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Ethical Responsibilities and Policies

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BEYOGLU EYE JOURNAL

CONTENTS VOLUME 10 ISSUE 3 YEAR 2025 ISSN 2459 - 1777

ORIGINAL ARTICLES

Swept-Source Optical Coherence Tomography and Optical Coherence Tomography Angiography Findings in Patients with Solar Retinopathy

Kucuk E, Yesilyurt H, Zor KR, Ozer O, Coban Karatas M 127

Outcomes of Laser Hyaloidotomy in Premacular Hemorrhage: Identifying Predictors of Treatment Success and Need for Vitrectomy

Venkatesh R, Prabhu V, Hande P, Tendulkar K 134

Incidence of Retinopathy of Prematurity Between 2021 and 2024: Results from a Single Center

Kizilay O, Karaca S, Oto BB, Celik G 142

The Role of Serum Vitamin and Mineral Levels in Benign Essential Blepharospasm: A Comparative Study

Yakut B, Atac A, Yilmaz A, Onder F 149

Exploring Health Tourism and Corneal Refractive Surgery: Insights From a Single Referral Center

Akbas YB, Koc AA 154

Comparison of the Depth of the Stromal Demarcation Line and Clinical Outcomes in Corneal Crosslinking Treatment with Hydroxypropyl Methylcellulose-Based and Vitamin E-TPGS-Based Riboflavin Solutions

Ulutas HG, Balikci Tufekci A 159

Comparison of the Accuracy, Comprehensiveness, and Readability of ChatGPT, Google Gemini, and Microsoft Copilot on Dry Eye Disease

Colak D, Yakut B, Agin A 168

Comparative Detector Analysis for the Identification of Academic Articles Synthesized by Artificial Intelligence in the Field of Ophthalmology

Kaya Ergen S 175

Selenium: Could It Be the Game-Changer for Ocular Surface and Anterior Chamber in Graves' Disease?

Kiyat P, Semiz G 181

CASE REPORT

Primary Localized Conjunctival Amyloidosis Mimicking Lymphoma

Coskun B, Ucaryilmaz Ozhamam E, Yuksel N 188

DOI:10.14744/bej.2025.93206
Beyoglu Eye J 2025; 10(3): 127-133

Original Article

Swept-Source Optical Coherence Tomography and Optical Coherence Tomography Angiography Findings in Patients with Solar Retinopathy

Erkut Kucuk, Huseyin Yesilyurt, Kursad Ramazan Zor, Omer Ozer, Muge Coban Karatas

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Abstract

Objectives: Solar retinopathy is a retinal disease caused by exposure to ultraviolet radiation from sunlight, primarily affecting the outer retinal layers, including photoreceptors and the retinal pigment epithelium. This cross-sectional study aimed to present the optical coherence tomography (OCT) and OCT angiography (OCTA) findings in patients with solar retinopathy.

Methods: Fourteen eyes from 11 patients with a history of solar exposure during a partial solar eclipse were included. OCT and OCTA were performed and parameters including central macular and choroidal thickness, outer retinal defect thickness, retinal pigment epithelium (RPE)-Bruch membrane thickness, outer retinal defect area on en face OCT, OCTA foveal avascular zone area, and vessel density in the central fovea were measured. Their correlation with the visual acuity (VA) was investigated.

Results: Hyporeflective outer retinal defects including the ellipsoid and interdigitation zones were observed in all eyes in B scan and en face structural OCT. OCTA indicated a normal vascular pattern with no choriocapillaris flow deficits corresponding to the outer retinal defects. A significant positive correlation was found between VA and RPE-Bruch membrane thickness under the outer retinal defect. There was no significant relationship between VA and other OCT and OCTA parameters.

Conclusion: The outer retina is affected in solar retinopathy. En face structural OCT enables the measurement of the area of outer retinal defect. The significant relationship between VA and RPE-Bruch membrane thickness suggests that this may be an indicator of severity.

Keywords: Optical coherence tomography angiography, optical coherence tomography, solar retinopathy

Introduction

The detrimental effects of staring at the sun have been acknowledged for a long time. The term used to characterize the retinal damage due to exposure to ultraviolet (UV) from solar radiation referred to as solar retinopathy (1). Evaluating solar retinopathy prevalence is not easy because many individuals who engage in unprotected sun viewing do not seek medical attention. Also diagnosing a patient with this pathology in the chronic phase proves challenging even evaluated by an ophthalmologist (1,2). The outer retinal layers including photoreceptors and the retinal pigment epithe-

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lium (RPE) are especially susceptible to the toxicity of UV radiation from sunlight (3). UV radiation primarily induces damage to the retina through the photochemical pathway (4). In the photochemical pathway, chemical damage occurs through various mechanisms, including the generation of reactive oxygen species and oxygen-dependent toxicity (1,2,4). Generation of free radicals results in lipid peroxidation and damage to tissues. The prognosis for solar retinopathy is generally positive, with most cases experiencing full recovery. Nonetheless, a notable proportion of patients may encounter persistent consequences, such as diminished visual acuity (VA) and lifelong central/paracentral scotomas. Despite the subjective improvement observed, there are irreversible changes in the external retina that can be demonstrated through retinal imaging in the majority of cases (2,5).

Optical coherence tomography (OCT) has emerged as a cornerstone in the diagnosis of various retinal disorders including solar retinopathy, offering high-resolution cross-sectional images that reveal alterations in the retinal layers and the RPE. This modality is very useful in detecting subtle retinal changes in solar retinopathy (6,7). OCT imaging studies mostly report defects in the outer retinal layers, mostly in photoreceptor and RPE cells (8,9). The abnormalities observed in the ellipsoid zone (EZ) and interdigitation zone (IZ) are occasionally referred to as outer retinal holes or defects (5,9). The studies reported a discrepancy between OCT findings and VA in patients with solar retinopathy, and the features detected through OCT demonstrated only a limited correlation with VA (5,9). OCT angiography (OCTA) is a valuable non-invasive imaging technique for identifying vascular abnormalities in retinal diseases, offering detailed insights into the retinal vasculature. There is a limited body of research on OCTA findings in patients with solar retinopathy (10). This study aims to present the OCT and OCTA findings in patients with solar retinopathy and explore the relationship between OCT and OCTA parameters and VA.

Methods

This cross-sectional study was conducted at the Ophthalmology Department of Niğde Ömer Halisdemir University Training and Research Hospital. The study was conducted in alignment with the principles set forth in the Declaration of Helsinki. The Non-Interventional Clinical Research Ethics Committee of Niğde Ömer Halisdemir University granted approval for the research (No: 2023/84). Comprehensive details regarding the procedures were communicated to all participants or their parents/legal representatives, and informed consent was obtained through written documentation as well as verbal communication.

The clinical identification of solar retinopathy was based on a patient's reported history of direct sunlight exposure during eclipse without eye protection, coupled with the subsequent onset of symptoms like a scotoma in the visual field or a discernible decline in VA. The diagnostic confirmation involved the utilization of OCT to visualize the presence of outer retinal damage in the affected eyes. Individuals with pre-existing retinal conditions or a history of retinal surgeries were excluded from the study. All participants underwent a comprehensive ophthalmologic assessment, encompassing the evaluation of best-corrected VA, biomicroscopic examination of the anterior segment, measurement of intraocular pressure, and examination of the fundus. For retinal imaging, color fundus photography was performed using TRC-50DX retinal camera (Topcon Corporation, Tokyo, Japan). OCT and OCTA imaging were performed using Triton™ DRI swept-source OCT (Topcon Corporation, Tokyo, Japan).

Analysis of OCT and OCTA Images

For OCT imaging, a radial macular scan was conducted using a 1,024 × 12 scan protocol, incorporating 12 radial scan lines centered on the fovea. Each of these lines comprised 1,024 A-scans, each with a length of 6 mm. IMAGEnet 6 software (Topcon Medical Systems, Inc.) was used for analysis. The software can produce thickness maps based on the conventional early treatment diabetic retinopathy study grid. This grid comprises inner and outer rings with diameters of 1–3 mm and 3–6 mm, respectively, producing nine sectors that include inner and outer sectors for each of the temporal, superior, inferior, and nasal regions, along with a central sector. Macular and choroidal thickness values were derived from the measurements obtained in the central sector of the thickness maps. The thickness of outer retinal defects (vertical depth) and the thickness of the RPE-Bruch membrane were also measured from OCT scans passing through the fovea. The OCT device's internal software measurement tool was used for these measurements.

Patients underwent OCTA imaging with a volume scan pattern of 3 mm × 3 mm, centered on the fovea. Automated segmentation of the device was employed to delineate specific retinal and choroidal layers, including the superficial capillary plexus (SCP) (from the internal limiting membrane to 15.6 μm below the junction between the inner plexiform and inner nuclear layers, IPL/INL), the deep plexus (from 15.6 μm below IPL/INL to 70.2 μm below IPL/INL), the outer retina (extending from 70.2 μm below IPL/INL to the Bruch membrane, BM), and the choriocapillaris (from BM to 20.8 μm below BM). The SCP and deep capillary plexus (DCP) slabs of each eye were analyzed using open-access software ImageJ/Fiji (11). The area of the foveal avascular zone (FAZ) was manually measured in square millimeters for the superficial (SCP) and DCP using the freehand tool in ImageJ. This involved connecting points along the edge of the capillary network in the foveal area. The vascular density (VD) of the

SCP was automatically measured using IMAGEnet 6 software (Topcon Medical Systems, Inc.). The software generates a VD map featuring a central region enclosed by a 1 mm diameter circle, surrounded by a ring with diameters of 1 to 2.5 mm. For our analysis, we focused on the vessel density within the central area. Vessel density values were determined as the ratio of the angiography signal to the total area in this specified region.

Structural en face OCT images of the outer retina were examined and the area of the hyporeflectivity seen in the outer retina was measured using OCT device's internal software measure tool.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences version 20.0 (IBM Corporation, Armonk, NY). Descriptive statistics for quantitative data were expressed as means±standard deviations, and qualitative data were presented as percentages. Spearman's correlation analysis was employed to evaluate the association between VA and the measured parameters obtained from OCT and OCTA. Statistical significance was defined as $p<0.05$.

Results

Individuals with a prior experience of observing the partial solar eclipse on October 25, 2022, and subsequently reporting issues such as scotoma in the visual field or reduced VA were subjected to evaluation upon presenting to the ophthalmology department. The study comprised 14 eyes from 11 patients (7 males and 4 females), who had examination and imaging results consistent with solar retinopathy. The average age of the study participants was 30.4±16.2 years, with a range from 13 to 55 years. The mean duration from solar exposure to presentation was 60.8±35.5 days, ranging from 21 to 135 days. Three cases exhibited bilateral solar retinopathy, while in 8 cases, unilateral solar retinopathy was present. The anterior segment examination revealed normal findings in all eyes. Fundus examination disclosed the absence of foveal reflex in four eyes, while the remaining eyes exhibited no abnormalities. The VA in the 11 affected eyes varied between 20/80 and 20/20, with five eyes having a Snellen VA of 20/20.

All eyes exhibited a focal outer retinal defect on B-scan SS-OCT, characterized by the absence of the EZ and interdigitation zone in the fovea (Fig. 1). The external limiting membrane anterior to the lesion displayed mild hyperreflectivity. There were no abnormalities detected in the inner retinal structures within the fovea. The mean vertical depth of the outer retinal defect was 54.2±8.5 µm, with a range extending from 33 to 65.0 µm, and the mean thickness of the RPE-Bruch membrane was 37.4±5.4 µm ranging from 26.0 to 49.0 µm (Fig. 2). In en face structural OCT, a focal defect in the outer retina was present in all affected eyes. The shape of this defect differed among the eyes affected. The mean area of the defect was 13.14±6.24 μm^2 ranging from 3.51 to 22.59 μm^2 (Fig. 3). The mean central macular thickness was 219.9±17.48 µm and the mean central choroidal thickness was 329.4±74.0 µm.

The OCTA results indicated a typical normal vascular pattern in the retinal layers. The superficial and deep capillary plexi showed no signs of non-perfusion or dilatation, and there were no observed flow deficits corresponding to the outer retinal defects in the choriocapillaris (Fig. 4). The mean superficial FAZ area was 0.341±0.137 mm^2 and the mean deep FAZ area was 0.437±0.136 mm^2. The mean vessel density in the central fovea for the superficial retinal layer was 18.3±6.1%.

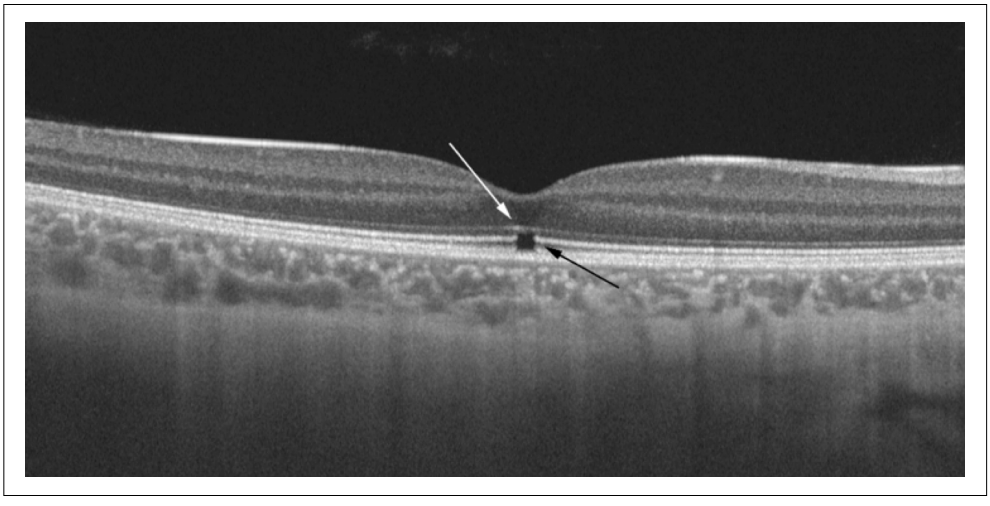

Figure 1. Optical coherence tomography image of a patient showing a focal outer retinal defect (black arrow) and mild hyperreflectivity of the external limiting membrane anterior to the defect (white arrow).

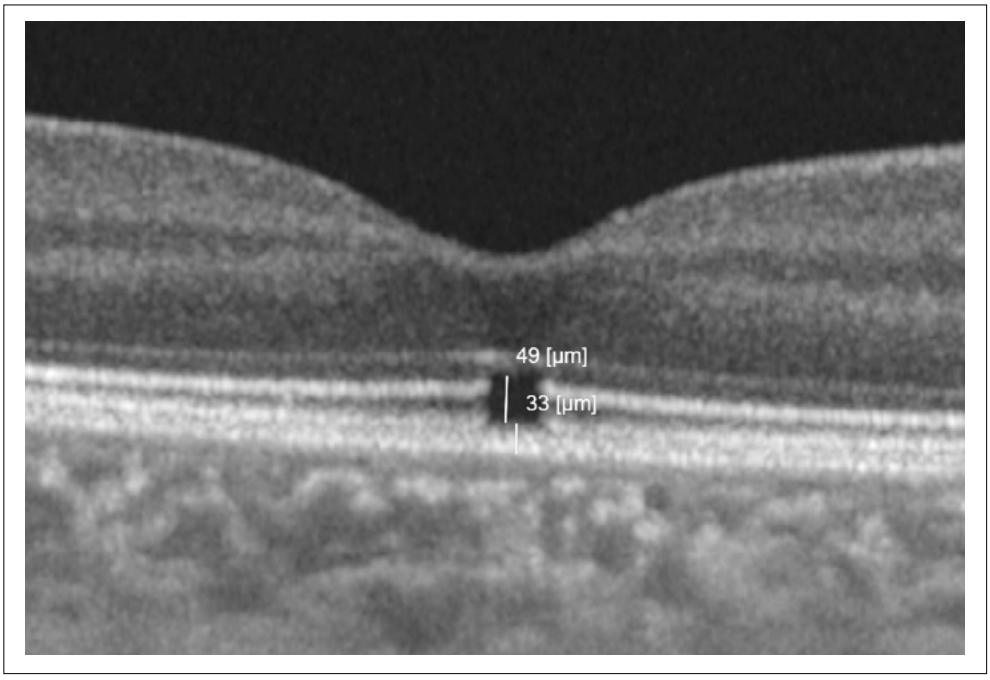

Figure 2. This optical coherence tomography image illustrates the measurement of the vertical depth of the outer retinal defect and the thickness of the retinal pigment epithelium-Bruch membrane under the defect.

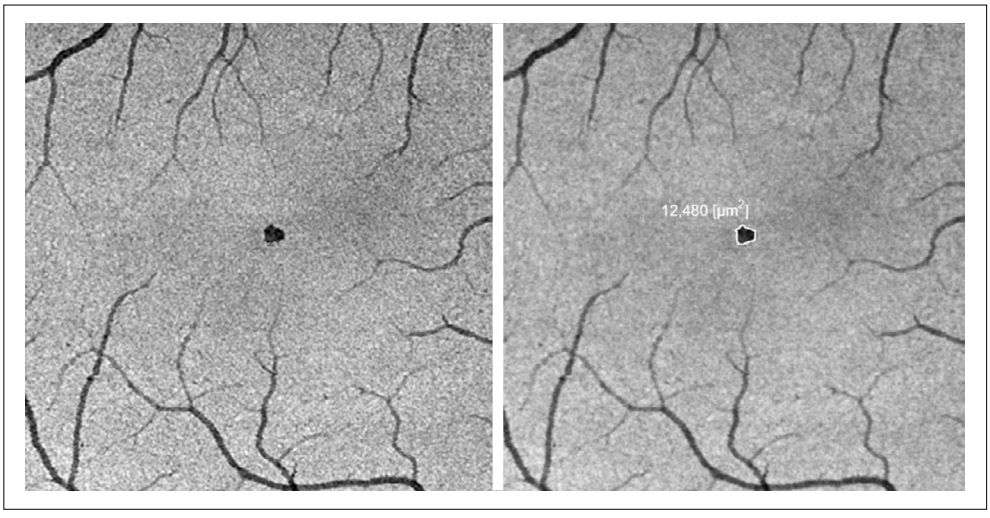

Figure 3. En face structural optical coherence tomography of a patient showing a focal defect in the outer retina accompanied by measurement of the defect area.

Spearman's correlation analysis was performed to assess the relationship between VA (logMAR) and the measured parameters from OCT and OCTA (Table 1). The results revealed a significant moderate positive correlation between VA and RPE-Bruch membrane thickness (r_s [12] = 0.57, p=0.032). However, no significant relationship was observed between VA and the other evaluated parameters.

Discussion

In this study, we presented the clinical and structural findings observed in a group of individuals with solar maculopathy. Outer retinal defects were observed in all affected eyes, as indicated by both B-scan and en face OCT. The defects included the EZ and interdigitation zone in the outer retina. Previous studies (5,12,13) also reported that the outer retinal layers were mostly affected by solar retinopathy. Mild

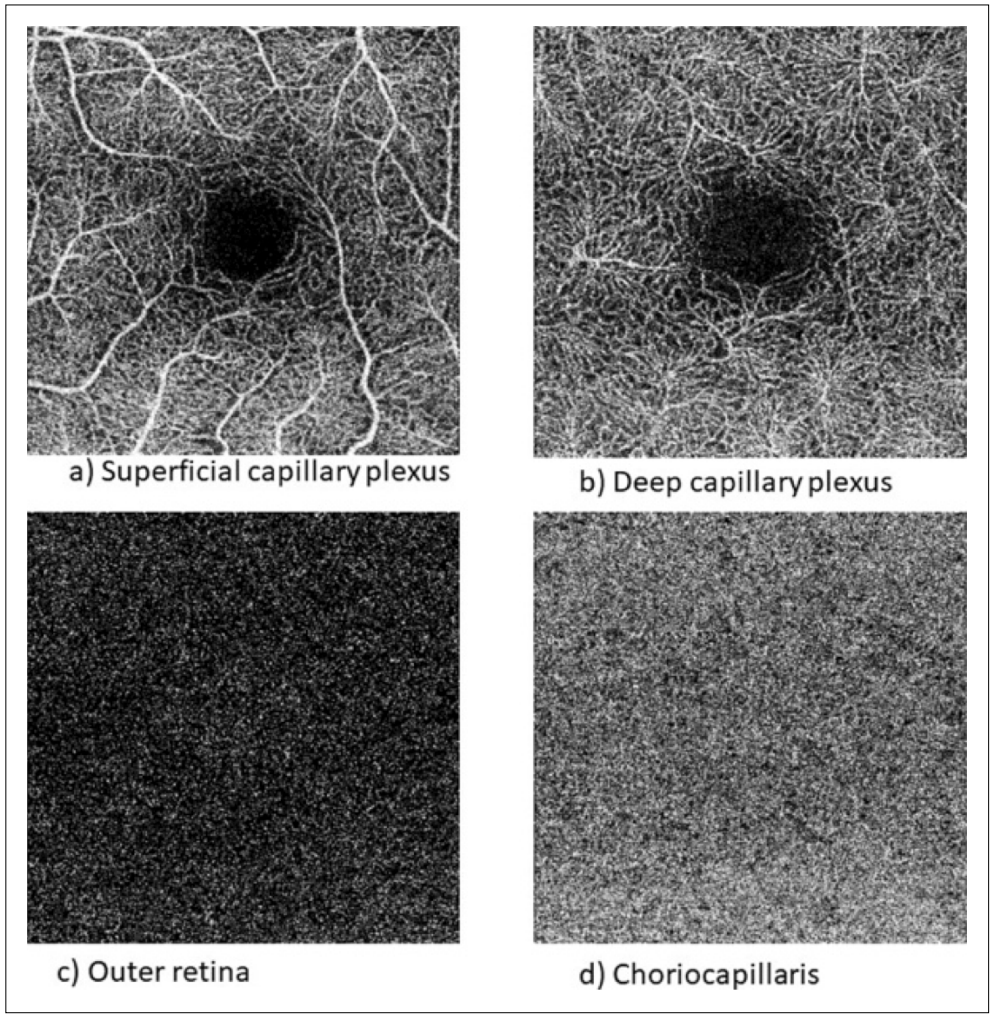

Figure 4. En face optical coherence tomography angiography images of a patient showing a typical normal vascular pattern in the retinal layers. Superficial capillary plexus **(a)**, deep capillary plexus **(b)**, outer retina **(c)**, choriocapillaris **(d)**.

Table 1. Spearman rank correlations for visual acuity and OCT-OCTA parameters

OCT and OCTA parameters	Correlation coefficient	p
Central macular thickness (μm)	-0.23	0.427
Central choroidal thickness (μm)	-0.25	0.382
Outer retinal defect thickness (μm)	-0.19	0.518
RPE-Bruch membrane thickness (μm)	0.57	0.032
Defect area on en face OCT (μm^2)	0.03	0.925
OCTA FAZ area (SCP) (mm^2)	0.31	0.283
OCTA FAZ area (DCP) (mm^2)	0.28	0.334
Vessel density in the central fovea	-0.33	0.257

RPE: Retinal pigment epithelium; FAZ: Foveal avascular zone; SCP: Superficial capillary plexus; DCP: Deep capillary plexus; OCT: Optical coherence tomography; OCTA: Optical coherence tomography angiography.

hyperreflectivity of the external limiting membrane was also present in the affected eyes in our study. This finding was also reported by Chen et al. (14) We did not observe changes in the inner retinal layers in the current study. While certain studies did not detect inner retinal injury, others reported damage to the inner retinal layer at a lower rate in cases of solar retinopathy (5,6). Damage to the inner retinal layers was also proposed as a risk factor for poorer VA in patients with solar retinopathy (12).

We used en face structural OCT to identify and measure the area of the outer retinal defect. The study eyes exhibited hyporeflective outer retinal defects of varying sizes. Several other studies, (8,15) primarily comprising case reports, similarly described hyporeflective circular focal defects in the outer retina in en face OCT images. En face OCT imaging is suggested as a more effective imaging technique, given its comprehensive coverage of the macular region, thereby minimizing the risk of overlooking macular lesions. It has the

capability to confirm the existence of outer retina defects in solar retinopathy, even in cases where the B-scan OCT scan fails to traverse the foveal defect (15). It was proposed as a sensitive means to measure the extent of EZ loss, allowing for longitudinal tracking (8). In a case study, Wu et al. (16) described a circular zone of hyperreflectivity in the en face OCT image of the outer retina, along with central hyporeflectivity in a patient with acute solar retinopathy. In addition, a corresponding change was noted in the choriocapillaris region, appearing as a hyporeflective area. These observations were not evident in our case series. The disparity may stem from the acute nature of their case, contrasting with our series that comprised patients with a minimum of 3 weeks since solar exposure.

OCTA imaging indicated a typical normal vascular pattern in the retinal vascular layers, with no flow deficits corresponding to the outer retinal defects observed in the choriocapillaris layer in this study. There is limited research employing OCTA in individuals with solar retinopathy, and the available studies predominantly consist of case reports (1). In a case of acute solar retinopathy, Wu et al., (16) reported that OCTA images of the patient were normal. In a patient with chronic solar retinopathy, Goduni et al. (8) observed relatively symmetrical FAZs and slight vessel tortuosity using OCTA, with the superficial and DCP appearing normal. In a case of acute photic retinopathy induced by a laser pointer, Tabatabaei et al., (17) noted that OCTA revealed a typical vascular pattern in retinal layers but exhibited a distinct low-signal area in the choriocapillaris layer. The difference in OCTA findings between our findings and this laser-induced maculopathy case may be due to lasers' higher energy levels, potentially causing thermal or disruptive damage. Solar maculopathy, on the other hand primarily caused by photochemical damage, involves cellular harm from reactive oxygen species, with the local temperature increase insufficient to induce thermal damage (1,18,19). The reports also indicate that the damage induced by lasers is more severe and thermal effects may extend beyond the RPE to involve the choriocapillaris (20,21).

We calculated Spearman rank correlations to examine the correlations between VA and OCT-OCTA parameters. In the correlation analysis, the only parameter with a statistically significant correlation with VA was the RPE-Bruch membrane thickness under the outer retinal defect. No significant relationships were observed between VA and the other evaluated parameters. Some of the previous studies have reported a correlation between VA and foveal thickness (6,22). Other research has indicated that visual symptoms may not consistently align with findings observed through OCT (9). In a study involving patients with photic retinopathy caused by sun gazing and welding, Kumar et al. (5) found a weak correlation between the thickness and horizontal dimensions of the outer retinal defect and VA. Their conclusion was that ultrastructural features assessed through OCT have limited correlation with either initial or eventual VA. We also assessed central macular thickness, central choroidal thickness, outer retinal defect thickness, and defect area, finding no correlation with VA. OCTA superficial and deep FAZ area and vascularity were also not correlated with VA. Regarding RPE, it was suggested that in cases of severe photochemical damage extending to the RPE, the probability of recovery decreases, and a tendency for progressive RPE remodeling may emerge (8). The observed correlation between the thinning of the RPE-Bruch membrane and reduced VA in our study suggests that it may indicate more severe damage resulting from solar retinopathy, leading to lower VA.

There are some limitations and strengths of the study. First, the study involved a relatively small sample size, comprising 14 eyes from 11 patients. A larger cohort might enhance the generalizability of the findings and provide a more comprehensive understanding of solar retinopathy but it is crucial to note that solar retinopathy is relatively rare, making it challenging to gather a larger cohort. Second, the study design is cross-sectional, limiting the ability to establish causation or explore changes over time. Longitudinal studies would be valuable in tracking the progression or resolution of structural changes. Another limitation of our study is that FAZ measurements for both the superficial and deep capillary plexuses were performed manually using the freehand tool in ImageJ. Although automated methods are available, we chose manual measurement to ensure greater control over FAZ boundary delineation and to overcome potential segmentation artifacts. Nevertheless, manual tracing may introduce observer-dependent variability. In addition, the vertical measurement of outer retinal defect thickness encompassed multiple microstructural components – such as the EZ, interdigitation zone, myoid zone, and photoreceptor outer segments – which may limit the ability to interpret the specific contribution of each individual layer. The strengths of the study include the comprehensive approach used in the study, combining clinical examination with OCT and OCTA to provide a thorough evaluation of solar maculopathy. In addition, our study focused exclusively on solar retinopathy cases, excluding other causes of photic retinopathy, which adds specificity to our research.

