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Original Articles

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Case Report

Letters to the Editor

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AT A GLANCE

2026 Issue 3 at a Glance:

Esteemed colleagues,

In the third issue of 2026, the Turkish Journal of Ophthalmology features five original research articles, one review, one case report, and five letters to the editor addressing highly engaging and current topics. We believe you will find these articles beneficial.

The original research section begins with a study by Yalçındağ et al. titled "Determination of the Non-Invasive Tear Break-Up Time Cut-Off Point for Diagnosis of Dry Eye Disease and Its Correlation with Other Dry Eye Tests." The authors identified a threshold value of the tear break-up time test for use in the differential diagnosis of evaporative and mixed-type dry eye disease, emphasizing that this test has high diagnostic sensitivity and specificity and correlates with other clinical tests (See pages 148-157).

In their study titled "Refractive and Visual Outcomes in Unilateral Duane Retraction Syndrome: Influence of Ocular Motility," Ünlü et al. reported that patients with unilateral Duane retraction syndrome had lower visual acuity and higher spherical refraction values on the affected side. They further noted that cylindrical refraction values were associated with abnormal head position and deviation type in these patients (See pages 158-165).

Devebacak et al. present a study titled "Accuracy of Contemporary Intraocular Lens Calculation Formulas Based on Swept-Source OCT Biometry in Eyes with Capsular Tension Ring," in which they determined that the Barrett Universal II formula yielded the lowest mean absolute error and median absolute error, followed by the Holladay II formula. However, a slight hyperopic shift was demonstrated across all evaluated formulas (See pages 166-171).

In their study titled "MicroRNA Profiles Targeting Angiopoietin-1, Angiopoietin-2, and TEK Receptor Tyrosine Kinase-2 Genes Associated with Angiogenesis in Proliferative Diabetic Retinopathy," Sancar et al. discussed the increased expression of certain microRNA subtypes in the vitreous. They suggested that this increase may be related to decreased Angiotensin-1 levels and that these microRNAs could serve as indicators of vascular changes in the pathogenesis of proliferative diabetic retinopathy (See pages 172-179).

Demirayak et al. present a survey study titled "Assessment of Dietary Nutritional Profile in Turkish Patients with Age-Related Macular Degeneration." In their sample of 530 patients, they determined that only 19.3% consumed the recommended amounts of omega-3 rich foods. Additionally, over half of the patients did not consume fish weekly, and recommended intake of foods rich in lutein/zeaxanthin, beta-carotene, and antioxidants was reported by 63.6%, 41.7%, and 4.7% of patients, respectively. The proportion of patients using micronutrient supplements regularly was determined to be 35.5%. Highlighting the low frequency of antioxidant use, the authors emphasized the need to raise awareness among both patients and ophthalmologists regarding this issue (See pages 180-186).

This issue's review, by Taşkıran Çömez, is titled "Unseen Consequences: The Expanding Burden of Iatrogenic Dry Eye Disease in Surgical and Cosmetic Practice." The article includes a detailed discussion of dry eye disease developing after surgery, cosmetic procedures, pharmacological treatments, and the use of medical devices, with emphasis on the potential for preoperative ocular surface examination to substantially reduce the burden of iatrogenic dry eye disease (See pages 187-197).

In the case report of this issue, titled "Modification of the Temporal Inverted Internal Limiting Membrane Flap in Macular Hole Surgery: Envelope Technique," Tatlıpınar proposed that utilizing a window in the internal limiting membrane (ILM) to stabilize the inverted ILM flap in large macular holes may yield a higher success rate compared to the original method (See pages 198-202).

The letters to the editor section includes pieces titled "Out of Sight, Out of Chamber: PreserFlo® MicroShunt Dislocation Following Office-Based Needling" by Garcia-Risco et al. (See pages 203-207), "Unilateral Idiopathic Retinal Venous Beading" by Karslıoğlu et al. (See pages 208-210), "Presentation of Bilateral Optic Disc Coloboma–Morning Glory Syndrome in Mother and Son, with Retinitis Pigmentosa in the Father" by İslambekov et al. (See pages 211-215), a letter from Çağlar regarding the article "Long-Term Intravitreal Dexamethasone Implant Monotherapy in Naïve Patients with Diabetic Macular Edema" (See pages 216-217), and the reply from Karataş et al. (See pages 217-219).

We hope that the valuable articles in this year's third issue will capture your interest and make significant, inspiring, and lasting contributions to your daily practice.

On behalf of the Editorial Board,

Hande Taylan Şekeroğlu, MD

Original Article

Determination of the Non-Invasive Tear Break-Up Time Cut-Off Point for Diagnosis of Dry Eye Disease and Its Correlation with Other Dry Eye Tests

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Abstract

Objectives: To determine optimal cut-off values for first and average non-invasive tear break-up time (NIBUT-f and NIBUT-av, respectively) in dry eye disease (DED), as well as evaluate their correlation with other tests.

Materials and Methods: This retrospective study included 46 patients with DED and 35 healthy controls. All subjects were assessed using the Ocular Surface Disease Index questionnaire. NIBUT measurements and meibography images were obtained using the Sirius topography device. The conventional diagnostic tests Schirmer-I, tear break-up time (TBUT), ocular surface staining (OSS), Marx line score, and lid wiper epitheliopathy (LWE) grade were performed.

Results: The cut-off values of NIBUT-f and NIBUT-av for DED diagnosis were identified as 10.7 and 12.2 seconds, respectively. The area under the curve (AUC) was 0.93 (95% confidence interval [CI]: 0.889–0.992) for NIBUT-f and 0.92 (95% CI: 0.872–0.985) for NIBUT-av. For the differentiation between evaporative and mixed DED subtypes, the NIBUT-av cut-off value was 7.2 seconds, with an AUC of 0.63 (95% CI: 0.512-0.743). NIBUT-av showed a positive correlation with TBUT ($p<0.001$, $r=0.905$) and Schirmer-I ($p<0.001$, $r=0.403$) but a negative correlation with OSS ($p<0.001$, $r=-0.700$), meibomian gland loss ($p<0.001$, $r=-0.601$), LWE grade ($p<0.001$, $r=-0.597$), and Marx line score ($p<0.001$, $r=-0.539$).

Conclusion: NIBUT is a highly sensitive and specific non-invasive diagnostic tool for DED that correlates with other ocular surface and meibomian gland function tests.

Keywords: Non-invasive tear break-up time (NIBUT), dry eye disease, cut-off value

Cite this article as: Yalçındağ E, Akıngöl Z, Bağatur Vurgun E, Akkaya Turhan S, Toker E. Determination of the Non-Invasive Tear Break-Up Time Cut-Off Point for Diagnosis of Dry Eye Disease and Its Correlation with Other Dry Eye Tests. Turk J Ophthalmol. 2026;56:148-157

This study was presented at the 55th National Congress of the Turkish Ophthalmology Association (04.11.2021-Antalya).

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Introduction

The Tear Film and Ocular Surface Dry Eye Workshop II (TFOS DEWS II) defines dry eye disease (DED) as a multifactorial condition of the ocular surface characterized by disrupted tear film homeostasis, accompanied by ocular symptoms. The etiology involves tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities.[1] The global estimated prevalence of DED ranges from 5% to 50%, reflecting variations across different populations.[2] DED is increasingly extending beyond the typical adult demographic to affect younger individuals, indicating a rising potential for widespread impact in the years ahead.[3] According to the TFOS DEWS II diagnostic algorithm, initial triage questions and a comprehensive analysis of risk factors precede the performance of specific diagnostic tests to confirm DED.[4] Diagnostic testing involves assessments of symptomatology

as well as the measurement of homeostasis markers, which are critical in establishing a definitive diagnosis. To this end, tear film osmolarity, ocular surface staining (OSS), and tear break-up time (TBUT) are employed to assess tear film homeostasis. A positive finding in any of these tests, in conjunction with screening questionnaires, conclusively confirms a diagnosis of DED.[4]

TBUT is defined as the duration between a complete blink and the first disruption in the tear film.[4] The initial method for assessing TBUT (using fluorescein) was introduced nearly 50 years ago and has become established in clinical practice.[5] This technique involves instilling sodium fluorescein dye into the tear film, allowing disruptions to be detected using a slit-lamp biomicroscope under cobalt blue light. A benchmark of 10 seconds has been traditionally accepted as the threshold between a normal and unstable tear film.[5] However, fluorescein inherently alters tear film stability, and measurement variability is highly dependent on the practitioner's technique, which impedes the reliability of the TBUT protocol.[6,7,8]

Accordingly, non-invasive tear break-up time (NIBUT) methods have emerged as the preferred method over conventional TBUT, and the use of TBUT is recommended only in cases where NIBUT is not feasible or accessible.[9] NIBUT is the interval from the completion of a full blink to the first disruption in the reflection of a pattern (such as grid, mire, or Placido disc) projected onto the tear film.[10,11] A NIBUT cut-off value of 10 seconds has been suggested as indicative of DED in examinations of the reflection of an illuminated grid pattern.[11] However, studies have presented divergent findings regarding cut-off values obtained through automated measurement systems, with some reporting shorter[12,13] or longer[14,15,16] durations. In addition, modern devices incorporating videokeratography systems analyze videos to derive first and average NIBUT values.[17,18] Despite these advancements, there is no consensus in the literature regarding the most suitable device, reference value, or appropriate cut-off threshold.

Therefore, our primary objective in the current study was to determine the optimal cut-off values for both the first and average NIBUT (NIBUT-f and NIBUT-av, respectively) in patients diagnosed with DED, as well as to evaluate the correlation between invasive and non-invasive diagnostic tests in these patients. Furthermore, we compared the results of DED patients and healthy controls across conventional diagnostic tests, including Schirmer-I, TBUT, OSS, Marx line score, lid wiper epitheliopathy (LWE) grade, and meibography.

Materials and Methods

This retrospective study was conducted with the approval of the Marmara University Faculty of Medicine's Ethics Committee (date: 15.11.2024; protocol code: 09.2024.1296) and in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all subjects.

Patients aged 18 years or older presenting to the Ophthalmology Clinic of Marmara University Pendik Training and Research Hospital with complaints of dry eye were included in the study. The exclusion criteria were the presence of an active ocular infection or allergy, contact lens wear, and a history of ocular surgery within the last 3 months.

All examinations were performed according to a predefined clinical protocol with a fixed sequence to minimize test-to-test interference. Non-invasive assessments, including NIBUT and meibography imaging, were conducted prior to invasive procedures such as Schirmer-I, TBUT, and OSS. This retrospective study included only patients whose clinical examinations were performed by a single ophthalmologist (E.Y.). All Sirius topography measurements were routinely obtained by the same trained technician using the same device and standardized protocol, and the data were retrospectively reviewed for the purposes of this study. Only one eye from each patient was included in the analysis. When both eyes met the inclusion criteria, the eye with more severe clinical findings was selected.

Diagnostic Tests for DED

The Turkish version of the Ocular Surface Disease Index (OSDI) questionnaire, consisting of 12 questions in 3 sections, was administered to all subjects.[19] The OSDI score was calculated according to the following formula:

OSDI = (sum of scores for all questions answered × 25) / total number of questions answered

NIBUT measurements were conducted using the Sirius topography device (Costruzione Strumenti Oftalmici, Florence, Italy), which operates on the Placido-disc principle. During the measurement, patients were instructed to blink twice and keep their eyes open for as long as possible, in line with the device's prompts. NIBUT-f and NIBUT-av values were automatically recorded by the device's software. Measurements were repeated three times for each eye, and the average of the three values was calculated.

To assess the meibomian glands, images were captured using the Phoenix Meibography Imaging module of the Sirius topography device following the eversion of the upper and lower eyelids. After the borders of the tarsal conjunctiva and the meibomian glands were manually delineated, the software calculated the percentage of gland loss. The area of meibomian gland loss was graded as

follows: grade 0 indicates no loss, grade 1 indicates a loss of up to 25%, grade 2 indicates a loss of 26-50%, grade 3 indicates a loss of 51-74%, and grade 4 indicates a loss of 75% or more.

After these non-invasive tests, the Schirmer-I test was performed without anesthesia using a Whatman 41 filter paper strip marked up to 35 mm. The rounded tip of the paper was placed in the conjunctival sac at the junction of the temporal and middle thirds of the eyelid without contacting the cornea, to prevent reflex tear activity. Both eyes were evaluated concurrently, and the length of the wetted segment of the filter paper was measured after a duration of 5 minutes.

A fluorescein strip, wetted with a drop of saline and shaken to remove excess liquid, was gently applied to the inferior bulbar conjunctiva to stain the ocular surface. The tear film was subsequently evaluated using a biomicroscope with a cobalt blue filter. Patients were instructed to blink several times and then keep their eyes open for as long as possible. The TBUT was recorded at the first appearance of disruption in the tear film.

OSS was assessed following fluorescein application, using a cobalt blue filter on a biomicroscope. Staining of the nasal conjunctiva, temporal conjunctiva, and cornea was evaluated based on the Oxford grading scheme.[20]

For the evaluation of LWE, a mixture of 2% fluorescein and 1% lissamine green was applied to the conjunctival sac, and the upper and lower eyelid margins were examined. The lesions were graded on a scale of 0-3 based on the width and height of the staining, as described by Korb et al.[21]

During the fluorescein and lissamine-green staining, the mucocutaneous junction of the lower eyelid was examined under a slit lamp, and the Marx line score (also known as the Yamaguchi score) was calculated.[22] The lower eyelid was divided into three imaginary sections to evaluate the relationship between the mucocutaneous junction and the meibomian gland orifices: a score of 0 was assigned if there was no intersection, 1 if the Marx line reached the gland orifices at certain points, 2 if the Marx line intersected with all gland orifices, and 3 if the Marx line extended anterior to the gland orifices. The scores from the inner, middle, and outer sections were summed to calculate the final score.

DED Diagnosis and Classification

DED diagnosis required OSDI ≥13 plus at least one positive homeostasis marker (TBUT <10 s or OSS positivity). Patients diagnosed with DED were subsequently categorized into three subtypes: aqueous-deficient, evaporative, and mixed. The diagnostic algorithm and DED subgroup classifications are summarized in Table 1.

Statistical Analysis

A post-hoc power analysis was conducted using G*Power software based on the observed difference in NIBUT-av values between the DED group (7.7±3.4 s, n=46) and the control group (15.1±2.9 s, n=35). The calculated effect size was large (Cohen's d=2.42). With this effect size, the post-hoc analysis yielded a statistical power of 1.00 at α=0.05.

All data in this study were analyzed using SPSS v20 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to describe patient characteristics, with data presented as mean ± standard deviation. The Shapiro-Wilk test was employed to assess the normality of the data distribution. Variables with normal distribution were analyzed using parametric tests, whereas variables not conforming to normality were analyzed using non-parametric tests. An independent-samples t-test was performed to compare continuous variables for the evaporative and the mixed types of DED. Receiver operating characteristic (ROC) curve analysis was conducted to determine the optimal cut-off values of NIBUT-f and NIBUT-av for the diagnosis of DED, and sensitivity, specificity, and the area under the curve (AUC) were calculated. For ROC analyses, optimal cut-off values were selected by maximizing the Youden index (J = sensitivity + specificity − 1), which identifies the operating point offering the best combined sensitivity and specificity. The correlations between NIBUT-av and other DED diagnostic tests were assessed using Spearman's rank correlation analysis. To further evaluate independent associations, a multivariate linear regression analysis was performed with NIBUT-av as the dependent variable and TBUT, Schirmer-I test, OSS score, Marx line score, LWE grade, and meibomian gland loss as independent variables. A *p value* of less than 0.05 was considered statistically significant.

Table 1. DED subgroup classification

Aqueous-deficient	Evaporative	Mixed
Schirmer-I test <10 mm F-TBUT <10 s	Meibomian gland loss ≥ grade 1 LWE ≥ grade 1 Marx line score ≥1	Criteria of both groups

DED: Dry eye disease, F-TBUT: Fluorescein tear break-up time, LWE: Lid wiper epitheliopathy

Results

The study included 83 participants with a mean age of 47.2±15.5 years (range 18-85 years); 54 (65.1%) were female and 29 (34.9%) were male. Of these, 48 patients (57.8%) were diagnosed with DED and 35 (42.2%) were in the control group. Within the DED group, 35 patients (72.9%) were female and 13 (27.1%) were male. In the control group, 19 subjects (54.3%) were female and 16 (45.7%) were male. Among those diagnosed with DED, 2 (4%) had aqueous-deficient DED, 23 (48%) had evaporative DED, and 23 (48%) had mixed DED. The two patients with aqueous-deficient DED were excluded from further analyses due to the small sample size for that subgroup. Therefore, the final analyzed cohort comprised 81 participants (46 with DED and 35 controls).

Table 2 shows the characteristics of DED patients and the control group. Compared to the controls, DED patients exhibited significantly lower NIBUT-av, NIBUT-f, TBUT, and Schirmer-I values, while their OSS score, LWE grade, Marx line score, and meibomian gland loss grade were significantly higher (p<0.001).

Table 3 presents the results of the subgroup analysis of patients with DED, specifically comparing the evaporative and mixed types of DED. The evaporative DED group showed significantly higher NIBUT-av, TBUT, and Schirmer-I test values, but notably lower OSS scores, Marx line scores, and LWE grades.

NIBUT-f and NIBUT-av Cut-Off Values for DED Diagnosis

ROC curve analysis identified the cut-off values for the diagnosis of DED as 10.7 seconds for NIBUT-f and 12.2 seconds for NIBUT-av. The AUC was 0.93 (95% confidence interval [CI]: 0.889-0.992) for NIBUT-f and 0.92 (95% CI: 0.872-0.985) for NIBUT-av (Figure 1). At these cut-off values, the sensitivity was 89% (95% CI: 79.7%-96.6%) and the specificity was 88% (95% CI: 74.0%-95.5%) for both parameters. At the selected operating points for overall DED detection, the Youden index was 0.77 (0.89 + 0.88 – 1) for both NIBUT-f and NIBUT-av. In addition, when ROC analysis was performed to differentiate evaporative and mixed DED subtypes, the cut-off value for NIBUT-av was determined to be 7.2 seconds; the sensitivity, specificity,

Table 2. Test results of the DED and control groups

	DED group (n=46)	Control group (n=35)	p
NIBUT-av (s)	7.7±3.4 (2.7-17)	15.1±2.9 (5.1-17)	<0.001
NIBUT-f (s)	5.9±3.7 (1.1-17)	14.6±3.4 (4.7-17)	<0.001
TBUT (s)	6.2±2.6 (1-14)	12.2±2.6 (5-16)	<0.001
Schirmer-I (mm)	9.8±5.4 (1-21)	15.3±4.7 (6.5-26)	<0.001
OSS score	0.91±0.98 (0-5)	0.02±0.16 (0-1)	<0.001
Marx line score	3.9±2.7 (0-9)	1.3±1.7 (0-6)	<0.001
LWE grade	0.66±0.78 (0-3)	0.04±0.18 (0-1)	<0.001
Meibomian gland loss grade	1.6±0.67 (0-4)	0.8±0.65 (0-3)	<0.001

Data presented as mean ± standard deviation (range). DED: Dry eye disease, NIBUT-av: Average non-invasive tear break-up time, NIBUT-f: First non-invasive tear break-up time, TBUT: Tear break-up time, OSS: Ocular surface staining, LWE: Lid wiper epitheliopathy

Table 3. DED subgroup analysis

	Evaporative (n=23)	Mixed (n=23)	p
NIBUT-av (s)	8.5±4.2 (2.4-17)	6.5±3.4 (2.2-17)	0.015
NIBUT-f (s)	6.3±4.9 (1.1-17)	5.1±3.7 (1.1-17)	0.698
TBUT (s)	7.2±2.7 (3-14)	5.1±2.5 (1-10)	0.003
Schirmer-I (mm)	14.8±4.3 (10-25)	4.9±2.2 (1-9)	<0.001
OSS score	0.5±0.6 (0-3)	1.3±1.1 (0-5)	<0.001
Marx line score	3.2±2.5 (0-9)	5.0±2.4 (1-9)	0.028
LWE grade	0.3±0.5 (0-2)	1±0.8 (0-3)	<0.001
Meibomian gland loss area (%)	29.7±12.7 (8.7-66.5)	33.5±13.2 (14.5-69.4)	0.796

Data presented as mean ± standard deviation (range). DED: Dry eye disease, NIBUT-av: Average non-invasive tear break-up time, NIBUT-f: First non-invasive tear break-up time, TBUT: Tear break-up time, OSS: Ocular surface staining, LWE: Lid wiper epitheliopathy

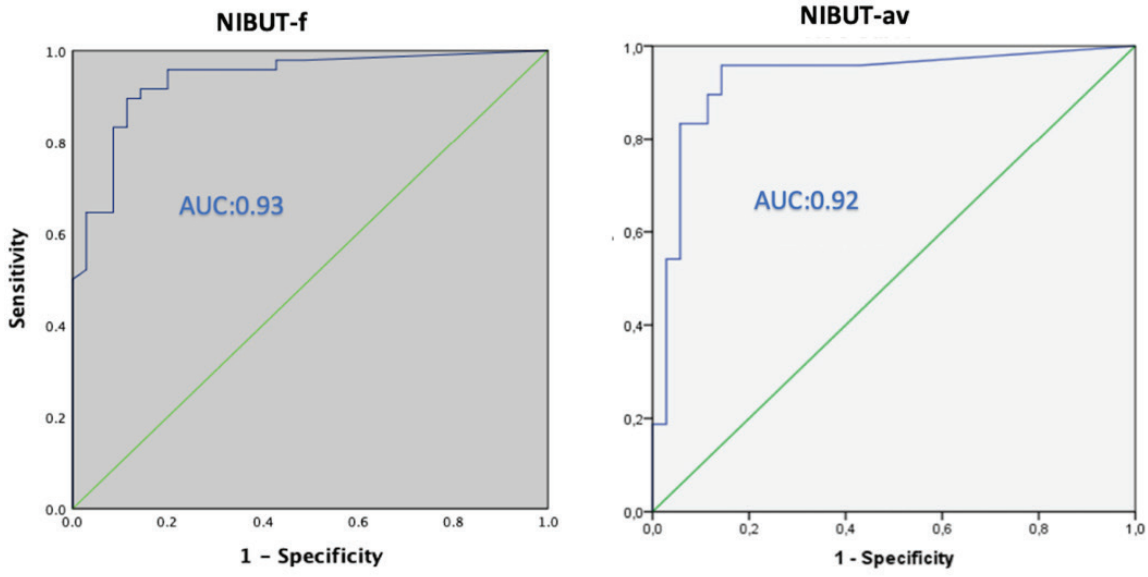

Figure 1. Receiver operating characteristic (ROC) curve analysis for first and average non-invasive break-up times (NIBUT-f and NIBUT-av) in dry eye disease patients
AUC: Area under the ROC curve

and AUC were 56% (95% CI: 36.8%-74.4%), 58% (95% CI: 40.9%-72.0%), and 0.63 (95% CI: 0.512-0.743), respectively (Figure 2). In the DED subgroup ROC analysis, the Youden index at the selected cut-off was 0.14 (0.56 + 0.58 – 1), reflecting limited discriminatory performance.

Correlation of NIBUT with Other Dry Eye Diagnostic Tests

Figure 3 illustrates the correlations between NIBUT-av and other DED diagnostic tests. A statistically significant and very strong positive correlation was observed between NIBUT and TBUT (r=0.905, 95% CI: 0.843-0.940, p<0.001). NIBUT also showed a moderate positive correlation with Schirmer-I test values (r=0.403, 95% CI: 0.202-0.575, p<0.001). In contrast, significant negative correlations were found between NIBUT and OSS score (r=-0.700, 95% CI: -0.809 to -0.553, p<0.001), meibomian gland loss (r=-0.601, 95% CI: -0.733 to -0.434, p<0.001), LWE grade (r=-0.597, 95% CI: -0.730 to -0.425, p<0.001), and Marx line score (r=-0.539, 95% CI: -0.690 to -0.359, p<0.001).

A multivariate linear regression analysis was performed to identify independent predictors of NIBUT-av. The overall model was statistically significant (R^2=0.795, p<0.001). Among the evaluated parameters, TBUT emerged as the only independent predictor of NIBUT-av (β=0.907, p<0.001). Other variables, including Schirmer-I test, OSS score, Marx line score, LWE grade, and meibomian gland loss, were not independently associated with NIBUT-av (all p>0.05) (Table 4).

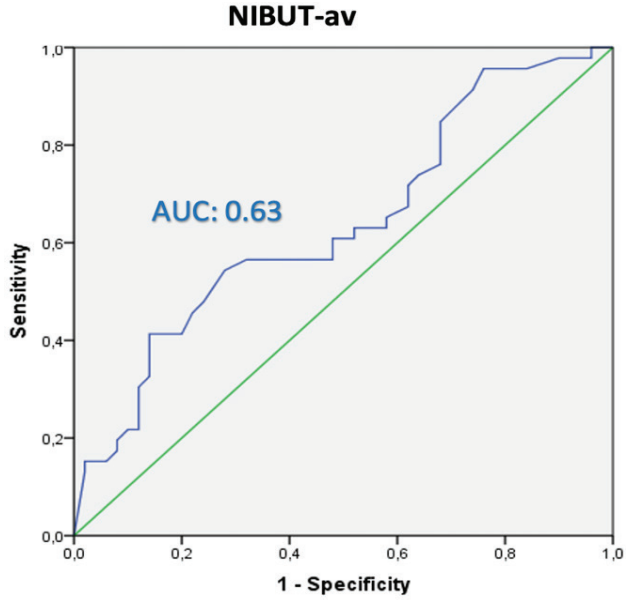

Figure 2. Receiver operating characteristic (ROC) curve analysis for average non-invasive break-up time (NIBUT-av) in evaporative dry eye disease patients
AUC: Area under the ROC curve

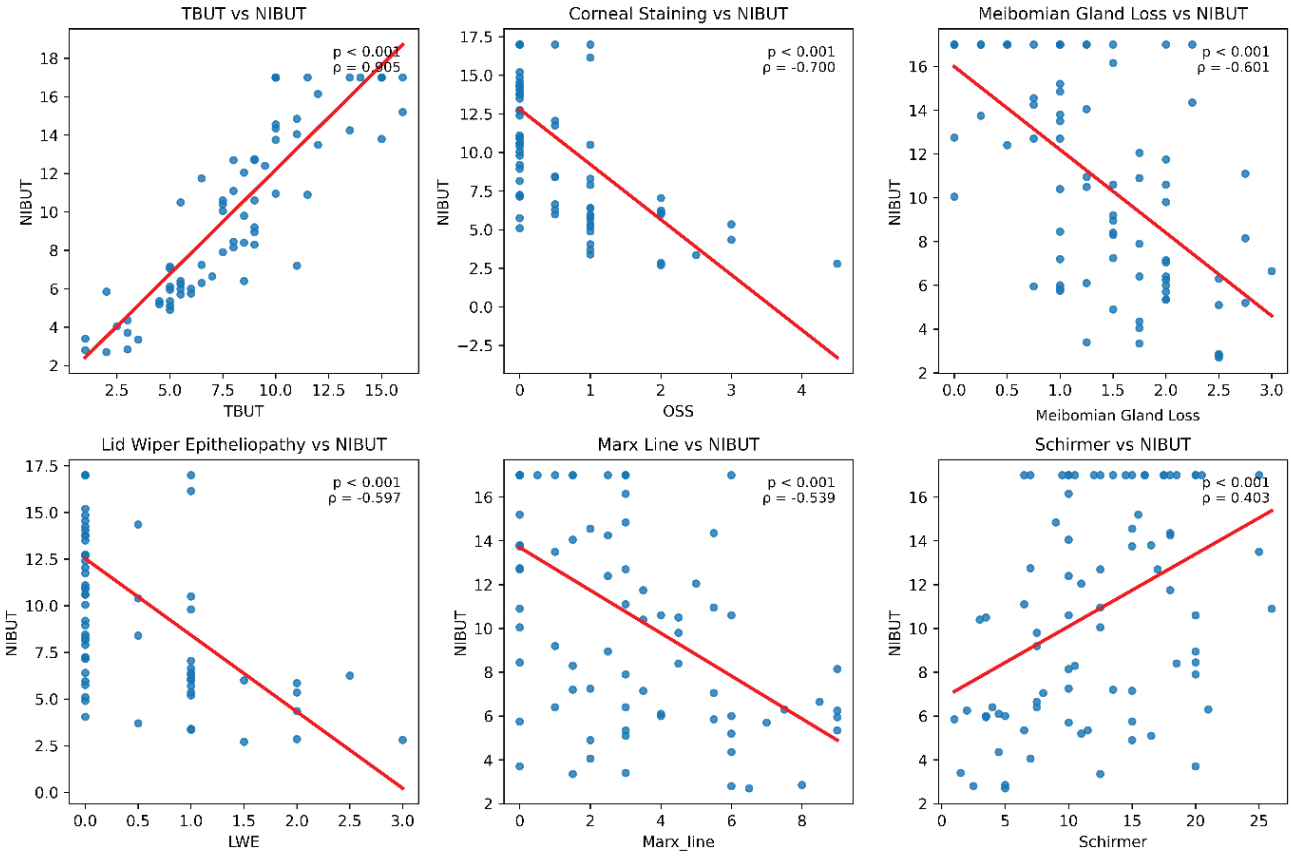

Figure 3. Correlation of non-invasive break-up time (NIBUT) with other dry eye diagnostic tests
TBUT: Tear break-up time, OSS: Ocular surface staining, LWE: Lid wiper epitheliopathy

Table 4. Multivariate linear regression analysis of factors associated with NIBUT-av			
Variable	**β (standardized coefficient)**	**Standard error**	**p**
TBUT (s)	0.907	0.085	**<0.001**
Schirmer-I (mm)	-0.041	0.058	0.488
OSS score	-0.732	0.584	0.215
Marx line score	-0.079	0.136	0.568
LWE grade	0.174	0.777	0.825
Meibomian gland loss	-0.842	0.446	0.063
NIBUT-av: Average non-invasive tear break-up time, TBUT: Tear break-up time, OSS: Ocular surface staining, LWE: Lid wiper epitheliopathy			

Discussion

This study aimed to determine the optimal NIBUT-f and NIBUT-av cut-off points for DED diagnosis and subgroup differentiation, as well as the correlation of these non-invasive measures with conventional clinical diagnostic methods. While several studies in the literature have compared NIBUT measurements across different devices,[23,24,25] we utilized the Sirius topography system for our automated assessments. We found that although the NIBUT cut-off value demonstrated high sensitivity and specificity for diagnosing DED overall, its ability to differentiate between evaporative and mixed subtypes was limited.

