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Editorial

Celebrating the Third Year of the Journal of Archives of Ophthalmological Research

As we enter the third year of the Archives of Ophthalmological Research, we take a moment to reflect on the remarkable strides we've made since our inception. Over the past year, we celebrated significant milestones, such as publishing major research studies and fostering a thriving community of researchers and professionals. Your continued support has been instrumental, and as we move forward, we are thrilled to share several exciting developments with our readership.

This year, one of the most notable changes is the inclusion of international authors. This expansion marks an important step in broadening the scope of the research we publish, ensuring that our journal reflects a truly global perspective on ophthalmology. We are committed to promoting diversity in thought and research, and the addition of authors from around the world will significantly enrich the quality of our content.

In addition, we have renewed our editorial board to better meet the evolving needs of our community. The new board consists of highly respected and experienced experts from various fields of ophthalmology, bringing fresh perspectives, innovative research, and advanced expertise. This update will help us uphold the rigorous scientific standards and robust peer-review process that our journal is known for.

Looking ahead, our commitment to making the Journal of Archives of Ophthalmological Research a premier platform for scientific knowledge remains unwavering. We are dedicated to publishing impactful studies that advance our understanding of ophthalmic diseases and their treatments. As always, we rely on your continued contributions to help us reach this goal.

With these exciting changes in place, we begin this new year with renewed enthusiasm and commitment. We look forward to another year of enhanced collaboration, innovation, and progress in the field of ophthalmology.

Thank you for your steadfast support. Together, we will continue to push the boundaries of scientific discovery.

With our deepest respect,
Prof. Uğur ACAR
Editor-in-Chief

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Original Article

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Evaluation of the efficacy, safety, patient comfort, and preference of the fixed combination of brinzolamide 1%/timolol 0.5% in patients with pseudoexfoliation glaucoma

Hatice Ergün*[1], Özlem Evren Kemer[2]

[1]Department of Ophthalmology, Kayseri City Training and Research Hospital, Kayseri, Turkiye
[2]Department of Ophthalmology, Ankara Bilkent City Hospital, Ankara, Turkiye

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ABSTRACT

Aims: The efficacy and safety of the fixed combination of brinzolamide 1%/timolol 0.5% (BTFC) have previously been demonstrated in primary open-angle glaucoma (POAG). The aim of this study was to evaluate the efficacy, adverse effect profile, and patient preference of BTFC in patients with pseudoexfoliation glaucoma (PXG), whose treatment approach is similar to POAG but whose clinical management is more challenging for various reasons.

Methods: A total of 37 eyes of 27 patients followed with a diagnosis of PXG were retrospectively analyzed. Intraocular pressure (IOP) values during the previous treatment period, the untreated baseline period, and at 1, 3, and 6 months after initiation of BTFC were evaluated. In addition, the efficacy, adverse effects, and patient preference related to BTFC were assessed.

Results: BTFC achieved a significant reduction of 33.4%-37.2% in IOP compared with baseline in PXG patients (p<0.001), and this effect was sustained throughout the 6-month follow-up. The most frequently reported adverse effect associated with BTFC was burning–stinging sensation (77%). While 48.1% of patients rated BTFC as very good and 51.9% as good, 51.9% preferred BTFC, whereas 18.5% preferred their previous treatment.

Conclusion: The findings indicate that BTFC is an effective treatment option preferred by patients with PXG, owing to its comparable efficacy and adverse effect profile relative to other antiglaucomatous therapies.

Keywords: Pseudoexfoliation glaucoma, brinzolamide/timolol, primary open-angle glaucoma

INTRODUCTION

Pseudoexfoliation glaucoma (PXG) is one of the most common causes of secondary open-angle glaucoma, developing as a result of the accumulation of pseudoexfoliative fibrillar material in the anterior segment of the eye, and is generally characterized by higher intraocular pressure (IOP) levels and a more aggressive clinical course.[1] The treatment approach for patients with PXG is similar to that for patients with primary open-angle glaucoma (POAG). However, because PXG patients typically present with higher IOP levels at the time of diagnosis and exhibit greater 24-hour IOP fluctuations, their response to medical therapy is often poorer compared with POAG patients.[2] Therefore, fixed-combination therapies are frequently preferred over monotherapy in this patient group.

Although several treatment options are available, fixed-dose combinations are currently used more frequently in both POAG and PXG patients. Most studies evaluating these combinations in the literature have been conducted in POAG populations. In a study by Mary S. Galose et al.,[3] both the brinzolamide 1%/timolol 0.5% fixed combination (BTFC) and the dorzolamide 2%/timolol 0.5% fixed combination (DTFC) were reported to provide a significant and clinically meaningful reduction in IOP.[3] Another study evaluating BTFC demonstrated that it is a safe and effective treatment option for lowering IOP in patients with POAG.[4]

Studies focusing exclusively on PXG patients are limited in number. In a study including 60 patients diagnosed with PXG, both DTFC and BTFC were shown to be effective in reducing IOP.[5] In another study conducted by Mustafa Eliacık et al.,[6] DTFC was reported to achieve a significant reduction in IOP at the end of the third month in PXG patients. Although the efficacy of both fixed combinations in PXG has been demonstrated, differences in tolerability and effectiveness may influence patient preference. Studies conducted in POAG populations have shown that BTFC is better tolerated than DTFC; additionally, other studies have reported that BTFC is associated with less topical discomfort, improvement in signs of ocular surface disease, and potentially better treatment adherence compared with DTFC.[7,8]

*Corresponding Author: Hatice Ergün, haticeergun2022@gmail.com

Based on the available evidence, there is a lack of sufficient and comprehensive data in the literature evaluating the efficacy, tolerability, and patient preference of BTFC exclusively in PXG patients. Given that the IOP-lowering efficacy of both BTFC and DTFC has previously been demonstrated in PXG, and that BTFC has been reported to be better tolerated in POAG populations, it may be anticipated that BTFC would exhibit comparable tolerability and clinical efficacy in PXG patients, which may in turn influence patient preference.

The aim of the present study was to evaluate the IOP-lowering efficacy, adverse-effect profile, and patient preference of BTFC in patients with PXG, in comparison with other antiglaucomatous therapies.

METHODS

Ethics

This study was approved by the Clinical Researches Ethics Committee of Ankara Numune Training and Research Hospital (Date: 04.12.2013, Decision No: 56/2013). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Due to the retrospective nature of the study, the ethics committee waived the requirement for individual informed consent.

This study included 37 eyes of 27 patients who were followed in the Glaucoma Unit of our clinic with a diagnosis of PXG and treated with BTFC. Clinical and follow-up data were retrospectively reviewed from patient medical records. The patients included in the study had discontinued their treatments for various reasons and had not attended follow-up visits for at least 28 days; therefore, they could not be monitored during this period. Upon re-presentation, BTFC therapy was initiated in patients in whom elevated IOP was detected.

Patients were evaluated across a total of five distinct periods. The first period was defined as the phase during which antiglaucomatous treatments other than BTFC were used. The second period was defined as the baseline period, during which patients had completely discontinued all IOP-lowering therapies and had not attended follow-up for at least 28 days. Follow-up evaluations after the initiation of BTFC were conducted at 1 month, 3 months, and 6 months.

At all study periods, best-corrected visual acuity measured using the Snellen chart was recorded and converted to the logMAR scale for statistical analysis. Anterior segment examinations were performed using slit-lamp biomicroscopy, and angle assessments were carried out with a Goldmann gonioscopy lens. Fundus examinations were conducted using standard clinical methods. IOP measurements were performed in the morning hours (09:00-12:00) using Goldmann applanation tonometry.

At the sixth-month follow-up visit, patients were questioned regarding potential adverse effects related to BTFC use. Additionally, patients were asked to rate BTFC as “poor,” “moderate,” “good,” or “very good,” and to indicate their treatment preference between BTFC and their previous IOP-lowering therapy. In patients who discontinued BTFC, the reasons for treatment discontinuation were recorded.

Patients with a history of ocular trauma or intraocular surgery within the preceding six months, ocular infection or inflammation within the previous three months, uncontrolled diabetes mellitus or hypoglycemia, severe cardiovascular, renal, or hepatic disease, and pregnant patients were excluded from the study.

Statistical Analysis

The data were performed using IBM SPSS Statistics for Windows version 23.0. Continuous variables were expressed as mean±standard deviation and median [minimum-maximum], while categorical variables were presented as numbers and percentages. The normality of continuous variables was assessed using the Shapiro-Wilk test. Changes in IOP over time were analyzed using repeated-measures analysis of variance for normally distributed variables. The assumption of sphericity was evaluated using Mauchly’s test; when the sphericity assumption was violated, the Greenhouse-Geisser correction was applied. For variables that did not meet normality assumptions, the Friedman test was used. Post hoc pairwise comparisons between baseline or previous IOP-lowering therapy and BTFC at 1, 3, and 6 months were performed using Bonferroni or Dunn corrections, as appropriate. A p value <0.05 was considered statistically significant. A post hoc power analysis was performed. Assuming a moderate effect size (Cohen’s d=0.5), a two-sided alpha level of 0.05, and a paired-samples t-test design, the sample size of 37 eyes yielded a statistical power of 0.84.

RESULTS

The mean age of the patients included in the study was 68.7±9.7 years; 59.3% of the patients were male and 40.7% were female. The demographic characteristics of the patients, as well as visual acuity and biomicroscopic examination findings, are presented in detail in Table 1.

Table 1. Demographic characteristics, visual acuity, and biomicroscopic examination findings of the patients

Demographic characteristics		Treated eye	
Female, n (%)	11 (40.7)	Right, n (%)	6 (22.2)
Male, n (%)	16 (59.3)	Left, n (%)	11 (40.7)
Total patients, n (%)	27 (100)	Bilateral, n (%)	10 (37.03)
Age (years), mean (SD)	68.7±9.7	Visual acuity (LogMAR), mean (SD)	0.64±0.79
Hypertension, n (%)	11 (40.7)	Presence and type of cataract, n (%)	28 (75.6)
Diabetes mellitus, n (%)	7 (25.9)	Nuclear cataract, n (%)	25 (67.6)
Coronary artery disease, n (%)	5 (18.5)	Cortical cataract, n (%)	3 (8.1)
Thyroid disease, n (%)	3 (11.1)	Pseudophakia, n (%)	4 (10.8)
Rheumatoid arthritis, n (%)	1 (3.7)	Total eyes, n (%)	32 (86.5)
Family history of glaucoma, n (%)	10 (37.0)	Cup-to-disc ratio, mean (SD)	0.66±0.24
Smoking, n (%)	3 (11.1)		

SD: Standard deviation

In the pre-BTFC period, the most frequently used IOP-lowering agents were prostaglandin analogues, accounting for 29.7% of treatments. Evaluation of treatment regimens revealed that 37.8% of the patients were receiving monotherapy, 27.0% were treated with DTFC, 40.5% were receiving combination therapy, and 35.1% were on multiple-drug therapy. Subgroups of previous IOP-lowering treatments are summarized in Table 2.