Conclusion

In conclusion, our study assesses clinical and structural findings in solar maculopathy, revealing consistent outer retinal defects, especially in the ellipsoid and interdigitation zones. En face structural OCT proves valuable for precise evaluation, offering advantages over traditional B-scan OCT ca-

pabilities. OCTA showed a normal vascular pattern with no choriocapillaris flow deficit corresponding to the outer retina defects. The correlation analysis indicates a significant link between VA and RPE-Bruch membrane thickness under the outer retinal defect, suggesting its potential as an indicator of severity. At present, no proven treatment exists, making prevention of solar retinopathy the most effective strategy. Further research is needed to understand long-term effects and refine diagnostic and management strategies for solar retinopathy.

Disclosures

Ethics Committee Approval: This study was approved by the Niğde Ömer Halisdemir University Ethics Committee (Date: 10.11.2023, Number: 2023/84) and conducted in accordance with the tenets of the Declaration of Helsinki.

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

Conflict of Interest: None declared.

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Peer-review: Externally peer-reviewed.

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Original Article

Outcomes of Laser Hyaloidotomy in Premacular Hemorrhage: Identifying Predictors of Treatment Success and Need for Vitrectomy

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Abstract

Objectives: This study aimed to evaluate the outcomes of laser hyaloidotomy (LH) in treating premacular hemorrhage (PMH) and identify factors influencing treatment success.

Methods: In this retrospective cohort study, patients with PMH of any etiology treated with LH were included. Patient demographics and PMH characteristics were documented. Treatment efficacy was assessed based on successful hyaloid puncture, blood drainage into the vitreous cavity, and the need for pars plana vitrectomy (PPV).

Results: A total of 56 eyes from 51 patients (36 males, 15 females; mean age: 46.32±15.07 years) underwent LH for PMH (all cases had subhyaloid hemorrhage). The median symptom duration was two days (range: 0–30 days). The mean time interval between advising and performing LH was 4.92±12.82 days. Pretreatment visual acuity ranged from counting fingers to 6/36. LH was successful in 14 eyes (25%), while 42 eyes (75%) failed, primarily due to non-drainage of PMH (32 eyes, 76%) or persistent vitreous hemorrhage (10 eyes, 24%). PMH secondary to proliferative diseases universally requires PPV. PMH located within the retinal arcades or closer to the presumed fovea was more likely to necessitate PPV (p=0.001).

Conclusion: LH demonstrated limited efficacy, particularly in PMH associated with proliferative diseases or in those confined within the inferior retinal arcade. These cases frequently required early PPV. Incorporating vitrectomy into the initial treatment strategy may optimize outcomes for specific PMH subgroups.

Keywords: Hyaloidotomy, laser, outcomes, premacular hemorrhage, vitrectomy

Introduction

Premacular hemorrhage (PMH) causes profound vision loss and is defined as blood accumulation beneath the posterior hyaloid (subhyaloid) space or beneath the internal limiting membrane (ILM) (sub-ILM) space in the macular region, including the fovea (1,2). It can be caused by several factors, including proliferative retinal vascular diseases such as proliferative diabetic retinopathy and retinal vein occlusions, as well as non-proliferative retinal or choroidal vascular diseases such as rupture of retinal artery macroaneurysm and polypoidal choroidal vasculopathy, arteriovenous communication of the retina, and blood dyscrasias (3-5). Non-vascular disorders that cause premacular bleed include trauma, laser in situ keratomileusis, Valsalva, Terson's syndrome, and Purtscher's retinopathy (6-10). The distinction between subhyaloid hemorrhage (SHH) and sub-ILM hemorrhage is crucial in clinical practice, as these entities differ in both clinical presentation

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and optical coherence tomography characteristics. Recognizing these differences is essential, as the underlying etiologies and management strategies vary significantly between the two conditions (11).

Various treatment modalities for PMH have been described, with the primary goal of clearing the hemorrhage from the foveal region and improving visual acuity. Observation, laser hyaloidotomy (LH), pneumatic displacement of hemorrhage by intravitreal injection of gas and tissue plasminogen activator, and pars plana vitrectomy (PPV) are some of the procedures currently available (12-14). When planning treatment for a PMH, several factors are usually taken into consideration. These include the patient's presenting visual acuity, the level of the PMH (sub-hyaloid or sub-ILM), obscuration of the fovea, the cause of the hemorrhage (proliferative or non-proliferative), the extent of the hemorrhage (> or <3DD), the height of the hemorrhage, and finally, the patient's single-eyed status (3-5). Though spontaneous resolution of the PMH is possible in most cases, it can take several weeks or months depending on the dimensions and total volume of blood present, which can be incapacitating to the patient when it occurs bilaterally or in single-eyed patients. Furthermore, prolonged contact with hemoglobin and iron may result in poor visual outcomes due to pigmentary macular changes or the formation of epiretinal membranes, as well as toxic damage to the retina (13). As a result, observation as a form of treatment is usually reserved for cases with a small amount of blood (<3DD) or pure sub-ILM bleed (15). Active non-surgical interventions such as LH or pneumatic displacement with gas injection are planned to rapidly clear or displace preretinal blood from the foveal region, prevent secondary retinal damage due to the presence of long-standing blood, improve visual acuity, and eliminate the need for PPV. There are numerous papers in the literature (anecdotal case reports and case series) that discuss the utility and outcomes of neodymium-doped yttrium aluminum garnet LH for various etiologies (3-5,14). These studies, however, do not give readers specific guidelines on when to consider LH or other treatment options for the initial management of PMH.

In this study, we will review our series of PMH cases treated with LH and identify the key factors that may influence the outcome of this treatment modality.

Methods

Patients above 18 years, with recently diagnosed (<1-month duration) PMH and without significant vitreous hemorrhage of any etiology, attending the retina clinic of a tertiary eye care hospital in South India between June 2017 and May 2024 were included in this retrospective cohort study. The study was conducted as per the Declaration of Helsinki, and all the necessary details related to the study were supplied to the Institutional Review Board and Ethics committee of Narayana Nethralaya (EC Ref. No: C/2019/03/04). Age, gender, etiology, interval between symptoms and presentation to retina clinic, and interval between presentation and active intervention, pre- and post-treatment visual acuity, need and reason for surgical intervention, and total follow-up duration were all recorded. Optical coherence tomography imaging was performed in all cases to determine the predominant location of the PMH (subhyaloid or sub-ILM), and fundus fluorescence angiography was used as needed. Only eyes that showed blood confined to the subhyaloid space–with typical convex dome-shaped elevation, and absence of ILM draping or cleavage lines suggestive of sub-ILM localization–were included in the LH group. The dimensions of the hemorrhage were measured on the color fundus photographs obtained on the Optos® Daytona machine (UK) using the device's in-built calipers. The horizontal and vertical dimensions of the hemorrhage, as well as the vertical distance from the presumed foveal center to the inferior-most boundary of the hemorrhage were noted.

The treating retina specialist presented the patient with three management options for PMH: observation, LH, and primary PPV. Observation was preferred for: (A) eyes with hemorrhages <3-disc diameters not involving the fovea; (B) elderly or monocular patients with guarded visual prognosis or unfit for laser, and (C) patient refusal of laser intervention. Primary PPV was considered for: (A) patients with large dense hemorrhage (>6-disc diameters) obscuring the fovea and located in eyes with known proliferative retinopathy or associated traction and (B) patient preference for quicker visual recovery. The potential risks, expected outcomes, and subsequent steps were thoroughly discussed with the patient. Informed consent was obtained from all patients undergoing LH and PPV.

For LH, a Q-switched Nd: YAG laser (Ellex Super Q, Ellex, USA) was utilized, emitting a single laser burst through a well-dilated pupil via a slit-lamp delivery system. A Goldmann three-mirror contact lens (Volk) was employed to precisely focus the laser energy on the posterior hyaloid membrane. The perforation was strategically created near the inferior and most dependent edge of the PMH while avoiding retinal blood vessels and the fovea. Initial laser energy was set at 2 mJ and was incrementally increased by 1 mJ, up to a maximum of 10 mJ, as needed. The number of laser spots applied varied from one to five, depending on the response, to ensure effective perforation of the hyaloid and facilitate blood drainage into the vitreous cavity.

The LH procedure was initially performed by a senior vitreoretinal fellow (≥18 months of experience) and, in cases of unsuccessful attempts, was subsequently re-attempted by the attending faculty. Treatment success after LH was defined as successful drainage of blood from the premacular

space into the vitreous, with no subsequent requirement for PPV. The procedure was deemed unsuccessful if a posterior hyaloid puncture could not be created despite multiple attempts or if blood failed to drain into the vitreous cavity following a successful puncture.

PPV was performed as a primary intervention in select cases of PMH or as a secondary procedure following LH failure. Secondary PPV was considered after a minimum of 4 weeks of follow-up post-LH, if there was: (A) Persistent non-clearing vitreous hemorrhage; (B) recurrent hemorrhage, and (C) failure of blood drainage into the vitreous.

The time interval between LH and subsequent PPV, when required, was also documented.

Statistical Analysis

All data were analyzed using GraphPad Prism version 9.4.1 (681) for Windows, GraphPad Software, San Diego, California, USA, www.graphpad.com. The Kolmogorov-Smirnov normality test showed the data sets to be of the non-parametric variety, and hence only non-parametric statistical tests were used in this study. Quantitative variables between the 2 groups were analyzed using the Mann–Whitney U test, and Chi-square test was used to compare the categorical data between the 2 groups. $P<0.05$ were considered statistically significant.

Results

For this study, 84 eyes of 78 patients presenting with PMH were included. Six patients had bilateral PMH. There were 56 (72%) males and 22 (28%) females in the study. The average age of the patients was 43.68±14.08 years. Mean duration of symptoms was 13.06±6.05 days. Causes of PMH at presentation are included in Table 1.

In 24 (29%) eyes, the PMH was observed at presentation. 54 (64%) eyes underwent LH, and 6 (7%) eyes underwent PPV at the initial presentation. Eighteen of the 24 (75%) eyes that were observed initially showed resolution of the PMH over a period ranging from 2 to 5 months. In the remaining 6 (25%) eyes, LH was attempted in 2 (33%) eyes, whereas PPV was performed in 4 (67%) eyes for non-resolving PMH after a median period of 3.25 weeks. In total, 56 eyes underwent LH in the study. Analysis of these 56 eyes was performed further in this study.

Table 1. Causes of premacular hemorrhage at presentation

Causes	No. of eyes (n=84)
Proliferative diabetic retinopathy (n, %)	22 (26)
Valsalva retinopathy (n, %)	18 (21)
Trauma (n, %)	14 (17)
Branch retinal vein occlusion (n, %)	11 (13)
Ruptured retinal artery macroaneurysm (n, %)	8 (10)
Polypoidal choroidal vasculopathy (n, %)	5 (6)
Blood dyscrasias (n, %)	5 (6)
Terson's syndrome (n, %)	1 (1)

LH Group

This study included 56 eyes from 51 patients, with five patients presenting bilateral PMH. The etiologies of bilateral PMH included proliferative diabetic retinopathy (n=3), trauma (n=1), and Valsalva retinopathy (n=1). The cohort comprised 36 males (71%) and 15 females (29%), with a mean age of 46.32±15.07 years. The median duration of symptoms was 2 days (range: 0–30 days). The mean interval between recommending and performing LH was 4.92±12.82 days (range: 0–58 days). Pre-treatment visual acuity ranged from counting fingers close to the face to 6/36. The mean vertical distance between the presumed fovea and the inferior boundary of the PMH was 5.211±2.63 mm. The mean maximum vertical and horizontal diameters of the PMH were 10.64±5.171 mm and 11.83±6.504 mm, respectively. All eyes in this cohort exhibited hemorrhage predominantly in the subhyaloid space on optical coherence tomography, with no cases of sub-ILM hemorrhage observed.

Outcomes of LH

There was no drainage of blood from the premacular space in 32 of the 56 (57%) eyes that had LH. Ten (42%) of the 24 eyes where blood was successfully drained from the premacular space into the vitreous required PPV later for non-resolving vitreous hemorrhage. To summarize, 14 (25%) eyes had treatment success after LH, while 42 (75%) eyes had treatment failure. Following a successful LH, the visual acuity ranged from 6/6 – 6/18. Table 2 provides information and analysis of the factors based on whether or not blood was successfully drained from the premacular space into the vitreous cavity after LH. PMH >7 days duration encountered more frequent treatment failures ($p=0.001$). The treatment success did not differ significantly when LH was performed in a young patient (≤40 years) compared to an older patient (>40 years). When all the proliferative and non-proliferative causes of PMH were combined, and the treatment outcomes were compared between the two groups, proliferative causes of premacular bleeding failed to drain into the vitreous cavity after LH (100% vs. 39%; $p\leq0.001$).

There was a requirement for performing PPV in 42 (75%) of the 56 eyes that underwent LH. Ten (24%) eyes required PPV for non-clearing vitreous hemorrhage, while the remaining 32 (76%) eyes required PPV for failure to drain PMH into the vitreous space and, in some cases, for the development of additional tractional retinal detachment. PPV was required in all cases of PMH caused by proliferative diseases. Table 3

Table 2. Univariate analysis of factors associated with success or failure of drainage of blood into the vitreous cavity from the premacular subhyaloid space after laser hyaloidotomy

	Drainage success (n=24) (%)	Drainage failure (n=32) (%)	p
Duration of symptoms			
≤7 days	16 (67)	7 (22)	0.001
>7 days	8 (33)	25 (78)	
Age			
≤40 years (n=30)	11 (37)	19 (63)	0.565
>40 years (n=21)	10 (33)	11 (67)	
Valsalva retinopathy (n=16)	11 (69)	5 (31)	0.018
Proliferative diabetic retinopathy (n=10)	0 (0)	10 (100)	0.003
Trauma (n=11)	8 (63)	3 (27)	0.041
Branch retinal vein occlusion (n=7)	0 (0)	7 (100)	0.016
Retinal artery macroaneurysm (n=6)	3 (50)	3 (50)	>0.999
Blood dyscrasias (n=3)	2 (67)	1 (33)	0.571
Polypoidal choroidal vasculopathy (n=2)	0 (0)	2 (100)	0.501
Terson's syndrome (n=1)	0 (0)	1 (100)	>0.999
Non-proliferative causes (n=39)	24 (61)	15 (39)	<0.001
Proliferative causes (n=17)	0 (0)	17 (100)	

Table 3. Comparison of premacular dimensions between eyes that required PPV and eyes that did not require PPV after laser hyaloidotomy

	Eyes where PPV not needed (n=14)	Eyes where PPV needed (n=42)	p
Vertical distance of the hemorrhage from the presumed fovea to the inferior-most boundary of the PMH (mm)	9.465±4.632	4.165±1.287	0.001
Maximum vertical dimension of detached subhyaloid space (mm)	10.64±5.171	9.256±6.125	0.567
Maximum horizontal dimension of detached subhyaloid space (mm)	12.07±7.125	11.45±6.981	0.725

mm: Millimetre; PPV: Pars plana vitrectomy; PMH: Premacular hemorrhage.

compares the pre-treatment dimensions of the premacular SHH between those who required PPV and those who did not after LH. Figure 1 demonstrates the case examples of patients treated with LH for PMH and reasons for its failure, while Figure 2 demonstrates the case examples of patients successfully treated with LH, observation, and primary PPV for PMH.

Complications after LH

Tractional retinal detachment occurred in 7 of 10 (70%) eyes with proliferative diabetic retinopathy and 5 of 7 (71%) eyes with branch retinal vein occlusion due to contraction of the posterior hyaloid membrane and subsequent traction on the fibrovascular membrane. PPV was used to treat these cases. In cases where the PMH was successfully drained, no other complications such as increased intraocular pressure, epiretinal membrane formation, retinal and choroidal hemorrhage, macular hole, or retinal break formation were observed.

PPV Outcomes in Eyes Treated with LH

Out of a total of 84 eyes included in the study, 52 (62%) eyes underwent PPV at some point during the course of treatment. These included 42 (81%) eyes after failed LH, 6 (14%) eyes at the initial presentation itself, and 4 (5%) eyes after an initial period of observation. Thirty of the 42 (71%) eyes that required PPV after LH underwent surgery after a period ranging from 2–4 months. The visual acuity of these patients by the last follow-up visits improved to ≥ 6/18 in 87% (n=26) eyes.

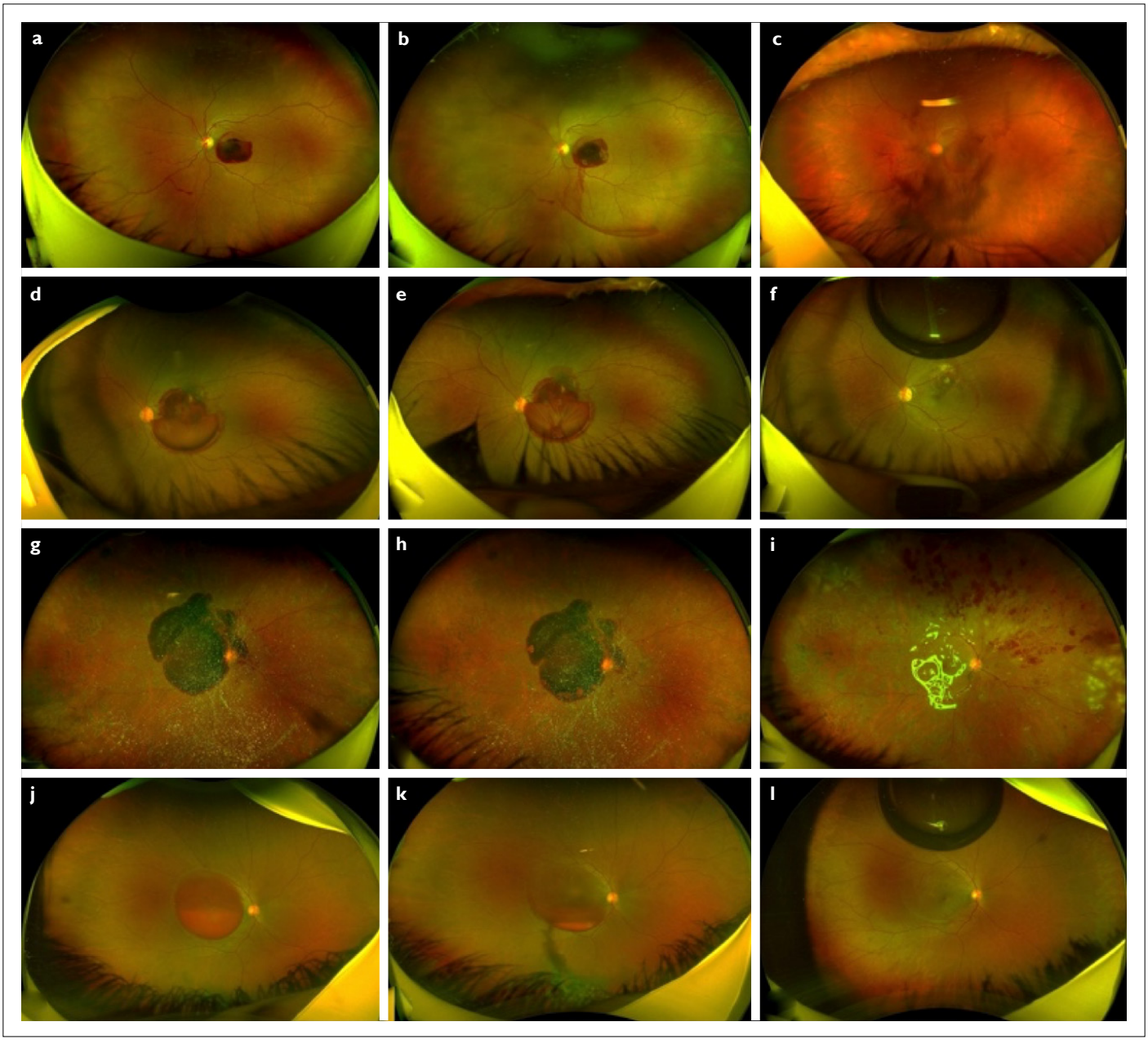

Figure 1. Reasons for treatment failure after laser hyaloidotomy (LH) for premacular subhyaloid hemorrhage (SHH) depicted with the help of case illustrations: Row 1: **(a-c)** Premacular SHH limited to the posterior pole within the retinal arcades demonstrated successful drainage of the premacular blood into the vitreous cavity following LH requiring pars plana vitrectomy (PPV) for non-clearing vitreous hemorrhage. Row 2: **(d-f)** After LH, premacular SHH caused by a non-proliferative superotemporal retinal artery macroaneurysm failed to drain blood into the vitreous cavity. The failure in this case illustration was due to the inability of the laser to successfully puncture the posterior hyaloid membrane. Row 3: (g-i) Treatment for a dense premacular bleed by LH brought on by proliferative diabetic retinopathy was unsuccessful because it was not possible to puncture the retrohyaloid membrane. Later, PPV was performed on the patient to treat the premacular hemorrhage. Row 4: **(j-l)** Following LH, premacular blood from Valsalva retinopathy with SHH restricted to the retinal arcades revealed insufficient drainage of the SHH. The patient underwent PPV at the end and displayed improved visual acuity.

Discussion

This study examined the outcomes of LH in eyes with PMH from various causes and identified factors that can help a clinician predict success or failure after LH. The study revealed five significant observations: (a) Better LH outcomes can be achieved if symptoms last for <1 week; (b) patient's age has no bearing on the success of LH; (c) higher chances of treatment failure in eyes with PMH secondary to proliferative diseases; (d) localized PMH confined within the retinal

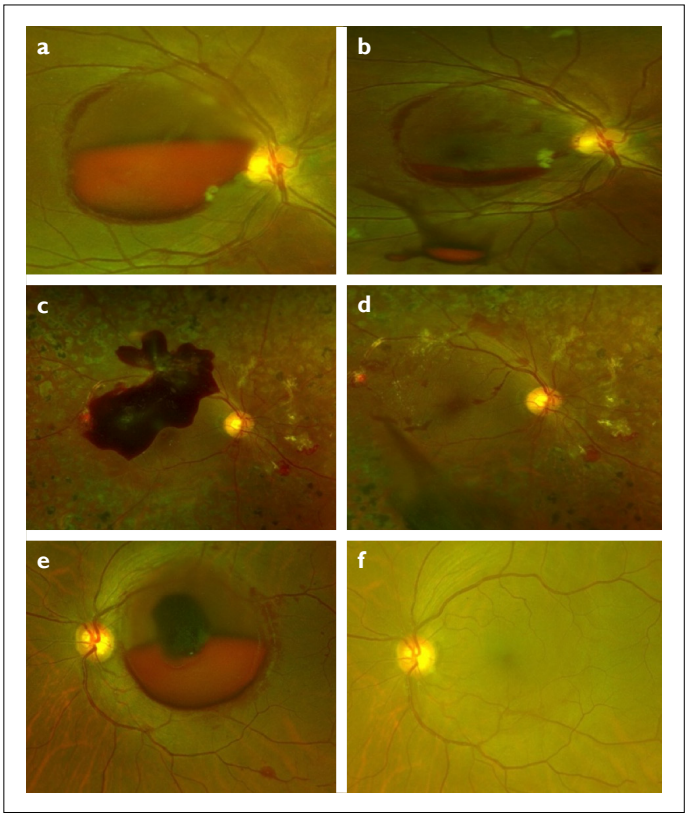

Figure 2. Case illustrations depicting successful management of premacular bleed following laser hyaloidotomy (LH), observation, and primary pars plana vitrectomy (PPV): Row 1: **(a, b)** Successful management of dense premacular bleed secondary to Valsalva retinopathy treated with yag-LH. Row 2: **(c, d)** Complete resolution of premacular bleed, sparing the foveal center in a patient with proliferative diabetic retinopathy with no active management. Row 3: **(e, f)** Successful management of dense premacular bleed secondary to Valsalva retinopathy treated with primary PPV. Patient achieved early visual rehabilitation following surgery.

arcades required more PPV after LH; and (e) improved visual outcomes after PPV. According to the findings, non-invasive LH has a limited role in the management of PMH in the current era when compared to a safer microincision PPV.

Blood located in the subhyaloid space typically lacks clotting factors (13). The presence of blood in this space produces a characteristic boat-shaped configuration due to the red blood cell sedimentation in the most dependent inferior portion of the detached posterior hyaloid (16). Conversely, a PMH with blood located in the sub-ILM space remains confined, limiting displacement and increasing the risk of direct retinal damage by the laser itself. Therefore, these cases are less amenable to laser treatment. The most common reasons for the failure of PMH following LH include the sub-ILM heme and clogging of the puncture site by sedimented red blood cells (3-5,17).

On the other hand, vitreous hemorrhage differs from SHH in several aspects, including rapid clot formation, slower clot lysis, red blood cell hemolysis, prolonged persistence of erythrocytes, and the absence of a polymorphonuclear response (18,19). The vitreous collagen matrix promotes rapid clotting and impedes hemorrhage resolution by preventing passive diffusion, delaying the inflammatory cellular response. Consequently, hemolytic blood remains in the vitreous cavity for an extended duration, leading to compromised visual quality. Moreover, prolonged intraocular heme retention increases the risk of complications such as proliferative vitreoretinopathy, ghost cell glaucoma, and hemolytic glaucoma (18). Thus, despite successful drainage of blood from the premacular space into the vitreous cavity, the eye remains at an elevated risk of complications and persistent visual impairment. Consequently, in cases of PMH, active surgical intervention through PPV may facilitate faster visual recovery and reduce the risk of complications associated with long-standing, non-resolving vitreous hemorrhage (20).

An important finding in this study was the absence of disparity in LH outcomes between young and elderly eyes. The outcomes are expected to differ significantly due to the substantial variation in the clinical, histological, and ultrastructural composition of the posterior hyaloid membrane, which is dependent on the age of the patient (21).

One significant finding in the current study was the inability of laser perforation of the posterior hyaloid membrane in eyes with proliferative retinopathy, such as diabetic retinopathy and retinal vein occlusion. Puncture of the posterior hyaloid membrane, on the other hand, was successful in eyes without proliferative diseases, such as trauma, Valsalva retinopathy, and other non-proliferative causes. The difference in the composition of the posterior hyaloid membrane between these two groups of diseases could explain this. Hyalocytes are sentinel macrophages that live in the posterior vitreous cortex, just ahead of the ILM. Hyalocytes contribute to increased cellular proliferation after abnormal posterior vitreous detachment and vitreoschisis, which are common in proliferative retinopathies, resulting in macular pucker and fibrous/fibrovascular proliferations (22). In addition, in proliferative retinopathies, new vessels style on the posterior (retinal) surface of the posterior hyaloid membrane, causing changes in the posterior hyaloid membrane itself (23,24). Furthermore, after LH in proliferative diseases, the posterior hyaloid membrane may contract, causing increased traction on the neovascular tissue and retina, leading to further bleeding, tractional retinal detachment, retinal break formation, and combined retinal detachment (25). As a result, it is prudent not to consider LH as a treatment option in PMH caused by proliferative retinopathies due to increased chances of drainage failure and increased risks of post-laser complications.

In our study, we assessed the vertical extent of the SHH–measured from the presumed foveal center to its inferior margin–as a surrogate for hemorrhage size and its potential for spontaneous or facilitated clearance. Our findings suggest that LH was more effective when the SHH extended beyond the inferior retinal arcade, allowing the drained blood to disperse into the larger inferior vitreous cavity. Conversely, when the hemorrhage was confined to the macular region, particularly within the inferior retinal arcade, the likelihood of requiring PPV remained high, even in cases where LH technically succeeded in creating drainage. This may be attributed to limited vitreous liquefaction and impaired clearance dynamics over the posterior pole, which results in stagnation of the drained hemorrhage in the visual axis. The persistent vitreous opacity continues to compromise central vision, both in terms of acuity and subjective visual quality.

