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Research Articles

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Ziya KAPRAN
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PRISMA statement of preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/);

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al., for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/);

STROBE statement, a checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/);

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

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Study Limitations: This section should state which data and analyses could not be included in the study, discuss limitations of the study, and give recommendations for future studies.

Conclusion: Highlights the results obtained and conclusions that can be drawn from the study.

Acknowledgements: Any technical or financial support or editorial contributions (statistical analysis, English/Turkish evaluation) towards the study should appear at the end of the article.

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Case reports should present cases which are rarely seen, feature novelty in diagnosis and treatment, and contribute to our current knowledge. The first page should include the title in Turkish and English, an unstructured Turkish summary up to 150 words in length and a corresponding English abstract not exceeding 175 words, and keywords in both languages. The main text should include the introduction, case presentation, discussion, and references. The main text should not exceed 1500 words, excluding references. For case series of 3 or more, the main text should not exceed 2000 words, excluding references.

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CONTENTS

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EDITORIAL

Esteemed Colleagues,

In the second issue of 2023, the Turkish Journal of Ophthalmology features six original studies, one review, and three case reports.

In their study titled "**The Effect of Mask Use on the Ocular Surface During the COVID-19 Pandemic**", Dikmetaş et al. evaluated the relationship between the clinical signs and symptoms of dry eye and the duration of mask use in healthy individuals using regular face masks. The study included 35 patients with no additional ophthalmologic pathology who were divided into two groups, those with ≤6 hours/day of mask use (group 1) and >6 hours/day of mask use (group 2), and compared in terms of Ocular Surface Disease Index (OSDI) score, ocular surface staining with fluorescein, and tear break-up time (TBUT). OSDI values were similar in the two groups, while TBUT was less than 10 seconds in 50% of the eyes in group 1 and 65% of the eyes in group 2. In addition, evaluation of corneal staining according to Oxford staging showed that staining was more severe in patients who wore masks for >6 hours/day. The authors emphasized that prolonged mask use leads to adverse ocular surface changes.

In their study titled "**Clinical Approach to Ocular Cicatricial Pemphigoid**", Çiftçi et al. retrospectively evaluated the medical records of 11 patients diagnosed with ocular cicatricial pemphigoid (OCP). Conjunctival involvement was detected in all eyes included in the study, and eyelid involvement was detected in 14 eyes (63.63%). Eighteen eyes (81.81%) had corneal involvement, most commonly persistent corneal epithelial defect (n=8). According to the Tauber staging system, 7 (31.81%) eyes were stage 2, 8 (36.36%) were stage 3, and 7 (31.81%) were stage 4. Of the 9 patients who underwent biopsy, 6 (66.66%) were histopathologically diagnosed with OCP. Systemic involvement was observed in 5 (45.45%) of the 11 patients, with oral mucosal involvement being the most frequent (18.18%).

In a study by Malkoç Şen and Serbest Ceylanoğlu titled "**Factors Affecting the Incidence of Ptosis After Trabeculectomy**", 312 patients (339 eyes) who underwent trabeculectomy surgery with mitomycin C were evaluated retrospectively and ptosis was detected in 35 (10.3%) of the 339 eyes. Of these, 30 eyes (8.8%) of 30 patients had transient ptosis and 5 eyes (1.5%) of 4 patients had permanent ptosis. Preoperative duration of antiglaucoma drug use, antiglaucoma drugs used, time between trabeculectomy and needling, and ocular massage did not differ significantly between the groups, whereas rates of needling and eye itching due to antiglaucoma drug-related allergy were significantly higher in patients with ptosis.

In a study by Erdem et al. titled "**An Association Between the Intestinal Permeability Biomarker Zonulin and the Development of Diabetic Retinopathy in Type II Diabetes Mellitus**", blood zonulin levels were examined in 33 patients with type II diabetes with no diabetic retinopathy (DR), 28 patients with nonproliferative DR, 28 patients with proliferative DR, and 32 healthy individuals. Zonulin levels were significantly higher in the proliferative DR group compared to the other three groups, as well as in the non-DR and nonproliferative DR groups compared to the control group. The authors stated that high zonulin levels may have an important role in the development of DR, especially in the transition to the proliferative stage.

In their study titled "**Choroidal Vascularity Index and Choroidal Thickness Changes Following Renal Transplantation**", Aksoy et al. investigated changes in choroidal vascularity index (CVI), subfoveal choroidal thickness (SFCT), glomerular filtration rate (GFR), intraocular pressure (IOP), and mean arterial pressure (MAP) in 49 patients who underwent kidney transplantation. While there was a significant difference in GFR and SFCT measurements before and after renal transplantation ($p<0.001$), there were no differences in CVI ($p=0.09$), MAP ($p=0.14$) and IOP ($p=0.84$) measurements.

In a cross-sectional study titled "**Audiometric Evaluation of the Relationship between Sensorineural Hearing Loss and Chronic Glaucoma**", Gülyeşil et al. aimed to evaluate sensorineural hearing function in chronic glaucoma patients and compare the results with healthy individuals. The ocular findings and audiometry results of 24 primary open-angle glaucoma (POAG) patients (group 1, 24 ears), 22 patients with pseudoexfoliative glaucoma (PEG) (group 2, 22 ears), and 21 healthy individuals (group 3, 21 ears) followed for more than 5 years were compared. Group 1 had significantly higher hearing thresholds at 500 and 1,000 Hz compared to group 3, while hearing thresholds at all tested frequencies were higher in group 2 compared to group 3. The authors emphasized the possible coexistence of hearing problems in patients with chronic glaucoma and pointed out the importance of performing routine ocular and otolaryngological examinations in older adults.

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EDITORIAL

The review by Atan et al. titled "**The Effect of Blindness on Biological Rhythms and the Consequences of Circadian Rhythm Disorder**" examines the circadian rhythm disorders caused by blindness and emphasized the need to evaluate sleep problems and plan treatment approaches accordingly in visually impaired individuals.

The case report titled "**Coincident Acute Macular Neuroretinopathy and Paracentral Acute Middle Maculopathy in COVID-19**" by Yılmaz Çebi et al. describes the clinical course of a 29-year-old woman with both acute macular neuroretinopathy and paracentral acute middle maculopathy after COVID-19 infection.

A case series by Yalçınbayır et al. titled "**Different Cases, Different Manifestations of Post-COVID-19 Retinal Artery Occlusion: A Case Series**" is significant in terms of showing that occlusion of the retinal arterial system can occur at different levels following COVID-19 infection. The first case was central retinal artery occlusion (CRAO) with sudden loss of vision, the second was inflammatory peripheral retinal artery occlusion, vasculitis, and uveitis that did not affect vision, and the third was CRAO with progression from orbital cellulitis to orbital apex syndrome.

The other case series in this issue is by Gülpınar İkiz et al., titled "**Flap-Related Complications Following Temporal Inverted Internal Limiting Membrane Flap for Macular Hole Repair**". Their study evaluated three patients with flap-related complications after vitrectomy and temporal inverted flap surgery for the repair of macular holes. The first patient exhibited the "flap closure pattern" followed by delayed spontaneous closure of the macular hole, the second patient developed flap contracture and a nasally located epiretinal membrane after early postoperative closure of the macular hole, and in the third patient, early postoperative flap dislocation was observed.

We hope that the articles selected for this issue will provide you interesting and enjoyable reading.

Respectfully on behalf of the Editorial Board,

Hakan Özdemir, MD

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Turk J Ophthalmol 2023;53:74-78

Original Article

The Effect of Mask Use on the Ocular Surface During the COVID-19 Pandemic

Özlem Dikmetaş, Hilal Toprak Tellioğlu, İzlem Özturan, Sibel Kocabeyoğlu, Ali Bülent Çankaya, Murat İrkeç

Hacettepe University Faculty of Medicine, Department of Ophthalmology, Ankara, Türkiye

Abstract

Objectives: The new coronavirus disease 2019 (COVID-19) pandemic emerged in Wuhan, China in October 2019 and spread rapidly all over the world, making extended mask use an inescapable rule of daily life. Literature data indicate that the use of face masks increases the symptoms of dry eye in addition to preventing the spread of COVID-19. The aim of our study was to evaluate the relationship between the clinical signs and symptoms of dry eye and the duration of mask use in healthy individuals using regular face masks.

Materials and Methods: Thirty-five patients aged 20-60 years with no additional ophthalmologic pathology were included in the study. Participants were stratified by duration of face mask use: ≤6 hours/day (group 1) and >6 hours/day (group 2). The patients were assessed with the Ocular Surface Disease Index (OSDI) questionnaire, fluorescein ocular surface staining, and tear break-up time (TBUT) to evaluate the effect of extended mask use on the ocular surface.

Results: A total of 62 eyes of 35 patients, 20 women (57.1%) and 15 men (42.9%), were included in the study. The two mask use duration groups had similar OSDI values (p=0.736). When the ocular surface staining pattern was examined according to the Oxford scale, 50% (10/20) of the eyes in group 1 were assessed as stage 1 and the other 10 eyes as stage 0. In group 2, 47.6% (20/42) of the eyes were assessed as grade 1, 11.9% (5/42) as grade 2, and 4.7% (2/42) as grade 3.

Conclusion: Prolonged face mask use was shown to cause decreased TBUT and increased ocular surface staining even in healthy individuals. Further studies are needed to investigate changes in the tear film after extended daily mask use.

Keywords: COVID-19, mask use, ocular surface, dry eye

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Introduction

Novel coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1,2] COVID-19 has affected and continues to affect millions of people. Although various vaccines have been studied and applied to prevent the spread of COVID-19 infection, their long-term effects and protectiveness have not been ascertained. Despite ongoing vaccination in various parts of the world, the disease has not been eradicated due to continued transmission and the fact that the vaccination rate has not yet reached 100%.[3] Social distancing, hygiene rules, and the use of personal protective equipment (face masks, visors) are still the most effective ways to prevent the spread of COVID-19 infection.[1,2]

COVID-19 infection is usually spread by close contact or droplet transmission.[4] Although the benefit of using face masks is still a matter of debate, regulatory recommendations led to a rapid increase in their use, especially in enclosed environments where sufficient physical distance cannot be maintained.[1]

In the Tear Film and Ocular Surface Workshop II (TFOS DEWS II) study, dry eye was defined as a multifactorial ocular surface disease characterized by loss of tear homeostasis and subsequent tear instability, hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities.[5] Dry eye disease can be associated with many different clinical symptoms such as ocular pain, dryness, burning, stinging, and foreign body sensation. The Ocular Surface Disease Index (OSDI) was adapted to Turkish by Irkeç et al.[6] and enables the evaluation of subjective symptoms.

The purpose of a face mask is to prevent air from the mouth and nose to spread. However, gaps between the mask and face cause the exhaled air to move upward, creating airflow over the corneal surface.[7] This current accelerates evaporation of the corneal tear film, causing dry spots on the ocular surface. This chain of events results in ocular surface damage and mask-related dry eye disease.[8] The resulting clinical picture demonstrates that prolonged mask use is one of the factors in ophthalmologists' more frequent encounters with ocular symptoms during the pandemic, and has given rise to a new term: mask-associated dry eye.[8,9,10]

Mask-associated dry eye is the most prominent ocular condition associated with masks and may exacerbate existing symptoms in patients who have previously been diagnosed with dry eye, use contact lenses, have low corneal tear quality, have postmenopausal dry eye symptoms, or have undergone eye surgery such as refractive surgery.[9]

To date, studies in the literature examining this subject in different populations have shown that dry eye symptoms may be associated with mask use.[7,8,9,10,11,12] These studies have shown that the feeling of ocular irritation increases with regular mask use.[13] D. E. White, an American ophthalmologist, first described the concept of mask-associated dry eye (which he abbreviated as MADE) on his blog in June 2020.[14] Since then, research has increased in this direction. However, prevalence studies and research into ocular surface staining and quality of life indices are limited and insufficient.[11]

In this study, we aimed to evaluate the relationship between the clinical signs and symptoms of dry eye disease and the duration of mask use in healthy individuals using regular face masks.

Materials and Methods

Ethical approval was obtained from the Hacettepe University Faculty of Medicine Scientific Research Ethics Committee (GO: 20/1023) and the study was conducted in accordance with the ethical principles and practices stated in the Declaration of Helsinki. The study included 35 healthy individuals who presented to the ophthalmology department of Hacettepe University between February 2021 and April 2021 and underwent routine ophthalmologic examination. Patients with signs of retinal pathology, glaucoma, and uveitis were excluded from the study. Each participant's demographic characteristics (e.g., gender, age), comorbidities, contact lens use, ocular surface staining characteristics, fluorescein break-up time, and Schirmer 1 test results were recorded. All participants in the study wore surgical face masks in the standard manner. Those who practiced any additional interventions (e.g., taping on the nose, use of double masks) were excluded from the study. The participants' daily durations of mask use and screen exposure were recorded.

The participants were divided into two groups based on the duration of mask use: ≤6 hours/day (group 1) or >6 hours/day (group 2) at least 5 days per week for the last year. Group 2 included people who wore their mask continuously for the >6-hour period, removing them only during meal breaks. Individuals whose screen exposure time did not exceed an average of 5 hours/day were included in the study.[15] All patients underwent a detailed dilated ophthalmological examination. The patients' Schirmer 1 test, tear break-up time (TBUT), and ocular surface staining patterns were examined. Ocular surface staining was graded from 0 to 5 on the Oxford scale. In addition, symptoms were assessed by administering the OSDI questionnaire. The OSDI survey results ranged from 0 to 100 and were categorized as normal (0-12), mild (13-22), moderate (23-32), and severe (33-100) dry eye.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 23 (IBM Corp, Armonk, NY, USA) software. The Shapiro-Wilk goodness of fit test was used to test whether distributions of numerical variables conformed to normal distribution. Normally distributed numerical variables were presented using descriptive statistics such as mean and standard deviation, while non-normally distributed numerical variables were given using descriptive statistics such as median and interquartile range (IQR). Both the right and left eyes of the

participants were included in the study. Due to the covariance structure between the eyes, generalized estimating equation (GEE) analysis was used to analyze variables affected by mask duration. Level of statistical significance was $p<0.05$.

Results

The study included 35 patients who presented to the ophthalmology department of Hacettepe University for eye examination between February 2021 and April 2021. A total of 62 eyes of the 35 participants were included. GEEs were used to avoid any bias in the results. There were 20 eyes of 10 patients in group 1 (mask use ≤6 hours/day) and 42 eyes of 25 patients in group 2 (mask use >6 hours/day). The median age of the study participants was 43.5 years (IQR: 26-60) in group 1 and 27 years (IQR: 23-29) in group 2. Analysis of the duration of mask use by gender showed that 35% of the women in the study were in group 1 and 65% were in group 2. Similarly, 33.3% of the men in the study were in group 1 and 66.7% were in group 2. The participants' descriptive data and ocular surface findings are summarized in **Table 1.** Both groups had similar OSDI scores (p=0.618). The mean Schirmer 1 test result was 12.25±1.82 mm/5 min (range: 8.68-15.82) in group 1 and 19.47±1.46 mm/5 min (range: 16.59-22.35) in group 2. The difference between the two groups was statistically significant (p=0.002). TBUT was less than 10 seconds in 50% (10/20) of eyes in group 1 and 65% (27/42) of eyes in group 2. However, there was no statistically significant difference between the two groups in terms of TBUT (p=0.736). When the ocular surface staining pattern was examined according to the Oxford scale, 50% (10/20) of the eyes in group 1 were assessed as stage 1 and the other 10 eyes as grade 0. In group 2, 47.6% (20/42) of the eyes were assessed as grade 1, 11.9% (5/42) as grade 2, and 4.7% (2/42) as grade 3 **(Figure 1)**.

Discussion

In this study, we observed that at least half of the subjects using regular daily facial masks had TBUT less than 10 seconds and increased ocular surface staining, but these findings were not reflected in the OSDI results. OSDI scores were similar in both groups. The expected decrease in Schirmer test results with longer duration of mask use was also not observed. TBUT did not differ according to the duration of facial mask use. Oxford scoring showed a marked shift toward dry eye disease with prolonged mask use. Because there was no subgroup analysis according to duration of screen exposure, only people with less than 5 hours of daily screen exposure were included in this study. This threshold was used based on a report by Al Tawil et al.[15] that screen exposure of up to 5 hours was less associated with ocular surface findings.

In a study assessing 67 eyes with the OSDI, Scalinci et al.[7] showed that OSDI scores increased significantly in individuals who used a mask for at least 6 hours or more 5 days a week for the previous 2 months. They observed that individuals who used masks for shorter periods of time had a lower OSDI score.

