle, iris, or retina,
- History of uveitis, chronic intraocular inflammation, or ocular infection,
- Prior use of antiglaucoma drugs other than PGAs,
- Iridocorneal angle grade ≤2 on gonioscopy according to the Shaffer classification, angle neovascularization, or peripheral anterior synechiae,
- Lens opacity greater than grade 2 according to the Age-Related Eye Disease Study classification.[22]

Ophthalmological Assessment

All participants underwent a comprehensive ophthalmic examination, including best-corrected visual acuity (BCVA) measurement using a Snellen chart and IOP measurement with Goldmann applanation tonometry. Iridocorneal angle assessment was performed using the Latina SLT goniolens (Ocular Instruments, Bellevue, WA, USA). Additionally, slit-lamp biomicroscopic anterior segment examination and dilated fundus examination were performed. Visual field assessment was performed using the Humphrey Field

Analyzer 3 (Carl Zeiss Meditec, Dublin, CA, USA) with the 24-2 Swedish Interactive Threshold Algorithm Standard strategy, and MD and visual field index (VFI) values were recorded. Peripapillary retinal nerve fiber layer (ppRNFL) thickness was measured using the CIRRUS™ HD-OCT system (version 8.0.0.518; Carl Zeiss Meditec, Dublin, CA, USA).

Selective Laser Trabeculoplasty

SLT was performed by the same experienced clinician using a Q-switched Nd:YAG laser (Ellex Solo™ SLT Laser, Ellex Inc., Adelaide, Australia). The laser system operated at a wavelength of 532 nm with a pulse duration of 3 ns and spot diameter of 400 µm. Following topical anesthesia with 0.5% proparacaine hydrochloride (Alcaine™, S.A. Alcon-Couvreur N.V., Puurs, Belgium), the Latina SLT goniolens (Ocular Instruments, Bellevue, WA, USA) was used to visualize the trabecular meshwork. The entire trabecular meshwork (360°) was treated, targeting the pigmented trabecular meshwork. The initial energy was set at 0.9 mJ/pulse and titrated upward in 0.1-mJ increments until microcavitation bubbles were observed, indicating the appropriate energy level. A total of 100 non-overlapping laser spots were applied.

All participants were prescribed topical loteprednol etabonate (Lotemax®, Bausch & Lomb Inc., Tampa, FL, USA) 4 times daily for 5 days after SLT. Patients already receiving PGA therapy were instructed to continue their existing antiglaucoma treatment following the procedure.

Anterior Segment Optical Coherence Tomography Evaluation

In all participants, AS-OCT measurements were obtained before SLT, 1 week after SLT, and 1 month after SLT. Images were acquired using the MS-39 AS-OCT device (Phoenix software version 4.1.1.5; CSO, Florence, Italy), which integrates Placido disk topography with a spectral-domain OCT system. The MS-39 system provides a scan length of 16 mm and an axial resolution of 3.6 µm with an infrared superluminescent diode light source at a wavelength of 850 nm.

Each AS-OCT scan comprises 25 B-scans, each consisting of 1024 A-scans, acquired in approximately 1 second. All measurements were obtained by the same experienced technician between 10:00 AM and 12:00 PM under the same lighting conditions.

For AS-OCT analysis, the meridional cross-section along the 0°-180° axis was selected. The scleral spur, posterior corneal surface, and line tangent to the anterior iris surface were automatically identified by the device software. The angle opening distance (AOD) was measured as the perpendicular distance from the scleral spur to the anterior iris surface at 250 µm, 500 µm, and 750 µm, and recorded as AOD250, AOD500, and AOD750, respectively. The trabecular-iris space area (TISA) was automatically calculated by the device software as the area bounded by the AOD line, the posterior corneal surface, and the anterior iris surface, and was reported as TISA250, TISA500, and TISA750 (Figure 1). The anterior chamber angle (ACA) was calculated as the angle between the line passing through the scleral spur and the line along the anterior iris surface.

Iris thickness was measured at 1000 µm, 2000 µm, and 3000 µm from the pupillary margin (Figure 1). All measurements were analyzed separately for the temporal and nasal quadrants. Additionally, central corneal thickness (CCT) and anterior chamber depth (ACD) were obtained from MS-39 AS-OCT topography scans.

Statistical Analysis

Statistical analysis was performed using SPSS Statistics v22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation, and categorical variables as frequency and percentage. The normality of quantitative data distribution was assessed using the Kolmogorov-Smirnov test. For normally distributed data, one-way repeated measures analysis of variance (ANOVA) followed by the Bonferroni post-hoc test was used to compare the three repeated measurements within the same subjects. Non-normally distributed data were analyzed using the Friedman test followed by post-hoc Wilcoxon signed-rank test with Bonferroni correction. Correlations between variables were assessed using the Pearson correlation coefficient. A p value of <0.05 was considered statistically significant.

The required sample size was calculated assuming an effect size of 0.25 with 85% power and a 95% confidence level, yielding a minimum of 31 subjects (G*Power version 3.1.9.4, University of Düsseldorf, Germany).

Results

The mean age of the patients was 64.4±8.53 (range: 48-75) years. Nineteen participants (59.3%) were male and 13 (40.6%) were female. Eight patients had intermediate PEXG and 24 patients had early PEXG. The mean BCVA was 0.094±0.10 (range: 0.0-0.30) logarithm of the minimum angle of resolution. Ten patients (31.2%) were treatment-naïve, while 22 patients (68.7%) were using PGA therapy. No changes were made to the medication regimen of PGA-treated patients during the 1-month post-SLT period. The

patients' baseline mean visual field MD was -3.84±3.28 dB and mean VFI was 91.72±9.05. The mean baseline ppRNFL thickness was 85.77±12.54 µm.

Mean baseline IOP was 23.47±3.56 mmHg and decreased significantly to 17.81±2.62 mmHg at 1 week and 16.12±2.57 mmHg at 1 month post-SLT (all p<0.001). No significant change was observed in CCT or ACD (p>0.05) (Table 1).

Changes in angle parameters and iris thickness following SLT are presented in Table 2. Temporal and nasal ACA values increased significantly at both week 1 and month 1 compared with baseline (temporal: p=0.013 and p<0.001; nasal: p=0.022 and p<0.001, respectively). In the temporal quadrant, AOD250, AOD500, AOD750, TISA250, TISA500, and TISA750 values increased significantly at month 1 compared to baseline (p=0.007, p=0.006, p=0.038, p=0.005, p=0.002, and p=0.005, respectively). At week 1, only TISA500 was significantly higher than baseline (p=0.020). No significant change in temporal iris thickness was observed following SLT (p>0.05). In the nasal quadrant, AOD250, AOD500, AOD750, TISA500, and TISA750 values increased significantly at month 1 compared with baseline (p=0.007, p=0.009, p=0.029, p=0.003, and p=0.033, respectively). No significant changes in these parameters were observed at week 1 (all p>0.05). Nasal iris thickness also showed no significant change following the procedure (all p>0.05) (Table 3).

There was no significant correlation between IOP change at 1 month post-SLT and baseline MD, VFI, mean ppRNFL thickness, or changes in ACA, AOD, and TISA values at month 1 (all p>0.05) (Table 2).

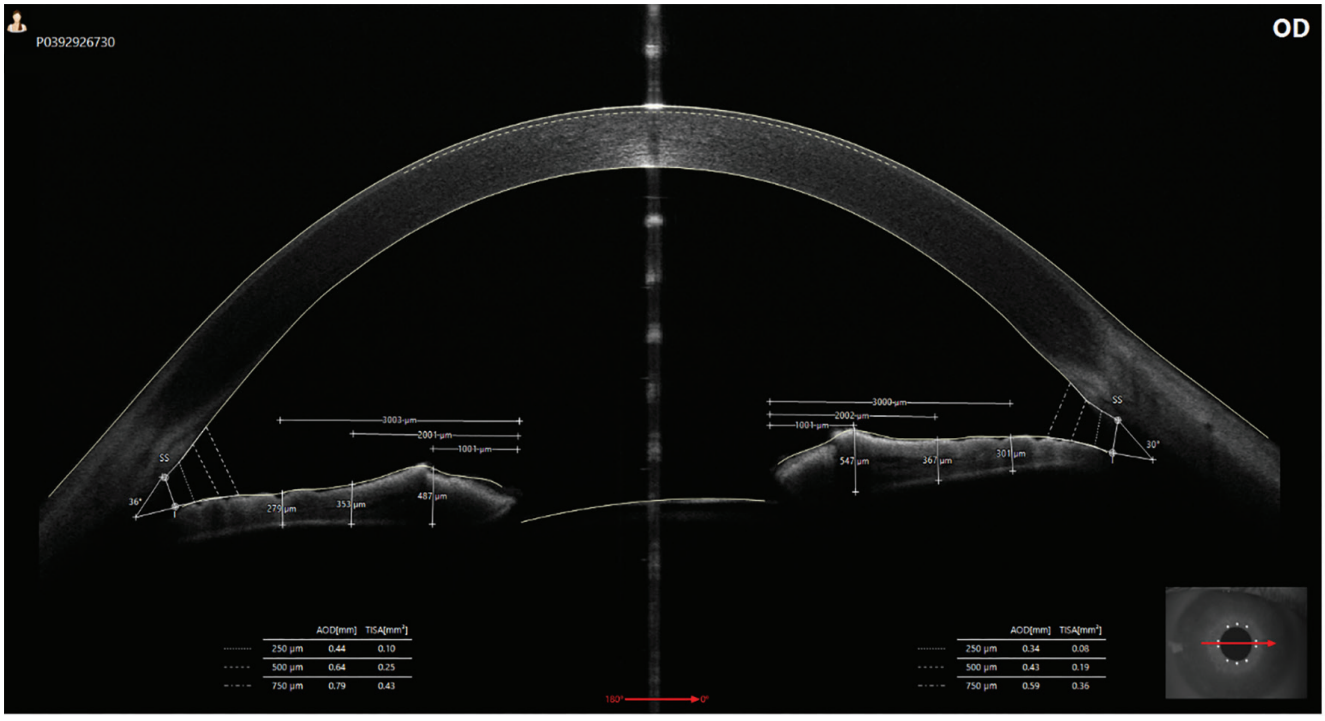

Figure 1. Measurement of iridocorneal angle parameters and iris thickness using anterior segment optical coherence tomography

Table 1. Intraocular pressure, central corneal thickness, and anterior chamber depth before and after selective laser trabeculoplasty

Variables	Pre-SLT	1 week post-SLT	1 month post-SLT	p^{α}	Paired comparisons		
					p^{β}	p^{γ}	p^{δ}
IOP (mmHg)	23.47±3.56	17.81±2.62	16.12±2.57	**<0.001**	**<0.001**	**<0.001**	**<0.001**
CCT (µm)	543.39±36.10	547.68±35.38	543.65±36.51	0.162	0.170	0.999	0.549
ACD (µm)	2995.78±511.76	2985.84±527.93	3012.13±511.07	0.240	0.999	0.719	0.338

p^{α}: Comparison of all three measurements, p^{β}: Pre-SLT vs. 1 week post-SLT, p^{γ}: Pre-SLT vs. 1 month post-SLT, p^{δ}: 1 week post-SLT vs. 1 month post-SLT, IOP: Intraocular pressure, CCT: Central corneal thickness, ACD: Anterior chamber depth, SLT: Selective laser trabeculoplasty

Table 2. Correlation of IOP change from baseline with changes in ppRNFL, MD, VFI, and anterior chamber angle parameters at 1 month after selective laser trabeculoplasty		
	ΔIOP (mmHg)	
	Correlation coefficient (r)	**p value**
ppRNFL (μm)	0.255	0.166
MD (dB)	0.065	0.732
VFI (%)	0.037	0.847
ΔTemporal ACA (°)	0.019	0.919
ΔNasal ACA (°)	-0.032	0.864
ΔTemporal AOD250 (mm)	0.122	0.508
ΔTemporal AOD500 (mm)	0.264	0.144
ΔTemporal AOD750 (mm)	0.151	0.409
ΔNasal AOD250 (mm)	0.225	0.215
ΔNasal AOD500 (mm)	0.269	0.136
ΔNasal AOD750 (mm)	0.152	0.406
ΔTemporal TISA250 (mm)	0.333	0.063
ΔTemporal TISA500 (mm)	0.328	0.067
ΔTemporal TISA750 (mm)	0.189	0.219
ΔNasal TISA250 (mm)	0.042	0.821
ΔNasal TISA500 (mm)	0.026	0.889
ΔNasal TISA750 (mm)	0.138	0.451

ppRNFL: Peripapillary retinal nerve fiber layer thickness, MD: Mean deviation, VFI: Visual field index, IOP: Intraocular pressure, ACA: Anterior chamber angle, AOD: Angle opening distance, TISA: Trabecular-iris space area