Therefore, in cases where SHH is localized within the macula and does not extend beyond the arcades, LH may offer limited clinical benefit. In such scenarios, primary observation (for small, non-visually significant hemorrhages) or early PPV (for visually disabling hemorrhages) may be more appropriate strategies. This tailored approach may help reduce treatment delays, avoid redundant interventions, and improve both anatomical and functional outcomes.

In the current study, PPV was used as the primary treatment option for PMH in 7% of the eyes, whereas LH was used in 64% of the eyes. Furthermore, 75% of the eyes where LH was attempted required PPV to resolve the PMH or non-resolving vitreous hemorrhage. All proliferative causes of PMH for which LH was initially attempted were later treated with PPV. Furthermore, 87% of cases improved in visual acuity (>6/18) following PPV in the study. These findings highlight PPV's high anatomical and functional success rate in PMH management and suggest that it be considered much earlier in the treatment algorithm, despite being more invasive than LH. These findings are supported by Ghali et al.'s (26).

publication, which concluded that PPV was a beneficial surgical treatment for PMH of various pathologies, ensuring rapid visual recovery with no serious side effects.

The study has the advantage of evaluating the results of a large number of patients treated with LH for PMH from a single center. Furthermore, the study identified factors that may influence treatment outcomes following LH. However, the study is a retrospective one and does not include a head-to-head comparison between observation, LH, and PPV for PMH management in a prospective, randomized clinical trial design.

Conclusion

This study provides a comprehensive analysis of key PMH attributes that may be an important factor to consider when managing PMH. Based on our findings, LH should be avoided in eyes with PMH due to proliferative causes. PPV should be included much earlier in the PMH treatment algorithm.

Disclosures

Ethics Committee Approval: This study was approved by the Narayana Nethralaya Ethics Committee (Date: 27.03.2019 Number: C/2019/03/04) and conducted in accordance with the tenets of the Declaration of Helsinki.

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Original Article

Incidence of Retinopathy of Prematurity Between 2021 and 2024: Results from a Single Center

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Abstract

Objectives: Retinopathy of prematurity (ROP) is a multifactorial disease characterized by abnormal vascularization of the immature retina. Although the most important risk factors are gestational age (GA) and birth weight (BW), the quality of neonatal intensive care also affects its incidence. This study aimed to evaluate the incidence of ROP and the need for treatment in infants screened for ROP according to the 2021 Turkish Prematurity Screening Guidelines for Retinopathy.

Methods: Records of premature babies screened for ROP at a single center between January 2021 and December 2024 were retrospectively evaluated. The results of the examinations, need for treatment, and hospital centers where premature infants were examined in accordance with the new guidelines were recorded.

Results: Between 2021 and 2024, 8,503 premature infants were screened for ROP at our clinic. A total of 1,623 infants were diagnosed with ROP, and 147 were treated using either laser photocoagulation or intravitreal bevacizumab. The number of babies with a BW over 1,700 g who were screened for ROP was 6,581; of these, 738 (11.21%) developed ROP, and 28 babies (0.42%) were treated. The number of babies born at ≥34 weeks' GA and who were screened for ROP was 4,029; of these, 173 (4.29%) developed ROP, and one baby (0.024%) was treated. Among the 1,623 patients diagnosed with ROP, 147 were treated, and 1,476 had spontaneously regressed ROP.

Conclusion: Significant ROP requiring treatment may occur in infants born at >34 weeks of gestation and/or with a BW ≥1,700 g.

Keywords: Birth weight, gestational age, retinopathy of prematurity, screening guideline

Introduction

Retinopathy of prematurity (ROP) is a multifactorial pathology characterized by abnormal vascularization of the immature retina and retinal vascular network of premature infants (1). Higher rates of preterm births and limited resources in underdeveloped and developing countries have increased the incidence of this disease. ROP is a major cause of childhood blindness; therefore, timely screening and diagnosis of premature infants are crucial for identifying those requiring treatment (2,3).

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Advancements in assisted reproductive techniques and perinatal care have increased the survival rates of premature infants, thereby increasing the incidence of ROP (4). Although low gestational age (GA) and birth weight (BW) are major risk factors, the quality of neonatal intensive care units (NICUs) greatly influences ROP occurrence (5). Universal criteria for screening programs cannot be established because of variations in NICU standards among countries. Instead, guidelines provide recommendations based on national conditions and scientific data. Each country should develop screening guidelines tailored to its specific NICU standards. For example, in low- to middle-income countries, such as India, screening criteria (GA ≤34 weeks; BW ≤2,000 g) differ from those in the United States (GA ≤30 weeks; BW ≤1,500 g) and the United Kingdom (GA ≤31 weeks; BW ≤1,501 g) owing to variations in perinatal and postnatal risk factors (6-8). In developed countries, ROP occurs primarily in preterm infants born at <32 weeks of gestation; however, in developing countries, it can also be observed in infants born at ≥34 weeks (9). Therefore, it is crucial for each country to establish a screening protocol based on NICU standards. A retrospective analysis of ROP cases plays a significant role in shaping these guidelines.

This study aimed to evaluate the incidence of ROP and the need for treatment in infants according to the screening criteria updated in the 2021 Turkish ROP Guidelines (TPRR) (10). The study also compared treatment rates among different centers for infants diagnosed with ROP. The objective was to determine the percentage of infants diagnosed with and treated for ROP after the screening criteria were extended from GA < 32 weeks to GA <34 weeks and from BW ≤1,500 g to BW ≤1,700 g in the 2021 TPRR update. This study highlights the significance of modifying screening criteria to identify infants at risk of blindness because of ROP.

Methods

Premature infants evaluated in our ROP screening and treatment center were included in this study. Medical records of 8,503 premature infants who underwent ROP screening between January 2021 and December 2024 were retrospectively reviewed. This study was approved by the Ethics Committee of the Zeynep Kamil Maternity and Children's Disease Training and Research Hospital (Decision No: 91, Date: December 25, 2024) and adhered to the principles of the Declaration of Helsinki.

Infants included in the screening met the criteria of the 2021 TPRR update: GA <34 weeks and BW ≤1,700 g. In addition, infants with GA ≥34 weeks or BW >1,700 g who received cardiopulmonary support or were deemed at risk for ROP by their primary pediatrician were included in the study. This study included infants hospitalized in our NICU and those referred to our hospital after follow-up in other NICUs. Infants who did not complete screening examinations or had congenital corneal and/or retinal abnormalities were excluded.

The GA and BW of all infants were recorded from the patients' files. The presence and type of treatment were also recorded. The NICU stay at another center was also noted. In this study, infants with type 1 ROP (Early Treatment for ROP classification) were categorized into Group 1, those with aggressive ROP (A-ROP) (International Classification of ROP, Third Edition) into Group 2, and those diagnosed with ROP who did not receive treatment into Group 3.

As a standard, the initial screening examination was performed at 4 weeks of age or corrected to 31 weeks of postmenstrual age. Families were informed before the ROP examination. Pupils were dilated before examination using 2–3 drops of 2.5% phenylephrine and 0.5% tropicamide at 5-min intervals. Topical proparacaine (0.5%) was applied before using the lid speculum. Indirect binocular ophthalmoscopy was performed using 20- and 28-diopter lenses. Detailed retinal examinations were performed with scleral indentation. The presence of plus/preplus disease, retinal vascularization (zone), disease stage, extent, and other findings were recorded for each eye according to the "International Classification of ROP, Third Edition" (11). Screening intervals and termination were determined according to the 2021 TPRR update (10).

ROP was managed based on the Early Treatment for ROP study (12). Intravitreal bevacizumab (IVB) injections (Altuzan 100 mg/4 mL vial, F. Hoffmann-La Roche Ltd., Kaiseraugst, Switzerland) and/or laser photocoagulation (LFC) were administered for A-ROP and type 1 ROP requiring treatment. The parents were informed orally and in writing, and consent forms were signed before treatment.

Statistical Analysis

All analyses were conducted using Statistical Package for the Social Sciences (SPSS) version 26.0 (SPSS, Chicago, IL, USA). Normal distribution was evaluated using the Shapiro-Wilk test. Descriptive statistics for normally distributed quantitative data are expressed as mean±standard deviation. For nonparametric data, the median and interquartile ranges were used. Categorical variables (including sex) were compared using Pearson's Chi-squared or Fisher's exact test. Continuous variables (such as age and BW) were analyzed using the two-sample t-test or Mann-Whitney U-test. Correlations between parameters were assessed using Spearman's rank correlation analysis.

Results

A total of 8,503 premature infants were screened for ROP between January 2021 and October 2024. Among these, 1,623 infants were diagnosed with ROP, and 147 were treated with either LFC or IVB. The characteristics of each group are presented in Table 1.

Table 1. Distribution of gestational age and birth weight in patients

	Premature babies screened for ROP (n=8503)	Patients with ROP diagnosis (n=1623)	Patients treated for ROP (n=147)
Girls/boys	4051/4344	753/870	65/78
Median gestational age at birth (IQR) (range)	34 (3) gw (23–38)	32 (4) gw (23–38)	29 (5) gw (23–36)
Median birth weight (IQR) (range)	2,000 (795) g (340–4,700)	1,650 (800) g (370–3,900)	1,120 (650) g (370–3,600)

gw: Gestational weeks; g: Grams; IQR: Interquartile range; ROP: Retinopathy of prematurity.

Among the 1,623 infants diagnosed with ROP, 147 received treatment, and 1,476 showed spontaneous regression of the disease. Of the included patients, 113 (7%) had type 1 ROP, 34 (2.1%) had A-ROP, and 1,476 (90.9%) were diagnosed with other forms of ROP (Table 2). The distribution of disease severity according to GA and BW is shown in Table 3 and Figure 1.

GA and BW were significantly lower in the treated group than in all infants diagnosed with ROP ($p<0.001$). Both GA and BW were negatively correlated with ROP severity (Spearman's rho = −0.307, $p<0.001$, and −0.269, $p<0.001$, respectively). No correlation was observed between sex and the need for ROP treatment.

Of the 147 treated infants, 113 (76.9%) were diagnosed with type 1 ROP and 34 (23.1%) with A-ROP. Among the treated infants, 97 (66%) had a history of NICU admission to another center, whereas 50 (34%) were followed up in our NICU. Infants from other NICUs had significantly higher GA and BW than those of infants in our center ($P < 0.001$) (Table 4). Among the treated patients, 111 (75.5%) received IVB, 32 (21.8%) underwent LFC, and four (2.7%) required both treatments (Table 5).

When the screening criteria were expanded from GA ≤32 weeks to GA ≤34 weeks, an additional 2,409 infants were screened for ROP. Among them, 487 (20.2%) developed ROP, with 34 (1.41%) classified as having stage 3 disease. Six (0.25%) infants were treated with IVB, five (0.2%) with LFC, and one (0.04%) received both IVB and LFC. Expanding the BW criteria from ≤1,500 g to ≤1,700 g resulted

Table 2. Retinopathy of prematurity types in patients diagnosed with retinopathy of prematurity (n = number of patients)

	Group 1 (n=113)	Group 2 (n=34)	Group 3 (n=1476)
Birth weight			
<700 g	10	7	34
701–1,000 g	32	12	160
1,001–1,250 g	16	5	160
1,251–1,500 g	22	4	227
1,501–1,700 g	8	3	186
1,701–2,000 g	18	3	291
>2,000 g	7	0	418
Gestational age			
<26 gw	11	14	32
26–28 gw	34	7	177
29–30 gw	26	5	231
31–32 gw	32	5	389
33–34 gw	9	3	475
>34 gw	1	0	172

Gw: Gestational weeks; g: Grams.

Table 3. Stages in retinopathy of prematurity in patients diagnosed with retinopathy of prematurity, categorized by gestational age and birth weight (n = number of patients)

	Stage 1 (n: 1204)	Stage 2 (n: 180)	Stage 3 (n: 239)
Birth weight			
<700 g	22	9	20
701–1,000 g	110	28	66
1,001–1,250 g	119	25	37
1,251–1,500 g	179	32	42
1,501–1,700 g	154	18	25
1,701–2,000 g	254	31	27
>2,000 g	366	37	22
Gestational age			
<26 gw	19	11	27
26–28 gw	119	29	70
29–30 gw	177	34	51
31–32 gw	314	57	55
33–34 gw	420	33	34
>34 gw	155	16	2

Gw: Gestational weeks; g: Grams.

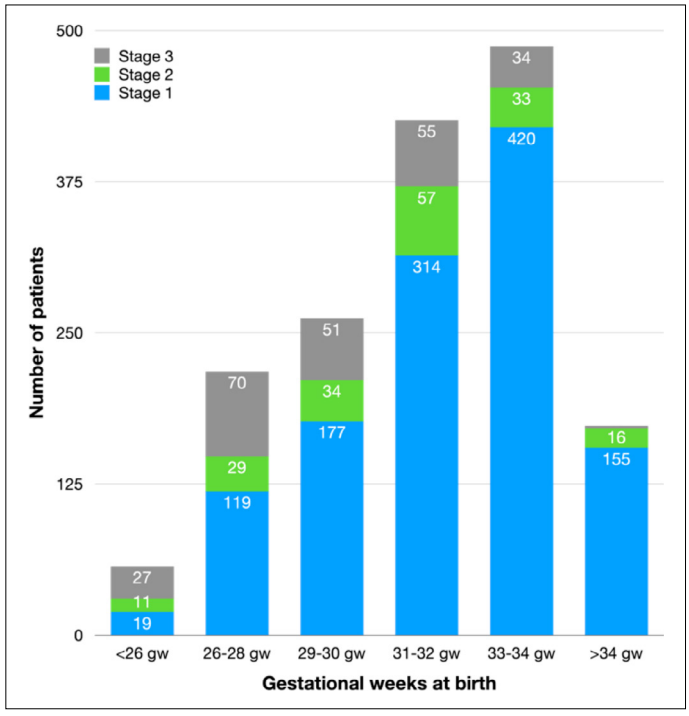

Figure 1. Distribution of retinopathy of prematurity severity according to gestational age.
gw: gestational week.

in the screening of 600 additional infants, of whom 197 (32.8%) developed ROP. Twenty-five (4.16%) patients developed stage 3 or higher ROP. Eight (1.3%) patients received IVB, and three (0.5%) underwent LFC.

The number of babies born at >34 weeks GA who were screened for ROP was 4,029; among these, 173 (4.29%) developed ROP, and one baby (0.024%) was treated with LFC for ROP. The number of babies with a BW >1,700 g who were screened for ROP was 6,581; among these, 737 (11.2%) developed ROP, and 28 babies (0.42%) were treated. Among these 28 infants, 14 (0.21%) were treated with IVB, 13 (0.2%) with LFC, and one (0.015%) with IVB followed by LFC.

Discussion

ROP screening criteria vary depending on the developmental status of countries and may even differ among centers within the same country (13). In countries where survival rates have improved but neonatal care remains inadequate, the incidence of ROP is high. In low- to middle-income countries, such as India, this rate has been reported to range between 20% and 30% (14). Meena et al. (14) reported an ROP incidence of 26.9%, whereas Raffa et al. (2) reported 29.5% in Saudi Arabia. Ding et al. (15) reported an ROP incidence of 11.8% in 2,040 infants screened between 2017 and 2021. However, the rate is low in developed countries. Bhatnagar et al., (16) in their study of 125,212 infants screened in the United States between 2003 and 2019, reported ROP incidences of 4.4% in 2013 and 8.1% in 2019. Similarly, Cudjoe et al. (17) reported an ROP incidence of 4.6% among 12,942 infants screened between 2009 and 2018.

In our study, 8,503 infants were screened between 2021 and 2024, of whom 1,623 (19.08%) were diagnosed with ROP, and 147 (1.72%) received treatment for ROP. We believe that the relatively low proportion of treated infants was due to the large number of screened infants. The screening criteria in our country include infants born at <34 weeks and ≤1,700 g, which represents a broad range. In developed countries, screening includes infants ≤30 weeks and ≤1,500 g, whereas in developing countries, the criteria can extend up to 34 weeks and 1,750 g (15).

Table 4. Comparison of gestational age and birth weight between patients admitted to different neonatal intensive care units (NICUs)

	NICU stay at another Center (n=97)	NICU stay at the same Center (n=50)	p
Mean gestational age at birth ±STD (range) (gw)	29.34±2.85 (23–36)	27.54±2.89 (23–33)	<0.001*
Mean birth weight ±STD (range) (g)	1356.08±523.88 (530–3600)	1035.42±428.42 (370–1980)	<0.001**

*Mann-Whitney U-test. **Independent samples t-test. Gw: Gestational weeks, g: Grams.

Table 5. Gestational age and birth weight of patients who underwent retinopathy of prematurity treatment

	IVB (n=111)	LFC (n=32)	IVB+LFC (n=4)
Mean gestational age at birth ±STD (range)*	28.29±2.87 (23–34)	30.44±2.55 (25–36)	27.25±4.71 (24–34)
Mean birth weight ±STD (range)**	1166.22±460.48 (370–3,600)	1534.42±555.29 (625–2,900)	1,186.25±905.33 (530–2,500)

*in gestational weeks. **in grams. IVB: Intravitreal bevacizumab; LFC: Laser photocoagulation.

Our study included a diverse patient population: infants born and followed up in our hospital, infants born in other centers who were referred to our hospital for screening, and infants transferred to our hospital for ROP treatment after being screened and followed up elsewhere. The significant difference in GA and BW between infants followed up in our NICU and those from other centers ($p<0.001$) suggests that the quality of NICU care varies even between centers within the same region (Table 4).

Consistent with other studies, our findings demonstrated that the incidences of ROP and severe ROP decreased with increasing GA and BW (2,18-20). Among infants born before 32 weeks, 59.3% developed ROP, compared to 30% of those born between 33 and 34 weeks and 10.7% of those born after 34 weeks. According to BW, 54.6% of infants weighing <1,700 g developed ROP, whereas 45.4% of those weighing >1,700 g were affected. A similar trend was reported in a retrospective study by Bas et al., (1) which included 15,745 infants in our country and indicated a high prevalence of ROP among premature infants with low GA and BW.

A 12-year retrospective study in Northern China reported an ROP diagnosis in 16.16% of 7,832 preterm infants, with 7.8% of these cases falling outside the screening criteria specified by the Chinese Medical Association. Of these patients, 1.11% required treatment for severe ROP (18). This rate is comparable to that in developing countries. Similarly, our study identified infants outside of the screening criteria who developed and required treatment for ROP. We attribute the high number of infants screened beyond 34 weeks and 1,700 g to neonatologists and pediatricians referring all potentially at-risk infants for ROP examinations. Although this can lead to unnecessary examinations and stress in neonates, especially in developing countries, it is crucial to prevent misdiagnosis.

Our study confirmed the presence of ROP in mature infants in our country. We believe that the relatively higher incidence compared with that of other clinics is because of our role as a referral center for ROP diagnosis and treatment, receiving complex cases from other institutions. Similarly, Araz-Ersan et al. (21) demonstrated that severe ROP may develop in mature and large infants in our country. Likewise, in other developing countries, ROP and severe ROP can occur at any stage in infants with high GA and BW (1,22,23). In our study, 11.2% of infants weighing >1,700 g and 4.29% of those born at >34 weeks GA developed ROP.

According to the TPRR 2016 guidelines, screening was recommended primarily for infants born ≤32 weeks and/or ≤1,500 g. Compared with the 2016 guidelines, the TPRR 2021 update led to the screening of an additional 2,409 infants born at 33–34 weeks and 600 infants weighing 1,501–1,700 g. Among them, 12 infants born at 33–34 weeks and 11 infants weighing 1,501–1,700 g required treatment, highlighting the importance of the updated criteria.

Dericioğlu et al. (24) reported an ROP incidence of 14.1% and a severe ROP incidence of 0.6% in 1,784 preterm infants weighing >1,500 g. Another study conducted before the update of the ROP guidelines suggested screening criteria of ≤33 weeks and ≤1,770 g based on data from 1,241 infants (25). These findings support the occurrence of severe ROP in mature and large infants in Türkiye.

A comparative retrospective study by Kaya Güner et al., (26). covering the 2 years before and after the TPRR 2021 guideline update, revealed that the number of infants diagnosed with ROP increased post-update (19.3% vs. 21.4%, respectively), whereas the number of infants requiring treatment decreased (3.9% vs. 2.1%, respectively). The incidence of treatment-requiring ROP is lower in developed countries and is influenced by socioeconomic development and healthcare quality. Adams et al. (27) reported a treatment-requiring ROP incidence of 4% in a prospective study of 8,112 infants weighing <1,500 g in the UK, with a mean GA of 25 weeks and mean BW of 706 g. Barjol et al., (28) in a retrospective study conducted in France between 2011 and 2018, reported a treatment-requiring ROP incidence of 2.6% among 2,246 infants, all born at <31 weeks GA. Similarly, Freitas et al. (29) reported an ROP incidence of 33.9% and a treatment-requiring rate of 5% among 602 patients. However, Romo-Aguas et al. (30) reported a higher rate, with 26.2% of the 503 neonates screened between 2011 and 2017 requiring treatment, reflecting Mexico's NICU development status.

Study Limitations

In addition to low GA and BW, other risk factors contribute to ROP development, including the duration and concentration of oxygen therapy, mechanical ventilation, asphyxia, cardiorespiratory issues, bronchopulmonary dysplasia, intracranial hemorrhage, sepsis, number of blood transfusions, and slow postnatal weight gain. Some infants in our study were followed up and treated in NICUs at other centers and presented to our outpatient clinic after discharge. The lack of data on these additional risk factors is a limitation of this study. Furthermore, our large sample size and the higher incidence of ROP and treatment-requiring cases are likely due to our experience as a specialized ROP clinic and the large number of patient referrals.

Conclusion

Our study highlights the incidence and treatment needs of ROP in infants weighing <1,700 g and born at <34 weeks GA, as well as in more mature infants outside these criteria in our country.

Disclosures

Ethics Committee Approval: This study was approved by the Zeynep Kamil Maternity and Children's Disease Training and Research Hospital Ethics Committee (Date: 25.12.2024, Number: 91) and conducted in accordance with the tenets of the Declaration of Helsinki.

Informed Consent: The parents were informed orally and in writing, and consent forms were signed before treatment.

Conflict of Interest: None declared.

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Original Article

The Role of Serum Vitamin and Mineral Levels in Benign Essential Blepharospasm: A Comparative Study

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Abstract

Objectives: This study aims to compare serum levels of folic acid, Vitamin B12, 25-hydroxy (OH) Vitamin D, calcium (Ca), zinc (Zn), phosphorus, and magnesium (Mg) between patients with benign essential blepharospasm (BEB) and healthy controls and to examine their associations with disease severity and frequency.

Methods: A retrospective study was conducted on 20 patients with BEB (13 females, 7 males) and 25 healthy controls (15 females, 10 males) from our clinic. Serum levels of folic acid, Vitamin B12, 25-OH Vitamin D, Ca, phosphorus, Mg, and Zn, as well as ophthalmologic examination results, were analyzed. BEB severity and frequency were assessed using the Jankovic Rating Scale (0–4).

Results: Serum levels of Vitamin B12, folic acid, Zn, Ca, phosphorus, and Mg were within normal limits for both groups. However, serum Vitamin D levels were below normal in both groups. No significant differences were found between the BEB and control groups regarding serum Vitamin B12, 25-OH Vitamin D, Ca, phosphorus, Mg, and Zn levels ($p>0.05$). Notably, serum folic acid levels were significantly lower in the BEB group compared to controls (6.19±2.75 vs. 8.95±4.10, $p=0.011$). In addition, a significant negative correlation was observed between serum folic acid levels and Jankovic severity ($r=-0.378$, $p=0.011$) and frequency scores ($r=-0.392$, $p=0.008$).

Conclusion: These findings suggest that folic acid may play a role in BEB pathogenesis. Further studies are needed to explore the underlying mechanisms and potential benefits of micronutrient supplementation in BEB management.

Keywords: Benign essential blepharospasm, folic acid, jankovic rating scale, micronutrients

Introduction

Benign essential blepharospasm (BEB) is a rare neurological condition characterized by involuntary contractions of the orbicularis oculi muscles surrounding the eyes. This results in excessive blinking, eye closure, and visual impairment (1). The spasms can be distressing, making it hard or even unfeasible for those affected to participate in daily activities, such as reading, driving, or sustaining eye contact during conversations (2). Despite being classified as "benign," BEB can lead to significant morbidity by affecting vision, social interactions, and emotional health.

The low prevalence of essential blepharospasm, with an estimated incidence of 0.10% among individuals, (3) has led to a limited understanding of its underlying mechanisms. The specific etiology of BEB remains unidentified, but increasing evidence suggests the involvement of various factors, including genetic predisposition, environmental triggers, and

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neurochemical imbalance (4). Conventionally, neurology has defined this condition as a result of neurotransmitter imbalances and basal ganglia dysfunction (5). Recent studies have started to examine the potential impact of micronutrient status, specifically essential vitamins and minerals, on the development of BEB (6-8).

Micronutrients play a critical role in various physiological processes, including cognitive functions, serving as cofactors, and modulating oxidative stress (9). The majority of vitamins and essential minerals are not produced by the body and must be acquired through diet. A deficiency in specific micronutrients leads to several alterations in nervous system development.

Vitamin B12 and folic acid are essential for numerous physiological functions, including neuron function, neurotransmitter regulation, and DNA synthesis. These processes are crucial to the development of movement disorders, such as BEB, and various neurological and neuromuscular problems have been linked to deficits in these vitamins (10).

Calcium (Ca) is an essential component in signal transmission across the neuronal membrane and nerve terminal, and it also participates in several cellular processes, including apoptosis. The discharge of Ca from the sarcoplasmic reticulum is vital for muscle contraction (11). Vitamin D regulates the absorption of Ca and phosphate (P). Hypophosphatemia and Vitamin D insufficiency are both linked to muscle weakness (12). Magnesium (Mg) is vital in numerous metabolic processes due to its involvement in various enzymes. On the contrary, Mg serves as a physiologic Ca channel blocker (13). A notable correlation between serum Mg levels and muscle strength has been documented (14).

Synaptic zinc (Zn) is essential for neuronal transmission, significantly contributing to neurogenesis, cognition, memory, and learning. Recent studies indicate that the disruption of Zn homeostasis is related to several central nervous system diseases (15).

This study aims to compare the serum levels of Vitamin B12, folic acid, 25-OH Vitamin D, Ca, Mg, P, and Zn in patients with BEB to those of healthy individuals and to determine the relationship between these micronutrient levels and the intensity and frequency of BEB symptoms, as evaluated using validated clinical rating scales.

Methods

This retrospective case–control study included 20 BEB patients (13 females and 7 males) who were followed up and treated periodically with botulinum toxin injections for BEB in the department of oculoplastic surgery and 25 age- and gender-matched healthy individuals (15 females and 10 males). The study was conducted in the ophthalmology department of the Haseki Training and Research Hospital, from October 2023, to December 2023. Demographic data, clinical characteristics, and medical history were obtained from the medical records of all participants. We conducted complete neurological exams on all the patients to rule out any underlying neurological conditions. Both patients and controls using supplements, including Vitamin B12, folic acid, Ca, phosphorus (P), Mg, Vitamin D, and Zn, and patients with a history of thyroid and parathyroid surgery were not involved in the study. The blood tests were conducted within 3 months before the ophthalmological examination.

In our laboratory, the normal ranges of serum concentration were between 8.6 and 10.0 mg/dL for Ca, 1.6 and 2.6 mg/dL for Mg, 2.5 and 4.5 mg/dL for P, 15 and 55.5 ng/mL for 25-OH Vitamin D, 197 and 771 ng/L for Vitamin B12, 3.89 and 26.8 g/L for folic acid, and 70 and 114 g/dL for Zn.

The severity and frequency of BEB were evaluated using the Jankovic Rating Scale (JRS), which assigns scores ranging from 0 to 4 (16).

The study was carried out in compliance with the principles stated in the Declaration of Helsinki and obtained clearance from the local ethics committee (173–2023). Informed consent was obtained from all participants before data collection.