Krolo et al.[9] also demonstrated in a study including 203 participants that OSDI score increased with the duration of mask use in patients who had a previous dry eye diagnosis. However, their study only described the worsening of dry eye using OSDI scoring. Unlike other studies, our study included the OSDI as

Table 1. Demographic and ocular surface characteristics according to daily duration of mask use

	Duration of mask use		
	Group 1, ≤6 hours (n=20)	**Group 2, >6 hours (n=42)**	**p***
Age (years), median (IQR)	43.5 (26-60)	27 (23-29)	0.150
Schirmer (mm/5 min), mean ± SD (range)	12.25±1.82 (5-30)	19.47±1.46 (5-35)	0.002
OSDI, mean ± SD (range)	17.58±2.71 (0-31)	15.74±2.51 (0-38)	0.618
Tear break-up time, n (%)			0.736
≤10 s	10 (50)	27 (65)	
>10 s	10 (50)	17 (35)	
Ocular surface staining, n (%)			-
Grade 0	10 (50)		
Grade 1	10 (50)	20 (47.6)	
Grade 2		5 (11.9)	
Grade 3		2 (4.7)	

n: Number of eyes, IQR: Interquartile range (25^{th}-75^{th} percentiles), SD: Standard deviation, OSDI: Ocular Surface Disease Index. *Obtained using generalized estimating equations

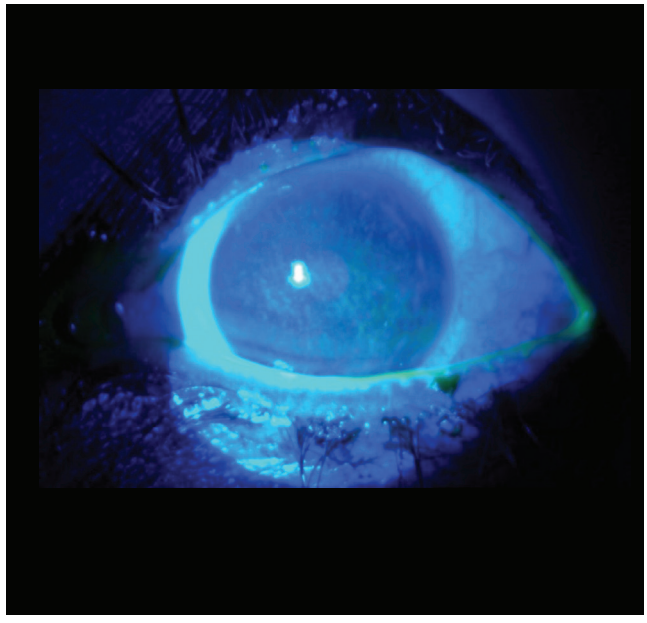

Figure 1. A patient with an OSDI score of 23 showing ocular surface staining
OSDI: Ocular Surface Disease Index

well as the Schirmer test, TBUT, and Oxford scoring, thereby allowing a more objective evaluation. In addition, the inclusion of only individuals with healthy ocular surfaces in the study design increases the reliability of the results.

Moshirfar et al.[8] observed that OSDI scores increased over time with mask use in individuals with no previous dry eye complaints, They also reported that ocular surface complaints increased after uncomplicated cataract surgery.

The most recent TFOS-DEWS II diagnostic pathway is based mainly on clinical symptoms, TBUT, osmolarity, and ocular surface staining.[16] The Schirmer test is not used as a primary assessment. For this reason, Schirmer results, which were also included in our study, should not be considered a direct exclusion criterion for dry eye.

Ocular surface osmolarity has recently been evaluated as one of the main dry eye diagnostic criteria. In mask-associated dry eye disease, it is also possible that mask-mediated intermittent breathing on the ocular surface triggers both irritation and inflammation of the ocular surface.[17] Therefore, the hypothesis that it disrupts osmolarity and consequently leads to ocular and clinical findings has been proposed in other studies, but no quantitative study has been conducted to test this hypothesis.[10] Giannaccare et al.[18] found that OSDI scores were consistent with the idea that abnormal surface evaporation resulting from uncontrolled air flow over the ocular surface may be involved in the pathophysiology of dry eye. Studies should also be conducted on the pathophysiological role of tear osmolarity.

Study Limitations

The main limitations of this study are that it was conducted with a small number of eyes and the duration of the study was short. In addition, the inability to obtain data pertaining to the left eyes of 8 of the patients was another limiting factor. Screen exposure is also known to be an important cause of dry eye and was increased during the pandemic, but people with different screen exposure times were not included in this study. In addition, not analyzing tear osmolarity changes is an important limitation in terms of explaining the etiopathogenesis.

Conclusion

In this study, face mask use was shown to cause decreased TBUT and ocular surface staining even in healthy individuals. Supporting these findings with more comprehensive future studies will help clarify the etiopathogenesis.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the local ethics committee of the Faculty of Medicine (GO: 20/1023).

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Concept: M.İ., Ö.D., Design: M.İ., Ö.D., Data Collection or Processing: Ö.D., H.T.T., İ.Ö., A.B.Ç., Analysis or Interpretation: Ö.D., S.K., A.B.Ç., Literature Search: H.T.T., İ.Ö., Writing: Ö.D., H.T.T., İ.Ö.

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

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Original Article

Clinical Approach to Ocular Cicatricial Pemphigoid

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Abstract

Objectives: To evaluate the demographic data, ocular and systemic findings, clinical management, and outcomes of patients with ocular cicatricial pemphigoid (OCP).

Materials and Methods: The medical records of 11 patients diagnosed as having OCP in the ophthalmology department of Ege University between 2008 and 2021 were evaluated retrospectively.

Results: The patients' mean follow-up time was 14±5.76 months. All eyes (100%) had conjunctival involvement and 18 (81.81%) had corneal involvement. According to the Tauber staging system, 7 (31.81%), 8 (36.36%), and 7 (31.81%) of the eyes were stage 2, 3, and 4, respectively. The diagnosis was confirmed in 6 (66.66%) of 9 patients who underwent biopsy. Amniotic membrane transplantation was performed in 7 eyes, entropion surgery in 2 eyes, and electrocauterization for trichiasis in 5 eyes. Systemic involvement was observed in 45.45% (5/11) of patients, most commonly oral mucosal involvement (18.18%). Review of medical records showed that alkylating agents, steroids, and dapsone were used in patients treated before 2020. Mycophenolate mofetil was preferred to be used in combination with corticosteroids. Although treatment responses before mycophenolate mofetil usage could not be evaluated well because of loss to follow-up, 4 (66.66%) of 6 patients who received steroid treatment combined with mycophenolate mofetil showed partial or complete clinical remission. No serious side effects and drug withdrawal were observed.

Conclusion: OCP is a sight-threatening autoimmune disease that affects older adults. Although positive biopsy results are valuable for diagnosis, negative results do not exclude the diagnosis. The main treatment is systemic immunosuppressives. Disease activity can be suppressed, especially with early initiation of drug therapy. These patients require a multidisciplinary approach. Especially in the presence of isolated ocular findings, ophthalmologists should be able to make the decision to start immunosuppressive treatment, and systemic treatment should not be delayed.

Keywords: Ocular cicatricial pemphigoid, mycophenolate mofetil, cicatricial conjunctivitis, immunofluorescence

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Introduction

Mucous membrane pemphigoid is an autoimmune disease characterized by accumulation of immunoglobulin (Ig) A, IgG, IgM, and/or complement components along the epithelial basal membrane region of mucosal surfaces such as the oral cavity, nasal cavity, esophagus, larynx, and eye.[1] The clinical picture in which mucous membrane pemphigoid primarily affects the eye is called ocular cicatricial pemphigoid (OCP).[2] Although ocular involvement may be unilateral at first, bilateral and asymmetrical involvement is observed over time.[3] There are multiple assessment algorithms for disease stage and progression. The Tauber staging system enables a multidimensional evaluation, as it combines both fornix depth and conjunctival cicatrization assessment in grading.[4] Although the diagnosis can be made clinically, it is supported by biopsy.[5] Systemic immunosuppression is the foundation of treatment.

The aim of this study was to retrospectively evaluate the demographic characteristics, ocular and systemic findings, clinical management, and outcomes of patients with OCP who were followed up in the ophthalmology clinic of Ege University Hospital between 2008 and 2021.

Materials and Methods

Medical records pertaining to 22 eyes of 11 patients with OCP who were followed up in the cornea unit of the Ege University Department of Ophthalmology between 2008 and 2021 were evaluated retrospectively. We excluded patients with cicatrizing conjunctivitis due to secondary causes such as chemical injury or drug use and those with conditions that may be associated with cicatrizing conjunctivitis, including oculodermal diseases such as toxic epidermal necrosis/Stevens-Johnson syndrome and bullous pemphigoid, and rheumatological diseases such as systemic lupus erythematosus and Sjögren's syndrome. The study was approved by the Ege University Faculty of Medicine Ethics Committee and was carried out in accordance with the Declaration of Helsinki.

Demographic data; ocular and systemic findings; Tauber disease stage; conjunctival, skin, or mucosal biopsy results; and treatment preferences and response were evaluated. Best corrected visual acuity (BCVA) in logMAR, lid and eyelash examination to detect pathologies such as entropion, ectropion, trichiasis, and distichiasis, and a slit-lamp examination involving a detailed evaluation of the cornea and conjunctiva were included in the ocular findings. The Tauber staging system for OCP was proposed in 1992 by Tauber et al.[4] Stage 1 is subconjunctival scarring and fibrosis; stage 2 consists of fornix foreshortening of 0-25% (stage 2a), 25-50% (2b), 50-75% (2c), or 75-100% (2d) without symblepharon; stage 3 involves horizontal symblepharon of 0-25% (stage 3a), 25-50% (3b), 50-75% (3c), or 75-100% (3d); and stage 4 is ankyloblepharon. The need for surgical intervention and which surgical procedures were performed were recorded. The frequency of systemic involvement was evaluated. In addition, the effectiveness, adverse effect profile, and remission/recurrence rates of systemic mycophenolate mofetil therapy, which is currently the preferred treatment, were evaluated in 6 patients.

Results

The median age of the patients was 76 years (range: 53-87) and the female:male ratio was 8:3. Mean BCVA was 1.9±0.97 logMAR (range: 0.3-3) before treatment and 1.74±0.95 logMAR (range: 0.2-3) after treatment. The mean follow-up time was 14±5.76 months. The patients' data are summarized in **Table 1.**

Fourteen (63.63%) of the 22 eyes had lid involvement, which was entropion in 5 eyes (22.72%). Conjunctival involvement was present in all eyes (100%). **Figure 1** is an anterior segment photograph showing inferior fornix shortening. Eighteen eyes (81.81%) had corneal involvement, most commonly persistent epithelial defect (n=8). **Figure 2** shows anterior segment photographs of a patient with bilateral corneal erosion. Amniotic membrane transplantation was performed in 7 eyes but was not effective in preventing recurrence of corneal erosions in 5 (71.42%) of them. Recurrent corneal erosion was observed at a mean of 28.8±9.88 days (range: 18-42) after amniotic membrane transplantation.

According to the Tauber staging system, 7 (31.81%) of the eyes were stage 2, 8 (36.36%) were stage 3, and 7 (31.81%) were stage 4. Nine of the 11 patients underwent biopsy for histopathologic examination. In 2 patients with data from before 2011, the diagnosis was made clinically and immunosuppressive treatment was initiated urgently because the disease was advanced and there was no suspected differential diagnosis. Conjunctival biopsy was performed in 6 patients, oral mucosa biopsy in 2 patients, and scalp biopsy in 1 patient. In 2 (33.33%) of the conjunctival biopsies, there was no subepithelial separation and no accumulation was detected in immunofluorescence (IF) examination. In the other 4 conjunctival biopsies (66.66%), ulceration and/or subepithelial separation were observed on the surface, but IF examination was inconclusive as an intact dermo-epidermal junction was not observed. Subepithelial/subepidermal separation was observed in 2 non-conjunctiva mucosal biopsies

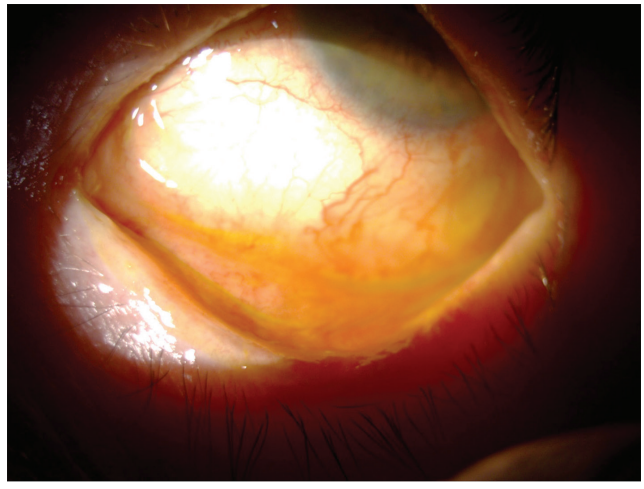

Figure 1. Anterior segment photograph showing inferior fornix shortening

Table 1. Demographic data of the patients, pre- and post-treatment disease stage and visual acuities, biopsy results, and systemic and surgical treatment details

Patient no.	Eye	Age (years)/ gender	BCVA, logMAR (initial)	BCVA, logMAR (post-treatment)	Tauber grade (initial)	Tauber grade (post-treatment)	Biopsy	IF	Surgical treatment	Systemic treatment	Systemic involvement	Follow-up time (months)
1	Right	62/female	0.5	0.3	2b	2a	Conjunctiva, Tunica propria not observed	Negative	Electrocauterization	MM, methylprednisolone	None	18
	Left		0.3	0.5	3a	3a			AMT			
2	Right	65/female	2.3	1.8	3a	3a	Conjunctiva, Epithelium not observed	Intact DEJ not observed	AMT	MM, methylprednisolone	Oral mucosa	20
	Left		0.7	0.5	3d	3c			AMT			
3	Right	72/male	2.8	2.3	3d	3c	Conjunctiva, Subepithelial separation not observed Superficial ulceration	Negative	None	MM, methylprednisolone	None	19
	Left		2.8	2.3	3d	3d			Electrocauterization			
4	Right	87/female	3	3	4	4	Oral mucosa, Subepithelial separation	Negative	None	Cyclophosphamide	Skin, esophagus	14
	Left		2.8	2.8	4	4			None			
5	Right	76/female	0.5	0.2	2d	2c	Conjunctiva, Subepithelial separation not observed	Negative	Electrocauterization	MM, methylprednisolone	None	22
	Left		1.8	1.8	2d	2d			AMT			
6	Right	85/female	1	1.3	3a	3c	--	--	None	Methylprednisolone	None	12
	Left		1.3	1.3	2b	2d			None			
7	Right	79/male	3	3	4	4	Scalp, Subepidermal separation	Negative	None	Azathioprine methylprednisolone	Skin	14
	Left		1.3	1	3d	3d			None			
8	Right	79/female	2.8	2.8	4	4	--	--	Electrocauterization	Methylprednisolone	None	10
	Left		0.3	0.2	2a	2a			None			
9	Right	53/female	2.8	2.3	2d	2d	Conjunctiva, Subepithelial separation	Intact DEJ not observed	AMT	MM, methylprednisolone	Oral mucosa	15
	Left		2.3	1.8	2d	2d			AMT			
10	Right	87/female	2.3	2.3	4	4	Oral mucosa, Subepithelial separation	Linear IgA accumulation	None	Dapsone	Oral mucosa	7
	Left		2.3	1.8	4	4			Entropion surgery			
11	Right	74/male	2.3	2.3	3b	3b	Conjunctiva, Subepithelial separation	--	Electrocauterization	MM, methylprednisolone	None	3
	Left		2.8	2.8	4	4			AMT, entropion surgery			

AMT: Amniotic membrane transplantation, DEJ: Dermo-epidermal junction, BCVA: Best corrected visual acuity, IF: Immunofluorescence examination, MM: Mycophenolate mofetil

and the scalp biopsy, while linear IgA accumulation at the dermo-epidermal border was observed in one of the oral mucosal biopsies. Although histopathological findings supporting the diagnosis of OCP were observed in 6 (66.66%) of the 9 patients who underwent biopsy, the results of IF examination were not significant. Of the conjunctival biopsies, 2 had no intact dermo-epidermal junction, 2 had subepithelial separation, and 2 had no subepithelial separation and IF accumulation. **Figure 3** shows conjunctival biopsy samples stained with hematoxylin and eosin.

Surgery was performed only in the event of complications. Amniotic membrane transplantation was performed in 7 eyes, entropion surgery in 2 eyes, and electrocauterization due to trichiasis in 5 eyes. Amniotic membrane transplantation was performed to treat epithelial erosions and for ocular surface reconstruction in 7 eyes with recurrent epithelial erosions and possible risk of corneal melting despite topical and systemic treatment and inadequate response to bandage contact lens application.

Systemic involvement was observed in 5 (45.45%) of the 11 patients, with oral mucosal involvement being most frequent (18.18%). One patient had a history of dilation for esophageal stenosis.