Table 3. Iridocorneal angle parameters and iris thickness before and after selective laser trabeculoplasty							
Variables	**Pre-SLT**	**1 week post-SLT**	**1 month post-SLT**	**p^{α}**	**Paired comparisons**		
					p^{β}	**p^{γ}**	**p^{δ}**
Temporal angle							
ACA (°)	34.03±4.55	35.50±5.19	38.03±5.48	**<0.001**	0.013	**<0.001**	**<0.001**
AOD250 (mm)	0.443±0.19	0.462±0.18	0.497±0.17	**0.001**	0.340	**0.007**	**0.037**
AOD500 (mm)	0.580±0.23	0.632±0.24	0.646±0.24	**0.004**	0.071	**0.006**	0.935
AOD750 (mm)	0.775±0.28	0.801±0.30	0.839±0.34	**0.029**	0.785	**0.038**	0.335
TISA250 (mm^2)	0.102±0.05	0.108±0.05	0.117±0.05	**0.003**	0.952	**0.005**	0.101
TISA500 (mm^2)	0.241±0.10	0.262±0.11	0.276±0.11	**<0.001**	**0.020**	**0.002**	0.388
TISA750 (mm^2)	0.430±0.18	0.461±0.18	0.484±0.19	**0.002**	0.058	**0.005**	0.372
IT1000 (μm)	421.84±87.65	421.69±87.70	409.34±99.39	0.247	0.999	0.551	0.569
IT2000 (μm)	384.56±84.03	380.56±88.84	373.88±82.86	0.302	0.999	0.232	0.999
IT3000 (μm)	384.37±55.72	383.19±79.48	383.84±71.16	0.979	0.999	0.999	0.999
Nasal angle							
ACA (°)	33.34±5.18	35.66±4.74	36.81±4.79	**<0.001**	**0.022**	**0.001**	0.174
AOD250 (mm)	0.435±0.17	0.453±0.18	0.476±0.20	**0.005**	0.428	**0.007**	0.192
AOD500 (mm)	0.571±0.20	0.588±0.20	0.625±0.23	**0.002**	0.500	**0.009**	0.091
AOD750 (mm)	0.735±0.24	0.769±0.26	0.805±0.31	**0.010**	0.215	**0.029**	0.187
TISA250 (mm^2)	0.100±0.04	0.102±0.05	0.108±0.06	0.244	0.999	0.191	0.923

Table 3. Continued

Variables	Pre-SLT	1 week post-SLT	1 month post-SLT	p^{α}	Paired comparisons		
					p^{β}	p^{γ}	p^{δ}
TISA500 (mm^2)	0.230±0.09	0.243±0.08	0.256±0.10	**0.003**	0.195	**0.003**	0.288
TISA750 (mm^2)	0.422±0.17	0.428±0.15	0.455±0.18	**0.012**	0.999	**0.033**	0.127
IT1000 (μm)	467.28±85.31	462.09±84.84	456.03±81.59	0.136	0.999	0.189	0.577
IT2000 (μm)	411.69±68.36	407.19±69.15	400.56±71.39	0.349	0.999	0.713	0.999
IT3000 (μm)	398.75±66.62	391.03±58.49	379.12±64.49	0.055	0.789	0.132	0.269

p^{α}: Comparison of all three measurements, p^{β}: Pre-SLT vs. 1 week post-SLT, p^{γ}: Pre-SLT vs. 1 month post-SLT, p^{δ}: 1 week post-SLT vs. 1 month post-SLT, ACA: Anterior chamber angle, AOD: Angle opening distance, TISA: Trabecular-iris space area, IT: Iris thickness, SLT: Selective laser trabeculoplasty

Discussion

Our study demonstrated a significant reduction in IOP at both 1 week and 1 month following SLT in patients with PEXG. Previous studies have reported that the trabecular meshwork exhibits more intense pigmentation in PEXG compared to POAG.[3,23] The elevated IOP in PEXG is believed to result from obstruction of the trabecular meshwork by pigment and pseudoexfoliation material.[4,5] It has been suggested that this increased pigmentation may be one of the factors contributing to a better early response to SLT in PEXG.[5,7,10] However, although short-term studies have reported a more pronounced early IOP reduction in PEXG, long-term follow-up studies have found no significant difference in sustained IOP reduction between PEXG and POAG.[24,25]

AS-OCT enables objective, quantitative, and reproducible assessment of the iridocorneal angle, ACD, and iris morphology.[11,13] Widening of iridocorneal angle parameters has been reported following iris-targeted laser procedures such as iridotomy and iridoplasty, as well as after Nd:YAG capsulotomy applied to the posterior lens capsule.[15,16,17,18,19,26,27] In the present study, AS-OCT revealed significant increases in ACA, AOD, and TISA values at 1 month post-SLT in patients with PEXG. Özer et al.[20] evaluated ACA parameters in 50 POAG and ocular hypertension patients for 1 month and observed a significant increase in both nasal and temporal ACA, AOD, and TISA values, with no significant change in CCT or ACD. Our findings are consistent with those reported by Özer et al.[20] The absence of significant changes in CCT and ACD in our study may be attributable to the application of laser energy exclusively to the trabecular meshwork.[20] Indeed, no change in ACD has been reported even in primary angle-closure glaucoma following laser iridoplasty or peripheral iridotomy.[14,17]

The demonstration of Schlemm's canal expansion following SLT in previous studies may explain the observed increase in angle parameters.[28,29] However, iridocorneal angle parameters were not concurrently evaluated in those studies. Although angle parameters were quantitatively measured in our study, Schlemm's canal could not be measured due to image quality limitations. Future studies simultaneously evaluating both Schlemm's canal and iridocorneal angle parameters following SLT may provide a better understanding of the underlying anatomical changes. However, the IOP-lowering effect of SLT cannot be explained primarily by anatomical changes. SLT is thought to induce cytokine release, matrix metalloproteinase activation, and macrophage recruitment through the selective absorption of low-energy laser pulses by pigmented trabecular cells.[3,9,20,30] These processes facilitate trabecular debris clearance, extracellular matrix remodeling, and enhanced aqueous humor outflow. The presence of pseudoexfoliation material may also contribute to this process. Evidence suggests that the cellular and immune mechanisms driving changes in the trabecular meshwork are central to this effect.[9] Alvarado et al.[9] demonstrated that post-SLT cytokine and chemokine expression increased Schlemm's canal endothelial permeability. A subsequent study showed that SLT weakened intercellular junctions between Schlemm's canal endothelial cells, similar to PGAs.[31] Therefore, when evaluating SLT efficacy, cellular and cytochemical mechanisms should be considered before anatomical changes.[9,20]

Regarding iris morphology, a study using ultrasound biomicroscopy in POAG patients reported a transient increase in iris thickness at day 3 and week 1 following SLT, with no significant difference at 1 month.[32] This transient thickening has been attributed to post-SLT cytokine release. In our study, no significant change in iris thickness was observed. This finding is likely attributable to the inherent selectivity of SLT, which targets pigmented cells within the trabecular meshwork without causing thermal damage to the iris, although postoperative topical corticosteroid use may also have contributed. Similarly, Ayala et al.[33] reported no significant increase in anterior chamber flare following SLT. No significant change in iris

thickness has been reported even following laser iridoplasty and peripheral iridotomy, procedures in which the iris is directly targeted.[14,34] However, it has been hypothesized that post-SLT corticosteroid use may suppress the beneficial inflammatory response (i.e., cytokine release, macrophage activation, and matrix metalloproteinase activity) integral to SLT's mechanism of action, potentially reducing laser efficacy.[9,33] Nevertheless, randomized controlled trials have reported that post-SLT corticosteroid use does not adversely affect IOP reduction outcomes.[35,36]

In the present study, no significant association was found between post-SLT IOP reduction and baseline MD, VFI, or ppRNFL thickness, which is consistent with previous reports.[10,37] Lee et al.[10] reported no significant difference in baseline visual field parameters between PEXG eyes with successful and unsuccessful SLT outcomes. Gillmann et al.[37] demonstrated that baseline ppRNFL thickness did not predict the magnitude of IOP reduction following SLT. Furthermore, no significant correlations were found between IOP change and changes in ACA, AOD, or TISA values.

Study Limitations

Although our study is the first study to evaluate anterior segment parameters following SLT in patients with PEXG, it has several limitations. These include the relatively small sample size, the lack of a POAG or healthy control group, and the follow-up period being limited to only 1 month. An additional limitation is that measurements were restricted to the temporal and nasal quadrants, as eyelid interference in vertical quadrant sections made identification of the scleral spur difficult and precluded calculation of AOD and TISA, thereby hindering the evaluation of changes in the superior and inferior quadrants of the iridocorneal angle. Consequently, our results may not have fully captured potentially greater structural effects arising from gravity-dependent pigment accumulation in the inferior quadrant. Similarly, the study by Özer et al.,[20] which evaluated iridocorneal angle parameters using AS-OCT in POAG patients who underwent SLT, was also limited to horizontal cross-sections. Another limitation is that the study group comprised both treatment-naive patients and those already receiving PGA therapy. The pre-existing modification of trabecular outflow by PGAs may have masked the additional effect of SLT.[31] Finally, concurrent assessment of Schlemm's canal dimensions alongside the other parameters would have provided valuable additional information. However, as previously noted, the quality of the acquired images did not technically allow evaluation of Schlemm's canal.

Conclusion

SLT is an effective IOP-lowering treatment option for patients with PEXG. Similar to findings reported in POAG, significant widening of iridocorneal angle parameters occurs in patients with PEXG following SLT.[20] However, the absence of a correlation between these anatomical changes and IOP reduction supports the view that the primary mechanism of SLT involves cellular and biochemical alterations rather than mechanical angle widening. The mechanical widening of the iridocorneal region following SLT may represent a secondary consequence of the cellular and biochemical changes induced by the procedure. A more comprehensive understanding of these mechanisms requires prospective studies with larger sample sizes, extended follow-up periods, and concurrent assessment of both the iridocorneal angle and Schlemm's canal.

Ethics

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Türkiye, Ankara Etlik City Hospital Ethics Committee (decision no: AEŞH-EK-2025-224, date: 3/9/2025).

Informed Consent: Written informed consent was obtained from all participants prior to enrollment.

Declarations

Authorship Contributions

Surgical and Medical Practices: B.D.Y.E., Concept: B.D.Y.E., S.B., Design: B.D.Y.E., S.B., Data Collection or Processing: B.D.Y.E., S.B., Analysis or Interpretation: S.B., Literature Search: B.D.Y.E., S.B., Writing: S.B.

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Review

Large Language Models in Ophthalmology: A Bibliographic Analysis

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Abstract

This study evaluated the distribution of research on the use of large language models (LLMs) in ophthalmology through a bibliographic analysis of articles retrieved from PubMed through November 2024. Studies were categorized into four main areas of LLM application: clinical decision-making (further divided according to subspecialties), education, patient interactions, and miscellaneous applications. Descriptive statistics were used to analyze the distribution of studies by ophthalmic subspecialty, geographical region, journal quality, and author characteristics, including gender and scholarly impact (h-index and i10-index). The findings revealed that clinical decision-making was the most common application (43.7%), with the majority of studies in this subgroup focusing on the retina (39.5%). Geographically, most of the research originated from North America (48.3%), followed by Asia (29.9%) and Europe (20.7%). Most studies were published in high-impact journals (Q1 journals: 74.7%), particularly for those related to clinical decision-making in retina (80.0%), glaucoma (100%), and multiple subspecialties (87.5%). Gender disparities were evident across all author roles, with female authors accounting for only 29.9% of first authors, 25.3% of last authors, and 26.4% of corresponding authors. The results suggest a need for greater diversity in terms of gender and geographic representation in LLM research in ophthalmology to promote inclusive progress in the field.

Keywords: Large language models, ophthalmology, bibliographical analysis

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Introduction

In recent years, artificial intelligence (AI), particularly in the form of large language models (LLMs), has revolutionized many aspects of science and become an integral part of research.[1] Models such as ChatGPT, BERT, and LLaMA utilize millions of parameters and draw from diverse data sources, including books, articles, and other text-based materials, to generate human-like text responses.[2] These LLMs differ architecturally: ChatGPT uses autoregressive transformers focused on generative language tasks; BERT employs bidirectional transformers for contextual understanding; and LLaMA has a standard decoder-only transformer architecture with minor adaptations, avoiding mixture-of-experts models to maximize training stability.[3,4,5] Despite these differences, all are commonly used for generating responses.

While AI has been utilized in medicine for decades, LLMs are now transforming diagnostics through image analysis and enhancing clinical decision-making by efficiently processing vast amounts of data, clinical information, and patient records, paving the way for precision medicine.[6] Over the past few years, LLMs have become increasingly adopted across various medical specialties, including radiology, internal medicine, pediatrics, cardiovascular medicine, and many others.[7,8,9] Research related to LLMs has increased significantly since 2023, reflecting a growing interest in their capabilities and applications. Ophthalmology, in particular, has been at the forefront of AI-related research, with growing interest in leveraging LLMs to advance patient care.[10]

However, LLM-related research also faces several limitations and challenges. First, LLMs are predominantly trained on English-language data, which may affect the reliability of their responses when applied to non-English

languages. As a result, research is often concentrated in regions where English is widely spoken. Regional disparities are evident across all AI studies, with the majority of publications and grants dominated by the US and China, which together have been shown to account for approximately 50% of all publications from 2014 to 2023.[11] Additionally, the AI Index Report (2024) showed that novel AI models developed in 2023 primarily originated in the US, followed by China and Europe, further highlighting the geographical gap in AI research.[12] This unequal distribution in research output is accompanied by other disparities within the field, including gender representation. The latest Global Gender Gap Report (2024) by the World Economic Forum revealed that only 22% of professionals in AI are women, a gender gap which is reflected in AI-related research.[13]

Given these known disparities in AI-related research, this study aimed to provide a closer look at LLM-related studies in ophthalmology. We performed a bibliographic analysis to evaluate the distribution of research on LLMs in ophthalmology, focusing on gender, academic impact, and the geographical origin of the studies.