Statistical analysis was conducted utilizing the Statistical Package for the Social Sciences version 25. Descriptive statistics involving means and standard deviations were determined for continuous variables. Group comparisons between essential blepharospasm patients and controls were performed using independent t-tests for continuous variables and Chi-square tests for categorical variables. A P-value below 0.05 was deemed statistically significant.

Results

The demographic properties of 20 BEB patients and 25 age- and gender-matched control cases are given in Table 1. The range of age was 44 to 87 for the BEB group and 45 to 84 for the control group. Table 2 summarizes the results of serum Vitamin B12, folic acid, Ca, P, Mg, 25-OH Vitamin D, and Zn concentrations. Serum Vitamin B12, folic acid, Ca, P, Mg, and Zn levels were within normal limits, while 25-OH Vitamin D levels were below normal limits in both groups. There was no significant difference between the BEB and control groups regarding the seeked parameters except for the mean serum folic acid level, which is significantly lower in the BEB group (p=0.011) (Fig. 1).

Table 1. Demographic properties of study participants

	BEB (n=20)	Control (n=25)	p
Sex (F/M)	13/7	15/10	0.487
Age	59.75±9.80	62.04±9.19	0.204

BEB: Benign essential blepharospasm; F: Female; M: Male.

Table 2. Laboratory data of study participants

	BEB (n=20)	Control (n=25)	p
Vitamin B12	363.10±188.56	336.16±170.95	0.698
25-hydroxy (OH)-Vitamin D	13.72±7.52	11.68±5.51	0.560
Folic acid	6.19±2.75	8.95±4.10	0.011
Zinc	83.15±17.41	81.66±16.01	0.854
Calcium	9.54±0.37	9.36±0.45	0.181
Phosphorus	3.42±0.72	3.50±0.49	0.499
Magnesium	1.94±0.19	2.01±0.16	0.232

BEB: Benign essential blepharospasm.

Clinical assessments were conducted to evaluate the severity of blepharospasm symptoms in the patient group in conjunction with serum vitamin measurements. The mean JRS severity and frequency scores were 2.6±0.5 and 2.1±0.4, respectively, for the BEB patients. Serum folic acid levels were negatively correlated with both Jankovic severity and frequency scores (Table 3).

Discussion

The findings of this study revealed that the levels of evaluated micronutrients were within normal limits for both the BEB and control groups except 25-OH Vitamin D. While serum folic acid levels were within laboratory normal limits in both groups, BEB patients had significantly lower folic acid levels compared to controls, and there was a negative correlation between the Jankovic severity and frequency score and folic acid levels. This observation suggests there may be a link between folic acid levels and BEB.

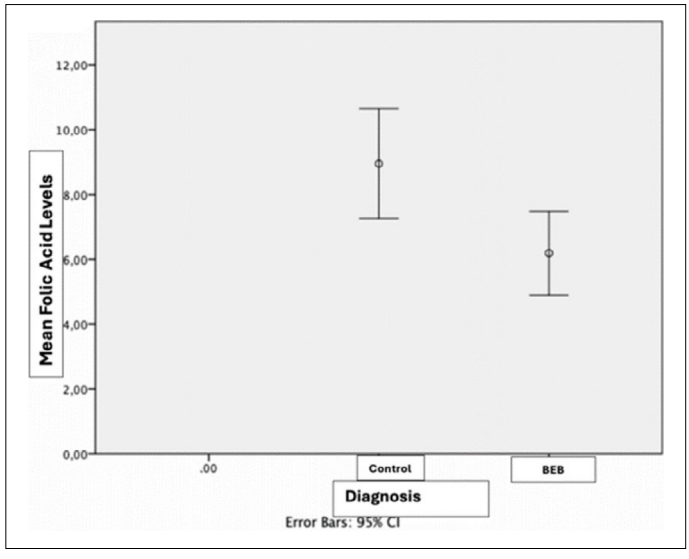

Figure 1. The mean folic acid levels of the benign essential blepharospasm and control groups.

Table 3. The correlation of serum Vitamin B12, 25-OH Vitamin D, and folic acid levels with Jankovic severity and frequency scores

	JSS		JFS	
	r	p	r	p
Vitamin B12	0.050	0.745	0.079	0.606
25-hydroxy (OH)-Vitamin D	0.164	0.282	0.199	0.191
Folic acid	-0.378	0.011	-0.392	0.008

JSS: Jankovic Severity Score; JFS: Jankovic Frequency Score.

BEB is characterized by involuntary contractions of the orbicularis oculi muscles and frequently other protractor muscles. In severe cases, it leads to functional blindness (5). The annual incidence is estimated at approximately 0.1/1,000 individuals, and although it is infrequent, the disease has a significant impact on quality of life (3). The precise etiology of BEB remains unclear. The primary form of BEB typically has a gradual onset and is more common in middle-aged females. In contrast, secondary BEB is linked to lesions in the basal ganglia, brainstem, and thalamus. One of the characteristic features of BEB is focal dystonia, which is characterized by disproportionate muscle contractions that may be isolated or generalized. This neurological movement disorder is associated with repetitive movements, forceful contractions, and, in some cases, painful abnormal postures. Dysfunctions in basal ganglia and cerebellar circuits, as well as disturbances in mitochondrial function, dopamine signaling, and Ca homeostasis, play a role in the pathogenesis of dystonia, including BEB (17,18).

Ca, Mg, P, and Vitamin D are essential for neuromuscular function, significantly involving muscle contraction and neurotransmission. Ca modulates the interaction between excitation and contraction, neurotransmitter release, and muscle contraction by sarcoplasmic reticulum signaling. In contrast, Mg modulates Ca channels, stabilizes neuronal excitability, and facilitates ATP metabolism, which energizes muscular activity. P, an essential element of ATP and creatine P, supports energy-dependent muscular functions, and Vitamin D regulates Ca-P homeostasis by improving intestinal absorption and supporting bone and muscle health (19). Previous studies have highlighted the potential significance of these micronutrients in movement disorders. For instance, Serefoglu Cabuk et al. (7) indicated markedly reduced serum Ca levels in BEB patients compared to controls, suggesting a possible correlation between Ca deficit and dystonic activity. Nevertheless, they did not observe significant differences in Mg, P, or 25-OH Vitamin D levels among the groups. Eroğul et al., (8) observed lower Ca and 25-OH Vitamin D levels in BEB patients in comparison with controls, despite noting

the need for further prospective studies to understand these correlations better. Pratty et al. (20) examined the correlation between acute dystonic reactions and serum Ca levels in patients with acute psychosis. They concluded that no association was seen between acute dystonia and serum Ca. The widespread Vitamin D deficiency observed in both groups may be attributed to factors, such as limited sun exposure, dietary habits, or lifestyle common in our population.

Ca channel dysfunctions and intracellular Ca signaling abnormalities have been linked to dystonia, reflecting disturbances in basal ganglia and cerebellar circuits (17). Mg's function as a Ca antagonist may additionally affect dystonic activity by modulating synaptic transmission and muscle excitability (14). While the present study did not reveal significant variations in serum Ca, Mg, P, and 25-OH Vitamin D levels, localized deficiencies or imbalances in neuronal tissue may still contribute to dystonic mechanisms. This underscores the necessity for advanced imaging and cerebrospinal fluid studies to investigate micronutrient balance in BEB patients. Further research addressing intracellular Ca and Mg modulation, along with the role of Vitamin D in neuromuscular stability, can clarify their contributions to BEB.

Zn is an essential trace element that plays a pivotal role in many neurological functions, including neurotransmitter synthesis, modulation of synaptic activity, and protection of neuronal structure (21). Zn is known for its interaction with glutamatergic and GABAergic systems, which is crucial for motor control. Changes in Zn levels can disturb the excitatory-inhibitory balance in neural circuits, thereby playing a role in the pathophysiology of dystonic movements (15). In addition, Zn's antioxidant properties reduce oxidative stress, a factor that leads to neuronal dysfunction. In the literature, some studies revealed that Zn deficiency and also accumulation may lead to neurotoxicity and neuronal cell death, both resulting in neurological disorders (21,22). However, to the best of our knowledge, this is the first study that evaluated the serum Zn levels in BEB patients.

Vitamin B12 deficiency has been associated with multiple neurological diseases, such as peripheral neuropathy, myelopathy, and dystonia. The role of Vitamin B12 in dystonic mechanisms is mainly related to its function in lowering homocysteine levels, a neurotoxic molecule that may affect dopamine metabolism, provoke oxidative stress and lead to mitochondrial malfunction (6). Obeid et al. (6) emphasized the contribution of hyperhomocysteinemia, resulting from B12 deficiency, increased oxidative damage, and neuroinflammation, both of which may exacerbate dystonic symptoms (6). Our study found no significant differences in serum B12 levels between BEB patients and controls, indicating that overt systemic B12 insufficiency may not be a primary factor in BEB. Erogul et al. (8) noted markedly reduced B12 levels in BEB patients compared with controls (8). However, since serum 25-OH Vitamin D and Ca levels were also lower in BEB patients, it is difficult to tell which of these components is specifically linked to the disease.

In our study, folic acid levels in BEB patients were found to be significantly lower than in controls, and this finding suggests a potential role in the pathophysiology of the disease. As discussed previously, Vitamin B12 affects homocysteine metabolism by facilitating its remethylation with methionine. Folic acid acts as a critical cofactor in this process, contributing to methylation reactions that are essential for DNA synthesis, neurotransmitter regulation, and myelin maintenance. Folic acid deficiencies can lead to elevated homocysteine levels, which are associated with neurotoxicity through oxidative stress, endothelial dysfunction, and excitotoxicity, all of which may contribute to the neuronal damage and abnormal neuromuscular activity observed in dystonia. High homocysteine levels resulting from folic acid or B12 deficiencies may disrupt dopamine metabolism and basal ganglia function, potentially exacerbating dystonic symptoms (6). Specifically, in patients with BEB, abnormalities in neurotransmitter balance, Ca signaling, and oxidative stress pathways have been suggested as contributing factors. Folic acid deficiency may increase susceptibility to BEB by exacerbating these underlying dysfunctions. The clinical assessment of BEB severity using the JRS revealed a spectrum of symptom severity among patients. This variability underscores the heterogeneous nature of essential blepharospasm, where some individuals experience milder symptoms while others experience more debilitating manifestations. The negative correlation between folic acid levels and BEB severity and frequency warrants further investigation to determine whether lower folic acid concentrations are associated with more severe blepharospasm symptoms.

Although our study provides important information, it has limitations, such as the retrospective methodology, the small sample size, and the limited age range of participants. Further research with a prospective study design and larger study groups should comprehensively examine the processes by which folic acid affects blepharospasm and evaluate the potential of supplementation as a treatment option.

Conclusion

The study indicated that serum levels of Vitamin B12, folic acid, Ca, P, Mg, and Zn were normal in both BEB patients and control subjects. In contrast, Vitamin D levels were subnormal in both groups. While our findings highlight the potential importance of folic acid in BEB, isolating its specific role remains challenging, as Vitamin B12, Vitamin D, and Ca deficiencies have also been observed in BEB patients. Future research should aim to directly assess homocysteine levels,

along with the combined effects of Vitamin B12 and folic acid supplementation, to understand their contributions to BEB better. Investigation of methylation patterns, oxidative stress markers, and cerebrospinal fluid metabolite profiles may further clarify the relevant molecular pathways and identify therapeutic targets for intervention.

Disclosures

Ethics Committee Approval: This study was approved by the Haseki Training and Research Ethics Committee (Date: 04.10.2023 Number: 173–2023) and conducted in accordance with the tenets of the Declaration of Helsinki

Informed Consent: Informed consent was obtained from all patients.

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Original Article

Exploring Health Tourism and Corneal Refractive Surgery: Insights From a Single Referral Center

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Abstract

Objectives: The purpose of this study was to compare the characteristics, clinical outcomes, and complications of health tourism patients who underwent corneal refractive surgery with the local patient group.

Methods: This retrospective study analyzed the medical records of 736 health tourism patients and 853 local patients who presented for corneal refractive surgery. Patient demographics, type of laser procedure, visual and refractive outcomes, complications, and follow-up period were recorded.

Results: The mean ages of health tourism patients and local patients were 27.1±5.9 and 26.3±5.3 (p=0.216), respectively. The percentage of patients who underwent surgery was significantly higher among health tourism patients (91.0%) compared to local patients (78.2%) (p<0.01). There were no significant differences in uncorrected distance visual acuity, corrected distance visual acuity, or spherical equivalent at the 3-month post-operative examination. The median follow-up period for health tourism patients was 1 (1–360) day, while for local patients, it was 360 (30–1080) days (p<0.001). The percentage of patients who received laser-assisted *in situ* keratomileusis surgery was significantly higher in the health tourism group (89.9% vs. 82.0%, p<0.001). There were no significant differences in perioperative or early post-operative complications.

Conclusion: Health tourism patients were more likely to have undergone surgery and had a significantly shorter follow-up period. This may particularly affect the follow-up of the long-term complications.

Keywords: Complications, Corneal refractive surgery, Health tourism, Laser *in situ* keratomileusis, Photorefractive keratectomy

Introduction

Health tourism involves deliberate travel to another country for specialized medical care. Motivations for seeking medical treatment abroad are numerous, ranging from financial considerations, such as seeking more affordable treatment, to accessing care that is unavailable in their own country. Evidence regarding risk is often limited and speculative, providing little guidance for decision-making. The reporting can be biased and sensationalist, often produced by individuals with insufficient expertise in such procedures. In addition, concerns arise about the reliability of complication reporting due to the heavy investment in advertising and the association with financial gain.

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Refractive surgery is a widely performed eye procedure throughout the world (1-4). Laser refractive surgery has been shown to have excellent visual outcomes and safety profiles, supported by extensive scientific evidence over the past several decades (5). The impact of refractive surgery on patients goes beyond achieving freedom from glasses. The procedure has been shown to enhance quality of life, work productivity, and daily performance (6).

Studies have published the outcomes of health tourism, particularly in the fields of cosmetic and transplantation surgery (7-10). Health tourism has seen substantial growth in recent years, particularly in Türkiye, with a notable increase in ophthalmic surgical procedures (11,12). Interventions such as refractive surgery, cataract extraction, and corneal transplantation are performed with a high level of surgical expertise. However, the scientific data supporting the long-term outcomes of these procedures remain limited. Due to the relatively short follow-up durations commonly associated with health tourism patients, the potential for post-operative complications cannot be overlooked. This study aims to describe the patient demographics, clinical outcomes, and complications of corneal refractive surgery in health tourism patients at a single referral center and compare them with the local patient group.

Methods

This retrospective study included all patients who were seeking corneal refractive surgery and admitted to Medical Park Florya Hospital between July 2020 and January 2024. The study adhered to the tenets of the Declaration of Helsinki and was approved by the Aydın University Ethics Committee (46-2024) and hospital management. Written informed consent was obtained from the patients. Pre-operative inclusion criteria were age >20 years, myopia and spherical equivalent <−8.00D, astigmatism <−4.00D, hyperopia <+4.00D, minimum residual stromal thickness of 300 microns, <40% tissue altered, and at least 1 year of stable refraction. Exclusion criteria were <480 microns central corneal thickness, suspicious corneal tomography, clinical or subclinical keratoconus, severe ocular surface disease, glaucoma, and cataract.

The patients were divided into two groups: Health tourism and local patients. Health tourism patients are defined as individuals residing outside of Türkiye who travel to the country specifically to receive medical care. Patient demographics, type of surgery, visual and refractive outcomes, follow-up time, and complications were obtained through chart review. The surgeries were performed by the same surgeon, and all patients received either wave front optimized transepithelial photorefractive keratectomy (PRK) with mitomycin C or femtosecond laser-assisted *in situ* keratomileusis (LASIK). The excimer laser utilized in all procedures was the WaveLight EX500 (Alcon Laboratories, Fort Worth, TX, USA) while the femtosecond laser was the IntraLase (Abbott Medical Optics Inc., Santa Ana, California). A bandage contact lens was placed in all procedures, followed by topical ophthalmic antibiotic drops. Postoperatively, all patients received topical moxifloxacin 0.5% eyedrops (Vigamox, Alcon Laboratories, Fort Worth, TX, USA.) 4 times daily for 1 week. Loteprednol etabonate 0.5% eyedrops (Lotemax, Bausch and Lomb, Rochester, NY, USA) were administered 4 times daily and tapered over 4 weeks in all LASIK procedures. They were also used 4 times daily for 1 month in all PRK procedures, with tapering over a further 4 weeks. In addition, all patients were instructed to use preservative-free artificial tears at least 4 times daily for a minimum of 6 months. All patients were advised to have post-operative follow-up visits at day 1 (LASIK) or 3 (PRK), month 1, month 3, month 6, month 12, and then annually.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences version 22.0 for Windows (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean and standard deviation, or median and range. The normality of the data was assessed using the Shapiro-Wilk test. Student's t-test and Mann–Whitney U-test were used to compare continuous variables, while Chi-square test was used for categorical variables. Statistical significance was considered for $p<0.05$.

Results

The records of 1589 patients were reviewed, of whom 1304 underwent corneal refractive surgery. The health tourism group consisted of 736 (46.3%) patients, while the local group had 853 (53.7%) patients. Figure 1 shows the geo-

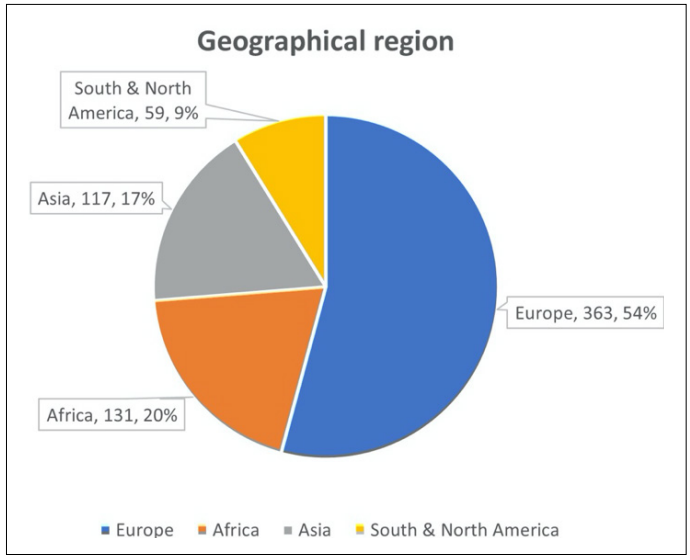

Figure 1. The distribution of patients undergoing corneal refractive surgery for health tourism purposes is categorized by geographical region.

graphic distribution of patients who underwent corneal refractive surgery as part of health tourism. The majority of patients in Europe were from Germany (78.2%), while in Asia, the majority were from the Arabian Peninsula (76.1%). The demographics and characteristics of the patients are shown in Table 1. The surgery rate was 91.0% for health tourism patients and 78.2% for local patients (p<0.01). There were no significant differences between the two groups in terms of gender, age, or laterality. The rate of LASIK surgery was significantly higher in the medical tourism group (89.9% vs. 82%, p<0.001). At post-operative month 3, there were no significant differences in uncorrected distance visual acuity (0.01±0.03 vs. 0.02±0.04 LogMAR, p=0.316), corrected distance visual acuity (−0.01±0.03 vs. 0.01±0.05 LogMAR, p=0.658), and standard error (−0.10±0.33 vs. −0.16±0.41 Diopters, p=0.231) between health tourism and local patients, respectively. The follow-up period for the health tourism group was significantly shorter, with a median of 1 (1–360) day, compared to the local patients who had a median follow-up period of 360 (30–1080) days (p<0.001). Table 2 shows the compliance rates of patients with post-operative examinations. Following the initial post-operative examination, local patients demonstrated significantly higher compliance rates than health tourism patients (p<0.001 for all visits).

In terms of complications, 3 patients (0.4%) in the health tourism group and 5 patients (0.8%) in the local group (p=0.43) had to switch to the PRK technique due to suction problems during the operation. On the 1st day after the operation, 6 patients (0.9%) in the health tourism group (four with flap striae and two with diffuse lamellar keratitis) and 2 patients (0.3%) in the local group (due to flap striae) underwent flap re-lifting and interface irrigation (p=0.18). Post-LASIK ectasia was detected in one patient (0.2%) in the local group and corneal collagen crosslinking was performed. Eight patients (1.2%) in the health tourism group and 14 patients (2.2%) in the local group (p=0.15) underwent enhancement for the residual refractive error after a waiting period of 3 months.

Discussion

Refractive surgery is a frequently performed procedure in health tourism due to high patient satisfaction and perceived low complication rates (13,14). However, it is crucial to communicate post-operative care and management decisions effectively to all patients undergoing these procedures, as most will be leaving the country soon after surgery. Hospitals and intermediary companies have an obligation to provide timely and appropriate treatment for any complications that may arise, although the patient is a tourist.

According to a published article on health tourism in Türkiye, the majority of patients seek ophthalmologic care, with refractive and cataract surgeries being the most commonly performed procedures (12). Most of these treatments are provided in private hospitals, and Istanbul has been identi-

Table 1. Demographics and characteristics of the patients

	Total (n=1589)	Health tourism (n=736)	Local (n=853)	p
Patients who underwent CRS (%)	1304/1589 (82.1)	670/736 (91.0)	634/853 (74.3)	<0.001
Type of surgery (LASIK, %)	1122/1304 (86.0)	602/670 (89.9)	520/634 (82.0)	<0.001
Age (years) (mean±SD)	26.7±5.4	27.1±5.9	26.3±5.3	0.216
Gender (Female, %)	789/1304 (60.5)	391/670 (58.4)	398/634 (62.8)	0.103
Laterality (Unilaterally, %)	43/1304 (3.3)	25/670 (3.7)	18/634 (2.8)	0.367
Follow-up (days) (median [min-max])	30 (1–1080)	1 (1–360)	360 (30–1080)	<0.001

P-values were calculated using Student's t-test, Mann–Whitney U-test, and Chi-squared test. CRS: Corneal refractive surgery, LASIK: Laser-assisted in situ keratomileusis.

Table 2. Compliance rates of patients with post-operative examinations

	Day 1 or 3	Month 1	Month 3	Month 6	Month 12
Health tourism patients (%)	670/670 (100)	246/670 (36.7)	102/670 (15.2)	27/670 (4.0)	25/670 (3.7)
Local patients (%)	634/634 (100)	593/634 (93.5)	536/634 (84.5)	521/634 (82.4)	497/634 (78.4)
P-values	1	<0.001	<0.001	<0.001	<0.001

P-values were calculated using Chi-squared test.

fied as the leading destination for health tourists in this contex t(12). A separate study has identified Türkiye as a prominent destination for health tourism, particularly in ophthalmology (15). The impetus for this trend is attributable to several factors, including its strategic geographic location, cost-effectiveness, perceived safety, and accessible transportation infrastructure (15). Furthermore, government-supported investments have contributed to the strengthening of Türkiye's competitive position in the global health tourism market (15).

In our study, we found that the indication rates for corneal refractive surgery were significantly higher in health tourism patients (91% vs. 78.2%, p<0.001). There appear to be two primary reasons for this. First, some health tourism patients are excluded before arrival due to reports of refractive error and/or corneal topography from their home country. Second, as health tourism patients are often highly motivated to undergo medical procedures and may travel to other countries to do so, it is possible that they may be more willing to take risks even after being informed of the potential dangers. These factors are believed to increase surgery rates. Furthermore, on reviewing the surgical technique rates, we see that the LASIK rate is significantly higher in the health tourism group (89.9% vs. 82%, p<0.001). It is well known that LASIK surgery is more advantageous than PRK in terms of patient comfort and early visual rehabilitation (16). Therefore, LASIK may be a suitable option for health tourism patients seeking both medical treatment and comfort while travelling, unless absolutely contraindicated. In addition, as previously stated, these patients may have a higher likelihood of considering the relative risks of LASIK.

One of the significant issues related to health tourism is the relatively short follow-up time. In our study, the local patients had a median follow-up time that was significantly longer than that of the health tourism patients. Most health tourism patients returned to their home countries after the first post-operative visit and naturally had lower compliance with the post-operative follow-up schedule than local patients (Table 2). This poses a significant challenge for health tourism patients, particularly in detecting long-term complications of corneal refractive surgery. We found no significant difference in peroperative and early post-operative complications between the two groups. Post-LASIK ectasia was observed in one patient in the local group and in none of the patients in the health tourism group. This could be a source of confusion, as post-LASIK ectasia may have been underdiagnosed in health tourism patients who did not adhere to the follow-up schedule. As is known, post-LASIK ectasia can be identified through corneal tomography during routine follow-up, even in the absence of clinical signs. Therefore, it is possible that ectasia in health tourism patients is underdiagnosed due to the short follow-up period.

Comparing enhancement rates between groups, they appear to be slightly lower in the health tourism group, although not significantly. Due to time constraints, most patients in the health tourism group are unable to have a preoperative cycloplegic refraction. Therefore, in the theory, they may be more likely to be overcorrected than the local patient group, resulting in a lower undercorrection rate and a lower enhancement rate. Furthermore, although all health tourism patients are able to communicate with the surgeon in the post-operative period even if they are not examined, some residual refractive errors may still be underdiagnosed.

To the best of our knowledge, this is the first study that compares and reports outcomes of health tourism for corneal refractive surgery. However, the study has potential limitations. First, the long-term complications of the procedures in health tourism patients are unknown, as many patients return to their home country early. As lenticule extraction surgery was not performed at the clinic where the study was conducted, there are no available data on this procedure.

Conclusion

Health tourism patients were found to have a higher rate of undergoing corneal refractive surgery, likely due to their higher motivation, despite being informed of all associated risks. However, it is important to bear in mind that there are various complications that can occur in such cases and that the post-operative follow-up period is limited. To address this issue, hospitals specializing in health tourism should obtain certification and establish agreements with clinics in patients' home countries to provide follow-up care before their arrival in the destination country. We believe that improving the conditions for health tourism patients will help to reduce the disparities between them and local patients.

Disclosures

Ethics Committee Approval: This study was approved by the Aydın University Ethics Committee (Date:05.06.2024, Number: 46-2024) and conducted in accordance with the tenets of the Declaration of Helsinki.

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Original Article

Comparison of the Depth of the Stromal Demarcation Line and Clinical Outcomes in Corneal Crosslinking Treatment with Hydroxypropyl Methylcellulose-Based and Vitamin E-TPGS-Based Riboflavin Solutions

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Abstract

Objectives: This study aims to compare the visual and topographic results and the depth of demarcation line in patients who underwent epithelial-off-cross-linking (CXL) with riboflavin solutions containing D alpha-tocopheryl polyethyleneglycol 1000 succinate (Vitamin E-TPGS) and 1.1% hydroxypropyl methylcellulose (HPMC).

Methods: Patients with progressive keratoconus, 26 treated with HPMC (Group 1) and 34 treated with Vitamin E-TPGS (Group 2), were evaluated retrospectively. Best corrected visual acuity, spherical equivalent, refractive cylinder, and corneal topography parameters (keratometry of flat and steep meridians (K1 and K2), maximum keratometry (Kmax), central, thinnest, and apical corneal thickness) at baseline and post-operative follow-up visits were compared (1, 3, 6, and 12 months). Corneal stromal demarcation line depth (DLD) was measured centrally, nasally, and temporally (1.5 mm and 3 mm distance from the center of the cornea) by anterior segment optical coherence tomography at 1 month post-operatively, and changes in endothelial cell density (ECD) at 6 months were compared between the two groups.

Results: There was no difference between the two groups in terms of age and gender. The mean DLD was deeper in group 1 (325.95±76.55 μm) than in group 2 (267.94±54.2 μm) (p=0.002). In the 3rd month, K1, K2, and Kmax changes, while a decrease was observed in Group 1 compared to the baseline; an increase was observed in Group 2 (all p<0.05). At the end of the 1 year, K1, K2, and Kmax were decreased in both groups. There was no difference in ECD change between baseline and 6 months in both riboflavin solutions (p=0.12).

Conclusion: HPMC-based riboflavin appears to be associated with a deeper demarcation line than Vitamin E-TPGS-based riboflavin. While a decrease in K values was observed in the earlier period in HPMC, no difference was observed between Vitamin E-TPGS and HPMC at the 12th month in terms of efficacy. Both riboflavin solutions were safe for the endothelium.