When the general medical records of the patients were examined, it was seen that alkylating agents, steroids, and dapsone were used in patients treated before 2020. We noted that with emerging evidence of its effectiveness in OCP, the use of mycophenolate mofetil in combination with corticosteroids became preferred. Mycophenolate mofetil (CELLCEPT 500 mg, Roche, Milano, Italy) was administered orally at a dose of 1,000 mg/day divided into 2 doses. Patients underwent hemogram and kidney and liver function tests before treatment, once a month for the first 3 months of treatment, and every 3 months thereafter. Treatment responses in the period before mycophenolate mofetil treatment could not be assessed well due to patient loss to follow-up. However, partial or complete clinical remission was observed in 4 (66.66%) of 6 patients who received combined steroid and mycophenolate mofetil therapy. Due to the progressive nature of the disease, we evaluated remission and determined that Tauber disease stage did not progress after treatment and there was no increase or decrease in BCVA values, similar to the literature.[6] Systemic involvement was present in 2 (33.33%) of the 6 patients who received this treatment. Treatment responses could not be evaluated in one of the patients who received mycophenolate mofetil therapy because they died as a result of aspiration pneumonia (patient 11) and in another patient who developed concomitant secondary bacterial keratitis (patient 1). No serious adverse effects or drug discontinuation were observed in any of the patients. One patient experienced diarrhea early in treatment and needed only supportive treatment. During follow-up, recurrence in the form of recurrent corneal epithelial defect was observed in 4 (33.33%) of 12 eyes. Comparisons of clinical data between patients using mycophenolate mofetil and other systemic immunosuppressants are summarized in **Table 2.**

Although systemic immunosuppression formed the basis of treatment, all patients used artificial tears containing sodium hyaluronate (Eyestil 0.15%, Sifi, Catania, Italy); cyclosporine drops (RESTASIS® 0.05%, Allergan, Irvine, CA, USA); and topical loteprednol (Lotemax 5 mg/mL, Bausch & Lomb, Tampa, FL, USA) or fluorometholone (Flarex 0.1%, Novartis, Puurs, Belgium), which are surface-active corticosteroids, during exacerbations. Corticosteroid dose was increased in the early postoperative period in patients who underwent surgery.

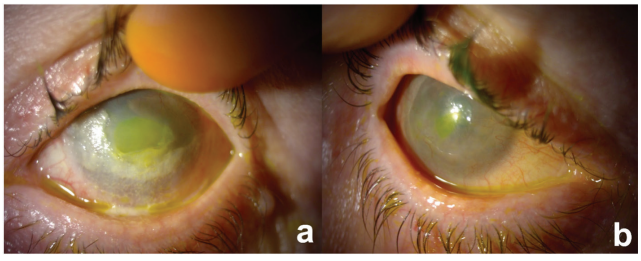

Figure 2. a) Anterior segment photograph showing the recurrence of fluorescein-stained corneal erosion in the left eye of a patient who underwent amniotic membrane transplantation due to recurrent corneal erosion. b) Anterior segment photograph of the same patient's right eye showing corneal vascularization and fluorescein-stained central erosion

Table 2. Comparison of clinical data of patients using mycophenolate mofetil and other systemic immunosuppressants

	Mycophenolate mofetil	Other treatments
Conjunctival involvement	12/12 (100%)	10/10 (100%)
Corneal involvement	11/12 (91.66%)	7/10 (70%)
Lid involvement	5/12 (41.66%)	9/10 (90%)
Tauber stage ≥3	7/12 (58.33%)	8/10 (80%)
Systemic involvement	2/6 (33.33%)	3/5 (60%)

Discussion

OCP is a rare autoimmune disease that usually affects older adults and is characterized by progressive inflammation and cicatrization of the conjunctiva. Its incidence has been reported at rates varying from 1/20,000 to 1/46,000 in the literature.[7] Patients are usually diagnosed in the 7th decade and the condition is more common in women.[7,8] In this study, 8 (72.72%) of the 11 patients were women and the median

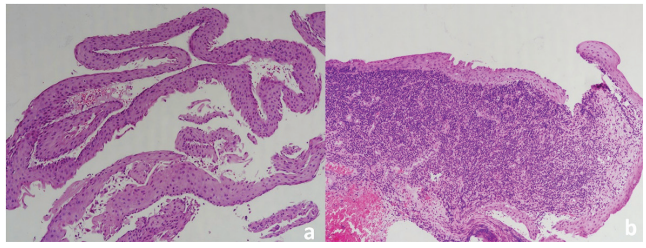

Figure 3. a) Conjunctival biopsy showing only the epithelial area, separated from the subepithelial area (H&E x200). b) Conjunctival biopsy with intense inflammatory cell infiltration in the tunica propria and no subepithelial separation (H&E x100)

age was 76 (range: 53-87). Thus, the demographic data were consistent with the literature. Similarly, systemic involvement has been reported in approximately 50% in the literature and was observed in 45.45% of the patients in our study.[5] The most common extraocular finding is oral mucosal involvement, with desquamative gingivitis usually observed. Patients may present initially to a dentist.[9] In our study, oral mucosal involvement was present in 2 of the 5 patients with systemic involvement.

The Tauber staging system for OCP was preferred in this study because it includes both the degree of conjunctival cicatrization in the Foster system and fornix shortening used in the Mondino system.[4]

The ocular findings of the disease vary. In a cohort study with 34 eyes, the most common clinical finding was conjunctival involvement (100%), followed by corneal involvement (88%) and lid involvement (71%).[10] In the present study, the frequency of conjunctival involvement was 100%, but the frequency of corneal (81.81%) and lid (63.63%) involvement was lower compared to the literature. The lower rates of corneal and lid involvement may be explained by the relatively high proportion of patients with early-stage disease.

The diagnosis is generally delayed because initial findings of the disease are non-specific.[11] In a retrospective study of 51 patients, it was reported that 83% of patients were at clinical stage 3 or higher at diagnosis.[12] In our study, 68.18% of the patients were stage 3 or above. The relatively low number of patients in the advanced stage may be attributed to the high clinical suspicion in our center, which is an important criterion in the early diagnosis of the disease.

The combination of clinical findings and IF confirmation is very valuable in the diagnosis of OCP. Conventional histological examination is insufficient, and demonstrating immune deposit accumulation in the conjunctival basement membrane by direct IF is the gold standard in the diagnosis. Despite adherence to proper sampling techniques, the sensitivity of the direct IF technique in the literature varies widely between 20% and 87%.[7,13] In this study, biopsy tissues were collected appropriately and transferred for pathological examination.[14] Histopathological findings supporting the diagnosis of OCP were observed in 6 (66.66%) of 9 biopsied patients, while immune accumulation was detected in 1 (20%) of the 5 biopsies in which the dermo-epidermal junction in IF examination of 7 biopsies. IF examination in patients with OCP reveals IgG, complement C3, and to a lesser extent linear IgA accumulation in the epithelial basement membrane zone.[15] Differential diagnosis from linear IgA disease cannot be made pathologically but can be made clinically. Although linear IgA disease was considered in the differential diagnosis of the patient with linear IgA accumulation in oral mucosal biopsy, evaluation together with their dermatological and ocular findings was consistent with OCP. Positive biopsy is a valuable finding, but negative biopsy results do not exclude the diagnosis.

Although the prognosis of surgical outcomes is unfavorable in OCP patients, surgery may be required in some cases, such as entropion, which causes ocular surface irritation.[16] Cataract surgery can be performed under adequate immunosuppressive therapy to increase vision, but keratoplasty is recommended only for tectonic purposes, as it has a very poor prognosis due to limbal stem cell deficiency, insufficient lid function, and dry eye.[17] In this study, cataract surgery was not planned because none of the patients had cataract severe enough to impact visual prognosis. In addition, limbal allograft transplantation can be considered for limbal stem cell deficiency and the associated visual impairment. However, the procedure is not preferred due to the inflammatory nature of the disease and the fact that the 1-year success rate in allograft applications is around 50%.[18] In our study, amniotic membrane transplantation was performed in 7 eyes for recurrent corneal erosion and ocular surface reconstruction, 2 eyes underwent entropion surgery, and 5 underwent electrocauterization. Despite performing the surgical interventions after suppressing the inflammatory process, amniotic membrane transplantation failed to prevent the recurrence of corneal ulcerations in 5 eyes (71.42%). Considering that even minor conjunctival traumas can accelerate disease progression in these patients, the 8/0 Vicryl sutures and surgical manipulations made during amniotic membrane transplantation may have triggered inflammation. Barabino et al.[19] reported that of 9 eyes with advanced OCP, 6 eyes (66.7%) exhibited goblet cells and restoration of the normal conjunctival epithelium on impression cytology performed 4 weeks after amniotic membrane transplantation. In our study, the patients were only assessed clinically after surgery, and the lack of cytological examination may have resulted in a limited evaluation of response. It has been suggested that during the treatment of corneal ulcerations in OCP patients, amniotic grafting should be performed only on the corneal surface to avoid surgical manipulation of the conjunctiva.[20]

Systemic immunosuppression is the foundation of treatment. Mild to moderate inflammation can be suppressed with dapsone.[8] However, because of the need for close follow-up and some serious side effects such as hemolytic anemia and hepatitis, dapsone therapy is now being replaced by mycophenolate mofetil. Mycophenolate mofetil was preferred as the first-line treatment option in our clinic. In a retrospective study of 23 patients treated with mycophenolate mofetil, clinical remission was reported in 82.6% of patients within 12 months.[21] In our study, partial or complete clinical remission was documented in 66.66% of patients receiving mycophenolate mofetil therapy. The lower remission rate in our study may be explained by the small number of patients (one of whom died) and the relatively short follow-up period.

Study Limitations

Limitations of this study include its retrospective study design and the limited sample size. Larger prospective studies on this subject are needed.

Conclusion

OCP is a rare, sight-threatening disease that affects older people. Although positive biopsy results are very valuable in the diagnosis, negative results do not rule out the disease. The main treatment is systemic immunosuppressives, and disease activity

can be suppressed with early initiation of therapy. This disease requires a multidisciplinary approach; in patients with isolated ocular findings, ophthalmologists should be able to make immunosuppressive treatment decisions and systemic treatment should not be delayed.

Ethics

Ethics Committee Approval: Ege University Medical Research Ethics Committee, 22-IT/20.

Informed Consent: Obtained.

Peer-review: Internally and externally peer reviewed.

Authorship Contributions

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

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Original Article

Factors Affecting the Incidence of Ptosis after Trabeculectomy

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Abstract

Objectives: The aim of this study was to investigate the incidence of postoperative ptosis after primary trabeculectomy and the possible factors contributing to ptosis.

Materials and Methods: A total of 312 patients (339 eyes) who underwent trabeculectomy with mitomycin-C between 2015 and 2020 were retrospectively evaluated. Patients who had regular follow-up for at least 6 months and no history of ptosis or ptosis surgery were included. Age, sex, glaucoma type, preoperative and postoperative intraocular pressure, preoperative and postoperative antiglaucoma medications, number of antiglaucoma drops, duration of antiglaucoma medication use, history of eye itching due to antiglaucoma medication-associated allergy, duration of follow-up, postoperative needling, needling time, and ocular massage were recorded. Ptosis was defined as ≥2 mm reduction in margin-reflex distance 1 from preoperative levels. Ptosis that had not improved for at least 6 months was considered persistent ptosis. Multivariate logistic regression was used to determine potential predictors of ptosis development.

Results: Ptosis after trabeculectomy was observed in 35 of 339 eyes (10.3%). Thirty eyes of 30 patients (8.8%) had transient ptosis and 5 eyes of 4 patients (1.5%) had persistent ptosis. Preoperative duration of antiglaucoma medication use, drug(s) used (prostaglandin analogs, beta-blockers, alpha-2 agonists, carbonic anhydrase inhibitors, or combinations of these), needling time, and ocular massage after trabeculectomy did not differ significantly between groups ($p>0.05$). Needling and eye itching due to antiglaucoma medication-associated allergy were significantly higher in patients with ptosis ($p<0.05$).

Conclusion: Ptosis after trabeculectomy is an important problem for glaucoma patients. It has been observed that needling and a history of eye itching due to antiglaucoma drug-associated allergy may increase the risk of ptosis.

Keywords: Medication-associated allergy, glaucoma, needling, ptosis, trabeculectomy

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Introduction

In the literature, the incidence of ptosis following intraocular surgery is reported to be 10-11.4%.[1,2] Despite its high frequency, ophthalmologists underestimate the impact of this complication on patients' quality of life. Postoperative ptosis is a multifactorial condition that may develop transiently due to eyelid edema, eyelid or intraorbital hematoma, ocular inflammation, and neurogenic causes, but persistent ptosis can also occur as a result of dehiscence or disinsertion of the levator aponeurosis.[3,4,5] Although it often improves within months of surgery, ptosis may be permanent and require corrective surgery. This complication is reported to be more common after glaucoma surgery than after other anterior segment surgeries.[2]

Trabeculectomy is one of the most common glaucoma surgeries in the world. Ptosis after trabeculectomy has been reported at rates between 8% and 19%.[6,7,8,9,10] The higher rate may be related to the effect of manipulations performed to create adequate surgical space during trabeculectomy or to chronic bleb irritation.[2] Ptosis can severely impair quality of life in glaucoma patients, causing astigmatism and impairing vision by increasing existing visual field defects, and it also makes it difficult to measure intraocular pressure (IOP) by applanation tonometry.[7,8,9,10,11] It is important to know the risk factors and take precautions in glaucoma patients, as well as to inform patients about this issue before trabeculectomy.

The present study aimed to investigate the incidence and possible risk factors of ptosis after trabeculectomy, a filtration surgery.

Materials and Methods

The medical records of 339 eyes of 312 patients who underwent trabeculectomy with antimetabolite were retrospectively reviewed. Patients who were followed up and surgically treated by the same ophthalmologist (E.M.S.) in both the glaucoma and oculoplastic surgery clinics between January 2015 and May 2020 were included. The study was conducted in accordance with the tenets of the Declaration of Helsinki and received ethics committee approval. Written informed consent form was obtained from the patients whose images were used.

We included patients who had been followed up regularly for at least 6 months after trabeculectomy. Exclusion criteria included inadequate documentation, history of ptosis or ptosis surgery, history of intraocular surgery within 6 months, and combined surgeries. All patients were white.

The following data were obtained from the patients' medical records: age, sex, pre- and postoperative IOP, glaucoma type (primary open angle glaucoma, pseudoexfoliation glaucoma, primary angle closure glaucoma, or secondary glaucoma), antiglaucoma drug used preoperatively (prostaglandin analogs [PGA], beta-blockers, alpha 2 agonists, carbonic anhydrase inhibitors, or combinations thereof), number of antiglaucoma drops, the duration of antiglaucoma medication use, history of eye itching due to antiglaucoma medication-associated allergy, duration of follow-up, whether needling was done after trabeculectomy, needling time, and ocular massage, and ptosis (transient or persistent). Ptosis was defined as a ≥2 mm decrease in margin-reflex distance 1 (MRD1), and patients with upper eyelid defect in visual field test were included. Ptosis that developed after trabeculectomy and resolved spontaneously within 6 months was considered transient ptosis. Ptosis that lasted more than 6 months was classified as persistent ptosis.

All procedures (trabeculectomy and ptosis surgery) were performed by one experienced surgeon (E.M.S.). All patients underwent trabeculectomy with mitomycin C (MMC) under sub-tenon local anesthesia using the same surgical instruments and technique and only a corneal traction suture. Fornix-based conjunctival incisions with square scleral flaps were made and 0.2 ng/mL MMC was applied beneath the scleral flap for 2 minutes. The scleral flap was made in the superior nasal quadrant. Follow-up examinations were scheduled by the same ophthalmologist at postoperative 1, 2, and 7 days; 2, 4, 6, and 8 weeks; 3, 6, 9, and 12 months, and every 4-6 months thereafter.

In case of increased IOP and decrease in bleb height, ocular massage was performed by the bleb with a cotton-tipped applicator under slit-lamp biomicroscopy. The massage was continued until swelling of the bleb and dispersion of aqueous humor under the conjunctiva was observed. A speculum was not placed for this procedure. Patients were taught how to do ocular massage over the lower eyelid and were advised to perform it nightly before sleeping while looking up. The bleb was evaluated 1 week later to determine whether to continue the ocular massage. Needling was performed in the operating room by the same surgeon using a sterile surgical drape and speculum.

Statistical Analysis

Statistical analyses were performed with IBM SPSS Statistics version 22.0 (IBM, Armonk, NY, USA). Categorical data were presented as frequency and percentages and continuous data were presented as the mean ± standard deviation. The Shapiro-Wilk's test and histograms were used to evaluate for normal distribution of the data. In the comparison between groups with and without ptosis, parameters with normal distribution were evaluated with the independent samples t-test, and those without normal distribution were evaluated with the Mann-Whitney U test. For categorical variables, the chi-square test was used. Multivariate logistic regression was used to determine potential predictors of ptosis development for variables with a p value ≤0.20. A p value 0.05 was considered statistically significant.

Results

A total of 339 eyes of 312 patients that underwent trabeculectomy with MMC were retrospectively included in this study. The total number of eyes with ptosis was 35 (10.3%). Transient ptosis was observed in 30 eyes (8.8%) and persistent ptosis in 5 eyes (1.5%). All cases of ptosis were aponeurotic; none of the patients had levator dysfunction. **Figure 1A** shows a patient with left aponeurotic ptosis 6 months after trabeculectomy with inferior and superior arcuate defects in the visual field. **Figure 1B** shows the visual field assessed after

lifting the left eyelid, demonstrating that the patient will benefit from ptosis surgery. **Figures 1C and 1D** show photographs before and after ptosis surgery, respectively.

The patients' characteristics are presented in **Table 1.** There were no statistical differences between patients with and without ptosis after trabeculectomy in terms of mean age (p=0.91), sex (p=0.38), or duration of follow-up (p=0.06). IOP did not differ significantly between the groups.