The first NIBUT measurement reported in the literature was conducted by Mengher et al.,[11] who used an instrument attached to a slit lamp biomicroscope that projected a rectangular grid pattern onto the cornea. Today, automated measurements can be performed using various devices. Based on NIBUT measurements obtained with the Sirius topography device, we determined cut-off values for DED diagnosis to be 10.7 seconds for NIBUT-f and 12.2 seconds for NIBUT-av, with AUC values of 0.93 and 0.92, respectively. We also analyzed the evaporative group specifically, for which the cut-off value was 7.2 seconds with an AUC of 0.63.

Kim et al.[23] investigated NIBUT values, tear break-up locations, and break-up patterns across DED subtypes using a Keratograph 5M. The cut-off values for DED diagnosis were determined to be 4.84 seconds for NIBUT-f and 8.62 seconds for NIBUT-av. In their study, the AUC values for DED diagnosis were reported as 0.671 and 0.640. However, when individual ROC analysis was performed for the aqueous-deficient type and the non-evaporative type, an increase in AUC values was observed. In contrast, in our study, the AUC value decreased when only the evaporative type was evaluated.

A study by Hong et al.[12] using a Keratograph reported the NIBUT cut-off value to be 2.65 seconds, with an AUC of 0.825. Additionally, in a study conducted by Muhafiz and Demir[17] with contact lens wearers, a TBUT of less than 10 seconds was accepted as indicative of tear instability. Based on Sirius topography measurements before contact lens wear, the cut-off values for NIBUT-f and NIBUT-av were identified as 8 seconds and 12.65 seconds, respectively. These values are similar to our cut-off values. Furthermore, they reported AUC values of 0.842 and 0.810, respectively.

In a different study conducted with DED patients, NIBUT measurements were performed on the same subjects using both a DR-1 and a Keratograph 5M. The cut-off values for DED diagnosis were found to be 3.9 seconds with the DR-1, compared to 6.31 seconds for NIBUT-f and 8.63 seconds for NIBUT-av with the Keratograph 5M (AUC values of 0.725, 0.720, and 0.748, respectively).[24] Further supporting this concept, a recent study by Zeri et al.[25] demonstrated that NIBUT measurements obtained from different non-invasive devices are not interchangeable, even within subjects. The authors showed that despite strong correlations between measurements, significant differences exist between devices due to variations in Placido disc configuration, illumination systems, and analysis algorithms. These findings indicate that agreement between devices does not necessarily imply equivalence, and that absolute NIBUT values—and consequently diagnostic cut-off thresholds—are inherently device-dependent. In this context, the relatively higher cut-off values observed in our study using the Sirius topography system should be interpreted within the technical framework of this specific device. Therefore, our results support the concept of device-specific cut-off values, emphasizing that NIBUT thresholds derived from one platform should not be directly extrapolated to others. This device dependency represents an important limitation in terms of clinical generalizability and highlights the need for either device-specific normative databases or standardization across measurement systems. The notable differences in cut-off values may be attributed to the measurements being taken with different devices. To the best of our knowledge, no other study has determined NIBUT cut-off values using Sirius topography in patients diagnosed with DED, and further studies comparing the measurements of the different devices could provide valuable guidance.

In our study, we compared evaporative and mixed types of DED and observed that in the mixed-type DED group, the NIBUT-av, TBUT, and Schirmer-I values were significantly lower, whereas the OSS, Marx line score, and LWE grade values were significantly higher. However, no significant difference was found between the subgroups for NIBUT-f and meibomian gland loss. Therefore, our findings suggest that NIBUT-av may be a more appropriate option for subgroup analysis than NIBUT-f.

Although there was a significant difference in NIBUT-av values between patients with evaporative and mixed-type dry eye, the relatively low AUC value (0.63) in the ROC analysis reflects the limited ability of NIBUT-av to distinguish between the evaporative and mixed subtypes of DED. Since both subtypes are characterized by tear film instability and consequently low NIBUT values, this is expected to result in significant overlap. However, the mixed subtype exhibited more severe clinical findings, consistent with the coexistence of aqueous deficiency and evaporative mechanisms. The limited discriminatory ability likely reflects the heterogeneous nature of DED, the presence of meibomian gland dysfunction as a dominant component in both groups, and the fact that NIBUT primarily measures tear film stability and may not capture subtype-specific differences. Additionally, the relatively small subgroup size and the device- and algorithm-dependent nature of NIBUT measurements may also have contributed to this poor performance.

In a subgroup analysis of DED patients by Lemp et al.,[26] Schirmer-I values for the evaporative and mixed types were reported as 16.3 mm and 3.2 mm, respectively, while the TBUT values were 4.4 seconds and 3.2 seconds, respectively. Additionally, higher grade corneal and conjunctival staining was observed in the mixed type. In

our study, the evaporative and mixed groups had Schirmer-I values of 14.8 mm and 4.9 mm and TBUT values of 7.2 seconds and 5.1 seconds, respectively. In another study, lower Schirmer-I and TBUT values, as well as higher OSS scores, were reported for the mixed type compared to the evaporative type.[23] Although the mentioned studies contain differences in their diagnostic criteria for subgroup analysis, their results are consistent with our findings.

The observed differences between evaporative and mixed DED subgroups may be explained by their underlying pathophysiological mechanisms. Evaporative DED is primarily associated with increased tear evaporation due to meibomian gland dysfunction, while aqueous tear production is relatively preserved, which may result in higher Schirmer-I values and less pronounced ocular surface damage. In contrast, mixed-type DED involves both increased evaporation and aqueous tear deficiency, leading to greater tear film instability, hyperosmolar stress, and more severe ocular surface involvement, as reflected by higher OSS, Marx line, and LWE scores.[27]

In the current study, NIBUT was compared with other DED tests and a positive correlation was observed with TBUT and Schirmer-I ($r=0.905$, $p<0.001$ and $r=0.403$, $p<0.001$, respectively). However, NIBUT showed negative correlations with OSS, meibomian gland loss, LWE grade, and Marx line score ($r=-0.700$, $r=-0.601$, $r=-0.597$, $r=-0.539$, respectively; all $p<0.001$). A study by Hong et al.[12] produced similar findings, reporting that NIBUT correlated with TBUT and Schirmer-I ($r=0.550$, $p<0.001$ and $r=0.405$, $p<0.001$, respectively). Additionally, Ozulken et al.[15] found that NIBUT measured using Sirius topography correlated with TBUT and Schirmer-I ($r=0.947$, $p<0.001$ and $r=0.166$, $p=0.030$, respectively). Karakılıç and Taşkiran Çömez[28] also found a positive correlation between NIBUT and TBUT ($r=0.473$, $p<0.001$).

In addition to correlation analysis, a multivariate regression model was constructed to determine independent predictors of NIBUT. Although several parameters showed significant correlations with NIBUT in univariate analysis, only TBUT remained an independent predictor in the multivariate model. This finding can be explained by the shared pathophysiological basis of DED parameters, particularly tear film instability. TBUT, as a direct measure of tear film break-up, likely reflects the core mechanism underlying NIBUT measurements, whereas other parameters such as OSS, LWE, Marx line score, and meibomian gland loss represent downstream or secondary manifestations. Therefore, the lack of independent association in multivariate analysis does not indicate a lack of relationship but rather suggests overlapping biological pathways among these variables. This result further supports the validity of NIBUT as a non-invasive surrogate for tear film instability.

Traditionally, TBUT measurement is a subjective method performed invasively using dye or strip application. With advancements in technology, non-invasive measurements can now be performed with objectivity and reproducibility. Future studies conducted with Sirius topography can utilize the cut-off values we obtained, with their high sensitivity and specificity. Its strong correlation with TBUT supports its applicability. Additionally, the NIBUT measurements obtained in our study demonstrated positive correlations with Schirmer-I values while showing negative correlations with meibomian gland loss, OSS score, LWE grade, and Marx line score. These findings highlight the potential of NIBUT as an objective, non-invasive, and effective diagnostic tool for DED.

Study Limitations

This study has several limitations. Due to its retrospective design, formal masking procedures were not implemented. However, clinical examinations and device-based measurements were performed independently by different individuals, and the examining clinician was not aware of the Sirius measurement results at the time of evaluation, which may have reduced potential measurement bias. In addition, inter-observer and intra-observer variability were not prospectively assessed, and therefore some degree of measurement variability cannot be excluded. Furthermore, due to the retrospective nature of the study, only two patients with pure aqueous-deficient DED were identified, which precluded a separate subgroup analysis for this category. Consequently, the exclusion of the aqueous-deficient subgroup of DED patients limits the generalizability of our findings to all subtypes of DED. Another limitation is that tear osmolarity and inflammatory biomarker testing, particularly tear MMP-9, were not assessed. Although our diagnostic approach was based on accepted TFOS DEWS II principles, the absence of these complementary measures may have reduced diagnostic completeness and limited characterization of tear film homeostasis and ocular surface inflammatory status. Consequently, some borderline cases or inflammation-predominant DED phenotypes may have been under-recognized or misclassified.

Conclusion

NIBUT demonstrated high sensitivity and specificity for the diagnosis of DED in our study population. It is a non-invasive and repeatable method that shows good correlation with other tests assessing ocular surface and meibomian gland function. However, its diagnostic performance appears to be lower when distinguishing between DED

subtypes. These findings should be interpreted with caution due to the retrospective design, relatively small sample size, and single-center nature of the study. Larger prospective, multicenter studies are warranted to further validate these findings and better evaluate the clinical utility of NIBUT in subclassifying DED.

Ethics

Ethics Committee Approval: This retrospective study was conducted with the approval of the Marmara University Faculty of Medicine's Ethics Committee (date: 15.11.2024; protocol code: 09.2024.1296) and in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from all subjects.

Declarations

Authorship Contributions

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

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Original Article

Refractive and Visual Outcomes in Unilateral Duane Retraction Syndrome: Influence of Ocular Motility

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Abstract

Objectives: To compare the refractive profiles and clinical characteristics of affected and fellow eyes in unilateral Duane retraction syndrome (DRS), emphasize subtype-related variations, and assess the impact of motility restriction and ocular findings on refractive status.

Materials and Methods: This retrospective cross-sectional study included 191 patients with unilateral DRS, comprising type I (n=162), type II (n=7), and type III (n=22). Best-corrected visual acuity (BCVA), cycloplegic autorefraction, astigmatism classification, and ocular alignment/motility findings were analyzed across DRS subtypes.

Results: The mean age at examination was 6.67±7.13 years, and 62.3% of the patients were female. Amblyopia was observed in 23.0% of patients, anisometropia in 18.6%, and abnormal head posture in 52.7% of patients. Esotropia (42.0%) was more prevalent than exotropia (11.7%), and the majority of patients (61.4%) exhibited grade 4 horizontal limitation. Compared with fellow eyes, DRS eyes exhibited a substantially lower BCVA (p<0.001), higher spherical power (p=0.025), and greater cylindrical power (p<0.001). In both DRS (60.7%) and non-DRS (72.3%) eyes, the predominant pattern was with-the-rule astigmatism. There were no discernible variations in astigmatism subtypes among motility limitation grades or DRS subtypes. The cylindrical refractive error was independently associated with abnormal head posture (p=0.007) and horizontal deviation type (p=0.029) according to multiple regression analysis.

Conclusion: Unilateral DRS is characterized by diminished visual function and increased refractive error, with cylindrical outcomes affected by head posture and type of deviation. The findings highlight the importance of integrating motility parameters into refractive evaluation and surgical planning in DRS.

Keywords: Duane retraction syndrome, refraction, astigmatism, ocular motility

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Introduction

Duane retraction syndrome (DRS) is a rare congenital cranial dysinnervation and ocular motility disorder characterized by anomalous innervation of the lateral rectus muscle by branches of the oculomotor nerve in the setting of an absent or hypoplastic abducens nerve.[1] This miswiring leads to a limitation in horizontal movement, most commonly in abduction, accompanied by globe retraction and narrowing of the palpebral fissure on attempted adduction. Vertical gaze abnormalities, particularly upshoots and downshoots, may present as associated clinical features. Based on electromyographic findings, Huber[2] classified DRS into three subtypes: Type I, characterized by limited abduction with near-normal adduction; Type II, defined by limited adduction with near-normal abduction; and Type III, which presents with limitations in both abduction and adduction.

The refractive error profile of DRS consistently demonstrates astigmatism, most commonly with-the-rule (WTR) as the predominant finding, whereas against-the-rule

(ATR) and oblique astigmatism show variable distribution across subtypes.[3] Khorrami-Nejad et al.[4] reported that affected eyes in unilateral DRS exhibited higher levels of astigmatism compared with fellow eyes in a large patient cohort. In contrast, Yuzbasıoglu et al.[5] found no significant differences in spherical, cylindrical, or spherical equivalent values, and further showed that the grade of ocular motility restriction was not significantly correlated with refractive errors, suggesting that restriction severity alone does not determine refractive status. Nevertheless, characteristic subtype-specific patterns, such as an increased prevalence of ATR in Types II and III, indicate that motility profiles may be associated with distinct refractive configurations.[3]

While movement restriction grade has been analyzed previously,[5] the potential influence of additional ocular motility findings, such as vertical deviation and type of horizontal deviation as well as abnormal head posture, on refractive status has not been systematically evaluated. In this study, we aimed to assess refractive errors and clinical characteristics in a large cohort of unilateral DRS patients, comparing affected and fellow eyes, identifying subtype-specific differences, and examining the combined effects of movement restriction grade and other ocular motility findings on refractive components.

Materials and Methods

Patient Selection

We retrospectively reviewed the medical records of patients diagnosed with DRS at Dokuz Eylül University Hospital, İzmir, between January 2000 and January 2024. Patients with a confirmed diagnosis were eligible for inclusion, while those with a history of ocular or cranial trauma, prior ocular surgery, high ametropia (spherical equivalent > ±6.00 diopter [D]), or other ocular/systemic disorders that could affect refractive status or ocular motility (e.g., keratoconus, thyroid eye disease, neuromuscular disorders) were excluded. Patients with high ametropia were not included because extreme refractive values may disproportionately influence the overall distribution and introduce instability in regression analyses. This approach was adopted to enable a more homogeneous assessment of refractive patterns specific to DRS. Patients with incomplete or inconsistent ophthalmologic examination data were also excluded. Demographic data and ophthalmic examination findings were collected from the records.

This study followed the Declaration of Helsinki, with approval from the Dokuz Eylül University Institutional Research Ethics Committee (decision no 2024/42-30, dated December 18, 2024). Informed consent was waived due to the retrospective nature of the study.

Ophthalmic Examination

All patients underwent a comprehensive ophthalmological examination, including best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, fundus examination, and ocular motility assessment. BCVA was measured using a Snellen chart at a distance of 4 meters. Cycloplegic autorefraction was performed with a Nidek ARK-530 device 30 minutes after instillation of 1% cyclopentolate in both eyes, and measurements included sphere, cylinder, and axis values. For consistency of analysis, all cylindrical values were converted to the positive cylinder format, and subsequent calculations were performed using these values. Astigmatism was classified as WTR (steep meridian within 90±30 degrees), ATR (steep meridian within 180±30 degrees), or oblique (steep meridian outside WTR and ATR ranges). The spherical equivalent was calculated as the spherical value plus half of the cylindrical value. Anisometropia was defined as an interocular spherical equivalent difference of at least one D, and amblyopia was defined as a BCVA difference of two or more lines between the eyes or a BCVA of 20/30 or worse in either eye.

Ocular motility was evaluated with duction and version testing. In cooperative patients, ocular alignment was assessed using the prism cover test at both distance (6 m) and near (40 cm) in primary gaze. In younger or uncooperative children, alignment was evaluated using the Hirschberg or Krimsky methods. The manifest horizontal deviation in the primary gaze position was used for analysis. Primary and secondary deviations were not analyzed separately. Strabismus was defined as a manifest horizontal deviation greater than 5 prism D, while vertical deviation was defined as hypertropia or hypotropia greater than 2 prism D. Although these thresholds were used for clinical classification, quantitative deviation measurements were not consistently available for all patients; therefore, deviation magnitude was not included in the statistical analyses. Patients with no observable deviation in primary position were considered orthotropic. Patients were classified according to the Huber classification system (Types I-III), as described above. In addition to Huber's original classification, an exotropic variant Type IV, described in subsequent reports, was also included in the classification. This subtype is characterized by primary position exotropia with a compensatory contralateral head turn, full abduction, absent adduction, and simultaneous abduction of both eyes during contralateral gaze. The presence of upshoots, downshoots, and abnormal head posture was recorded during orthoptic evaluation.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 28.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as mean ± standard deviation for continuous variables and as frequencies and percentages for categorical variables. The normality of data distribution was assessed using the Shapiro-Wilk test. Comparisons of continuous variables between the affected (DRS) and unaffected (non-DRS) eyes were conducted using paired samples t-tests for normally distributed data. Differences in categorical variables, such as astigmatism subtypes across groups, were analyzed using the chi-square test. For comparisons among more than two independent groups (e.g., refractive components across DRS subtypes), one-way analysis of variance (ANOVA) was employed for normally distributed variables, followed by Tukey's Honestly Significant Difference (HSD) post-hoc test when appropriate.

Associations between the grade of horizontal duction limitation and astigmatism subtype were evaluated using the chi-square test. To identify factors independently associated with cylindrical refractive error in the affected eye, a multiple linear regression model was constructed, incorporating ocular motility characteristics and other relevant clinical parameters as predictor variables. For multiple linear regression analysis, multicollinearity was assessed using variance inflation factor (VIF) values. Regression assumptions including linearity, homoscedasticity, and normality of residuals were evaluated using standard residual diagnostic plots. A p value <0.05 was considered statistically significant for all analyses.

Results

A total of 191 patients diagnosed with unilateral DRS were included in the analysis. The mean age at examination was 6.67±7.13 years (range: 1-35 years). Of the participants, 119 (62.3%) were female and 72 (37.7%) were male. The right eye was affected in 54 cases (28.3%), whereas the left eye was affected in 137 cases (71.7%). Regarding clinical subtype distribution, Type I was the most common, observed in 162 patients (84.8%), followed by Type III in 22 patients (11.5%) and Type II in 7 patients (3.7%).

Anisometropia was present in 33 patients (18.6%), and amblyopia was detected in 40 patients (23.0%). Abnormal head posture was observed in 99 patients (52.7%). Vertical deviation was present in 7 patients (3.7%). Regarding horizontal deviation patterns, 79 patients (42.0%) had esotropia and 22 patients (11.7%) had exotropia.

Regarding the degree of horizontal limitation, most patients (61.4%) had grade 4 abduction/adduction limitation, followed by grade 3 (17.5%), grade 2 (15.9%), and grade 1 (5.3%) limitation (n=189).

Refractive Characteristics Across DRS Subtypes

Among the refractive components, only the spherical values of the non-DRS eyes showed a significant difference across subtypes (p=0.019). Post-hoc analysis for the non-DRS eye sphere values revealed a statistically significant difference between Type I and Type III subgroups (p=0.023, Tukey HSD). No other pairwise comparisons reached statistical significance. Among DRS subtypes, the spherical equivalent in non-DRS eyes showed a trend toward significance (p=0.056). No other significant differences were identified across subtypes in terms of BCVA or refractive components in DRS eyes. A detailed comparison of visual acuity and refractive parameters between DRS and non-DRS eyes, as well as across unilateral DRS subtypes, is provided in Table 1.

In DRS eyes, WTR astigmatism was the most common pattern, observed in 82 cases (60.7%), followed by oblique astigmatism in 24 cases (17.8%) and ATR astigmatism in

Table 1. Analysis of visual acuity and refractive components across unilateral DRS subtypes

	Eye	Total (n=191) (Mean ± SD)	Type I (n=162) (Mean ± SD)	Type II (n=7) (Mean ± SD)	Type III (n=22) (Mean ± SD)	p
BCVA	DRS eye	0.84±0.23	0.84±0.21	0.90±0.15	0.77±0.30	0.374
	Non-DRS eye	0.92±0.14	0.91±0.13	1.00±0.00	0.93±0.14	0.235
Sphere	DRS eye	0.61±1.72	0.77±1.65	0.54±2.64	0.01±1.78	0.236
	Non-DRS eye	0.42±1.49	0.63±1.55	-0.12±0.78	-0.39±1.12	**0.019**
Cylinder	DRS eye	0.80±0.72	0.75±0.57	0.75±0.57	1.08±1.34	0.184
	Non-DRS eye	0.58±0.58	0.52±0.46	0.79±0.57	0.82±0.91	0.064
SE	DRS eye	1.01±1.73	1.14±1.70	0.91±2.60	0.55±1.61	0.425
	Non-DRS eye	0.71±1.49	0.90±1.58	0.27±0.69	0.01±1.01	0.056

DRS: Duane retraction syndrome, BCVA: Best-corrected visual acuity, SD: Standard deviation, SE: Spherical equivalent

29 cases (21.5%) (n=135). No significant difference was observed between the affected eyes of unilateral DRS types and astigmatism subtypes. Table 2 presents the relationship between DRS type and astigmatism subtype in the affected eye.

Comparison Between Affected and Fellow Eyes

Paired samples analysis demonstrated a statistically significant difference in BCVA between DRS and non-DRS eyes (0.84±0.23 vs. 0.92±0.14, p<0.001). The mean spherical power was significantly higher in DRS eyes compared to non-DRS eyes (0.67±1.73 D vs. 0.48±1.53 D, p=0.025). Similarly, the cylindrical power was significantly greater in DRS eyes than in non-DRS eyes (0.80±0.71 D vs. 0.58±0.55 D, p<0.001).

In DRS eyes, the most prevalent pattern was WTR astigmatism, identified in 82 cases (60.7%). In non-DRS eyes, WTR astigmatism was also predominant (72.3%), while ATR astigmatism and oblique patterns were found in 25 (19.2%) and 11 (8.5%) cases, respectively (n=130).

Impact of Ocular Motility Parameters on Astigmatism

The distribution of astigmatism subtypes was similar across ocular motility limitation grades, with WTR astigmatism being the most common in all grades, and the degree of limitation did not significantly affect subtype distribution, as shown in Table 3. To further explore the potential influence of ocular motility characteristics and related clinical factors on refractive cylinder magnitude in the DRS eye, multiple linear regression analysis was performed. The overall model was statistically significant (F=3.600, p=0.027), explaining 56.2% of the variance in cylindrical value (R^2=0.562; adjusted R^2=0.406). Abnormal head posture (β=0.754, p=0.007), and the type of horizontal deviation (esotropia/exotropia) (β=-0.622, p=0.029) were independently associated with cylindrical refractive error. In contrast, ocular motility restriction grade (p=0.117) and vertical deviation (p=0.051) did not reach statistical significance. Multicollinearity analysis showed acceptable values with VIF values ranging between 1.35 and 2.08. The results of the multiple linear regression analysis are presented in Table 4.

Discussion

This study evaluated refractive characteristics, visual acuity, and ocular motility parameters in a large cohort of patients with unilateral DRS. By analyzing both affected and fellow eyes and incorporating multiple ocular motility-related variables, we were able to identify factors independently associated with refractive error patterns. To our knowledge, no previous study has simultaneously assessed the influence of movement restriction grade, abnormal head posture, vertical deviation, and horizontal deviation type on refractive components in DRS.

Table 2. Astigmatism subtypes in affected eyes according to DRS classification

DRS type	WTR astigmatism n (%)	ATR astigmatism n (%)	Oblique astigmatism n (%)	Total n (%)
Type I	71 (62.8)	22 (19.5)	20 (17.7)	113 (100.0)
Type II	2 (33.3)	4 (66.7)	0 (0.0)	6 (100.0)
Type III	9 (56.3)	3 (18.8)	4 (25.0)	16 (100.0)
Total	82 (60.7)	29 (21.5)	24 (17.8)	135 (100.0)

p=0.078 represents the overall chi-square test comparing the distribution of astigmatism subtypes (WTR, ATR, oblique) across DRS subtypes. DRS: Duane retraction syndrome, ATR: Against-the-rule, WTR: With-the-rule

Table 3. Distribution of astigmatism subtypes based on limitation grade in DRS

Horizontal ocular motility limitation grade	WTR astigmatism n (%)	ATR astigmatism n (%)	Oblique astigmatism n (%)	Total n (%)	p
1	4 (66.7)	2 (33.3)	0 (0.0)	6 (100.0)	0.731
2	13 (59.1)	6 (27.3)	3 (13.6)	22 (100.0)	
3	16 (69.6)	4 (17.4)	3 (13.0)	23 (100.0)	
4	49 (58.3)	17 (20.2)	18 (21.4)	84 (100.0)	
Total	82 (60.7)	29 (21.5)	24 (17.8)	135 (100.0)	

p value represents the overall chi-square test comparing the distribution of astigmatism subtypes (WTR, ATR, oblique) across different grades of ocular motility limitation. DRS: Duane retraction syndrome, WTR: With-the-rule, ATR: Against-the-rule

Table 4. Multiple linear regression analysis of factors associated with cylindrical value in DRS eyes					
Predictor variable	**B (unstandardized)**	**SE**	**β (standardized)**	**t**	**p**
Horizontal deviation	-0.429	0.176	-0.622	-2.438	**0.029**
Abnormal head posture	0.780	0.248	0.754	3.149	**0.007**
Vertical deviation	0.783	0.368	0.477	2.130	0.051
Ocular motility restriction grade	-0.199	0.119	-0.409	-1.671	0.117
Model statistics: R^2=0.562, Adjusted R^2=0.406, F=3.600, p=0.027. DRS: Duane retraction syndrome, SE: Standard error					

In our cohort, only the spherical values of the non-DRS eyes differed significantly across DRS subtypes, with a difference between Type I and Type III, whereas other refractive parameters showed no variation. Khorrami-Nejad et al.[4] investigated refractive conditions and amblyopia rates in 582 patients with DRS and reported the highest hyperopic spherical values in Type I and the lowest in Type III in both DRS and non-DRS eyes. They also noted higher cylindrical values in Type II and Type III compared with Type I non-DRS eyes. In another study, Khorrami-Nejad et al.[3] compared astigmatism in 312 DRS patients and found similar spherical and cylindrical values between affected and fellow eyes in unilateral cases. They further showed that WTR astigmatism was more common in Type I DRS, whereas ATR astigmatism predominated in Type III.

These subtype-specific restriction patterns may influence binocular vision and visual development. Distinct visual inputs from each eye can result in discrepancies in refractive error in the fellow, non-DRS eye. To better understand the refractive error observed in these eyes, the role of emmetropization must be taken into consideration. Emmetropization is the developmental process by which the eye adjusts its optical power and axial length to reduce refractive error. It functions as an interocular rather than an entirely independent monocular process. Therefore, the emmetropization of one eye may be influenced by motility restriction in the other, potentially explaining the presence of refractive error in non-DRS eyes.[6,7] Moreover, strabismus itself may interfere with the normal course of emmetropization, further contributing to refractive anomalies.[8]

The spherical difference observed between Type I and Type III non-DRS eyes may also be theoretically related to convergence mechanisms and binocular vision. Marella et al.[9] investigated convergence in DRS subtypes and reported that patients with Type III DRS exhibited poorer convergence compared with those with Type I, and it was also observed that patients with DRS had poorer binocular vision than healthy individuals. However, as convergence was not assessed in our study, no direct conclusions can be drawn regarding this association.