Keywords: Crosslinking, demarcation line, keratoconus, vitamin E TPGS-based riboflavin

Introduction

Keratoconus is usually chronic and progressive cornea thinning and steepening due to the stroma's biomechanical instability. It is manifested by irregular astigmatism and decreased visual acuity (1). It usually begins in the 2nd and 3rd decades of life. Corneal involvement often has a bilateral and asymmetrical clinical manifestation (2). Corneal cross-linking (CXL) treatment was effective in arresting progression in the

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early stages of the disease in an animal experimental study conducted in 1997 (3). CXL treatment, which increases the biomechanical and biochemical stiffness of the cornea, was first applied to human patients in 2003 (4). The conventional CXL technique (CCXL), also known as the Dresden protocol, is applied with ultraviolet-A (UVA) irradiation (370 nm light at 3 mW/cm^2) for 30 min after epithelial peeling and instillation of 0.1% riboflavin in 20% dextran solution (vitamin B2). The UV ray diameter is 7 mm, and the total energy applied is 5.4 J/cm^2 (5). After demonstrating the effectiveness of the Dresden protocol, various techniques were developed to increase the safety and effectiveness of CXL and shorten the treatment time, such as accelerated and customized technics. The accelerated CXL (ACXL) method, which transmits high UVA radiation in a shorter time, the transepithelial epi-on CXL method applied with chemical enhancers, and the iontophoresis CXL method, in which the penetration of the riboflavin solution is increased by using a small electric current, are examples of commonly used methods (6).

A wide variety of riboflavin formulations are currently available on the market. They contain additional components designed to increase the riboflavin penetration into the stroma (6). The osmolarity of riboflavin solutions affects the corneal thickness and is the reason for preference in achieving safe corneal thickness. In recent years, riboflavin solutions containing D alpha-tocopheryl polyethylene-glycol 1000 succinate (Vitamin E-TPGS) based riboflavin has been used in the market. It has been shown that Vitamin E-TPGS increases riboflavin permeability and also provides photoprotection against free radicals formed during photo-induced processes (7).

UVA light energy is known to be effective in corneal regions where riboflavin is absorbed. The cross-linking effect was more effective in the anterior half of the stroma due to the reduction in UVA radiation throughout the depth of the corneal stroma (8). It is said that changes in riboflavin application time and concentration have little effect on the depth of corneal stromal penetration (9). Seiler et al. (10) suggested the demarcation line as an indicator of the depth and efficacy of CXL treatment. Some studies state that the effectiveness of CXL is related to the depth of the demarcation line (11,12). Different results were observed when the demarcation line depths (DLDs) formed with different CXL protocols were compared (12-15).

In this study, we aimed to compare the visual and topographic results, DLD, and endothelial cell density (ECD) after epi-off ACXL with riboflavin solutions containing Vitamin E-TPGS and 1.1% hydroxypropyl methylcellulose (HPMC).

Methods

This retrospective study was conducted in a tertiary hospital's Cornea unit of the Ophthalmology department. Patients who received CXL treatment for progressive keratoconus between January 2020 and January 2022 were included in the study. The hospital ethics committee approved the study (2011-KAEK-25 2022/06-15), and the authors adhered to the principles of the Declaration of Helsinki in all protocols. Corneal topographic (Sirius Topography, CSO, Florence, Italy) data, together with the presence of irregular myopic astigmatism and biomicroscopic examination findings (central or paracentral steepening, Fleischer ring, apical scarring, and Vogt lines) were used for the diagnosis of keratoconus. Progressive keratoconus was defined by the presence of one of the following criteria within the past 1 year (16). An increase of more than 1.0 D in astigmatism, a decrease in corneal thickness of more than 25 microns, an increase of more than 1.0 D in the steepest corneal axis, and a decrease in visual acuity by one line on the Snellen chart. Patients with the following criteria were excluded from the study: The thinnest corneal thickness on topography is <370 microns, presence of corneal scar or opacity, history of infective keratitis, pregnancy or lactation period, presence of chronic, topical, and systemic drug use and presence of autoimmune and connective tissue disease. In addition, patients with a post-operative follow-up period of <1 year and patients with significant post-operative corneal haze were not included in the study.

A complete ophthalmologic examination, including best corrected visual acuity, spherical equivalent, cylindrical value, intraocular pressure, biomicroscopic, and fundoscopic examination of the patients included in the study, pre-operative, post-operative 1 month, 3 months, 6 months, and 12 months were recorded. Flat (K1), steep (K2), and maximum keratometry (Kmax) values and thinnest (TCT), apex (ACT), and central corneal (CCT) thickness values were recorded from the corneal topography parameters evaluated in all examinations of the patients. In addition, corneal ECD was recorded by specular microscopy (NSP-9900, NonconRobo, Konan, Japan) pre-operatively and 6 months post-operatively. One month after the CXL procedure, corneal crossline images obtained with the anterior segment module of Optovue optic coherence tomography (iVue; Optovue Inc., Fremont, CA, USA) were examined. The distance measured between the outer surface of the corneal epithelium and the hyperreflective line in the stroma using the caliper instrument of the device was defined as the DLD. DLD was measured from the cornea's center and the nasal and temporal regions at 1.5- and 3-mm distances from the center. The average DLD value of the five measured points was recorded. Figures 1 and 2 show DLD measurements on anterior segment optical coherence tomography (OCT) of both groups.

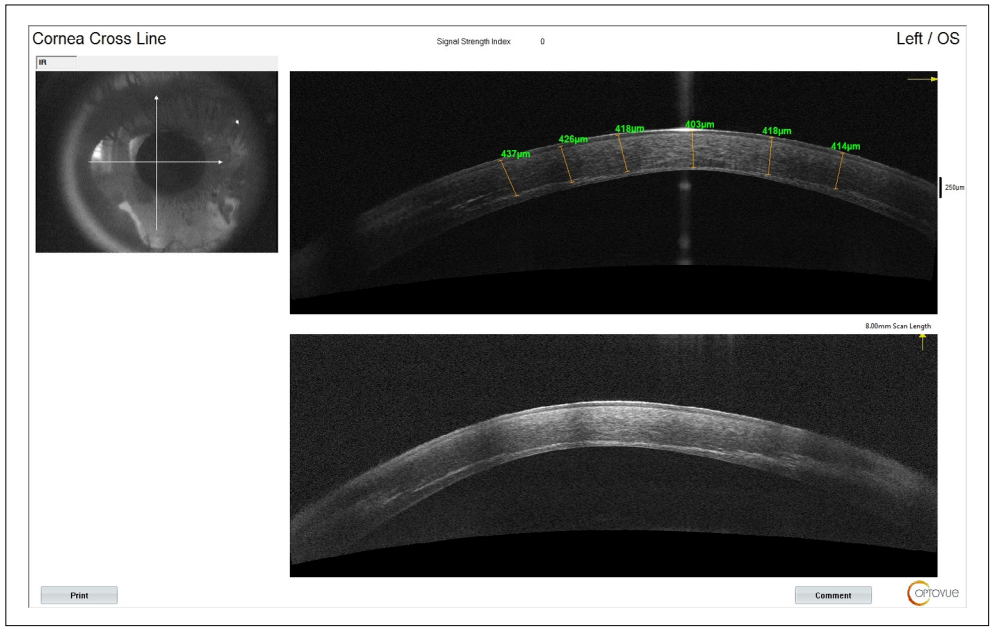

Figure 1. Demarcation line depth measurements of patients in the hydroxypropyl methylcellulose group at the 1st post-operative month.

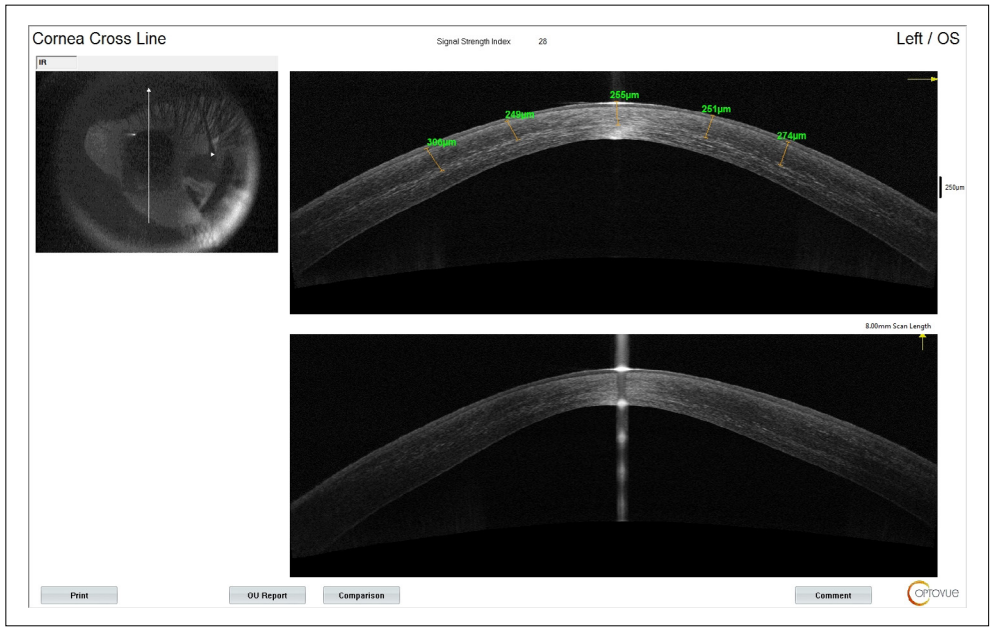

Figure 2. Demarcation line depth measurements of patients in the Vitamin E TPGS group at the 1st post-operative month.

In this retrospective study, patients who had CXL with two different riboflavin solutions available in the hospital pharmacy at different times were divided into two groups. There was no specific feature in choosing riboflavin for the patients. Group 1 consisted of patients treated with riboflavin with HPMC (MedioCROSS® M Avedro 0.1% riboflavin, HPMC 1.1%) and Group 2 with riboflavin with Vitamin E-TPGS (Ribofast® Iromed 0.1% riboflavin, Vitamin E-TPGS).

Pre-operative and post-operative changes in both groups' ophthalmological examination findings and corneal topographic data were compared. In addition, the changes in corneal ECD and DLD values were compared. The correlation between DLD and the change in post-operative values was evaluated.

Surgical Technique

After topical anesthetic drops, 10% diluted ethyl alcohol was applied to the corneal epithelial surface for 15 s with a

9 mm ring. The corneal epithelium was debrided. Patients treated with 1.1% HPMC and 0.1% isotonic riboflavin were instilled every 2 min for 30 min. A 0.1% isotonic riboflavin drop with Vitamin E-TPGS was instilled every 30 s for 15 min. The UVA device (Peschke trade CCL-Vario Cross-linking system, Switzerland) was adjusted to be at an appropriate distance from the eye, and the beam was focused on the corneal center. Nine mW/cm^2 of 370 nm UVA (total 5.4 j/cm^2) was applied to all cases for 10 min as ACXL.

After the cornea was rinsed with sterile saline, a drop of moxifloxacin hydrochloride (0.5%; Vigamox, Alcon Laboratories, Fort Worth, TX) was instilled, and a soft contact lens was inserted. As a post-operative treatment, topical antibiotics (0.5% moxifloxacin hydrochloride) and artificial tears were given to all patients 5 times a day on the 1st day. On the 2nd day, a topical steroid (0.1% dexamethasone) was added to the treatment. If the cornea was completely epithelialized on the 3rd or 4th day, the bandage contact lens was removed. After the 2nd week, only artificial tears and topical loteprednol drops were applied 3 times a day for 1 month. All patients were examined on the 1st day, 1st week, 1st, 3rd, 6th, and 12th months after the procedure.

Statistical Analysis

Power analysis was performed using the G*Power 3.1.9.6 program to calculate the sample size. When the effect size of the difference between the groups in terms of DLD measurement was determined as 0.479, with a power level of 80% and a significance level of 5%, the minimum number of patients to be included in the study in each group was determined as 26.

The data were examined by the Shapiro–Wilk test to determine whether or not it presents a normal distribution. The results were presented as mean±standard deviation, median (minimum–maximum), or frequency and percentage. Normally distributed data were compared with independent samples t-tests, and Mann-Whitney U tests were used for non-normally distributed data. Repeated measurements were compared between groups by calculating the difference (Change=last measure first measure) according to the baseline measurement. Categorical variables were compared using Pearson's Chi-square, Fisher's exact, and Fisher-Freeman-Halton tests between groups. The Pearson correlation coefficient was calculated for the relationship between variables. Statistically, the significance level was accepted as α=0.05. Statistical analyses were performed with the IBM Statistical Package for the Social Sciences (SPSS) version 28.0 (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp.).

Results

Sixty eyes of 60 progressive keratoconus patients, 24 females, and 36 males, were included in this study. The patients were divided into two groups according to the riboflavin solutions used during ACXL. Group 1 consisted of 26 patients treated with HPMC-based riboflavin solution, and Group 2 consisted of 34 patients treated with CXL with Vitamin E-TPGS-based riboflavin solution. There was no statistically significant difference between the two groups in the patient's demographic characteristics, pre-operative ophthalmological examination, and topographic parameters. Demographic data and pre-operative examination findings of the patients are summarized in Table 1. While the median Kmax value decreased by −0.03±1.52 D in Group 1 in the post-operative 3rd month, it increased by 1.18±1.62 D in Group 2. The difference is statistically significant (p=0.01). Mean Kmax changes at 1 year post-operatively were −0.45±1.33 D and −0.44±1.53 D in Group 1 and Group 2, respectively, and there was no difference between the two groups (p<0.05). Table 2 shows the changes in keratometry values from the baseline at the post-operative 1st, 3rd, 6th, and 12th months.

Mean DLD measurements were statistically higher (p=0.002) in the HPMC group compared to the HPMC and Vitamin E-TPGS groups (325.95±76.5 and 267.94±54.2 μm, respectively). The value of the DLD in all regions in the post-operative 1st month of both groups is shown in Table 3.

In the correlation analysis of DLD and keratometry values, there was a weak positive correlation between the DLD and the change in Kmax value at 6 months (r=0.371, p=0.009). No significant correlation was detected in all any of the other parameters shown in Table 4.

Discussion

The effectiveness and safety of the CCXL procedure have been proven in many studies since 2003. Riboflavin is absorbed by corneal tissue through drops applied every 2 min for 30 min. UVA radiation is irradiated at three mW/cm^2 for 30 min (5.4 J/cm^2 energy dose). Free oxygen radicals formed as a result of the interaction of riboflavin molecules absorbed in the tissue and UVA light rays strengthen corneal biomechanics by creating covalent bonds within and between collagen fibers. Over the years, different techniques have been tried to shorten the surgery time without reducing the effect of CXL. With the ACXL protocol, successful results can be achieved in strengthening the corneal tissue by exposing it to higher-intensity UVA in a shorter time (17,18). Shortening the surgery time may reduce corneal dehydration and cause fewer complications, such as infection. Riboflavin solutions containing Vitamin E TPGS have recently been commercially

Table 1. Comparison of demographic data and baseline findings of both groups

Parameters	Group 1 (HPMC) n=26	Group 2 (Vitamin E-TPGS) n=34	p*
Age (years), Mean±SD	23.37±7.13	23.97±6.79	0.739
Gender M:F	12:14	22:12	0.151
BCVA	0.51±0.27 (0.05–1.0)	0.51±0.27 (0.05–1.0)	0.747
SE (D)	−4.12±2.71 (−0.5–−11.0)	−4.64±2.7 (1.0–−13.0)	0.341
Cylinder (D)	−3.28±−2.29 (−0.27–−5.5)	−2.75±1.48 (−0.18–−5.5)	0.469
Kmax (D)	53.47±4.91 (46.59–64.20)	54.64±5.33 (44.84–75.53)	0.383
K1 (D)	45.04±2.25 (41.56–50.82)	44.98±2.91 (40.73–55.92)	0.727
K2 (D)	48.12±2.27 (43.99–52.12)	47.73±3.33 (43.25–58.90)	0.254
TCT	462.85±38.97 (383–546)	455±49.50 (369–567)	0.273
ACT	478.93±40.25 (391–565)	470.30±49.20 (370–579)	0.259
CCT	476.19±40.91 (400–569)	467.12±52.34 (371–576)	0.466
ECD	2563.64±339 (1721–2907)	2855±309.71 (2119–3401)	0.018

SD: Standard deviation; HPMC: Hydroxypropyl methylcellulose; Vitamin E-TPGS: D alphatocopheryl polyethylene-glycol 1000 succinate; M: Male; F: Female; BCVA: Best corrected visual acuity; SE: Spherical equivalent; Kmax: Maximum keratometry; K1: Flat keratometry; K2: Steep keratometry; TCT: Thinnest corneal thickness; ACT: Apical korneal thickness; CCT: Central corneal thickness; ECD: Endothelial cell density.

Table 2. Comparison of changes in Keratometric values in the 1st, 3rd, 6th, and 12th months post-operatively compared to the baseline

Variables	Group 1 (HPMC)		Group 2 (Vitamin E-TPGS)		p
	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	
Change in Kmax					
1 month	1.10±2.01	0.86 (-1.88-7.52)	1.26±1.83	1.48 (-3.15-4.8)	0.757
3 months	−0.03±1.52	−0.24 (−2.58–3.08)	1.18±1.62	1.15 (−1.54–5.75)	0.010
6 months	0.02±1.42	−0.19 (−2.48–2.89)	−0.33±1.99	−0.03 (−5.5–3.50)	0.492
12 months	−0.45±1.33	−0.59 (−3.83–2.26)	−0.44±1.53	−0.52 (−3.42–2.67)	0.973
Change in K1					
1 month	0.39±1.01	0.22 (−1.17–4.44)	0.41±0.68	0.45 (−0.91–2.57)	0.368
3 months	−0.26±0.48	−0.24 (−1.12–0.57)	0.18±0.59	0.29 (−1.04–2.20)	0.006
6 months	−0.21±0.62	−0.26 (−1.31–1.96)	−0.38±0.55	−0.41 (−1.68–0.33)	0.717
12 months	−0.61±0.52	−0.46 (−1.31–1.96)	0.60±0.91	−0.62 (−3.61–1.13)	0.831
Change in K2					
1 month	0.34±0.89	0.48 (−2.06–2.06)	0.79±0.91	0.77 (−0.71–4.12)	0.064
3 months	−0.20±0.62	−0.16 (−1.20–1.44)	0.22±0.78	0.18 (−1.26–3.07)	0.022
6 months	−0.26±0.71	−0.22 (−1.48–1.82)	−0.29±0.67	−0.21 (−2.02–0.65)	0.841
12 months	−0.58±0.82	−0.57 (−2.96–0.75)	−0.50±1.01	−0.48 (−3.47–1.96)	0.708

SD: Standard deviation, HPMC: Hydroxypropyl methylcellulose, Vitamin E-TPGS: D alphatocopheryl polyethylene-glycol 1000 succinate, BCVA: Best corrected visual acuity, Kmax: Maximum keratometry, K1: Flat keratometry, K2: Steep keratometry, TCT: Thinnest corneal thickness, ACT: Apical corneal thickness, CCT: Central corneal thickness.

Table 3. The values of the demarcation line depth in all regions in both groups at post-operative 1st month

	Group 1 (HPMC)	Group 2 (Vitamin E-TPGS)	p
DLD nasal 1	351.92±73.6	292.58±71.4	0.002
DLD nasal 2	336.29±85.6	270.81±58.6	0.002
DLD central	335.22±83.4	267.02±55.7	<0.001
DLD temporal 1	328.66±93.4	259.93±59.1	0.002
DLD temporal 2	322.58±89.4	260.48±67.7	0.004
DLD mean	325.95±76.5	267.94±54.2	0.002
Change in ECD 1 month	-115.25±297.12	-348.66±374.87	0.127

HPMC: Hydroxypropyl methylcellulose; Vitamin E-TPGS: D alphatocopheryl polyethylene-glycol 1000 succinate; DLD: Demarcation line depth; ECD: Endothelial cell density.

Table 4. Correlation between demarcation line depth and keratometry values of all patients

	DLD nasal		DLD central		DLD temporal	
	r	p	r	p	r	p
Change in Kmax 1 month	0.110	0.420	0.167	0.214	0.113	0.406
Change in Kmax 3 month	0.037	0.799	0.055	0.702	0.030	0.838
Change in Kmax 6 month	0.371	0.009	0.349	0.014	0.355	0.013
Change in Kmax 12 month	0.172	0.252	0.172	0.248	0.133	0.378
Change in K1 1 month	0.176	0.195	0.193	0.151	0.174	0.199
Change in K1 3 month	–0.046	0.754	–0.116	0.421	–0.106	0.469
Change in K1 6 month	0.042	0.776	0.067	0.649	0.113	0.443
Change in K1 12 month	0.164	0.277	0.081	0.590	0.147	0.330
Change in K2 1 month	–0.126	0.353	–0.098	0.467	–0.102	0.453
Change in K2 3 month	–0.026	0.858	–0.042	0.771	–0.057	0.695
Change in K2 6 month	0.163	0.268	0.263	0.068	0.311	0.031
Change in K2 12 month	0.165	0.273	0.161	0.281	0.189	0.208

DLD: Demarcation line depth; Kmax: Maximum keratometry; K1: Flat keratometry; K2: Steep keratometry.

available to increase riboflavin penetration into the cornea. The protocol for saturating Vitamin E TPGS-based solutions onto the cornea is to instill them every 30 s for 15 min. Vitamin E TPGS accelerates the stromal penetration of riboflavin, so shorter application times are sufficient, and the solution needs to be instilled at more frequent intervals due to its low osmolarity (19).

ACXL protocol using Vitamin E TPGS-based riboflavin solution significantly shortens the surgery time. A few studies in the literature compare the effectiveness of riboflavin solutions containing Vitamin E TPGS. In the study of Carusa et al., (19) which used Vitamin E TPGS-based riboflavin, the CCXL protocol was compared with a customized accelerated CXL (CFXL) protocol. No difference between the two protocols was detected in the biomechanical parameters, refractive, and topographic results of the cornea. In the CFXL group performed using the epi-on technique, the Kmax value decreased by −0.99±0.34 D at the 12th month compared to the baseline. In the present study, the Kmax value decreased by −0.44±1.53 D in the 12th month in the group that received epi-off ACXL with Vitamin E TPGS. Crosslinking performed with Vitamin E TPGS-based riboflavin solution also appears effective in halting keratoconus progression with epi-on and epi-off techniques. Rupano et al. (20) compared patients who underwent CCXL using HPMC and dextran-based riboflavin solutions. Kmax change in the HPMC group compared to the baseline values at 1st, 6th, and 12th months were found to be 3.32±4.89, −0.20±2.22, and −0.45±2.35 D, respectively. In

the present study, the change in Kmax values in the HPMC group from baseline to the 1st, 6th, and 12th months were found to be 1.10±2.01, 0.02±1.42, −0.45±1.33 D, respectively. The 12th-month results were similar, even though they were conducted with CCXL and ACXL methods.

In our study, when we compared the refractive and topographic results of the Vitamin E TPGS and HPMC groups after CXL, best corrected visual acuity (BCVA) was higher in the Vitamin E TPGS group in the 1st and 3rd months than in the HPMC group. However, the change in Kmax values in the 3rd month was significantly lower in the HPMC group (−0.03±1.52 D in the HPMC group vs. Vitamin E TPGS group 1.18±1.62 D, p=0.010). Considering the amount of change in the values in the 12th month, similar results were obtained as Kmax −0.45±1.33 D in the HPMC group and −0.44±1.53 D in the Vitamin E TPGS group (p=0.973). It can be said that CXL treatment with Vitamin E TPGS-based riboflavin solutions shortens the duration of surgery and is as effective as HPMC-based riboflavin solution, even if an increase in K values is observed without a decrease in BCVA in the early post-operative period.

The demarcation line detected after CXL represents the transition zone between anterior stromal keratocytes' apoptosis with UVA rays and unaffected keratocytes in the posterior stroma. Determination of the demarcation line is important in terms of maintaining endothelial safety, especially in eyes with thin corneas (21). In this study, the depth of demarcation line detected at the post-operative 1st month was 325.95±76.5 μm in the HPMC-based riboflavin group and 267.94±54.2 μm in the Vitamin E TPGS-based riboflavin group. Both riboflavin solutions were safe for the endothelium.

In the literature, different results have been shown in studies evaluating DLDs after ACXL and CCXL methods. Hagem et al. (22) found the DLD in the OCT evaluation as 296±54 μm in the CCXL group and 160±41 μm in the ACXL group. They did not detect any difference in Kmax and visual acuity values at the end of the 12th month. Brittingham et al. (23) said the ACXL protocol reduces the visibility and depth of the demarcation line and negatively affects topographic results. The DLD has been proposed as an objective marker to determine the effectiveness of treatment. Kyminious et al. (15) found DLD to be 350.78±49.34 μm in the CCXL group and 288.46±42.37 μm in the ACXL group (p=0.005). They argued that DLD could be an indicator of treatment effectiveness. Unlike the studies mentioned above, Spadeo et al. (24) found similar DLD values in ACXL and CCXL protocols.

In studies comparing HPMC and dextran-based riboflavin solutions, deeper DLD was found in corneas using HPMC riboflavin (25,26). Malhotra et al. (25) found the DLD to be 308.22±84.19 μm in the HPMC group and 235.33±64.87 μm in the dextran group. They thought that both riboflavin solutions were safe for the endothelium. In the study of Özek et al., (27) DDL was compared in CXL performed with hypotonic and dextran-free isotonic riboflavin. DLD was found to be 180.32±10.26 μm in the hypotonic riboflavin group and 287.21±15.01 μm in the isotonic riboflavin group (p<0.05). They conclude that the use of hypotonic riboflavin causes swelling of the cornea and causes more superficial DLD after CXL. Balıkçı et al. (28) evaluated pachymetry values before and after the instillation of Vitamin E TPGS and 1.1% HPMC-based riboflavin solutions to evaluate the increase in corneal stromal thickness during CXL. They argued that Vitamin E TPGS, used to increase the penetration of riboflavin into the corneal tissue during CXL treatment, significantly increases the corneal thickness compared to HPMC and creates a safer tissue thickness for UVA. In the present study, it was observed that a more superficial demarcation line was formed in epi-off CXL performed with Vitamin E TPGS-based riboflavin solution. Hypotonic riboflavin solutions swell the cornea and create a more superficial DLD. Vitamin E TPGS-based riboflavin solution applied with the epi-off method creates a more superficial DLD by swelling the corneal stroma, such as hypotonic riboflavin. Vitamin E TPGS-based riboflavin solution can be preferred more safely than HPMC in thin corneas because its treatment effectiveness is similar, the depth of the demarcation line is superficial, and the corneal thickness increases significantly during the procedure. The limitations of this study are its retrospective design, short-term follow-up, random selection of patients into groups, and small number of patients.

Conclusion

This study is the first in the literature to evaluate DLD in CXL performed with Vitamin E TPGS-based riboflavin. Both riboflavin solutions were observed to be effective in halting keratoconus progression and safe for endothelial cells in the 1st-year results. Similar clinical results were obtained with the Vitamin E TPGS-based riboflavin solution, although with a more superficial DLD. There is still no consensus in the literature as to whether DLD is an indicator of treatment effectiveness. Different results have been shown in studies. In this study, no significant relationship was found between DLD and treatment effectiveness. Long-term studies with a larger number of patients and a prospective design are needed for definitive evidence.

Disclosures

Ethics Committee Approval: This study was approved by the SBÜ Bursa Hospital Ethics Committee (Date: 06,15,2022, Number: 2011-KAEK-25) and conducted in accordance with the tenets of the Declaration of Helsinki.

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Original Article

Comparison of the Accuracy, Comprehensiveness, and Readability of ChatGPT, Google Gemini, and Microsoft Copilot on Dry Eye Disease

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Abstract

Objectives: This study compared the performance of ChatGPT, Google Gemini, and Microsoft Copilot in answering 25 questions about dry eye disease and evaluated comprehensiveness, accuracy, and readability metrics.