Table 2. Subgroups and classification of previous intraocular pressure-lowering treatments

Treatment subgroup	Number of eyes, n (%)
None	2 (5.4)
PGA	11 (29.7)
Betaxolol 2.5%	3 (8.1)
DTFC	3 (8.1)
PGA/timolol 0.5%	5 (13.5)
DTFC+brimonidine 0.15%	2 (5.4)
PGA+brimonidine 0.15%	5 (13.5)
PGA+DTFC	3 (8.1)
PGA+dorzolamide 2%+brimonidine 0.15%	1 (2.7)
PGA+DTFC+brimonidine 0.15%	2 (5.4)
Total	37 (100)
Treatment category	**Number of eyes, n (%)**
Monotherapy	14 (37.8)
Combination therapy	15 (40.5)
DTFC-containing regimens	10 (27.0)
Multiple-drug therapy	13 (35.1)

DTFC: Dorzolamide 2%/timolol 0.5% fixed combination, PGA: Prostaglandin analogues (bimatoprost 0.03%, latanoprost 0.005%, travoprost 0.004%)

Compared with baseline IOP values, BTFC therapy resulted in statistically significant reductions in IOP at 1, 3, and 6 months, with decreases of 33.4%, 37.2%, and 36.4%, respectively ($p<0.001$ for all). In contrast, when compared with previous IOP-lowering therapies, reductions in IOP at 1, 3, and 6 months were 0.77%, 8.85%, and 7.19%, respectively, and these differences did not reach statistical significance ($p=0.482$, $p=0.051$, and $p=0.174$, respectively). All IOP values, as well as absolute and percentage changes, are presented in **Table 3**.

Adverse effects related to BTFC use were observed in approximately 33.3% of the patients, with the most frequently reported adverse effect being a burning-stinging sensation, accounting for 77.7% of reported events. All adverse effects associated with BTFC are listed in **Table 4**.

When patients evaluated BTFC in terms of comfort, all participants (100%) reported satisfaction with the treatment, rating it as good or very good. Accordingly, 51.9% of the patients indicated a preference for BTFC therapy. Findings related to comfort assessment and treatment preference are presented in **Tables 5**, **6** and **Figure**.

Table 4. Adverse effects observed after BTFC use

		n	%
Patients with adverse effects		9	33.3
Adverse effects	Blurred vision	2	22.2
	Metallic taste	1	11.1
	Burning-stinging sensation	7	77.7
	Ocular redness	2	22.2
	Dizziness	1	11.1

BTFC: Brinzolamide 1% / timolol 0.5% fixed combination

Table 5. Evaluation of BTFC in terms of comfort

Comparison with previous therapy	n	%
Very good	13	48.1
Good	14	51.9
Moderate	0	0
Poor	0	0

BTFC: Brinzolamide 1% / timolol 0.5% fixed combination

Table 6. Treatment preference of the patients

Treatment preference	n	%
BTFC	14	51.9
Previous IOP-lowering therapy	5	18.5
No preference	8	29.6

BTFC: Brinzolamide 1%/timolol 0.5% fixed combination, IOP: Intraocular pressure

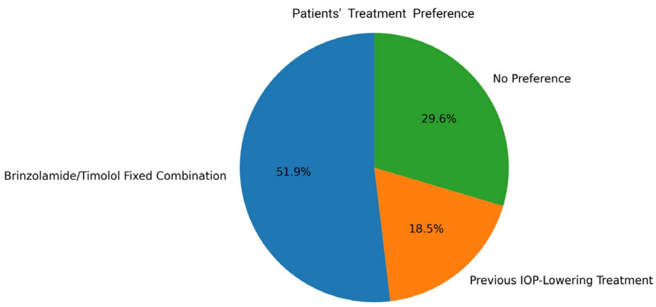

Figure. Treatment preference of the patients

IOP: Intraocular pressure

Table 3. Comparison of intraocular pressure values at 1, 3, and 6 months after initiation of BTFC according to baseline and previous therapy

Baseline		BTFC			p (baseline vs 1st month)	p (baseline vs 3rd month)	p (baseline vs 6th month)
		1st month	3rd month	6th month			
Mean IOP (mmHg Hg)	27.3±6.9	17.5±3.5	16.4±3.2	16.7±3.8			
Mean change in IOP (mmHg)		-9.84	-10.48	-10.21	p<0.001	p<0.001	p<0.001
Mean percentage change in IOP (%)		-%33.4	-%37.2	-%36.4			
Previous IOP-lowering treatment		BTFC			p (previous IOP-lowering therapy vs 1st month)	p (previous IOP-lowering therapy vs 3rd month) 1st month	p (previous IOP-lowering therapy vs 6th month) 3rd month
		1st month	3rd month	6th month			
Mean IOP (mmHg)	18.6±5.2	17.5±3.5	16.4±3.2	16.7±3.8			
Mean change in IOP (mmHg)		-1.14	-2.55	-2.27	p= 0.482	p=0.051	p=0.174
Mean percentage change in IOP (%)		-%0.77	-%8.85	-%7.19			

BTFC: Brinzolamide 1% / timolol 0.5% fixed combination, IOP: Intraocular pressure

DISCUSSION

The main finding of the present study is that BTFC may be considered a preferred treatment option among patients with PXG, given its comparable efficacy and adverse-effect profile when compared with other antiglaucomatous therapies.

PXG is a more severe and progressive form of glaucoma, characterized by higher IOP levels and marked fluctuations in the diurnal IOP curve; consequently, it exhibits a more resistant clinical course to medical therapy.[2] Although treatment is generally initiated with monotherapy, dual or multiple combination therapies are frequently required at an early stage, particularly in the management of PXG, to achieve lower and more stable IOP levels. DTFC and BTFC are commonly used in many glaucoma patients, either as direct fixed combinations or as components of multiple combination regimens added to other therapies. Consistent with the literature, our study demonstrated that most PXG patients were receiving combination or multiple therapies, with DTFC being the most frequently used agent among combination treatments. Previous studies including patients with PXG and POAG have shown that both DTFC and BTFC, which are widely used in combination therapy, provide effective IOP reduction.[5,9] Another study reported that BTFC is an effective treatment option and provides additional IOP reduction regardless of prior therapy.[10] In our study, BTFC therapy in patients with PXG was associated with a statistically significant reduction in IOP compared with baseline values. However, when BTFC was compared with previous IOP-lowering therapies, no statistically significant additional reduction in IOP was observed at any follow-up visit, indicating that the efficacy of BTFC was comparable rather than superior to that of prior treatments. Given the heterogeneity of prior treatment regimens and the absence of direct head-to-head drug comparisons, we believe that the efficacy outcomes observed after switching to BTFC should be interpreted with caution.

Although the efficacy of combination therapies has been well established, differences exist in their adverse-effect profiles. The majority of the available literature involves POAG and ocular hypertension (OHT) populations, in which PXG patients have often been evaluated only as a subgroup. In patients with POAG or OHT, DTFC and BTFC have been shown to provide comparable IOP-lowering efficacy; however, BTFC has been associated with less ocular irritation. Moreover, switching from DTFC to BTFC has been reported to be well tolerated, without negatively affecting IOP control or treatment adherence, and may represent an appropriate therapeutic alternative, particularly for glaucoma patients experiencing burning or stinging sensations.[11-14] Similarly, a common finding across other studies in comparable populations is that DTFC is more frequently associated with ocular irritation, whereas BTFC is more commonly linked to blurred vision.[15,16] Although the majority of the patients included in the study did not report any adverse effects, the most frequently reported adverse effect was a burning-stinging sensation, followed by blurred vision and ocular redness, both observed at similar frequencies. On the other hand, several studies have also evaluated the tolerability of these therapies and patient preference. In the study by Lanzl et al.,[10] the existing IOP-lowering treatments of patients diagnosed with POAG, OHT, and PXG were replaced with BTFC, and both IOP levels and treatment tolerability were assessed. At the end of the study, 87.2% of patients reported a positive treatment response (good/very good). When treatment preference was evaluated, 75.9% of patients indicated a preference for BTFC, 8.6% preferred to continue their previous therapy, and 15.5% reported no noticeable difference between treatments. In studies including POAG and OHT populations, the reported preference for BTFC has ranged from 60% to 79.2%,[16-18] and BTFC use has been associated with lower levels of patient-reported ocular discomfort.[18] In our study, all patients evaluated the transition to BTFC favorably, rating it as good or very good, and overall, nearly half of the PXG patients demonstrated a preference for BTFC over their prior therapies. The apparent discrepancy between the relatively high frequency of reported burning-stinging sensations and the universally favorable comfort ratings may be explained by the transient and mild nature of these symptoms. In addition, comfort was assessed as a global patient-reported outcome rather than a symptom-specific measure, which may have contributed to this observation. Furthermore, patients may have perceived these effects as less bothersome than those experienced with their previous treatments, particularly regimens involving DTFC or multiple topical agents. DTFC has a pH of 5.6, whereas BTFC has a pH of 7.2, which is more compatible with physiological ocular pH. This difference in pH may represent a potential explanation for the improved short-term ocular comfort and higher patient preference observed with BTFC in our study. Indeed, previous reports have suggested that the more pronounced ocular burning and stinging associated with DTFC use may be related to differences in pH.[19] Another possible contributing factor may be differences in the concentrations of the preservative benzalkonium chloride contained in combination formulations. Benzalkonium chloride has been shown to induce subclinical conjunctival inflammation and exacerbate ocular surface disease.[20] In our study, approximately one-third of patients had been using more than one topical preparation in their prior treatment regimens, which may have resulted in higher cumulative exposure to benzalkonium chloride. This increased exposure may have contributed to greater ocular irritation and, consequently, to a preference for BTFC therapy. In addition, switching from regimens involving two or more topical agents to a single fixed combination such as BTFC reduces the number of instilled drops, potentially improving ease of use and treatment adherence, which may further influence patient preference in favor of BTFC.