We found that DRS eyes had significantly poorer visual acuity and higher spherical and cylindrical refractive errors than their fellow eyes, a difference that may be attributed to anisometropic and strabismic amblyopia. Consistently, the amblyopia rate in our study was in line with previous reports.[10,11] Fixation is generally favored by the dominant eye, primarily determined by ocular alignment and relative visual acuity, which may contribute to the observed interocular differences in refractive parameters.[12] According to our findings, the presence of DRS was associated with an increased risk of hypermetropia in the affected eyes relative to their contralateral counterparts. Kekunnaya et al.[13] reported similar results and additionally observed shorter axial lengths in DRS eyes. Khorrami-Nejad et al.[3] also reported lower BCVA and higher cylinder values in affected eyes compared with fellow eyes, consistent with our results. These findings may be explained by abnormal innervation patterns or concurrent activation of the horizontal recti in DRS, which may generate mechanical forces on the globe, leading to corneal deformation and astigmatism. Our hypothesis is that aberrant innervation, co-contraction of the horizontal rectus muscles, and globe retraction in DRS may indirectly affect the ocular surface and visual development, thereby contributing to refractive patterns. Nonetheless, since these factors were not statistically assessed in the current study, a direct causal relationship cannot be determined. Moreover, the shorter axial length commonly observed in affected eyes predisposes them to hypermetropic refractive errors. Young et al.[14] similarly reported higher astigmatism values in DRS eyes compared to non-DRS eyes. However, Yuzbasıoglu et al.[5] found no significant differences in spherical or cylindrical refractive errors between DRS and non-DRS eyes. Given the congenital nature of DRS, early initiation of care and consistent follow-up in children may be particularly important for the timely detection and management of refractive errors and amblyopia.

In this study, WTR astigmatism was the most common subtype in both DRS and non-DRS eyes, with no significant difference in distribution. A previous study reported higher rates of WTR astigmatism in Type I DRS eyes and higher rates of ATR astigmatism in Type II and Type III DRS eyes.[3] However, Young et al.[14] demonstrated that DRS eyes

exhibited higher rates of ATR astigmatism, while WTR astigmatism occurred at similar frequencies. Additionally, oblique astigmatism was found to be more prevalent in DRS eyes compared with fellow eyes.

Wang et al.[15] conducted a large-scale study of 21,415 children aged 5-13 years and found that WTR astigmatism was the most common pattern, whereas ATR and oblique astigmatism were less frequently observed. These results are consistent with our findings. Other researchers have proposed that increased eyelid pressure may also influence astigmatism and corneal topography.[16] Osaki et al.,[17] for example, investigated patients with hemifacial spasm and showed that botulinum toxin type A treatment reduced astigmatism by temporarily decreasing eyelid tension, thereby lessening the mechanical interaction between the cornea and eyelids. Based on this rationale, one might expect a higher prevalence of different astigmatism types in DRS and its subtypes compared with healthy individuals. Nevertheless, our findings were consistent with those reported in the general healthy population. The absence of a notable difference in astigmatism subtype distribution may suggest that DRS-related mechanical factors, including globe retraction, palpebral fissure narrowing, and horizontal rectus co-contraction, are inadequate alone to modify the overall astigmatic axis pattern, or that their effects may be mitigated by individual variations in corneal and lenticular components. However, it should be noted that the cylindrical values obtained by autorefractometry reflect total astigmatism. In the absence of corneal topographic measurements, the corneal and lenticular components of astigmatism could not be distinguished. Therefore, interpretations regarding mechanical effects should not be regarded as direct evidence, but rather as possible pathophysiological explanations.

Although the grade of ocular motility restriction did not significantly influence astigmatism subtype distribution, multiple linear regression analysis showed that abnormal head posture and the type of horizontal deviation were independently associated with cylindrical refractive error. The potential mechanism linking aberrant head posture to cylindrical refractive error may involve chronic compensatory head positioning, which may alter the habitual gaze position and the relationship between the eyelid and the cornea. In DRS, atypical head posture is mostly utilized to preserve binocular single vision and reduce diplopia; yet, extended non-primary gaze posture may alter palpebral fissure morphology, eyelid pressure distribution, and ocular surface biomechanics. These factors may contribute to changes in total astigmatism; however, the lack of corneal topography and quantitative head posture assessments in this investigation precludes the establishment of a direct causal relationship. There are limited studies in the literature examining changes in astigmatism and its subtypes in relation to ocular motility restriction. Yuzbasıoglu et al.[5] found no significant differences in astigmatism among different levels of movement restriction, consistent with our results. Abnormal head posture plays a crucial role in enabling DRS patients to sustain binocular vision, and it was observed in 52.7% of our patients, a rate comparable to previous reports.[18,19] Yeniad and Gezer[20] investigated the association between corneal topography and abnormal head posture in DRS and hypothesized that abnormal head position may result from distortions in corneal contour and lid structure, thereby reducing astigmatism and improving visual acuity.

In 2011, the Multi-Ethnic Pediatric Eye Disease Study and the Baltimore Pediatric Eye Disease Study Groups examined 9,970 children aged 6 to 72 months and established a correlation between astigmatism and strabismus, particularly exotropia.[21] The relationship between strabismus and astigmatism has also been investigated in studies assessing refractive errors before and after horizontal muscle surgery. Karakosta et al.[22] reported that astigmatism may increase or shift its axis toward WTR astigmatism. These results may underscore the importance of careful surgical planning, as the potential risk of postoperative astigmatism progression must be considered. Accordingly, the main contribution of our study is not merely to demonstrate the presence of refractive error but to identify its association with cylindrical refractive error and specific motility-related clinical features, particularly abnormal head posture and horizontal deviation type.

Study Limitations

The retrospective design may have introduced selection bias. Additionally, visual acuity measurements were analyzed in their original decimal (Snellen) format as documented in the medical records, rather than being converted to logarithm of the minimum angle of resolution values. Although age was initially included in the regression model, it was not found to be an independent predictor of cylindrical refractive error. Nevertheless, the wide age range may still influence refractive development, including emmetropization and astigmatic axis changes, and should be considered when interpreting the results. Moreover, the absence of corneal topography data limits our ability to distinguish whether the source of astigmatism is corneal or lenticular in origin. Therefore, the corneal origin of the observed astigmatism could not be directly demonstrated, and the interpretations regarding mechanical effects should be considered speculative and limited to possible pathophysiological explanations.

Another limitation is the absence of precise measurement of the degree of abnormal head posture, as well as the lack of a quantitative analysis assessing its correlation with refractive error. Furthermore, the distribution of participants across DRS subtypes was not well balanced, which may have reduced the robustness of subtype-specific comparisons. In addition, refractive examinations were performed at a single time point, precluding evaluation of longitudinal changes in refractive status. Patients with high ametropia were excluded to reduce the influence of extreme refractive values and improve the interpretability of regression analyses; however, this may limit the generalizability of the findings to DRS patients with high ametropia. Standardized quantitative deviation measurements and consistent documentation of the fixing/dominant eye were also unavailable, preventing analysis of deviation magnitude and potentially affecting the interpretation of visual acuity outcomes and interocular comparisons. Although affected-fellow eye comparisons partially controlled for individual variability, the fellow eye cannot be considered a fully independent healthy control; therefore, the findings should be interpreted primarily as interocular differences. Finally, as the study was conducted in a single tertiary referral center, the findings may not be fully generalizable to broader populations.

Conclusion

This study confirms that unilateral DRS eyes tend to exhibit poorer visual acuity and greater refractive error magnitude compared to fellow eyes, with WTR astigmatism being the predominant subtype in both. While movement restriction grade alone was not associated with astigmatism type, abnormal head posture and horizontal deviation type emerged as independent predictors of cylindrical refractive error. These findings underscore the importance of a comprehensive evaluation of ocular motility parameters when assessing refractive status in DRS, with potential implications for both refractive correction strategies and surgical planning.

Ethics

Ethics Committee Approval: This study followed the Declaration of Helsinki, with approval from the Dokuz Eylül University Institutional Research Ethics Committee (decision no 2024/42-30, dated December 18, 2024).

Informed Consent: Informed consent was waived due to the retrospective nature of the study.

Declarations

Authorship Contributions

Surgical and Medical Practices: A.Y., A.T.B., Concept: B.H.Ü., Ö.U.F., C.D.E., Design: B.H.Ü., Ö.U.F., C.D.E., Data Collection or Processing: B.H.Ü., Analysis or Interpretation: B.H.Ü., C.D.E., Literature Search: B.H.Ü., Writing: B.H.Ü., Ö.U.F., C.D.E., A.Y., A.T.B.

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Original Article

Accuracy of Contemporary Intraocular Lens Calculation Formulas Based on Swept-Source OCT Biometry in Eyes with Capsular Tension Ring

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Abstract

Objectives: To compare the refractive prediction accuracy of contemporary intraocular lens (IOL) calculation formulas based on swept-source optical coherence tomography (OCT) biometry in cataract surgery with capsular tension ring (CTR) implantation, and to assess for systematic postoperative refractive tendencies.

Materials and Methods: This retrospective study included 98 eyes of 92 patients who underwent phacoemulsification with in-the-bag IOL and CTR implantation. Preoperative biometry utilized swept-source OCT (ARGOS, Alcon). Refractive prediction accuracy was evaluated for the Barrett Universal II, Haigis, SRK/T, and Holladay II formulas. Main outcomes included mean prediction error, mean absolute error (MAE), median absolute error (MedAE), and percentages of eyes within ±0.25, ±0.50, and ±1.00 diopter (D).

Results: The mean age was 73.0±8.1 years, and the mean axial length was 23.03±1.04 mm. Barrett Universal II yielded the lowest MAE and MedAE (0.36±0.34 D and 0.24 D, respectively), followed by Holladay II (0.40±0.32 D and 0.30 D). Higher MAE was observed with SRK/T (0.45±0.37 D) and Haigis (0.54±0.45 D). MAE differed significantly among the formulas ($p<0.001$), with pairwise comparisons showing that Barrett Universal II and Holladay II performed similarly ($p>0.05$) and better than both Haigis and SRK/T (all $p\leq0.003$). The highest percentage of eyes within ±0.25 D was observed with Barrett Universal II (52.04%), whereas Holladay II showed the highest percentage within ±0.50 D (69.39%), and the two formulas tied within the ±1.00 D range (both 92.86%). Prediction errors were positive for all formulas, indicating a mild hyperopic shift.

Conclusion: In eyes undergoing cataract surgery with CTR implantation, Barrett Universal II and Holladay II showed more favorable refractive prediction accuracy than Haigis and SRK/T. A mild hyperopic shift was observed across all formulas. This finding may be clinically relevant when selecting the target refraction or IOL power in these eyes.

Keywords: Capsular tension ring, cataract surgery, intraocular lens calculation, swept-source optical coherence tomography, refractive outcome

Introduction

Cataract surgery is currently regarded as a refractive surgical procedure.[1] Therefore, accurate intraocular lens (IOL) power calculation is crucial for achieving optimal visual outcomes. With increasing patient expectations, even minor refractive errors have become clinically significant. Despite advances in biometric technologies and IOL power calculation formulas, refractive prediction errors still occur.[2] These errors are often associated with inadequacies in axial length measurement, keratometry, or the prediction of effective lens position.[3]

Capsular tension rings (CTRs) are commonly used in eyes with zonular weakness.[4] Typical indications include pseudoexfoliation (PEX) syndrome, trauma, and high myopia.[5] CTR implantation increases the stability of the capsular bag and helps maintain IOL centration.[6] Furthermore, it allows surgery to be performed more safely in eyes with compromised zonular support.[7] However, CTR implantation can alter the geometry and tension of the capsular bag.[6] These changes can affect the effective lens position, leading to unpredictable deviations in refractive

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outcomes.[8] In eyes with PEX, where CTRs are frequently used, it has been reported that the change in anterior chamber depth following phacoemulsification may be more pronounced compared to normal eyes.[9] Therefore, the prediction accuracy of existing IOL calculation formulas in eyes implanted with a CTR must be specifically evaluated from a clinical perspective.[8]

Modern optical biometry devices based on swept-source optical coherence tomography (OCT) provide reliable and reproducible measurements.[10] These devices offer better signal penetration, allowing for accurate axial length measurement even in eyes with dense cataract.[11] They can also improve the accuracy of IOL power calculations by providing detailed anterior segment parameters.[10] Numerous modern IOL calculation formulas have been developed to enhance refractive accuracy.[12] These formulas incorporate multiple biometric variables and utilize advanced theoretical models to better predict effective lens position.[12] However, because capsular bag dynamics may be altered in eyes that have undergone CTR implantation, the predictive performance of these formulas may differ from that in standard eyes. Therefore, it is important to specifically evaluate the accuracy of contemporary IOL calculation formulas in eyes implanted with a CTR.

The aim of this study was to compare the refractive prediction accuracy of contemporary IOL calculation formulas using preoperative swept-source OCT biometry in eyes undergoing cataract surgery with CTR implantation, and to evaluate systematic refractive tendencies that may emerge postoperatively in this patient cohort.

Materials and Methods

This retrospective, single-center study was conducted in the ophthalmology department of a tertiary university hospital. The study was approved by the Dokuz Eylül University Non-Interventional Research Ethics Committee (approval no: 2025/42-22, date: 01.12.2025) and was conducted in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective nature of the study.

The medical records of patients who underwent phacoemulsification and IOL implantation combined with CTR implantation were reviewed retrospectively for inclusion. Only eyes with in-the-bag IOL implantation and available postoperative refraction data between 1 and 3 months were included. Patients with a history of corneal refractive surgery were excluded. Eyes with irregular astigmatism, combined ocular surgery, corneal pathology affecting keratometry, or sulcus, anterior chamber, or scleral-fixated IOL implantation were also excluded. Furthermore, we excluded eyes that developed intraoperative or postoperative complications that could affect refractive outcomes, as well as eyes with missing postoperative refractive data. For patients who underwent bilateral surgery, both eyes were included if they met the eligibility criteria.

Preoperative biometry was performed using a swept-source OCT-based biometer (ARGOS, Alcon, Fort Worth, TX, USA). Axial length, keratometry values, and anterior chamber depth were recorded. IOL power calculations were performed using the Barrett Universal II, Haigis, SRK/T, and Holladay II formulas. All eyes were implanted with an SA60AT model foldable posterior chamber IOL in the capsular bag (Alcon Laboratories, Inc., Fort Worth, TX, USA). The predicted postoperative refraction value was recorded for each formula. For constant optimization, an independent optimization cohort comprising 50 eyes that underwent uneventful phacoemulsification with the implantation of the same IOL model, without a CTR, was evaluated. The mean prediction error (MPE) of each formula in this cohort was considered the formula-specific correction value and subtracted from the prediction errors in the CTR cohort to obtain the optimized prediction error.[13]

The difference between the postoperative spherical equivalent and the predicted spherical equivalent was defined as the prediction error. For each formula, the MPE, mean absolute error (MAE), and median absolute error (MedAE) were calculated. Additionally, the percentages of eyes with a prediction error value within ±0.25 D, ±0.50 D, and ±1.00 diopter (D) were determined. Subgroup analyses were based on the absolute prediction error of the Barrett Universal II formula. These analyses were performed according to CTR diameter, axial length, anterior chamber depth, mean keratometry, and IOL power. Furthermore, absolute prediction errors were compared between eyes with and without PEX.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics software (version 25.0; IBM Corp., Armonk, NY, USA). The normality of the data distribution was assessed using the Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation or median, depending on their distribution. Absolute prediction errors were compared among the formulas using the Friedman test, and post hoc pairwise comparisons were performed when significant differences were detected. For subgroup analyses, the independent samples t-test or Mann-Whitney U test was used, depending on the data distribution. Categorical data were presented as numbers and percentages. A p value < 0.05 was considered statistically significant. To evaluate whether the inclusion of both eyes of the same patient

affected the results, a sensitivity analysis was performed by randomly selecting one eye from each patient (n=92).

Results

The study included a total of 98 eyes of 92 patients. The mean age was 73.0±8.1 years, and the mean axial length was 23.03±1.04 mm. The demographic characteristics and biometric data of the patients are summarized in Table 1. In the optimization cohort of 50 eyes without CTR, the MPE was close to zero for all formulas (Barrett Universal II: +0.03 D, Haigis: +0.05 D, Holladay II: −0.06 D, SRK/T: +0.04 D).

MPE values were +0.21±0.45 D for Barrett Universal II, +0.24±0.66 D for Haigis, +0.32±0.49 D for SRK/T, and +0.19±0.48 D for Holladay II. Positive MPE values in all formulas indicated a mild hyperopic shift. MAE values ranged from 0.36±0.34 D to 0.54±0.45 D among the evaluated formulas. The lowest MAE values were observed with Barrett Universal II (0.36±0.34 D) and Holladay II (0.40±0.32 D), followed by SRK/T (0.45±0.37 D) and Haigis (0.54±0.45 D). MedAE was lowest for Barrett Universal II (0.24 D). This was followed by Holladay II (0.30 D), SRK/T (0.33 D), and Haigis (0.44 D).

Table 1. Demographic data and biometric characteristics of the patients

Variable	Value
Eye, n	98
Patients, n	92
Age (years), mean ± SD	73.03±8.10
Gender, male/female, n	46/52
Side, right/left, n	54/44
Axial length (mm), mean ± SD	23.03±1.04
Anterior chamber depth (mm), mean ± SD	3.13±0.43
Mean keratometry (D), mean ± SD	44.12±1.55
CTR diameter, 10-12 mm/11-13 mm, n	68/30

SD: Standard deviation, D: Diopter, CTR: Capsular tension ring

The difference in MAE among the formulas was statistically significant (p<0.001). In post-hoc pairwise comparisons, both Barrett Universal II and Holladay II demonstrated significantly lower MAE values compared to Haigis (both p<0.001) and SRK/T (p<0.001 and p=0.003, respectively). There was no statistically significant difference between Barrett Universal II and Holladay II (p=0.164), or between SRK/T and Haigis (p=0.131).

The percentage of eyes with prediction error values within ±0.25 D was highest for Barrett Universal II (52.04%), followed by Holladay II (41.84%), SRK/T (38.78%), and Haigis (32.65%). Within the ±0.50 D range, Holladay II showed the highest percentage (69.39%), followed by Barrett Universal II (67.35%), SRK/T (65.31%), and Haigis (56.12%). Within ±1.00 D, Barrett Universal II and Holladay II tied at the highest percentage (92.86%), followed by SRK/T (91.84%) and Haigis (85.71%).

Subgroup analysis based on CTR diameter using the Barrett Universal II formula revealed similar refractive outcomes between the groups. The MAE was 0.38±0.35 D in eyes implanted with 10-12 mm rings (n=68) and 0.32±0.32 D in eyes implanted with 11-13 mm rings (n=30). There was no statistically significant difference between the groups (p=0.566). Additional subgroup analyses based on axial length, anterior chamber depth, mean keratometry, and IOL power also showed no significant differences in refractive outcomes (all p>0.05).

Regarding CTR indications, PEX syndrome was present preoperatively in 72 (73.5%) of the 98 eyes included in the study. No significant difference in MAE was detected between eyes with and without PEX (p>0.05 for all formulas). The refractive outcomes for each formula are presented in Table 2. In the sensitivity analysis performed to evaluate the effect of including bilateral eyes (n=92), the relative ranking and statistical significance of the comparisons among formulas were maintained (Friedman χ^2=24.97; p<0.001).

Table 2. Refractive outcomes of intraocular lens calculation formulas

Formula	MPE (D)	MAE (D)	MedAE (D)	≤0.25 D (%)	≤0.50 D (%)	≤1.00 D (%)
Barrett Universal II	+0.21±0.45	0.36±0.34	0.24	52.04	67.35	92.86
Holladay II	+0.19±0.48	0.40±0.32	0.30	41.84	69.39	92.86
SRK/T	+0.32±0.49	0.45±0.37	0.33	38.78	65.31	91.84
Haigis	+0.24±0.66	0.54±0.45	0.44	32.65	56.12	85.71

MPE: Mean prediction error, D: Diopter, MAE: Mean absolute error, MedAE: Median absolute error

Discussion

This study evaluated the refractive outcomes and prediction accuracy of contemporary IOL calculation formulas in eyes that underwent cataract surgery combined with CTR implantation. Preoperative measurements were obtained using swept-source OCT biometry. Overall, the refractive outcomes were acceptable, although a mild hyperopic shift was observed with all formulas. Barrett Universal II and Holladay II stood out among the evaluated formulas with lower absolute error values, while Haigis and SRK/T were associated with higher absolute prediction errors.

The formula used for IOL power calculation is an important factor affecting the accuracy of the refractive outcome. In the literature, it has been reported that formulas incorporating different biometric parameters can provide lower prediction errors in certain patient groups compared to classic formulas.[14] It has been suggested that changes in anterior segment biometric parameters such as anterior chamber depth may influence the prediction error of IOL calculation formulas and may be associated with a hypermetropic prediction bias.[15] In studies based on swept-source OCT biometry, acceptable refractive outcomes were also achieved with formulas commonly used in clinical practice, such as Barrett Universal II, Haigis, SRK/T, and Holladay II.[16,17] In the present study, these formulas were compared in eyes implanted with a CTR. While Barrett Universal II demonstrated the lowest MAE and MedAE values, Holladay II also showed comparable absolute error.

There has been limited research specifically examining the accuracy of refractive estimation in eyes that have undergone CTR implantation. A recent study showed that Barrett Universal II provided lower absolute error values compared to Haigis and SRK/T in highly myopic eyes implanted with a CTR, and the percentage of eyes within ±0.25 D was highest with this formula.[18] Our findings are partially consistent with that study. In the current series, Barrett Universal II exhibited lower absolute error values compared to Haigis and SRK/T. However, Holladay II yielded results similar to Barrett Universal II, with no statistically significant difference between the two formulas. This finding suggests that both Barrett Universal II and Holladay II may be clinically viable options in CTR-implanted eyes measured with swept-source OCT.

Studies using swept-source OCT biometry in routine cataract surgery have reported high refractive accuracy with different IOL calculation formulas. Savini et al.[17] compared the refractive prediction performance of various formulas, including Barrett Universal II and Holladay II, and showed that acceptable results could be obtained with contemporary biometry devices. In the current series, Barrett Universal II was superior in terms of the percentage of eyes within ±0.25 D of target refraction, while Holladay II showed the highest percentage in the ±0.50 D range, and there was no difference between the two for the ±1.00 D range. This outcome suggests that both formulas can provide successful results at different accuracy thresholds in eyes with a CTR.

In our study, the MPE was found to be positive for all formulas, indicating a mild hyperopic shift. Although similar findings have been reported in previous studies related to CTRs, there is no definitive consensus on this matter. A study of patients with PEX revealed a hyperopic tendency both in eyes with and without CTR implantation, with the authors concluding that no specific modification to the formula was necessary solely due to CTR implantation.[19] Intraoperative OCT-based studies have shown that postoperative IOL position is a major source of uncertainty in refractive prediction.[20] Our results parallel these observations. Although the hyperopic shift was mild, it was consistently detected across all formulas. This finding could be taken into clinical consideration during target refraction planning for eyes undergoing CTR implantation. Furthermore, because postoperative anterior chamber depth was not evaluated in the current series, the relationship among CTR implantation, effective lens position, and refractive outcome can only be interpreted indirectly.

A previous study in highly myopic eyes reported that CTR implantation had no marked and consistent effect on refractive outcomes but could enhance the precision of refractive prediction.[21] Another more recent study demonstrated that implantation of a 13 mm CTR in eyes with long axial myopia did not significantly affect formula selection.[22] Similarly, no significant difference was detected in our subgroup analysis based on CTR diameter. Comparable refractive outcomes were obtained with Barrett Universal II in eyes implanted with 10-12 mm and 11-13 mm CTRs. Additional subgroup analyses based on axial length, anterior chamber depth, mean keratometry, and IOL power also revealed no significant differences. These findings suggest that, within the sample limits of our study, CTR diameter and the evaluated biometric variables did not significantly impact refractive prediction accuracy.

Study Limitations

This study has certain limitations, including its retrospective, single-center design. Moreover, due to the lack of postoperative anterior chamber depth data, the relationship between CTR implantation and effective lens position and refractive error could not be directly established. Therefore, deductions regarding effective lens position in our study are indirect, and prospective

studies involving intraoperative or postoperative OCT-based measurements are needed to directly evaluate this mechanism. Another limitation is that next-generation formulas such as Kane and EVO 2.0 were excluded from this study because they are not included in the software of the ARGOS biometry device. Further studies should examine the predictive accuracy of these formulas in CTR-implanted eyes.

Conclusion

When evaluated with contemporary IOL calculation formulas, cataract surgery combined with CTR implantation can yield acceptable refractive outcomes. Among the evaluated formulas, Barrett Universal II and Holladay II yielded lower absolute prediction errors, whereas Haigis and SRK/T were associated with higher absolute errors. Additionally, a mild but consistent hyperopic shift was observed across all formulas. This may have clinical significance in the planning of target refraction and IOL power in eyes undergoing CTR implantation.

Ethics

Ethics Committee Approval: The study was approved by the Dokuz Eylül University Non-Interventional Research Ethics Committee (approval no: 2025/42-22, date: 01.12.2025) and was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: The requirement for informed consent was waived due to the retrospective nature of the study.

Declarations

Authorship Contributions

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

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Original Article

MicroRNA Profiles Targeting Angiopoietin-1, Angiopoietin-2, and TEK Receptor Tyrosine Kinase-2 Genes Associated with Angiogenesis in Proliferative Diabetic Retinopathy

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Abstract

Objectives: This study aims to assess the concentrations of angiopoietin-1, angiopoietin-2, and Tie-2, which are implicated in the pathophysiology of proliferative diabetic retinopathy (PDR), in the vitreous fluid and to evaluate the expression profiles of microRNA (miR)-145-5p, miR-542-3p, miR-5195-3p, miR-126-3p, miR-211-3p, and miR-204-5p.

Materials and Methods: The study included 25 patients with PDR and 25 non-diabetic individuals as controls. Vitreous angiopoietin-1, angiopoietin-2, and Tie-2 levels were measured using enzyme-linked immunosorbent assay (ELISA). miRNA expression levels were evaluated using real-time polymerase chain reaction.

Results: Vitreous angiopoietin-1 and 2 levels were significantly lower in the PDR group when compared to controls ($p<0.05$). The PDR group also had a lower angiopoietin-1/angiopoietin-2 ratio and higher Tie-2 levels, but these differences did not reach statistical significance ($p>0.05$). Significantly higher levels of miR-126-3p and miR-204-5p were detected in the PDR group ($p<0.05$), whereas miR-211-3p, miR-5195-3p, miR-542-3p, and miR-145-5p did not show statistically significant differences ($p>0.05$).

Conclusion: Our data demonstrate that increased miR-204-5p and miR-126-3p expression may be associated with angiogenesis-related alterations in PDR. These findings provide insight into PDR-related angiogenesis and suggest that these microRNAs may represent potential biomarkers of disease-related vascular alterations.

Keywords: Proliferative diabetic retinopathy, microRNA, angiopoietin-1, angiopoietin-2, receptor tyrosine kinase-2

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Introduction

As a microvascular complication of diabetes, diabetic retinopathy (DR) results in substantial visual consequences in adults.[1] Clinically, DR progresses from a non-proliferative stage to a proliferative form. Non-proliferative diabetic retinopathy (NPDR) involves microvascular alterations confined to the retina, whereas proliferative diabetic retinopathy (PDR) reflects an advanced disease stage involving aberrant intraocular vessel growth and the development of fibrovascular tissue at the vitreoretinal interface. Both stages contribute substantially to irreversible vision loss.[2]

The pathogenesis of PDR is closely linked to retinal ischemia and the subsequent upregulation of angiogenic signaling pathways. Beyond vascular endothelial growth factor (VEGF), the angiopoietin/Tie2 (Ang/Tie2) axis is an important mediator regulating vascular stability and pathological angiogenesis in the diabetic retina.[3,4] Angiopoietin-1 (Ang-1), primarily produced by perivascular cells, activates the Tie2 receptor and promotes vessel maturation and stabilization by enhancing endothelial cell survival, intercellular adhesion, and barrier integrity.[5]

In contrast, angiopoietin-2 (Ang-2) is generally considered a context-dependent antagonist of Tie2 and contributes to vascular destabilization and pericyte dropout, thereby sensitizing the vasculature to pro-angiogenic cues.[6] Diabetic retinal stressors, particularly hypoxia, hyperglycemia, and oxidative stress, have been shown to increase Ang-2 expression, and hypoxic conditions also enhance VEGF signaling. The combined action of Ang-2 and VEGF facilitates endothelial activation, sprouting, and neovascular growth, promoting the progression of PDR.[7]

The expression of various genes is post-transcriptionally regulated by microRNAs (miRNAs), a family of non-coding RNAs.[8] These regulators recognize and bind to the 3′ untranslated regions of target transcripts, thereby hindering their translation into proteins.[9] Through these regulatory actions, miRNAs participate in a wide range of biological mechanisms, including angiogenic regulation; cellular differentiation, proliferation, and growth; apoptosis; and embryonic development. Therefore, miRNA downregulation or dysfunction, as well as the dysregulation of miRNA targets, is believed to contribute to various diseases. Moreover, studies are ongoing to investigate the transcriptional regulation of miRNAs and their roles in several eye diseases and retinal neovascularization.[10] The abnormal expression and altered activity of numerous retinal miRNAs have been associated with the etiology of common retinal disorders, including PDR.