Methods: The artificial intelligence (AI) platforms answered 25 questions derived from the American Academy of Ophthalmology's Eye Health webpage. Three reviewers assigned comprehensiveness (0–5) and accuracy (−2 to 2) scores. Readability metrics included Flesch-Kincaid Grade Level, Flesch Reading Ease Score, sentence/word statistics, and total content measures. Responses were rated by three independent reviewers. Readability metrics were also calculated, and platforms were compared using Kruskal–Wallis and Friedman tests with *post hoc* analysis. Reviewer consistency was assessed using the intraclass correlation coefficient (ICC).

Results: Google Gemini demonstrated the highest comprehensiveness and accuracy scores, significantly outperforming Microsoft Copilot ($p<0.001$). ChatGPT produced the most sentences and words ($p<0.001$), while readability metrics showed no significant differences among models ($p>0.05$). Inter-observer reliability was highest for Google Gemini (ICC=0.701), followed by ChatGPT (ICC=0.578), with Microsoft Copilot showing the lowest agreement (ICC=0.495). These results indicate Google Gemini's superior performance and consistency, whereas Microsoft Copilot had the weakest overall performance.

Conclusion: Google Gemini excelled in content volume while maintaining high comprehensiveness and accuracy, outperforming ChatGPT and Microsoft Copilot in content generation. The platforms displayed comparable readability and linguistic complexity. These findings inform AI tool selection in health-related contexts, emphasizing Google Gemini's strengths in detailed responses. Its superior performance suggests potential utility in clinical and patient-facing applications requiring accurate and comprehensive content.

Keywords: Artificial intelligence, ChatGPT, dry eye disease, Google Gemini, Microsoft Copilot

Introduction

Dry eye disease (DED) is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles (1-4). The prevalence of DED varies widely, with estimates ranging from 5% to 50% of the adult

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population (2). The impact of DED is substantial, affecting millions worldwide and leading to discomfort, visual impairment, and a diminished quality of life (5). The variability in its presentation and the lack of a universally accepted diagnostic criterion further complicate its understanding and management (6).

The digital age has seen a surge in individuals turning to online resources for health information, and artificial intelligence (AI) chatbots have emerged as potential tools to provide readily accessible medical knowledge (7). However, the accuracy, comprehensiveness, and readability of the information provided by these AI platforms, especially for intricate medical conditions like DED, remain a critical concern. In addition to providing health information to patients, AI chatbots are increasingly integrated into medical education, supporting both undergraduate and postgraduate learners. These tools offer interactive learning experiences, assist in knowledge reinforcement, and serve as accessible resources for quick clinical reference, making them valuable for healthcare professionals and non-specialist users alike.

This study addresses this concern by evaluating the performance of three leading AI chatbots, ChatGPT, Google Gemini, and Microsoft Copilot, in answering a diverse set of questions about DED. The questions, formulated based on the American Academy of Ophthalmology's Eye Health webpage, encompass various aspects of the disease, including its definition, symptoms, causes, risk factors, diagnosis, treatment options, and impact on daily life. By systematically assessing the responses generated by these AI platforms for accuracy, comprehensiveness, and readability, we seek to provide a nuanced understanding of their capabilities and limitations in the context of DED. The study also examined inter-reviewer consistency in evaluating AI-generated responses, aiming to enhance the reliability and reproducibility of the evaluation process. Ultimately, this research endeavors to shed light on the potential and challenges of AI chatbots in disseminating accurate and comprehensible medical information about DED. By providing a comprehensive assessment of their performance, we hope to empower both healthcare providers and patients to make informed decisions about utilizing AI chatbots as adjuncts in the pursuit of improved patient education and healthcare outcomes. The insights gained from this study will contribute to the ongoing dialogue about the role of AI in healthcare communication, fostering a more informed and judicious use of these tools.

Methods

Data Source: Twenty-five questions were created based on the AAO Eye Health webpage and used to prompt each AI platform. Although these questions were not pilot-tested or formally validated, they were derived from a reputable patient information source to ensure clinical relevance and clarity. The questions cover a wide range of topics, including definitions, symptoms, causes, risk factors, diagnosis, treatment, and impact on daily life. The questions were designed to assess the AI platforms' ability to provide accurate, comprehensive, and readable information on this complex topic. Since the study does not involve any procedures related to patients, ethical committee approval is not required. The questions are highlighted in Table 1.

- AI platforms: Three prominent AI platforms were selected for evaluation:
- ChatGPT: A large language model developed by OpenAI, known for its conversational abilities and general knowledge.
- Google Gemini: A cutting-edge AI model developed by Google, designed to excel in natural language understanding and generation tasks.
- Microsoft Copilot: An AI-powered code completion and generation tool developed by Microsoft that is also capable of providing information on various topics.

Evaluation

- Independent reviewers: Three ophthalmologists with expertise in DED independently assessed the responses generated by each AI platform. This ensured an unbiased and expert evaluation of the information provided. All responses were anonymized before evaluation, and reviewers were blinded to the identity of the AI model that generated each response to minimize potential bias.
- Comprehensiveness: Each response was rated on a scale of 0 to 5, where 0 indicated no relevant information, and 5 indicated a fully comprehensive answer that addressed all aspects of the question.
- Accuracy: Each response was rated on a scale of −2 to 2, where −2 indicated utterly inaccurate information, 0 indicated partially accurate or incomplete information, and 2 indicated exact information.
- Readability metrics: To assess the readability of the AI-generated responses, several established metrics were calculated.
- Flesch–Kincaid grade level (FKGRL): This metric estimates the U.S. school grade level required to understand the text.
- Flesch reading ease score (FRES): This metric indicates how easy the text is to read, with higher scores representing easier readability.
- Average words per the sentence: This metric measures the average length of sentences in the text.
- Average syllables per word: This metric assesses the complexity of words used in the text.
- Total number of sentences: This metric provides the total count of sentences in the response.

Table 1. Patient-oriented questions on dry eye disease answered by ChatGPT, Google Gemini, and Microsoft Copilot

1.	What is the definition of dry eye disease?
2.	What are the common symptoms of dry eye disease?
3.	What are the primary causes of dry eye disease?
4.	What are the main tests used in the diagnosis of dry eye disease?
5.	How is the Schirmer test performed, and what does it measure?
6.	What are the effects of tear film layer disruption on vision?
7.	What is the prevalence of dry eye disease?
8.	What are the risk factors for dry eye disease?
9.	What is blepharitis, and how is it related to dry eye disease?
10.	What are the components of the tear film layer, and what functions do they serve?
11.	What are the primary treatment methods for dry eye disease?
12.	What is the long-term prognosis for dry eye disease?
13.	What are the effects of computer use on dry eye disease?
14.	What autoimmune diseases are associated with dry eye disease?
15.	How does dry eye disease affect the daily lives of patients?
16.	How is the tear break-up time (TBUT) test performed, and what does it measure?
17.	What corneal findings may be observed in patients with dry eye disease?
18.	How does contact lens use affect dry eye disease?
19.	How do hormonal changes impact dry eye disease?
20.	What are the effects of environmental factors on dry eye disease?
21.	How are Lissamine Green and Rose Bengal dyes used, and what do they measure?
22.	What is the prevalence of dry eye syndrome in children and adolescents?
23.	What pharmacological treatments are used in the management of dry eye disease?
24.	What are the non-pharmacological treatment methods for dry eye disease?
25.	What are the social and economic impacts of dry eye disease?

- Total number of words: This metric gives the total word count of the response.

Statistical Analysis

All statistical analyses were conducted using Statistical Package for the Social Sciences Statistics 23 (IBM Corp., Armonk, New York, USA). Initially, descriptive statistics (mean±standard deviation) were calculated for each variable across the three AI platforms. The Shapiro–Wilk test was conducted to evaluate the normality of the data for each variable. As the variables were not normally distributed, the Kruskal–Wallis test was used to compare differences among the three models. This test was used for Comprehensiveness, Accuracy, total number of sentences, and total number of words to evaluate whether at least one platform performed significantly differently from the others. If the Kruskal–Wallis test revealed a significant difference, Mann–Whitney U tests were conducted as *post-hoc* pairwise comparisons to identify which AI platforms differed from one another. This test was applied separately for each pair of platforms (ChatGPT vs. Google Gemini, ChatGPT vs. Microsoft Copilot, and Google Gemini vs. Microsoft Copilot). Bonferroni correction was applied to control for Type I error (adjusted P-value threshold: $p<0.0167$ for three comparisons. To analyze differences in FKGRL and FRES scores, a Friedman test was conducted, as these metrics were assessed across all three AI platforms on the same dataset. To assess inter-rater agreement in comprehensiveness and accuracy scores, the intraclass correlation coefficient (ICC) was calculated for each AI platform separately. A statistical significance threshold of $p<0.05$ was used.

Results

Google Gemini demonstrated the highest comprehensiveness ($p<0.001$) and accuracy ($p=0.003$) scores among the three AI platforms, followed by ChatGPT, while Microsoft Copilot consistently underperformed. Although Gemini

outperformed ChatGPT in comprehensiveness (p=0.014), their accuracy scores did not differ significantly (p=0.280) (Fig. 1). Readability scores such as FKGRL and FRES showed no significant differences among models (p=0.468 and p=0.289, respectively), but ChatGPT produced significantly longer responses in terms of sentence count and total word count (both p<0.001) (Table 2). Copilot had a higher average syllables-per-word score than ChatGPT (p=0.007) (Table 3 and Fig. 2). Inter-observer agreement was strongest for Gemini (ICC = 0.701, p<0.001) and weakest for Copilot (ICC = 0.495, p=0.022), suggesting greater consistency in expert evaluation for Gemini (Table 4 and Fig. 3).

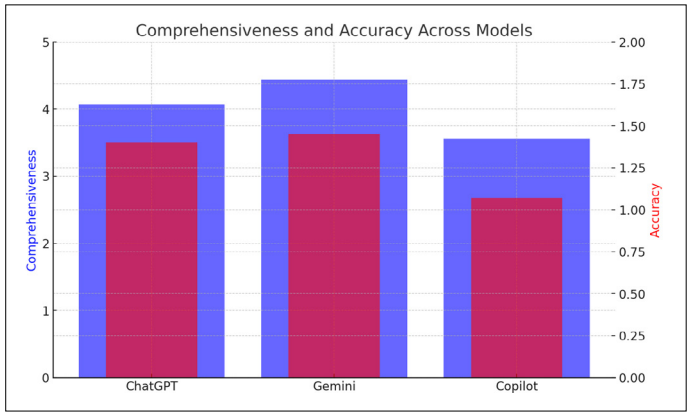

Figure 1. Comprehensiveness and accuracy across models. The blue bars represent the mean Comprehensiveness scores (left y-axis), while the red bars indicate the mean Accuracy scores (right y-axis) for each artificial intelligence model (ChatGPT, Gemini, and Copilot). Comprehensiveness scores (blue) range from 0 to 5, and accuracy scores (red) range from -2 to +2.

Discussion

Our study provides a comprehensive comparison of ChatGPT, Google Gemini, and Microsoft Copilot in answering DED-related questions, assessing their performance in terms of accuracy, comprehensiveness, readability, and inter-observer reliability. The findings highlight key differences in how these AI platforms generate medical information, offering valuable insights for both healthcare professionals and patients seeking reliable online health content.

Consistent with previous research on AI-generated medical information, ChatGPT and Google Gemini demonstrated comparable accuracy, confirming the ability of large language models to provide medically relevant responses. However, our study uniquely underscores the substantial differences in response comprehensiveness, with Google Gemini significantly outperforming both ChatGPT and Microsoft Copilot. Google Gemini's more detailed responses may enhance understanding of complex DED concepts, but they also introduce the potential risk of information overload, which could be challenging for some users. While extensive answers can be beneficial for professionals or highly engaged patients, they may also make it harder for general users to extract key takeaways efficiently.

Microsoft Copilot, initially developed for code generation, performed the weakest in both accuracy and comprehensiveness. This result reinforces the importance of task-specific AI tools. It highlights the need for users to carefully consider an AI model's intended purpose before relying on it for medical information. The significant performance gap between Microsoft Copilot and the other two platforms suggests that general-purpose AI models may not always be suitable for specialized domains such as medical education and patient counseling.

Table 2. Descriptive statistics and group comparisons of AI models

Metric	ChatGPT (mean±SD)	Gemini (mean±SD)	Copilot (mean±SD)	Range (min-max)	X^2	p
Comprehensiveness	4.07±0.55	4.44±0.56	3.56±0.61	2–5	21.72	<0.001*
Accuracy	1.40±0.32	1.45±0.50	1.07±0.52	–1–2	11.76	0.003*
Total sentence count	3.24±2.79	1.48±0.96	1.12±0.44	0–14	29.20	<0.001*
Total word count	47.04±13.26	25.04±7.32	20.56±10.50	7–90	43.08	<0.001*
Average sentence length	21.68±15.15	19.66±5.72	18.09±3.88	5–86	5.63	0.060
Average syllables per word	1.84±0.24	1.93±0.26	1.99±0.31	1.3–3.0	7.45	0.024*
FKGRL	15.11±4.89	15.91±4.50	15.39±4.81	7.12–27.17	1.52	0.468
FRES	28.14±16.78	21.38±21.30	21.49±23.06	–48.99–76.05	2.21	0.331

*Statistically significant. FRES: Flesch reading ease score; higher scores indicate easier readability, FKGRL: Flesch–Kincaid grade reading level; indicates U.S. school grade level required for comprehension, Avg. syllables/word: Average number of syllables per word, X^2: Kruskal–Wallis H test statistics, used for group comparison of non-normally distributed variables, Accuracy (–2 to +2), Comprehensiveness (0–5). SD: Standard deviation

Table 3. *Post-hoc* comparisons for statistically significant variables

Metric	Comparison	p	Direction of difference
Comprehensiveness	Gemini versus ChatGPT	0.014*	Gemini > ChatGPT
	ChatGPT versus Copilot	<0.001*	ChatGPT > Copilot
	Gemini versus Copilot	<0.001*	Gemini > Copilot
Accuracy	Gemini versus ChatGPT	0.280	No significant difference
	ChatGPT versus Copilot	<0.001*	ChatGPT > Copilot
	Gemini versus Copilot	<0.001*	Gemini > Copilot
Total sentence count	ChatGPT versus Gemini	<0.001*	ChatGPT > Gemini
	ChatGPT versus Copilot	<0.001*	ChatGPT > Copilot
	Gemini versus Copilot	0.014*	Gemini > Copilot
Total word count	ChatGPT versus Gemini	<0.001*	ChatGPT > Gemini
	ChatGPT versus Copilot	<0.001*	ChatGPT > Copilot
	Gemini versus Copilot	0.014*	Gemini > Copilot
Average syllables per word	ChatGPT versus Gemini	0.086	No significant difference
	ChatGPT versus Copilot	0.007*	Copilot > ChatGPT
	Gemini versus Copilot	0.210	No significant difference

*Statistically significant.

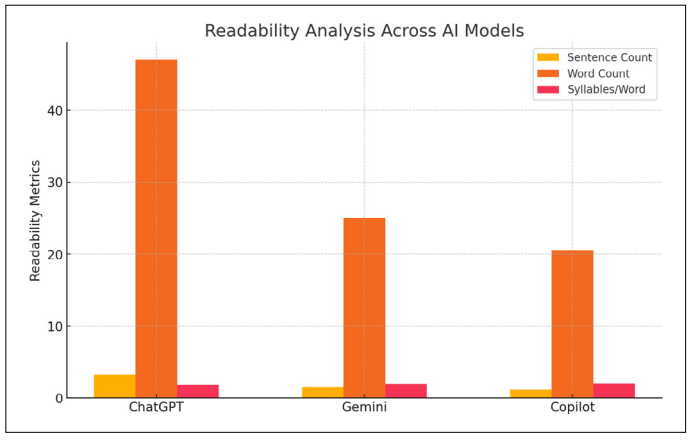

Figure 2. Readability analysis across artificial intelligence models. Readability metrics across the three models. Yellow bars represent the average sentence count, orange bars represent the average word count, and pink bars represent the average syllables per word for responses generated by each model.

Readability remains a critical factor in ensuring that AI-generated health information is accessible to a diverse audience. While ChatGPT produced the highest number of sentences and words, potentially making its responses more detailed, our analysis found no significant differences among the platforms in FKGRL and FRES readability scores. This suggests that, despite variations in response length, all three models generated content that is generally suitable for educated laypersons. However, given the well-documented correlation between readability and patient comprehension, further refinements in AI-generated medical content may be necessary to ensure accessibility for individuals with lower health literacy.

A particularly noteworthy finding of our study is the variation in inter-observer reliability. Google Gemini exhibited the highest agreement among evaluators (ICC = 0.701), suggesting that its responses were perceived as more consistently accurate and comprehensive across different reviewers. ChatGPT followed with moderate reliability (ICC = 0.578), while Microsoft Copilot had the lowest agreement (ICC = 0.495), indicating higher variability in how its responses were evaluated. This reinforces the notion that specific AI models may produce more stable and trustworthy outputs, which is a crucial consideration for both medical professionals and AI developers aiming to refine chatbot performance.

This finding aligns with studies demonstrating the efficacy of large language models in providing medically relevant information (1,2). However, our study uniquely highlights the significant difference in response length between these two platforms. While both ChatGPT and Google Gemini provided accurate and comprehensive answers, Google Gemini consistently generated more extensive responses. This may offer a deeper understanding of DED concepts, but it also raises concerns about information overload for some users. Microsoft Copilot, designed primarily for code generation, exhibited the lowest performance in this medical context, reinforcing the importance of task-specific AI mod-

Table 4. Inter-observer reliability

Model	Single measures ICC	Average measures ICC	p	Reliability level
ChatGPT	0.314	0.578	0.005*	Moderate
Gemini	0.439	0.701	<0.001*	High
Copilot	0.247	0.495	0.022*	Low to moderate

*Statistically significant. ICC: Intraclass correlation coefficient.

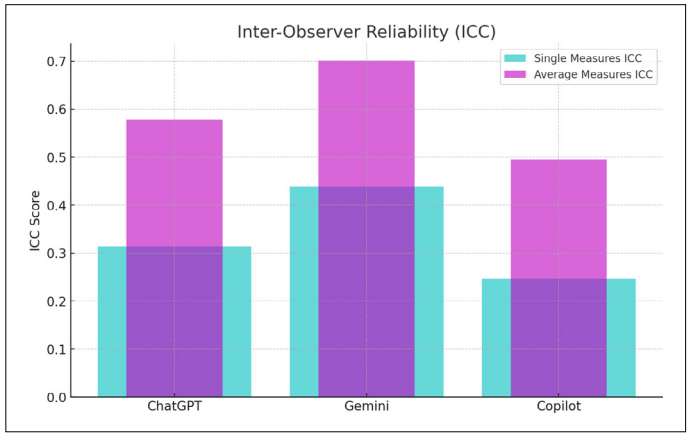

Figure 3. Inter-observer reliability (ICC). Turquoise bars show the single measures ICC, and purple bars show the average measures ICC for inter-observer agreement on scoring across the three artificial intelligence models.

els. Users should carefully consider an AI tool's intended purpose before relying on it for medical information. Our readability analysis revealed that ChatGPT generated significantly more sentences and words than both Google Gemini and Microsoft Copilot, suggesting that response length may impact readability perceptions. However, there were no significant differences among the platforms in terms of FKGRL and FRES readability scores, indicating that all three produced text suitable for educated laypersons. However, the complexity of the language used may pose a challenge for individuals with lower health literacy. This aligns with the broader concern raised in the literature regarding the need for AI-generated health information to be tailored to diverse audiences (5-7). Interestingly, Google Gemini exhibited the highest inter-reviewer consistency, indicating greater agreement among experts regarding the quality of its responses. This finding suggests that Google Gemini may be a more reliable in providing consistent and trustworthy information.

Haddad et al. (8) highlighted that ChatGPT's responses often required a higher level of education for comprehension compared to other platforms, which may hinder patient understanding. This complexity in readability is particularly concerning, given that many patients seek straightforward information about their conditions. The correlation between readability and patient comprehension is well-documented, with studies indicating that overly complex materials can lead to confusion and misinformation (9). Therefore, it is essential for AI tools to balance detail with accessibility to ensure that patients can quickly grasp the information provided. The reliance on AI chatbots for medical information is particularly pertinent in the context of chronic conditions such as glaucoma. Guler and Ertan Baydemir reported that approximately 43% of glaucoma patients utilize the Internet for medical information, highlighting the need for high-quality, reliable content (10). This shift in patient behavior underscores the importance of ensuring that AI-generated information is not only accurate but also presented in a manner that is easily digestible for patients with varying levels of health literacy. Moreover, the potential of AI chatbots in medical education has been explored in various studies. Haddad et al. (8) assessed the ability of ChatGPT to answer ophthalmology-related questions across different levels of training, indicating its utility as a supplementary educational tool for medical professionals. This aligns with findings from Davis et al., (9) who evaluated the application of AI in generating patient-centered information in other medical fields, suggesting a broader applicability of AI in enhancing patient education across specialties. The integration of AI into medical education and patient information dissemination could significantly improve the quality of care provided to patients. Desideri et al. (11) work further contributes to this discourse by examining the accuracy and applicability of AI chatbots in providing information about age-related macular degeneration. Her study categorized patient inquiries into general medical advice and pre- and post-intravitreal injection advice, revealing that while AI platforms provided accurate information, there were notable gaps in comprehensiveness and specificity (11). This highlights the necessity for continuous refinement of AI tools to ensure they meet the diverse informational needs of patients effectively. In addition, a study conducted by Guler and Ertan Baydemir evaluated the accuracy of responses provided by ChatGPT to 50 frequently asked questions by glaucoma patients, demonstrating a high level of concordance among ophthalmologists and generally accurate responses without observed significant inaccuracies

with potential harm (10). The research examined ChatGPT's overall accuracy in responding to typical patient inquiries related to glaucoma, highlighting its potential to address medical concerns and alleviate patient anxieties promptly. Despite the promising capabilities of AI chatbots, challenges remain in ensuring the accuracy and readability of the information they provide. The variability in performance among different platforms, as demonstrated by our study, suggests that continuous evaluation and refinement of AI tools are necessary to enhance their effectiveness in clinical settings. In addition, the complexity of responses generated by AI underscores the importance of tailoring information to meet the needs of diverse patient populations (8).

Conclusion

Our study has several limitations. The relatively small sample size of questions and reviewers may not fully capture the nuances of AI performance across a broader range of medical topics. Although the 0.4-point difference in mean accuracy was statistically significant, its clinical relevance remains context-dependent and may vary based on the complexity of the medical topic and the informational needs of the user. Since all prompts and responses were in English, the findings may not be generalizable to non-native speakers or multilingual populations. Language proficiency and cultural context could affect both comprehension and perceived quality of AI-generated content. Furthermore, the study did not assess qualitative attributes such as tone, empathy, or perceived trustworthiness of the responses, which may play a critical role in patient engagement and trust in AI-generated health content. Our comparative study reveals that while ChatGPT and Google Gemini can provide accurate and comprehensive information on DED, Google Gemini tends to offer more extensive responses. Microsoft Copilot, while proficient in other domains, may not be the optimal choice for complex medical queries. All platforms produced text suitable for educated laypersons, but further efforts are needed to improve readability for diverse audiences. This research emphasizes the importance of selecting the appropriate AI chatbot for specific tasks and highlights the potential of AI in revolutionizing healthcare communication. However, continued research and development are necessary to optimize AI's role in providing accessible, accurate, and user-friendly medical information. Future research should expand the scope of inquiry and explore objective DED measures of AI performance.

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Original Article

Comparative Detector Analysis for the Identification of Academic Articles Synthesized by Artificial Intelligence in the Field of Ophthalmology

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Abstract

Objectives: The increasing use of large language models, such as ChatGPT, in academic writing has raised significant ethical concerns within the academic community. This study explores the potential challenges posed by the ability of artificial intelligence (AI) to produce realistic, evidence-based academic texts and investigates whether these challenges can be effectively controlled.

Methods: Three original articles in the field of ophthalmology were provided as input to ChatGPT-4o to generate introduction sections. A total of 50 introduction texts were synthesized from 150 original articles. These AI-generated texts were analyzed using AI detectors (GPTZero, Writer, CorrectorApp, and ZeroGPT) and a plagiarism detector. In addition, the ability of AI detectors to differentiate between original and AI-generated texts was evaluated.

Results: There was a statistically significant difference in AI detector probabilities between original and AI-generated texts ($p<0.001$ for all detectors). GPTZero demonstrated a sensitivity of 100% and a specificity of 96% in distinguishing original from AI-generated texts, outperforming all other AI detectors. However, paraphrased AI-generated texts significantly reduced the detection accuracy of GPTZero ($p<0.001$).

Conclusion: ChatGPT-4o demonstrated the ability to synthesize new texts with referenced citations within seconds, capable of bypassing plagiarism detectors. However, AI detectors showed limitations in achieving absolute accuracy and occasionally misclassified original texts. Even with the most accurate AI detectors, a simple paraphrasing method significantly compromised prediction accuracy, highlighting the need for improved detection strategies and ethical oversight.

Keywords: Artificial intelligence detection, Artificial intelligence ethic, ChatGPT-4o, large language models, research policy

Introduction

Large language models (LLMs) are complex neural network-based transformative models that create natural, conversational content that is often difficult to distinguish from human-written text (1). ChatGPT is built on the largest of such models, generative pre-trained transformer-3 (GPT-3), and millions of people started using this tool, which OpenAI (San Francisco, CA, USA) released for free in November 2022 (2,3).

In the last few years, articles that include artificial intelligence (AI) tools such as ChatGPT as authors in their research have been entering the literature (4). Concerns are growing in academia about the misuse of AI chatbots for scientific paper writing, and some reputable scientific journals have reported that they have banned the use of ChatGPT for scientific article writing (5,6). However, there is no universal policy yet.

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Recently, various studies have been published investigating the potential of distinguishing abstracts prepared by AI (7-9). As a result of these studies, it was found that none of the human examinations and AI detector scans were perfect discriminators (7-10). While the functionality of existing AI detectors is just being discussed, OpenAI has released ChatGPT-4 (March 2023) and introduced the PDF upload feature in this version. An important point here is that when AI is prompted to generate a scientific article using references from the literature, it may produce incomplete or fabricated information due to its limited access to external sources and inability to verify content. The PDF upload feature will provide AI with the opportunity to increase the accuracy and credibility of the text it produces. As AI and AI detectors rapidly improve, continuous effort is needed to evaluate their performance.

In this study, it was requested that ChatGPT-4o (Version May 2024), the latest version released to the market, read and analyze three different original articles submitted to the literature with similar titles in the field of ophthalmology and synthesize an introduction with appropriate references. A total of 50 AI-generated texts were scanned in AI detectors, and their functionality was investigated. At the same time, the original texts were scanned by these detectors to investigate the possibility of misidentification.

Besides this study, which test the latest version of ChatGPT, no other study has been found in the literature in which AI chatbots have produced scientific synthesis text from more than one scientific article. The aim of this study is to draw attention to the potential threat of AI-generated texts, whose accuracy has not been examined, to the ophthalmology academy.

Methods

A total of 150 original articles, three each under similar titles, were sourced from PubMed and collected from February 2012 to November 2021 issues of six high-impact open-access journals (Eye and Vision, Investigative Ophthalmology and Visual Science, Retina, Translational Vision Science and Technology, Clinical Ophthalmology, and BMJ Open Ophthalmology). Articles with similar titles have been uploaded to ChatGPT-4o (OpenAI, San Francisco, CA, Version May 2024), the latest version on the market. The prompt given to the model was "Based on the introduction in the three articles provided, please synthesize an introduction for a new article. Cite references that contain actual articles using the Harvard reference style." 50 AI-generated texts were obtained by opening a new session each time. Ethical approval was not required because the study did not involve human participants and used only publicly available data. Sample prompts and AI-generated texts are available in the supplementary material.