The patients' glaucoma types, antiglaucoma medication usage, needling rate and timing, ocular massage, and history of eye itching are summarized in **Table 1.** Needling after trabeculectomy and history of eye itching due to antiglaucoma medication-associated allergy were considered clinically significant factors associated with increased ptosis. Needling was performed once in this study. The mean time between trabeculectomy and needling was 4.6±1.3 weeks in the patients with ptosis and 5.9±1.7 weeks in the patients without ptosis (p=0.18). None of the patients had postoperative procedures such as laser suture lysis, bleb revision, or compression suture. Levator aponeurosis advancement was performed within a year in all patients with persistent ptosis. No bleb failure was observed after ptosis surgery.

Multivariate logistic regression was used to identify potential and final predictors of ptosis development after trabeculectomy. When age, sex, eye itching, postoperative ocular massage, needling, needling time, and PGA use were evaluated in multivariate logistic regression analysis, only preoperative history of eye itching due to antiglaucoma medication-associated allergy (odds ratio [OR]=2.52, 95% confidence interval [CI]: 0.032-0.202, p=0.0001) and needling (OR=1.41, 95% CI: 0.098-0.608, p=0.002) were found to be predictive of ptosis development (**Table 1**).

Discussion

In the present study, we investigated the incidence of ptosis after trabeculectomy and the factors that may be associated with this complication. In order to avoid the possible influence of surgeons and surgical techniques on outcomes, we included only patients operated on by the same surgeon with the same technique and surgical instruments. Combined surgeries were excluded to evaluate only the effect of trabeculectomy. In this study, the incidence of ptosis after trabeculectomy was 10.3%, which is comparable to previous studies (8-19%).[6,7,8,9,10] The incidence of persistent ptosis was 1.5%. We determined that eye

Table 1. Univariate and multivariate regression analysis of factors associated with ptosis after trabeculectomy

Parameters	Ptosis (34 patients, 35 eyes)	No ptosis (278 patients, 304 eyes)	Univariate analysis p-value (95% CI for OR)	Multivariate analysis p-value (95% CI for OR)
Age (years)	62.0±16.3	63.09±15.1	0.686 (0.982-1.028)	0.91 (0.531-20.738)
Sex (n female/male)	17/18	171/133	0.388 (0.676-2.743)	0.38 (0.901-1.057)
Duration of follow-up (months)	27.8±17.4	34.3±20.2	0.072* (0.998-1.037)	0.325 (0.965-1.112)
Preop IOP (mmHg)	22.3±10.9	23±6.7	0.925 (0.908-1.112)	
Postop IOP (mmHg)	13.0±2.9	11.7±2.5	0.287 (0.572-1.180)	
Glaucoma type (%) POAG PXG PACG Secondary	 31.4 42.9 2.9 22.9	 21.1 51.0 3.6 24.4	 0.388 (0.046-3.241) 0.689 (0.085-5.583) 0.733 (0.041-13.050) 0.411 (0.046-3.712)	
Number of preop antiglaucoma medications	2.24±0.7	2.23±0.7	0.983 (0.569-1.781)	
Preop duration of antiglaucoma medication use (months)	12.5±6.6	13.4±9.8	0.243 (0.990-1.109)	
Antiglaucoma drug used (%) PGA Beta-blocker Carbonic anhydrase inhibitor Alpha-2 agonist	 28.6 42.3 40.8 53.2	 41.0 39.1 47.3 51.1	 0.155* (0.266-1.235) 0.264 (0.328-1.357) 0.332 (0.698-2.902) 0.658 (0.423-1.722)	0.544 (0.460-4.370)
Preop history of eye itching due to antiglaucoma medication-associated allergy (%)	54.3	6.6	**0.0001*** (7.540-37.713)	**0.0001**** (9.803-73.528)
Postop ocular massage (%)	22.9	13.3	0.134* (0.818-4.535)	0.71 (0.193-3.067)
Postop needling (%)	62.9	20.7	**0.0001*** (3.085-13.565)	**0.002**** (0.098-0.608)
Postop needling time (weeks)	4.6±1.3	5.9±1.7	0.288 (0.890-1.479)	

Data are expressed as mean ± SD or percentage of eyes. IOP: Intraocular pressure, Preop: Preoperative, Postop: Postoperative, POAG: Primary open angle glaucoma, PXG: Pseudoexfoliation glaucoma, PACG: Primary angle closure glaucoma, PGA: Prostaglandin analog, OR: Odds ratio, CI: Confidence interval, SD: Standard deviation *p≤0.20, **p<0.05, significant results are shown in bold

itching due to allergy to antiglaucoma medication and needling might be related to the development of ptosis. Patients with and without ptosis showed no significant differences in age, sex, duration of follow-up, glaucoma type, antiglaucoma medication number and duration of use, type of antiglaucoma agent, or ocular massage.

There are few prospective studies in the literature reporting ptosis after trabeculectomy.[7,8] Jampel et al.[8] reported that ptosis after trabeculectomy is one of the most important postoperative complications and had an incidence of 12% in the first month. However, ptosis was assessed subjectively, and the prevalence of ptosis at 6 months was not reported.[8] The mean follow-up time of the ptosis group in our study was 28 months. In another prospective study, the incidence of ptosis after trabeculectomy with MMC performed by the same surgeon using the same technique was reported to be 19%.[7] Naruo-Tsuchisaka et al.[7] reported that the mean follow-up time was only 6 months, and argued that the presence of an intraoperative traction suture in the peripheral cornea or a postoperative procedure (laser suture lysis, needling, transconjunctival scleral flap suture, or compression suture) did not affect the incidence of ptosis. In addition, the reason for the higher rate compared with other studies was not reported.[7] Among retrospectively designed studies, the incidence of ptosis after trabeculectomy was 10.7% in a study by Song et al.[9] and 12.5% in a study by Fukushima et al.[10] According to Song et al.,[9] there was no association between ptosis and cataract surgery, type of conjunctival flap, or previous ocular surgery, but the role of antiglaucoma drugs or any information about the surgeons were not reported. In our study, we included only trabeculectomy procedures to standardize the operation time. Fukushima et al.[10] reported that deepening of the upper eyelid sulcus (DUES) may be an important predictor of ptosis after trabeculectomy and that

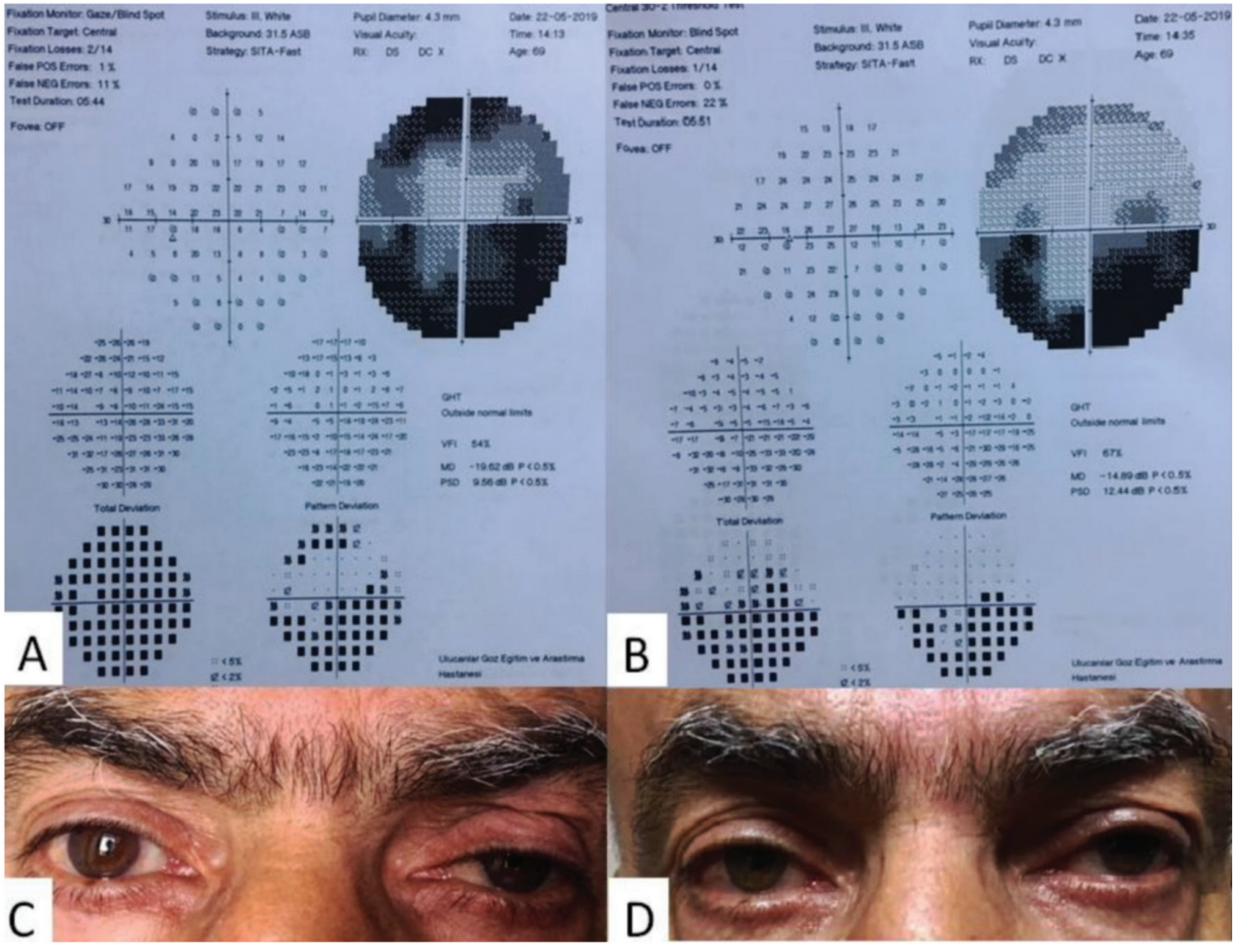

Figure 1. Evaluation of a 69-year-old male patient who had persistent ptosis on following trabeculectomy. A) Superior and inferior arcuate defects were detected on visual field after trabeculectomy. B) The visual field test was repeated 15 minutes later while lifting the left eyelid. On the second test, the inferior arcuate defect (associated with glaucoma) remained while the superior visual defect (due to ptosis) was absent. This indicated that ptosis surgery would benefit the patient and significantly improve his quality of life. C) Left persistent ptosis after trabeculectomy (MRD1: 1 mm). D) The left upper ptosis improved after levator aponeurosis advancement
MRD1: Margin-reflex distance 1

there was no difference between the ptosis and non-ptosis groups in terms of glaucoma types, number of antiglaucoma drugs, or postoperative needling times.

In addition, traction of the levator muscle complex by bridle sutures or forceps, eyelid speculum, and excessive infraduction may increase the rate of ptosis after trabeculectomy.[5,12] We chose corneal traction sutures and the same surgical instrumentation for all procedures. Many factors have been investigated in all these studies, but there is no clear consensus on the risk factors for this important complication. This may be attributable to the preference of different surgical techniques and surgical instruments, different surgeons, or different follow-up approaches.

Chronic eye itching is one of the known causes of aponeurotic ptosis.[13] Trauma to the levator muscle complex due to eye itching or ocular massage may lead to easier detachment of the already weakened aponeurosis in patients undergoing trabeculectomy. Manipulation of the bleb by needling is another procedure that may cause trauma to the levator complex in these patients. A comparison of the aforementioned factors has not been published in the literature. In our study, a higher rate of ptosis was observed in patients with needling and eye itching. Although needling is a short procedure, eyelid edema, minor trauma from the procedure or the blepharostat, and inflammation may have caused ptosis. In addition to the trauma to the levator aponeurosis during trabeculectomy, these mechanisms might have contributed to the development of ptosis. Needling was performed 4-5 weeks after trabeculectomy in our study and may cause a second separation of the levator aponeurosis, which was already traumatized during trabeculectomy. Any intervention in the early period after trabeculectomy can cause further separation of the aponeurosis. In patients with ptosis, the time between surgery and needling was approximately 1.3 weeks earlier than in those without ptosis. However, this difference did not prove to be statistically significant.

The development of an allergic reaction to antiglaucoma medication results in eye redness, dryness, tearing, chronic irritation, and eye itching.[14,15,16,17,18] In such cases, the patient is expected to cause mechanical eyelid trauma. To our knowledge, there are no data on ptosis associated with a history of allergy to antiglaucoma medication. Eyelid rubbing due to an allergic reaction may cause aponeurotic ptosis in patients who either exert excessive force on their eyelids or have an intrinsically weak levator aponeurosis. Itching may also be considered a minor and persistent trauma. Although the type of glaucoma drug used was not associated with the development of ptosis in our study, the literature data indicates that most allergies are caused by the alpha-2 agonist and PGA groups.[14,15,16,17,18] In patients with eye itching caused by an allergy to topical antiglaucoma medication, it should be replaced with another antiglaucoma drug known to be less allergenic, and treatment with both topical and oral antiallergic drugs should be provided depending on symptom severity.

Ocular massage is a simple technique used to treat early bleb failure after trabeculectomy. Although no significant difference was found between the groups with and without ptosis in our study, these patients should be advised to be careful with massage.

One of the most preferred agents in glaucoma treatment is PGAs, but they are associated with many side effects involving the ocular appendages. Prostaglandin-associated periorbitopathy (PAP) has been reported after the use of PGA and includes eyelid pigmentation, eyelash changes, dermatochalasis, orbital fat atrophy, enophthalmos, narrow orbit, levator dysfunction, DUES, and ptosis.[19,20,21] In addition, a possible association between PGA exposure and failure of ptosis surgery has been reported.[22] In the study by Fukushima et al.,[10] PGA was used in all cases in both the blepharoptosis and non-blepharoptosis groups, but other antiglaucoma drugs were not discussed. In our study, no significant difference was found between the use of PGA and other antiglaucoma agents (beta-blockers, alpha-2 agonist, and carbonic anhydrase inhibitors) in the development of ptosis. The reason for this could be the high awareness of PAP and the replacement of PGA with another agent as soon as DUES is noticed. It is very important to keep in mind the periorbital side effects of PGA use and ensure glaucoma specialists are aware of this issue.

Study Limitations

Although this study evaluated a large number of parameters in 339 eyes after trabeculectomy, it has several limitations. Firstly, it was a retrospective study. Another limitation is that we did not evaluate bleb morphology and characteristics or DUES, which may be risk factors for ptosis. A prospective study investigating the influence of bleb morphology would certainly be beneficial. Because of the shortcomings of this study, we are conducting a prospective study examining these parameters. The strengths of this study are that all trabeculectomy procedures were performed by the same surgeon using the same technique and surgical instruments, and we evaluated many factors such as age, sex, glaucoma type, preoperative antiglaucoma drug use, ocular itching associated with antiglaucoma treatment, duration of follow-up, and postoperative needling, needling time, and ocular massage. Moreover, transient and persistent ptosis were evaluated separately. The mean duration of follow-up was long, at 31.05 months.

Conclusion

This study reports the incidence and factors contributing to ptosis after trabeculectomy. It is well known that ptosis is one of the most important complications after trabeculectomy. According to our findings, preoperative ocular itching due to allergies to antiglaucoma medications and postoperative needling may increase ptosis after trabeculectomy. We recommend raising awareness of related factors to prevent ptosis, which affects the quality of life of glaucoma patients.

Ethics

Ethics Committee Approval: University of Health Sciences Türkiye, Ankara Training and Research, Hospital, E-21-619.

Informed Consent: Written informed consent was obtained from the patient whose images were used.

Peer-review: Externally peer reviewed.

Authorship Contributions

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

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Original Article

An Association Between the Intestinal Permeability Biomarker Zonulin and the Development of Diabetic Retinopathy in Type II Diabetes Mellitus

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Abstract

Objectives: Increased intestinal permeability (IP) and gut microbiota dysbiosis have been implicated in low-grade chronic inflammation, which is an important factor in the pathogenesis of diabetic retinopathy (DR). This study aims to demonstrate the relationship between the IP biomarker zonulin and DR in patients with type 2 diabetes mellitus (T2DM).

Materials and Methods: This study was conducted with a total of 89 T2DM patients, including 33 non-DR, 28 with non-proliferative DR (NPDR), and 28 with proliferative DR (PDR), and 32 healthy controls. Zonulin levels were determined from blood samples using an enzyme-linked immunosorbent assay kit.

Results: There was no difference between the four groups in terms of age (p=0.236), gender (p=0.952), and body mass index (p=0.134) of the participants. Zonulin levels were significantly higher in the PDR group compared to the other three groups, as well as in the non-DR and NPDR groups compared to the control group. In multivariate logistic regression analysis, zonulin was found to be an independent predictor of DR (odds ratio: 1,781, 95% confidence interval: 1,122-2,829, p=0.014).

Conclusion: Our study showed that elevated zonulin levels may play a significant role in the development of DR, particularly during the transition to the proliferative stage. This suggests that regulation of IP could be one of the targets of DR treatment. More studies are needed to determine whether a eubiotic gut microbiota and IP have a direct relationship with DR.