Methods

A comprehensive literature search was conducted on PubMed to identify studies involving the use of LLMs in ophthalmology published up until November 2024. The search terms used were *large language models* AND *ophthalmology* OR *retina* OR *glaucoma* OR *cornea* OR *uvea* OR *pediatric ophthalmology* OR *neuro-ophthalmology*. The search results yielded a total of 194 studies. Only original investigations were included in the final analysis. Studies not related to LLMs or ophthalmology, review articles, meta-analyses, and commentaries were excluded from the final list.

Included studies were categorized into four groups based on their primary focus and application:

• Clinical Decision-Making Applications: Studies that investigated the use of LLMs in clinical decision-making and assessed LLM responses in diagnosing, managing, or providing clinical support for ophthalmic conditions. This category was further divided into ophthalmic subspecialties including retina, glaucoma, cornea/anterior segment, uveitis, neuro-ophthalmology, and pediatrics. Studies that encompassed more than one ophthalmic subspecialty or general ophthalmology were categorized as "multiple subspecialties."

• Educational Applications: Studies that explored the use of LLMs in educational contexts, including their application in answering board-style questions and developing educational materials for both patients and clinicians.

• Patient Interaction Applications: Studies that focused on how LLMs are used to improve patient communication and respond to frequently asked questions about ocular health, such as in the format of a chatbot.

• Miscellaneous Applications: Studies that explored other applications of LLMs in ophthalmology that do not neatly fit into other categories, particularly those that are highly technical in nature.

The initial categorization of studies was conducted by the first author and reviewed by the senior author. Discrepancies were resolved by discussion and consensus.

Descriptive statistics were used to analyze the distribution of studies by application type, ophthalmic subspecialty, geographical region, journal quality, and author characteristics. The geographic regions were determined based on the United Nations World Population Prospects, which divides the world into six continental regions: Africa, Asia, Europe, Latin America and the Caribbean, North America, and Oceania.[14] Geographical region was assigned according to the first author's affiliated institution. Journal quality was classified into quartiles Q1, Q2, Q3, and Q4 as retrieved from SCImago. Author characteristics included gender and scholarly impact. Gender information was obtained from institutional websites or professional profiles. Scholarly impact was assessed using the h-index and i10-index, both retrieved from Google Scholar. The h-index is a metric that measures the scientific impact of an author's publications, defined as the maximum value of h for which the author has published at least h papers, each of which has been cited no fewer than h times.[15] In contrast, the i10-index is a related metric used by Google Scholar that counts the number of publications with at least 10 citations.[16]

Results

Overall Results

A total of 87 original research studies were included in the final evaluation. In terms of application type, the most common was clinical decision-making (n=38, 43.7%), followed by educational applications (n=22, 25.3%), patient interaction applications (n=18, 20.7%), and miscellaneous applications (n=9, 10.3%) (Table 1). Within the clinical decision-making category, studies related to the retina were most prevalent, accounting for 15 studies (39.5%), while pediatrics had the least, with only 1 study (2.6%). Notably, research encompassing multiple subspecialties accounted for 21.1% of the studies in this group (n=8). There were

moderate contributions from glaucoma, cornea/anterior segment, uveitis, and neuro-ophthalmology. The number of studies in each category is presented in Table 2.

The geographic distribution of studies based on first author's affiliated institution revealed that the majority of research originated from North America (n=42, 48.3%), followed by Asia (n=26, 29.9%) and Europe (n=18, 20.7%). Oceania was represented by a single study (1.1%) from Australia, while no research related to LLMs in ophthalmology was reported from Latin America and the Caribbean or Africa. The distribution of studies by region is presented in Table 3 and Figure 1.

The majority of studies were published in high-impact journals, with 65 studies (74.7%) in Q1 journals, 10 studies (11.5%) in Q2 journals, and 9 studies (10.3%) in Q3 journals. In addition, 4 studies (4.6%) were not assigned a quartile, of which 3 were pre-prints in clinical decision-making. Most studies were published in 2024 (n=71, 81.6%), followed by 15 studies (17.2%) in 2023 and 1 study (1.1%) in 2022.

Gender disparity was evident for all author roles, with women accounting for only 29.9% of first authors, 25.3% of last authors, and 26.4% of corresponding authors (Figure 2). As expected, last and corresponding authors generally had greater scholastic impact than first authors. The average h-indices for last and corresponding authors were 39.7±37.7 and 28.7±33.7, respectively, compared to 8.9±6.2 for first authors ($p<0.001$). Similarly, the average i10-indices for last and corresponding authors were 147.1±254.2 and 94.4±222.2, compared to 12.0±14.9 for first authors ($p=0.005$) (Table 4).

We also evaluated the publications according to each application category, and the results of this in-depth analysis are as follows:

Clinical Decision-Making

Studies within this category were published from a diverse range of countries across several continents, although the majority of them still originated from the USA (n=17, 44.7%). Most studies were published within the past year in 2024 (n=32, 84.2%). Gender disparities were evident across all subgroups, most notably in the cornea/anterior segment subspecialty, where there were no women as first, last, or corresponding authors (Table 5).

Most studies were published in high-impact journals, particularly within the retina, glaucoma, and multiple subspecialties subgroups, with 80.0%, 100%, and 87.5% appearing in Q1 journals, respectively. The cornea/anterior segment and uveitis subgroups had a mix of Q1, Q2, and/or Q3 journals. Notably, no studies were published in Q4 journals. A detailed list of the studies in this category is provided in the supplementary material (Supplementary Table 1).[17-54]

Table 1. Distribution of studies according to application types (n=87)

Category	Number of studies	Percentage
Clinical decision-making	38	43.7%
Educational applications	22	25.3%
Patient interaction applications	18	20.7%
Miscellaneous applications	9	10.3%

Table 2. Distribution of studies within the clinical decision-making category (n=38)

Clinical decision-making	Number of studies	Percentage
Retina	15	39.5%
Glaucoma	6	15.8%
Cornea/anterior segment	3	7.9%
Uveitis	3	7.9%
Neuro-ophthalmology	2	5.3%
Pediatrics	1	2.6%
Multiple subspecialties	8	21.1%

Table 3. Geographical distribution of studies according to first author's affiliated institution (n=87)

Region/ continent	Country	Number of studies	Percentage
North America	United States	38	43.7%
	Canada	4	4.6%
Europe	United Kingdom	9	10.3%
	Germany	3	3.5%
	Switzerland	2	2.3%
	Italy	2	2.3%
	Romania	1	1.1%
	Finland	1	1.1%
Asia	China	12	13.8%
	Singapore	4	4.6%
	Türkiye	4	4.6%
	India	3	3.5%
	Japan	1	1.1%
	Israel	1	1.1%
	Jordan	1	1.1%
Oceania	Australia	1	1.1%
Africa		0	0%
Latin America and the Caribbean		0	0%

Educational Applications

Of the 22 studies, North America contributed the largest share (45.5%), with 8 studies from the USA and 2 from Canada. Europe accounted for 31.8% of the studies, with 6 studies from the UK and 1 study from Germany. Asia contributed 5 studies (22.7%), with 2 from China and 1 each from Türkiye, Israel, and Japan. Most of these studies were published in Q1 journals (72.7%), followed by Q3 journals (18.2%) and Q2 journals (9.1%), with the majority published in 2024 (n=18, 81.8%). Gender disparity was also evident in this group, with male dominance in all author roles. Women accounted for 4 first authors (18.2%), 1 last author (4.5%), and 3 corresponding authors (13.6%).

Patient Interaction Applications

Studies in this group were primarily from Asia (44.4%), followed by North America (38.9%), Europe (11.1%), and Oceania (5.6%). The majority of the studies were published in Q1 journals (66.7%), with smaller portions in Q2 and Q3 journals. Female authors were overall more represented in this category, accounting for 33.3% of first authors, 5.6% of last authors, and 44.4% of corresponding authors.

Miscellaneous Applications

Of the 9 studies, North America made the largest contribution, accounting for 66.7% of the studies, with 6 studies originating from the USA. Türkiye, India, and Finland contributed the remaining studies, each providing one. The distribution of author roles was nearly balanced for first and corresponding authors, with 44.4% of first authors being men and 55.6% women, while 55.6% of corresponding authors were men and 44.4% were women. However, last authors were still predominantly male (66.7%).

The distribution of gender and geographical regions for first and last authors across educational applications, patient interaction applications, and miscellaneous applications is detailed in Table 6. A comprehensive list of studies in the other categories and overall journal metrics are provided in the supplementary material (Supplementary Tables 2 and 3).[55-103]

Discussion

LLMs are generative AI systems that perform natural language processing in order to understand human text and speech.[104,105] ChatGPT, BERT, and LLaMA are commonly used LLMs that employ deep learning (DL) techniques to engage in meaningful conversations with users.[104] These applications provide access to vast amounts of knowledge and may also help patients access medical information relevant to their specific conditions, assess the urgency of their symptoms, or be directed to the appropriate subspecialty.[106]

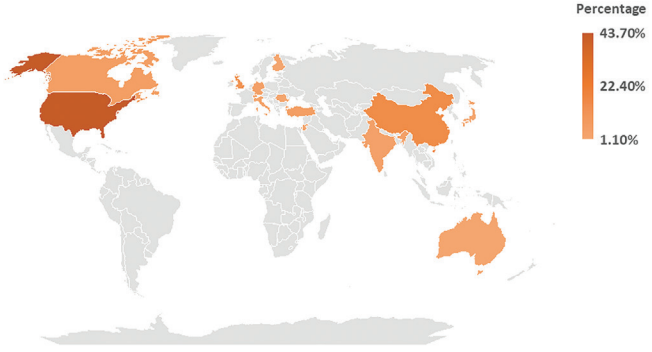

Figure 1. Heat map distribution of global LLM-related studies in ophthalmology
LLM: Large language model

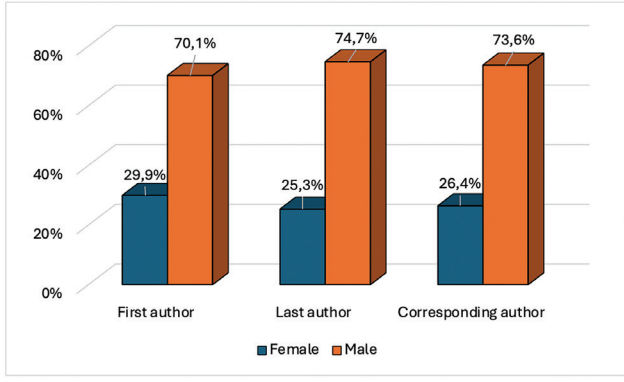

Figure 2. Gender distribution among authorship roles (presented as percentage)

Table 4. Distribution of genders and scholastic impact factors (h-index and i10-index) across first, last, and corresponding author roles

Author role	Female	Male	h-index (Mean ± SD)	i10-index (Mean ± SD)
First author	26 (29.9%)	61 (70.1%)	8.9±6.2	12.0±14.9
Last author	22 (25.3%)	65 (74.7%)	39.7±37.7	147.1±254.2
Corresponding author	23 (26.4%)	64 (73.6%)	28.7±33.7	94.4±222.2

SD: Standard deviation

Table 5. Detailed distribution of gender and geographical region of studies according to the first and last authors' affiliated institutions for clinical decision-making applications