The following four AI detectors were tested: GPTZero (https://gptzero.me/), ZeroGPT (https://www.zerogpt.com/), Writer (https://writer.com/ai-content-detector/), and CorrectorApp (https://corrector.app/ai-content-detector/). These programs, which can be used online for free, evaluate the probability of the given text being human or an AI production. To detect plagiarism, the introductions created by ChatGPT were scanned in "Plagiarism Checker" (https://plagiarismdetector.net/), which is a free web scanning plagiarism detection tool. All of these tools are software that offer a percentage probability from 0 to 100 when evaluating the probability of the text being human-written or AI-generated. Increasing value indicates a higher probability of AI production. Finally, 50 AI-generated texts were rewritten in the QuillBot program (https://quillbot.com/paraphrasing-tool), which offers paraphrasing tool features, and these texts were retested by GPTZero.

Statistical Analysis

All statistical analyses were performed using IBM Statistical Package for the Social Sciences, version 25.0 (IBM Corp., Armonk, NY, USA). The convenience of the data to normal distribution was evaluated using the Kolmogorov–Smirnov and Shapiro–Wilk normality tests. Variables were presented as mean±standard deviation and median (interquartile range [IQR]). A comparison of the probabilities given by the detector software for the original and ChatGPT-generated texts was made with a 2-sided Mann–Whitney U test. The Friedman test was used to compare the detectors with each other. Pearson's r effect size value was calculated for the Mann–Whitney U-test. Kendall's W effect size value was calculated for the Friedman test. For two-sided hypothesis testing, statistical significance was set at $p<0.05$.

Online-Only Supplemental Material Description

The article includes online-only supplementary material, and this material provides detailed examples of ChatGPT-generated text based on academic articles in ophthalmology. It includes synthesized introductions and reference citations, demonstrating the methodology and outcomes of AI-assisted content creation in this field.

Results

The likelihood of 100 texts (50 original and 50 ChatGPT-generated) being written by AI was evaluated, and a statistically significant difference was found in the probabilities detected by the AI detectors ($p<0.001$, all). The results were as follows: GPTZero (100% [IQR, 98.0–100%] vs. 2% [IQR, 1.00–3.00%]; $p<0.001$); Writer (15.5% [IQR, 12.0–18%] vs. 0% [IQR, 0.00–3.00%]; $p<0.001$); ZeroGPT (86.72% [IQR, 60.88–100%] vs. 24.28% [IQR, 0.00–66.03%]; $p<0.001$); CorrectorApp (85.91% [IQR, 58.77–100%] vs. 26.44% [IQR, 0.00–71.86%]; $p<0.001$) (Table 1 and Fig. 1).

Table 1. Comparative evaluation of the probabilities found by artificial intelligence text detectors for original texts and ChatGPT-generated texts (%)

AI-detector	Texts	n	Mean±SD	Median (Q1–Q3)	Z	p[a]	r[b]
ZeroGPT	ChatGPT-generated	50	80.11±21.26	86.72 (60.88–100.00)	–5.823	<0.001	0.58
	Original	50	36.50±35.47	24.28 (0.00–66.03)			
GPTZero	ChatGPT-generated	50	99.10±2.08	100.00 (98.00–100.00)	–8.908	<0.001	0.89
	Original	50	3.12±4.25	2.00 (1.00–3.00)			
Corr.App	ChatGPT-generated	50	76.94±24.18	85.91 (58.77–100.00)	–5.235	<0.001	0.52
	Original	50	38.41±35.57	26.44 (0.00–71.86)			
Writer	ChatGPT-generated	50	16.34±10.03	15.50 (12.00–18.00)	–8.397	<0.001	0.84
	Original	50	1.70±3.11	0.00 (0.00–3.00)			

Test statistics: Mann–Whitney U test; [a]Significant P-values (<0.05) are shown in bold; [b]Pearson r effect size value; SD: Standard deviation.

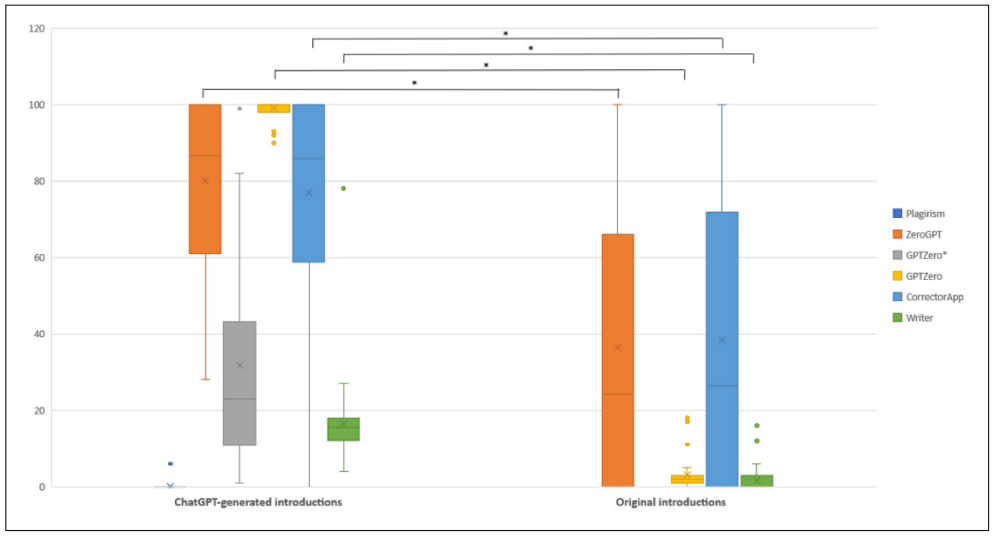

Figure 1. Percentage estimates of artificial intelligence (AI) text detectors giving ChatGPT-generated and original texts as AI generation.

When the effect size values were examined, it was seen that the AI detector that gave the most successful results was GPTZero (r=0.89). The average of the probabilities given by GPTZero for AI-generated texts is 99.10±2.08, whereas for original texts, this average is 3.12±4.25. When the AI-generated texts were paraphrased and evaluated again with GPTZero, it was observed that there was a statistically significant decrease in the probability in the second evaluation (100% [IQR, 98.0–100%] vs. 23% [IQR, 10.75–43.25%]; p<0.001) between the two evaluations of the same texts (Table 2).

Based on effect size, GPTZero was the most accurate detector (r=0.89). Its average probability for AI-generated texts was 99.10±2.08, whereas for original texts it was 3.12±4.25. After paraphrasing the AI-generated texts and re-evaluating them with GPTZero, a significant decrease was observed (100% [IQR, 98.0–100%] vs. 23% [IQR, 10.75–43.25%]; p<0.001) (Table 2).

When the results of AI detectors evaluating AI-generated texts were examined, it was seen that there was a statistically significant difference between them (p>0.05) (Table 2). Mean rank values for the Friedman test were found as follows: GPTZero: 5.63; ZeroGPT: 5.01; CorrectorApp: 4.23; GPT-Zero (post-paraphrase evaluation): 2.77; Writer: 2.35. While the Plagiarism Detector program gave a 0% plagiarized score in 49 of the 50 introductions produced with ChatGPT, it presented a 6% plagiarized percentage for only one text.

The comparison of the probabilities given by AI detectors for original introductions is presented in Table 3. According to these results, it was seen that there was a significant statistical difference between GPTZero and ZeroGPT (p=0.04), between Writer and ZeroGPT (p<0.001), and

Table 2. Evaluation of ChatGPT-generated texts by AI text detectors (%)

AI-detector	Mean±SD	Min-max.	Median (Q1–Q3)	p[q]
ZeroGPT	80.11±21.26	27.95–100.00	86.72 (60.88–100.00)	<0.05[b,t]
GPTZero	99.10±2.08	90.00–100.00	100.00 (98.00–100.00)	<0.05[a,x,y]
Corr.App	76.94±24.18	0.00–100.00	85.91 (58.77–100.00)	<0.05[c,x,z]
Writer	16.34±10.03	4.00–78.00	15.50 (12.00–18.00)	<0.05[a,b,c]
GPTZero*	31.84±25.91	1.00–99.00	23.00 (10.75–43.25)	<0.05[y,z,t]

Test statistics: Friedman test; [q]Significant P-values (<0.05) are shown in bold. GPTZero*: Post-paraphrase evaluation; [a]Between Writer and GPTZero; [b]Between Writer and ZeroGPT; [c]Between Writer and Corr.App; [x]Between Corr.App and GPTZero; [y]Between GPTZero* and GPTZero; [z]Between GPTZero* and Corr.App; [t]Between GPTZero* and ZeroGPT; AI: Artificial intelligence; SD: Standard deviation.

Table 3. Evaluation of ChatGPT-generated texts by AI text detectors (%)

AI-detector	Mean±SD	Min-Max	Median (Q1–Q3)	p[q]
ZeroGPT	36.50±35.47	0.00–100.00	24.28 (0.00–66.03)	<0.05[k,m]
GPTZero	3.12±4.25	0.00–18.00	2.00 (1.00–3.00)	<0.05[k]
Corr.App	38.41±35.57	0.00–100.00	26.44 (0.00–71.86)	<0.05[n]
Writer	1.70±3.11	0.00–16.00	0.00 (0.00–3.00)	<0.05[m,n]

Test statistics: Friedman test; [q]Significant P-values (<0.05) are shown in bold; [k]Between GPTZero and ZeroGPT; [m]Between Writer and ZeroGPT; [n]Between Writer and Corr.App; AI: Artificial intelligence.

between Writer and Corr.App (p<0.001). The mean rank order for the Friedman test was found as follows: ZeroGPT: 3.04; CorrectorApp: 2.93; GPTZero: 2.34; Writer: 1.69.

ROC curves for scores of AI detectors are presented in Figure 2 and Table 4. According to the results, ZeroGPT had an area under the receiver operating characteristic (AUROC) curve of 0.84 for detecting generated introductions. At the optimal cutoff (95.39%), maximizing sensitivity and specificity, ZeroGPT had a sensitivity of 38% and a specificity of 94% in differentiating original versus generated introductions. GPTZero had an AUROC curve of 1.000 for detecting AI-generated texts. At the optimal cutoff (17.5%), maximizing sensitivity and specificity, GPTZero had a sensitivity of 100% and a specificity of 96% in differentiating original versus generated introductions. CorrectorApp had an AUROC curve of 0.802 for detecting generated introductions. At the optimal cutoff maximizing sensitivity and specificity (94%), CorrectorApp had a sensitivity of 32% and a specificity of 94% in differentiating original versus generated introductions. The Writer had an AUROC curve of 0.981 for detecting generated introductions. At the optimal cutoff maximizing sensitivity and specificity (12.5%), Writer had a sensitivity of 68% and a specificity of 98% in differentiating original versus generated introductions.

Discussion

Writing an original academic article requires researchers to spend a long time on processes such as collecting information, analyzing it with critical thinking, and accurately referencing the data. The possibility of using LLM as an author in scientific research has brought up ethical and accuracy problems (11). Although AI facilitates language-related challenges and eases the writing process for researchers, it also raises concerns about the inclusion of unreliable studies or inadequately reviewed systematic reviews into the scientific literature.

In the study, three original scientific articles, different in each new chat, were uploaded to CHATGPT-4o, and it was asked to read and analyze these articles and write an introduction with their references. While 33 of these 50 introductions produced by ChatGPT showed only the uploaded articles in their references, it was seen that in 17 texts, some other references were added to the text. When checked, all of these references were taken from actual articles in the literature that the main articles referenced, with authors and publication titles matching. Even though the references were real articles from the correct year and journal, it was seen that in some places, the sentences that they claimed to be

Table 4. Receiver operating characteristics analysis to predict the probability of texts being AI or human-written

	AUC (% 95)	Cut off	p	Sensitivity (%)	Specificity (%)
ZeroGPT	0.836 (0.756–0.916)	95.39	<0.001	38	94
GPTZero	1.000 (1.000–1.000)	17.5	<0.001	100	96
CorrectorApp	0.802 (0.716–0.889)	93.995	<0.001	32	94
Writer	0.981 (0.955–1.000)	12.5	<0.001	68	98

AI: Artificial intelligence; AUC: Area under the curve.

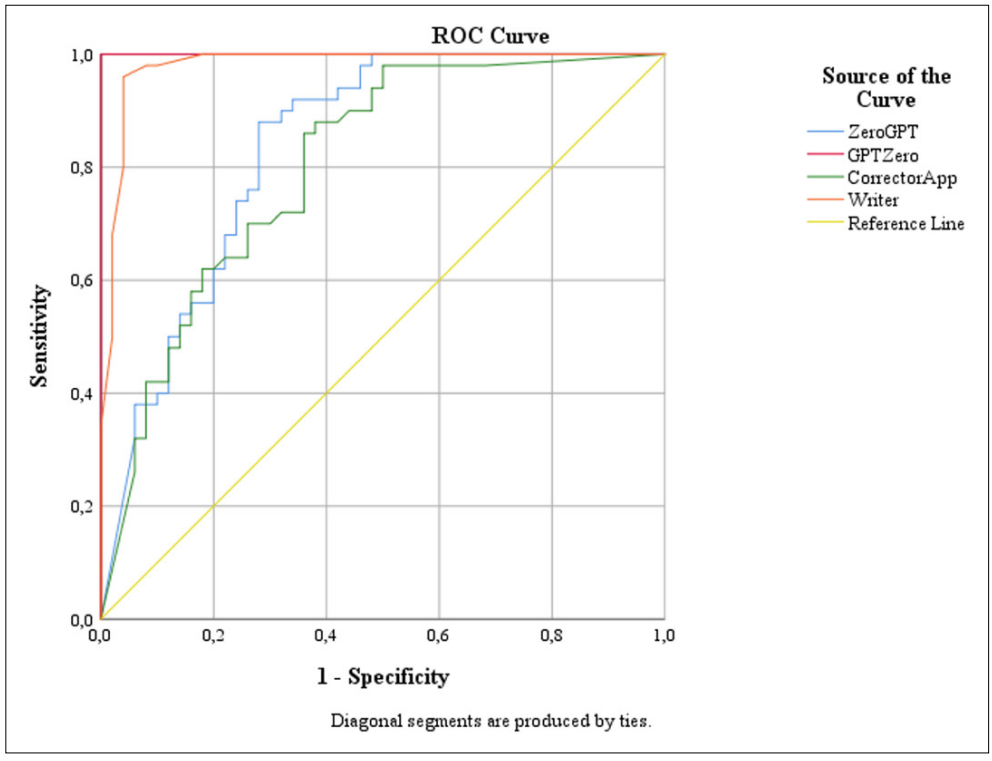

Figure 2. Receiver operating characteristic curve for scores of artificial intelligence text detectors.

relevant were not included in the referred articles, and the content of another article could be referred to a different article. Accepting seemingly evidence-based texts without careful examination could undermine trust in the scientific literature in the future. At this point, the effectiveness of detectors developed to detect texts produced by AI is worth examining. In the study, four AI detectors and a plagiarism detector program were used to detect plagiarism.

The plagiarism detection tool gave a 0% plagiarism score in 49 of 50 texts. Among the AI detectors whose functionality was examined, it can be said that GPTZero predicts AI-generated texts more accurately than all other detectors except ZeroGPT (Table 2). We see that the prediction probability of GPTZero, which works with an accuracy rate of nearly 100%, decreases significantly when the texts are simply paraphrased (QuillBot program) with an effort that takes seconds ($p<0.001$). This situation draws attention to the difficulty of detecting the texts produced when an AI robot is used for fraudulent research.

Another important point here was the possibility that AI detectors could mistakenly show human-written texts as AI production. It has been observed that the writer program, which has the lowest mean rank in detecting AI-generated texts, gives more accurate predictions than CorrectorApp and ZeroGPT in predicting the original texts, but it cannot be said that any tool works with near-perfect accuracy, raising the risk of unfair accusations against authors.

In this study, where the effectiveness of more than one AI detector was compared, the latest version of ChatGPT, 4o, was tested. While the AI-generated texts were initially

evaluated without any modifications, they were subsequently paraphrased to simulate potential human editing, and the impact on AI detector prediction probabilities was assessed. Furthermore, there are several limitations in the study. First, the content of the produced texts was not examined with a critical approach, so how original the content produced by AI was and how balanced and synthesized the subjects were not examined in this article. Therefore, no manual human control was provided to the texts. Another limitation of the study is the possibility that ChatGPT may produce a different response to the same prompt each time. Future studies could be expanded with a larger number of AI texts and plagiarism detectors, and to areas outside the field of ophthalmology.

Conclusion

This study highlights the growing challenges and ethical dilemmas associated with the use of AI, particularly LLMs such as ChatGPT-4o in academic writing. While AI demonstrates impressive capabilities in synthesizing and referencing texts, the inaccuracies in citation content and the ability of simple paraphrasing techniques to bypass even the most advanced AI detectors underscore the limitations of current AI detectors. Furthermore, the risk of AI misclassifying human-written texts and the potential for fraudulent research to infiltrate scientific literature emphasize the urgent need for improved detection systems and rigorous human oversight. As AI continues to advance, researchers and academic institutions must prioritize the development of robust ethical guidelines and reliable tools to ensure the integrity of academic research. Future studies should explore broader applications, test additional AI detectors, and critically evaluate the originality and synthesis quality of AI-generated content.

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Original Article

Selenium: Could It Be the Game-Changer for Ocular Surface and Anterior Chamber in Graves' Disease?

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Abstract

Objectives: To evaluate the effects of selenium supplementation on ocular surface parameters and anterior segment architecture in euthyroid Graves' disease (GD) patients without ophthalmopathy.

Methods: This cross-sectional study included 218 consecutive euthyroid GD patients without clinical manifestations of Graves' ophthalmopathy (GO). Patients underwent comprehensive ophthalmological examination, including the Ocular Surface Disease Index (OSDI) questionnaire, tear film break-up time (T-BUT), Oxford scale scoring, and Pentacam Scheimpflug imaging for anterior segment parameters assessment. Selenium intake was questioned, and based on selenium intake, participants were divided into two groups: the selenium intake group (n=106), receiving selenium supplementation (100 µg twice daily for 6 months) with standard anti-thyroid therapy, and the control group (n=112), receiving only standard anti-thyroid therapy.

Results: The mean age was 45.7±7.8 years (range: 30–61) in the selenium intake group (n=106; 48 females, 58 males) and 46.1±7.5 years (range: 30–60) in the control group (n=112; 52 females, 60 males), with no significant difference between groups (p=0.821 for age, p=0.904 for gender distribution). The mean duration of selenium supplementation was 11.4±4.2 months. The selenium group showed significantly better ocular surface parameters, with lower OSDI scores and higher T-BUT values compared to the control group (p<0.001 for both). Oxford staining scores were lower in the selenium group, though not statistically significant (p=0.244). Pentacam analysis revealed significantly higher anterior chamber volume (p=0.024) and central corneal thickness (p<0.001) in the selenium group, while anterior chamber depth and angle width were higher but not statistically significant (p=0.322 and p=0.276, respectively).

Conclusion: Selenium supplementation is associated with better ocular surface parameters and different anterior segment architecture in euthyroid GD patients without ophthalmopathy. Clinical associations observed in these cases may be related to selenium's antioxidant and anti-inflammatory properties through glutathione peroxidase and thioredoxin reductase activity, suggesting selenium as a potentially beneficial therapeutic approach for ocular surface integrity in GD.

Keywords: Graves' disease, ocular surface, selenium supplementation

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Introduction

Graves' disease (GD) is an autoimmune condition in which antibodies bind to the thyrotropin receptor and stimulate thyroid hormone production, representing the majority of hyperthyroidism cases (1). The most frequent extrathyroidal manifestation of GD is Graves' ophthalmopathy (GO), which is an immune-mediated inflammatory disorder affecting orbital tissues, where autoantibodies target thyroid-stimulating hormone receptors expressed on orbital fibroblasts (2). This leads to various clinical manifestations, including proptosis, eyelid retraction, corneal exposure, periorbital edema, and potentially optic neuropathy.

Selenium, an essential trace element highly concentrated in the thyroid gland, plays a pivotal role in maintaining endocrine function through its integration as selenocysteine into various proteins. It is crucial for the function of antioxidant enzymes like glutathione peroxidases and thioredoxin reductases, which protect the thyroid gland by neutralizing reactive oxygen species (ROS) produced during hormone synthesis (3). While these selenoprotein-dependent antioxidant systems effectively manage ROS levels in healthy individuals, patients with autoimmune thyroid disorders, including GD, often have increased oxidative stress, creating enhanced selenium requirements (4). In the pathophysiology of GD, where oxidative stress contributes to the pathogenesis, selenium's antioxidant and immunomodulating properties have emerged as therapeutically significant. This understanding has led to important clinical applications, with the European Thyroid Association/European Group on Graves' Orbitopathy now recommending 6 months of selenium supplementation for mild GO cases (5), as it reduces disease progression and improves quality of life (6,7).

Dry eye is a common complication in GO, where proptosis and upper eyelid retraction cause increased evaporation from the ocular surface, exacerbating tear film instability, resulting in reduced tear break-up time and elevated ocular surface disease scores (8). Studies suggest that ocular surface problems and dry eye can occur in GD patients even without active ophthalmopathy, indicating other possible underlying mechanisms affecting ocular health before ophthalmopathy develops (9,10).

Considering the inflammatory pathogenesis and soft tissue involvement in GD, subtle changes in corneal architecture and anterior segment parameters may be present even in patients without clinical ophthalmopathy. Pentacam (Oculus Inc., Wetzlar, Germany), a rotatory Scheimpflug imaging system, provides non-invasive, rapid, and reproducible measurements of multiple anterior segment parameters, including anterior chamber depth, volume, angle width, central corneal thickness, and corneal volume, offering potential for detecting these subtle alterations in anterior segment architecture (11).

Despite the well-known relationship between GO and ocular surface alterations, and the potential for anterior segment changes secondary to inflammatory processes, the effects of selenium supplementation on ocular surface parameters and anterior segment architecture have not been evaluated in euthyroid GD patients without ophthalmopathy. This study aims to assess these parameters, thereby expanding our understanding of selenium's effects in this specific patient population.

Methods

This study was approved by the institutional review board of Buca Seyfi Demirsoy Training and Research Hospital (approval number: 2025/416) and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants.

The study included 218 consecutive euthyroid GD patients under regular follow-up at the Department of Endocrinology and Metabolism, İzmir Buca Seyfi Demirsoy Training and Research Hospital. Only patients without clinical manifestations of GO were enrolled in the study. Euthyroid status was confirmed through thyroid function tests. Demographic data were collected from all participants.

Patients with any signs of GO or a history of compressive optic neuropathy were excluded from the study. Additional exclusion criteria comprised any systemic disease other than GD that could affect measurements, use of systemic medications except antithyroid agents, history of ocular surgery, and ophthalmological conditions requiring medical treatment (e.g., glaucoma). Patients with refractive errors beyond ±3 diopters, media opacities affecting image quality (e.g., cataract), non-euthyroid thyroid hormone levels, or a history of steroid treatment or orbital radiotherapy were also excluded from the study.

All participants underwent comprehensive ophthalmological examination by the same ophthalmologist (P.K.), including best-corrected visual acuity measurement using a Snellen chart, intraocular pressure measurement with applanation tonometry, and anterior-posterior segment evaluation with slit-lamp biomicroscopy.

Evaluation of dry eye included assessment with the Ocular Surface Disease Index (OSDI) questionnaire, tear film break-up time (T-BUT) measurement, and Oxford scale scoring. The OSDI score was calculated using the formula: OSDI = (sum of scores) × 25 / (number of questions answered). T-BUT was assessed by instilling fluorescein into the inferior fornix and measuring the time until the first break in the tear film under cobalt blue illumination, with the mean of three consecutive measurements recorded. Corneal and conjunc-

tival staining was evaluated using fluorescein under a cobalt blue filter and graded according to the Oxford scale (grades A to >E, corresponding to scores 0 to 5).

Anterior segment parameters were evaluated using Pentacam Scheimpflug imaging (Oculus Inc., Wetzlar, Germany) under standardized dark conditions without pupil dilation. Parameters analyzed included anterior chamber depth, volume, and angle width, along with central corneal thickness, corneal volume, and pupil diameter. To ensure measurement consistency, all examinations were performed by a single ophthalmologist (P.K.).

After the measurements, patients were questioned regarding selenium supplementation status and, based on selenium intake, participants were divided into two groups: the selenium intake group (n=106) received selenium supplementation (100 µg twice daily for 6 months) in addition to standard anti-thyroid medical therapy, while the control group (n=112) received standard anti-thyroid medical therapy alone. The duration of selenium supplementation was also recorded for all patients in the selenium intake group. The selenium supplementation protocol (100 µg twice daily) was chosen based on the European Thyroid Association/ European Group on Graves' Orbitopathy (EUGOGO) guidelines, which recommend this specific dosing regimen for mild Graves' ophthalmopathy management (5,6).

Statistical Analysis

IBM Statistical Package for the Social Sciences version 25 (SPSS Inc., Chicago, IL, USA) was used for statistical purposes. Categorical variables were expressed as frequencies and percentages, and numerical variables were expressed as means and standard deviations. Kolmogorov-Smirnov tests were used to determine whether the data were normally distributed. Independent t-test was used to evaluate differences in normally distributed data. Mann-Whitney U test was used to determine differences in non-normally distributed data. A p-value less than 0.05 was considered statistically significant. For statistical purposes, values from the left eyes were analyzed in both the study and control groups.

Results

The mean age was 45.7±7.8 years (range: 30–61) in the selenium intake group (n=106; 48 females, 58 males) and 46.1±7.5 years (range: 30–60) in the control group (n=112; 52 females, 60 males), with no significant difference between groups (p=0.821 for age, p=0.904 for gender distribution). The mean duration of selenium supplementation was 11.4±4.2 months (range: 6–18 months) in the selenium supplementation group.

The selenium supplementation group demonstrated significantly better ocular surface parameters compared to the non-selenium group. Mean OSDI scores were significantly lower, and T-BUT values were significantly higher in the selenium group compared to the non-selenium group (p<0.001 for both parameters). Oxford staining scores were lower in the selenium group, though this difference was not statistically significant (p=0.244).

Pentacam analysis revealed differences in anterior segment parameters between groups. The selenium group demonstrated significantly higher anterior chamber volume (p=0.024) and central corneal thickness (p<0.001). Although anterior chamber depth and angle width were higher in the selenium group, these differences did not reach statistical significance (p=0.322 and p=0.276, respectively). No significant differences were observed in corneal volume or pupil diameter between groups (p=0.534 and p=0.266, respectively) (Table 1).

Table 1. Comparison of ocular surface parameters and anterior segment measurements between groups

	Selenium Group (Mean±SD)	Non-selenium Group (Mean±SD)	p
OSDI Score	18.67±19.91	54.60±31.56	<0.001
T-BUT (seconds)	14.20±5.51	9.88±5.07	<0.001
Oxford Staining Score	0.44±0.70	0.55±0.79	0.244
Anterior Chamber Depth (mm)	2.80±0.22	2.59±0.52	0.322
Anterior Chamber Volume (mm³)	155.47±23.43	139.97±38.05	0.024
Anterior Chamber Angle Width (°)	37.89±5.89	33.19±7.44	0.276
Pupil Diameter (mm)	2.94±0.58	2.92±0.79	0.266
Central Corneal Thickness (µm)	558.90±23.34	530.16±28.63	<0.001
Cornea Volume (mm³)	60.89±2.85	59.17±3.01	0.534

OSDI, Ocular Surface Disease Index; T-BUT, tear film break-up time; SD, standard deviation.

Discussion

Selenium's critical role in thyroid function is well established through its high thyroid tissue concentration and essentiality in antioxidant enzyme systems (3,4). *In vitro* studies have shown that selenium helps to reduce orbital fibroblast proliferation while protecting them from oxidative stress-induced damage and decreasing inflammatory cytokine production (12,13). Selenium also demonstrates anti-inflammatory effects through reduction of tumor necrosis factor-α and inhibition of nuclear factor-κB activation. These antioxidant and anti-inflammatory properties are especially important in GD patients, who require increased selenium levels to compensate for elevated oxidative stress (3).