Keywords: Diabetic retinopathy, inflammation, intestinal permeability, gut microbiota, zonulin

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Introduction

Diabetic retinopathy (DR) is a multifactorial disease, and the pathogenetic mechanisms behind it are still unclear in certain regards. The complex interaction of immunological, vascular, neuronal, and low-grade chronic inflammation (LGCI)-related pathways plays a role in the development and progression of DR.[1,2] LGCI, one of these variables, has lately garnered increased scientific interest. The pathogenic processes involved in LGCI are thought to be just as responsible for the development of DR as hypertension and hyperglycemia.[3,4]

Recent studies have shown that LGCI-related diseases such as obesity, inflammatory bowel syndrome, liver cirrhosis, depression, type 1 diabetes mellitus (T1DM), and type 2 diabetes mellitus (T2DM) are associated with intestinal barrier dysfunction, increased intestinal permeability (IP) (leaky gut), and gut microbiota dysbiosis (GMD).[5,6,7] The LGCI response has been attributed to an inflammatory immune reaction triggered by antigens bypassing the intestinal barrier as a result of GMD and increased IP.[8] Thus, increased IP and GMD leading to LGCI via gut-derived endotoxins (metabolic endotoxemia) is believed to be an essential component of DR pathophysiology.[9,10]

Human zonulin, the eukaryotic counterpart of the zonula occludens toxin discovered during vaccination studies against *Vibrio cholerae*, is a protein weighing 47 kDa and the only physiological mediator known to regulate IP. This is accomplished by reversibly opening the intestinal tight junctions (TJs).[11] Serum zonulin levels correlate linearly with IP and can be utilized as a biomarker for intestinal barrier function.[12] There is significant evidence that the gut microbiota (GM) influences the barrier function of the intestinal mucosa, which regulates the permeability of the gastrointestinal tract.[13] As a result, serum zonulin levels are also an important indicator of GMD.[8,13]

Studies conducted to date have shown that zonulin is also associated with a wide range of diseases characterized by chronic inflammation and oxidative stress.[14,15,16] The purpose of this study was to evaluate the association between DR and serum levels of the IP biomarker zonulin.

Materials and Methods

This research was carried out in the Ophthalmology department of the Ordu University Training and Research Hospital between November 2019 and May 2020. Individuals diagnosed with T2DM who applied to the internal medicine clinic were referred to the ophthalmology clinic for an eye and vision examination, and eligible patients were included in the research. The control group was recruited from healthy individuals referred for routine eye examination following an assessment at the internal medicine clinic. The criteria for the diagnosis of T2DM are based on American Diabetes Association guidelines.[17] All participants underwent a complete ophthalmologic examination and assessment of retinopathy status by fundus photography, fluorescein angiography, and optical coherence tomography. Guidelines on Diabetic Eye Care were used for DR diagnostic criteria and grading.[18] Non-proliferative DR (NPDR) was identified based on the presence of any characteristic lesion such as microaneurysms, hemorrhages, hard exudates, cotton wool spots, intraretinal microvascular abnormalities, and venous beading. PDR was identified based on the presence of neovascularization, vitreous hemorrhage, or tractional retinal detachment.

The exclusion criteria for the study were as follows: T1DM, pregnancy, acute or chronic infectious disease, severe hypertension, heart failure, liver or kidney disease, cancer, body mass index (BMI) percentile over 95%, and other long-term complications of diabetes. All study procedures were carried out following the Helsinki Declaration. The study was approved by the Ordu University Faculty of Medicine Ethics Committee (decision no: 2019-160) and informed written consent was obtained from all participants.

Eighty-nine participants with T2DM (32 men, 57 women) and 32 age-, gender-, and BMI-matched adult healthy controls without pre-existing ocular disease (11 men, 21 women; group 1) were included in the study. Participants with T2DM were divided into three groups according to clinical ocular examination findings: 33 in the non-DR group (group 2), 28 in the NPDR group (group 3), and 28 in the PDR group (group 4). Clinical and demographic information was recorded and BMI was calculated for each participant.

Blood samples were taken from all subjects after an overnight fast. After blood samples were centrifuged at 3,000 rpm for 10 minutes at 4 °C, the serum was separated and stored at -80 °C until the time of testing. Glycated hemoglobin (HbA1c), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and creatinine levels in the studied samples were recorded. Zonulin levels were measured using a human zonulin enzyme-linked immunosorbent assay (ELISA) kit (Sunred®, China, 201-12-5578). All samples were tested by the same researcher blinded to the clinical trial.

Statistical Analysis

The IBM SPSS for Windows (v 23.0, IBM Corp, Armonk, NY, USA) package program was used for statistical analysis. Power analysis for parametric and non-parametric tests was performed using G*power software (d=0.5, α=0.05, power=80%). Therefore, the study was conducted with a sufficient sample size. The Shapiro-Wilk test was used to evaluate the distribution of data. Numerical variables were expressed as mean and standard deviation and categorical variables as numbers. One-Way analysis of variance (ANOVA) and Kruskal-Wallis variance analysis were used for multi-group comparison of continuous variables. Tukey's test was used to make comparisons between groups in post-hoc analysis. Logistic regression analysis was used to calculate predictors of DR. Receiver operating characteristic (ROC) analysis was used to determine the sensitivity and specificity of zonulin for DR.

Results

The mean age of the participants was 62.10±10.0 years in group 1, 60.24±8.72 years in group 2, 62.77±5.88 years

in group 3, and 64.42±9.51 years in group 4. There was no difference between the four groups in terms of the age (p=0.236), gender (p=0.952), and BMI (p=0.134) of the participants. There were also no significant differences in TG, TC, HDL-c, LDL-c, and creatinine between the groups. There was no statistically significant difference in metformin usage or HbA1c levels among the T2DM groups (groups 2, 3, and 4). The demographic and clinical features of the participants are given in **Table 1.**

The groups differed significantly in terms of T2DM duration and serum zonulin levels. The mean duration of T2DM was 7.58±2.75 years in group 2, 9.94±4.77 years in group 3, and 11.85±8.87 years in group 4. The mean zonulin level was 4.65±0.85 ng/mL in group 1, 5.33±1.58 ng/mL in group 2, 5.26±0.67 ng/mL in group 3, and 11.85±6.87 ng/mL in group 4 (**Table 2**). In post-hoc analysis, disease duration was significantly longer in group 4 than groups 2 and 3 but did not differ significantly between groups 2 and 3. Serum zonulin level was significantly higher in group 4 than in the other groups and in groups 2 and 3 compared to the control group. Again, there was no significant variation in zonulin levels between groups 2 and 3. **Figure 1** shows the distribution of serum zonulin concentrations in the groups.

In multivariate logistic regression analysis, zonulin was found to be an independent predictor of DR (odds ratio: 1.781, 95% confidence interval: 1.122-2.829, p=0.014) (**Table 3**).

ROC curve analysis for zonulin is shown in **Figure 2**. The area below the ROC curve of zonulin for distinguishing DR was 0.657 (p=0.003). The optimal cut-off value was 10.27, with a sensitivity of 65.2% and a specificity of 58.3%.

Discussion

Zonulin, the precursor to haptoglobin (HP) 2, leads to epidermal growth factor receptor activation through PAR2. Similar to the modulating effect of epidermal growth factor in actin cells in the intestines, zonulin has a regulatory effect on the TJs, enabling them to open and thereby increasing IP.[19] Circulating zonulin is considered a biomarker of IP and GM.[8] Increased IP and GMD have recently been shown to play a role in the development of many diseases, including T2DM.[5,6,7] Jayashree et al.[16] showed that increased serum lipopolysaccharide (LPS) and zonulin levels were associated with T2DM. LPSs produced by intestinal bacteria pass into the systemic circulation as a result of increased IP. LPS is thought to be a significant contributor to LGCI.[16] LGCI and concomitant blood cell aggregation in the tissue are believed to contribute to neurodegeneration and microvascular damage in DR, although the exact processes are not fully known.[20] According to Simonsen et al.,[21] serum LPS levels were associated with severe DR in T1DM patients, and bacterial endotoxemia was a risk factor for DR. Studies in humans and animals conducted in recent years have suggested that changes in the GM and increased IP may pose a new risk factor for the development of DR.[9,10]

The main findings of this study were that there was a strong association between PDR and high serum zonulin levels, and T2DM patients with and without NPDR had considerably higher serum zonulin levels than the healthy control group. There was also a significant difference between the non-DR T2DM group (group 2) and the control group (group 1), consistent with previous studies.[22] Zonulin levels were also shown to be linked to NPDR, but there was a similar relationship in the non-DR T2DM group. High zonulin levels were found to be an independent predictor of DR using multivariate logistic regression analysis in this study. However, its sensitivity and specificity are relatively low according to our ROC curve analysis, and further studies are required to understand whether it will prove beneficial for the prediction of DR in routine use. These findings suggest that T2DM patients with high zonulin levels are strong candidates for progression to the proliferative stage of DR. Also, it points out that increased IP

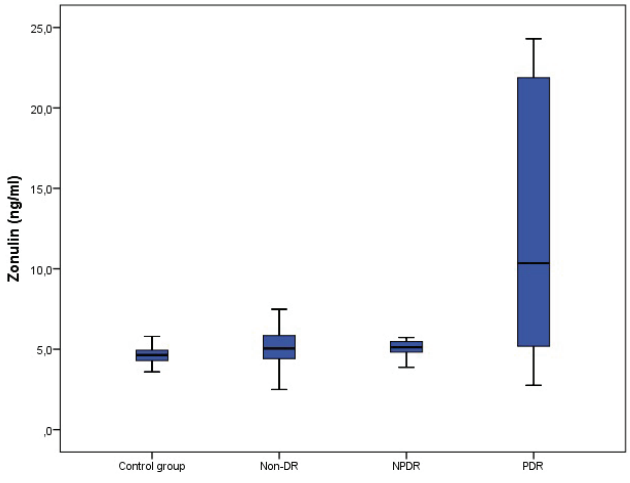

Figure 1. The distribution of serum zonulin concentrations in the study groups
Non-DR: No diabetic retinopathy, NPDR: Non-proliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy

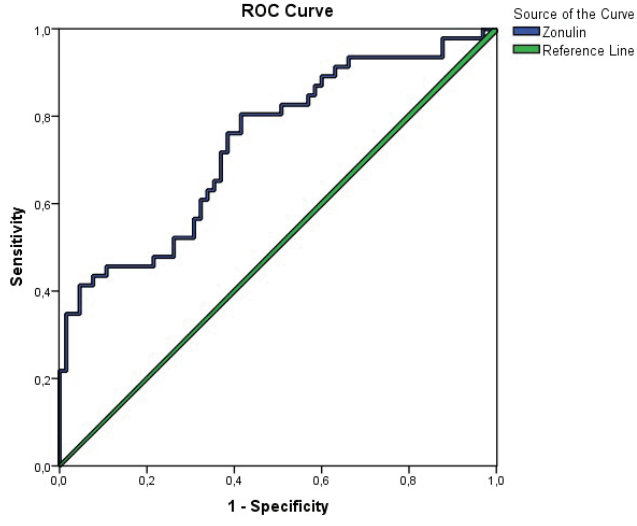

Figure 2. Receiver operating characteristic (ROC) curve analysis of zonulin as a predictor of diabetic retinopathy

Table 1. Clinical features and demographic data of the participants

	Control group n=32	Non-DR group n=33	NPDR group n=28	PDR group n=28	p value
Age (years)	62±10.0	60.2±8.7	62.7±5.8	64.4±9.5	0.236
Gender (female/male)	21/11	20/13	17/11	17/11	0.952
BMI (kg/m^2)	29.8±6.3	32.7±4.1	31.8±4.3	30.6±3.4	0.134
Duration of DM (years)	-	7.58±2.75[a]	9.94±4.77[a]	11.85±8.87[b]	**0.002***
Use of metformin (using/not using)	-	9/24	2/16	7/21	0.401
HbA1c [mmol/mol (%)]	-	59.0±30.1 (7.58±2.75)	64.0±13.6 (8.02±1.24)	66.0±18.1 (8.22±1.66)	0.189
Triglycerides (mg/dL)	144.8±79.3	167.7±67.9	159.8±61.5	168.7±86.0	0.313
HDL-c (mg/dL)	51.5±15.4	45.7±10.7	44.5±14.4	47.6±12.5	0.284
LDL-c (mg/dL)	129.5±32.8	122.7±39.6	110.5±27.3	127.0±35.4	0.425
Creatinine (mg/dL)	0.82±0.19	0.79±0.14	0.96±0.42	0.91±0.34	0.365

Data presented as mean ± standard deviation or number. BMI: Body mass index, DM: Diabetes mellitus, HDL-c: High-density lipoprotein cholesterol, LDL-c: Low-density lipoprotein cholesterol, Non-DR: No diabetic retinopathy, NPDR: Non-proliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy
*Matching letters indicate no significant difference, different letters indicate a significant difference between the groups

Table 2. Comparison of serum zonulin levels between groups

	Control group n=32	Non-DR group n=33	NPDR group n=28	PDR group n=28	p value
Zonulin (ng/mL)	4.65±0.85	5.33±1.58[a]	5.26±0.67[a]	11.85±8.87[b]	**0.001***

Non-DR: No diabetic retinopathy, NPDR: Non-proliferative diabetic retinopathy, PDR: Proliferative diabetic retinopathy
*Significant difference between the groups in one-way ANOVA. [a]Zonulin level is significantly higher in groups 2 and 3 than the control group in post-hoc analysis ($p<0.05$). There is no difference between groups 2 and 3 ($p>0.05$). [b]Zonulin level is significantly higher in group 4 than the other three groups in post-hoc analysis ($p<0.05$)

Table 3. Logistic regression analysis to identify possible factors associated with diabetic retinopathy

	Odds ratio	95% CI	p
Age (years)	0.924	0.887-1.016	0.813
BMI (kg/m^2)	0.948	0.911-1.128	0.902
HDL-c (mg/dL)	0.968	0.933-1.005	0.092
Zonulin (ng/mL)	1.781	1.122-2.829	**0.014**

BMI: Body mass index, HDL-c: High-density lipoprotein cholesterol, CI: Confidence interval

should be considered in the pathogenesis of DR. We identified only one study in the literature comparable to ours. Sirin et al.[23] examined the relationship between zonulin and DR but observed no association, contrary to our results. Additionally, the time interval after DM diagnosis did not differ significantly between non-DR and NPDR but was significant for the development of PDR in the current study. This indicates that longer diabetes duration is related to high zonulin levels. Prolonged diabetes is likely to have effects on GM that are difficult to reverse.

According to prior research, several variables, including age, obesity, and dyslipidemia, have an influence on serum zonulin levels.[24,25] The average BMI of all groups in our study shows that the participants were overweight and obese. However, as there was no significant difference in BMI between groups, including the control group, this factor is not expected to affect the study results.

Rahman et al.[26] reported that there was a direct association between the blood-brain barrier (BBB) and zonulin via the TJs, like in the intestine. Subsequently, zonulin has been associated with a wide range of central nervous system diseases and psychiatric diseases. As in the BBB, TJs are also found in the basic skeleton of the retina-blood barrier (RBB), and there is evidence that vascular endothelial growth factor-mediated pathological mechanisms contribute to the development of DR by disrupting the structure of TJs.[27,28] Accordingly, it is also possible that circulating zonulin has a direct effect on the retina in the transition from NPDR to PDR, acting on TJs in the RBB structure. Nevertheless, this association needs to be supported with more evidence based on controlled studies.

Although zonulin is still regarded as the best measure of IP in most recent studies,[29,30] some researchers have reported contradictory information concerning zonulin. When Scheffler et al.[31] conducted their study on obese individuals, they divided them into groups based on the genes encoding HP. Naturally, they did not expect to detect zonulin in individuals carrying the homozygous HP1 allele. After detecting zonulin in these patients' blood, the researchers deepened their studies. They eventually determined that commercial ELISA kits did not measure zonulin, but rather a structurally identical protein family. However, Scheffler et al.[31] found zonulin to be upregulated in diabetic and obese patients, as in previous studies. Other studies also warn researchers that what is measured with commercial zonulin ELISA kits is not zonulin.[32,33] There are also claims that zonulin does not accurately reflect IP.[34] Power et al.[35] investigated the correlation between lactulose/mannitol ratio and zonulin in first-degree relatives of Crohn's patients known to have increased IP. As a result, they found that there was no correlation between lactulose/mannitol ratio, which is a good indicator of IP, and zonulin. Consequently, it is a fact that zonulin is a target molecule in LGCI-related diseases, although there are conflicting findings.

Study Limitations

There are some limitations to this study. One is that it was conducted with a small group. In addition, because there is a wide range of drug groups and diseases that can cause GMD and increased IP, it was not possible to include all of them in the exclusion criteria. Moreover, the individuals' eating habits were not documented in this study. Dietary records in may offer new insights in future GMD and IP studies. Also, the participants were limited to a single ethnic group, and the results may not be valid for other ethnic groups. HP genotyping would have been useful in our study because of the controversy surrounding zonulin kits, but we were unable to do this. Although the use of zonulin as an indicator of IP is controversial, for many researchers zonulin is still the most important indicator of IP.