Limitations

This study has several limitations. First, its single-center, retrospective design and relatively small sample size may limit the generalizability of the findings. Second, the use of a non-randomized within-subject design, in which each patient served as their own control, together with the absence of a parallel control group, restricts the ability to perform direct head-to-head comparisons and to draw causal inferences regarding the superiority of BTFC over other antiglaucomatous therapies. In addition, the assessment of patient comfort and preference using subjective scales, rather than objective measures of ocular surface disease such as tear break-up time or ocular surface staining scores, necessitates cautious interpretation of conclusions suggesting greater acceptability of BTFC compared with other treatments.

Moreover, IOP measurements were obtained between 09:00 and 12:00. Given the well-documented diurnal fluctuations in IOP in PXG, peak IOP values may have been missed, which represents an additional limitation of the study. Furthermore, the frequent underrepresentation of PXG patients in the literature has resulted in limited availability of comparable data, making comprehensive comparisons with previous studies more challenging.

When these limitations are taken into account, the findings suggest that BTFC may represent a well-tolerated and patient-accepted therapeutic option in PXG; however, larger prospective controlled studies with greater sample sizes are required to confirm these observations.

CONCLUSION

In this study, the finding that BTFC demonstrates an efficacy and adverse-effect profile comparable to other antiglaucomatous therapies suggests that it may represent a suitable and potentially preferred treatment option for patients with PXG. In the existing literature, PXG patients have generally been evaluated within the broader context of POAG rather than as a distinct group. Accordingly, the present study is among the first to directly assess the efficacy, tolerability, and patient preference associated with BTFC specifically in patients with PXG.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Clinical Researches Ethics Committee of Ankara Numune Training and Research Hospital (Date: 04.12.2013, Decision No: 56/2013).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Author Contributions Concept: HE, ÖE; Design: HE, ÖE; Control: HE, ÖE; Data Collection and/or Processing: HE, ÖE; Analysis and/or Interpretation: HE, ÖE; Literature Review: HE, ÖE; Article Writing: HE, ÖE; Critical Review: HE, ÖE.

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Original Article

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Public interest in ophthalmic imaging: a Google Trends analysis of diagnostic modalities from 2005 to 2025

Elmas Yüksel Şükün*[1], Abdullah Şükün[2]

[1]Department of Ophthalmology, Alanya Training and Research Hospital, Antalya, Turkiye

[2]Department of Radiology, Başkent University Alanya Research and Application Center, Antalya, Turkiye

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ABSTRACT

Aims: This study aimed to evaluate the evolution of public interest in ophthalmic imaging modalities between 2005 and 2025 using Google Trends data, with comparisons across countries, languages, and disease-related contexts.

Methods: Google Trends was used to analyze relative search volume (RSV) data for eight ophthalmic imaging modalities: optical coherence tomography (OCT), optical coherence tomography angiography (OCTA), fluorescein angiography, fundus photography, ocular ultrasound, corneal topography, orbital computed tomography (CT), and orbital magnetic resonance imaging (MRI). Terms were searched in both Turkish and English. Five countries were assessed: Turkiye, the United States, Germany, India, and Japan. Compound Annual Growth Rate (CAGR) was calculated for each term. Comparative analyses were performed by language, disease focus (e.g., macular degeneration, diabetic retinopathy), and pre- versus post-COVID-19 periods.

Results: Most imaging terms showed a notable rise in RSV, particularly OCT, fundus photography, and OCTA. The highest CAGR was seen for OCT (+8.1%, India). Turkish terms had consistently lower RSV than their English equivalents, although substantial growth was observed for searches corresponding to OCT and fluorescein angiography after 2015. COVID-19 led to a temporary decline in search activity, followed by a strong rebound. Corneal topography and ocular ultrasound showed more modest but steadily increasing interest.

Conclusion: Public interest in ophthalmic imaging has significantly increased over two decades. The growing attention to OCT and OCTA reflects rising awareness of non-invasive retinal diagnostics. Lower interest in Turkish terms highlights the need to improve local-language health education. Digital data tools like Google Trends may serve as valuable instruments in tracking and enhancing ophthalmic public health awareness.

Keywords: Google trends, ophthalmic imaging, public awareness, digital epidemiology, health literacy

INTRODUCTION

Advancements in ophthalmic imaging have fundamentally transformed the diagnosis and monitoring of ocular diseases. Modalities such as optical coherence tomography (OCT), optical coherence tomography angiography (OCTA), fluorescein angiography, corneal topography, and ocular ultrasonography are now integral components of contemporary ophthalmic practice, particularly in the evaluation of retinal and anterior segment disorders. Despite their widespread clinical use, the extent to which the general public is aware of these imaging technologies - and how this awareness has evolved over time-remains incompletely understood.[1-4]

With the increasing reliance on internet-based resources for health-related information, online search behavior has emerged as a valuable proxy for assessing public interest and awareness. Google Trends, a freely accessible tool that analyzes the relative popularity of search queries over time, has been increasingly utilized in digital epidemiology to explore public engagement with health conditions, diagnostic tools, and medical services.[5-7] Several studies have applied this approach in ophthalmology, primarily focusing on specific diseases or clinical services; however, data specifically examining imaging-focused search trends across multiple ophthalmic modalities remain limited.

The present study aims to evaluate temporal trends in public interest in major ophthalmic imaging modalities using Google search data from 2005 to 2025. By analyzing variations across countries, languages, and disease-related contexts, this study seeks to provide a comprehensive overview of how public

*Corresponding Author: Elmas Yüksel Şükün, dr.elmas.yuksel@gmail.com

awareness of ophthalmic imaging technologies has evolved over two decades. Unlike prior studies that have focused on individual diseases or isolated diagnostic tools, this analysis systematically compares multiple imaging modalities within a unified digital epidemiology framework, thereby contributing novel insights into public engagement with ophthalmic diagnostics.

METHODS

Ethics

This study used publicly available, aggregated data from Google Trends and did not involve any human participants or identifiable personal information. Therefore, ethics committee approval and informed consent were not required, in accordance with the principles of the Declaration of Helsinki.

Study Design

This study was designed as a retrospective digital epidemiology analysis based on publicly available Google Trends data collected between January 2005 and December 2025. The study followed established principles of infodemiology and digital health surveillance.

Search Term Selection

Ophthalmic imaging modalities were selected based on their widespread clinical use in routine ophthalmic practice and their established roles in the diagnosis and monitoring of retinal, anterior segment, and orbital diseases. The final list of search terms was determined through a review of ophthalmology textbooks, clinical guidelines, and prior Google Trends-based ophthalmology studies.

The following imaging modalities were analyzed using both English and Turkish equivalents to capture language-related differences in public search behavior:

- Optical coherence tomography
- Optical coherence tomography angiography
- Fluorescein angiography
- Fundus photography
- Ocular ultrasound
- Corneal topography
- Orbital computed tomography
- Orbital magnetic resonance imaging

In addition, selected disease-related search terms commonly associated with these imaging modalities were included for exploratory descriptive comparison with modality-specific search trends: macular degeneration, diabetic retinopathy, glaucoma, retinopathy of prematurity (ROP), optic neuritis, and eye tumor.

Country Selection

Five countries-Turkiye, the United States, Germany, India, and Japan-were selected to represent diverse geographic regions, healthcare systems, population sizes, and levels of digital health engagement. These countries were chosen to allow comparison between developed and developing healthcare settings and to capture variation in ophthalmic service utilization and public health awareness across different regions.

Data Collection

Relative Search Volume (RSV) data were obtained from Google Trends (https://trends.google.com). Search parameters were standardized as follows:

- Time range: 2005-2025
- Regions: Turkiye, United States, Germany, India, Japan
- Category: Health
- Search type: Web search

RSV values were normalized by Google Trends on a scale from 0 to 100, representing the relative popularity of each term over time.

Pre-and Post-COVID-19 Period Definition

To assess the potential impact of the COVID-19 pandemic on public interest in ophthalmic imaging, the study period was divided into two segments: pre-COVID (January 2005 to December 2019) and post-COVID (January 2020 to December 2025). This classification was based on the global recognition of COVID-19 as a public health emergency by the World Health Organization in early 2020. The pandemic caused widespread disruptions to routine ophthalmologic care and may have influenced the volume and pattern of health-related search behaviors. Therefore, this segmentation allows for a clearer understanding of the pandemic's effect on public interest trends.

Statistical and Trend Analysis

RSV time-series data were extracted from Google Trends and visualized to evaluate temporal trends in public interest. Long-term growth patterns were quantified using the Compound Annual Growth Rate (CAGR), which was calculated as follows:

CAGR=(RSV_final/RSV_initial)^(1/n)-1

where RSV_final represents the RSV at the end of the study period, RSV_initial represents the RSV at the beginning of the study period, and n denotes the number of years between these two time points. CAGR was used to summarize the overall direction and magnitude of long-term trends while reducing the influence of short-term or seasonal fluctuations.

Comparative analyses were performed across:

- Imaging modality versus disease-related search terms
- English versus Turkish search queries
- Pre-COVID-19 (2005-2019) and post-COVID-19 (2020-2025) periods

The pre- and post-pandemic division was applied to evaluate the impact of COVID-19-related healthcare disruptions on public interest in ophthalmic imaging.

CAGR values were primarily intended to describe within-modality temporal trends rather than to enable direct comparisons between modalities with different data availability periods (e.g., OCTA, which became searchable only after 2016). Therefore, cross-modality comparisons of growth rates should be interpreted with caution.

Readability Analysis

To assess the accessibility of online ophthalmic imaging information, the readability of content containing the terms "OCT" and "OCTA" on the top 10 Turkish-language eye health websites was evaluated. Readability was measured using the Ateşman Readability Formula and the Flesch-Kincaid Grade Level, both of which are validated tools for assessing text complexity.[8,9]

RESULTS

General Search Trends for Imaging Modalities

Between 2005 and 2025, global interest in ophthalmic imaging modalities demonstrated a steady and significant upward trend. Among all terms, OCT had the highest RSV, with particularly high interest observed in India and the United States.

Significant increases were also noted in fundus photography, fluorescein angiography, OCT angiography (OCTA), and corneal topography, especially after 2010. Although OCTA became visible in the Google Trends database only after 2016, it exhibited a rapid rise in search volume over a short period.

In Turkiye, search volumes for the relevant terms were generally lower compared to their English counterparts. However, search terms corresponding to OCT and fluorescein angiography demonstrated a notable upward trend after 2015.

Corneal topography and ocular ultrasonography had relatively lower RSV values, but their trend lines indicated a gradually increasing level of public awareness.

The updated CAGR values based on 2005–2025 data and the countries with the highest growth are summarized in Table.