The involvement of miRNAs in PDR pathogenesis has attracted growing attention due to their potential utility in disease treatment and biomarker identification.[8,11] Recent meta-analyses indicate that circulating miRNAs can distinguish PDR from NPDR, although existing evidence is largely based on serum or plasma samples and does not fully capture the angiogenic microenvironment at the vitreoretinal interface.[12]

The selected miRNAs (miR-145-5p, miR-542-3p, miR-5195-3p, miR-126-3p, miR-211-3p, and miR-204-5p) were chosen based on *in silico* target prediction tools (e.g., TargetScan and miRWalk) and previous literature indicating their potential interactions with *Ang-1, Ang-2*, and *Tie-2*–related pathways, as well as their reported relevance to angiogenesis and retinal vascular disorders.

This study focuses on quantifying the vitreous expression levels of these miRNAs that target *Ang-1, Ang-2,* and *Tie2* genes, seeking to uncover the underlying molecular mechanisms of PDR in comparison to non-diabetic controls.

Materials and Methods

All experimental procedures were approved by the Trakya University Faculty of Medicine Scientific Research Ethics Committee (protocol code: TÜTF-BAEK 2020/273, decision no: 14/22, date: 14.09.2020). We enrolled 25 patients with PDR and 25 individuals without diabetes from the Department of Ophthalmology, Trakya University Faculty of Medicine. For the PDR group, HbA1c levels were measured to document glycemic status and to confirm diabetes mellitus. The diagnosis of PDR was established based on the presence of retinal neovascularization, vitreous hemorrhage, and fibrovascular proliferative tissue.

General exclusion criteria for both groups included age-related macular degeneration, a history of complicated cataract surgery, and uveitis. Additionally, individuals with diabetes mellitus or other retinal vascular disorders were excluded from the control group. For the PDR group, further exclusion criteria comprised a history of surgery for retinal detachment, epiretinal membrane, or macular hole, and having received intravitreal injections within the previous three months.

In both groups, vitreous specimens were obtained intraoperatively during pars plana vitrectomy (PPV). Because vitreous sampling from completely healthy individuals is not ethically feasible, control specimens were obtained from patients undergoing PPV for conditions not associated with retinal vascular pathology (rhegmatogenous retinal detachment, macular hole, epiretinal membrane). This approach is consistent with previously published vitreous studies, in which control samples were typically obtained from patients undergoing vitrectomy for non-vascular retinal conditions, due to ethical limitations in obtaining vitreous fluid from healthy individuals.

Vitreous Sample Collection

Each participant underwent conventional three-port 23-gauge PPV performed by the same senior surgeon under local anesthesia. At the beginning of the procedure, before initiating intraocular infusion, approximately 0.5 mL of vitreous humor was aspirated from the central vitreous cavity using a syringe attached to the vitrectomy cutter. Any residual irrigation fluid within the cutter tubing was expelled before sample collection. Vitreous samples were clarified by centrifugation and stored at -80 °C until further analysis.

Isolation of miRNA and cDNA Synthesis

After thawing the vitreous samples, total RNA including miRNAs was isolated using a commercial miRNA isolation kit (High Pure miRNA Isolation Kit, Roche Diagnostic GmbH, Mannheim, Germany). RNA quantity and purity were measured spectrophotometrically. Complementary DNA (cDNA) was synthesized from the isolated RNA using an miRNA-specific cDNA synthesis kit (miRNA All-In-One cDNA Synthesis Kit, Abm, Canada). Synthesized

cDNA was kept at -20 °C for subsequent polymerase chain reaction (PCR) analysis.

Quantitative Real-Time PCR Analysis (qRT-PCR)

The expression levels of miRNAs were analyzed using an qRT-PCR (StepOne, Applied Biosystems, USA). Normalization of miRNA expression levels was performed using RNU6B as an endogenous control. The primer sequences for the miRNAs and RNU6B are provided in Table 1. Quantitative PCR assays for miRNA expression were conducted in 20-µL reaction mixtures containing Bright Green miRNA qPCR Master Mix-No Dye (Abm, Canada), gene-specific primers, cDNA template, and nuclease-free water. qPCR amplification was conducted using standard thermal cycling parameters recommended by the manufacturer to ensure reliable and reproducible amplification.

Determination of Ang-1, Ang-2, and Tie2 Levels in Vitreous Samples

After samples were equilibrated to room temperature, enzyme-linked immunosorbent assay (ELISA)-based quantification was performed to determine vitreous levels of angiogenic pathway components, including angiopoietins and the Tie2 receptor (ANG-1 ELISA kit, Cat. no. E1222Hu BTLAB; ANG-2 ELISA kit, Cat. no. E1221Hu BTLAB; TEK ELISA kit, Cat. no. SEA126Hu, USCN, respectively). Optical density measurements were obtained with a microplate reader (Thermo Multiscan Go Microplate, USA), and concentrations of all assessed angiogenic components were expressed in ng/mL.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics (version 25.0, IBM Corp., Armonk, NY, USA). Power calculations were conducted with PASS software targeting 80% power at α=0.05. Data normality was assessed using the Shapiro-Wilk test. Depending on distribution characteristics, comparisons were performed using the independent samples t-test or the Mann-Whitney U test. Data were presented as mean ± standard deviation or median (interquartile range), as appropriate. miRNA expression levels were normalized to RNU6B and quantified using the $2^{-\Delta\Delta Ct}$ method.[13] Correlation analyses between miRNA expression levels and angiopoietin concentrations were performed using Spearman's rank correlation coefficient. A p value <0.05 was considered statistically significant. Given that multiple comparisons were performed, the possibility of type I error cannot be excluded. No formal correction was applied due to the exploratory nature of the study and limited sample size; therefore, the findings should be considered hypothesis-generating.

Results

In the PDR group, 12 patients (48%) had vitreous hemorrhage and 13 patients (52%) had tractional retinal detachment. The mean diabetes duration in the PDR patients was 20 years (20.0±9.5). In the control group, 18 patients (72%) had rhegmatogenous retinal detachment, 4 (16%) had epiretinal membrane, and 3 (12%) had idiopathic macular hole. The study groups did not differ significantly in terms of age or gender (p>0.05). Patients with PDR exhibited higher HbA1c levels compared to controls (p<0.05). Demographic characteristics of the study population are summarized in Table 2.

Vitreous concentrations of Ang/Tie2 axis components

A significant reduction in the vitreous levels of both angiopoietins was observed in the PDR group (p<0.05; Figure 1). Assessment of the relative Ang-1 to Ang-2 ratio in vitreous samples revealed a lower value in patients with PDR (2.08±0.43 ng/mL vs. 2.20±0.58 ng/mL), although the difference was not statistically significant (p=0.412). Tie2 levels were higher in the PDR group (8.87±2.03 ng/mL) when compared with controls (8.16±2.20 ng/mL), but this increase also remained non-significant (p>0.05).

Table 1. miRNA primer sequences

Primer	Base sequence
hsa-miR-145-5p	5'-GUCCAGUUUUCCCAGGAAUCCCU-3'
hsa-miR-542-3p	5'-UCGGGGAUCAUCAUGUCACGAGA-3'
hsa-miR-5195-3p	5'-AUCCAGUUCUCUGAGGGGGCU-3'
hsa-miR-126-3p	5'-UCGUACCGUGAGUAAUAAUGCG-3'
hsa-miR-211-3p	5'-GCAGGGACAGCAAAGGGGUGC-3'
hsa-miR-204-5p	5'-UUCCCUUUGUCAUCCUAUGCCU-3'
RNU6B	5'-AACGCTTCACGAATTTGCGT-3'

Vitreous miRNA Expression Patterns in PDR and Controls

We quantified six miRNAs in PDR patients and non-diabetic controls using qRT-PCR. We found that vitreous miR-204-5p and miR-126-3p were notably increased in PDR patients relative to controls, demonstrating fold changes of 3.72 (p=0.02) and 2.63 (p=0.022), respectively. Vitreous miR-542-3p levels were approximately 1.57-fold higher in the PDR group, but this increase did not reach statistical significance (p=0.17; Figure 2). In contrast, miR-211-3p, miR-145-5p, and miR-5195-3p exhibited lower expression levels in the PDR group, again with no significant intergroup differences being identified (p>0.05; Figure 2). Spearman correlation analysis performed within the PDR group revealed no significant correlation between miR-126-3p/miR-204-5p expression levels and Ang-1/Ang-2 concentrations (p>0.05). However, a moderate positive correlation was observed between miR-126-3p and miR-204-5p expression levels (r=0.508, p=0.009). No significant correlations were observed between miRNA expression levels and Hemoglobin A1c (HbA1c) values (p>0.05)

Discussion

The present findings highlight the potential involvement of the Ang/Tie2 signaling axis in the development of PDR and suggest that selected miRNAs may be associated with alterations in the intraocular angiogenic environment rather than directly regulating these pathways. Additionally, we examined the expression profiles of miR-145-5p, miR-542-3p, and miR-5195-3p, which target the *Ang-2* gene in vitreous fluid.

In one study, the vitreous expression levels of both angiopoietins were reported to be increased in PDR patients relative to controls.[14] Similarly, Tsai et al.[15] identified elevated vitreous Ang-1 and Ang-2 concentrations in PDR patients compared to control subjects and NPDR cases. Conversely, Patel et al.[16] observed decreased levels

Table 2. Demographic parameters of control and proliferative diabetic retinopathy (PDR) groups

	PDR (n=25)	Control (n=25)	p
Age (years), mean ± SD	56.7±8.83	58.64±12.15	0.72
Sex, n (%) Male Female	 19 (76) 6 (24)	 18 (72) 7 (28)	0.76
HbA1c (%), mean ± SD	9.56±1.40	5.40±0.58	0.001

HbA1c: Hemoglobin A1c, n: Number of people, SD: Standard deviation

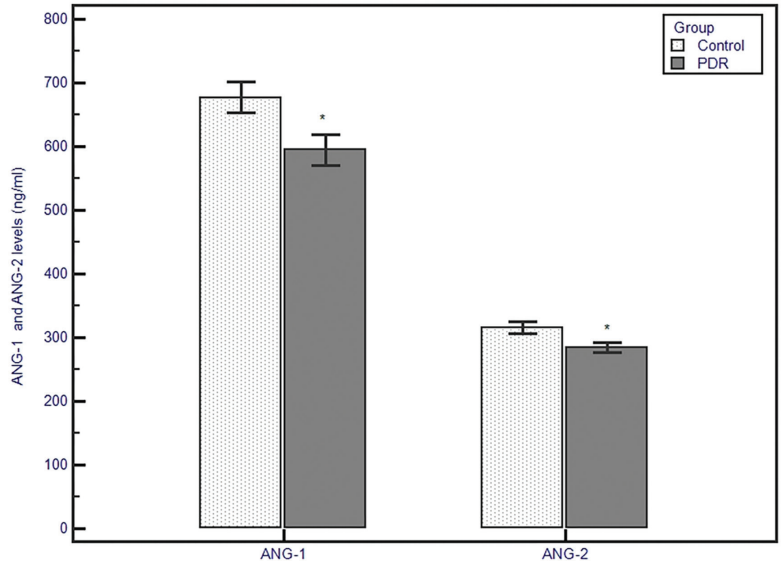

Figure 1. Vitreous concentrations of angiopoietin-1 (Ang-1) and angiopoietin-2 (Ang-2) in patients with proliferative diabetic retinopathy (PDR) and controls
**p<0.05 compared to the control group; data are presented as mean ± SD*
SD: Standard deviation

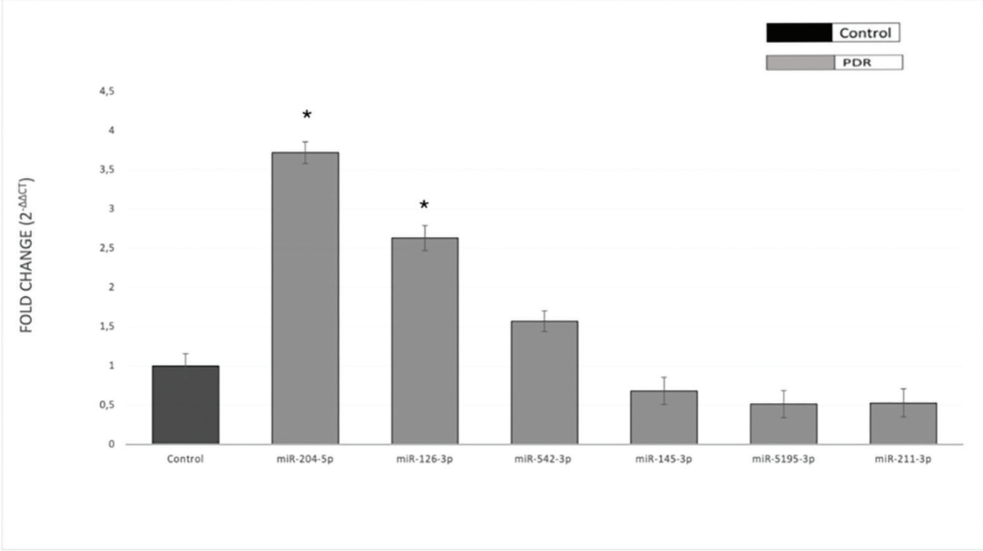

Figure 2. Relative expression levels of vitreous miRNAs in patients with proliferative diabetic retinopathy (PDR) compared to controls
**p<0.05 compared to the control group; data are presented as mean ± SD*
SD: Standard deviation

of these angiogenic factors in the vitreous fluid of PDR patients compared to the control group. The latter study is consistent with our findings of lower vitreous expression levels of both Ang-1 and Ang-2 in PDR patients relative to controls. Differences in control group composition, particularly the inclusion of eyes with non-vascular retinal disorders, may also contribute to variability in reported vitreous angiopoietin levels across studies.

Thus, the literature data regarding Ang-1 and Ang-2 regulation in the vitreous pathophysiological mechanisms of PDR are contradictory. Some studies indicate that measuring only one angiopoietin level is not sufficient to evaluate the balance in the angiogenesis process.[4,5,14] Therefore, Wang et al.[17] determined the Ang-1/Ang-2 ratio and found it was significantly decreased in PDR compared to moderately severe NPDR and more severe DR. Other studies have similarly demonstrated shift toward Ang-2 in PDR relative to controls.[4,14] A reduced Ang-1/Ang-2 ratio was also observed in the current study, consistent with the literature. Our findings support that changes in angiopoietin levels shift the balance towards neovascularization and affect the pathogenesis of PDR. The finding of reduced vitreous Ang-1 and Ang-2 levels in the PDR group contrasts with several previous studies reporting elevated levels in PDR. This discrepancy may be related to differences in disease stage, clinical phenotype, the presence of vitreous hemorrhage or tractional retinal detachment, and the heterogeneous nature of the control group. In our cohort, 48% of patients had vitreous hemorrhage and 52% had tractional retinal detachment, both of which may influence the intraocular molecular environment. Therefore, our angiopoietin findings should be interpreted within the specific clinical and methodological context of this study, and may reflect disease heterogeneity or sampling-related differences rather than a uniform biological response.

In line with this, a lower Ang-1/Ang-2 balance in patients with PDR has been associated with impaired endothelial vascular integrity. Accordingly, maintaining this balance may be important for vascular homeostasis, although its therapeutic implications require further investigation.

According to Pramanik et al.,[18] miR-126-3p levels were lower in vitreous and plasma samples from patients with NPDR than in non-DR controls. Similarly, experimental studies using streptozotocin (STZ)-induced diabetic rat models demonstrated reduced retinal miR-126-3p levels, suggesting that this miRNA may be involved in the early pathogenesis of DR by regulating the expression of VCAM-1, VEGF, and Ang-1.[19] In contrast, our study revealed a notably elevated miR-126-3p expression in the vitreous fluid of patients with PDR, accompanied by a concomitant decrease in Ang-1 levels relative to controls. Considering the protective role of Ang-1 in Tie2-mediated vascular stabilization, the observed inverse relationship between elevated miR-126-3p expression and reduced Ang-1

levels suggests a mechanism that may contribute to the maintenance of pathological angiogenesis in PDR. Our findings align with the observations of Liu et al.,[20] who reported significantly increased miR-126 expression in the vitreous, plasma, and proliferative membranes of patients with PDR, with expression levels increasing in parallel with disease severity. Other vitreous-based studies have also demonstrated upregulation of miR-126-3p in PDR compared with controls and suggested an association with increased VEGF levels and angiogenic activity.[21] Although Ang-1 levels were reduced in the same group, no significant correlation was detected between miR-126-3p expression and Ang-1 concentrations. Therefore, any potential relationship between miR-126-3p and Ang-1/Tie2 signaling in PDR remains indirect and cannot be interpreted as a causal interaction. These findings suggest that miR-126-3p may be associated with angiogenic alterations in advanced disease stages rather than directly regulating Ang-1 expression.

Regarding miR-204-5p, Kot and Kaczmarek[22] and Yan et al.[23] reported significant decreases in exosomal miR-204-5p in the vitreous of patients with PDR. In contrast, our analysis of total vitreous miRNA revealed that miR-204-5p expression was notably increased in PDR patients compared to controls. This elevation is consistent with experimental observations in STZ-induced diabetic models, where retinal miR-204-5p levels surpassed those found in non-diabetic controls, suggesting early involvement in the disease process.[24] The discrepancy between exosomal and total vitreous levels suggests that total vitreous miRNA levels may more accurately reflect retinal tissue-level pathology. Furthermore, Kather et al.[25] reported that decreased miR-204-5p expression leads to increased Ang-1 expression, thereby promoting corneal neovascularization, while Zhang et al.[26] demonstrated that Ang-1 is a direct target of both miR-204 and miR-211 in EA.hy926 endothelial cells. In the current study, miR-204-5p expression was increased in vitreous samples from PDR patients, whereas miR-211 expression showed a non-significant decreasing trend. Although experimental studies have identified Ang-1 as a potential target of miR-204-5p, we did not observe a significant correlation between miR-204-5p expression and Ang-1 levels. Therefore, the observed upregulation of miR-204-5p in PDR should be interpreted as an association rather than evidence of direct regulatory activity. Similarly, although several miRNAs evaluated in this study have been reported to target angiogenic pathways, no significant correlations were observed between miRNA expression levels and Ang-1 or Ang-2 concentrations in our dataset. This lack of association suggests that the relationship between miRNAs and angiopoietin signaling in PDR may be complex, indirect, or context-dependent, potentially involving multiple regulatory layers.

In addition, no significant correlation was identified between miRNA expression levels and HbA1c values, indicating that vitreous miRNA expression may be more strongly influenced by local intraocular mechanisms rather than systemic glycemic status.

In the present study, vitreous miR-542-3p levels showed a 1.57-fold increase in patients with PDR compared with controls, although this difference was not statistically significant ($p>0.05$). Zhang et al.[27] investigated the circSIRT2/miR-542-3p/VASH1 regulatory network in subretinal fibrosis models and elucidated the functional roles of miR-542-3p. However, they did not evaluate endogenous miR-542-3p levels in human vitreous fluid. Thus, to our knowledge, our study provides the first data regarding vitreous miR-542-3p expression in PDR. Extensive evidence indicates that miR-542-3p suppresses angiogenesis by directly targeting and negatively regulating Ang-2 expression.[28,29] Moreover, disruption of the NEAT1–miR-542-3p–Ang-2 regulatory axis has been shown to increase Ang-2 expression and exacerbate pathological angiogenesis.[30] Taken together, these results indicate that miR-542-3p may contribute to the post-transcriptional control of Ang-2 and potentially influence angiogenic pathways in ocular vascular disorders. In this context, the non-significant increase in miR-542-3p expression observed in our study may represent a compensatory regulatory response aimed at limiting Ang-2-mediated angiogenic activity underlying PDR pathogenesis.

Regarding miR-5195-3p, a previous study investigating retinal pigment epithelial cell damage showed that miR-5195-3p expression was reduced in retinal epithelial cells exposed to high-glucose conditions compared to controls.[31] However, the expression of miR-5195-3p in the human vitreous remains unexplored in the existing literature. Our miRWalk-based predictions highlight a potential interaction with Ang-2, suggesting that this miRNA acts as a key signaling component in the pathological vascularization characteristic of PDR.

Wang et al.[32] demonstrated that miR-145-5p directly targets Ang-2 and may exert an inhibitory effect on angiogenic signaling. In addition, miR-145-5p has been implicated in ocular angiogenesis, with its expression reported to be upregulated in the retinas of mice with oxygen-induced retinopathy.[33] More recently, miR-145-5p has been shown to contribute to endothelial dysfunction in DR by suppressing PDZK1 under hyperglycemic conditions.[34] Although exosomal miR-145-5p has been detected in the vitreous fluid of patients with pathological

myopia, our study is the first to evaluate vitreous miR-145-5p expression in PDR. In our study, vitreous miR-145-5p expression was decreased in PDR patients compared with controls (fold change: 0.71). Given that Ang-2 is a validated target of miR-145-5p and a key pro-angiogenic mediator in PDR, reduced vitreous miR-145-5p levels may facilitate Ang-2-driven pathological angiogenesis within the vitreous microenvironment. Our findings indicate that dysregulated miR-145-5p expression may contribute to PDR pathogenesis in a compartment-specific manner.

Overall, the results of this study should be considered exploratory and hypothesis-generating. The observed alterations in miRNA expression and angiopoietin levels may reflect complex regulatory processes involved in PDR, but do not establish causal relationships.

Study Limitations

These findings should be interpreted in the context of several limitations. Primarily, the modest sample size may have limited the statistical power to detect significant differences in vitreous miRNA expression, despite the presence of potentially relevant biological effects. Another important limitation of this study is the use of a heterogeneous control group consisting of patients with rhegmatogenous retinal detachment, macular hole, and epiretinal membrane. Although these conditions are not primarily angiogenic, they may alter the vitreous molecular environment and therefore act as potential confounding factors in vitreous biomarker analysis. In addition, multiple comparisons were performed without formal adjustment, which may increase the risk of type I error. The lack of stratification according to disease activity or clinical phenotype (e.g., presence of vitreous hemorrhage or tractional retinal detachment) may further limit the interpretation of the findings. Finally, the cross-sectional design precludes causal inference and limits the ability to assess temporal relationships between miRNA expression and angiogenic alterations.

Accordingly, future investigations with larger patient cohorts are required to confirm these observations and delineate temporal changes in vitreous miRNA expression during disease progression.

Conclusion

The present study demonstrates that differentially expressed miRNAs may be involved in the molecular mechanisms underlying PDR. Our findings suggest that altered vitreous expression of miR-126-3p and miR-204-5p may be associated with angiogenesis-related changes in PDR. However, given the exploratory design, limited sample size, and control group characteristics, particularly the use of a heterogeneous non-healthy control group, these findings should be interpreted cautiously and require confirmation in larger, well-designed studies.

Notably, to the best of our knowledge, this study is the first to evaluate the vitreous expression levels of miR-145-5p, miR-5195-3p, and miR-542-3p in patients with PDR, thereby contributing novel data to the existing literature. Nevertheless, further experimental and clinical studies are warranted to clarify the signaling pathways and functional roles of the significantly dysregulated miRNAs identified in this study.

Ethics

Ethics Committee Approval: All experimental procedures were approved by the Trakya University Faculty of Medicine Scientific Research Ethics Committee (protocol code: TÜTF-BAEK 2020/273, decision no: 14/22, date: 14.09.2020).

Informed Consent: Informed consent was obtained from all participants.

Declarations

Authorship Contributions

Surgical and Medical Practices: İ.A., S.A.Ö., Concept: L.A., Design: L.A., Data Collection or Processing: L.A., H.S., İ.A., S.A.Ö., Analysis or Interpretation: L.A., H.S., İ.A., S.A.Ö., Literature Search: L.A., H.S., Writing: L.A., H.S., İ.A., S.A.Ö.

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Original Article

Assessment of Dietary Nutritional Profile in Turkish Patients with Age-Related Macular Degeneration

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Abstract

Objectives: To evaluate the dietary nutritional profile according to the suggestions of the Age-Related Eye Disease Study 2 (AREDS2) in Turkish patients with age-related macular degeneration (AMD).

Materials and Methods: The study included patients diagnosed with non-neovascular AMD in one or both eyes and who underwent routine follow-up in retina clinics at tertiary centers in İstanbul between May 12 and May 27, 2025. An ocular nutrition questionnaire prepared according to AREDS2 suggestions was translated into Turkish. The survey was conducted among our cohort after its reproducibility and validity were confirmed. Consumption of fish-shellfish, hazelnut-walnut-peanut, eggs, leafy greens, red pepper, carrot-pumpkin, and peppers-green tea-strawberry-citrus (eicosapentaenoic acid, docosahexaenoic acid, omega 3, lutein, zeaxanthin, beta-carotene, and antioxidant-rich foods, respectively), micronutrient supplementation, smoking, physical activity, anxiety about vision loss, education level, and monthly income were recorded.

Results: A total of 530 patients from 7 clinics who answered all questions were evaluated. Adequate consumption of omega-3-rich foods consumption was reported by 19.3% of participants, whereas 57.2% reported no fish intake in the last week. Adequate consumption of foods rich in lutein/zeaxanthin, beta-carotene, and antioxidants was reported by 63.6%, 41.7%, and 4.7% of patients, respectively, and regular micronutrient supplementation was reported by 35.5%. Of the patients, 23.6% reported high anxiety about vision loss, 69.8% reported elementary or lower education, and 64.9% had a 20,000 TRY or lower monthly income. Micronutrient intake was positively associated with anxiety (p=0.0001) and education (p=0.02) but not with monthly income (p=0.1).

Conclusion: According to this first report in Turkish patients with AMD which was evaluated nutrition profile based on AREDS2 suggestions, patients showed low adherence to AREDS recommendations for micronutrient intake and lifestyle modifications. Awareness among patients and ophthalmologists needs improvement.

Keywords: Age-related macular degeneration, dietary nutrition, micronutrition

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Introduction

Age-related macular degeneration (AMD) is a leading cause of vision loss in older adults, and preventing blindness due to AMD is becoming increasingly important as the global population ages.[1] Treatment with anti-vascular endothelial growth factor is effective in treating the neovascular form of AMD; however, there is no reliable treatment for non-neovascular AMD.

The Age-Related Eye Disease Study (AREDS) showed that high doses of vitamins C and E, beta-carotene, and zinc supplements could reduce the risk of developing advanced AMD by 25% after 5 years.[2] AREDS2 evaluated the effect of adding lutein plus zeaxanthin and omega-3 long-chain polyunsaturated fatty acids to the AREDS formulation in further reducing the risk of progression to advanced AMD. According to the exploratory analysis of AREDS2, protection against progression to AMD was observed in patients with the lowest dietary intake of lutein plus zeaxanthin.[3] Moreover, healthy lifestyle behaviors, such as a nutritious diet, physical activity, and avoidance of smoking, were associated with 71% lower odds of developing AMD.[4]

Dietary supplementation is currently considered the only effective means of preventing progression to advanced forms of AMD. Nevertheless, adherence to AREDS recommendations seems unsatisfactory. Several studies have evaluated adherence to AREDS recommendations in different countries.[5,6,7,8] However, there are no published data concerning the Turkish population. Therefore, we aimed to evaluate the dietary nutritional profile of Turkish patients with AMD according to the AREDS2 recommendations and determine the extent of adherence to AREDS2 nutritional and lifestyle recommendations.

Materials and Methods

This multicenter cross-sectional study protocol was approved by the Institutional Review Board of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (protocol number: 2025/121, decision no: 2025-08-03, date: 04/24/2025) and was conducted in accordance with the principles outlined in the Declaration of Helsinki. Informed consent was obtained from all participants. Patients diagnosed with non-neovascular AMD in one or both eyes and examined during routine follow-up visits in retina clinics at seven education and research hospitals in İstanbul between May 12 and May 27, 2025, were included.

An ocular nutrition questionnaire developed in accordance with AREDS2 dietary recommendations was translated into Turkish and adapted for this study (Table 1).[9] First, the survey was conducted with five patients in each research clinic as a pilot study to evaluate readability, clarity, and reliability. We also assessed face validity through pilot testing.[10] After reproducibility was observed, the survey was administered to our cohort. Consumption of fish/shellfish, nuts/walnuts/peanuts, eggs, leafy greens, red pepper, carrot/pumpkin, peppers/green tea/strawberry/citrus (foods rich in eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA], omega-3, lutein, zeaxanthin, beta-carotene, and antioxidants), micronutrient supplement use, systemic diseases, smoking status, physical activity, anxiety about vision loss, education level, and monthly income were recorded. The patient's age, diagnosis, and follow-up duration were also recorded.

Statistical Analysis

All statistical analyses were performed using IBM SPSS for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as frequencies and percentages for categorical variables. Associations between micronutrient supplement intake and categorical variables, including anxiety level, education level, and monthly income, were evaluated using the chi-square test or Fisher's exact test where appropriate. The level of statistical significance was set at $p<0.05$.

Results

In total, 530 patients who answered all questions were evaluated. Demographic and clinical data are summarized in Table 2.