Conclusion

The results of this study showed that participants with T2DM had high levels of serum zonulin. Moreover, serum zonulin levels were much higher in participants with PDR than in participants with NPDR and those without DR. Accordingly, IP regulation and GM remodeling may be one of the main goals in the treatment of DR. In addition, zonulin or a structurally similar protein family, as claimed in some studies, may serve as a direct target molecule in the treatment of DR. More studies are needed to determine whether there is a direct association between a eubiotic GM and IP or between zonulin and DR.

Ethics

Ethics Committee Approval: Ordu University Clinical Research Ethics Committee (decision no: 2019-160).

Informed Consent: Written consent for the study was obtained from all participants.

Authorship Contributions

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

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Original Article

Choroidal Vascularity Index and Choroidal Thickness Changes Following Renal Transplantation

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Abstract

Objectives: This study aimed to evaluate changes in subfoveal choroidal thickness (SFCT), choroidal vascularity index (CVI), estimated glomerular filtration rate (GFR), mean arterial pressure (MAP), and intraocular pressure (IOP) after renal transplantation.

Materials and Methods: A total of 49 renal transplantation patients were included in this prospective study. CVI and SFCT on enhanced-depth imaging optic coherence tomography (EDI-OCT), MAP at the cubital fossa, GFR, and IOP were measured preoperatively and at postoperative 1 week and 1 month. In the analysis of EDI-OCT images, luminal area (LA) and stromal area of the choroid were determined using the image binarization method. CVI was defined as the ratio of LA to total choroid area. The effects of GFR, IOP, and MAP on CVI and SFCT were investigated.

Results: The study included 23 women (47%) and 26 men (53%) with a mean age of 26.28±8.25 years (range: 18-52). Changes between preoperative, postoperative 1-week, and postoperative 1-month GFR values, CVI, and SFCT measurements were evaluated. There were significant differences between preoperative and postoperative GFR and SFCT measurements ($p<0.001$), but no significant differences between preoperative and postoperative CVI ($p=0.09$), MAP ($p=0.14$), or IOP ($p=0.84$) measurements.

Conclusion: The present study demonstrated that SFCT increased significantly with GFR, while there was no change in CVI values.

Keywords: Binarization, renal transplantation, glomerular filtration rate, choroidal thickness, choroidal vascularity index

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Introduction

Chronic renal failure is among the top health issues worldwide.[1] In the 1970s, dialysis was considered the most appropriate treatment of chronic renal failure.[2] However, increased success in renal transplantation surgery together with improved survival rates and quality of life has caused a shift of opinion.[3] New advancements in surgical methods and postoperative immunosuppression after renal transplantation has greatly increased renal allograft survival rates. Renal transplantation is now the primary choice of treatment in end-stage renal failure.[4,5]

Ocular pathologies are detected in over 50% of renal transplantation patients. These include posterior subcapsular cataract, opportunistic ocular infections, steroid-induced raised intraocular pressure, and primary disease-related vascular complications.[6] The choroid is a highly vascular tissue that supplies blood to the outer layers of the retina and plays a major role in the pathogenesis of many primary and secondary diseases involving the posterior segment of the eye.[7,8] In addition to toxemia of pregnancy, pheochromocytoma, and malignant hypertension, renal diseases have also been associated with hypertensive choroidopathy.[9] Increased systemic blood pressure has also been shown to reduce choroidal thickness.[10]

Previous studies have reported reduced choroidal thickness following hemodialysis in patients with chronic renal failure. This change has been attributed to changes in diastolic blood pressure.[11] Another study indicated that changes in choroidal thickness were associated with changes in systolic blood pressure.[12] Hypertension is a common occurrence after renal transplantation.[13] Drugs listed among the risk factors for hypertension after renal transplantation include cyclosporine A/G, corticosteroids, and tacrolimus.[13,14]

Choroidal vascularity index (CVI) has been recently proposed as a new marker in addition to subfoveal choroidal thickness (SFCT) for the evaluation of choroidal changes with optical coherence tomography (OCT).[15,16] CVI is a new imaging tool for the measurement and analysis of the choroidal vascular system by quantifying both the luminal and stromal choroidal components. Numerous reports have been published so far regarding CVI and its potential applications in healthy eyes as well as in the evaluation and management of several chorioretinal diseases. In addition, CVI measurement has been shown to be a more stable parameter that has lower inter-assay variability and is less dependent on physiological factors compared to choroidal thickness.[17] According to one study, there was a significant decrease in SFCT after hemodialysis in patients with end-stage renal failure, whereas no change in CVI was observed in the same population.[18]

To the best of our knowledge, changes in choroidal thickness following renal transplantation have not been studied before. CVI is known to be important in monitoring disease progression and prognosis in patients.[19] The present study was conducted to investigate the importance of CVI and SFCT measurements in renal function alterations. This prospective study aimed to evaluate alterations in the choroid in terms of SFCT and CVI following renal transplantation, and to correlate these parameters with the estimated glomerular filtration rate (GFR), mean arterial pressure (MAP), and intraocular pressure (IOP).

Materials and Methods

This prospective study was conducted on patients admitted to the ophthalmology department between July 2015 and April 2017 who were scheduled to undergo renal transplantation in the general surgery department for end-stage renal disease secondary to causes not related to diabetes and hypertension (e.g., recurrent kidney infection, polycystic kidney disease, prolonged urinary tract obstruction, glomerulonephritis). The study received ethics approval from the Başkent University Faculty of Medicine Scientific Research Projects Advisory Board (project no: KA16/271).

Study Sample

A total of 49 right eyes of 49 patients (23 women, 26 men) diagnosed with end-stage renal disease and who were hospitalized for renal transplantation were included in the study. Complete ophthalmological examination and assessments of CVI, SFCT, IOP, GFR, and MAP were conducted preoperatively and at 1 week and 1 month postoperatively. Patients were administered a postoperative treatment protocol comprising acetyl salicylic acid (100 mg; Bayer, İstanbul, Turkey), trimethoprim/sulfamethoxazole (40 mg/200 mg; Deva, Tekirdağ, Türkiye), valganciclovir (450 mg; Roche, Mississauga, Canada), tacrolimus (0.1 mg/kg; Astellas Pharma, Killorglin, Ireland), prednisolone (1.5 mg/kg; Gensenta, İstanbul, Türkiye), and mycophenolate (30 mg/kg; Koçakfarma, Tekirdağ, Türkiye).

Slit-lamp anterior segment and dilated fundus examinations were performed and visual acuity, IOP, GFR, CVI, SFCT, and MAP were assessed in all patients. Patients with additional macular or choroidal disease, myopia ≥3 diopters (D) or hypermetropia ≥+3 D, history of ocular or orbital surgery, ocular inflammation, diabetes mellitus, and systemic hypertension were not included in the study.

IOP was measured with a non-contact pneumotonometer (Reichert 7; Reichert Inc., New York, USA). Systemic blood pressures were manually measured from the cubital fossa separately by both researchers. MAP was calculated as follows: diastolic blood pressure +1/3 (systolic blood pressure-diastolic blood pressure). All measurements were obtained by the same researchers (M.A., L.A.).

The patients were consecutively operated in this study. Only two patients with cataract were excluded, because they did not have high quality choroidal measurements due to cataracts. There was no kidney rejection or any complications during follow-up.

Ophthalmic Imaging

Choroidal imaging was non-invasively obtained with spectral domain enhanced depth imaging OCT (EDI-OCT, Heidelberg Spectralis, Heidelberg, Germany). All participants were examined during the same part of the day (between 9:30

and 10:00 AM) to eliminate the effects of physiological diurnal alterations. The images were obtained after pupil dilation, using a horizontal scan centered on the fovea (**Figure 1 A1,B1,C1**).

Choroidal thickness was assessed as the distance between the outer margin of the hyperreflective retinal pigment epithelium (RPE) and choroid-sclera interface (CSI).[20] Patients with visible and measurable choroid were included in the study and choroidal thickness was manually measured in EDI-OCT images of the subfoveal cross-section by two different researchers (M.A., L.A.). The program's measurement feature was used to measure the vertical line between the RPE and CSI to determine choroidal thickness (**Figure 2**).

For CVI measurement, the binarization method was utilized for all scans acquired. Image processing was performed using open-source software (http://fiji.sc/) and analyzed as described by Agrawal et al.[16] Briefly, z scans were viewed using the ImageJ version 1.53a platform and total choroid area (TCA), which was added to the region of interest (ROI) manager, was selected

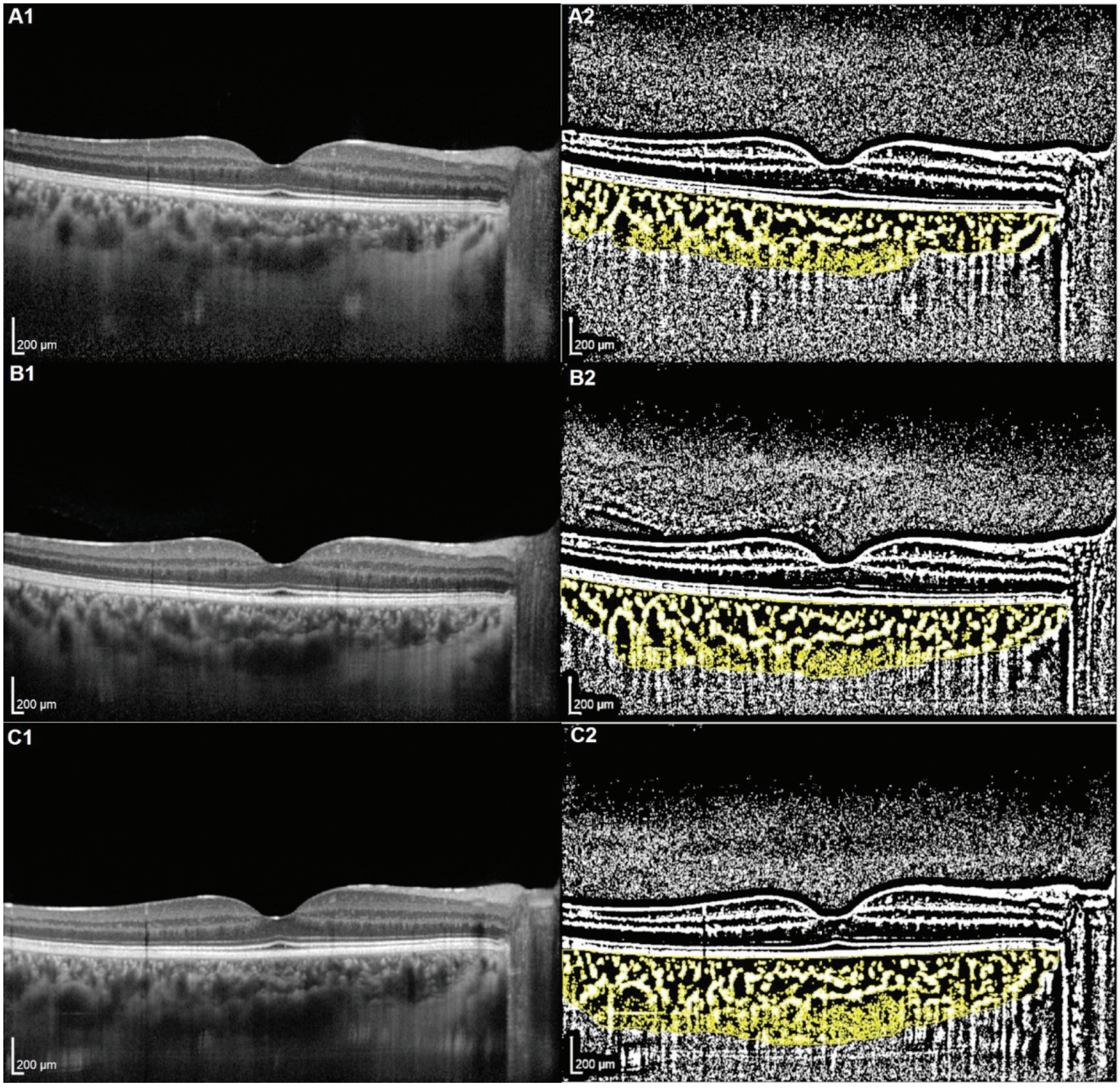

Figure 1. Left: Images from horizontal scans centered on the central foveal region in a participant preoperatively (A1) and at postoperative 1 week (B1) and 1 month (C1). Right: Choroidal vascularity index measurements from the same images using ImageJ software. The luminal area (dark pixels) is represented as yellow lines using the color threshold tool, and stromal area is represented as bright pixels

using the polygon tool. After converting the image to 8-bit, Niblack's auto local thresholding was employed, which provided the mean pixel value with standard deviation for all points. On EDI-OCT scans, the luminal area (LA) was indicated by using the color threshold (**Figure 1 A2,B2,C2**). To determine the LA within the selected polygon, both areas in ROI manager were selected and combined using the "AND" operation of ImageJ. The composite third area was added to the ROI manager. The first area corresponded to the total selected choroid, and the third composite area indicates the LA or vascular area. The CVI value was obtained as the ratio of LA to TCA. The light color pixels indicated stromal area, which was calculated by subtracting the LA from the TCA.

Both SFCT and CVI values were examined separately by two researchers (M.A., L.A.) who were blinded to the patients' clinical data. The mean values of the measurements obtained by the two researchers were used for statistical analysis.

The intraobserver and interobserver reliability of the SFCT and CVI values was assessed using intraclass correlation coefficients (ICC) with a 95% confidence interval (CI). ICC values between 0.75 and 0.90 were regarded as satisfactory and values greater than 0.90 as excellent.

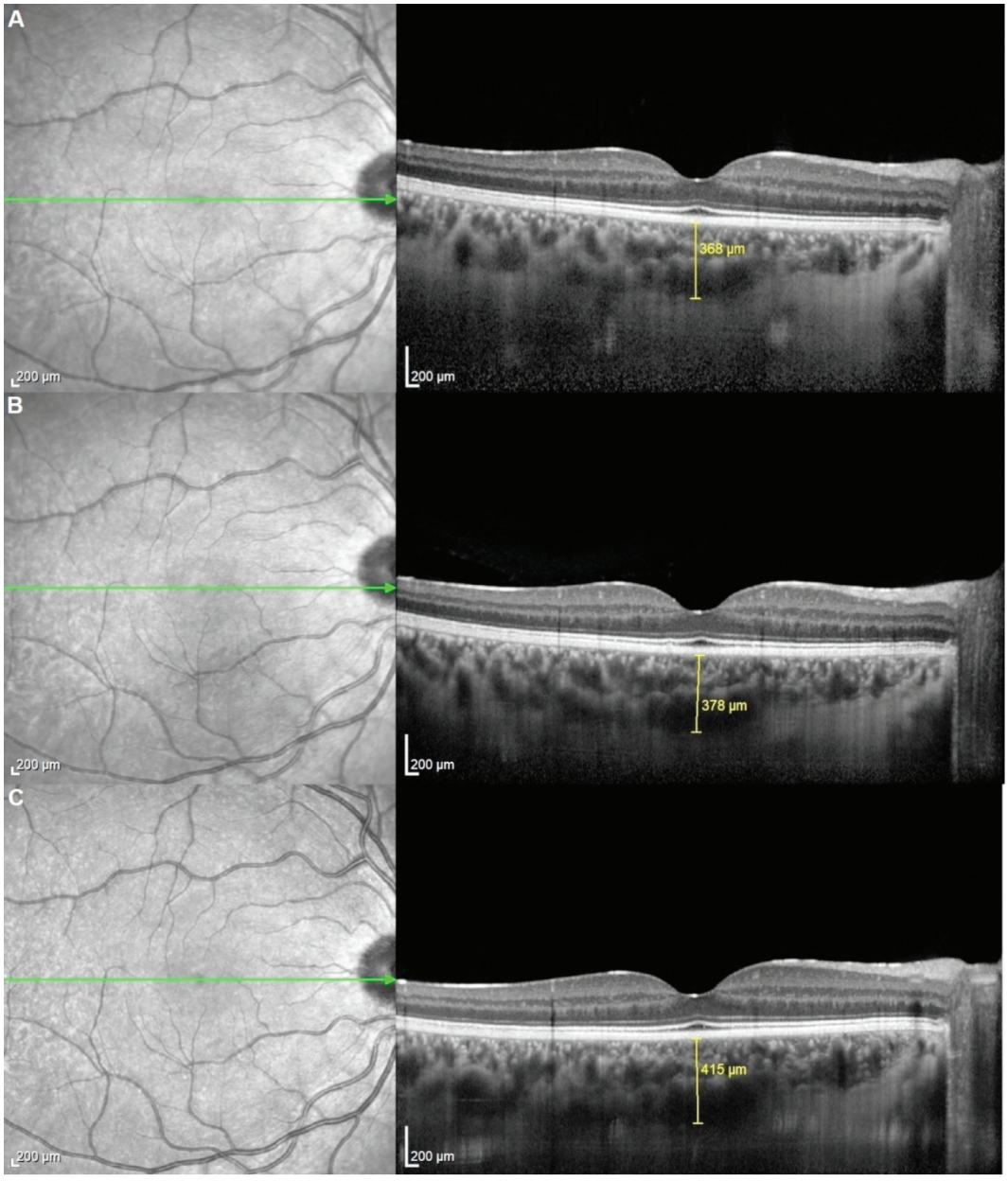

Figure 2. Image of SFCT measurement centered on the central foveal region in a participant preoperatively (A) and at postoperative 1 week (B) and 1 month (C)
SFCT: Subfoveal choroidal thickness

Statistical Analysis

IBM SPSS Statistics 22.0 (IBM Corp., Armonk, NY, USA) was used for statistical analyses. Power analysis was performed for the repeated-measures analysis of variance (ANOVA) method, in which the sample size was determined as at least 49 individuals in each group. In this case, the power of the test was approximately 80.5%. As the data met the parametric test criteria, repeated-measures ANOVA and Bonferroni test were used for analysis. Correlations between parameters were assessed using Pearson correlation analysis.