Table. CAGR by term (2005-2025) and country with highest growth

Imaging modality	CAGR (2005-2025)	Country with highest growth
OCT	+8.1%	India
Fundus photography	+5.6%	United States
Fluorescein angiography	+3.4%	Turkiye
OCTA	+3.1%*	Germany
Corneal topography	+2.7%	Japan
Ocular ultrasound	+2.2%	India
Orbital CT	+1.6%	Turkiye
Orbital MRI	+0.9%	Germany

CAGR: Compound Annual Growth Rate, OCT: Optical coherence tomography, OCTA: Optical coherence tomography angiography. *OCTA data available only after 2016

DISCUSSION

This study examined long-term patterns in online search interest for ophthalmic imaging modalities using Google Trends data from 2005 to 2025. Consistent with findings from earlier digital epidemiology studies, our results indicate a marked increase in search activity related to retina-focused diagnostic tools-particularly OCT, fluorescein angiography, fundus photography, and more recently, OCTA.[10,11] Importantly, Google Trends reflects online search behavior and relative interest rather than validated health literacy, clinical utilization, or diagnostic uptake; therefore, these results should be interpreted as changes in public information-seeking behavior rather than direct evidence of increased use or understanding of imaging modalities. In contrast to prior studies that focused on general ophthalmology terms or specific conditions, the present study uniquely emphasizes the diagnostic modality level, offering modality-based insights across multiple countries and languages.

OCT emerged as the most frequently searched term in all regions, which is consistent with its widespread use in contemporary retinal imaging. OCTA, though visible in Google Trends only after 2016, exhibited rapid growth-suggesting increasing online information-seeking related to non-invasive imaging of retinal microvasculature, especially in the context of age-related macular degeneration (AMD) and diabetic retinopathy.[12,13]

Interestingly, corneal topography showed the highest CAGR in Japan. This trend may be linked to the rising demand for refractive surgeries such as LASIK and implantable contact lenses (ICL), as well as early detection of corneal ectatic disorders like keratoconus.[14] Similarly, ocular ultrasound had a notable growth rate in India, likely reflecting the continued relevance of low-cost, accessible imaging technologies in low-resource settings.[15]

In Turkiye, online search interest in imaging modalities has increased substantially since 2015, particularly for OCT and fundus photography. This pattern may reflect expanding access to retinal diagnostics, increased digital outreach by private hospitals, and greater dissemination of visual medical content through social media. However, the RSV of Turkish-language search terms remained lower than their English counterparts, which may relate to a preference for English medical terminology, bilingual search behavior, and clinician-driven information seeking using standard English terms, as well as the limited availability of local-language ophthalmic resources.[16]

Moreover, the readability analysis may suggest that a substantial portion of Turkish-language ophthalmic resources requires relatively advanced reading levels, which could influence online information-seeking patterns and may partly relate to the lower RSV observed for Turkish-language queries.

A temporary decline in RSV was observed during the early phase of the COVID-19 pandemic, aligning with widespread disruptions in outpatient services and public hesitancy toward non-urgent healthcare visits. This observation supported our pre-/post-COVID segmentation. The increase in search activity after 2021 suggests renewed health information-seeking related to ophthalmic diagnostics following the acute phase of the pandemic.[6]

Limitations

This study is subject to several limitations inherent to Google Trends-based analyses. First, search data reflect public interest but not actual clinical utilization or diagnosis. Second, Google Trends does not provide demographic information such as age or gender, limiting interpretability. Third, only a selected set of keywords was included, potentially excluding related queries using synonyms or informal language. Additionally, other popular search engines (e.g., Yandex, Baidu) were not assessed, potentially limiting generalizability in certain regions. Lastly, newer technologies like OCTA were not searchable before 2016, limiting long-term comparison. Accordingly, CAGR should be interpreted primarily as a within-modality summary of long-term trend direction rather than for direct comparisons between modalities with different availability periods.

In addition, disease-related search terms were included for exploratory descriptive comparison only; no formal statistical association analyses were performed between specific diseases and imaging modalities.

CONCLUSION

This study shows an overall increase in online search interest in ophthalmic imaging modalities over the past two decades, particularly for non-invasive retinal techniques such as OCT and OCTA. The analysis also indicates differences across countries and languages, including lower relative search activity for Turkish-language terms. The temporary decline during the early COVID-19 period and subsequent rebound likely reflect the pandemic's impact on health information-seeking behavior. Importantly, these findings represent changes in search behavior and relative interest rather than validated health literacy, clinical utilization, or diagnostic uptake. Nevertheless, digital data tools such as Google Trends may be useful for monitoring public information-seeking patterns and informing targeted ophthalmic health communication strategies.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study used publicly available, aggregated data from Google Trends and did not involve any human participants or identifiable personal information. The refore, ethics committee approval were not required.

Informed Consent

This study used publicly available, aggregated data from Google Trends and did not involve any human participants or identifiable personal information. Therefore, informed consent was not required.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

Concept: EYŞ, AŞ; Design: EYŞ; Control/Supervision: EYŞ; Data Collection and/or Processing: AŞ; Analysis and/or Interpretation: EYŞ; Literature Review: EYŞ, AŞ; Writing the Article: EYŞ; Critical Review: EYŞ, AŞ.

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Review

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The retinal pigment epithelium: the silent guardian and mother of photoreceptors

Mehmet Çıtırık
Department of Ophthalmology, Ankara Etlik City Hospital, Ankara, Turkiye

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ABSTRACT

The retinal pigment epithelium (RPE) is a highly specialized, polarized monolayer that sustains photoreceptor survival through metabolic coupling, chromophore regeneration, phagocytosis, ion and fluid transport, immune regulation, and trophic factor secretion. Although historically viewed as a structural support layer, modern molecular, imaging, and therapeutic evidence positions the RPE as the central regulator of outer retinal homeostasis. This review synthesizes structural biology, developmental polarity, cellular stress responses, retinal degenerative diseases, imaging biomarkers, and emerging therapies through a unifying maternal paradigm. We propose that the RPE functions biologically as the "mother" of photoreceptors-nourishing, cleansing, protecting, and responding dynamically to injury. Clinical and experimental data from age-related macular degeneration (AMD), retinitis pigmentosa (RP), Stargardt disease, and RPE-targeted gene therapy support the conceptual re-centering of retinal disease around RPE dysfunction.

Keywords: Phagocytosis, photoreceptor support, retinal pigment epithelium, visual cycle, vitamin A metabolism

INTRODUCTION

The vertebrate retina is frequently described as a neuronal tissue optimized for phototransduction. However, photoreceptors exist in a uniquely dependent relationship with the retinal pigment epithelium. Strauss1 described the retinal pigment epithelium (RPE) as indispensable for visual function, emphasizing that photoreceptors cannot sustain phototransduction without RPE-mediated support. Bok[2] earlier characterized the RPE as a "versatile partner in vision," highlighting its multifaceted responsibilities.

Unlike neurons supplied by direct vasculature, photoreceptors lack an intrinsic blood supply and rely entirely on the RPE for nutrient delivery, waste removal, chromophore recycling, and environmental regulation.[1,3] Each RPE cell supports dozens of photoreceptors, establishing a marked asymmetry of dependence.[3]

This structural and metabolic interdependence supports a maternal conceptualization: the RPE sustains photoreceptor survival through continuous caregiving functions. Disease states frequently reveal that RPE dysfunction precedes and amplifies neuronal degeneration.

STRUCTURAL ARCHITECTURE

Outer Blood-Retina Barrier

The RPE forms the outer blood-retina barrier (oBRB) via apicolateral tight junctions composed of claudins, occludin, and zonula occludens (ZO-1).[3,4] This barrier establishes immune privilege and regulates molecular exchange between the choroidal circulation and neural retina.[1,4] Barrier breakdown is an early feature of age-related macular degeneration (AMD) and inflammatory retinal disease.[1-4] Disruption of ZO-1 and cytoskeletal reorganization compromises selective permeability and promotes edema.

Apical Microvilli and Photoreceptor Coupling

The apical RPE surface extends elongated microvilli that ensheath photoreceptor outer segments, expanding surface area approximately threefold.[3,5] These structures facilitate retinoid exchange, ion regulation, and phagocytosis.

A distinctive feature of RPE polarity is the apical localization of Na^+/K^+-ATPase, reversed relative to classical epithelia.[3] This polarity adaptation optimizes ion transport within the subretinal space.

Corresponding Author: Mehmet Çıtırık, mcitirik@hotmail.com

Basal Infoldings and Bruch's Membrane Interface

Basal infoldings form a labyrinthine interface with Bruch's membrane and the choriocapillaris, increasing membrane surface area for nutrient transport.[1,3] Glucose, retinoids, and water traverse this interface via glucose transporters (GLUT) transporters, aquaporins, and ion channels.[1,6]

Kirchhof and Ryan[7] demonstrated differential permeance between retina and RPE, establishing hydrostatic forces that contribute to retinal adhesion. Age-related thickening of Bruch's membrane impairs exchange and predisposes to AMD.[8,9] These structural specializations and their functional and pathological correlates are summarized in **Table 1**.

Table 1. Structural specializations of the RPE and functional significance

Structural domain	Key components	Functional role	Disease relevance
Tight junctions	Claudins, ZO-1	Outer blood-retina barrier	AMD barrier failure
Apical microvilli	Na^+/K^+-ATPase, CRALBP	Visual cycle, ion balance	RP, AMD
Basal infoldings	GLUT-1, aquaporins	Nutrient & water exchange	Bruch's thickening
Melanosomes	Melanin	Light absorption	Aging depigmentation

AMD: Age-related macular degeneration, RP: Retinitis Pigmentosa

FUNCTIONAL BIOLOGY: THE MATERNAL TASKS

Visual Cycle and Vitamin A Metabolism

Phototransduction requires continuous regeneration of 11-cis-retinal. The RPE mediates this process through RPE65-dependent isomerization.[1,6] Mutations in RPE65 result in Leber congenital amaurosis and autosomal recessive retinitis pigmentosa (RP).[6]

The success of RPE65 gene therapy confirms that restoration of RPE metabolism partially rescues photoreceptor function, even after significant degeneration.[6]

Phagocytosis of Outer Segments

Photoreceptors shed distal outer segment discs daily. The RPE recognizes these membranes via αvβ5 integrin and activates Mer Tyrosine Kinase (MerTK) to initiate engulfment.[3,5] Failure of this pathway leads to accumulation of debris and secondary degeneration, as seen in the Royal College of Surgeons (RCS) rat model.[3] Lysosomal degradation intersects with autophagy. Impairment promotes lipofuscin accumulation and oxidative injury.[4,6]

Ion, Fluid, and Metabolic Coupling

The RPE maintains ionic homeostasis through Na^+/K^+-ATPase, Kir7.1 channels, chloride transporters, and aquaporins.[1,6] It delivers glucose to photoreceptors and removes lactate via monocarboxylate transporters.[1] Disruption results in subretinal fluid accumulation and detachment.[7]

Immune Modulation and Growth Factor Secretion

The RPE secretes vascular endothelial growth factor (VEGF) basally to support the choriocapillaris and pigment epithelium-derived factor (PEDF) apically to protect neurons.[4] It expresses complement regulators and inflammasome components such as NLR family pyrin domain containing 3 (NLRP3).[4] Chronic complement activation and inflammasome signaling contribute to AMD progression.[4,9] These interdependent maternal functions of the RPE-spanning retinoid cycling, phagocytosis, metabolic transport, and immune regulation-are schematically integrated in **Figure 1**.