Selenium supplementation has shown benefits in patients with GO in several studies. Marcocci et al. (6) reported improvements in quality of life and reduced ocular involvement and disease progression. Wang et al.'s study (14) confirmed these results. Additionally, Khong et al. (15) found lower selenium levels in GO patients compared to those with GD without ophthalmopathy in the Australian population. Potita et al. (16) found selenium supplementation improved eyelid and soft tissue symptoms in mild GO. In an Egyptian study, serum selenium levels were found to be lower in patients with GO compared to those with GD without ophthalmopathy, with levels progressively decreasing as disease severity increased (17).

However, it is important to acknowledge that not all studies have demonstrated consistent benefits of selenium supplementation in thyroid-related ocular conditions. The recent SeGOSS trial by Ahn et al. (18), a randomized controlled study of 84 patients with mild to moderate Graves' ophthalmopathy in selenium-sufficient regions, found no improvement in quality of life scores or clinical parameters at 6 months with selenium supplementation, despite some transient benefits observed at 3 months. This finding suggests that selenium's effectiveness may vary depending on baseline selenium status and geographic selenium sufficiency. Additionally, Halawa et al. (19) observed that while selenium status showed a significant negative correlation with Graves' disease, this correlation did not extend to Graves' ophthalmopathy specifically, implying that selenium's role may be more complex than initially thought. These conflicting results highlight the importance of considering baseline selenium status and patient selection criteria when evaluating selenium supplementation outcomes.

In this study of euthyroid GD patients without ophthalmopathy, significant differences were detected in ocular surface parameters between those receiving selenium supplementation and those who were not. The selenium supplementation group demonstrated significantly better OSDI scores and tear break-up time (T-BUT) values.

Although dry eye is a well-known condition in GO, studies by Kocabeyoglu et al. (20), Gürdal et al. (21), and Carreira et al. (22) have demonstrated significant ocular surface impairment in GD patients even without ophthalmopathy, with findings of higher OSDI scores and reduced T-BUT values. Additionally, Carreira et al. (22) found decreased corneal epithelial thickness regardless of ophthalmopathy status, suggesting subclinical chronic inflammation affects tear film stability and ocular surface integrity before obvious ophthalmopathy develops.

The pathogenesis of ocular surface disease in GD involves multiple inflammatory mechanisms. Lacrimal glands containing thyroid-stimulating hormone receptors become autoimmune targets, leading to increased tear film osmolarity, which triggers pro-inflammatory cytokines that damage the corneal surface (23,24). This process, combined with meibomian gland dysfunction and blinking abnormalities, creates an inflammatory cycle that compromises tear film stability before clinical ophthalmopathy develops (8,25).

The observed associations between selenium supplementation and improved ocular surface parameters may be related to its potential anti-inflammatory and antioxidant properties, though the exact mechanisms remain unclear. Oxidative stress plays a key role in GD pathogenesis, with studies showing elevated reactive oxygen species (ROS) in affected tissues, and selenium may help neutralize these through its antioxidant properties (4). The tear film stability improvements observed in our selenium group might be associated with selenium's anti-inflammatory effects, potentially reducing inflammatory mediators that disrupt ocular surface homeostasis. However, our cross-sectional design limits definitive conclusions about these mechanistic relationships. Supporting our findings, a recent study reported that selenium treatment in mild GO led to significant improvements in symptoms, including tearing, grittiness, and conjunctival congestion, compared to placebo during the first 6 months (26).

Regarding anterior segment measurements, Pentacam analysis revealed that the selenium group had significantly higher anterior chamber volume and central corneal thickness. Although anterior chamber depth and angle width were also higher in the selenium group, these differences did not reach statistical significance.

While there are no studies evaluating corneal thickness in GD patients without ophthalmopathy, previous studies have shown conflicting results regarding corneal thickness in GO. In our study, the non-selenium supplement group had thinner corneas, aligning with Bahceci et al. (27) and Bassiouny et al.'s (28) findings that showed corneal thickness

negatively correlating with thyroid hormone levels, despite Babić Leko et al. (29) reporting thicker corneas in GO. The higher corneal thickness observed in the selenium group may reflect potential anti-inflammatory properties, though causal relationships cannot be established from our study design. This hypothesis is supported by Zhang's (30) study, showing that inflammatory processes in GO lead to corneal thinning through soft tissue inflammation and fibrosis, with more pronounced thinning in moderate-severe cases. However, without baseline measurements, we cannot determine whether this represents a protective effect of selenium or pre-existing differences between groups.

Additionally, Chang et al. (31) reported that GO patients were found to have keratoconus-like changes, which aligns with our findings and suggests that selenium's anti-inflammatory properties may help prevent inflammation-induced corneal changes in our patient population.

The observed differences in anterior chamber parameters between groups are of uncertain clinical significance and require cautious interpretation. Our study found higher anterior chamber volume in the selenium-supplemented group, with non-significant trends toward increased anterior chamber depth and angle width. These findings partially align with Babić Leko et al.'s (29) observations of decreased anterior chamber parameters in patients with higher thyroid hormone levels. Selenium's anti-inflammatory and antioxidant properties may be associated with maintained anterior segment architecture, potentially through reduced inflammation and tissue remodeling (32), though prospective studies are needed to confirm these relationships.

This study has several significant limitations that must be acknowledged. First and most importantly, the cross-sectional design prevents establishment of causal relationships, and our findings should be interpreted as associations only. The lack of randomization introduces selection bias, as patients choosing selenium supplementation may differ systematically from those who do not in terms of health consciousness, dietary habits, and other protective behaviors that could independently affect ocular health. The absence of serum selenium level measurements represents a critical limitation, as selenium supplementation status was based solely on patient reporting without objective biochemical confirmation. This prevents assessment of actual selenium bioavailability, compliance, and baseline selenium status, which could significantly influence treatment response.

Additionally, baseline ocular surface and anterior segment parameters prior to selenium supplementation were not available, preventing assessment of whether groups had similar characteristics before treatment initiation. Although clinical assessments were performed prior to obtaining selenium supplementation history, the lack of complete blinding represents a potential source of observer bias. Other important confounding factors were not systematically assessed, including dietary selenium intake, systemic inflammatory markers, and potential subclinical ophthalmopathy that might not be detected by standard clinical examination.

It should be noted that our clinical recommendation follows the established 6-month selenium supplementation protocol as per EUGOGO guidelines (5,6), which has demonstrated an optimal benefit-to-risk ratio while minimizing potential adverse effects associated with prolonged high-dose selenium use, such as insulin resistance and hematological complications. The extended mean duration of selenium supplementation in our study occurred due to systemic factors affecting patients' follow-up schedules rather than by clinical design, as our protocol specifically recommends 6 months of treatment.

These limitations emphasize the need for well-designed randomized controlled trials with baseline measurements to establish the true therapeutic efficacy of selenium supplementation.

Conclusion

While studies have investigated the relationship between GD and ocular surface/anterior segment changes, and others have investigated selenium's effects in GD separately, this study uniquely combines these aspects by evaluating selenium's effects on both ocular surface and anterior segment parameters in GD without ophthalmopathy, demonstrating significant improvements in selenium-supplemented patients.

In conclusion, this study demonstrated associations between selenium supplementation and improved ocular surface parameters, as well as anterior segment differences, in euthyroid GD patients without ophthalmopathy. These findings suggest potential benefits that warrant further investigation. Prospective longitudinal studies with larger patient populations, longer follow-up periods, advanced imaging technologies, and detailed ocular surface assessments are needed to establish causal relationships and validate these preliminary findings.

Disclosures

Ethics Committee Approval: This study was approved by the Buca Seyfi Demirsoy Training and Research Hospital Ethics Committee (Date: 26.02.2025, Number: 2025/416) and conducted in accordance with the tenets of the Declaration of Helsinki.

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

Conflict of Interest: None declared.

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Case Report

Primary Localized Conjunctival Amyloidosis Mimicking Lymphoma

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Abstract

A 27-year-old healthy male presented to our clinic with complaints of redness and burning in his left eye for the past 6 months. Biomicroscopic examination revealed a salmon-colored, elevated, painless mass lesion involving the entire lower fornix conjunctiva of the left eye. A conjunctival incisional biopsy was performed due to suspicion of lymphoproliferative disease. Histopathological examination confirmed amyloidosis. Further investigations did not reveal any evidence of systemic amyloidosis, lymphoma, or other lymphoproliferative diseases. During the 18-month follow-up after surgery, no recurrence or new findings were observed in the patient's ophthalmologic or systemic evaluations. Amyloidosis in the periocular region can present with various clinical findings. Although a classic salmon-colored conjunctival mass initially may suggest lymphoproliferative diseases, conjunctival amyloidosis should be considered in the differential diagnosis.

Keywords: Conjunctiva, Lymphoma, Primary amyloidosis

Introduction

Conjunctival lesions range from benign, simple degenerative changes to malignant conditions such as lymphoma and melanoma. While the typical clinical features of these lesions can guide differentiation during examination, similarities can sometimes be misleading. Primary localized conjunctival amyloidosis is one of the rarest conditions among conjunctival lesions. Clinically, it can present with recurrent subconjunctival hemorrhage, a yellow-colored conjunctival mass, or lesions resembling pterygium (1). However, it is important to note that conjunctival amyloidosis can also present with conjunctival lesions of varying appearances. Herein, we present a case of primary localized conjunctival amyloidosis, which clinically resembled a lymphoproliferative lesion but was histopathologically diagnosed as amyloidosis.

Case Report

A 27-year-old male presented to our clinic with complaints of redness, swelling, stinging, and watering in the inner part of the left lower eyelid for the past 6 months. Biomicroscopic examination revealed a painless, elevated, salmon-

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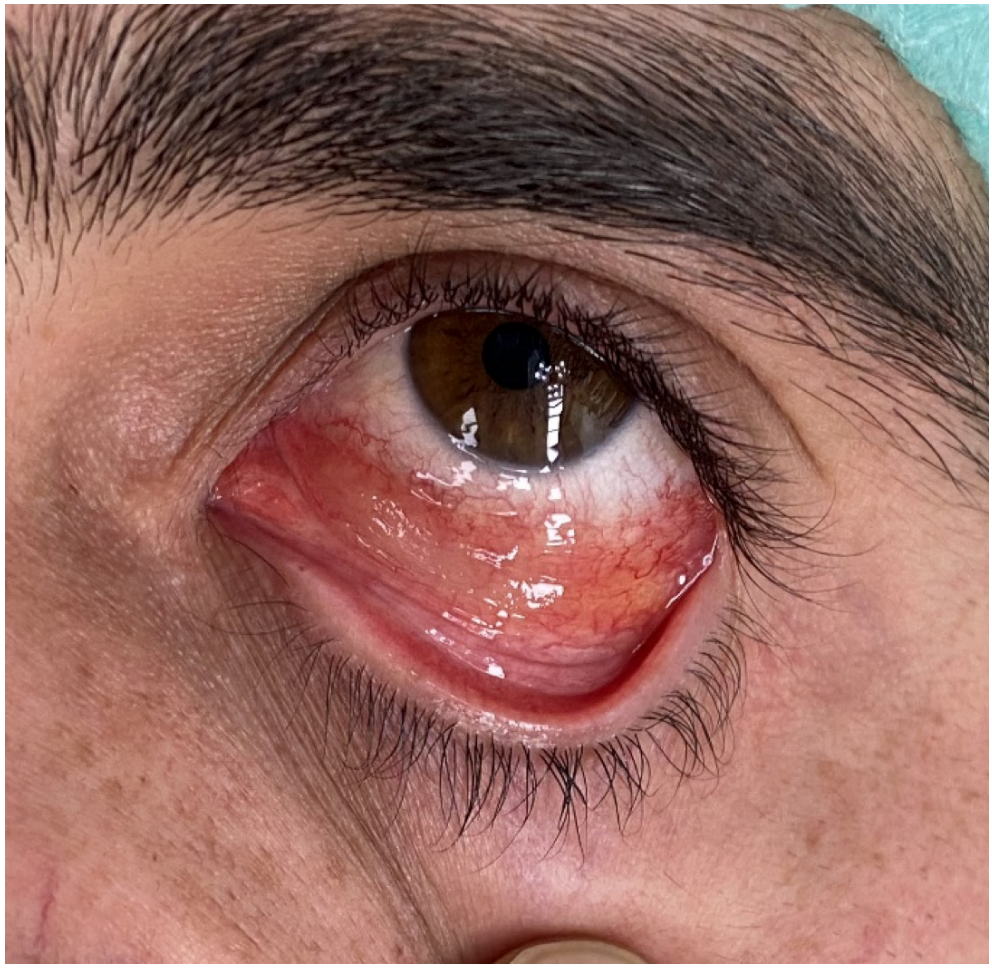

Figure 1. A salmon-colored, elevated lesion involving the entire inferior fornix conjunctiva and extending to the bulbar conjunctiva.

colored conjunctival mass lesion involving the entire lower fornix conjunctiva and extending to the bulbar conjunctiva on the left side, with indistinct borders and minimal surrounding hyperemia (Fig. 1). The other anterior segment and fundus examinations, as well as ocular movements, were normal bilaterally. Orbital magnetic resonance imaging showed no signs of orbital involvement. Due to its salmon color and rubbery consistency, an incisional biopsy was planned with a preliminary diagnosis of lymphoproliferative disease. The visible portion of the lesion along the lower fornix was excised, and the area was primarily closed. Histopathological evaluation revealed widespread and dense eosinophilic material throughout the stroma and vessel walls beneath the epithelium. An immunohistochemical study showed diffuse staining with Congo red, confirming a diagnosis of amyloidosis (Fig. 2). Figure 3 also demonstrates staining with Congo red with apple green birefringence. The patient was referred to the internal medicine clinic to investigate systemic involvement. Complete blood count (CBC), serum electrophoresis, β-2 microglobulin level, 24-h urine protein level, kidney and liver function tests, echocardiography, and abdominal ultrasonography were all normal, leading to a diagnosis of primary localized conjunctival amyloidosis. At the 4-month post-operative follow-up, there was no adhesion in the fornix, and the cosmetic appearance was satisfactory (Fig. 4). During the 18-month follow-up, no recurrence was observed. Written informed consent of the patient was taken for the publication of his clinical findings.

Discussion

Amyloidosis is a clinical condition characterized by the extracellular accumulation of a pathological protein material called amyloid. This material consists of amorphous, insoluble, misfolded fibrils with a beta-sheet structure and can accumulate in various tissues and organs. Depending on the extent of involvement, amyloidosis is classified as either systemic or localized. Based on the underlying etiology, it is further classified as either primary or secondary (2).

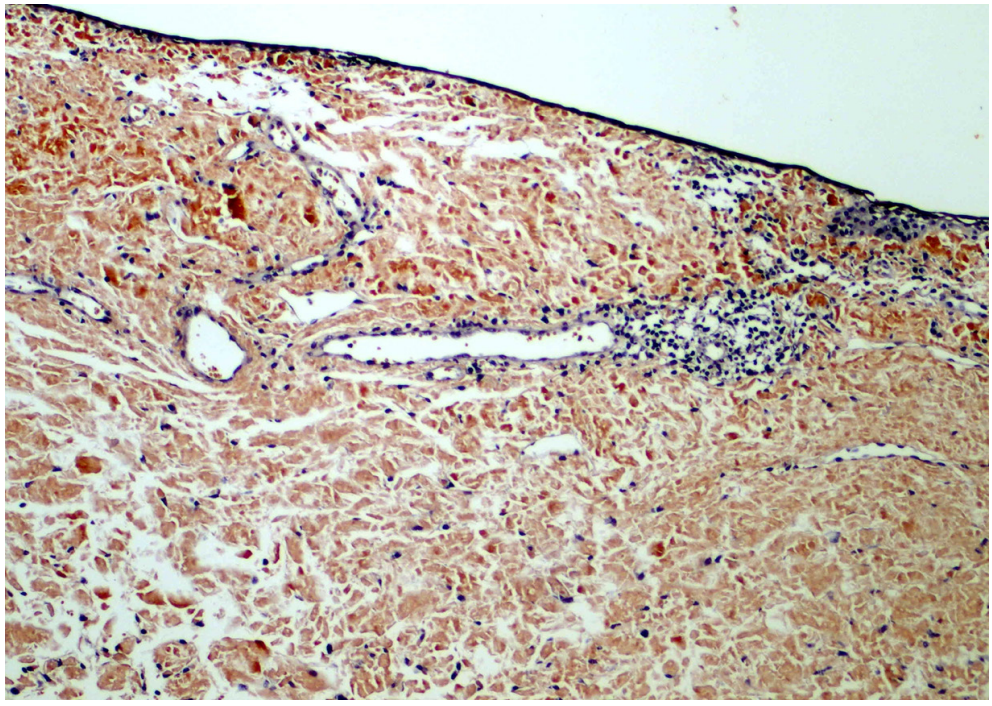

Figure 2. Brick red staining reaction with Congo red (×40).

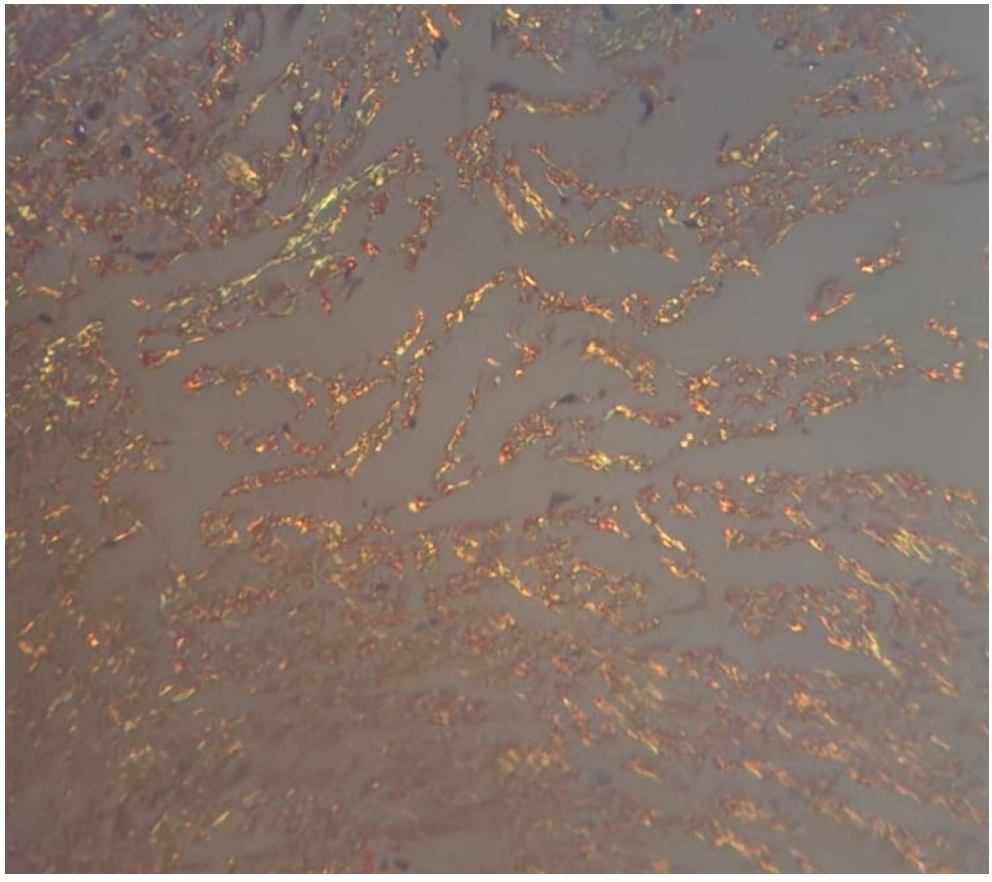

Figure 3. Congo red staining with apple green birefringence.

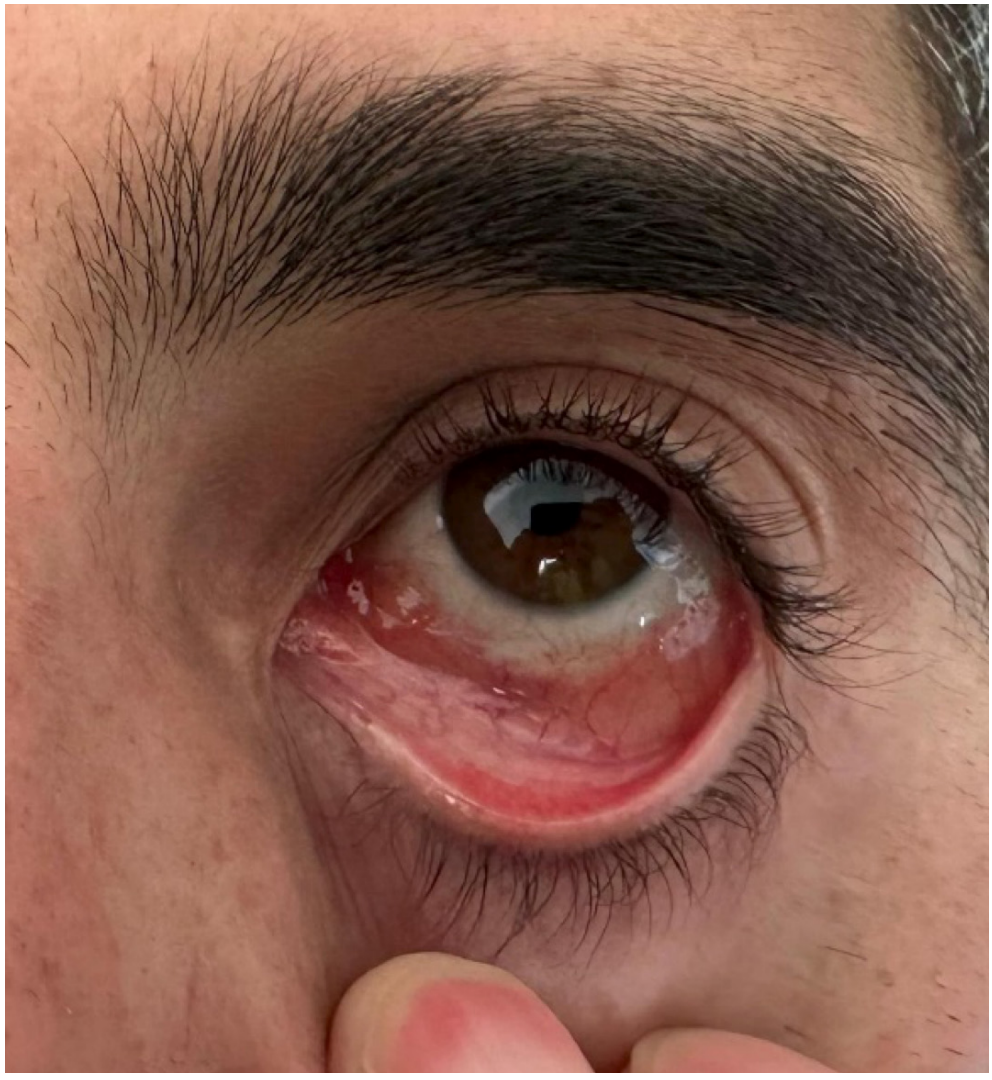

Figure 4. 4th month follow-up after surgery.

Localized conjunctival amyloidosis is a very rare form of the disease that can be either primary or secondary. Most commonly, conjunctival amyloidosis presents as primary localized, typically unilateral, and rarely shows systemic involvement. Secondary localized amyloidosis can develop due to chronic inflammation or as part of systemic conditions such as multiple myeloma, rheumatoid arthritis, leprosy, and familial Mediterranean fever. It is characterized by the accumulation of immunoglobulin-related protein (light chain amyloid) in the conjunctiva (1,3,4). Conjunctival amyloidosis generally occurs in middle-aged adults and shows no significant gender difference (2). The most common sites are the fornices (upper > lower) and the tarsal conjunctiva (5). Patients may present with conjunctival masses, pterygium-like lesions, or subconjunctival hemorrhage (1,3). Other ophthalmological involvements include the eyelid and orbit. These patients may present with blepharoptosis, entropion, eyelid masses, periorbital ecchymosis, periorbital edema, lacrimal gland involvement, extraocular muscle involvement, and proptosis (2). In this case, because the lesion exhibited a classic appearance suggestive of lymphoma, primary localized conjunctival amyloidosis was not initially considered due to its extreme rarity. The decision to perform a biopsy was primarily driven by the lesion's rapid development and characteristic "salmon patch" morphology. This case report highlights that, despite its uncommon occurrence, conjunctival amyloidosis can clinically mimic malignant lesions such as lymphoma, thereby posing a diagnostic challenge. Spitellie et al. (6) suspected lymphoproliferative disease in a 39-year-old female patient due to a painless, salmon-colored mass located under the left upper eyelid and involving the anterior orbit. The histopathological diagnosis was consistent with amyloidosis, and no systemic involvement was observed. In our case, only the lower fornix was involved with no orbital involvement. The lesion exhibited a salmon-colored appearance suggestive of lymphoproliferative disease. Since the lesion developed over a short period of 6 months,

orbital involvement may not yet have been observed. Cases where localized amyloidosis progresses to systemic disease have been reported, so this possibility should be kept in mind when monitoring a patient presumed to have localized amyloidosis (6). No systemic involvement was observed during the 18-month follow-up of our patient. In addition, Marsh et al. (7) reported a case of a 62-year-old patient diagnosed with localized conjunctival amyloidosis who subsequently developed extranodal lymphoma during follow-up. Therefore, long-term follow-up of these patients is crucial.

Histopathological evaluation is essential for diagnosis. Hematoxylin-eosin-stained sections show nodular accumulations of amorphous, homogeneous eosinophilic deposits in the substantia propria. Staining with Congo red reveals brick-red coloring, and under polarized light, amyloid deposits exhibit apple-green birefringence (8,9). Setoguchi et al. (10) detected low-grade B-cell lymphoma along with amyloid accumulation in the histopathological evaluation of a conjunctival lesion affecting the upper and lower eyelid fornices. They interpreted this as lymphoma cells transforming into plasma cells that produce amyloidogenic immunoglobulin light lambda chains.

Systemic evaluation of patients diagnosed with conjunctival amyloidosis is important. A comprehensive systemic evaluation at diagnosis should include CBC, serum protein electrophoresis with immunofixation, β-2 microglobulin level measurement, 24-h urine protein analysis, kidney and liver function tests, serum free light chain assay, abdominal ultrasonography, and echocardiography to thoroughly assess potential cardiac involvement. If clinically indicated, additional investigations such as bone marrow biopsy or PET-CT may be performed to exclude systemic or hematologic disorders (7).

Treatment options for adnexal and orbital amyloidosis include monitoring, excision, ocular surface reconstruction with amniotic membrane, cryotherapy, and even radiotherapy (3,9,11). Different treatment approaches can be applied depending on the location of the involvement, the presence of functional defects, and cosmetic expectations. In our case, the entire visible lesion was excised during the incisional biopsy stage. The ease of closing the conjunctiva in the fornix area allowed for ocular surface reconstruction without the need for an amniotic membrane. Follow-up examinations showed no recurrence or complications requiring intervention, such as symblepharon.

Ophthalmologic follow-up should include systematic slit-lamp examinations of the conjunctiva and fornices, detailed documentation, and sequential photography of any residual or newly developed conjunctival lesions. Evaluation should also address potential complications such as symblepharon or amyloid recurrence, along with assessment of intraocular pressure and posterior segment status to rule out secondary ocular involvement.

Importantly, conjunctival involvement may be the first clinical manifestation of systemic amyloidosis, with the ophthalmologist often being the first physician to recognize the disease. Therefore, ophthalmologists play a crucial role in initiating the diagnostic workup for this potentially systemic condition. All conjunctival lesions – especially those that mimic malignant processes or persist despite treatment – should be thoroughly evaluated with a high index of suspicion.

Conclusion

Conjunctival amyloidosis can present with various clinical features. Although rare, it should be considered in the differential diagnosis of all benign and malignant lesions of the conjunctiva. Since conjunctival involvement can occasionally be the first clue to a systemic amyloid disease, ophthalmologists have a vital role in early diagnosis. All diagnosed patients should be evaluated for systemic involvement or accompanying lymphoproliferative diseases and followed long-term.

Disclosures
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