	First author			Last author		
	Gender	**Geographical region**	**Top 3 countries of publication**	**Gender**	**Geographical region**	**Top 3 countries of publication**
Retina[17-31] (n=15)	Female: 4 (26.7%) Male: 11 (73.3%)	Asia: 6 (40.0%) Europe: 5 (33.3%) North America: 4 (26.7%) Africa: 0 (0%) Latin America/Caribbean: 0 (0%) Oceania: 0 (0%)	China: 5 (33.3%) UK: 3 (20.0%) USA: 3 (20.0%)	Female: 3 (20.0%) Male: 12 (80.0%)	Asia: 6 (40.0%) Europe: 5 (33.3%) North America: 4 (26.7%) Africa: 0 (0%) Latin America/Caribbean: 0 (0%) Oceania: 0 (0%)	China: 5 (33.3%) UK: 4 (26.7%) USA: 3 (20.0%)
Glaucoma[32,33,34,35,36,37] (n=6)	Female: 2 (33.3%) Male: 4 (66.7%)	North America: 4 (66.7%) Asia: 1 (16.7%) Europe: 1 (16.7%) Africa: 0 (0%) Latin America/Caribbean: 0 (0%) Oceania: 0 (0%)	USA: 4 (66.7%) China: 1 (16.7%) Italy: 1 (16.7%)	Female: 0 (0%) Male: 6 (100%)	North America: 4 (66.7%) Asia: 1 (16.7%) Europe: 1 (16.7%) Africa: 0 (0%) Latin America/Caribbean: 0 (0%) Oceania: 0 (0%)	USA: 4 (66.7%) China: 1 (16.7%) Italy: 1 (16.7%)
Cornea/anterior segment[38,39,40] (n=3)	Female: 0 (0%) Male: 3 (100%)	North America: 2 (66.7%) Europe: 1 (33.3%) Asia: 0 (0%) Africa: 0 (0%) Latin America/Caribbean: 0 (0%) Oceania: 0 (0%)	USA: 2 (66.7%) Germany: 1 (33.3%)	Female: 0 (0%) Male: 3 (100%)	North America: 2 (66.7%) Europe: 1 (33.3%) Asia: 0 (0%) Africa: 0 (0%) Latin America/Caribbean: 0 (0%) Oceania: 0 (0%)	USA: 2 (66.7%) Germany: 1 (33.3%)
Uveitis[41,42,43] (n=3)	Female: 2 (66.7%) Male: 1 (33.3%)	Asia: 1 (33.3%) Europe: 1 (33.3%) North America: 1 (33.3%) Africa: 0 (0%) Latin America/Caribbean: 0 (0%) Oceania: 0 (0%)	Singapore: 1 (33.3%) Switzerland: 1 (33.3%) USA: 1 (33.3%)	Female: 2 (66.7%) Male: 1 (33.3%)	Asia: 1 (33.3%) Europe: 1 (33.3%) North America: 1 (33.3%) Africa: 0 (0%) Latin America/Caribbean: 0 (0%) Oceania: 0 (0%)	Singapore: 1 (33.3%) UK: 1 (33.3%) USA: 1 (33.3%)
Neuro-ophthalmology[44,45] (n=2)	Female: 1 (50%) Male: 1 (50%)	North America: 2 (100%) Asia: 0 (0%) Europe: 0 (0%) Africa: 0 (0%) Latin America/Caribbean: 0 (0%) Oceania: 0 (0%)	USA: 2 (100%)	Female: 0 (0%) Male: 2 (100%)	North America: 2 (100%) Asia: 0 (0%) Europe: 0 (0%) Africa: 0 (0%) Latin America/Caribbean: 0 (0%) Oceania: 0 (0%)	USA: 2 (100%)

Table 5. Continued

	First author			Last author		
	Gender	Geographical region	Top 3 countries of publication	Gender	Geographical region	Top 3 countries of publication
Pediatrics[46] (n=1)	Female: 0 (0%) Male: 1 (100%)	North America: 1 (100%) Asia: 0 (0%) Europe: 0 (0%) Africa: 0 (0%) Latin America/Caribbean: 0 (0%) Oceania: 0 (0%)	USA: 1 (100%)	Female: 0 (0%) Male: 1 (100%)	North America: 1 (100%) Asia: 0 (0%) Europe: 0 (0%) Africa: 0 (0%) Latin America/Caribbean: 0 (0%) Oceania: 0 (0%)	USA: 1 (100%)
Multiple subspecialties[47,48,49,50,51,52,53,54] (n=8)	Female: 1 (12.5%) Male: 7 (87.5%)	North America: 5 (62.5%) Asia: 3 (37.5%) Europe: 0 (0%) Africa: 0 (0%) Latin America/Caribbean: 0 (0%) Oceania: 0 (0%)	USA: 4 (50%) China: 3 (37.5%) Canada: 1 (12.5%)	Female: 3 (37.5%) Male: 5 (62.5%)	North America: 5 (62.5%) Asia: 3 (37.5%) Europe: 0 (0%) Africa: 0 (0%) Latin America/Caribbean: 0 (0%) Oceania: 0 (0%)	USA: 4 (50.0%) China: 3 (37.5%) Canada: 1 (12.5%)

As AI applications continue to grow in medicine, there has also been a rising interest in their use within ophthalmology. Over the past year, ophthalmology has seen an increase in the diverse applications of LLMs, ranging from clinical decision-making to enhancing patient interactions. The purpose of our study was to explore the current state of LLM research in ophthalmology through a bibliographic analysis.

We observed that most of the LLM studies in ophthalmology focused on clinical decision-making, with the majority aimed at retinal applications. This interest in clinical decision-making applications is not surprising, as LLMs have shown promise in assisting with complex diagnostic and treatment decisions. However, there is still significant uncertainty regarding how LLMs could be integrated into actual patient care from a regulatory standpoint.[107] While the reasons for the high number of retina-related LLM publications are not entirely clear, we speculate that it may be due to the history of DL applications in ophthalmology. DL-based image analyses in ophthalmology have been spearheaded by the retina subspecialty. Therefore, the same group of researchers who focused on DL-based analysis of retinal images may have been early adopters of LLM-related research.[108]

Similarly, our research team has recently focused on LLMs. For example, we published a meta-analysis evaluating the accuracy of LLMs in answering board-style questions.[55] In addition, we further examined the impact of integrating retrieval-augmented generation in enhancing LLM performance on both text-based and image-based board-style questions.[109,110] Another area of interest has been the difference in performance between different LLMs in answering questions related to social determinants of health in ophthalmology.[111]

Furthermore, our current study also demonstrates that LLMs possess significant scientific merit, as evidenced by their increasing presence in top-tier publications in recent years. These studies present substantial scholarly impact, with a notable number appearing in top-tier Q1 journals. We observed that glaucoma-related applications exhibited the greatest scientific impact in clinical decision-making, as reflected by their high h-index and i10-index values, along with their strong presence in Q1 journals. However, overall, the most scientifically impactful applications were those involving algorithms trained for educational purposes, such as evaluating their performance in clinical knowledge exams compared to professionals or developing educational materials. These studies demonstrated higher average h-index and i10-index values, with the majority published in Q1 journals. The high impact of educational applications in particular may be attributed to their adaptability across medical disciplines beyond ophthalmology, their potential

Table 6. Detailed distribution of gender and geographical region of studies according to the first and last authors' affiliated institutions for educational, patient interaction, and miscellaneous applications

	First author			Last author		
	Gender	Geographical region	Top 3 countries of publication	Gender	Geographical region	Top 3 countries of publication
Educational applications[55-76]	Female: 4 (18.2%) Male: 18 (81.8%)	North America: 10 (45.5%) Europe: 7 (31.8%) Asia: 5 (22.7%) Africa: 0 (0%) Latin America/Caribbean: 0 (0%) Oceania: 0 (0%)	USA: 8 (36.4%) UK: 6 (27.3%) Canada: 2 (9.1%) China: 2 (9.1%)	Female: 1 (4.5%) Male: 21 (95.5%)	North America: 12 (54.5%) Europe: 5 (22.7%) Asia: 5 (22.7%) Africa: 0 (0%) Latin America/Caribbean: 0 (0%) Oceania: 0 (0%)	USA: 9 (40.9%) Canada: 3 (13.6%) China: 2 (9.1%)
Patient interaction applications[77-94]	Female: 6 (33.3%) Male: 12 (66.7%)	Asia: 8 (44.4%) North America: 7 (38.9%) Europe: 2 (11.1%) Oceania: 1 (5.6%) Africa: 0 (0%) Latin America/Caribbean: 0 (0%)	USA: 7 (38.9%) Singapore: 3 (16.7%) Türkiye: 2 (11.1%)	Female: 8 (55.6%) Male: 10 (44.4%)	Asia: 8 (44.4%) North America: 7 (38.9%) Europe: 2 (11.1%) Oceania: 1 (5.6%) Africa: 0 (0%) Latin America/Caribbean: 0 (0%)	USA: 7 (38.9%) Singapore: 3 (16.7%) Türkiye: 2 (11.1%)
Miscellaneous applications[95,96,97,98,99,100,101,102,103]	Female: 5 (55.6%) Male: 4 (44.4%)	North America: 6 (66.7%) Asia: 2 (22.2%) Europe: 1 (11.1%) Africa: 0 (0%) Latin America/Caribbean: 0 (0%) Oceania: 0 (0%)	USA: 6 (66.7%) India: 1 (11.1%) Türkiye: 1 (11.1%)	Female: 3 (33.3%) Male: 6 (66.7%)	North America: 6 (66.7%) Asia: 2 (22.2%) Europe: 1 (11.1%) Africa: 0 (0%) Latin America/Caribbean: 0 (0%) Oceania: 0 (0%)	USA: 6 (66.7%) UK: 1 (11.1%) Türkiye: 1 (11.1%)

to enhance training outcomes, and their effectiveness in addressing educational gaps in medical training.

Despite the increasing prominence of LLMs, the underrepresentation of female authors remains an ongoing challenge. A recent study showed an increase in the proportion of women in research since 2018, from 33% to 37% of first authors and 27% to 30% of last authors.[112,113] However, gender disparity continues to be a significant issue, particularly in the field of AI. Similar to the literature, our study revealed a prominent gender gap in all author roles, with women accounting for only 29.9% of first authors, 25.3% of last authors, and 26.4% of corresponding authors. This gender distribution in our study suggests that despite recent efforts to increase female representation in academic publishing, significant barriers still exist for women in reaching key author roles. This underscores the need for continued efforts to promote gender equity. The notable underrepresentation of female authors likely reflects broader systemic issues, such as gender disparities in science, technology, engineering and mathematics education and leadership roles, limited mentorship opportunities for women in AI-driven medical research, and potential institutional biases.[114]

A similar disparity can be observed in the geographical distribution of studies. Research has shown that English-speaking countries, particularly the US (48.2%), dominate authorship in leading medical journals. In contrast, authors from developing countries remain underrepresented, although there has been an increase in geographical diversity in recent years.[115] Another recent study also highlighted a similar bias in the rejection of research submitted to journals. Compared to authors from institutions in non-Western countries, those from Western countries are 5.7% more likely to have their manuscript accepted after rejection. Additionally, authors from Western countries tend to publish 23 days faster, revise 5.9% less often, change co-authors 12.0% less frequently, and ultimately publish in journals with impact factors that are 0.8% higher.[11,116]

Consistent with the literature, our study revealed a similar disparity in the geographical origin of research based on first authorship. Overall, English-speaking countries dominated the research output, with the USA contributing 43.7% of the studies and the UK contributing to 10.3%. However, China ranked a strong second after the USA, contributing 13.8% of the studies, underscoring its significant contribution to the field. This suggests that while the USA and China are leading research in LLMs in ophthalmology, there is still a strong need for contributions from other regions, particularly in the development of applications tailored to the specific cultural and societal needs of those regions. This imbalance may be partly explained by the predominance of English-language data used for training LLMs.[117] Furthermore, it may also be attributed to the immense investment into fundamental AI infrastructure in the US and China, funding availability, and access to advanced technologies, all of which play a critical role in shaping the global distribution of LLM-related research.[118]

Study Limitations

This study also has limitations, particularly the use of PubMed as the sole platform for the literature search. While other databases such as arXiv and IEEE Xplore host a significant number of AI-related studies, we chose to include only those indexed in PubMed due to its high standards for peer-reviewed content, thereby ensuring the scientific rigor of the included articles. Additionally, we recognize that categorizing studies based on AI-related infrastructure or funding opportunities could offer a different perspective on the distribution of LLM-related research and should be explored in future studies.

Conclusion

The use of LLMs in ophthalmology is rapidly gaining interest, with the majority of studies published recently (in 2024) and in top-tier (Q1) journals. North America leads in publications, followed by growing contributions from Asia and Europe, while other regions, including Oceania, Latin America and the Caribbean, and Africa, remain underrepresented. A similar imbalance is observed in the gender distribution in authorship, with women being severely underrepresented across all key author roles. These geographic and gender inequities highlight significant gaps in global and demographic representation within LLM research in ophthalmology and demonstrate the need for further progress.

Declarations

Authorship Contributions

Concept: N.D.K., T.Y.A.L., Design: N.D.K., T.Y.A.L., Data Collection or Processing: N.D.K., T.Y.A.L., Analysis or Interpretation: N.D.K., T.Y.A.L., Literature Search: N.D.K., T.Y.A.L., Writing: N.D.K., T.Y.A.L.

Conflict of Interest: No conflict of interest was declared by the authors.

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Suture Revision for the Management of Postoperative Intraocular Pressure Spike Following Cyclodialysis Repair in Chronic Five-Year Hypotony

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Dear Editor,

Ocular blunt trauma can lead to cyclodialysis, which may resolve spontaneously or respond to conservative management.[1] However, interventional approaches may be required when the cleft is refractory to medical therapy.[2,3] Surgical closure of the cleft is generally effective at restoring intraocular pressure (IOP), but the occurrence of postoperative complications (such as severe IOP spikes) sometimes necessitates additional glaucoma surgery.[4,5]

This letter reports an unusual case of long-standing ocular hypotony due to a chronic cyclodialysis cleft. The case was further complicated by the development of severe, medically uncontrolled ocular hypertension following surgical cleft closure, which was managed by suture revision.