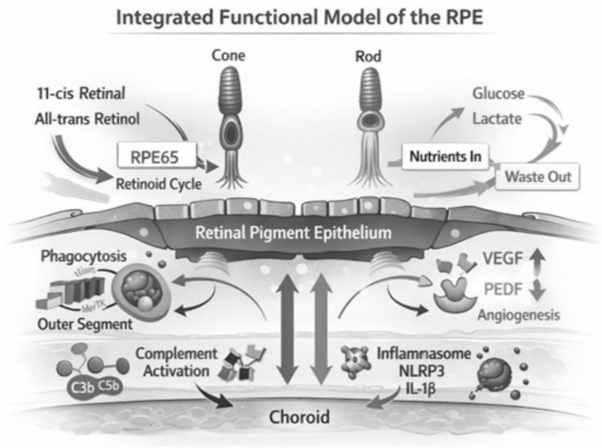

Figure 1. Integrated functional model of the RPE

Molecular Heterogeneity Revealed by Single-Cell Transcriptomics

Recent advances in single-cell RNA sequencing (scRNA-seq) and spatial transcriptomic technologies have revealed that the RPE is not a completely uniform epithelial layer but exhibits regional and functional heterogeneity. Transcriptomic analyses demonstrate differences in metabolic gene expression, oxidative stress responses, and visual cycle components across macular and peripheral RPE populations. Spatial mapping within intact retinal tissue further shows gradients of metabolic, inflammatory, and transport-related gene expression across the RPE layer. Notably, macular RPE displays distinct transcriptional signatures associated with lipid metabolism, mitochondrial function, oxidative stress resistance, and complement regulation. These regional molecular differences may contribute to the selective vulnerability of the macula in AMD and reinforce the concept that the RPE functions as a dynamic regulatory interface rather than a passive support layer.[10]

Aging: Maternal Exhaustion and Progressive Functional Decline of the RPE

The RPE operates under intense oxidative stress due to high oxygen consumption and light exposure.[1,9] With aging, mitochondrial Deoxyribonucleic acid (DNA) damage accumulates, reducing Adenosine triphosphate (ATP) production and increasing reactive oxygen species.[6]

Lipofuscin accumulation-particularly N-retinyl-N-retinylidene ethanolamine (A2E)-impairs lysosomal acidification and proteolysis.[6,9] Boulton and Dayhaw-Barker9 described age-related decline in RPE pigmentation and topographic vulnerability.

Recent metabolomic studies further highlight the metabolic specialization of the RPE. The RPE functions as a metabolic hub that coordinates glucose transport, lipid recycling, and mitochondrial oxidative phosphorylation. Mitochondrial biogenesis and quality control mechanisms are critical for sustaining ATP production required for phagocytosis and ion transport. Disruption of mitochondrial homeostasis has been increasingly implicated in early AMD pathogenesis, linking metabolic insufficiency with oxidative injury and impaired autophagy.[11]

Complement dysregulation further promotes sublethal injury.[4] Together, oxidative stress, lysosomal dysfunction, and immune activation erode RPE polarity and function. These converging mechanisms of oxidative, lysosomal, and immune-mediated injury and their structural consequences are summarized in **Table 2**.

Table 2. Mechanisms of age-related RPE degeneration

Mechanism	Molecular drivers	Structural consequence	Clinical outcome
Oxidative stress	ROS, mtDNA damage	Mitochondrial loss	Early AMD
Lipofuscin	A2E	Lysosomal dysfunction	Geographic atrophy
Complement activation	CFH variants	Membrane injury	Drusen
Inflammasome activation	NLRP3	Pyroptosis	RPE atrophy

DNA: Deoxyribonucleic acid, AMD: Age-related macular degeneration, A2E: N-retinylidene-N-retinylethanolamine, CFH: Complement factor H

Retinitis Pigmentosa: Migration as Maternal Response

In most forms of RP, photoreceptor degeneration precedes RPE pathology.[1] Histopathologic studies demonstrate that bone-spicule pigmentation results from RPE migration into the neural retina following photoreceptor loss.[1] Loss of photoreceptor-derived trophic signaling destabilizes RPE polarity and adhesion.[1-3] Detached RPE cells transdifferentiate and deposit melanin along retinal vessels. Within the maternal framework, this migration represents a reactive and maladaptive attempt to engage dying photoreceptors.[1-4] This sequential process of photoreceptor apoptosis, RPE polarity loss, intraretinal migration, and bone-spicule pigmentation is schematically illustrated in **Figure 2**.

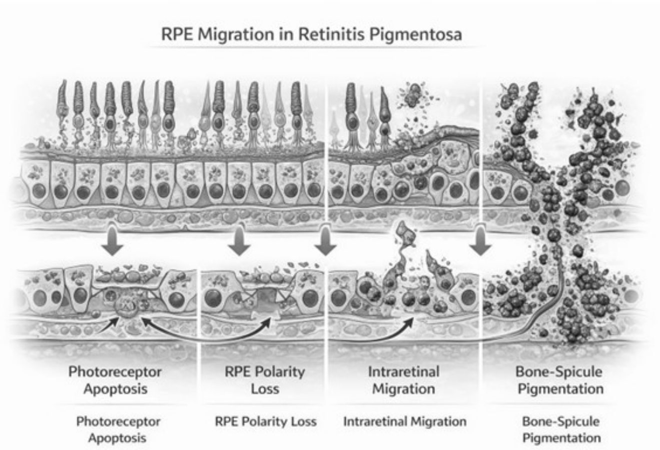

Figure 2. RPE migration in retinitis pigmentosa

RPE DYSFUNCTION IN DEGENERATIVE AND PROLIFERATIVE RETINAL DISEASES: MATERNAL FAILURE ACROSS PATHOLOGIES

If RP illustrates reactive maternal migration following photoreceptor death, age-related macular degeneration, pathologic myopia, and proliferative disorders illustrate progressive maternal exhaustion, mechanical stress, and maladaptive remodeling. Across these distinct clinical entities, a unifying principle emerges: RPE dysfunction destabilizes the outer retinal ecosystem.

Age-Related Macular Degeneration: Progressive Maternal Exhaustion

AMD represents the most extensively studied example of RPE-driven retinal degeneration. Although photoreceptor loss defines advanced disease, substantial evidence indicates that RPE dysfunction precedes and drives neuronal degeneration.[1,4,9] Aging RPE cells accumulate lipofuscin, particularly A2E, derived from incompletely degraded outer segment material.[6,9] Lipofuscin impairs lysosomal acidification, inhibits proteolytic enzymes, and generates reactive oxygen species under light exposure.[6] Concurrent mitochondrial DNA damage reduces ATP production and amplifies oxidative stress.[4,6] These changes compromise phagocytosis, visual cycle efficiency, and barrier integrity.

At the level of Bruch's membrane, age-related thickening and accumulation of basal deposits impair metabolic exchange between choriocapillaris and RPE.[9] Reduced permeability limits glucose delivery and waste removal, leading to chronic metabolic insufficiency. Complement dysregulation further accelerates RPE injury. The RPE expresses complement components and regulators; genetic variants affecting complement control predispose to sublethal RPE damage and drusen formation.[4] Chronic activation of the NLRP3 inflammasome promotes IL-1β release and pyroptotic cell death.[4]

In neovascular AMD, loss of RPE polarity disrupts directional secretion of VEGF and PEDF.[4] Normally, VEGF is secreted basally to support the choriocapillaris, while PEDF is secreted apically to maintain neuroprotection.[4] Polarity failure shifts this equilibrium toward pathologic angiogenesis.

Thus, AMD may be conceptualized not primarily as photoreceptor disease but as progressive maternal exhaustion culminating in secondary photoreceptor degeneration.

Pathologic Myopia: Mechanical Stretch and Maternal Thinning

Pathologic myopia introduces a distinct but equally revealing model of RPE vulnerability. Progressive axial elongation imposes chronic mechanical stretch on the RPE-Bruch's membrane-choroid complex.

Mechanical thinning of the RPE compromises barrier integrity and reduces metabolic buffering capacity. Bruch's membrane attenuation impairs nutrient transport and predisposes to focal atrophy. Loss of RPE melanin with age further reduces photoprotective capacity.[12]

Stretch-induced stress may alter RPE polarity and VEGF secretion patterns, increasing susceptibility to myopic choroidal neovascularization. In this context, maternal failure is not primarily metabolic but biomechanical: structural deformation disrupts the caregiving interface.

Proliferative Disorders: Loss of Maternal Identity

In proliferative vitreoretinopathy (PVR), RPE cells detach from Bruch's membrane, lose epithelial polarity, and undergo epithelial-mesenchymal transition (EMT).[3,4] Tight junction proteins such as ZO-1 are downregulated, cytoskeletal architecture reorganizes, and cells acquire migratory and contractile phenotypes.[3,4]

This represents not simply dysfunction but identity transformation. The RPE ceases to function as a polarized caregiver and becomes a fibrogenic participant in membrane formation. Such transdifferentiation illustrates the fragility of epithelial identity when polarity and environmental cues are lost.

Similarly, in diabetic retinopathy, inflammatory cytokines and hyperglycemic stress disrupt tight junctions and impair autophagy.[4,6] Although classically vascular, diabetic retinal disease includes significant RPE barrier compromise, contributing to edema.

Across AMD, pathologic myopia, and proliferative disease, a shared principle emerges: disruption of RPE polarity, metabolic competence, or structural integrity destabilizes photoreceptor survival. The shared and disease-specific mechanisms of RPE dysfunction across these conditions are comparatively summarized in **Table 3**.