Of the 530 respondents, an average of 19.3% reported adequate consumption of omega-3-rich foods according to AREDS recommendations, and 57.2% reported no fish intake in the previous week. Adequate consumption of foods rich in lutein/zeaxanthin, beta-carotene, and antioxidants was reported by 63.6%, 41.7%, and 4.7% of respondents, respectively. The results are summarized in Table 3.

Additionally, 35.5% of the participants reported regular use of micronutrient supplements and 26.8% reported regular physical activity. High anxiety about vision loss (score of 5) was reported by 23.6%. Of our cohort, 69.8% had a low education level (illiterate or primary school graduate), and 64.9% reported a monthly income of 20,000 TRY or less.

In the cross-tabulation analysis, a significant positive association was observed between micronutrient intake and both anxiety grade ($p=0.0001$) and education level ($p=0.02$). In addition, dietary modification after AMD diagnosis was significantly associated with both anxiety and education levels (both $p=0.001$). No significant relation was found between micronutrient intake and monthly income ($p=0.1$). However, fish consumption was positively

Table 1. Ocular nutrition questionnaire					
Please think a moment to reflect on what you ate last week and then answer the questions.					
	None	**1-2**	**3-4**	**5 or more**	
Sardines, mackerel, trout, salmon per week (1 fillet the size of a deck of cards)					
Shellfish (mussel, lobster, oysters) per week					
Walnut per week (2 walnuts)					
Egg per week (1 egg)					
Kale, spinach, broccoli, chard, lettuce, arugula per week (1 handful raw, 1 cup cooked)					
Red pepper per week (1/2 pepper)					
Carrots, pumpkin, sweet potato, turnip per week (1 cup)					
Hazelnut, peanut, almond per week (10 in a day)					
	Less than 8	**8-15**	**15 or more**		
Peppers, green tea, strawberry, kiwi, citrus per week (1 medium fruit or 1 cup)					
Do you follow a special diet?	No	Vegan	Gluten-free		
Do you take any special supplements, such as turmeric, saffron, maqui berry, grape seed	Yes	No			
Do you use any supplement for your AMD?	No	Not regularly	Regularly		
Systemic diseases	Diabetes	Hypertension	Hyperlipidemia		
Physical activity (at least 1 hour walking in a day)	None	Not regularly	Regularly (at least 3 days)		
Are you a current smoker?	No	Yes	…. pack(s)/day		
Are you an ex-smoker?	No	Yes	…. years		
Did you make any change to your diet after being diagnosed with AMD?	Yes	No			
Do you have anxiety about loss of your sight? Please rate your anxiety from 0 = none to 5 = severe ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5					
Education level	Illiterate				
	Elementary school	Middle school	High school		
	University	Postgraduate			
Monthly income	Under 20,000 TRY 20,000–50,000 TRY 50,000–100,000 TRY Over 100,000 TRY				

associated with monthly income and education level (p=0.0001 and p=0.004, respectively). Micronutrient intake and post-diagnosis diet modification were more frequent in female patients; however, the difference was not significant (p=0.05 and p=0.3, respectively).

According to fellow eye status, nut and egg consumption was significantly more common among patients with neovascular disease in the fellow eye (p=0.04 and p=0.001, respectively). This group also reported higher anxiety grade and a higher frequency of regular exercise (p=0.001 for both). Micronutrient supplementation and the use of additional supplements (e.g., turmeric/saffron) were significantly associated with neovascular AMD in the fellow eye (p=0.002 and p=0.026, respectively).

Discussion

To the best of our knowledge, adherence to the AREDS2 recommendations and lifestyle modifications in AMD has not yet been studied in the Turkish population. This study offers valuable insights into the nutritional habits

Table 2. Demographic and clinical data		
Age (years), mean ± SD, (range)		70.8±8.7 (43-97)
Follow-up time (months), mean		31.7
		Patients, n (%)
Fellow eye	Non-neovascular Neovascular	392 (74.0) 138 (26.0)
Stage of AMD	Intermediate Late	411 (77.5) 119 (22.5)
Gender	Female Male	299 (56.4) 231 (43.6)
SD: Standard deviation, AMD: Age-related macular degeneration		

and lifestyle characteristics of Turkish patients with AMD evaluated in the context of the AREDS2 recommendations. Our findings revealed suboptimal dietary patterns, particularly concerning intake of foods rich in omega-3 fatty acids, lutein/zeaxanthin, and antioxidants, as well as suboptimal micronutrient intake, which may have implications for disease progression and visual prognosis.

The relatively low frequency of omega-3-rich food consumption (19.3%), along with the fact that over half of the patients reported no fish intake during a typical week, aligns with existing evidence suggesting that Westernized or urban dietary patterns often lack sufficient long-chain polyunsaturated fatty acids, such as EPA and DHA. These essential fatty acids play critical roles in retinal integrity and anti-inflammatory mechanisms, potentially slowing the progression of AMD.[11,12] Despite moderate levels of lutein/zeaxanthin intake (63.6%), only a small proportion of participants reported adequate consumption of antioxidant-rich foods (4.7%). This finding is notable, considering that lutein and zeaxanthin are the primary macular pigments and enhance visual function and reduce oxidative stress.[13,14] Moreover, low antioxidant intake can compromise the ability of the macula to mitigate oxidative damage, which contributes to the pathogenesis of AMD.[15]

Regular micronutrient supplement usage was reported by only 35.5% of the participants, which appears insufficient when considering the robust evidence supporting the benefits of the AREDS and AREDS2 formulations in reducing the risk of AMD progression.[2,3] Similar survey-based studies from different countries reported micronutrient usage rates ranging from 38% to 83%.[4,5,14] More specifically, a study conducted in the USA found a rate of micronutrient intake of 42.5%, and a different study from the USA reported that 81% of patients had modified their diet according to the retina specialist's recommendations.[6,7] However, a 0% rate of smoking cessation was reported in the latter study. In a study from Italy, the researchers reported an AREDS-type oral supplementation rate of 40%.[8] The relatively lower adherence to micronutrient supplementation in our study may be associated with limited awareness, cost barriers, or a lack of physician recommendations, particularly in patients with lower socioeconomic and educational backgrounds.

A significant association was observed between micronutrient intake and both education level and anxiety regarding vision loss. Patients with lower education levels were less likely to consume recommended supplements, which may reflect the disparities in health literacy and access to nutritional information. Furthermore, participants with higher anxiety levels were more likely to use supplements, indicating self-initiated efforts to prevent visual deterioration. These findings are consistent with those of previous studies linking higher health-related anxiety to proactive health behaviors.[16,17]

Physical activity was also suboptimal (26.8%), despite growing evidence that an active lifestyle may be protective against AMD progression, possibly through systemic anti-inflammatory effects and enhanced vascular health.[18]

Some significant differences were found according to the status of fellow eye. Patients with neovascular involvement in the fellow eye were more likely to report higher consumption of eggs and nuts, regular exercise, micronutrient supplementation, the use of additional products such as turmeric or saffron, and higher anxiety, which may reflect increased disease awareness and perceived risk of visual loss. This heightened concern could also explain the greater adoption of health-related behaviors observed in this group. However, it remains unclear whether these habits were adopted earlier but were insufficient to mitigate disease progression, or represent adaptive responses after the diagnosis of advanced disease.

No significant correlation was found between monthly income and micronutrient intake. This finding could reflect the relative affordability of basic AREDS2 supplements in Türkiye or may indicate that non-economic barriers, such as education, awareness, or cultural factors, play a more prominent role.

Table 3. Nutrition profile and lifestyle characteristics of the participants according to AREDS2 recommendations (indicated by asterisks)

	None	1-2 days	3-4 days*	5 days or more*
Omega-3-rich foods				
Sardines, mackerel, trout, salmon	303 (57.2%)	194 (36.6%)	22 (4.2%)	11 (2.1%)
Shellfish (mussels, lobster, oysters)	519 (97.9%)	9 (1.7%)	2 (0.4%)	0 (0%)
Walnuts	109 (20.6%)	247 (46.6%)	99 (18.7%)	75 (14.2%)
Hazelnuts, peanuts, almonds	181 (34.2%)	244 (46%)	59 (11.1%)	46 (8.7%)
Lutein-rich foods				
Kale, spinach, broccoli, chard, lettuce, arugula	22 (4.2%)	185 (34.9%)	199 (37.5%)	124 (23.4%)
Egg	12 (2.3%)	166 (31.3%)	142 (26.8%)	210 (39.6%)
Zeaxanthin-rich foods				
Red pepper	199 (37.5%)	214 (40.4%)	65 (12.3%)	52 (9.8%)
Beta-carotene rich foods				
Carrots, pumpkin, turnip	74 (14.0%)	235 (44.3%)	152 (28.7%)	69 (13.0%)

Antioxidant-rich foods Peppers, green tea, strawberry, kiwi, citrus, other fruit	**<8** 395 (74.5%)	**8-14** 110 (20.8%)	**15*** 25 (4.7%)
Special diet	**No** 514 (97%)	**Vegan** 4 (0.8%)	**Gluten-free** 12 (2.3%)
Micronutrition usage	**None** 181 (34.2%)	**Not regularly** 161 (30.4%)	**Regularly*** 188 (35.5%)
Any special supplements as turmeric, saffron, maqui berry, grape seed	**No** 466 (87.9%)	**Yes** 64 (12.1%)	
Changed diet after AMD diagnosis	**No** 420 (79.2%)	**Yes** 110 (20.8%)	
Physical activity	**None** 228 (43.0%)	**Not regularly** 160 (30.2%)	**Regularly** 142 (26.8%)
Current smoker	**No** 455 (85.8%)	**Yes** 75 (14.2%)	
History of smoking	**No** 341 (64.3%)	**Yes** 189 (35.7%)	

Systemic diseases	**None** 166 (31.3%)	**DM** 68 (12.8%)	**HT** 104 (19.6%)	**HL** 20 (3.8%)
	DM+HT 72 (13.6%)	**DM+HL** 12 (2.3%)	**HT+HL** 37 (7%)	**DM+HT+HL** 51 (9.6%)

Anxiety about vision loss	**0** 73 (13%)	**1** 54 (10%)	**2** 63 (11%)	**3** 112 (21%)	**4** 103 (19%)	**5** 125 (23%)
Education level	**Illiterate** 78 (14%)	**Primary** 292 (55%)	**Elementary** 87 (16%)	**High Sch.** 50 (9%)	**University** 19 (3%)	**Postgrad.** 4 (0.8%)

Monthly income	**<20k TRY** 344 (64.9%)	**20-50k TRY** 167 (31.5%)	**50-100k TRY** 15 (2.8%)	**>100k TRY** 4 (0.8%)

AMD: Age-related macular degeneration, DM: Diabetes mellitus, HT: Hypertension, HL: Hyperlipidemia, TRY: Turkish lira

Study Limitations

This study has several limitations that should be acknowledged. First, as a questionnaire-based survey, the findings rely on self-reported data, which may be subject to recall bias and reporting inaccuracies. However, there is currently no other practical and easily applicable method to comprehensively assess dietary habits and lifestyle behaviors in such a large patient population. Second, the

study population consisted of patients residing in Istanbul, which may limit the generalizability of the results to the entire Turkish population. Nevertheless, Istanbul is a highly cosmopolitan city with diverse socioeconomic and cultural characteristics, and the findings are therefore likely to provide valuable insight into national trends. Third, seasonal variations in dietary habits may have influenced the results. For example, fish consumption may be lower during the summer months, when this study was conducted. Also, the absence of a subgroup analysis according to AMD stage is another limitation. Considering these factors, future studies including different seasons and a broader, nationwide population would be beneficial to further validate and expand upon the present findings.

Conclusion

Our findings highlight the urgent need for structured nutritional education and personalized counseling for patients with AMD. Ophthalmologists should be encouraged to integrate dietary and lifestyle guidance into AMD management protocols, especially in high-risk populations. In addition to having a duty of care to treat the neovascular complications of AMD as ophthalmologists, we must also strive to improve its prevention.

Ethics

Ethics Committee Approval: This multicenter cross-sectional study protocol was approved by the Institutional Review Board of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital (protocol number: 2025/121, decision no: 2025-08-03, date: 04/24/2025) and was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Informed Consent: Informed consent was obtained from all participants.

Declarations

Authorship Contributions

Surgical and Medical Practices: B.D., H.N.T., S.Ö.E., A.A., M.K., M.E., T.U., T.A.G., A.Ç., N.S., S.A.Ö., Ö.A.O., E.B., M.Ö., Concept: A.Ö., A.Ç., N.S., S.A.Ö., Ö.A.O., E.B., B.D., M.Ö., Design: B.D., H.N.T., S.Ö.E., A.A., M.K., M.E., T.U., T.A.G., Data Collection or Processing: B.D., H.N.T., S.Ö.E., A.A., M.K., M.E., T.U., T.A.G., A.Ç., N.S., S.A.Ö., A.Ö., E.B., M.Ö., Analysis or Interpretation: A.Ö., A.Ç., N.S., S.A.Ö., Literature Search: B.D., H.N.T., S.Ö.E., A.A., M.K., M.E., T.U., T.A.G., Writing: B.D., H.N.T., S.Ö.E., A.A., M.K., M.E., T.U., T.A.G., A.Ç., N.S., S.A.Ö., Ö.A.O., E.B., M.Ö., A.Ö.

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Review

Unseen Consequences: The Expanding Burden of Iatrogenic Dry Eye Disease in Surgical and Cosmetic Practice

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Abstract

Iatrogenic dry eye disease (DED) has emerged as a significant but overlooked complication in both ophthalmic surgery and aesthetic medicine. Characterized by disruption of tear film homeostasis, ocular surface inflammation, and neurosensory dysfunction, this condition may arise acutely or chronically following medical interventions. The Tear Film and Ocular Surface Society Dry Eye Workshop II and III reports have highlighted iatrogenic DED as a distinct clinical entity, underscoring its multifactorial etiology and the need for tailored risk mitigation strategies. Refractive procedures such as laser in situ keratomileusis and photorefractive keratectomy are frequently implicated due to corneal nerve transection and subsequent hypoesthesia, which impair blink dynamics and lacrimal gland feedback. Cataract surgery, though largely safe, contributes via surface desiccation, intraoperative light exposure, and topical medication toxicity. Oculoplastic interventions, including blepharoplasty, introduce mechanical alterations that disrupt eyelid function and tear film distribution. Moreover, the growing demand for periocular cosmetic procedures such as botulinum toxin injections and permanent eyeliner tattooing has introduced additional risks, particularly in individuals with preexisting meibomian gland dysfunction or marginal tear function. Emerging evidence suggests that the cumulative effect of repeated exposures and inadequate preoperative screening has led to a rise in persistent ocular surface morbidity. Prevention therefore necessitates a multidisciplinary approach encompassing ophthalmologists, dermatologists, plastic surgeons, and primary care providers. Systematic pretreatment ocular surface assessment, patient counseling, and adoption of minimally disruptive techniques are essential. By integrating evidence-based risk stratification into routine care, clinicians can significantly reduce the burden of iatrogenic DED and preserve long-term visual quality and patient satisfaction in the face of expanding therapeutic and cosmetic practices.

Keywords: Iatrogenic dry eye, ocular surface disease, refractive surgery, cataract surgery, blepharoplasty, botulinum toxin, cosmetic procedures, eyelid surgery

Introduction

Dry eye disease (DED) is a multifactorial and complex condition involving disruption of ocular surface homeostasis, characterized by tear film instability, hyperosmolarity, inflammation, and neurosensory dysfunction. As defined in the Tear Film and Ocular Surface Society Dry Eye Workshop (TFOS DEWS) II report by Craig et al.,[1] DED results from the loss of tear film homeostasis, presenting clinically as ocular discomfort, fluctuating vision, and signs of inflammation. Among its subtypes, iatrogenic DED remains underappreciated and refers specifically to tear film dysfunction and symptoms induced by medical or surgical interventions.

The DEWS III update expands upon this concept by incorporating recent data on epidemiology, diagnostic tools, and pathophysiologic mechanisms, emphasizing the increasing burden of iatrogenic triggers in routine practice.[2] Common contributors include anterior segment procedures (e.g., phacoemulsification, corneal refractive surgeries such as laser in situ keratomileusis [LASIK] and photorefractive keratectomy [PRK]), eyelid and periocular

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aesthetic surgeries (e.g., blepharoplasty), botulinum toxin (BoNT) injections, chronic use of preserved eye drops, and contact lens wear. Pharmacologic agents such as systemic retinoids, hormonal therapies, and antidepressants have also been linked to meibomian gland dysfunction (MGD) and aqueous deficiency.[3,4]

Importantly, iatrogenic DED is now understood not only as an acute postoperative complication but also as a chronic, often subclinical condition resulting from repeated or prolonged therapeutic exposure. Both intraoperative factors (e.g., corneal nerve disruption) and postoperative mechanisms (e.g., inflammation, tear film destabilization) contribute to its development.[5]

The DEWS III consensus strongly encourages the integration of iatrogenic risk profiling into clinical workflows, especially for surgical patients and those undergoing aesthetic procedures.[2] Risk is notably elevated in individuals with preexisting ocular surface instability, autoimmune diseases, and in older adults.[6] Among all causes, surgical interventions remain leading contributors, particularly anterior segment and oculoplastic procedures, due to their mechanical, neurotrophic, and anatomical impact on the ocular surface. This review aims to synthesize current understanding of iatrogenic DED by integrating DEWS frameworks with updated clinical evidence, outlining mechanisms, risk factors, and preventive strategies.

Methods

This narrative review synthesized peer-reviewed evidence on iatrogenic DED across surgical, cosmetic, pharmacologic, and device-related contexts. The author searched PubMed/MEDLINE, Embase, Scopus, and the Cochrane Library from January 1, 2000 to August 31, 2025, with no filter applied for study design at this stage. Core search strings combined terms and keywords related to dry eye and iatrogenic triggers, for example: (*dry eye* OR *ocular surface* OR *meibomian gland dysfunction*) AND (*refractive* OR *LASIK* OR *PRK* OR *SMILE* OR *cataract* OR *femtosecond* OR *blepharoplasty* OR *oculoplastic* OR *botulinum* OR *eyeliner tattoo* OR *contact lens* OR *preservative* OR *benzalkonium* OR *glaucoma drops* OR *isotretinoin* OR *intravitreal*). Searches were limited to English and Turkish literature.

Inclusion criteria: original clinical studies (randomized/non-randomized), cohort/case-control studies, large case series, systematic reviews, meta-analyses, consensus statements/guidelines (e.g., TFOS DEWS reports), and mechanistic or imaging studies with direct relevance to iatrogenic DED.

Exclusion criteria: non-peer-reviewed content, single-patient case reports unless clinically instructive for mechanisms, conference abstracts without full text, non-ocular surface endpoints, and duplicate publications.

The author screened titles/abstracts and reviewed full texts, as well as performed backward citation tracking of included articles and key consensus documents to identify additional eligible studies. Given the narrative scope, a qualitative appraisal focusing on study design, sample size, outcome definitions (e.g., Ocular Surface Disease Index [OSDI], tear break-up time [TBUT], Schirmer test, staining), and generalizability was conducted rather than a formal risk-of-bias meta-analysis.

Surgical Contributors to Iatrogenic Dry Eye Disease

Refractive Surgery

Refractive procedures, particularly LASIK and PRK, are well-established contributors to iatrogenic DED through their direct impact on corneal innervation. These surgeries often involve transection of subbasal nerve fibers, resulting in reduced corneal sensitivity and impaired reflex tear production. As demonstrated by Wilson and Ambrósio,[7] this post-LASIK corneal hypoesthesia can persist for as long as six months and contributes to both evaporative and aqueous-deficient subtypes of DED.

During the early postoperative period, transient dry eye symptoms are nearly universal. According to D'Souza et al.,[8] this occurs primarily due to corneal nerve transection, which leads to decreased stimulation of the lacrimal gland and reduced blink reflex. While PRK tends to damage the subbasal nerve plexus, LASIK often affects deeper stromal nerves, with both contributing to altered ocular surface homeostasis.[9]

The TFOS DEWS II Iatrogenic Report provides additional insight into these mechanisms. Gomes et al.[10] introduced the concept of "neurosensory block" to describe how corneal nerve injury impairs afferent signaling pathways essential for tear secretion and blink regulation. Preserved topical medications, particularly those containing benzalkonium chloride (BAK), can further destabilize the tear film by damaging epithelial microvilli and depleting goblet cells.[10]

In vivo confocal microscopy studies confirm that refractive surgery results in corneal nerve fiber transection, and follow-up imaging shows that nerve regeneration can take between 3 to 6 months, and even up to a year, to return to baseline status.[11,12] Identified surgical risk factors include flap configuration (e.g., hinge position, diameter, and thickness), size of the ablation zone, female sex, smoking, existing ocular surface disorders, and environmental exposures.[13]

Turu et al.[14] highlighted that LASIK-induced dry eye stems from both neurogenic and inflammatory mechanisms. Neurogenic elements involve corneal denervation, reduced sensory feedback, decreased tear secretion, and increased evaporation, while inflammatory factors involve cytokine-mediated epithelial injury. Confocal imaging has shown that stromal nerve density may decrease by up to 90% after LASIK, with only partial recovery at 1-year follow-up.[14]

D'Souza et al.[8] proposed a structured diagnostic and therapeutic algorithm for managing dry eye following refractive surgery. They emphasized that early identification of high-risk patients is key to reducing postoperative complications. Preoperative assessments should include objective measures such as Schirmer test, TBUT, and evaluation of ocular surface integrity and meibomian gland function. Subjective screening tools such as the OSDI, Dry Eye Questionnaire-5, and Impact of Dry Eye on Everyday Living are also valuable in detecting underlying dry eye before surgery.[15] In cases with subclinical signs of dry eye or lid margin abnormalities, postponing surgery and initiating ocular surface optimization therapies may improve long-term outcomes.

Small Incision Lenticule Extraction

Small Incision Lenticule Extraction (SMILE) is considered a significant technological progression in the field of corneal refractive surgery, offering high refractive accuracy while inducing less damage to corneal nerves when compared with traditional LASIK procedures.[16] In contrast to LASIK, which requires the creation of a corneal flap, SMILE involves the use of a femtosecond laser to sculpt an intrastromal lenticule that is extracted through a small peripheral incision. This technique leaves the anterior corneal architecture—including Bowman's layer and the subbasal nerve plexus—largely undisturbed, thereby helping preserve corneal sensitivity and tear film function and reducing the incidence of postoperative dry eye symptoms.[17]

Comparative studies analyzing the outcomes of SMILE and femtosecond LASIK have consistently shown similar levels of refractive correction. However, SMILE has demonstrated superior outcomes in terms of tear film stability and neurosensory recovery. Patients undergoing SMILE tend to experience faster improvement in dry eye symptoms, which often return to preoperative baseline by six months. In contrast, LASIK-treated patients frequently exhibit longer-lasting symptoms beyond this recovery window, likely due to greater corneal nerve disruption.[18,19]

Nonetheless, SMILE is not entirely exempt from iatrogenic effects. Some degree of subbasal nerve interruption occurs during lenticule dissection, which can transiently impair ocular surface function. Dry eye symptoms, although less frequent and severe than in LASIK, may still develop postoperatively, especially in patients with preexisting tear film instability or MGD.[20,21] Despite this, the relatively nerve-sparing nature of SMILE makes it a preferred option for patients considered at elevated risk for postoperative DED.

Evidence from D'Souza et al.,[8] Gomes et al.,[10] Turu et al.,[14] and studies specific to SMILE have led to a more nuanced understanding of post-refractive surgery dry eye that recognizes the multifactorial and evolving nature of the condition.[15,16,18]

Cataract Surgery

Although cataract surgery is generally regarded as a highly safe and effective procedure, it remains a prominent cause of both transient and persistent postoperative DED. In a broad narrative review by Mencucci et al.[22] representing the PICASSO Board, it was reported that up to 34% of patients without a prior history of ocular surface disease developed dry eye symptoms within the first 1 to 3 months following phacoemulsification surgery. Contributing factors include prolonged exposure to the intense illumination of the surgical microscope, ocular surface toxicity from preserved topical medications, and intraoperative desiccation of the cornea. Supporting these findings, Han et al.[23] and other authors demonstrated significant postoperative reductions in TBUT and Schirmer test scores, particularly in patients with marginal preoperative ocular surface parameters.[22,24]

Complementing this, Ishrat et al.[25] found that dry eye was more common after small-incision cataract surgery compared to standard phacoemulsification. They attributed this to increased tear film instability, reporting statistically significant differences in TBUT at 1 week, 1 month, and 3 months postoperatively.

Mencucci et al.[22] also detailed several intraoperative factors that exacerbate dry eye risk. These include the use of lid speculums that distort lid-globe congruity, the direct neuroepithelial trauma caused by corneal incisions, and the phototoxicity of microscope illumination, which reduces goblet cell density and promotes pro-inflammatory cytokine release. Larger and grooved incisions were particularly implicated in delayed epithelial healing and impaired nerve regeneration. Moreover, commonly used topical anesthetics and mydriatics, especially those preserved with BAK, have been shown to induce epithelial cell apoptosis, disrupt mucin production, and create a pro-inflammatory microenvironment even before the surgical procedure begins.[26,27,28,29]

Further evidence provided by Mencucci et al.[22] suggests that femtosecond laser-assisted cataract surgery (FLACS) may be associated with an even higher risk of postoperative

dry eye than conventional phacoemulsification. The longer duration of the procedure, elevated laser energy exposure, and the use of suction rings may collectively contribute to inflammatory edema, goblet cell dysfunction, and further destabilization of the tear film.[22,30]

One of the key conceptual contributions of the PICASSO Board was the proposal of the "3+2" pathophysiological model, which outlines three central mechanisms—tear film instability, epithelial damage, and ocular surface inflammation—alongside two aggravating factors: lid margin dysfunction and neurosensory impairment. This model serves as a framework for comprehensive diagnostic and therapeutic strategies that span preoperative, intraoperative, and postoperative phases, with the ultimate aim of preserving or restoring ocular surface homeostasis during cataract surgery.[22]

Wolffsohn et al.[4] also emphasized that thorough preoperative screening is essential for reducing the risk of postoperative complications. Recommended assessments include TBUT, OSDI scores, fluorescein staining, meibography, and point-of-care tests such as tear osmolarity and matrix metalloproteinase-9 measurements.[31]

These recommendations apply to both preoperative optimization and postoperative management. Preservative-free artificial tears, eyelid hygiene, warm compresses, and omega-3 fatty acid supplementation are appropriate in both periods to stabilize the tear film and address MGD. Topical anti-inflammatories should be used postoperatively (short courses of corticosteroids). When feasible, anti-inflammatory treatment should also be initiated preoperatively with immunomodulators (cyclosporine or lifitegrast) to reduce baseline inflammation and continued after surgery.[32] In refractory cases, punctal occlusion is considered after ocular surface inflammation is controlled, and pulsed light therapy is generally reserved for chronic/refractory MGD outside the immediate perioperative window.[4,20,30,32]

Oculoplastic Surgeries

Oculoplastic procedures, most notably blepharoplasty, can disrupt lid-globe congruity, impair blink dynamics, and adversely affect meibomian gland performance. Normal tear homeostasis requires coordinated aqueous production, blink-mediated distribution, and unobstructed drainage. Therefore, surgical alterations that weaken orbicularis function, modify eyelid position, or disturb lacrimal outflow can destabilize the tear film and precipitate ocular surface symptoms.[33,34,35,36,37,38,39] Blepharoplasty may alter eyelid positioning and compromise blink strength, while resection of the orbicularis oculi can induce scarring and neural injury, leading to incomplete blinking, reduced blink frequency, and lagophthalmos. These changes impair meibomian lipid secretion and further destabilize the tear film.[10,35,40,41] Zhang et al.[42] showed that even subtle trauma to the orbicularis during cosmetic blepharoplasty can inhibit blink-induced meibum expression, reduce lipid layer thickness, and destabilize the ocular surface.

Prospective data demonstrate transient but measurable postoperative tear film changes. Sanad et al.[33] reported significant declines in tear meniscus height and TBUT that typically returned to baseline by six months. In a large retrospective cohort (n=892), Prischmann et al.[34] noted dry eye complaints in ~26.5%, with higher risk when upper and lower lids were operated together versus single-lid procedures. As patient factors (age, sex, baseline tear status) and technique modulate symptom severity and duration, Hamawy et al.[35] recommended careful preoperative risk stratification and conservative skin excision. In patients with known DED, Saadat and Dresner[37] observed postoperative worsening in 8% and no change in 83% when anatomic structures were preserved, suggesting blepharoplasty can be performed with minimal risk in properly selected cases.