A 52-year-old man presented with decreased vision in his right eye and history of a severe motor vehicle accident 5 years earlier. On examination, best corrected visual acuity (BCVA) was hand motion in the right eye. IOP was 5 mmHg in the right eye and 15 mmHg in the left eye. Anterior segment examination of the right eye revealed an intumescent cataract and a markedly shallow anterior chamber. Fundus examination could not be performed due to media opacity. B-scan ultrasonography revealed no retinal or choroidal detachment. However, the axial length (AL) of the right eye was approximately 2 mm shorter than that of the left (22.15 mm vs. 23.99 mm). Gonioscopic evaluation was limited due to hypotony; the angle structures appeared indistinct and irregular secondary to trauma. Ultrasound biomicroscopy was recommended but declined by the patient. Anterior segment optical coherence tomography was subsequently performed; 360-degree scanning revealed a cyclodialysis cleft at the nasal angle and a blunt angle configuration in the inferior and temporal quadrants (Figure 1).

Phacoemulsification, cleft closure using the cross-chamber cyclopexy technique, and capsular tension ring (CTR) implantation in the sulcus were performed.[6] Following uneventful cataract removal, an approximately

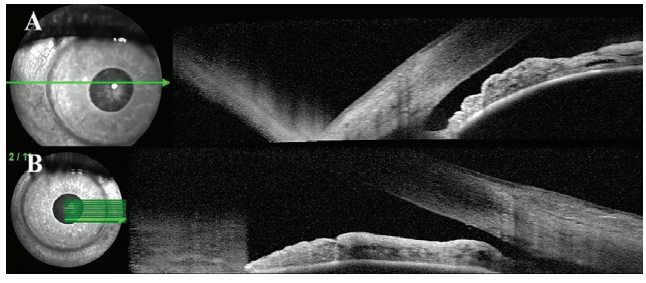

Figure 1. Anterior segment optical coherence tomography scans showing a blunt and widened angle configuration in the inferior and temporal quadrants (A), indicative of trabecular damage, and revealing a cyclodialysis cleft at the nasal angle (B)

Keywords: Intraocular pressure spike, hypotony, cyclodialysis, cyclopexy, trauma

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1-clock-hour cyclodialysis cleft (from 3 to 4 o'clock) was identified at the nasal angle using a Swan-Jacob gonioprism lens. The cleft area was identified and marked on the sclera. A double-armed 10-0 polypropylene suture was passed into the anterior chamber, exiting 1.5 mm posterior to the limbus at both outer edges of the cleft (Figure 2). The conjunctiva was closed after the suture was tightened and tied over the sclera. Prior to viscoelastic removal, a Morcher type 14A CTR was placed in the ciliary sulcus to ensure that no additional cyclodialysis areas were missed.

IOP was 55 mmHg on postoperative day 1. The patient was managed with maximum topical antiglaucomatous therapy. Systemic treatment included oral acetazolamide (Diazomid®, Sanofi Health Products, İstanbul, Türkiye) thrice daily and intravenous mannitol (5 mL/kg, Polifarma Pharmaceuticals, İstanbul, Türkiye) twice daily. No improvement in IOP was observed until the end of postoperative day 5, with a lowest recorded value of 45 mmHg. Gonioscopy revealed a closed cleft with a broadly and irregularly widened ciliary body band and indistinct angle structures, consistent with angle recession and trabecular damage (Figure 3). Due to severe, medically uncontrolled ocular pain and nausea associated with persistently elevated IOP, the 10-0 polypropylene suture used for cyclodialysis cleft closure was removed, given that a CTR had also been implanted in the sulcus during the initial surgery.

Following suture removal, the IOP rapidly decreased to 6 mmHg. At 12 weeks, BCVA improved to 0.6 (Snellen decimal), with an IOP of 14 mmHg in the right eye. However, a localized pupillary retraction was evident on the nasal side (Figure 4). Optical coherence tomography showed resolution of hypotony maculopathy (Figure 5). However, the AL was similar to the preoperative measurement (22.22 mm) and gonioscopy revealed a partially open cyclodialysis cleft smaller than the preoperative cleft area (Figure 6).

A notable postoperative event in this case was the rapid and severe IOP elevation to 55 mmHg, which was unresponsive to intensive medical therapy. Hypertensive episodes following cyclodialysis cleft closures are well documented, with reported incidence ranging from 48% to 84%.[7,8] This phenomenon is attributable to the abrupt cessation of abnormal aqueous outflow through the cleft and the subsequent reactivation of a previously compromised trabecular meshwork which may have become functionally atrophic during prolonged hypotony.

Post-cleft closure IOP spikes may be refractory to medical therapy and necessitate additional glaucoma surgery.[4,5] Ohtani et al.[4] reported a case in which Ahmed

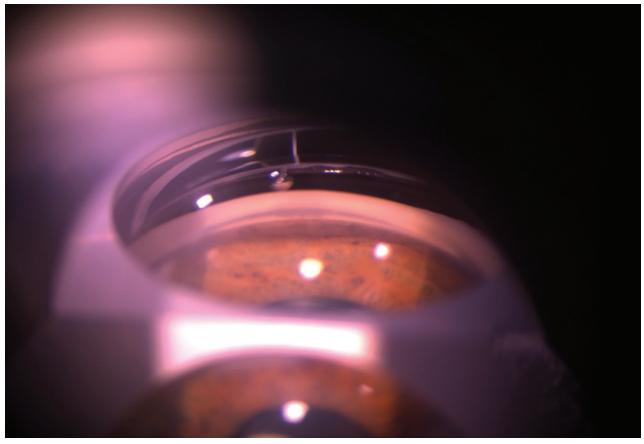

Figure 3. Gonioscopic image showing a broadly irregular and widened ciliary body band with indistinct angle structures at the inferior angle, consistent with angle recession and trabecular damage

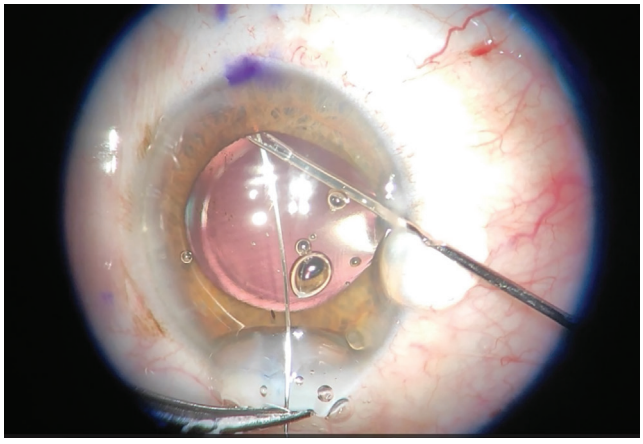

Figure 2. Intraoperative view showing cyclodialysis cleft closure using the cross-chamber cyclopexy technique following phacoemulsification

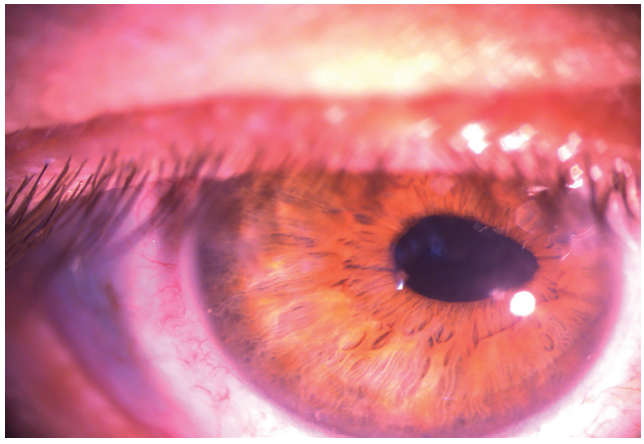

Figure 4. Anterior segment photograph taken three months after surgery shows localized nasal pupil retraction extending into the cyclodialysis cleft region

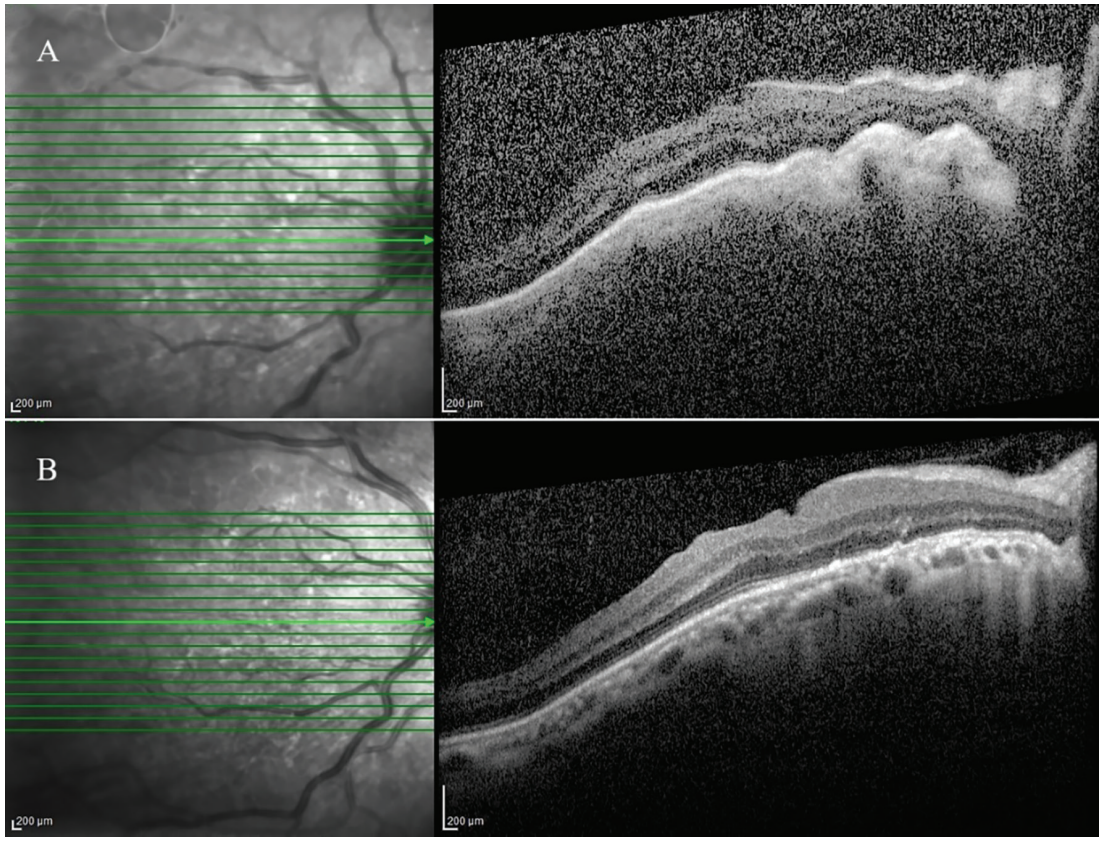

Figure 5. Optical coherence tomography demonstrated hypotony maculopathy on postoperative day 1 following suture removal (A), with notable improvement observed at the 3-month postoperative follow-up (B)

Figure 6. Gonioscopic examination demonstrated a partially reopened cyclodialysis cleft, smaller in extent than the preoperative lesion

glaucoma valve implantation was performed 14 days after direct internal cyclopexy due to persistent postoperative IOP elevation. In another study, both eyes required additional surgery following surgical cleft closure.[5] Similarly, this patient experienced medically uncontrolled elevated IOP with severe pain and nausea, necessitating further intervention. Additionally, the patient's ocular features (including the angle appearance consistent with recession and trabecular damage) and the prolonged hypotony, which can lead to trabecular dysfunction, warranted surgical revision instead of continued follow-up with antiglaucomatous medications. Suture removal (rather than a second IOP-lowering procedure) was performed as the sulcus CTR could facilitate cleft closure over time, while suture removal alone could effectively reduce IOP.

Trabecular dysfunction sustained by ocular hypotony is suggested to reverse following cleft closure, potentially contributing to gradual normalization of the IOP.[9] However, we consider this unlikely in patients with chronic hypotony lasting several years. In line with this view, Agrawal and Shah[7] hypothesized that microscopic aqueous drainage into the suprachoroidal space may persist despite clinically evident closure of the cyclodialysis cleft. In this case, final gonioscopy revealed a partially open cyclodialysis cleft (<0.5 clock hours) smaller than the preoperative cleft size. Therefore, we believe that the equilibrium between aqueous production and outflow is maintained by the residual cleft area rather than trabecular function recovery.

Based on this patient's experience, we recommend the use of adjustable sutures in incisional cyclodialysis closure surgeries. This technique, which permits aqueous drainage after loosening, may help reduce postoperative uncontrolled IOP spikes and the need for secondary glaucoma procedures.

Ethics

Informed Consent: Written informed consent was obtained from the patient.

Declarations

Authorship Contributions

Surgical and Medical Practices: A.M.K., Concept: A.M.K., Design: A.M.K., Data Collection or Processing: A.M.K., B.E.A., Analysis or Interpretation: A.M.K., Literature Search: A.M.K., Writing: A.M.K.