Table 3. RPE-centered pathophysiology across retinal diseases

Disease	Primary stressor	RPE dysfunction	Downstream consequence
AMD	Aging, complement dysregulation	Oxidative stress, lipofuscin, polarity loss	Geographic atrophy, CNV
Pathologic Myopia	Mechanical stretch	RPE thinning, VEGF imbalance	Atrophy, CNV
PVR	Inflammation, trauma	EMT, polarity loss	Fibrotic membranes
Diabetic Retinopathy	Hyperglycemia	Barrier breakdown, autophagy decline	Edema

AMD: Age-related macular degeneration, CNV: Choroidal neovascularization, PVR: Proliferative vitreoretinopathy, EMT: eEpithelial-mesenchymal transition

IMAGING THE RPE INTERFACE: VISUALIZING MATERNAL STRESS IN VIVO

Advances in multimodal retinal imaging have transformed the study of the RPE from a largely histologic discipline into a dynamic, in vivo science. Modern imaging techniques allow direct visualization of RPE morphology, polarity integrity, pigment distribution, and metabolic stress. Importantly, these technologies often detect RPE dysfunction before irreversible photoreceptor loss becomes clinically apparent.

Optical Coherence Tomography (OCT): Structural Integrity of the RPE Band

Spectral-domain and swept-source optical coherence tomography (OCT) provide high-resolution cross-sectional imaging of the outer retina and RPE–Bruch's membrane complex.[13,14] On OCT, the RPE appears as a hyperreflective band beneath the photoreceptor outer segments. Disruption, attenuation, or irregularity of this band is strongly associated with outer retinal degeneration.[14]

In AMD, OCT demonstrates several hallmark manifestations of RPE dysfunction, including: Pigment epithelial detachment (PED), Subretinal hyperreflective material, Focal RPE elevation, Geographic atrophy with complete RPE loss, Outer retinal tubulations secondary to chronic degeneration.[14]

Pigment epithelial detachment reflects altered hydrostatic and osmotic balance across the RPE-Bruch's membrane interface.[1,4] When metabolic exchange is impaired, fluid accumulates beneath the RPE, separating it from Bruch's membrane. This mechanical separation compromises polarity and disrupts directional secretion of trophic factors.

In advanced geographic atrophy, OCT reveals complete absence of the RPE band with increased choroidal signal transmission due to loss of melanin-containing cells.[4,9] These structural changes precede and predict overlying photoreceptor collapse. Thus, OCT provides a direct window into maternal structural integrity.

Fundus Autofluorescence (FAF): Mapping Metabolic Load

Fundus autofluorescence (FAF) exploits the intrinsic fluorescence of lipofuscin within RPE lysosomes.[6,15] Because lipofuscin accumulates as a byproduct of incomplete phagocytosis of photoreceptor outer segments, FAF serves as a metabolic map of RPE stress. Increased autofluorescence corresponds to lipofuscin overload and lysosomal dysfunction.[6,15] In contrast, decreased autofluorescence indicates RPE atrophy and cell loss. In Stargardt disease and AMD, patterned hyperautofluorescence frequently surrounds areas of geographic atrophy, suggesting zones of heightened metabolic strain preceding cell death.[6] These findings support the concept that lysosomal exhaustion is an early marker of maternal failure. FAF therefore visualizes not simply structure, but metabolic burden.

Multi-Contrast OCT and Melanin Mapping

Beyond conventional reflectivity imaging, multi-contrast OCT (MC-OCT) allows three-dimensional quantification of melanin within the RPE.[13,16] Miura et al[13] demonstrated that serous PED in AMD is associated with regional increases in RPE melanin thickness (≥70 µm), termed "RPE70".

This thickening likely reflects hypertrophic or activated RPE responding to mechanical and metabolic stress. In slope regions of PED, melanin redistribution may represent early remodeling before irreversible atrophy. Because melanin plays a critical role in light absorption and oxidative buffering, quantitative melanin mapping offers a functional biomarker of photoprotective capacity. MC-OCT thus extends structural imaging into pigment physiology.[12,16]

Adaptive Optics and Cellular-Level Visualization

Adaptive optics scanning laser ophthalmoscopy (AO-SLO) permits visualization of individual RPE cells in vivo.[4,18] In the healthy retina, RPE cells exhibit a regular hexagonal mosaic. Aging and degeneration are associated with: loss of hexagonal geometry, cell enlargement (compensatory hypertrophy), patchy mosaic disruption. These microstructural alterations reflect polarity destabilization and epithelial stress. AO imaging therefore captures early architectural breakdown of the maternal interface.[4,18]

Functional Testing: Visual Cycle Assessment

Structural imaging is complemented by functional testing of RPE-dependent processes. Dark adaptation kinetics provide a sensitive measure of visual cycle efficiency.[1] Because regeneration of 11-cis-retinal depends on RPE65-mediated enzymatic activity, delayed dark adaptation represents impaired maternal metabolic function. Electrooculography (EOG), which measures the Arden ratio, reflects RPE ion transport and barrier activity.[1] Reduced Arden ratios are characteristic of diffuse RPE dysfunction. Functional impairment often precedes overt structural collapse, reinforcing the importance of early RPE-directed assessment. The principal structural, metabolic, and functional imaging biomarkers of RPE dysfunction are summarized in Table 4.

Table 4. Imaging and functional biomarkers of RPE dysfunction

Modality	Biomarker	Biological process assessed	Disease relevance
OCT	RPE band disruption	Barrier integrity	AMD, RP
OCT	PED	Fluid transport failure	Neovascular AMD
FAF	Hyperautofluorescence	Lipofuscin overload	Stargardt, AMD
MC-OCT	RPE70 thickening	Melanin remodeling	Serous PED
AO-SLO	Mosaic irregularity	Cellular polarity loss	Aging, atrophy
Dark adaptation	Delayed recovery	Visual cycle dysfunction	Early AMD
EOG	Reduced Arden ratio	Ion transport defect	Diffuse RPE disease

OCT: Optical coherence tomography, RPE: Retinal pigment epithelium, AMD: Age-related macular degeneration, RP: Retinitis pigmentosa, PED: Pigment epithelium-derived, MC-OCT: Multi-contrast optical coherence tomography, AO-SLO: Adaptive optics scanning laser ophthalmoscopy, EOG: Electrooculography

Modern imaging has fundamentally altered the understanding of retinal degeneration. Rather than detecting only late-stage photoreceptor loss, contemporary modalities visualize RPE stress, metabolic overload, polarity disruption, and pigment remodeling at early stages. These findings reinforce the central thesis of this review: degeneration of the outer retina is frequently initiated at the level of the RPE. Imaging now allows clinicians to observe maternal distress before neuronal orphaning occurs. In doing so, it shifts both diagnosis and therapeutic strategy toward preservation of the caregiver.

EMERGING RPE-DIRECTED THERAPIES: RECONSTRUCTING THE MATERNAL INTERFACE

The increasing recognition of RPE centrality has reshaped therapeutic strategy. Rather than exclusively targeting neurons, modern interventions aim to restore or replace RPE function.

Gene Therapy: Restoring Metabolic Competence

RPE65 gene replacement therapy provides proof-of-concept that correcting RPE metabolic deficiency restores photoreceptor function.[6,19] Adeno-associated viral delivery of functional RPE65 reestablishes 11-cis-retinal production, improves rod-mediated vision, and demonstrates durable benefit. Beyond RPE65, investigational gene therapies target complements modulation, VEGF regulation, and intracellular trafficking pathways implicated in polarity maintenance.[4,6,19] The success of these strategies confirms a fundamental principle: rescuing the caregiver can stabilize dependent neurons.

Stem Cell-Derived RPE Transplantation

Because native RPE has minimal proliferative capacity, cell replacement has emerged as a rational approach. Human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs) can differentiate into polarized, pigmented RPE expressing RPE65 and capable of phagocytosis.[8,20] Clinical studies of stem cell-derived RPE transplantation in AMD and Stargardt disease demonstrate graft survival, pigmentation, and partial functional stabilization.[8,20] Scaffolds that restore epithelial polarity and Bruch's membrane contact improve integration. This approach does not merely replace cells-it seeks to reconstruct the maternal architecture of the outer retina.

Modulating Oxidative Stress and Mitochondrial Health

Given the central role of oxidative injury, therapeutic strategies aim to enhance NRF2 signaling, improve mitochondrial resilience, and restore autophagic flux.[4,6,21] Interventions targeting lysosomal acidification and lipofuscin reduction may preserve phagocytic competence.

Complement and Inflammasome Inhibition

Complement inhibition is now a major therapeutic frontier in AMD.[4,21,22] Recent therapeutic advances have translated complement biology into clinical practice. Complement inhibitors targeting C3 and C5 pathways have demonstrated the ability to slow geographic atrophy progression in AMD. These therapies highlight the importance of immune regulation at the level of the RPE-Bruch's membrane interface and further support the concept that protecting RPE integrity is central to preventing photoreceptor degeneration.[23] Targeting complement components or regulators seeks to prevent chronic RPE injury. Similarly, NLRP3 inflammasome inhibitors aim to suppress IL-1β-mediated pyroptosis and preserve RPE viability.[4,21,22]

Bioengineering and Precision Editing

Emerging strategies combine gene-corrected iPSC-derived RPE, biodegradable scaffolds, and controlled growth factor delivery systems.[8,19] CRISPR-based gene correction offers the potential to restore defective trafficking or polarity proteins in inherited RPE disorders. These approaches reflect a paradigm shift: rebuilding the maternal interface rather than merely treating downstream neuronal loss.[8,19,24] These complementary strategies for restoring metabolic competence, replacing damaged RPE, modulating immune injury, and enhancing mitochondrial resilience are conceptually integrated in Figure 3.

Across degenerative, mechanical, and proliferative retinal diseases, a recurring theme emerges: RPE dysfunction destabilizes the photoreceptor ecosystem. Whether through oxidative exhaustion (AMD), structural thinning (myopia), EMT transformation (PVR), or reactive migration (RP), the breakdown of maternal function precedes or amplifies neuronal degeneration. Modern imaging visualizes RPE stress before irreversible photoreceptor death.[1,13,25] Contemporary therapies increasingly target RPE metabolism, immune signaling, and structural integrity. The future of retinal therapeutics lies not solely in saving neurons but in preserving-or reconstructing-the caregiver that sustains them. Protecting the RPE means protecting vision.