Early postoperative perturbations are typically self-limited. Shao et al.[38] noted that OSDI and tear meniscus height were increased and Schirmer scores were reduced at week 1 after lower blepharoplasty and normalized by month 3. Using anterior-segment optical coherence tomography, they also documented a decreased cornea-lower lid angle and increased lower lid margin reflex distance at week 1. Both of these findings approached baseline by month 3, paralleling symptom resolution (dryness, epiphora, chemosis).[38]

Comparative studies contextualize the risk of postoperative DED. Aksu Ceylan and Yeniad[36] found greater decline in Schirmer test scores after blepharoplasty than after levator resection, attributing differences to orbicularis weakening with downstream effects on blink reflex and corneal sensitivity. Other eyelid surgeries such as ptosis repair and ectropion correction can also alter blink kinematics and tear physiology. In a series by Zhang et al.,[43] nearly 25% of patients exhibited postoperative blink pattern changes, most often those with preexisting lagophthalmos or facial nerve dysfunction, underscoring the role of eyelid closure in tear distribution. Full-thickness eyelid reconstruction data show that despite Schirmer and TBUT values comparable to controls, patients frequently report ocular discomfort, highlighting the importance of structural stability for tear film homeostasis.[44] In a cohort of 63 upper blepharoplasties, Mian et al.[45] observed reductions in Standard Patient Evaluation of Eye Dryness scores at 1 month and 1 year in both orbicularis-sparing and orbicularis-excising techniques, with no significant difference between approaches.

Lacrimal drainage pathology can also amplify the DED symptom burden. In patients with nasolacrimal duct obstruction and dry eye symptoms, silicone stent implantation achieved a 76.7% surgical success rate with significant improvements in Glasgow Benefit Inventory, particularly in general and social well-being.[46] These findings suggest that treating epiphora can enhance subjective comfort even without large changes in physical health scores. When lower lid retraction or malposition is anticipated, canthopexy or lateral canthal suspension provides needed support and reduces scleral show. Long-term series report lower malposition rates and improved ocular surface outcomes when using this approach.[47] During upper blepharoplasty, vigilance for lacrimal gland prolapse is essential, as unrecognized or traumatized gland tissue may depress aqueous production and worsen postoperative dryness, particularly in older patients or those with prior eyelid surgery.[48] Preventive measures include preoperative identification of high-risk patients, meticulous tissue-sparing technique to preserve eyelid mechanics and orbicularis integrity, and postoperative anti-inflammatory therapy with frequent lubrication. Adjunct lid margin therapies are advisable when MGD coexists.[10,35,40,41]

Cosmetic and Aesthetic Interventions

The growing popularity of periocular cosmetic procedures has introduced additional risk factors for iatrogenic DED. Treatments such as BoNT-A injections, permanent eyeliner tattooing, and eyelash extensions (EEs) are increasingly associated with adverse effects on tear film integrity, blink dynamics, and meibomian gland function.

Kocabeyoglu et al.[49] evaluated ocular surface changes in patients with blepharospasm receiving periocular BoNT-A injections. They reported that ocular surface test results improved 2 weeks after injection, started to deteriorate after 3 months, and almost returned to baseline after 6 months. In parallel with improvements in objective test results, subjective complaints also decreased within 2 weeks and increased between 3 and 6 months postinjection. The authors concluded that BoNT-A may have a temporary beneficial effect on ocular surface parameters in patients with blepharospasm, but the effect appears transient and may not apply universally.[49]

Despite some therapeutic benefit, the TFOS DEWS III report emphasized the potential iatrogenic consequences of cosmetic BoNT-A injections, particularly when administered near the lateral canthal area.[2] The toxin may interfere with blink force and amplitude due to its chemodenervation of the orbicularis oculi muscle, leading to lagophthalmos, incomplete blinking, or lower lid laxity, factors that can increase evaporative stress and destabilize the tear film.[6,50]

EEs represent another aesthetic modality with documented ocular surface implications. In a prospective study, Grupcheva et al.[51] demonstrated that the removal of EEs resulted in statistically significant improvements in both subjective symptoms and objective findings. Following EE removal, OSDI scores decreased from 33.4 to 26.7, TBUT increased from 11.25 to 13.96 seconds, and both blink frequency and corneal staining improved. These findings suggest that EEs may contribute to ocular surface instability by interfering with lid hygiene, reducing blink efficiency, and impairing meibomian gland expression. Importantly, discontinuing EEs led to measurable recovery in tear film stability and ocular comfort.

Consistent with these observations, Masud et al.[52] found that long-term use of EEs correlated with higher rates of meibomian gland dropout, lid margin irregularities, and diminished tear meniscus height when compared to control subjects. They attributed these effects to the combined mechanical and chemical irritation from repeated application, particularly due to cyanoacrylate-based adhesives. These changes were particularly detrimental in individuals with preexisting MGD, amplifying tear film instability and ocular surface inflammation.

Lee et al.[53] provided a detailed review of ocular complications arising from cosmetic eyelid tattooing, with a specific focus on permanent eyeliner tattoos. They reported a range of short- and long-term complications, including allergic reactions, eyelid edema, conjunctivitis, pigment migration, granuloma formation, and structural disruption of the meibomian gland orifices. The authors highlighted the need for stricter procedural guidelines and practitioner training, noting that tattoo placement too close to the mucocutaneous junction can result in permanent meibomian gland damage and chronic ocular surface disease.

These concerns were reflected in the TFOS DEWS III report by Stapleton et al.,[2] who included aesthetic procedures among the recognized contributors to iatrogenic DED. They advocated for pre-procedural ocular surface screening and routine postoperative follow-up for patients undergoing cosmetic interventions. Moreover, the report recommended interdisciplinary collaboration between dermatologists, plastic surgeons, and ophthalmologists to minimize ocular surface complications and ensure informed consent.

Taken together, these findings underscore that cosmetic procedures, despite being minimally invasive, can produce lasting disruptions in ocular surface homeostasis. Proper patient selection, clinician awareness, and preventive strategies are necessary to mitigate these risks.

Pharmacologic and Device-Related Triggers

Pharmacologic agents, particularly those administered topically in ophthalmology, represent a well-established category of contributors to iatrogenic DED. Among these, preservatives (especially BAK) have been studied extensively for their cytotoxic effects on the ocular surface.[3]

Beyond BAK, other excipients such as thiomersal and ethylenediaminetetraacetic acid may also contribute to ocular surface toxicity, especially in individuals with underlying dry eye conditions or known allergic sensitivities. The chronic administration of topical antiglaucoma medications poses particular concern in this regard. According to the findings of Mocan et al.,[54] patients receiving long-term treatment with prostaglandin analogs and beta-adrenergic blockers often present with signs of conjunctival hyperemia, punctate epithelial erosions, and MGD, features that collectively promote tear film instability and ocular surface disease.[55,56]

Systemic medications also contribute significantly to iatrogenic DED. Isotretinoin, a systemic retinoid commonly prescribed in dermatology, has been shown to induce meibomian gland atrophy, resulting in a marked reduction in lipid layer secretion. In parallel, systemic agents such as antihistamines, tricyclic antidepressants, selective serotonin reuptake inhibitors, and beta-blockers have been implicated in reduced aqueous tear production, further exacerbating tear film instability and evaporative stress in predisposed individuals.[4,57,58]

Furthermore, chemotherapeutic agents, particularly those targeting epidermal growth factor receptors, have been associated with direct injury to the ocular surface. These agents can deplete goblet cells, increase ocular surface inflammation, and impair epithelial regeneration, contributing to a cascade of tear film dysfunction and chronic ocular surface compromise.[59]

Contact lens use represents another prevalent and significant contributor to DED.[10,60] Estimates indicate that approximately half of soft contact lens users report symptoms consistent with contact lens-related dryness.[61] In a study conducted in Japan, Koh et al.[62] found that over 70% of individuals using soft contact lenses experienced ocular dryness.

Clinical awareness of contact lens discomfort has increased substantially since the publication of the TFOS DEWS II Contact Lens Discomfort Report.[63,64] The primary pathophysiologic mechanisms implicated in contact lens discomfort are inadequate tear distribution and increased mechanical interaction between the lens and ocular surface structures, leading to frictional damage.[65]

Prolonged contact lens wear (especially of rigid gas-permeable and soft contact lenses) has been associated with microtrauma to the ocular surface and disruption of tear film dynamics, including reduced tear exchange and compromised lipid spreading.[66,67] Tear film changes associated with soft contact lens usage include accelerated tear evaporation, reduced tear volume, instability of the pre-lens lipid layer, and compositional shifts in tear film content.[68]

Two reviews by Efron[69,70] highlighted both overt and subclinical inflammation associated with contact lens wear. They documented evidence of inflammatory responses even in users of modern lens materials, such as hydrogel and silicone hydrogel lenses, under routine conditions. Contact lens discomfort is a major reason for discontinuation of contact lens wear.[71]

Another often-overlooked source of iatrogenic DED is repeated intravitreal injection therapy. In a prospective study by Srinagesh et al.,[72] involving 12 patients undergoing multiple intravitreal anti-vascular endothelial growth factor injections, cumulative procedural exposure was associated with worsening ocular surface parameters, presumably due to repeated mechanical trauma and the inflammatory effects of antiseptics used perioperatively. Additionally, frequent use of topical antibiotics during the peri-injection period may exacerbate epithelial damage through direct cytotoxicity.[73,74]

Special consideration must also be given to patients receiving keratoprosthetic implants. In their retrospective study of patients with Boston Type I keratoprostheses, Zhang et al.[75] reported that aggressive management of the ocular surface (including intensive lubrication, punctal occlusion, and ongoing anti-inflammatory treatment) was essential to ensure prosthesis retention and prevent sterile keratolysis.

Management and Preventative Strategies

The effective prevention and long-term management of iatrogenic DED should follow an etiology-directed, stepwise algorithm that spans preoperative optimization, intraoperative protection, and severity-tiered postoperative care, along with continuous patient education. Stapleton et al.[2] emphasized within the TFOS DEWS III framework that routine ocular surface assessment (symptoms, TBUT, staining, meibography, osmolarity, validated questionnaires) should be integrated into preoperative planning for cataract, refractive, and oculoplastic candidates to identify subclinical instability early. In parallel, the recent TFOS DEWS III: Management and Therapy report synthesized first-line measures (replenish, conserve, stimulate the tear film), targeted meibomian gland interventions, anti-

inflammatory strategies, and advanced therapies within an evidence-based prescribing algorithm.[76] The interventions involved at each stage of this algorithm are outlined below.

Preoperative Optimization (Risk Modification): Address modifiable drivers, especially MGD, via lid hygiene education, regular warm compresses, and lid margin care. When feasible, modify systemic or topical regimens known to cause ocular surface toxicity. Lipid-enriched artificial tears and nutritional support (e.g., omega-3/omega-6) can improve lipid layer quality and symptom control.[77] For eyes with clinically significant inflammation or epithelial compromise, start targeted anti-inflammatory therapy to improve surgical readiness and recovery. Cyclosporine A or lifitegrast may be used to reduce T-cell–mediated inflammation and restore homeostasis.[6,78]

Intraoperative Protection (Iatrogenic Stress Minimization): Limit microscope light exposure and surface desiccation. Use preservative-free solutions when possible, and provide frequent non-preserved lubrication (or a moisture chamber) during longer cases. Technique choices that preserve corneal innervation and eyelid-globe congruity (e.g., thoughtful incision architecture, flap/ablation parameters, and preservation of orbicularis/eyelid position in oculoplastic procedures) reduce postoperative evaporative burden.

Postoperative Care (Severity-Tiered Management): Initiate preservative-free artificial tears promptly. Consider short, judicious corticosteroid courses for inflammatory phenotypes. Escalate when needed to punctal occlusion or autologous serum/platelet-rich plasma in refractory disease. Continue sustained lid-margin therapy for MGD-predominant phenotypes and consider in-office MGD procedures (thermal pulsation, meibum expression) where appropriate. Depending on etiology and severity, the TFOS DEWS III algorithm also recognizes the benefit of integrating adjunctive methods such as intense pulsed light, low-level light therapy, neuromodulation (nasal neurostimulation), scleral lenses for severe exposure/evaporative cases, and amniotic membrane in advanced epithelial disease.[76]

Patient Education (Cross-Cutting): Reinforce blink training, screen ergonomics, ambient humidity control, proper drop instillation, and adherence, which are the core tenets highlighted by TFOS DEWS III to sustain outcomes and reduce chronicity.[76]

Refractive Surgery (LASIK/PRK/SMILE): Screen preoperatively for borderline tear function and lid margin disease. Defer elective procedures when the ocular surface is unstable and optimize first. Technique selection that preserves innervation and prudent flap/ablation parameters support faster neurosensory recovery. Early postoperative lubrication is universal. Manage persistent neuropathic-inflammatory phenotypes with anti-inflammatory therapy and surface rehabilitation.

Cataract Surgery (Including FLACS): Conduct preoperative optimization of the ocular surface and avoid preserved perioperative drops when feasible (or switch to preservative-free/fixed combinations). Ensure intraoperative lubrication and minimize light exposure. Postoperatively, preservative-free tears plus short anti-inflammatory courses are first-line. Escalate in moderate-severe cases (e.g., punctal occlusion) while continuing MGD care.

Oculoplastic Procedures (e.g., Blepharoplasty, Ptosis Repair, Eyelid Reconstruction): Pre-select patients with fragile tear film or preexisting DED. Utilize surgical techniques that preserve orbicularis continuity, blink amplitude, and lid position. Provide intra-/postoperative edema control and frequent lubrication. Where lower lid malposition or retraction is anticipated, supportive canthal measures reduce scleral show and exposure. Vigilance for lacrimal gland prolapse is essential; inadvertent trauma risks aqueous deficiency.

Cosmetic Interventions (BoNT-A, EEs, Permanent Eyeliner): Ensure prior ocular surface screening and informed consent about DED risk. For BoNT-A, make dose/location choices that avoid excessive blink weakening. Monitor for transient changes and support with lubrication and lid margin care. For EEs, counsel on lid hygiene and consider discontinuation if they exacerbate symptoms. Eyelid tattooing should avoid the mucocutaneous junction to protect the meibomian gland orifices. Manage resultant lid margin inflammation promptly.

Chronic Topical Therapy (Especially Glaucoma): Prefer preservative-free or fixed-combination formulations to reduce cumulative BAK exposure. Monitor for signs of meibomian dysfunction and epithelial toxicity, and co-manage with surface-stabilizing therapy.

Contact Lens Wear and Procedure-Heavy Care Pathways (e.g., Repeated Intravitreal Injections, Keratoprosthesis): Recognize frictional/mechanical and inflammatory mechanisms. Optimize lens fit/wearing schedule and treat contact lens-related DED per established guidance. Around injection pathways, minimize epithelial insult from antiseptics/antibiotics and provide surface support. After keratoprosthesis, intensive lubrication, punctal occlusion, and sustained anti-inflammatory therapy may be necessary for device retention and surface integrity.

Discussion

Iatrogenic DED has become increasingly recognized as a substantial contributor to ocular surface dysfunction in the context of modern surgical techniques and pharmacological treatments. The multifaceted nature of its pathophysiology illustrates the inherent challenges in both prevention and therapeutic management. As substantiated by numerous prospective and retrospective investigations, the ocular surface demonstrates increased vulnerability to interventions that disturb anatomical integrity, impair neurosensory pathways, or trigger inflammatory responses.[7,22,25,77]

Epitropoulos[78] emphasized that refractive surgeries frequently precipitate the transition of patients from a subclinical status to overtly symptomatic DED following the procedure, especially among individuals with preexisting borderline tear function or unrecognized MGD.

Although cataract surgery is generally regarded as a safe and effective intervention, it also constitutes a common iatrogenic cause of DED. Importantly, there are studies reporting a significant association between MGD and cataract surgery, with asymptomatic MGD found to be twice as prevalent as symptomatic cases.[21,79]

Oculoplastic surgeries introduce a distinct set of challenges due to their direct alteration of eyelid architecture and blink dynamics.[80,81] Even minor modifications to eyelid position, blink amplitude, or orbicularis oculi muscle function can severely disrupt the eyelid's role in tear film distribution and ocular surface protection. The essential interdependence of eyelid mechanics, lacrimal gland secretion, and blinking function is prominently underscored in the TFOS DEWS III report and further corroborated by recent surgical outcome analyses. These studies consistently reveal that inadequate preservation of eyelid contour or orbicularis muscle continuity is closely linked to increased severity of dry eye symptoms in the postoperative period.[2,33,42]

This complex relationship is further exacerbated by the rising popularity of cosmetic procedures in the periocular region. As patient demand for such interventions continues to increase, the literature documenting their frequently underestimated negative consequences on the ocular surface environment is also increasing.[52,82,83]

Among these procedures, BoNT injections can impair blink completeness and frequency, thereby accelerating tear evaporation and compromising uniform tear distribution. This mechanism is particularly pertinent in elderly populations, in whom baseline tear production may already be marginal.[50] Similarly, cosmetic practices such as permanent eyeliner tattooing can provoke inflammation of the lid margin and worsen preexisting MGD, especially when performed without prior evaluation of ocular surface health.[53] Masud et al.[52] emphasized that healthcare providers must be aware of the potential adverse outcomes associated with these cosmetic enhancements, not only due to their capacity to damage the ocular surface but also because of their broader implications for visual function and postoperative satisfaction.

Given the expanding and evolving understanding of iatrogenic DED, it is evident that reducing its prevalence and severity demands more than only recognition. It requires the proactive implementation of comprehensive prevention strategies.

Conclusion

Iatrogenic DED represents a growing and underappreciated clinical challenge across ophthalmology and aesthetic medicine. Its etiology is inherently multifactorial, originating from surgical injury, pharmacologic toxicity, and cosmetic manipulation, and its effect on patient quality of life can be profound.

Fortunately, with the structured guidance provided by the TFOS DEWS II and III consensus frameworks, clinicians are now better equipped to recognize, prevent, and manage iatrogenic DED. Risk stratification, proactive screening, and tailored perioperative strategies are the cornerstones of effective care. Multidisciplinary collaboration among ophthalmologists, oculoplastic surgeons, dermatologists, plastic surgeons, and other care providers will be essential to alleviating long-term complications. By integrating evidence-based preventive strategies into standard practice, we can significantly reduce the incidence and impact of iatrogenic DED.

Declarations

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Case Report

Modification of the Temporal Inverted Internal Limiting Membrane Flap in Macular Hole Surgery: Envelope Technique

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Abstract

This case report aims to present a modification of the temporal inverted internal limiting membrane (ILM) flap technique in macular hole surgery. The inverted ILM flap technique was first described in 2010 and was shown to yield superior functional and anatomical outcomes in large macular holes compared to traditional ILM peeling. However, flap displacement can be a major concern with the inverted ILM flap technique. In the first case, a failed large macular hole after temporal inverted ILM flap surgery was reoperated, and flap displacement was observed as the reason for failure. The displaced ILM flap was inverted again and the superior corner of the flap was tucked under the small ILM defect in the upper nasal macular area to stabilize it. Hence, it is called as "envelope modification". Another patient with rhegmatogenous retinal detachment with coexistent macular hole underwent vitrectomy surgery with silicone oil. The retina was attached postoperatively, and the macular hole was closed with a flat-open pattern. During silicone oil removal, the envelope modification was used and the hole closed. Both patients had visual improvement. Although the inverted ILM flap technique is very effective for large macular holes, the modification described here may further improve the success rate.

Keywords: Macular hole, inverted ILM flap, modification

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Introduction

Idiopathic macular hole is one of the main vitreoretinal interface disorders, and removal of the internal limiting membrane (ILM) has become a critical surgical step in most macular hole surgeries. Pars plana vitrectomy with ILM peeling is a safe and effective procedure with a success rate up to 98%. However, macular hole size has been found to be inversely correlated with the surgical success rate.[1,2] Therefore, large macular holes (minimum diameter >400 µm) have less favorable surgical outcomes.

The inverted ILM flap technique was first described in 2010 by Michalewska et al.,[3] who reported the superiority of this technique in large macular holes compared to traditional ILM peeling in terms of both functional and anatomical results. However, the authors pointed out that flap displacement was an important limitation of this technique and concluded that new methods of maintaining the inverted flap on the macular surface should be investigated.

This study presents a novel modification of the inverted ILM flap surgery. To the best of my knowledge, this is the first report of this surgical technique.

Case Reports

Case 1

A 64-year-old female patient with a history of decreased vision in her right eye for 3 to 4 months presented to our clinic. Her vision in the right eye was counting fingers. Optical coherence tomography (OCT) revealed a large macular hole with a minimum diameter of 896 µm (Figure 1a). A 23-gauge pars plana vitrectomy with temporal inverted ILM flap combined with phacoemulsification and intraocular lens implantation was performed. Brilliant Blue

(BB) dye (Brilliant Peel 0.025%, Fluoron, Ulm, Germany) was used to stain the ILM and a temporal half ILM flap was created. The nasal side ILM was not peeled, and the rectangular temporal ILM flap was inverted over the nasal macula using a Tano scraper. A complete fluid-air exchange was performed, making sure that the ILM flap was in place, and 12% C_3F_8 gas was used as tamponade. The patient was advised to maintain a prone position for 5 days. However, the hole remained open after the surgery (Figure 1b), and revision surgery was performed at 6 weeks. During the reoperation, BB dye was used to visualize the original ILM flap, which was observed to be detached and folded over itself in the temporal macular area. To maintain the ILM flap in an inverted position on the macular surface, an "envelope modification" was performed by creating a small ILM window in the superonasal macular area (Figure 1c, Figure 2). A short vertical ILM window was fashioned using ILM forceps. The ILM flap was then inverted over the hole and its superonasal corner was tucked through the window using a Tano scraper. The ILM flap was observed closely during fluid-air exchange and it was seen to be completely immobile at the tucked edge. Gas tamponade (12% C_3F_8) was performed with prone positioning for 5 days. Significant inflammation was observed postoperatively and managed with topical steroids (Pred Forte 1%, Allergan, Westport, Ireland). OCT taken 3 weeks after the surgery showed a closed macular hole (Figure 1d). Final visual acuity was 0.2, possibly due to changes in the retinal pigment epithelium (RPE) at the hole base. The hole remained closed during an 18-month follow-up period.

Case 2

A 65-year-old female patient presented with loss of vision in the right eye for about 10 days. Her vision in the right eye was at the level of counting fingers, and she had a macula-off retinal detachment with a tear at the 10 o'clock position. Macular hole was not evident at the time of examination, possibly obscured by the bullous detachment. The patient underwent phaco-vitrectomy with silicone oil as endotamponade due to the necessity of air travel. A macular hole was clearly observed intraoperatively, and no special attempt was made to peel the ILM due to our previous experience in cases of rhegmatogenous retinal detachment cases with coexistent macular holes.[4] Additionally, ILM peeling may be challenging with a

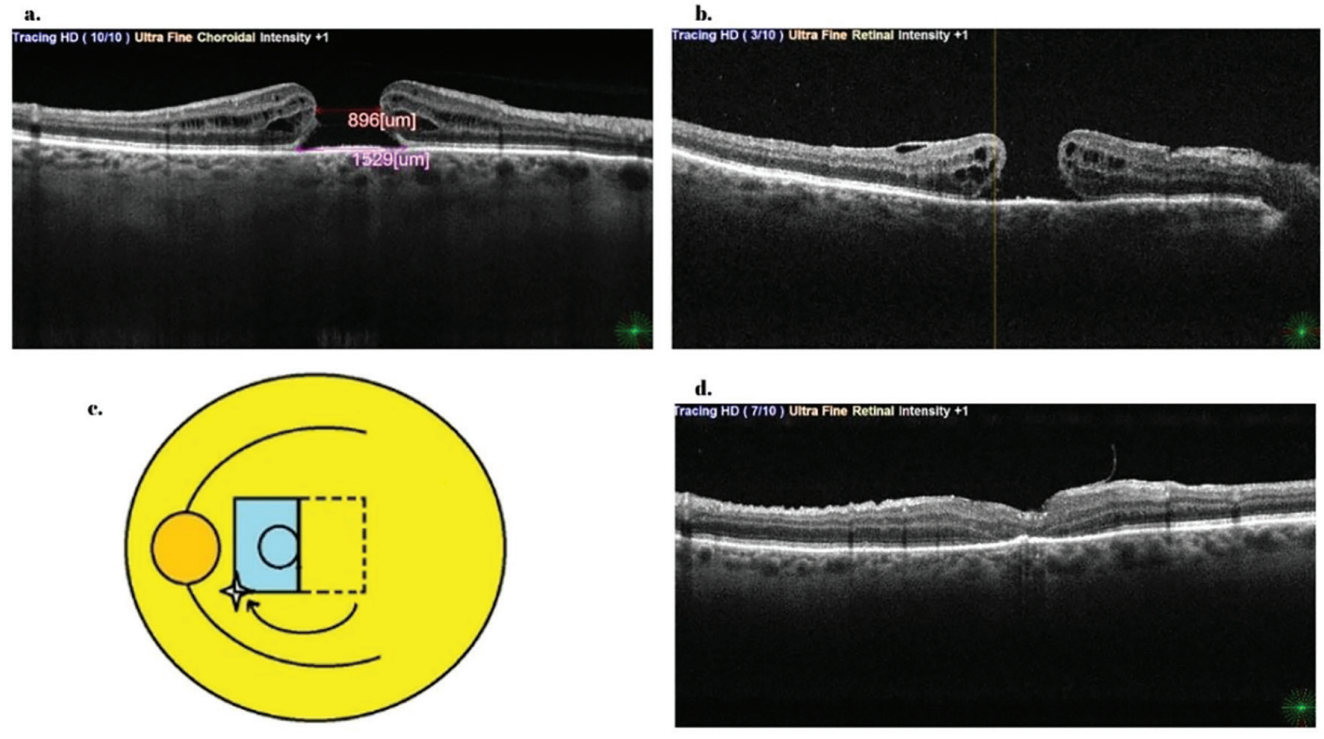

Figure 1. a) Preoperative optical coherence tomography (OCT) section depicting large macular hole. b) Postoperative OCT section showing an open macular hole with internal limiting membrane (ILM) flap returned to its original position on the temporal foveal area. c) Drawing of the modification (the star represents the ILM window in the superonasal macula, the blue rectangle indicates the inverted flap, and the arrow shows the tucked corner, surgeon's view). d) Postoperative OCT showing a closed macular hole with the inverted flap edge

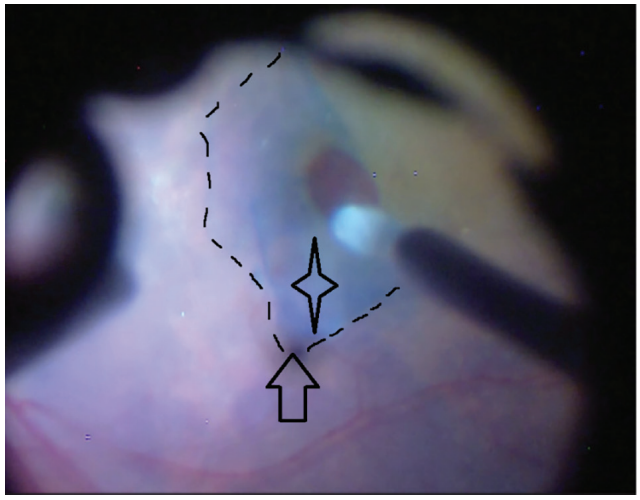

Figure 2. Still photo from the surgical video displaying the modification (arrow indicating the tucked corner and the star representing the ILM window in the superonasal macula, surgeon's view)
ILM: Internal limiting membrane

detached retina, and dyes can easily pass through the hole into the subretinal space, possibly causing toxicity. On the first postoperative day, the retina was attached and the hole was closed with flat-open pattern (Figure 3a). Visual acuity was 0.05 under silicone oil. After 2 months, OCT showed the hole edges had started to raise and round up (Figure 3b). Silicone oil removal was performed at 3 months, and the inverted ILM flap technique with envelope modification as described above was used to close the hole. Under 12% C_3F_8 gas with 5 days of prone positioning, the hole closed successfully with a U pattern (Figure 3c, d). Her final visual acuity was 0.2 and the hole remained closed during a 25-month follow-up period.