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Cyclodialysis as a Complication of Gonioscopy-Assisted Transluminal Trabeculotomy and its Management

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Dear Editor,

Cyclodialysis cleft is an uncommon but clinically significant cause of ocular hypotony. It can develop after ocular trauma or surgeries involving manipulation of the iris root, trabecular meshwork, or ciliary body. The condition has been reported following procedures such as cataract surgery, iridectomy, trabeculectomy, Kahook Dual Blade goniotomy, and microhook-assisted ab interno trabeculotomy.[1,2,3,4]

Although cyclodialysis cleft has been reported as a complication following gonioscopy-assisted transluminal trabeculotomy (GATT), its underlying mechanisms, diagnostic challenges, and optimal management strategies remain insufficiently characterized in the literature. GATT is a conjunctiva-sparing ab interno trabeculotomy technique that was first described by Grover et al.[1] and has since been reported to be effective even in advanced glaucoma cases.[5] Here we report a case of persistent hypotony caused by a cyclodialysis cleft following polypropylene suture-assisted GATT, which was successfully managed with direct cyclopexy followed by a repeat GATT to restore intraocular pressure (IOP) control.

A 33-year-old man with primary congenital glaucoma was referred for persistent hypotony in the right eye one month after GATT performed at another center. Best corrected visual acuity (BCVA) was 20/200 in the right eye and 20/20 in the fellow eye. IOP measured 7 mmHg in the right eye without medication and 13 mmHg in the left eye while on triple therapy. Both eyes were buphthalmic, and the right fundus exhibited hypotony maculopathy (Figure 1A, B). Despite advanced cupping, peripapillary retinal nerve fiber layer (RNFL) thickness appeared falsely preserved in the right eye, consistent with "green disease" secondary to hypotony, whereas the fellow eye demonstrated true RNFL loss (Figure 1C, D).

Gonioscopy demonstrated a superior cyclodialysis cleft extending from 12 to 2 o'clock (Figure 1E). This was confirmed by ultrasound biomicroscopy (UBM), which showed separation of the ciliary body from the scleral spur, along with supraciliary fluid (Figure 1F). Hypotony had persisted since the early postoperative period following the initial GATT surgery.

Persistent hypotony despite atropine (administered for 2 weeks) and argon laser photocoagulation led to the decision to perform direct transscleral suture cyclopexy. The surgical steps are shown in Figure 2. On postoperative day 1, IOP transiently increased to 42 mmHg, which was considered an expected indicator of successful cyclodialysis cleft closure.[6,7] The IOP spike was promptly managed with oral acetazolamide (Diazomid®, Sanofi, İstanbul, Türkiye) and intensive topical therapy including dorzolamide/

Keywords: Cyclodialysis cleft, gonioscopy-assisted transluminal trabeculotomy, hypotony, surgical repair

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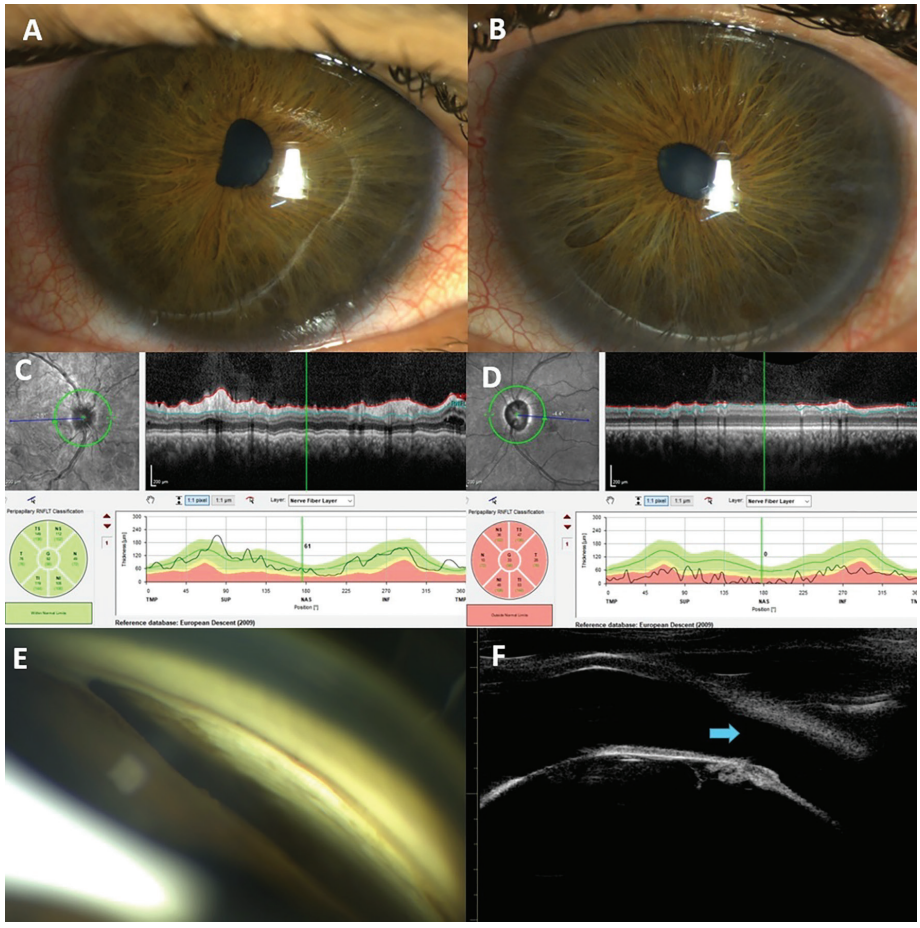

Figure 1. Buphthalmic appearance of the right (A) and left (B) eye. Optical coherence tomography analysis shows "green disease" in the right eye (C) and significant atrophy of the retinal nerve fiber layer in the left eye (D). Gonioscopy shows a cyclodialysis cleft extending from 12 o'clock to 2 o'clock (E). Ultrasound biomicroscopy confirms the presence of the cyclodialysis cleft (blue arrow) and suprachoroidal effusion (F)

timolol (Tomec®, Abdi İbrahim İlaç, İstanbul, Türkiye), brimonidine tartrate (Alphagan-P®, Allergan, Irvine, CA, USA), and bimatoprost (Lumigan®, Allergan, Irvine, CA, USA). No postoperative hyphema or intraocular bleeding was observed. IOP gradually decreased and stabilized around 24 mmHg under maximal tolerated medical treatment, with no evidence of further visual deterioration. UBM confirmed complete anatomical closure (Figure 3A, B). BCVA improved to 20/50.

Given the patient's young age and need for long-term pressure control, we opted to repeat GATT 2 weeks after the cyclopexy. Importantly, the trabecular meshwork remained structurally intact following cyclopexy (Figure 3C), allowing reestablishment of aqueous outflow through Schlemm's canal. During the revision surgery, visualization of the blue polypropylene suture (Prolene®, Ethicon Inc., Somerville, NJ, USA) confirmed correct canalization (Figure 3D). One week after repeat GATT, the IOP stabilized at 12 mmHg and remained between 12 and 16 mmHg on once-daily latanoprost (Xalatan®, Pfizer Inc., New York, NY, USA) throughout a 2-year follow-up period.

Several surgical approaches have been described for the management of cyclodialysis clefts, including argon laser photocoagulation, transscleral cryotherapy, cyclophotocoagulation, scleral buckling, and internal tamponade with gas or silicone oil.[8] While these methods aim to promote closure by inducing inflammation or reducing uveoscleral outflow, their success may be limited in cases of large, persistent, or anatomically well-defined clefts. Direct transscleral suture cyclopexy allows precise

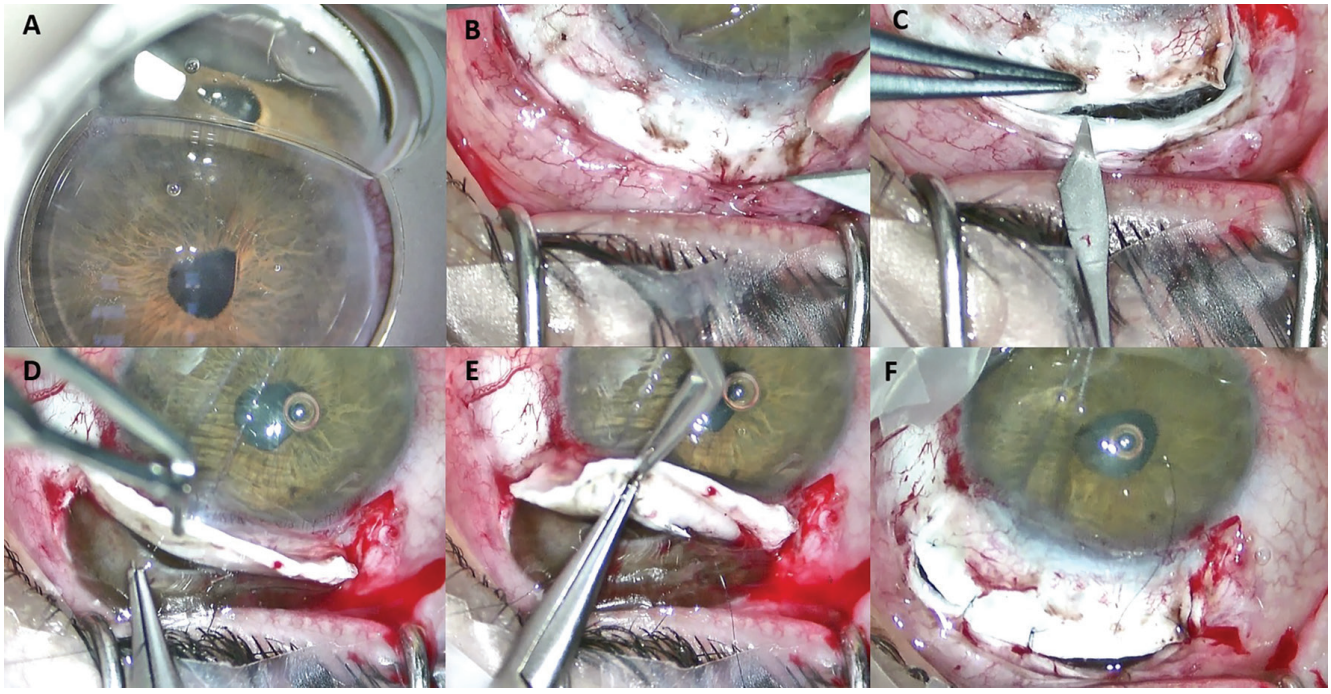

Figure 2. A) The superior border of the cleft was visualized using a surgical goniolens. B) Superior peritomy and scleral cauterization were performed. C) The sclerotomy area was created using a straight 15° micro-knife. D) 10/0 nylon suture was passed through the underlying ciliary body. E) Afterwards, the 10/0 nylon suture was passed through the corresponding inner wall of the sclera. F) The ciliary body and sclera were reapposed and the sclera was closed with 10/0 nylon suture

anatomical reapposition of the ciliary body to the scleral spur and is considered the most definitive surgical option, particularly in refractory cases. In the present case, given the clearly localized cleft, persistent hypotony, and failure of conservative measures, direct cyclopexy was preferred to achieve prompt and durable closure while preserving the angle anatomy for potential future angle-based surgery.

This case highlights two key clinical lessons. First, cyclodialysis cleft is a potential complication of GATT when the Prolene suture enters the suprachoroidal space rather than Schlemm's canal. In eyes with congenital glaucoma, anatomic variations such as angle dysgenesis, posterior displacement of the trabecular meshwork, and abnormal ciliary body insertion may increase the risk of posterior misdirection of the Prolene suture during GATT, potentially leading to cyclodialysis cleft formation. This risk can be mitigated through careful identification of the correct trabecular entry plane, assisted by blood reflux from Schlemm's canal or selective trabecular meshwork staining. Furthermore, in young patients with prominent iris processes, an initial incision inadvertently made into these structures may allow the Prolene suture to advance through a tunnel posterior to the trabecular meshwork. Subsequent traction on the suture during GATT may then result in separation of the ciliary body from the scleral spur, resulting in a cyclodialysis cleft.