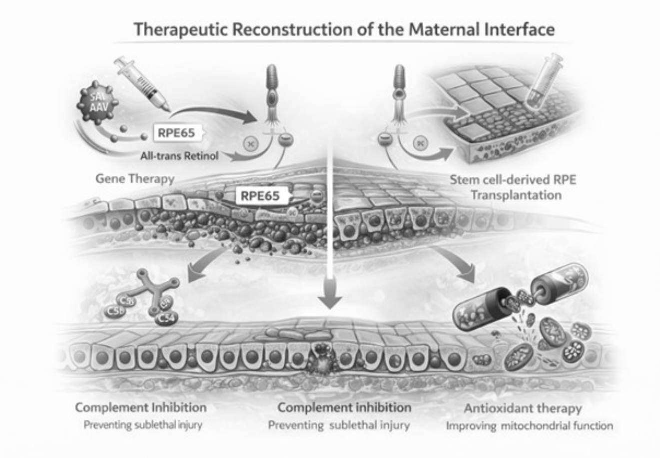

Figure 3. Therapeutic reconstruction of the maternal interface

RPE Organoids and Disease Modeling

Advances in stem-cell biology have enabled the generation of three-dimensional retinal organoids containing functional RPE layers. These organoid systems recapitulate many aspects of RPE polarity, pigmentation, and phagocytic activity. Importantly, organoid models allow investigation of disease mechanisms in inherited retinal degeneration and provide platforms for drug screening and gene-editing strategies. RPE organoids therefore represent a powerful bridge between basic molecular research and translational therapeutic development.[26,27]

CONCLUSION

The RPE is not a passive anatomical boundary but the central regulator of photoreceptor survival. It regenerates chromophore, clears debris, regulates ion balance, maintains immune privilege, and stabilizes retinal adhesion. Aging and disease represent progressive erosion of these maternal functions. Imaging now detects RPE stress before photoreceptor loss, and modern therapies increasingly target the RPE directly. Re-centering retinal biology around the RPE provides a unifying framework for understanding degeneration and guiding future intervention. Protecting the RPE means protecting vision.

ETHICAL DECLARATIONS

Peer Review Process

This review was externally peer-reviewed.

Conflict of Interest

The author declare no conflicts of interest.

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Author Contributions

The author is solely responsible for the conception, data collection, analysis, and writing of this manuscript.

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Case Report

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An aponeurotic blepharoptosis following uneventful cataract surgery: a case report

Nuhkan Görkemli, Mehmet Canleblebici*
Department of Ophthalmology, Kayseri State Hospital, Kayseri, Turkiye

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ABSTRACT

This case reports a 72-year-old female who developed delayed-onset, severe blepharoptosis three months following uncomplicated phacoemulsification under topical anesthesia. Despite an uneventful surgery and visual recovery (6/6), the patient presented with complete visual axis obstruction in the right eye. Preoperative examination had previously noted mild involutional changes, including bilateral mild ptosis and deep superior sulci. Clinical findings post-surgery confirmed levator aponeurosis dehiscence with preserved levator function. Following six months period of observation, the patient underwent successful levator aponeurosis reattachment, achieving satisfactory functional and cosmetic results. This case highlights that postoperative ptosis may still occur after modern cataract surgery, even when minimally invasive techniques and topical anesthesia is used, particularly in patients with pre-existing involutional eyelid changes. It emphasizes the necessity of thorough preoperative eyelid assessment and patient counseling regarding involutional risk factors to manage expectations and ensure timely intervention for optimal postoperative satisfaction.

Keywords: Blepharoptosis, cataract surgery, phacoemulsification, levator aponeurosis, involutional ptosis

INTRODUCTION

Cataract surgery is one of the most commonly performed ophthalmic procedures and is generally associated with good visual outcomes. However, postoperative complications involving the periocular adnexa may still occur and can adversely affect functional vision and patient satisfaction. One such complication is postoperative upper eyelid blepharoptosis, which, although often transient, may persist and lead to significant visual axis obstruction.[1,2]

Post-cataract blepharoptosis is typically attributed to a multifactorial etiology, including aponeurotic dehiscence of the levator palpebrae superioris, mechanical stress from eyelid speculums, postoperative inflammation, and patient-related involutional changes.[3] Even with modern cataract surgery techniques, postoperative blepharoptosis may still emerge as a clinically significant and functionally limiting complication.[1]

In this report, we present an elderly patient of persistent blepharoptosis with pre-existing involutional changes following uncomplicated cataract surgery, highlighting the diagnostic approach, clinical course, and management strategy, with a focus on practical considerations for prevention and treatment.

CASE

A 72-year-old female patient presented with decreased visual acuity in her right eye. On admission, best-corrected visual acuity (BCVA) was 6/18 in the right eye and 6/9 in the left eye using a metric Snellen chart. Intraocular pressure were 15 mmHg in both eyes. Slit-lamp examination of the anterior segment revealed bilateral corticonuclear cataracts, which were more advanced in the right eye. Fundus examination was unremarkable in both eyes.

Preoperative eyelid evaluation demonstrated a marginal reflex distance-1 (MRD-1) of 2 mm bilaterally, consistent with mild bilateral ptosis. Deep superior sulcus was noted in both eyes, suggestive of underlying involutional changes of the eyelid. There was no history of previous ocular surgery, trauma, contact lens use, or neuromuscular disease.

Cataract surgery with phacoemulsification was performed on the right eye under topical anesthesia using proparacaine hydrochloride (Alcaine®). The patient demonstrated good cooperation throughout the procedure. Uneventful phacoemulsification was completed, with a total surgical time of approximately 11 minutes. No intraoperative complications occurred.

Postoperatively, uncorrected visual acuity (UCVA) in the operated eye was 6/6 at the one-month follow-up visit, the patient's UCVA in the right eye remained 6/6, with normal anterior and posterior segment findings.

***Corresponding Author:** Mehmet Canleblebici, mehmetcl@hotmail.com

Three months after cataract surgery, the patient re-presented unhappily with complaints of impaired vision, primarily due to difficulty opening her right eye. She specifically reported that the inability to adequately elevate the upper eyelid had become her most disabling symptom.

On eyelid examination, a severe right-sided upper eyelid ptosis was observed, resulting in complete obstruction of the visual axis. The left upper eyelid position remained unchanged and did not interfere with the visual axis. MRD-1 in the right eye was markedly reduced compared with preoperative measurements. Levator function of the right upper eyelid was assessed and found to be moderately preserved (9 mm). A deeper superior sulcus, elevation on the right eye brow and worsening of the ptosis on downgaze were noted. (Figure 1). Additionally, extraocular muscle movements were full in all directions of gaze, pupillary reflexes were normal and symmetric. No diplopia, fatigability, or diurnal variation of ptosis was noted.

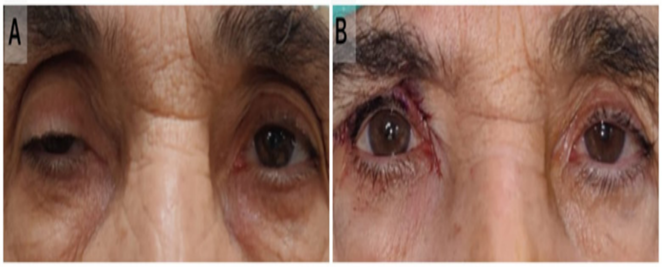

Figure 1. Clinical presentation of blepharoptosis and improvement after surgery

A) Preoperative clinical photograph demonstrating marked blepharoptosis of the right upper eyelid, with complete obstruction of the visual axis. Mild contralateral ptosis of the left upper eyelid is also evident but does not compromise the visual axis. B) Postoperative photograph following levator aponeurosis reattachment surgery, showing significant improvement in upper eyelid position on the right side, restoration of the visual axis, and satisfactory eyelid symmetry

Given the delayed onset of symptoms, preserved levator function, and clinical features suggestive of aponeurotic separation, a diagnosis of post-cataract iatrogenic aponeurotic blepharoptosis was made. After excluding neurogenic causes and allowing sufficient time for spontaneous recovery, surgical correction was recommended at sixth month.

The patient underwent levator aponeurosis reattachment surgery under local anesthesia. Through a standard upper eyelid crease incision, the levator aponeurosis was identified and found to be disinserted from the anterior surface of the tarsal plate. The aponeurosis was advanced and reattached to the tarsus using non-absorbable sutures, with intraoperative adjustment performed to achieve optimal eyelid height and contour. The procedure was completed without complications (Figure 2).

Postoperatively, eyelid position improved significantly, with restoration of the visual axis and satisfactory eyelid symmetry. No early or late postoperative complications were observed during follow-up. The patient reported marked functional and cosmetic satisfaction. Given the stable postoperative course, the patient was subsequently scheduled for routine follow-up and evaluation of cataract progression in the contralateral eye.

DISCUSSION

Blepharoptosis following cataract surgery is a well-recognized but often underestimated postoperative complication that may significantly impair functional vision and patient satisfaction. A recent meta-analysis reported an overall incidence of

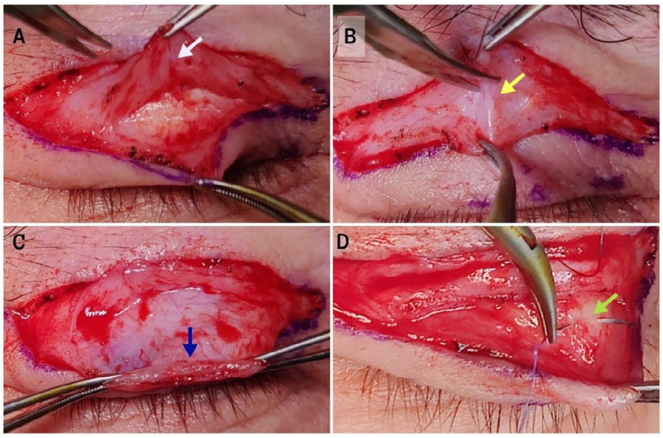

Figure 2. Demonstration of the levator aponeurosis reattachment surgery

A) The white arrow shows orbicularis oculi muscle was dissected. B) The yellow arrow shows orbital septum. C) The dissected levator muscle demonstrated with blue arrow. D) Suturing of the tarsus before reattachment of the levator muscle was presented with green arrow

postoperative ptosis of 11.4% (95% confidence interval: 10.1-12.8%) following ocular surgery.[4] The present case highlights the development of delayed-onset, visually significant blepharoptosis three months after uneventful cataract surgery performed under topical anesthesia.

The pathophysiology of post-cataract ptosis is multifactorial and includes aponeurotic dehiscence, anesthetic-related myotoxicity, mechanical stress from eyelid speculums, postoperative inflammation, and patient-related predispositions.[5,6] In the current case, several features support an aponeurotic mechanism as the primary etiology. Preoperatively, the patient demonstrated mild bilateral ptosis with reduced MRD-1 values and deep superior sulcus formation, suggesting pre-existing involutional changes of the levator aponeurosis. Cataract surgery likely acted as a precipitating factor, converting a subclinical condition into a functionally significant ptosis.[7] Clinicians should be aware of pre-existing involutional eyelid changes and counsel patients accordingly prior to cataract surgery.[7] Adequate preoperative counseling may help patients develop realistic expectations and improve psychological preparedness in the event that postoperative ptosis occurs.