Discussion

The surgical management of large macular holes has proven challenging despite ILM peeling. The surgical approach described by Michalewska et al.[3] utilizes an ILM flap as a scaffold to induce retinal gliosis within the macular hole, thereby augmenting hole closure. In 2015, Michalewska et al.[5] introduced the temporal inverted flap technique and compared it to the classic inverted ILM flap technique. The authors reported that the temporal inverted

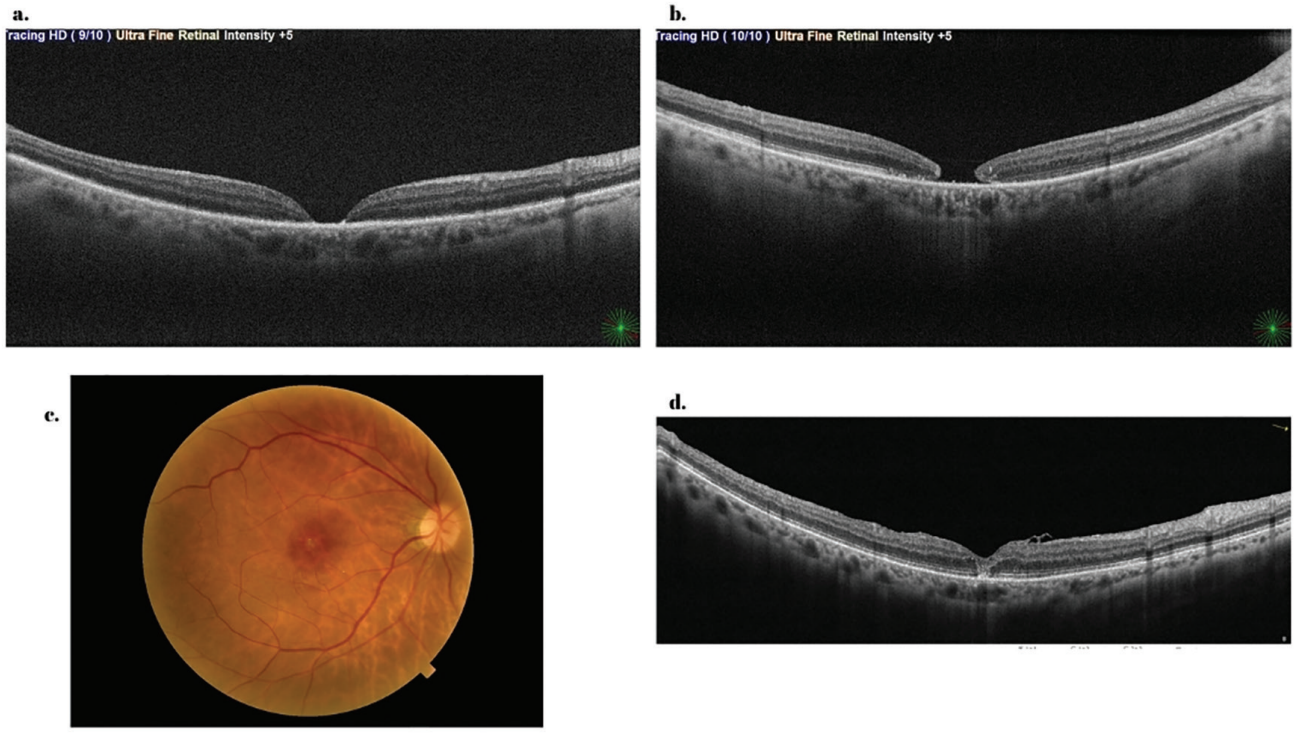

Figure 3. a) Attached retina with flat-open macular hole on postoperative day 1. b) After 2 months, the hole edges started to elevate and round up. c, d) Fundus photo and optical coherence tomography showing closed hole with the ILM flap edge on the nasal foveal area at last follow-up visit
ILM: Internal limiting membrane

flap would act as a scaffold for retinal gliosis at the roof of the macular hole without creating an obstacle at the base of the hole, unlike the trimmed ILM flaps in the original technique.

Flap displacement, however, may be a major concern when using the inverted ILM flap technique. In their original report, the authors stated that inverted ILM flaps had displaced spontaneously during fluid-air exchange in 7 of 50 eyes (14%).[3] They concluded that new techniques of maintaining the inverted ILM flap in position should be explored in the future. Although ILM flaps may be stable at the end of surgery, they can detach shortly afterwards due to fluid accumulation at the posterior pole. In a more recent study, the same group reported a 3.8% failure rate in inverted ILM flap procedures, and they repositioned the displaced ILM flap in the second surgery mostly using silicone oil as tamponade.[6]

The first patient in the current report needed the inverted ILM flap technique due to the large size of the macular hole. Although every step of the surgery was performed meticulously, the hole failed to close due to flap displacement. Since the stability of inverted ILM flap is somewhat unpredictable, the current report recommends a modification. The envelope technique involves creating a small vertical ILM window in the nasal macular area away from papillomacular bundle and tucking one of the corners of the inverted ILM flap through the window and under the unpeeled nasal ILM. This tucking ensures that the ILM flap stays in position during the fluid-air exchange and after the surgery. This approach worked very well in both patients, and the holes closed shortly in a U pattern. One may propose to tuck both corners of the flap, but the author believes that this will only add extra work, because tucking one corner is sufficient.

Despite the favorable anatomical outcomes, visual improvement was limited. This can probably be attributed to outer retinal/ellipsoid zone defect and RPE changes at the hole base in the first case. The RPE atrophy was believed to be due to repeat surgery, dye usage, and possibly significant inflammation after the second surgery. The author believes it is not related to the modification because the ILM flap was not in contact with the hole base, unlike in the classic inverted ILM technique. Although improved, visual acuity was also limited in the second case, likely due to underlying macula-off retinal detachment. No epiretinal membrane formation or fibrosis was observed during the follow-up period in both cases.

Different surgical techniques or adjuncts like perfluorocarbon liquids or viscoelastics have been used for flap stabilization.[7] Perfluorocarbon liquids have been utilized to "iron" the inverted ILM flap and prevent flap displacement during fluid-air exchange and afterwards. However, apart from the additional cost, these heavy liquids may cause toxicity. Additionally, it does not guarantee the stability of ILM flap, unlike the current modification.

This additional modification may be seen as unnecessary by some surgeons, but it may save both surgeon and patient from reoperation. This modified technique may be used in inverted ILM flap cases that failed due to flap displacement or can be used primarily in temporal inverted ILM flap surgeries according to the surgeon's discretion. The author proposes using a superior inverted ILM flap and tucking the temporal corner of the flap under the inferotemporal macular area. This may preserve the inferior visual field by moving the tucking area from the superior to inferior macula.

In conclusion, although the inverted ILM flap is a very effective surgical procedure for large macular holes, modifying the technique as described may augment the success rate. Larger studies are needed to determine whether the modified technique affects anatomical and visual results.

Ethics

Informed Consent: Due to the retrospective nature of the study, informed consent was not obtained.

Declarations

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

Financial Disclosure: The author declared that this study received no financial support.

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Out of Sight, Out of Chamber: PreserFlo® MicroShunt Dislocation Following Office-Based Needling

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Dear Editor,

The PreserFlo® MicroShunt (PMS) implant (Santen, Miami, USA) is a newer alternative to traditional glaucoma surgeries like trabeculectomy. While the PMS is typically less effective at lowering intraocular pressure (IOP) compared to trabeculectomy, it is favored for its superior safety profile, including fewer reinterventions[1,2] and a lower risk of hypotony.[3] However, the long-term success of PMS is influenced by fibrosis in the filtering bleb, which can increase IOP and lead to surgical failure.[4] Postoperative needling procedures are often used to address bleb failure and restore bleb function.[5] A rare and unique complication of PMS implantation is device dislocation, which can occur following needling procedures but has not been extensively documented in the medical literature. This article describes a case of PMS dislocation after an office-based needling procedure in a young patient.

Keywords: Minimally invasive glaucoma surgery, PreserFlo® MicroShunt, needling, device dislocation

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A 32-year-old man with a history of severe juvenile open-angle glaucoma in both eyes was monitored for ongoing IOP control. He had previously undergone multiple surgeries, including non-penetrating deep sclerectomy (NPDS) with revision and laser trabeculoplasty in the right eye, and NPDS, Ahmed valve implantation, cyclophotocoagulation, and revision in the left eye. Despite maximal topical therapy, IOP remained uncontrolled in the right eye. Preoperative examinations revealed visual acuity (Snellen decimal) of 0.7 in the right eye and 0.6 in the left eye, with IOPs of 40 mmHg and 15 mmHg, respectively. Both eyes showed signs of optic nerve damage, including significant pallor and thinning of the nerve fiber layer, as well as severe visual field involvement (Figure 1).

The patient had a prior history of hypotonic retinopathy after glaucoma surgery. Therefore, trabeculectomy was avoided, and ab externo PMS implantation was chosen for the right eye. The immediate postoperative course was uneventful, with an IOP of 9 mmHg and a well-formed bleb (Figure 2). However, at 5 weeks, IOP increased to 18 mmHg, and anterior segment optical coherence tomography (AS-OCT) revealed contact between the distal end of the PMS and Tenon's tissue (Figure 3A). A needling procedure was performed in the office to release the distal end (Figure 4). The PMS was localized using a cannula and pressure on the conjunctiva to visualize the end of the implant. A 30-gauge (G) needle was used to make fan-shaped movements to release adhesions around the PMS. After the procedure, AS-OCT confirmed fluid around the PMS tip (Figure 3B) and IOP dropped to 6 mmHg.

One month later, IOP remained below 14 mmHg, but 6 weeks post-needling, the patient presented with pain and a flattened bleb. IOP had risen to 50 mmHg, and the PMS was no longer visible in the anterior chamber (Figure 5A).

Gonioscopy confirmed that the device was absent (Figure 5B). The patient was started on topical treatment and oral acetazolamide to reduce IOP, and a surgical revision was scheduled. During the revision surgery, the PMS was found to be deformed, rigid, and completely displaced posteriorly. The device had migrated out of the anterior chamber and was now located in the sub-Tenon's space. The displaced PMS was removed, and a new PMS was implanted externally. Gonioscopy confirmed proper placement in the trabecular meshwork, and the device was guided with a 9-0 Prolene suture (Figure 6). The immediate postoperative course was uneventful, and 2 months after the revision, IOP remained stable at around 16 mmHg, decreasing to 12 mmHg after ocular massage.

For several years, needling with or without subconjunctival antimetabolite injections has become a standard procedure to address bleb failure after trabeculectomy and PMS implantation.[6] While needling is generally successful in restoring bleb function, it is not without risks. Although specific studies on complications after PMS needling are lacking, several case reports have described blood reflux,[7] endophthalmitis,[8] and device dislocation following needling with a 26G needle under the surgical microscope.[9] This article presents the first reported case of PMS dislocation following an office-based needling procedure.

There are no established guidelines or widely described techniques for performing needling after PMS implantation. In this case, the surgeon used a 30G needle and fan-shaped movements above and below the distal end of the PMS to release adhesions obstructing aqueous humor flow. The procedure was conducted in the office under topical anesthesia, and the surgeon did not notice that the PMS was being displaced. As IOP decreased, the surgeon failed to recognize the changes in the anterior chamber visibility of the PMS. We hypothesize that the PMS remained in contact with the anterior chamber for a few days but eventually migrated out of the chamber due to blinking and other eye movements. Over the following weeks, fibrosis obstructed the drainage pathway, resulting in increased IOP and pain.

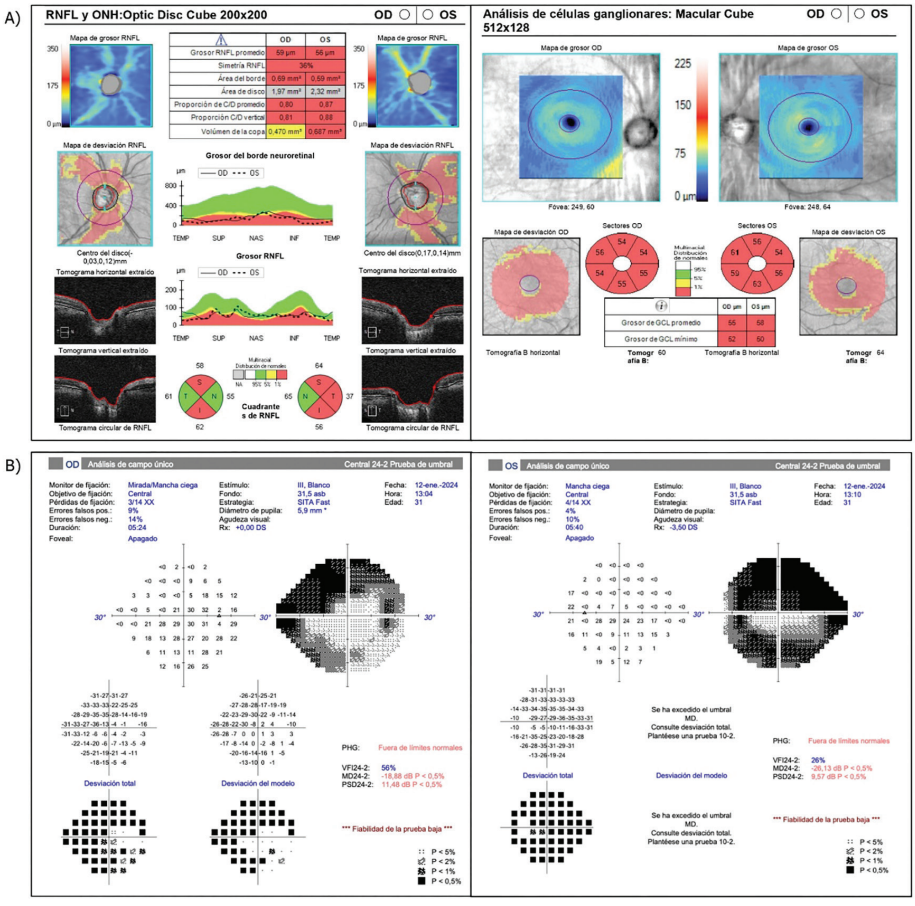

Figure 1. A) Optical coherence tomography showing retinal nerve fiber layer and ganglion cell layer thinning. B) Visual field testing demonstrating severe visual field loss in both eyes

This case underscores the challenges of performing needling after PMS implantation. Unlike trabeculectomy, PMS implantation places the bleb in a smaller, more posterior area of the eye. This creates difficulty in freeing the distal end of the device from Tenon's tissue while avoiding displacement during needle manipulation. Accurate localization of the end of the PMS is critical before performing needling. It is recommended to use a Hoskin lens or cannula and apply pressure to the conjunctiva to ensure proper visualization of the implant's tip. Additionally, performing the procedure in an operating room setting provides more tools and better control if complications such as displacement occur.

Partial displacement of a PMS within the anterior chamber may not lead to a loss of therapeutic effect. However, if the device completely exits the anterior chamber, the surgical procedure will fail. The implant's design allows for continued aqueous humor drainage until the drainage pathway becomes obstructed by fibrosis. This delayed failure makes diagnosis difficult, as the device may appear functional in the short term. When the PMS moves out of the anterior chamber, surgical revision is necessary.

In conclusion, minimally invasive glaucoma implants are increasingly important in glaucoma management. This case emphasizes that procedures to maintain bleb function carry potential complications. Special care during needling after PMS implantation is essential to prevent device dislocation, which can be difficult to diagnose and may ultimately result in surgical failure if the implant exits the anterior chamber.

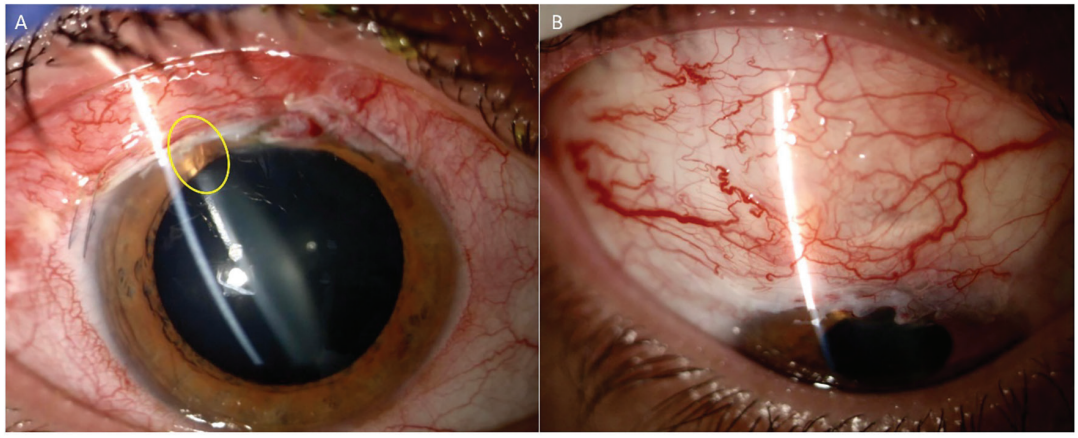

Figure 2. A) Twenty-four hours after the implantation of a PreserFlo® MicroShunt in the right eye, with the portion visible in the anterior chamber indicated in yellow. B) The bleb is well-formed one month after the surgery

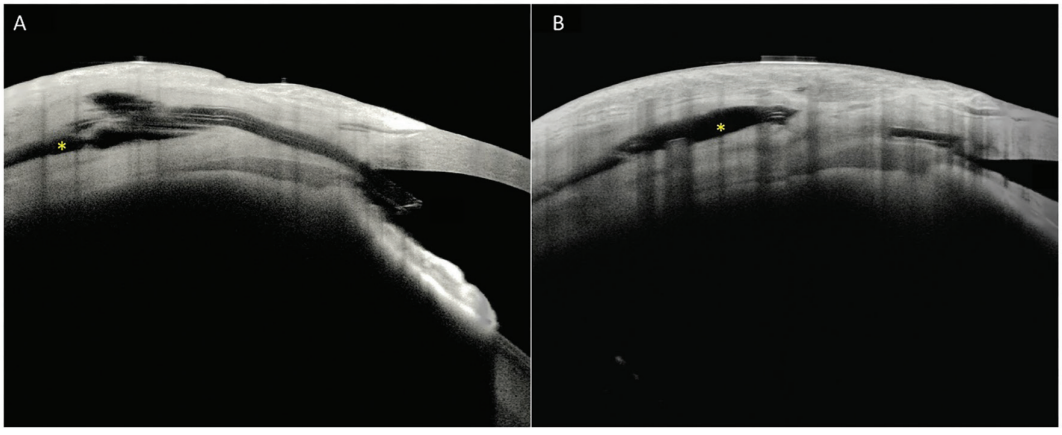

Figure 3. A) Before the needling procedure, anterior segment optical coherence tomography (AS-OCT) reveals the PreserFlo® MicroShunt and the patent lumen of the tract, with contact between the implant and Tenon's tissue observed at the distal end. The bleb is shallow (yellow asterisk). B) After the needling procedure, AS-OCT shows its effectiveness through the visualization of fluid around the distal end (yellow asterisk: hyporeflective area, consistent with fluid)

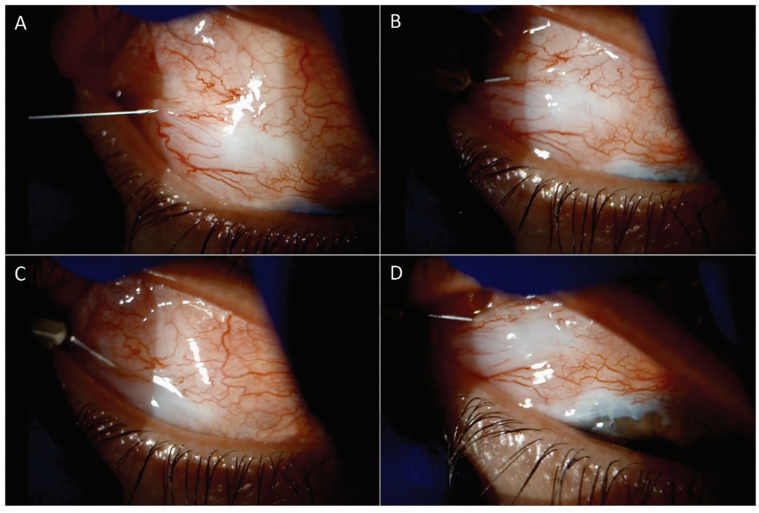

Figure 4. Needling procedure: a 30-gauge needle was used to create fan-shaped movements above and below the distal end of the implant to separate it from Tenon's capsule

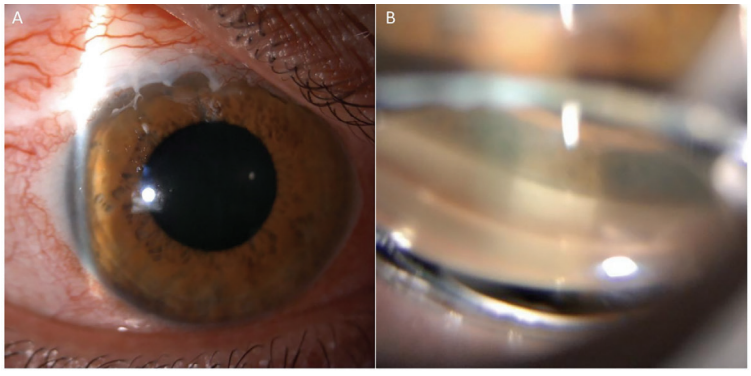

Figure 5. Six weeks after the needling procedure, the PreserFlo® MicroShunt is no longer visible on slit lamp examination (A) or gonioscopy (B)

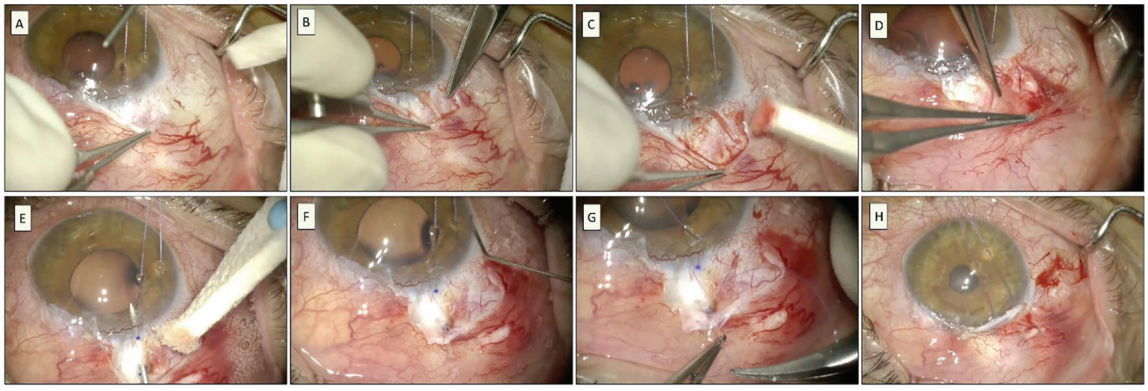

Figure 6. Bleb revision surgery. A) Fornix-based conjunctival peritomy was performed. B) Dissection was performed, revealing the displaced PreserFlo® MicroShunt (PMS). C) The PMS was pulled out, demonstrating how it was completely reversed, with the shorter part of the tube originally intended to be positioned posteriorly. D) Dissection was completed. E) A scleral tunnel was created using a 25-gauge needle. F) A new PMS was inserted ab externo. G) Filtration was confirmed and the implant was guided with 9-0 Prolene suture. H) The Tenon's capsule and conjunctiva were approximated and secured to the limbus with Vicryl sutures

Ethics

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

Declarations

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Surgical and Medical Practices: L.S.V., M.C., Concept: R.G.R., Design: C.P.A., Data Collection or Processing: T.G.S., Analysis or Interpretation: M.T., Literature Search: P.G.V., P.G.B.E., Writing: R.G.R.

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Unilateral Idiopathic Retinal Venous Beading

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Dear Editor,

Retinal venous beading is a rare retinal vascular anomaly characterized by segmental dilatation of the retinal veins. It is typically associated with systemic or ocular disorders such as hypertension, diabetes or central retinal vein occlusion (CRVO). Idiopathic retinal venous beading is exceedingly uncommon, especially unilateral presentations, and may serve as a clinical indicator of systemic disorders, particularly renal or metabolic diseases such as Fabry and Alport syndromes.[1]

This report presents a rare case of unilateral idiopathic retinal venous beading, outlines its differential diagnosis, and discusses potential pathophysiological mechanisms.

A 45-year-old woman presented for a routine ophthalmological evaluation with no specific complaints. Her medical history was notable for a stable, non-progressive pituitary microadenoma that had been under regular surveillance for several years.

On examination, best-corrected visual acuities were 20/20 in both eyes. Anterior segment examination was unremarkable, and intraocular pressures were measured as 16 mmHg in the right eye and 18 mmHg in the left eye.

Macular optical coherence tomography (OCT), optic nerve head OCT, and Humphrey 30-2 visual field testing were all within normal limits. Fundoscopic examination of the right eye revealed marked venous beading involving the superior and inferior temporal veins, with no associated hemorrhages, exudates, or macular edema but with additional vascular sheathing of the nasal vessels (Figure 1A). Ghost vessels and shunt vessels were observed nasal to the optic disc in the right eye, indicating a previous nasal branch retinal vein occlusion (BRVO) (Figure 1B). Fundus fluorescein angiography of the right eye revealed no leakage from the optic disc or retinal vessels but confirmed venous beading and retinal shunt vessels located nasally (Figure 1C). The left eye was entirely normal (Figure 1D, E).

Systemic evaluation, including blood pressure monitoring, complete blood count, and metabolic panel, was unremarkable. Family history was notable for paternal hypertension and fibromuscular dysplasia (FMD), with death from stroke at age 65. The patient's mother and sibling had a history of varicose veins.

Rheumatology reported borderline antinuclear antibody positivity with anti-polymyositis/scleroderma antibody, which was deemed clinically insignificant. Neurological assessment, including brain magnetic resonance imaging and magnetic resonance venography, was normal. Carotid Doppler ultrasound revealed a minimal fibrofatty plaque without clinical significance.

Multidisciplinary evaluation (internal medicine, neurology, rheumatology) showed no significant abnormalities. A diagnosis of unilateral idiopathic retinal venous beading with nasal BRVO was established, and the patient was advised regular follow-up and education on warning symptoms.

Keywords: Retinal venous beading, fibromuscular dysplasia, nasal branch retinal vein occlusion

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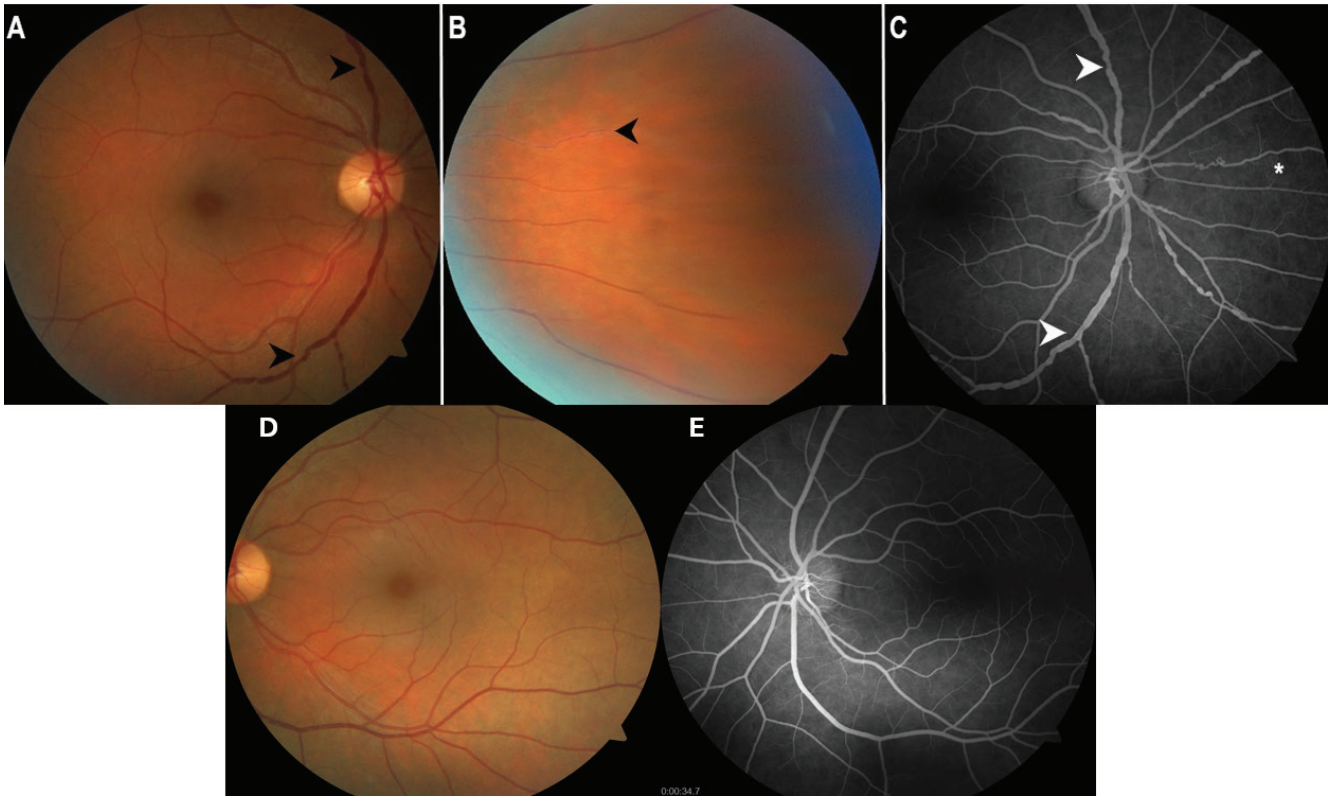

Figure 1. Fundus photographs of the right eye showed venous tortuosity and beading (A, black arrow head) and vascular sheathing in the nasal periphery (B, black arrow head). Fundus fluorescein angiography (C) demonstrated venous beading (white arrowheads) and retinal shunt vessels (white asterisk) indicating a previous venous occlusion. In the left eye, the color fundus photograph (D) and fluorescein angiography (E) appeared normal

Many causes of retinal venous beading have been described in the literature. As most cases are associated with systemic diseases, presentation is bilateral and characterized by flame-shaped retinal hemorrhages, retinal venous congestion and tortuosity, optic disc swelling, cotton wool spots, and macular edema.[1]

Previously, Meredith[1] reported inherited retinal venous beading. Prominent segmental beading of the retinal veins was observed in two male and three female family members across two affected generations. Additionally, various individuals exhibited focal retinal infarctions, surface retinal neovascularization, vitreous hemorrhages, microaneurysm formation, altered vascular permeability with lipid exudation, and localized edema. Renal disease was identified in two affected individuals during the fourth and fifth decades of life, respectively. Meredith[1] hypothesized that these retinal vascular abnormalities might be associated with Alport syndrome or Fabry disease.