Second, following successful cyclodialysis cleft repair, several surgical options can be considered for long-term IOP control, including trabeculectomy, implantation of a glaucoma drainage device, or repeat angle-based surgery. In the present case, repeat GATT remained a viable option for several reasons. One important consideration was the patient's young age, for which conjunctival preservation was prioritized to maintain future surgical options. In addition, gonioscopic and intraoperative findings demonstrated that the trabecular meshwork remained structurally intact after cleft repair, suggesting preserved functional potential despite the period of hypotony. Although prolonged hypotony may theoretically impair trabecular meshwork function, no structural collapse or scarring was observed in this case. Furthermore, given the patient's prior history of hypotony, avoiding bleb-forming procedures or permanent implants was considered advantageous. In this context, repeat GATT represented a reasonable and conservative approach to restore aqueous outflow while minimizing additional surgical morbidity. Nevertheless, we acknowledge that marked postoperative IOP elevations may pose a theoretical risk of further optic nerve damage or

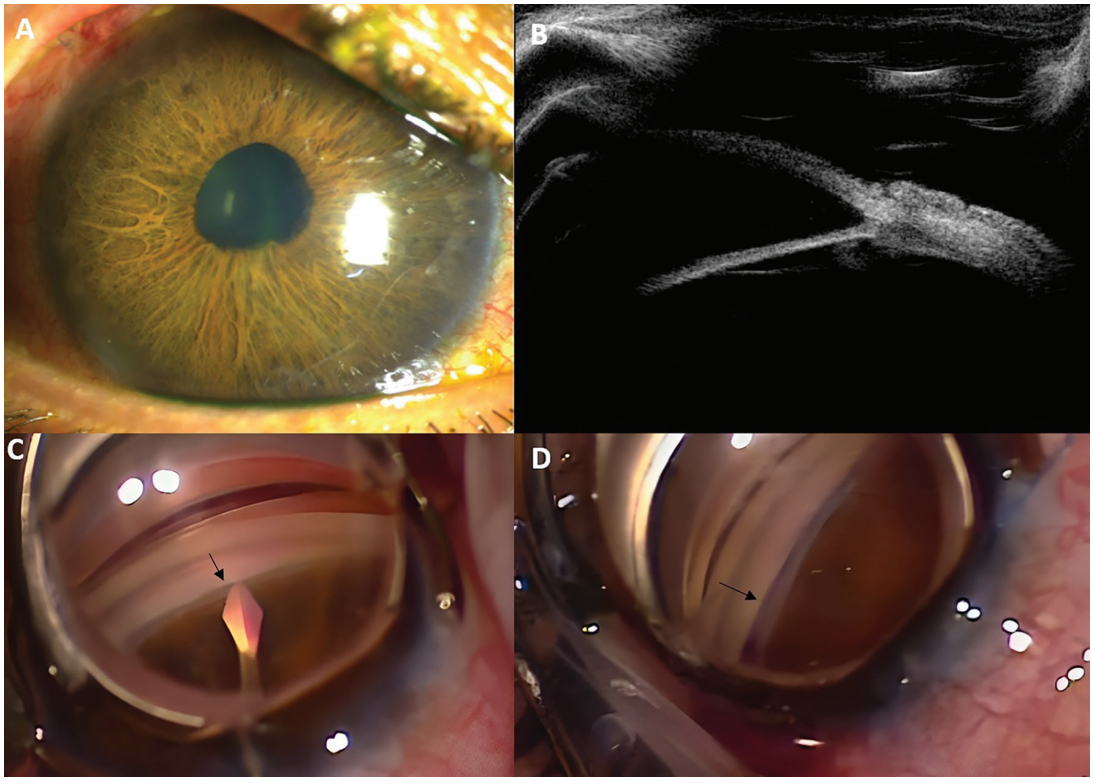

Figure 3. A) Two weeks after cyclodialysis repair, the cornea is clear and the iris appears normal. IOP is 24 mmHg with maximum tolerated medical treatment. B) Postoperative ultrasound biomicroscopy confirms complete closure of the cyclodialysis cleft and resolution of suprachoroidal effusion. C) A goniotomy incision made immediately adjacent to the previously repaired cleft area. The arrow shows the intact appearance of the trabecular meshwork overlying the area of cleft repair. D) Blue Prolene suture is seen in Schlemm's canal over the area of cleft repair (arrow)
IOP: Intraocular pressure

wipe-out phenomenon, particularly in eyes with advanced glaucoma. However, the pressure rise in our patient was transient, closely monitored, and rapidly controlled, and no additional functional loss was observed.

Early recognition of a cyclodialysis cleft is essential to prevent hypotony maculopathy. In eyes with severe hypotony and a shallow anterior chamber, direct visualization of a cyclodialysis cleft may not be feasible using gonioscopy or UBM alone. In such cases, temporary deepening of the anterior chamber with a viscoelastic agent followed by repeat gonioscopy may facilitate identification of the cleft and aid in accurate diagnosis. Once the cyclodialysis cleft is repaired, angle-based surgery can again be considered if the trabecular meshwork remains functional. Our case demonstrates that repeat GATT can provide lasting IOP control after successful cleft repair, and therefore represents an important management consideration.

Ethics

Informed Consent: Written informed consent was acquired from the patient in this case report.

Declarations

Authorship Contributions

Surgical and Medical Practices: Z.A., Concept: Z.A., A.Y.Ü., Design: Z.A., A.Y.Ü., Data Collection or Processing: Z.A., A.Y.Ü., Analysis or Interpretation: Z.A., A.Y.Ü., Literature Search: A.Y.Ü., Writing: A.Y.Ü.

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Enterobacter cloacae Keratitis in a Patient with Severe Dry Eye: A Rare Case Report and Review of the Literature

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Dear Editor,

Corneal ulcers are vision-threatening emergencies. Bacterial pathogens such as *Staphylococcus*, *Streptococcus,* and *Pseudomonas* are most frequently implicated in microbial keratitis.[1] The integrity of the corneal epithelium is critical in preventing infections, as it acts as a physical and immunological barrier.

Enterobacter cloacae is a Gram-negative rod in the Enterobacteriaceae family, commonly present in the environment and human gut microbiota. Although increasingly linked to nosocomial infections,[2] ocular involvement remains rare. The prevalence of *E. cloacae* keratitis ranges from 0.13% to 15.3%.[1,3] Most documented cases involve penetrating keratoplasty (PK), graft failure, chronic corneal edema, or topical corticosteroid use.[3,4,5,6]

Keywords: Corneal ulcer, *Enterobacter cloacae*, dry eye disease, topical corticosteroids

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Dry eye disease (DED) is a multifactorial disorder characterized by tear film instability, ocular surface inflammation, and neurosensory abnormalities.[7] Severe DED leads to disruption of the corneal epithelial barrier, impaired wound healing, and reduced resistance to pathogens. Topical corticosteroids or calcineurin inhibitors may exacerbate these effects.[8]

We present a rare case of *E. cloacae* keratitis that highlights the predisposing role of severe dry eye and topical corticosteroids and briefly review previously reported cases to contextualize the risk factors associated with this opportunistic infection.

A 77-year-old woman who did not use contact lenses presented with a 1-week history of pain, redness, and decreased vision in the right eye. Her best corrected visual acuity (BCVA) had declined from 20/25 to 20/32. She had a 3-year history of severe DED, with Schirmer test values of 4 and 3 mm, tear break-up time of 3 seconds, and grade II punctate keratitis in both eyes, together with meibomian gland dysfunction. No systemic predisposing conditions or previous ocular surgery were reported. The patient maintained adequate hygiene.

Treatment included warm compresses, lid hygiene, artificial tears (Thealoz Duo®; Laboratoires Théa, Clermont-Ferrand, France), and tear ointment (VitA-POS®; URSAPHARM Arzneimittel GmbH, Saarbrücken, Germany) at bedtime. Topical corticosteroid (dexamethasone 1 mg/mL, preservative-free; Dexafree®, Laboratoires Théa, Clermont-Ferrand, France) had been started 6 weeks earlier and was being tapered with a dose reduction every 10 days. At presentation, she was using fluorometholone 1 mg/mL (FML®, Allergan Pharmaceuticals, Westport, Ireland) once daily and cyclosporine A 0.05% eye drops (hospital-compounded formulation, Barraquer Ophthalmology Center Pharmacy, Barcelona, Spain) twice daily.

Slit-lamp examination showed mucous discharge, conjunctival hyperemia, and a 2-mm corneal ulcer with dense stromal infiltrate and surrounding calcium deposits in the inferior midperiphery (5 o'clock). No keratic precipitates were observed (Figure 1A).

Suspecting microbial keratitis, corneal scrapings were obtained for culture. Empirical treatment was begun with fortified cefazolin 50 mg/mL and amikacin 20 mg/mL eye drops (hospital-compounded formulation, Barraquer Ophthalmology Center Pharmacy, Barcelona, Spain) applied hourly while awake and ciprofloxacin 3 mg/g ointment (Oftacilox®, NTC Srl, Milan, Italy) at bedtime. Fluorometholone and cyclosporine A were discontinued.

Corneal cultures grew *E. cloacae* (Figure 1B) sensitive to amikacin, ciprofloxacin, and ceftazidime. After 1 week of treatment, the ulcer was controlled and the epithelial defect was closed. Thus, fortified cefazolin and amikacin were discontinued, and treatment was switched to ceftazidime 50 mg/mL (hospital-compounded formulation, Barraquer Ophthalmology Center Pharmacy, Barcelona, Spain) 5 times daily to reduce toxicity to the ocular surface, maintaining ciprofloxacin ointment every 12 hours. Medroxyprogesterone 20 mg/mL eye drops (hospital-compounded formulation, Barraquer Ophthalmology Center Pharmacy, Barcelona, Spain) were added to control inflammation.

After 1 month, infection was controlled but the calcium deposit enlarged (Figure 1C), causing a new epithelial defect. Conservative management with daily fluorometholone, tobramycin 3 mg/g ointment (Tobrex®, Novartis Pharma, Barcelona, Spain), and an eye patch was started. As no improvement occurred after 3 days, corneal curettage was performed, leaving 387 µm of residual stroma on anterior segment tomography (Figure 1D). The same regimen achieved complete epithelial closure within 1 week.

Maintenance treatment for severe DED was then resumed, including 50% autologous serum drops hourly, fluorometholone 1 mg/mL once daily, and cyclosporine A 0.05% twice daily to control chronic ocular surface inflammation.

At 7-month follow-up, stromal thinning and corneal haze persisted (Figure 1E), but BCVA improved to 20/25. Maintenance therapy continued with 6-month follow-up.

E. cloacae keratitis is rare; only 13 cases have been reported (Table 1). Most occurred in patients with a history of PK, graft failure, or prolonged topical corticosteroid use, often associated with corneal bullae, irregular ocular surface, or neurotrophic keratopathy. Gross and Meyer[4] noted reduced tear production as a possible factor. Rajarajan et al.[3] reviewed 7,787 infectious keratitis cases and identified *E. cloacae* in only 10 (0.13%): 9 following PK and 1 associated with bullous keratopathy. They suggested that epithelial bullae and an irregular corneal surface from graft failure may compromise the epithelial barrier, particularly when combined with long-term corticosteroid use. The most recent case, reported by Al Rasheed et al.,[6] occurred after corneal cross-linking with epithelial debridement, further emphasizing epithelial disruption as a major predisposing factor. Additionally, Feizi et al.[9] reported *E. cloacae* contamination in 7.02% of therapeutic bandage contact lenses, suggesting possible environmental exposure.

In our case, the absence of prior surgery, corneal decompensation, systemic disease, or contact lens use suggests that alternative risk factors must be considered. Severe DED is widely recognized to compromise epithelial integrity, impair tear film antimicrobial defense, and reduce corneal sensitivity, factors that collectively reduce ocular immunity.[7]

Interestingly, as shown in Table 1, no previously reported case of *E. cloacae* keratitis identified corticosteroid use as the sole risk factor. In all cases, topical corticosteroids were associated with epithelial barrier disruption such as post-surgical status, corneal bullae, graft failure, or chronic surface disease. This reinforces the idea that both epithelial compromise and local immunosuppression are required to trigger opportunistic keratitis.

Corticosteroids, while reducing ocular surface inflammation, further impair local defense mechanisms and increase susceptibility to opportunistic infections in eyes with already compromised epithelial integrity.[8] Our patient was using fluorometholone at presentation. Following TFOS DEWS III, medroxyprogesterone and autologous serum were used as corticosteroid-sparing therapy. Both provide regenerative and anti-inflammatory effects without relevant immunosuppression, making them appropriate for high-risk corneas.[7]

An additional complication was the formation of a calcium deposit at the ulcer site, delaying epithelial healing and requiring curettage. This was likely related to phosphate-containing fluorometholone (FML, Allergan). In compromised ocular surfaces, phosphate buffers may precipitate with calcium in the tear film, forming hydroxyapatite crystals.[10] Popiela and Hawksworth[10] noted this calcification can occur regardless of dosage or duration and advised avoiding phosphate-based drops in chronic ocular surface disease. This case highlights the need to critically evaluate the use of corticosteroids in DED.

In conclusion, this case suggests that severe DED and topical immunosuppression may suffice to trigger infection by an opportunistic pathogen such as *E. cloacae,* even without classical risk factors like PK or graft failure.