Results

A total of 49 eyes of 49 patients (23 women, 26 men) were included in the study. The mean patient age was 26.28±8.25 years (range: 18-52). All patients had visual acuity of 20/20 according to Snellen chart before and after renal transplantation. Preoperatively, the mean dialysis duration was 36.00±19.25 months. There were statistically significant differences between preoperative and postoperative 1-month, preoperative and postoperative 1-week, and postoperative 1-week and postoperative 1-month mean SFCT measurements and GFR values (p<0.001 all) (**Table 1, Figure 3**,4).

According to CVI measurements, there was no statistically significant difference between preoperative and postoperative 1-week or postoperative 1-month measurements (preoperative vs. postoperative 1-week: p=0.41; preoperative vs. postoperative 1-month: p=0.63; postoperative 1-week vs. postoperative 1-month: p=0.11) (**Table 1**).

The increase in SFCT was significant between preoperative and postoperative 1-week and postoperative 1-month, and also showed a strong positive correlation with the amount of change in GFR value (r=0.976, p<0.001 and r=0.711, p=0.009; respectively). The SFCT was not significantly correlated with MAP in the comparisons between preoperative and postoperative 1-week and between postoperative 1-week and postoperative 1-month values (r=0.101, p=0.368; r=0.124, p=0.416).

According to MAP values, there was no statistically significant difference between preoperative and postoperative 1-week or postoperative 1-month measurements (p=0.36 and p=0.19, respectively) (**Table 1**).

Mean preoperative IOP was 13.79±3.48 mmHg. Mean postoperative IOP was measured as 13.85±3.32 mmHg at 1 week and 13.81±3.32 mmHg at 1 month. There was no significant difference among preoperative, postoperative 1-week, and postoperative 1-month mean IOP values (p=0.84).

SFCT had ICC values of 0.918-0.951 for interobserver reliability and 0.928-0.971 for intraobserver reliability. For CVI, ICC values were 0.947-0.953 for interobserver reliability and 0.927-0.951 for intraobserver reliability (**Table 2**).

Discussion

To the best of our knowledge, this is the first study in the literature to evaluate preoperative and postoperative CVI and SFCT in renal transplantation. While CVI, MAP, and IOP values did not significantly change, there was significant increase in SFCT and GFR after renal transplantation.

Shin et al.[18] compared SFCT and CVI values before and after hemodialysis in patients with end-stage renal failure. Despite acute and severe fluid loss after hemodialysis, there was no significant change in CVI in their study population. Their study also demonstrated decrement in SFCT measurements. The present study demonstrated increase in SFCT following renal

Table 2. Intraclass correlation coefficients for CVI and SFCT measurements in the participants

	Interobserver variability (95% CI)	Intraobserver variability (95% CI)
CVI		
PO-1W	0.918 (0.911-0.942)	0.971 (0.959-0.977)
PO-1M	0.951 (0.929-0.978)	0.928 (0.912-0.968)
1W-1M	0.933 (0.891-0.964)	0.931 (0.906-0.975)
SFCT		
PO-1W	0.953 (0.932-0.984)	0.927 (0.908-0.949)
PO-1M	0.947 (0.929-0.963)	0.949 (0.931-0.976)
1W-1M	0.948 (0.931-0.969)	0.951 (0.923-0.965)

CI: Confidence interval, CVI: Choroidal vascularity index, SFCT: Subfoveal choroidal thickness, PO: Preoperative, 1W: Postoperative 1 week, 1M: Postoperative 1 month

Table 1. Statistical comparison of SFCT and CVI measurements, MAP, and GFR values

	Mean SFCT (SD), µm	Mean CVI (=LA/TCA) (SD)	Mean MAP (SD), mmHg	Mean GFR (SD), mL/min/1.73 m²
Preoperative (PO)	306.33 (±74.50)	65.42 (±2.19)	85.37 (±6.64)	9.02 (±4.50)
Postoperative 1 week (1W)	320.61 (±74.1)	65.59 (±2.24)	87.06 (±7.93)	61.03 (±15.48)
Postoperative 1 month (1M)	345.76 (±74.28)	65.29 (±2.11)	87.45 (±7.24)	68.2 (±17.90)
P value: PO vs. 1W	**<0.001***	0.41	0.36	**<0.001***
P value: PO vs. 1M	**<0.001***	0.63	0.19	**<0.001***
P value: 1W vs. 1M	**<0.001***	0.11	1.00	**<0.001***

SFCT: Subfoveal choroidal thickness, CVI: Choroidal vascularity index, LA: Luminal area, TCA: Total choroidal area, MAP: Mean arterial pressure, GFR: Glomerular filtration rate, SD: Standard deviation. *Statistically significant p values

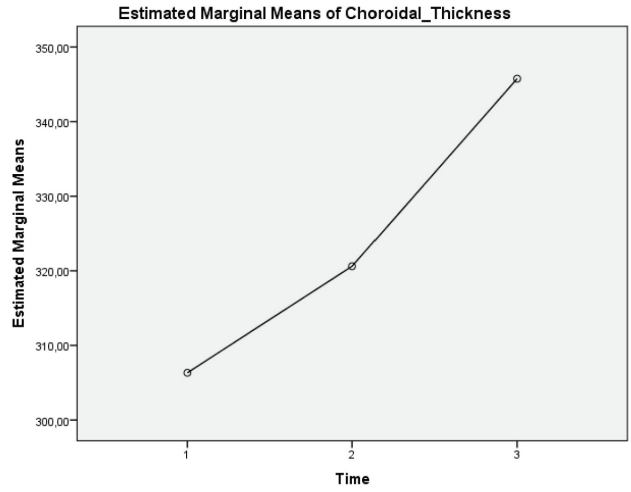

Figure 3. Change in choroidal thickness over time (1: Preoperative, 2: Postoperative 1 week, 3: Postoperative 1 month)

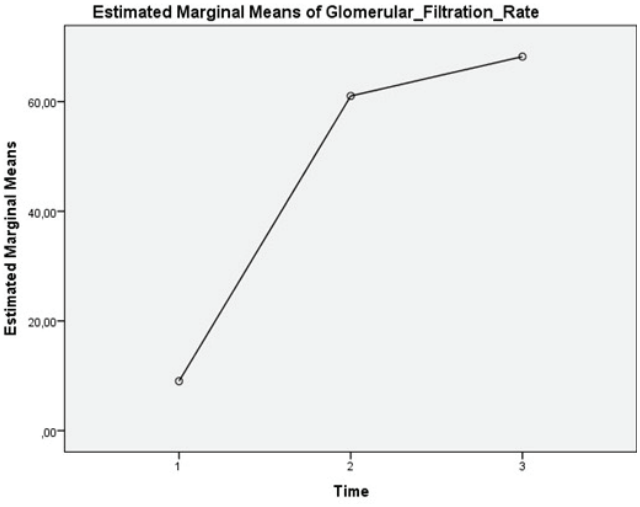

Figure 4. Change in glomerular filtration rate over time (1: Preoperative, 2: Postoperative 1 week, 3: Postoperative 1 month)

transplantation, while no difference was found in CVI values. These findings suggest that CVI values were more stable and less affected by physiological alterations compared to SFCT.[21]

Although studies have shown increased systemic blood pressure after renal transplantation, we did not observe a significant change in MAP in our study.[22,23] This inconsistency with the literature may be attributed to the treatment protocol including cyclosporine and tacrolimus. The second possible cause is that systemic blood pressure was remeasured in a short one-month follow-up period after the use of corticosteroids.

In this study, all patients received intravenous corticosteroid treatment after renal transplantation. Han et al.[24] investigated choroidal thickness 1 day, 1 week, and 1 month after pulse steroid treatment but detected no significant changes in choroidal thickness. Other studies reported significant reduced choroidal thickness after high-dose steroid treatment.[25,26] We believe that corticosteroid treatment given after renal transplantation does not increase choroidal thickness. Future studies on isolated postoperative treatment regimens after renal transplantation with different patient groups will help form a more accurate assessment.

In the present study, a significant increase in SFCT measurements was observed 1 week and 1 month postoperatively. In our previous report, IOLMaster 700 measurements were evaluated before and 1 month after renal transplantation. The study results demonstrated significant decrement in axial length despite significant thinning in central corneal thickness measurements at postoperative 1 month.[27] The present study demonstrated a significant increase in choroidal thickness. Therefore, the decrease in axial length measurements may be secondary to an increase in choroidal thickness.

The literature reports reduced choroidal thickness following hemodialysis. This has been attributed to changes in diastolic and systolic blood pressure.[11,12] In this study, while there was no change in systemic blood pressure after renal transplantation, follow-up showed increased choroidal thickness. Although choroidal thickness decreases after hemodialysis, it seems to increase after renal transplantation according to the results of the present study. This difference may be caused by hypotensive changes in systemic blood pressure after dialysis.[28] In addition, hemodialysis may have a more acute and rapid effect on a larger volume of blood compared to renal transplantation, leading to volume loss.[29] This may be due to acute and large fluid shifts that occur during dialysis.[18]

Although we found no change in blood pressure, choroidal thickness increased after renal transplantation. Increase in choroidal thickness independent from systemic blood pressure may be related to autonomic nervous system dysfunction in chronic renal failure. Since choroidal circulation has autonomic innervation, increased sympathetic activity in chronic renal disease may have contributed to choroidal thinning.[30] Improved renal functions after renal transplantation may lead to changes in autonomic regulation, thus leading to increased choroidal thickness after renal transplantation.[31] In our study, indicators of sympathetic activity were not examined. Future studies that evaluate sympathetic activity after renal transplantation are needed.

One study found that choroidal thickness is not associated with blood pressure in chronic renal failure. The same study revealed a correlation between choroidal thickness and GFR.[31] In addition, it is already known that preoperatively low GFR increases significantly after renal transplantation.[32] In this study, while there was no change in blood pressure, there was increased choroidal thickness after renal transplantation. In addition, there was a significant postoperative increase in GFR, which positively correlated with choroidal thickness. One likely cause of increased postoperative choroidal thickness may be increased GFR following renal transplantation, associated with reduced protein leakage (such as albumin) from the kidneys and increased vascular volume.[33] In light of these findings, GFR levels may be a useful tool for monitoring changes in choroidal thickness in patients with chronic renal disease.

The literature also showed that IOP was associated with choroidal thickness measurements. Hata et al.[34] indicated that elevated IOP following darkroom prone provocative test was associated with decreased choroidal thickness. In this study, we found no significant change in IOP after renal transplantation. This suggests that changes in SFCT are independent from IOP.

CVI, which was first introduced by Agarwal et al.,[16] is the ratio of LA to TCA, and a new parameter to quantitatively define choroidal vasculature. The current literature suggests that CVI is less variable and influenced by fewer physiological factors than choroidal thickness.[17] Iovino et al.[35] investigated choroidal changes in patients with central serous chorioretinopathy following photodynamic therapy and demonstrated a decrease in choroidal thickness but no change in CVI. They emphasized the decrease in both LA and TCA as an underlying reason for stable CVI. Similar to the literature, the present study showed increase in SFCT but no significant alteration in CVI.

Study Limitations

This study included patients with chronic renal failure secondary to various etiologies (other than diabetes and hypertension) who underwent renal transplantation. Increased choroidal thickness following renal transplantation is likely independent from diseases causing renal failure. Nevertheless, further studies with similar design on renal failure secondary to a single etiology will be more reliable and allow more accurate conclusions.

Furthermore, we believe this study should be repeated and supported by studies with longer follow-up period after renal transplantation. Drugs administered during postoperative treatment may have primarily affected measurements. The isolated use of these drugs and their effects on choroidal thickness should be evaluated separately for each drug.

Conclusion

The present study demonstrated that SFCT was affected by GFR, while no change occurred in CVI values. This suggests that CVI seems to be more stable parameter than SFCT. GFR is measured to evaluate renal functions in the follow-up of patients with end-stage renal disease. In light of our findings, we believe that SFCT measurements may also be used as an indicator of renal function.

Ethics

Ethics Committee Approval: The study received ethics approval from the Başkent University Faculty of Medicine Scientific Research Projects Advisory Board (project no: KA16/271).

Informed Consent: Obtained.

Peer-review: Internally peer reviewed.

Authorship Contributions

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

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Original Article

Audiometric Evaluation of the Relationship between Sensorineural Hearing Loss and Chronic Glaucoma

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Abstract

Objectives: To assess hearing function in chronic glaucoma patients in comparison to healthy individuals.

Materials and Methods: This cross-sectional study included 24 primary open-angle glaucoma (POAG) patients (24 ears) and 22 pseudoexfoliative glaucoma (PEG) patients (22 ears) who were followed for at least 5 years in the Afyonkarahisar Health Sciences University Ophthalmology Department, as well as 21 age- and gender-matched healthy individuals (21 ears, control group). Following a thorough ophthalmological examination that included visual acuity and intraocular pressure measurements, as well as anterior and posterior slit-lamp biomicroscopy, audiometry was performed in all participants to determine hearing function.

Results: Mean ages in the POAG, PEG, and control groups were 64.50±7, 66.90±4.51, and 64.38±4.36 years, respectively. The mean deviation in standard automated perimetry was -14.47±2.89 in the POAG group and -15.02±2.87 in the PEG group (p=0.306). When compared with the control group, the POAG group had significantly higher hearing thresholds at 500 (p=0.011) and 1,000 Hz (p=0.003), while the PEG group had significantly higher hearing thresholds at 250 (p=0.009), 500 (p=0.009), 1,000 (p=0.001), 2,000 (p=0.005), 4,000 (p=0.001), 8000 (p=0.010), and 10,000 Hz (p=0.009).

Conclusion: Both glaucoma and hearing loss are common chronic diseases that have an impact on the well-being of older people. Potential hearing problems in chronic glaucoma patients make routine ocular and otolaryngology examinations in older patients critical for prompt diagnosis and treatment.

Keywords: Primary open-angle glaucoma, pseudoexfoliative glaucoma, sensorineural hearing loss, audiometry, standard automated perimetry

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Introduction

Sensorineural hearing loss (SNHL) refers to hearing problems directly caused by cochlear, labyrinth, and central nervous system damage.[1] This disorder usually involves multiple pathologies not only in the inner ear, but also the auditory nerve. Hearing impairment refers to a hearing threshold of 21 decibels (dB) or higher in either ear. As a result, a person with normal hearing should have a sensitivity range of 0-20 dB across all frequencies, and it should be consistent at all ages.[2] SNHL is more common in people over the age of 65, with a prevalence of over 60%.[3,4] It may be associated with various etiological factors, including autoimmune ear disease, vascular diseases, noise, infection, and drug toxicity.[5] SNHL may also manifest features of vestibular schwannoma, which can only be ruled out by magnetic resonance imaging.[6] Most neurological diseases have the clinical presentation of a neurodegenerative mechanism that is nearly identical to SNHL. As a result, these patients may experience general neurological dysfunction that affects other organs.[7,8,9]

Glaucoma is a progressive optic neuropathy primarily associated with both visual field defects and high intraocular pressure (IOP).[10] Aside from primary open-angle glaucoma (POAG), there are several other types of open-angle glaucoma, including pigmentary glaucoma and pseudoexfoliative glaucoma (PEG).[11] POAG is a group of eye diseases with characteristic progressive changes in the optic nerve head and/or visual field loss.[12] POAG has no obvious cause, and glaucomatous changes may be directly related to high IOP or can also occur with IOPs lower than the population average. High IOP, advanced age, African ancestry, and a genetic predisposition to POAG are the most commonly reported risk factors.[13,14]

The most recognizable cause of secondary open-angle glaucoma is pseudoexfoliation (PEX) syndrome, which causes the deposition and accumulation of PEX material on the lens, iris, and other intraocular surfaces.[15] Although PEX syndrome is not always associated with glaucoma, patients with PEG have higher IOP at diagnosis than those with POAG, making the treatment of PEG relatively more difficult.[16]

Glaucoma patients have an increased risk of optic disc and retinal nerve tissue degeneration.[17] There is also some evidence of an association between SNHL and glaucoma.[3] As both diseases have related neurological degeneration characteristics, it is assumed that these conditions are more likely to coexist in a specific group of people. Therefore, the current study was designed primarily to assess hearing function in chronic glaucoma patients and compare the results with those of age- and gender-matched healthy individuals.