Fonseca and Dantas[2] and Keyser and Ferguson[3] reported isolated instances of retinal venous tortuosity and beading in their patients, with no other affected family members. They referred to these cases as an idiopathic form of retinal venous tortuosity.

In a 24-year-old man with no known pathological history, Konaté and Mariko[4] described an isolated instance of bilateral retinal venous tortuosity of unknown origin and without visual sequelae that was detected incidentally during a routine fundus examination.

A woman with retinal venous beading and conjunctival vascular aneurysms but no systemic anomalies or family history was the subject of an isolated case reported by Ehongo and Rasquin.[5]

A similar beading morphology is also observed in FMD, an arterial occlusive disorder that may also contribute to retinal venous pathology. The characteristic "string of beads" angiography sign in FMD occurs due to the development of muscle fibers and connective tissue inside arterial vessel walls, usually in the medial layer.[6] It typically affects young individuals and has been reported in multiple siblings across several families.

FMD most commonly involves small- and medium-sized arteries, including the carotid, renal, and vertebral

arteries.[7] Astrike-Davis et al.[8] described a patient with CRVO associated with FMD and hypertension, suggesting a synergistic effect on retinal vasculature. The central retinal vein shares a common adventitial sheath with the central retinal artery. Therefore, arterial pathology such as FMD may compress the vein, leading to occlusion.[7] Additionally, FMD may induce turbulent flow, predisposing to thrombus formation and CRVO.

Other reports of familial cases of retinal venous beading across successive generations support a hereditary pattern in some patients.[9,10] However, unilateral sporadic cases have also been described. Abdel-Hay and Raman[11] reported a case of sporadic unilateral retinal venous beading in 2018. Similar to our case, no comparable clinical findings were identified among the patient's family members. In the absence of associated ocular or systemic vascular disease, the authors suggested that this condition represents a sporadic vascular defect. Our findings are consistent with this interpretation, further supporting the notion that unilateral retinal venous beading may occur as an isolated, non-familial entity.

The venous changes observed in the nasal quadrant of the right eye suggested a previous nasal BRVO. However, rather than attributing the generalized venous beading pattern to a prior BRVO, we believe that this occlusive event may represent a secondary consequence of the underlying venous beading observed in our case. Furthermore, a history of retinal venous occlusion in the absence of systemic hypertension or metabolic disease also suggests that idiopathic retinal venous beading could serve as an early warning sign.

This case emphasizes the importance of comprehensive diagnostic evaluation and long-term follow-up in patients with idiopathic retinal venous beading. Regular follow-up is essential both for early detection of complications and to contribute to the long-term understanding of this rare entity. Given the potential risk of future vascular occlusions in critical organs, cardiology and neurology consultations and appropriate antiplatelet or anticoagulant therapy may be warranted.

Ethics

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

Declarations

Authorship Contributions

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

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Presentation of Bilateral Optic Disc Coloboma–Morning Glory Syndrome in Mother and Son, with Retinitis Pigmentosa in the Father

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Dear Editor,

Morning glory syndrome (MGS) and optic disc coloboma (ODC) are rare congenital optic disc (OD) anomalies that can be confusing and difficult to differentiate due to their similar presentations. MGS, first described by Kindler in 1970 and named for its resemblance to the morning glory flower, is characterized by a funnel-shaped, enlarged, and excavated OD.[1] Meanwhile, ODC appears as a sharply defined, white excavation within an enlarged OD and can occur in isolation or alongside other ocular anomalies, such as iris or chorioretinal coloboma (CC), particularly in patients with *PAX6* mutations.[2]

Retinitis pigmentosa (RP) is the most common form of inherited retinal degeneration, characterized by progressive photoreceptor disorders leading to photoreceptor cell death.[3] The disease can follow several modes of inheritance, including autosomal dominant, autosomal recessive, and X-linked patterns.[3]

Herein, we highlight a rare familial presentation involving bilateral OD anomalies in a mother and son, as well as CC in the son and RP in the father, and describe the associated genetic findings.

A family consisting of a 44-year-old woman, an 11-year-old boy, and a 40-year-old man visited our clinic. The woman came for a routine examination, while the boy presented with strabismus and the man reported low vision since childhood.

Upon evaluation, the woman's best corrected visual acuity (BCVA) was 20/50 in the right eye and 20/20 in the left. Fundus examination revealed bilaterally excavated, enlarged OD with peripapillary atrophy (Figure 1).

The 11-year-old son's BCVA was 20/25 bilaterally. Cycloplegic refraction revealed a bilateral hyperopic error of +2 diopters (D) in the 90-degree axis. Extraocular motility assessment indicated small-angle esotropia at distance and near fixation (10 prism diopters [PD] and 4 PD, respectively). Slit-lamp fundus examination revealed bilaterally excavated and enlarged ODs surrounded by an annulus of chorioretinal pigmentary deposition. Additionally, an area of chorioretinal atrophy was located between the OD and macula, and CC was observed inferiorly to the OD (Figure 2). His 8-year-old sibling had no detectable ocular or systemic abnormalities.

The visual acuity of the 40-year-old father was counting fingers at 2 meters bilaterally. Slit-lamp examination showed mild bilateral posterior capsular cataract. Fundus examination demonstrated attenuation of the retinal arteries, OD pallor, retinal atrophy, a bull's eye maculopathy pattern, and bone-spicule pigmentation changes, consistent with RP (Figure 3).

Keywords: Morning glory syndrome, optic disc coloboma, retinitis pigmentosa, choroidal coloboma, YAP1, BBS1

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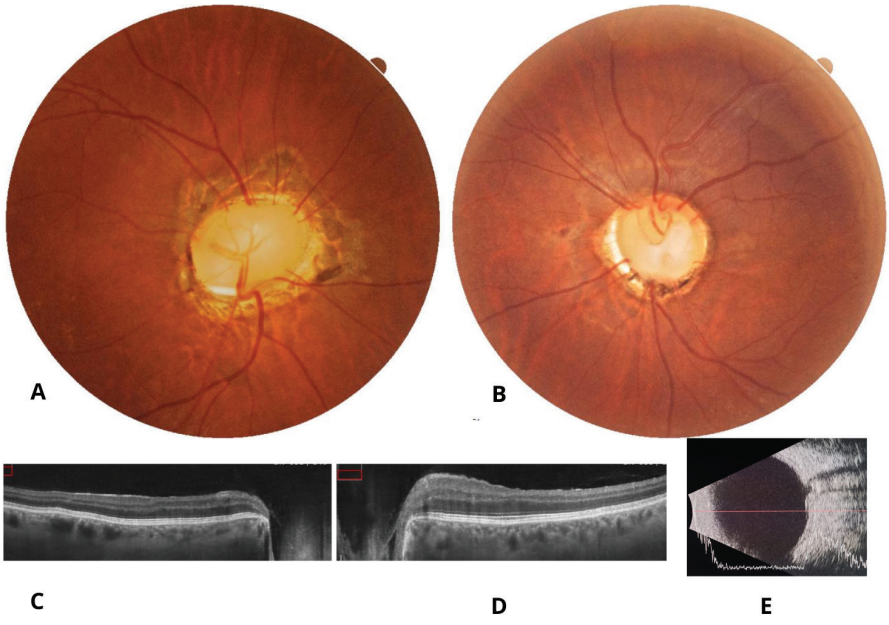

Figure 1. Fundus photographs of the mother's right (A) and left (B) eyes demonstrated bilaterally enlarged, excavated optic discs with surrounding peripapillary atrophy. Macular optic coherence tomography of the right (C) and left (D) eyes revealed significant excavation of the optic disc with preservation of retinal layers, consistent with bilateral optic disc anomaly. The B-scan image of the right eye revealed an excavation in the optic disc (E)

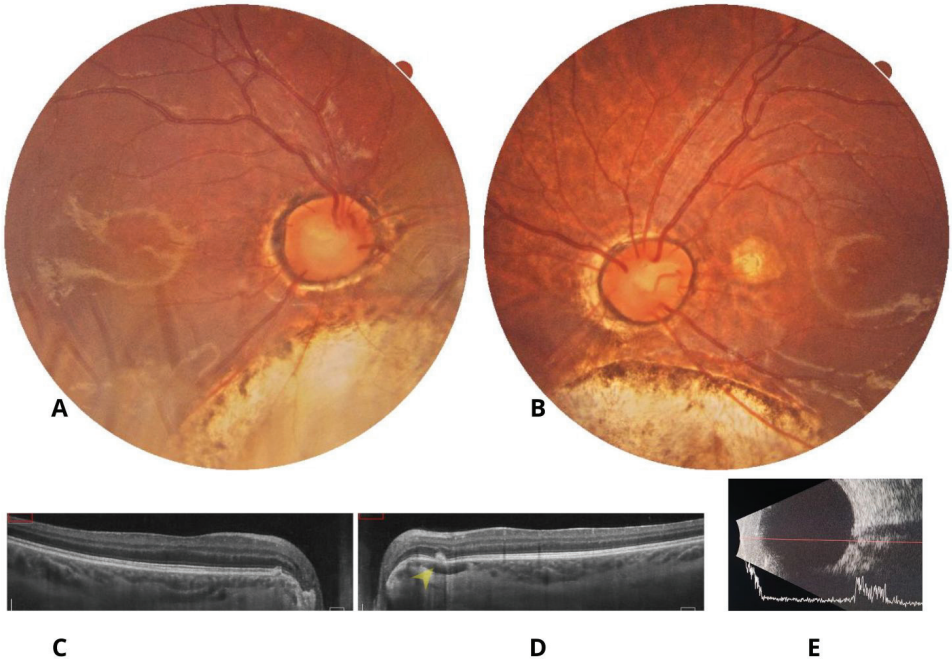

Figure 2. Fundus photographs of the 11-year-old son's right (A) and left (B) eyes showed bilaterally excavated, enlarged optic discs surrounded by an annulus of pigmentary deposition with chorioretinal coloboma inferiorly. Macular optic coherence tomography of the right (C) and left (D) eyes revealed areas of retinal pigment epithelial detachment (yellow arrowhead) with subretinal deposition surrounding chorioretinal atrophy, located between the optic disc and macula. The B-scan image of the right eye illustrated an excavation in the optic disc (E)

To investigate these clinical findings, whole exome sequencing (WES) and targeted variant analysis were performed for the family (Figure 4). The mother and affected son were heterozygous for a variant of uncertain significance in the *YAP1* gene according to the American College of Medical Genetics and Genomics (ACMG) criteria.[4] The unaffected sibling did not carry this variant. Furthermore, the father was homozygous for a pathogenic variant in the *BBS1* gene according to ACMG criteria. However, he exhibited no related systemic manifestations. Both the affected and unaffected sons were also heterozygous carriers of the *BBS1* variant.

Although the exact type of OD anomaly could not be definitively diagnosed, the mother's OD configuration resembled MGS, while the son's was consistent with ODC. The pathogenesis of these conditions differs. MGS may result from a primary mesenchymal abnormality, partial development of the lamina cribrosa, or incomplete closure of the posterior scleral wall, while ODC is caused by defective closure of the embryonic fissure.[1,2] In ODC, the defect is typically decentered inferiorly, reflecting the position of the embryonic fissure and abnormal exit of retinal vessels.[2] In contrast, MGS presents with central excavation and radial exit of the vessels.[2]

YAP1 (OMIM 606608) encodes Yes-associated protein 1, a key effector of the Hippo signaling pathway involved in the development, growth, repair, and homeostasis of multiple organs, including the eye.[5,6] Previous studies have linked *YAP1* variants to various ocular anomalies. DeYoung et al.[5] reported an association with uveal coloboma. Holt et al.[6] described a novel frameshift variant in the *YAP1* gene in a boy with bilateral CC. Meanwhile, Williamson et al.[7] identified novel missense and nonsense *YAP1* variants in families with both syndromic and non-syndromic coloboma. In the present case, both the mother and her affected son carried the identified *YAP1* variant, whereas the 8-year-old son, who exhibited no ocular or systemic abnormalities, did not carry this variant. Unfortunately, segregation analysis could not be extended to the maternal grandparents, as they were deceased. Therefore, the clinical relevance of the identified variant remains uncertain, although it is considered likely to be associated with the observed phenotype based on the available evidence.

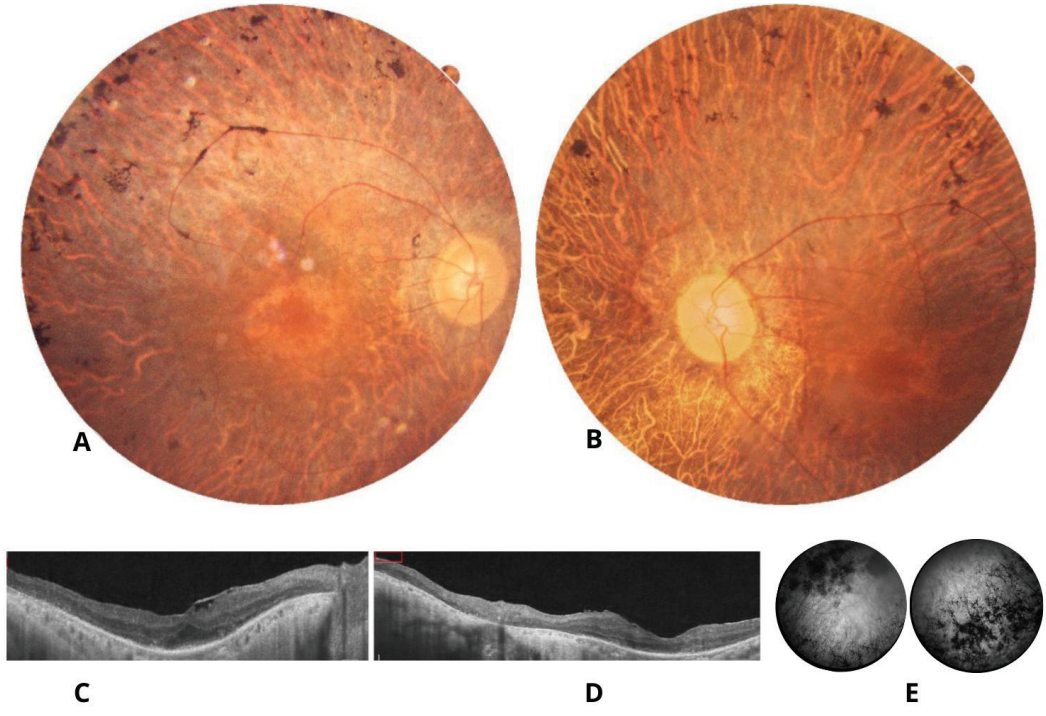

Figure 3. Fundus photographs of the 40-year-old father's right (A) and left (B) eyes revealed features consistent with advanced retinitis pigmentosa, including attenuation of retinal arteries, optic disc pallor, a bull's-eye maculopathy pattern, and extensive retinal atrophy. Macular optic coherence tomography of the right (C) and left (D) eyes demonstrated thinning of the outer retinal layers, loss of the ellipsoid zone, and atrophic changes in the retinal pigment epithelium (RPE). Fundus fluorescein angiography revealed multiple hyperfluorescent window defects observed in the mid-peripheral retina, corresponding to areas of RPE atrophy (E). Pigment clumping in a bone-spicule pattern appears as hypofluorescent areas due to blockage of choroidal fluorescence

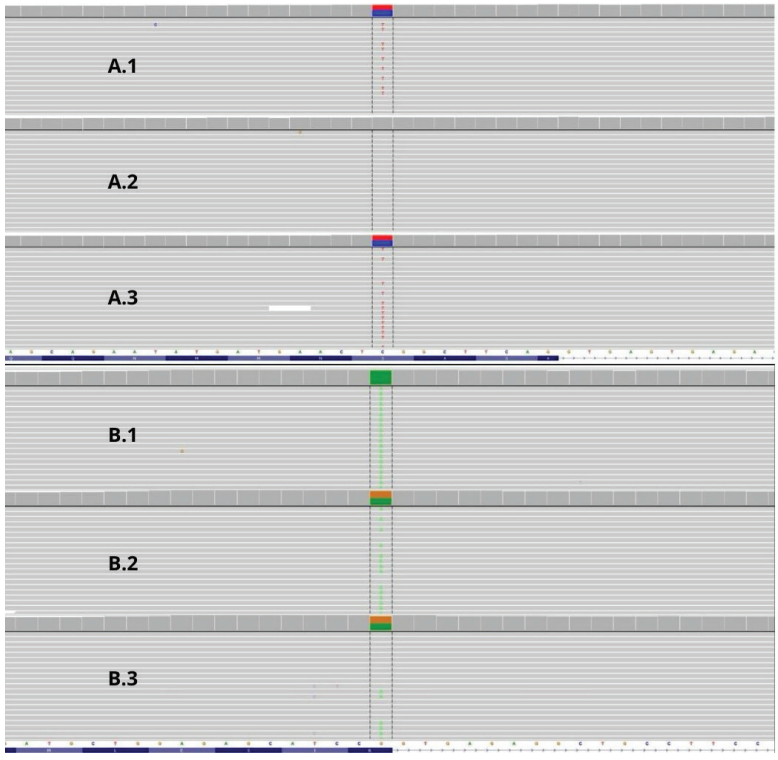

Figure 4. Integrative Genomics Viewer (IGV) images of next-generation sequencing (NGS) data illustrating the genomic region of the *YAP1*(NM_001130145.3):c.680C>T (p.Ser227Leu) variant in the mother (A.1), clinically unaffected son (A.2), and affected son (A.3). The mother and affected son were heterozygous for the variant, while the unaffected son carried the wild-type allele. IGV images of NGS data demonstrate the *BBS1*(NM_024649.5):c.479G>A (p.Arg160Gln) variant in the father (B.1) and his two children (B.2: unaffected son; B.3: son with optic disc anomaly). The father was homozygous for the variant, while both children were heterozygous

Pathogenic variants in the *BBS1* gene associated with RP can present as mild or even nonsyndromic forms of Bardet-Biedl syndrome (BBS).[3] According to WES analysis, the father was homozygous for this *BBS1* variant, whereas the affected son was heterozygous. This difference may partly explain the phenotypic variability observed between the father and son.

Clinically, the CC and OD anomaly observed in the son resembled ODC. This presentation may represent a type 3 fundus coloboma with OD involvement, as described by Gopal et al.[8] In addition, some studies have reported an association between RP and CC, which has been described as an autosomal dominant trait.[9,10] Meanwhile, CC has also been associated with BBS, as reported by Chattannavar et al.,[11] supporting our suggestion of a potential link between the father and son.

The presence of these unusual bilateral findings in the mother and son, both carrying a *YAP1* variant, along with the father's *BBS1*-associated RP, makes this case unique. It underscores the diagnostic challenge of distinguishing between MGS and ODC. Our patients lacked any systemic or neurological abnormalities, particularly cranial midline anomalies. The absence of these associated findings, together with the identification of a heterozygous *YAP1* variant, suggests that the observed phenotype is more consistent with ODC than MGS. Finally, the rare bilateral involvement in two family members raises the intriguing possibility that the son's CC is associated with the father's RP.

Ethics

Informed Consent: Written informed consent was obtained from all participants (and from the parents/legal

guardians for the minor participant) for publication of clinical data and images.

Declarations

Authorship Contributions

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

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Letter to the Editor Re: Long-Term Intravitreal Dexamethasone Implant Monotherapy in Naïve Patients with Diabetic Macular Edema

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Dear Editor,

I read the article titled "Long-Term Intravitreal Dexamethasone Implant Monotherapy in Naïve Patients with Diabetic Macular Edema" published in your journal with great interest.[1] I congratulate the authors for making a significant contribution to the literature by presenting the long-term outcomes of dexamethasone (DEX) implant monotherapy in the treatment of diabetic macular edema (DME) in a large cohort of treatment-naïve patients with a follow-up period of up to 80 months. The longitudinal follow-up over six years is highly enlightening, especially considering the "treatment fatigue" that the anti-vascular endothelial growth factor (VEGF) injection burden creates for both the patient and the healthcare system.[2]

As the authors note, despite the significant improvement in best-corrected visual acuity (BCVA) and the reductions in hyperreflective foci (HRF), pearl necklace sign, and intra-cystic hyperreflective material, the progressive increase observed in optical coherence tomography (OCT) markers such as disorganization of the retinal inner layers (DRIL), epiretinal membrane (ERM), and ellipsoid zone (EZ) damage presents a "functional-anatomical paradox" that must be addressed.[3] The authors attributed this phenomenon to natural disease progression and recurrent edema episodes caused by the pro re nata (PRN) treatment regimen, suggesting that a "treat-and-extend" regimen could mitigate this structural damage. This hypothesis could lead to a treat-and-extend protocol utilizing DEX alone or in combination with anti-VEGF therapy. DEX monotherapy is successful in reducing macular thickness. However, the "retinal stress" created by chronic inflammation or the edema-resolution cycles inherent in PRN regimens can cause permanent structural damage.[4] Did the rate of the structural defects demonstrated in the study accelerate after the third year, when the scheduled injection frequency was reduced to as low as 0.5 per year? If so, could this indicate that the retinal tissue had entered a "burn-out" phase rather than disease remission? A notable point is the dramatic reduction in the frequency of administered injections from the fourth year of the study onward. While this is encouraging for clinicians, in real-world data, the fine line between "treatment discontinuation" and "loss to follow-up" is not always clear. Administering 6.83 injections over a mean follow-up of 49 months indicates a remarkably low treatment burden for a chronic pathology like DME.

According to the study's findings, EZ-external limiting membrane (ELM) damage and HRF were among the independent factors influencing the final BCVA. This highlights the complex relationship between anatomical progression and functional outcomes. At this juncture, I would like to ask the authors the following question: Was there a correlation between the development of these structural defects detected on OCT and the frequency of injections, the intervals between follow-up visits, or the duration of treatment-free observation periods? The study included patients with ERM causing superficial traction, yet none underwent ERM surgery. Were there any differences

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in long-term outcomes between eyes with and without ERM, particularly in terms of DRIL and EZ-ELM integrity?

Meanwhile, a few methodological clarifications could further strengthen the interpretation of the findings: (1) It was stated that bilateral eyes were included in the analysis; clarifying whether a statistical approach was used for inter-eye correlation (two eyes from the same patient) would enhance the robustness of the results. (2) As two independent researchers evaluated the OCT findings, reporting inter-observer agreement (kappa/intraclass correlation coefficient) would be beneficial for reproducibility, especially for parameters such as DRIL and EZ-ELM integrity. (3) Finally, compared with the MEAD study, the cataract surgery rate in this cohort was remarkably high (97%), indicating that cataract development in patients scheduled for DEX implant monotherapy should be considered an inevitable "stage" of the treatment rather than a "side effect."[5] Was pseudophakic subgroup analysis or sensitivity analysis considered to mitigate the impact of lens status when interpreting visual gains over time?

The data shared by the authors will raise the need to re-evaluate the anti-VEGF-prioritized treatment paradigm in DME management for selected treatment-naïve cases.

Declarations

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Reply

We thank the author for their interest and valuable feedback regarding our study published in your journal. We believe that these constructive comments make important contributions to addressing the findings of our study from a broader perspective.

Regarding the author's first point, we thank them for highlighting this important issue. Indeed, despite the significant improvement in best-corrected visual acuity and the reduction in inflammatory optical coherence tomography (OCT) biomarkers, such as hyperreflective foci, pearl necklace sign, and intra-cystic hyperreflective material, the progression observed in the disorganization of the retinal inner layers (DRIL), epiretinal membrane (ERM), and ellipsoid zone (EZ) damage is a noteworthy finding. We consider this situation to be largely associated with the chronic progressive nature of the disease and the retinal stress caused by recurrent edema-resolution cycles that can occur during a pro re nata (PRN) treatment regimen.

This interpretation is also consistent with studies evaluating retinal thickness fluctuations in diabetic macular edema.[1,2] Previous studies have shown that greater fluctuations in retinal thickness are associated with poorer functional and structural outcomes, and that recurrent edema reactivations can exacerbate neuroretinal damage. Therefore, not only the anatomical thinning of the macula but also the provision of a more stable retinal microenvironment may be important. We also believe that the chronic nature of the disease and the edema-resolution cycles that can occur during PRN treatment regimens may contribute to progressive structural damage by creating cumulative retinal stress. In this context, proactive treatment approaches that can provide more continuous inflammation suppression and anatomical stability may theoretically offer advantages. The PRODEX study also highlighted the potential importance of dexamethasone (DEX) implants in providing more stable anatomical control.[3]

The structural changes reported in our study did not accelerate after the third year. The results are based on assessments made throughout the entire follow-up period. Therefore, there is no temporal analysis that can directly

demonstrate that the progression of DRIL, ERM, and EZ damage accelerates, particularly in the late phase when the number of injections is significantly reduced. However, the decrease in the number of injections over time cannot be solely explained by a "burn-out" phase. It is known that the need for anti-endothelial growth factor treatment can similarly decrease over time in diabetic macular edema. Furthermore, real-world studies utilizing the DEX implant have reported a reduction in scheduled injection frequency over the years. For example, the AUSSIEDEX study reported an average annual number of injections of approximately 2.5.[4] In this respect, our total number of injections over an average follow-up period of approximately 49 months is generally consistent with real-world data reported in the literature.

In our study, no specific correlation analysis was performed to evaluate the relationship of DRIL, EZ-external limiting membrane (ELM) damage, and ERM progression to injection frequency, follow-up intervals, or duration of treatment-free periods. Due to the retrospective real-world design, it is not always possible to definitively distinguish whether the treatment-free follow-up periods reflect disease stabilization, reduced need for treatment, or variability in follow-up/treatment.

Nevertheless, as discussed in our study, we believe that the recurrent edema episodes and associated retinal thickness fluctuations that can occur under PRN treatment regimens may contribute to cumulative retinal stress over time. Therefore, we think the relationship between injection frequency, treatment-free periods, and structural OCT progression should be evaluated through prospective and standardized follow-up protocols.

To better assess the potential impact of ERM on long-term retinal structural outcomes, we performed an additional subgroup analysis between eyes with and without ERM at the final follow-up visit. In the final follow-up evaluation, the DRIL rate was found to be 47.1% in eyes without ERM and 64.8% in eyes with ERM, and the difference between the two groups was not statistically significant (p=0.191). Similarly, at final follow-up, the EZ-ELM defect rate was 41.2% in eyes without ERM and 51.9% in eyes with ERM, and this difference did not reach statistical significance (p=0.443). Evaluated overall, it was observed that both DRIL and EZ-ELM defect rates increased over time, independent of the presence of ERM. This suggests that a statistically significant long-term impact on DRIL progression or the deterioration of EZ-ELM integrity could not be demonstrated in our study cohort.

Drawing attention to the methodological point regarding the inclusion of bilateral eyes in the analysis is also highly valuable. The inclusion of both eyes was preferred to reflect real-world clinical practice and to ensure the optimal evaluation of the available data in this long-term cohort. While inter-eye correlation is a known phenomenon in such studies, similar approaches have also been used in comparable real-world studies in the literature.[5,6,7] Considering the retrospective nature and sample size of our study, an additional statistical correction method was not applied.

We thank the author for their comment regarding the non-reporting of the inter-observer agreement analysis (kappa/intraclass correlation coefficient), despite the OCT findings being evaluated by two independent researchers. The main aim of our study was to evaluate long-term changes, and reproducibility analysis was not among the primary objectives. Nevertheless, consistency was targeted by ensuring the evaluations were conducted by experienced researchers in accordance with predefined criteria.

In our study, 40 (97%) of the 41 initially phakic eyes underwent phacoemulsification surgery during the follow-up period. This rate demonstrates that cataract development in patients scheduled for long-term DEX implant monotherapy is a clinically expected and important process that requires management. Similarly, the IRGREL-DEX study reported that 15 of 16 initially phakic eyes in the treatment-naïve diabetic macular edema group underwent cataract surgery during 24-month follow-up.[8]

The main reason for not including a pseudophakic subgroup or sensitivity analysis in our study was that almost all initially phakic eyes underwent cataract surgery during the follow-up period, making the cohort predominantly pseudophakic at the final follow-up. Therefore, performing a meaningful and balanced subgroup comparison based on lens status would be statistically limited. However, the impact of lens status was considered and discussed in the interpretation of the significant increase in visual acuity in our study. We are of the opinion that cataract surgery is an expected and manageable outcome of DEX implant therapy in long-term follow-up. Therefore, lens status may be an important confounding factor in the evaluation of visual outcomes.

We once again thank the author for their constructive contributions and believe that this valuable discussion will contribute to diabetic macular edema treatment approaches.

Declarations

Authorship Contributions

Design: F.K., Data Collection or Processing: Ö.A., T.U., A.M.Ö., Analysis or Interpretation: A.Ç., H.Ö., M.N.E., Literature Search: G.K., Writing: G.K.

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