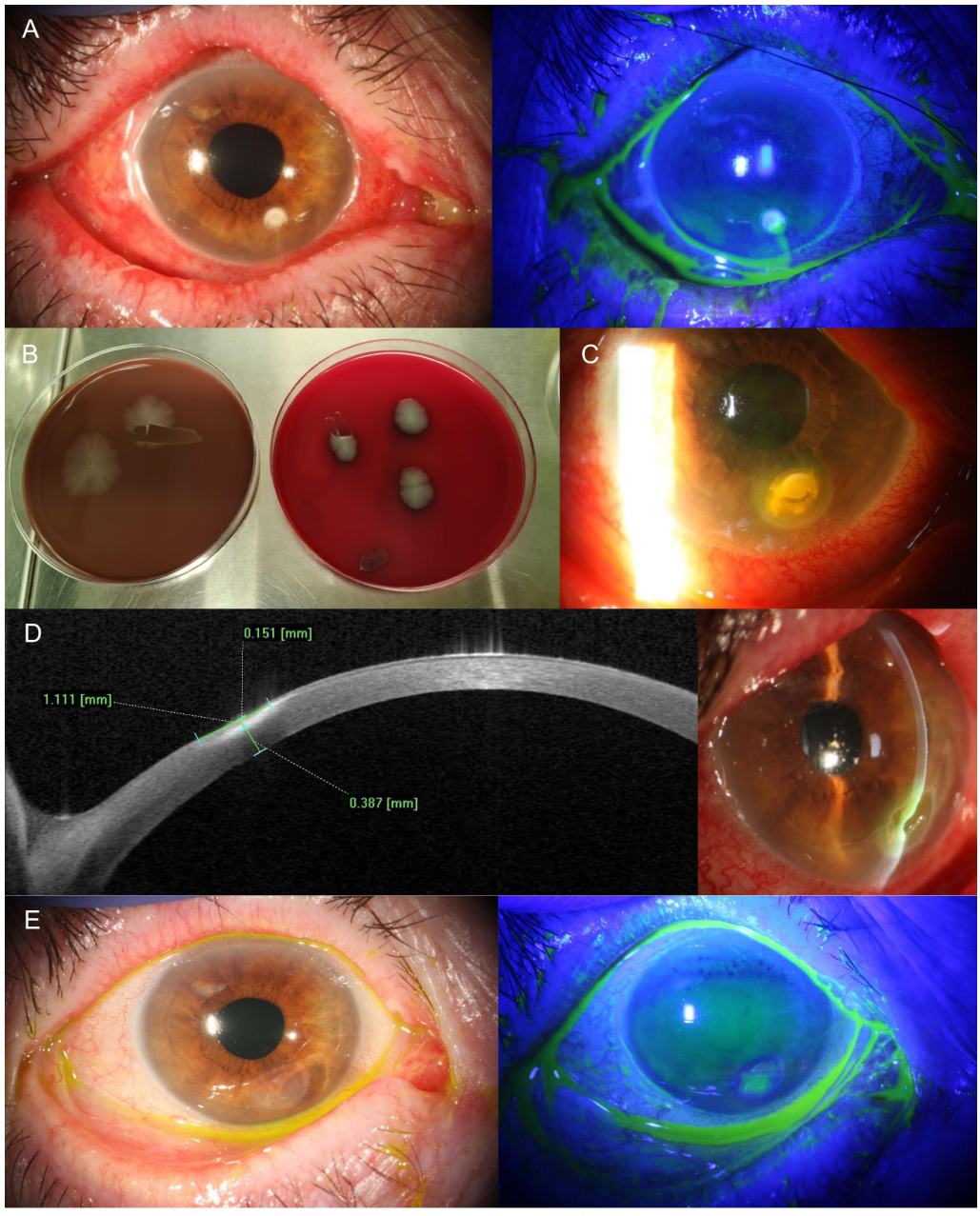

Figure 1. A) Slit-lamp exam at presentation showing corneal ulcer in the inferior midperiphery with dense infiltrates, calcium deposits and positive fluorescein staining. B) *Enterobacter cloacae* growth on chocolate agar (left) and blood agar (right). C) Slit-lamp photograph showing progressive calcium deposition hindering epithelial closure two months after initial treatment. D) Slit-lamp image (left) and anterior segment tomography (right) demonstrating focal corneal thinning. E) Slit-lamp exam at final follow-up showing no epithelial defect and fluorescein pooling due to residual surface irregularity

Table 1. Reported cases of *Enterobacter cloacae* keratitis in the literature and proposed risk factors

Cases	Gender/ age	Previous surgeries	Risk factors	Presenting VA	Ulcer size and morphology	Sensitive antibiotic	Final VA	Outcome/ duration (d)
Gross and Meyer[4] (1985)	F/70	-Extracapsular cataract extraction -PK for pseudophakic bullous keratopathy	-Chronic edema after graft rejection -Topical corticosteroid therapy -Tear insufficiency -Poor toilet hygiene and inadequate hand washing	HM at 15 cm	3.0x1.2 mm Dense, white stromal infiltrate	Gentamicin and sulfacetamide	NM	Residual edema secondary to previous graft rejection/7
Sharma et al.[5] (2020)	F/50	PK	NM except for surgery	HM close to face	Multifocal infiltrates of varying size	Ceftazidime	NM	Regraft/NM
Rajarajan et al.[3] (2021) (Case 1)	F/62	PK	-Failed PK -Corneal bullae and irregular ocular surface -Topical corticosteroid therapy	CF at 10 cm	6 mm^2 Patchy yellow	Ciprofloxacin	CF at 10 cm	Resolved/45
Rajarajan et al.[3] (Case 2)	M/45	PK	-PK -Corneal bullae and irregular ocular surface -Topical corticosteroid therapy -Neurotrophic keratopathy	CF at 10 cm	2.7 mm^2 Dense white	Ofloxacin	CF at 10 cm	Resolved/30
Rajarajan et al.[3] (Case 3)	M/41	PK	-Failed PK -Loose sutures -Topical corticosteroid therapy -Neurotrophic keratopathy	20/50	2.7 mm^2 Patchy white	Gentamicin, imipenem and chloramphenicol	20/100	Resolved/40
Rajarajan et al.[3] (Case 4)	M/58	PK	-Failed PK -Corneal bullae and irregular ocular surface -Topical corticosteroid therapy -Neurotrophic keratopathy	CF at 10 cm	1 mm^2 Patchy white	Ofloxacin	CF at 10 cm	Resolved/9
Rajarajan et al.[3] (Case 5)	M/55	PK	-Failed PK -Corneal bullae and irregular ocular surface -Topical corticosteroid therapy	HM	64 mm^2 Dense yellow	Amikacin	HM	Graft edema/ NM
Rajarajan et al.[3] (Case 6)	F/70	PK		CF at 10 cm	20.8 mm^2 Dense yellow	Chloramphenicol	NLP	Phthisis/120
Rajarajan et al.[3] (Case 7)	M/50	PK	-Failed PK -Topical corticosteroid therapy	Light perception	27.9 mm^2 Dense yellow	Gentamicin	HM	Scar/110
Rajarajan et al.[3] (Case 8a)	M/50	PK	-Failed PK -Corneal bullae and irregular ocular surface -Topical corticosteroid therapy	20/400	27.44 mm^2 Dense yellow	Azithromycin	CF at 10 cm	Regraft/60
Rajarajan et al.[3] (Case 8b)	M/50	PK		CF at 10 cm	9.5 mm^2 Dense yellow	Azithromycin	CF at 10 cm	Failed PK/45
Rajarajan et al.[3] (Case 9)	M/61	NM	-Corneal bullae and irregular ocular surface -Topical corticosteroid therapy	20/600	5.25 mm^2 Patchy white	Gatifloxacin	20/60	Scar/45
Al Rasheed et al.[6] (2023)	F/19	Corneal cross-linking for keratoconus	-Non-adherence to post-procedure medications -Corneal epithelium debridement	20/200	7.8 mm^2 Ring-shaped	Amikacin and moxifloxacin	20/40	Stromal haze and subepithelial scar/30
Cintas et al. (present case)	F/77	None	-Severe DED -Topical corticosteroid therapy	20/32	2 mm^2 Dense white with calcium deposits	Amikacin, ciprofloxacin and ceftazidime	20/25	Stromal thinning and corneal haze/70

CF: Counting fingers, d: Days, DED: Dry eye disease, F: Female, HM: Hand motion, M: Male, NLP: No light perception, NM: Not mentioned, PK: Penetrating keratoplasty, VA: Visual acuity

Evidence indicates that both epithelial disruption and corticosteroid use are usually required for the development of *E. cloacae* keratitis. Close monitoring of severe DED patients may prevent such infections.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of the case and accompanying images.

Declarations

Authorship Contributions

Surgical and Medical Practices: V.C., Concept: N.C., E.R.P., G.J., V.C., Design: N.C., E.R.P., G.J., V.C., Data Collection or Processing: V.C., Analysis or Interpretation: N.C., E.R.P., G.J., V.C., Literature Search: N.C., E.R.P., G.J., V.C., Writing: N.C., E.R.P.

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Letter to the Editor Re: Preferred Retinal Locus in Juvenile Macular Dystrophy

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Dear Editor,

We read with great interest the study by Erbezci et al.,[1] which examined the topographic and functional characteristics of preferred retinal loci (PRLs) in juvenile macular dystrophy using scanning laser ophthalmoscopy and microperimetry. The age-stratified analysis and fixation-tracking methodology provide meaningful contributions to the literature on eccentric fixation in inherited maculopathies. However, several aspects merit closer scrutiny to clarify the implications for low-vision rehabilitation.

The authors interpret the age-related shift in PRLs from nasal to superior locations as evidence of cortical adaptation. However, this inference assumes a unidirectional maturational trajectory rather than considering the role of structural lesion dynamics. Because younger patients in the cohort also exhibited significantly larger lesion sizes, the posterior anatomical displacement of PRLs may be a consequence of constrained viable retinal area rather than active cortical optimization.[2] Clinically, this distinction matters because spontaneous superior locus acquisition may not reflect training potential but rather lesion permissiveness, which may vary between individuals.

Additionally, the interpretation that superiorly located PRLs confer functional advantages for reading and mobility warrants more cautious framing. While lower visual field scotomas (associated with superior loci) can indeed facilitate tasks requiring downward gaze, the study did not assess near-vision outcomes such as reading speed, critical print size, or text navigation accuracy. Without these data, the presumed functional superiority remains speculative.[3] A more robust conclusion would require integrating continuous-text performance metrics that directly quantify task-relevant visual efficiency.

Moreover, although fixation stability was quantified via dispersion metrics, the clinical relevance of the measured values remains ambiguous. The study did not clarify whether the reported fixation instability of 2.15±1.43 degrees crosses any threshold predictive of rehabilitation responsiveness. In patients undergoing eccentric viewing training, fixation stability below 2° has been associated with better functional gains.[4] Without such a reference point, the measured stability values are difficult to translate into practical decision-making for visual therapy planning.

The observed correlation between PRL-fovea distance and lesion area reinforces the anatomical basis of eccentric fixation, yet its application to rehabilitation remains underdeveloped. Specifically, it remains unclear whether PRL relocation is feasible when eccentricity exceeds certain angular thresholds. Identifying a critical eccentricity limit beyond which perceptual and oculomotor recalibration becomes less effective could aid in triaging candidates for intensive vision training protocols.[5]

In summary, while this study advances our anatomical understanding of PRL characteristics in juvenile macular

Keywords: Juvenile macular dystrophy, preferred retinal locus, eccentric fixation, visual rehabilitation, scanning laser ophthalmoscopy

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dystrophy, its translational contribution would be strengthened by linking structural metrics to task-specific visual outcomes and therapeutic thresholds. Clarifying these relationships may inform individualized strategies for optimizing residual vision in young patients navigating educational and occupational demands.

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Reply

We thank the correspondents for their thoughtful comments on our article and the opportunity to clarify several points regarding preferred retinal locus (PRL) location in juvenile macular dystrophy (JMD).

First, we agree that the age-related shift in PRL location should be interpreted cautiously. In our cohort, younger patients tended to have both larger lesions and nasally located PRLs farther from the fovea. Therefore, the observed shift from nasal to superior PRL locations may reflect, at least in part, anatomical constraints related to lesion geometry and the distribution of viable eccentric retina, rather than cortical adaptation alone. However, these mechanisms need not be mutually exclusive. In our data, PRL-fovea distance was positively correlated with lesion dimensions, whereas PRL location itself was not significantly associated with lesion size or PRL-lesion distance. This suggests that structural factors likely constrain PRL development, while the contribution of adaptive cortical mechanisms remains to be clarified. In this respect, our findings should be considered hypothesis-generating rather than mechanistic.[1]

Second, regarding the presumed functional advantage of superior PRLs, we agree that this interpretation should be framed cautiously. Our study did not directly assess task-based performance. Nevertheless, previous work suggests that some eccentric retinal locations may be more favorable than others for reading. Reading during eccentric viewing has been reported to be better with the superior retina than with the inferior retina, and reading has also been shown to be faster when text is presented in the inferior visual field than in the left visual field.[2,3] These findings are consistent with the possibility that, in some circumstances, a superior retinal PRL may be advantageous for horizontal reading. However, because our study did not include direct reading-related outcome measures, this interpretation remains inferential rather than directly demonstrated.

Third, we acknowledge that the clinical meaning of the measured fixation stability values remains limited in the absence of validated rehabilitation thresholds. Our study was retrospective and was designed primarily to describe fixation behavior at presentation rather than to predict responsiveness to rehabilitation.

Finally, we agree that the possibility of an eccentricity threshold beyond which perceptual and oculomotor recalibration becomes less effective is clinically relevant. However, our study was not designed to determine a critical angular limit for PRL relocation or trainability. Whether increasing eccentricity constrains later rehabilitation potential likely depends on multiple interacting factors, including residual retinal sensitivity, fixation stability, task demands, and individual neuroplastic capacity.[1,4]

We are grateful for these comments, which help refine the interpretation of our work. We agree that structural lesion characteristics, task-specific outcomes, and longitudinal behavioral adaptation should all be considered when evaluating PRL development in JMD.

Declarations

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