Notably, the surgery was performed under topical anesthesia and completed within a relatively short duration, reducing the likelihood of myotoxic or neurogenic injury related to injectable anesthetic agents.[8] The delayed onset of symptoms further argues against transient postoperative edema or anesthetic effects, which typically resolve within weeks. In this case, it may be explained by gradual progression of a pre-existing involutional levator aponeurosis weakness. Mechanical stress during surgery may have initiated partial dehiscence, which subsequently progressed over time due to repetitive eyelid movements, chronic low-grade postoperative inflammation, or habitual eye rubbing. Such mechanisms may explain why clinically significant ptosis became evident several months after surgery rather than immediately in the early postoperative period. Although this was not a second-eye surgery in our patient, previous studies have suggested that second-eye cataract procedures may be associated with increased anxiety and stronger orbicularis muscle contraction during surgery. Excessive squeezing against the eyelid speculum may increase mechanical stress on a weakened levator aponeurosis and contribute to postoperative ptosis.[5]

Differential diagnosis is a critical step in evaluating postoperative ptosis. Neurogenic causes such as oculomotor nerve palsy, Horner syndrome, and myasthenia gravis must be excluded, particularly in elderly patients.[9] In this case, the absence of pupillary abnormalities, extraocular motility deficits, diurnal variability, or fatigability supported a mechanical rather than neurological etiology. The unilateral predominance of ptosis following surgery on the same side further strengthened the causal relationship with the cataract procedure.

Management of post-cataract ptosis generally begins with observation, as a significant proportion of cases resolve spontaneously within six months.[5] However, when ptosis persists beyond this period or causes visual axis obstruction, surgical intervention becomes necessary.[10] Given the preserved levator function and clinical findings consistent with aponeurotic separation, levator aponeurosis reattachment was selected as the treatment of choice in this patient.[2] This approach directly addresses the underlying structural defect and allows precise intraoperative adjustment of eyelid height and contour. The successful postoperative outcome in the present case confirms the effectiveness of this strategy when appropriate patient selection is performed.

This case underscores the importance of thorough preoperative eyelid assessment in patients undergoing cataract surgery. Subclinical ptosis, deep superior sulcus, and other signs of involutional change should be documented and discussed with patients preoperatively. Even with optimal surgical conditions, cataract extraction may unmask or exacerbate pre-existing eyelid instability. Awareness of this risk allows for realistic patient expectations and timely referral for oculoplastic evaluation when necessary.

CONCLUSION

In conclusion, this case demonstrates that visually significant blepharoptosis may develop months after uncomplicated cataract surgery, even under topical anesthesia. Cataract surgery can act as a triggering event in patients with pre-existing involutional eyelid changes, leading to aponeurotic dehiscence. Therefore, both surgeons and patients undergoing ocular surgery should be aware of this potential risk during the informed consent process. Moreover, operative techniques may be optimized to reduce the incidence of postoperative blepharoptosis. Careful diagnostic evaluation, appropriate timing of intervention, and tailored surgical management are essential to achieve favorable functional and cosmetic outcomes.

ETHICAL DECLARATIONS

Informed Consent

Written informed consent was obtained from the patient included in this report. Signed consent forms are retained by the authors and are available upon request.

Peer Review Process

This report underwent external peer review.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

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Author Contributions

Idea/Concept: NG, MC; Design: NG, MC; Control/Supervision: MC; Data Collection and/or Pro-cessing: NG, MC; Analysis and/or Inter-pretation: NG, MC; Literature Review: MC; Writing the Article: NG, MC; Critical Review: MC; Materials: MC.

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Letter to the Editor

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Re: "Open-globe injuries: associated findings, management, and visual outcomes"

Hakan Veli Savaş

Department of Ophthalmology, Karakoçan State Hospital, Elazığ, Turkiye

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Dear Editor,

We read with great interest the article by Kılıç et al.,[1] which characterizes adult open-globe injuries (OGI), management patterns, and visual outcomes in a single-center cohort. The authors' emphasis on early primary repair and the distribution of anterior/posterior segment findings adds valuable local data to the literature and will be informative for clinicians who support clinical decision-making and patient counseling at presentation.

In this context, we would like to offer several suggestions that may further strengthen the manuscript.

Prognostic stratification with Ocular Trauma Score (OTS): In addition to baseline/final visual acuity and zone-based results, incorporating the OTS would enhance between-study comparability and support clinical decision-making. OTS combines initial acuity with key injury variables [e.g., rupture, endophthalmitis, retinal detachment, relative afferent pupillary defect (RAPD)] to estimate probabilities of final vision categories and is widely adopted in OGI research and practice.[2]

Time-to-repair granularity within 24 hours: The manuscript highlights that all primary repairs were completed within the first 24 hours. Reporting finer time bands-e.g., <6 h, 6-12 h, and 12–24 h-and exploring their association with final vision or infection risk would add nuance. Contemporary evidence suggests earlier repair is associated with lower endophthalmitis risk.[3,4]

Infection prophylaxis reporting: Detailing systemic and intraocular antibiotic prophylaxis regimens (agents, routes, timing, duration) and tetanus prophylaxis would increase the paper's translational value. Recent reviews indicate heterogeneous practice patterns; while systemic antibiotics are common, intraocular antibiotics at primary repair may have stronger supporting evidence in high-risk scenarios.[5]

Imaging and intraocular foreign body (IOFB) detection: Because management and prognosis hinge on identifying IOFBs, we encourage reporting the usage rates of computed tomography (CT)/ultrasound (US), IOFB detection yield, and how imaging influenced surgical planning. Studies suggest CT is generally the preferred modality for rigid IOFBs, with sensitivity improving for larger fragments.[6]

Occupational prevention signals: Given the predominance of metal/wood injuries in many cohorts, specifying occupation categories, rural/urban origin, and personal protective equipment use could yield practical prevention messages for public health and workplace safety stakeholders.

Generalizability to pediatrics: Because this series focuses on adults, explicitly stating the limits of generalizability to pediatric OGI would help frame the scope and encourage complementary pediatric analyses.

In summary, Kılıç et al.[1] contribute meaningful data on adult OGI. We believe that adding OTS-based stratification, within-24-hour time-band granularity, explicit prophylaxis details, and imaging/IOFB metrics-supported by targeted analyses-would further enhance the manuscript's impact and its applicability to everyday decision-making.

ETHICAL DECLARATIONS

Peer Review Process

This letter was externally peer-reviewed.

Conflict of Interest

The author declare no conflicts of interest.

Financial Disclosure

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Corresponding Author: Hakan Veli Savaş, hakanvelisavas@hotmail.com

Author Contributions

The author is solely responsible for the conception, data collection, analysis, and writing of this manuscript.

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Archives of Ophtalmological Research

Letter to the Editor

Author reply "Open-globe injuries: associated findings, management, and visual outcomes"

Rasit Kılıç
Department of Ophthalmology, Faculty of Medicine, Tokat Gaziosmanpaşa University, Tokat, Turkiye

Dear Editor,

We would like to thank the authors for their thoughtful and constructive comments on our article and for their interest in our work. We appreciate the opportunity to clarify several points and to discuss potential areas for further enhancement. We respond to each comment below.

Prognostic stratification with the Ocular Trauma Score (OTS): We agree that the Ocular Trauma Score is a valuable and widely accepted prognostic tool in open globe injury (OGI) research and clinical practice. In our retrospective cohort, several OTS components-most notably relative afferent pupillary defect-were not consistently or reliably documented in the medical records, which precluded accurate post hoc calculation of OTS categories for all patients. For this reason, we focused our analyses on baseline and final visual acuity, injury zones, and major clinical variables that were uniformly available. We fully agree that prospective data collection incorporating complete OTS parameters would enhance between-study comparability and clinical interpretability, and we plan to include OTS-based stratification in future studies.

Time-to-repair granularity within the first 24 hours: We appreciate this suggestion. Although all primary repairs were performed within 24 hours, the exact timing from injury to surgery was not recorded with sufficient precision in a substantial proportion of cases to allow reliable subgrouping into narrower time bands (<6 h, 6-12 h, 12-24 h). We acknowledge that increasing evidence supports earlier repair, particularly with respect to reducing the risk of endophthalmitis. This limitation has now been recognized as an important consideration for future prospective investigations.

Infection prophylaxis reporting: The authors agree that detailed reporting of prophylactic regimens would increase the translational value of the study. In our clinic, systemic broad-spectrum antibiotics and tetanus prophylaxis are routinely administered according to institutional protocols, while intraocular antibiotics are reserved for selected high-risk cases at the discretion of the operating surgeon. However, due to heterogeneity in agents, dosing, and duration over the long study period, these data were not analyzed separately. We acknowledge this as a limitation and concur that standardized reporting of prophylaxis strategies would be highly valuable in future work.

Imaging and intraocular foreign body (IOFB) detection: We agree that identification of IOFBs is critical for management and prognosis. In our cohort, all patients with suspected open globe injury underwent computed tomography (CT) scanning as part of the initial evaluation. CT was the sole imaging modality used for IOFB assessment, and ocular ultrasonography was not performed in any case, in accordance with our institutional protocol and concerns regarding potential globe manipulation in the acute setting.

Occupational and prevention-related factors: We appreciate the emphasis on prevention. While the mechanism of injury was recorded, more granular data regarding occupation, rural versus urban setting, and use of personal protective equipment were inconsistently available in the retrospective records. We agree that inclusion of these variables could generate important public health and workplace safety insights and should be prioritized in prospective or registry-based studies.

Generalizability to pediatric populations: We agree that pediatric open globe injuries represent a distinct clinical and epidemiologic entity, and the findings of the present study should therefore be interpreted within the context of adult patients only. As explicitly stated in our Methods section, this series was intentionally limited to adults, reflecting differences in injury mechanisms, ocular tissue properties, management strategies, and visual prognosis between adults and children. Importantly, we have previously addressed pediatric globe injuries in a separate, dedicated publication, in which pediatric-specific epidemiological and clinical characteristics were analyzed. We believe that separating adult and pediatric cohorts allows for more accurate interpretation of outcomes within each population and avoids inappropriate extrapolation.

In summary, we thank the authors for their valuable comments, which highlight important directions for future research. We believe our study provides meaningful data on adult OGI outcomes, and we agree that incorporation of OTS-based stratification, finer time-to-repair analyses, standardized prophylaxis reporting, detailed imaging metrics, and prevention-focused variables would further enhance the impact and applicability of this field.

Sincerely,

on behalf of the authors