Materials and Methods

Study Participants

In this cross-sectional study, hearing function was assessed in 24 POAG patients (24 ears) and 22 PEG patients (22 ears) who had a mean deviation value lower than -12 dB in the Humphrey visual field test and had been followed for at least 5 years in the glaucoma unit of the Afyonkarahisar Health Sciences University Faculty of Medicine, Department of Ophthalmology. Hearing data from these groups were compared to those of 21 age- and gender-matched healthy individuals (21 ears, control group). The study procedure conformed to the ethical standards of the Helsinki Declaration and was approved by the Afyonkarahisar Health Sciences University Ethics Committee (approval number: 2020/520). All participants provided written informed consent prior to the study.

Inclusion and Exclusion Criteria

Participants aged 45 to 70 years old with best corrected visual acuity (BCVA) of 0.2 LogMAR or worse in each eye were referred to an otolaryngology clinic for an otological examination and hearing assessment. The study group consisted of pseudophakic or phakic male and female adults who had chronic POAG and PEG in either eye and no other ocular or systemic disease affecting visual system and who did not smoke or drink alcohol. Patients were also questioned about their history of glaucoma treatment, including both medical and surgical treatments. Subjects in the control group had IOP values lower than 21 mmHg in two readings and no ocular and/or systemic disease that could impair visual performance.

Exclusion criteria were: (a) the presence of any other type of glaucoma apart from POAG and PEG or any ocular or systemic condition associated with hearing physiology; (b) history of ear infection, surgery, tympanic membrane perforation, or exposure to ototoxic drugs or heavy noise; (c) the presence of an upper respiratory tract infection at the time of assessment; and (d) an evident perimetric sensitivity loss within the central 10° of the visual field according to pattern deviation plot.

Ocular Examination and Glaucoma Diagnosis

All participants underwent full ophthalmologic examination, including autorefraction (Canon R-F10m; Canon Inc., Tokyo, Japan), BCVA, and applanation tonometry (Goldmann; Haag-Streit AG, Köniz, Switzerland) measurements, as well as anterior and posterior slit-lamp biomicroscopy. All examinations were performed between 8:00 and 12:00 AM.

Glaucoma was diagnosed according to the International Society of Geographic and Epidemiological Ophthalmology (ISGEO) criteria.[18] POAG patients were classified as those who had an open and normal anterior chamber angle and met the ISGEO criteria. PEX syndrome was defined as the presence of PEX material in the anterior chamber angle and/or on the lens surface after pupil dilation, and PEG was defined as the presence of IOP greater than 21 mmHg as well as glaucomatous changes in both the optic nerve and visual field.

Standard automated perimetry (SAP) was performed with the Humphrey Field Analyzer HFAII (Carl Zeiss Meditec Inc, Dublin, CA, USA) using a 30-2 threshold program with Swedish Interactive Threshold Algorithm (SITA) standard strategy. The test was repeated a second time if the initial test was invalid. Test results were interpreted by comparison with the manufacturer's internal normative database. The results for visual field locations

were grouped into probability levels according to age-corrected normative values, shown on a grey scale. An irregular test result was defined as the presence of at least one low-sensitivity test point with p<1%, p<0.5%, or "not seen at maximum" on the total deviation plot.

Otolaryngologic and Audiometric Assessment

The hearing threshold for a specified ear was assessed with respect to ipsilateral ocular findings (i.e., the ear on the same side as the worse eye in POAG and the location of PEX in PEG). All participants were subjected to audiometry and noise annoyance tests to assess hearing function, and only ears with low hearing level were then studied. An otological examination was performed by an experienced otolaryngologist using a 4-mm 0-degree rigid endoscope (Xion GmbH, Berlin, Germany) and ML-150 light source (JRMed Trade Co., Seoul, South Korea). Hearing was assessed using the pure-tone average of thresholds at 250, 500, 1,000, 2,000, 4,000, 8,000, and 10,000 Hz. Hearing loss was defined as a dB level above 40 dB in one ear. All participants were asked if they had a history of noise exposure. Occupational noise exposure was defined as a history of loud noise (requiring a raised voice to be heard) at work for more than 3 months. Environmental noise exposure was defined as exposure to loud noise for more than 5 hours/week in any non-work setting.

Statistical Analysis

Statistical analysis was carried out using SPSS software (version 22, IBM Corp., Armonk, NY, USA). The Kruskal-Wallis test was used to compare the three independent groups because the study data did not show a normal distribution according to the Shapiro-Wilk test. In addition, the non-parametric Mann-Whitney U test with Bonferroni correction was used in pairwise comparisons to determine differences between groups in mean dB hearing levels at specific audiometric frequencies. Mann-Whitney U tests with p<0.0167 after Bonferroni correction were considered statistically significantly different.

Results

The mean ages of the POAG (64.50±7.45 years), PEG (66.90±4.51 years), and control (64.38±4.36 years) groups did not differ significantly (p>0.05) (**Table 1**). Eleven patients (45.8%) in the POAG group and 12 (54.5%) in the PEG group were pseudophakic (p=0.384). Two patients (8.3%) in the POAG group and 3 patients (14%) in the PEG group had a history of glaucoma filtration surgery (p=0.543). The mean logMAR BCVA values in the POAG and PEG groups were 0.61±0.49 and 0.69±0.51, respectively (p=0.217). When compared with the glaucoma groups, the control group had a significantly better logMAR BCVA of 0.00±0.00 (p<0.001 for both). Mean IOP did not differ statistically between the POAG and PEG groups (17.00±2.36 mmHg vs. 17.59±2.74 mmHg, p=0.202) but was significantly lower in the control group compared to both glaucoma groups (12.00±1.97 mmHg; p<0.001 for both). In the SAP analysis, the mean deviations were -14.47±2.89 and -15.02±2.87 in the POAG and PEG groups, respectively (p=0.306).

Audiometric Analysis

There were statistically significant differences among the three groups in hearing thresholds at 250 (p=0.039), 500 (p=0.012), 1,000 (p=0.002), 2,000 (p=0.012), 4,000 (p=0.004), 8,000 (p=0.003), and 10,000 Hz (p=0.021). In pairwise comparisons with the control group, the POAG group had significantly higher hearing thresholds at 500 (p=0.011) and 1,000 Hz (p=0.003), while the PEG group had higher hearing thresholds at all frequencies: 250 (p=0.009), 500 (p=0.009), 1,000 (p=0.001), 2,000 (p=0.005), 4,000 (p=0.001), 8,000 (p=0.010), and 10,000 Hz (p=0.009). The PEG group also had a higher hearing threshold at 8,000 Hz than the POAG group (p=0.002). There were no statistically significant differences in noise annoyance values among the three groups.

Discussion

This study demonstrated a significantly increased likelihood of SNHL in association with glaucoma. This relationship was significantly more pronounced in PEG than POAG patients, despite the fact that there was no age difference between them.

The relationship between glaucoma and SNHL is controversial. Although some studies reported a relationship between these two degenerative disorders, others reported no evidence of such a relationship.[19] One study found a significantly higher prevalence of SNHL in normotensive glaucoma patients.[20] In another study looking at the relationship between ocular diseases and SNHL, the prevalence of POAG was higher in the SNHL population, but SNHL was not significantly associated with increased glaucoma risk in covariate-adjusted models.[21] This is consistent with the current study findings that POAG patients had significantly higher hearing thresholds at 500 and 1,000 Hz in comparison to healthy individuals, suggesting a higher prevalence of concomitant hearing problems in these patients.

POAG is becoming more universally acknowledged as an age-related neurodegenerative disorder that can affect individuals predisposed to global neural damage. Optic and retinal nerve tissue degeneration is the most widely accepted glaucomatous feature. Furthermore, spiral ganglion neuron degeneration appears to be more closely connected to glaucoma development, because ganglion neurons are reduced in glaucoma patients while sensory cells are not.[22] Both POAG and SNHL appear to have common risk factors, neurodegenerative characteristics, and comorbidities. This suggests that SNHL patients may have a more vulnerable nervous system and an optic nerve more susceptible to damage than in healthy individuals, potentially leading to glaucoma progression.

A relationship between PEG and SNHL has also been reported.[23,24,25,26] However, no significant difference in hearing was observed between adults with PEG and age-matched controls in a study investigating the genetic and environmental causes of disease in older adults.[27] The authors of that study concluded by refuting Paliobei et al.'s[28] suggestion of adopting a multidisciplinary approach involving ear, nose, and throat

Table 1. Demographics of the study groups				
	POAG (n=24)	**PEG (n=22)**	**Control (n=21)**	**p value**
Age (years), mean ± SD (median, IQR)	64.50±7.45 (66, 58-72)	66.90±4.51 (66, 65-72)	64.38±4.36 (67, 62-67)	0.587*
Male:female ratio	12:12	11:11	12:9	0.863†

*Kruskal-Wallis test result, †Chi-square test result; n: Number of participants, POAG: Primary open-angle glaucoma, PEG: Pseudoexfoliative glaucoma, SD: Standard deviation, IQR: Interquartile range

specialists in the treatment of PEG and POAG patients. This contradicts the current study findings, particularly the increased likelihood of SNHL in association with PEG. Additionally, there is a much larger gap in mean ages between the current study and the study by Tryggvason et al.,[27] in which the mean ages were 77.4 years in PEG patients, 77.9 years in POAG patients, and 77.9 years in healthy individuals. The much older population in the Tryggvason et al.[27] study may explain their essentially insignificant and contradictory findings.

The general characteristic features of all types of glaucoma consist of retinal ganglion cell depletion, retinal nerve fiber layer thinning, and optic disc cupping.[29] The cell loss is not always limited to retinal ganglion cells, but may also extend to the lateral geniculate nucleus and visual cortex.[30,31] Previous studies reported that the loss of retinal ganglion cells and their axons as a result of glaucoma was followed by changes in glial cell, astrocyte, and retinal microglia cell counts.[32,33] Age-related SNHL was found to occur at a relatively high rate in age-related macular degeneration.[34] In addition, optic neuropathy and SNHL were shown to arise from more or less the same genetic defect.[35] However, few studies have focused on the relationship between glaucoma and SNHL. By taking into account the closely related features of these disorders in terms of neurological degeneration, the current study found an increased prevalence of SNHL in patients with glaucoma, most notably PEG, as opposed to only a minor manifestation in POAG. Given the concomitant neurological degeneration, this finding appears to support the early hypothesis of a clear relationship between these disorders.

POAG is characterized by unrestricted flow of aqueous humor to the trabecular meshwork and Schlemm's canal at the anterior chamber angle. In contrast, secondary open-angle glaucoma has a distinctive elevated outflow resistance through the trabecular meshwork and Schlemm's canal. The cause of this resistance is observable, as in pigmentary open-angle glaucoma and PEG, which can be identified by examining the ocular anterior segment.[36] PEX syndrome is an age-related disorder resulting in the formation and deposition of irregular extracellular fibrillar products.[37] Ocular PEX is now recognized as a part of a systemic disorder, as PEX material has been found in other body parts, including the skin, vasculature, and visceral organs such as the inner ear.[15] Thus, SNHL could be another extraocular symptom of PEX syndrome.

Analogous to the ocular anterior segment, the tectorial and basilar membranes of the inner ear are all products of the neuroectoderm. As such, accumulation of PEX materials on the tectorial and basilary membranes is also possible in PEX syndrome.[38] An abundance of PEX material on these structures can lead to elevated hearing threshold levels as a result of inner ear mechanoreceptor dysfunction, inevitably leading to hearing loss. Although SNHL has been linked to a variety of etiologies, the precise mechanism remains unknown. PEX materials that cause dysfunction of the mechanoreceptors of the inner ear have also been identified in the organ of Corti.[38] Precipitation of these materials may lead to significant changes in sound-induced vibration and impair the hearing process.[39] Yazdani et al.[26] reported a higher incidence of SNHL in PEX patients than in control subjects. Similarly, a high prevalence of SNHL in patients with PEX syndrome has been identified previously.[2,25,26,40] The current study supports prior findings regarding the prevalence of SNHL in PEX, specifically PEG. Furthermore, the current study has revealed a completely new finding: PEX syndrome was associated with a significant higher prevalence of SNHL at high frequency levels. SNHL seems to be associated with the presence of PEX material rather than glaucoma. If ocular PEX is representative of widespread PEX fibril distribution, then fibril deposition in the inner ear could demonstrate the association between PEX syndrome and SNHL. The presence of PEX fibrils in the organ of Corti may account for the clear relationship between PEX and the high hearing thresholds observed in this study.

The current study methodology has advantages as well, as more stringent participant exclusion criteria were used, and audiometric tests included a wide band of frequencies, encompassing the entire audible frequency spectrum. By revealing a higher likelihood of SNHL in PEG patients, the current study supports prior findings indicating that PEX syndrome may be a systemic disease affecting multiple tissues and organs.

Glaucoma subgroup analysis in a study by Chien et al.[3] revealed a significantly higher incidence of normotensive glaucoma and angle closure glaucoma in the SNHL group, while the incidence of POAG was only marginally increased. Steroids are a key alternative therapy for SNHL.[41] Hence, POAG is expected to become more common as a result of the IOP-raising effect of steroids, which is known as steroid-induced glaucoma.[42] Despite this, it was observed that the proportion of POAG patients who also had SNHL was not significantly higher, whereas patients with normotensive glaucoma were more prevalent in the SNHL group.[3] In the current study, however, there was a significant relationship between PEG and SNHL.

Similar to earlier studies, we found that SNHL and POAG coexisted less frequently. The preferential manifestation of SNHL and PEG is further evidence of the systemic nature of PEX syndrome. This finding lends support to the theory that a higher rate of glaucoma in SNHL patients is caused by a compromised nervous system rather than a result of steroid-related glaucoma.

Study Limitations

The current study has some limitations. First, the cross-sectional study design curtailed our ability to discover the processes underlying the relationship between hearing loss and glaucoma. Second, although we did not include patients with any ocular or systemic condition associated with hearing physiology, history of ear infection or surgery, tympanic membrane rupture, exposure to ototoxic drugs or heavy noise, and upper respiratory tract infection at the time of evaluation, there can sometimes be insufficient distinction between conductive hearing loss and SNHL. Therefore, we could not be completely certain that all patients with conductive hearing loss were excluded from the study. Third, residual confounding factors may have caused unexplained bias in the analysis. Fourth, although glaucoma patients were tested using Humphrey field analysis, which is a preferred approach for visual field testing, frequency-doubling technology is a quick, reliable, and large-scale screening technique sensitive enough to detect glaucomatous visual field abnormalities relatively earlier than SAP.[43] Fifth, participants were recruited based on ophthalmological examination using slit-lamp biomicroscopy. However, Kivelä et al.[44] stated that in some PEX cases, the accumulation of fibrillar products is not clinically observable but can be detected by histopathological examination. This fact could have contributed to some errors in control group sampling. Finally, the study population was just not large enough to improve the efficacy of the study.

While the current study has some drawbacks, it also has some advantages. So far as we know, this may be the first study to simultaneously evaluate seven different frequencies (250, 500, 1,000, 2,000, 4,000, 8,000, and 10,000 Hz) to determine pure-tone averages in the sample, which included patients and controls all of the same ethnicity. Ethnicity is an important factor in the selection of patients and controls, although an extensive investigation of this has not yet been conducted. In this case, European and American organizations have implemented international standards.[23] Based on the comparative findings of the current study and others globally that have shown comparable rates of SNHL in PEX patients, these standard systems appear to also be completely consistent with our population. Thus, there seems to be no need to set up study groups that include audiometric control measures in future Turkish studies. A high average age of study participants can be expected to influence hearing threshold results due to presbycusis. Fortunately, all of the groups in this study were roughly the same age, which might have mitigated the inherent bias in our results to some degree.

Conclusion

The current study has reaffirmed the relationship between SNHL and chronic glaucoma. Identifying concomitant hearing loss, particularly in chronic PEG patients, is essential for improving quality of life and thereby reducing the social burden of this patient group, whose quality of life is deteriorating due to long-term glaucoma therapy and irreversible visual loss. Routine ophthalmology and otolaryngology examinations in older adults may be critical for the early diagnosis and treatment of these disorders.

Ethics

Ethics Committee Approval: The study procedure conformed to the ethical standards of the Helsinki Declaration and was approved by the Afyonkarahisar Health Sciences University Ethics Committee (approval number: 2020/520).

Informed Consent: All participants provided written informed consent prior to the study.

Peer-review: Externally and internally peer reviewed.

Authorship Contributions

Concept: F.F.G., M.D., M.C.S., H.H.G., A.K., Ş.U., Design: F.F.G., M.D., M.C.S., H.H.G., A.K., Ş.U., Data Collection or Processing: F.F.G., M.D., M.C.S., H.H.G., A.K., Ş.U., Analysis or Interpretation: F.F.G., M.D., M.C.S., H.H.G., A.K., Ş.U., Literature Search: F.F.G., M.D., M.C.S., H.H.G., A.K., Ş.U., Writing: F.F.G., M.D., M.C.S., H.H.G., A.K., Ş.U.

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Review

The Effect of Blindness on Biological Rhythms and the Consequences of Circadian Rhythm Disorder

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Abstract

Various physiological systems and behaviors such as the sleep-wake cycle, vigilance, body temperature, and the secretion of certain hormones are governed by a 24-hour cycle called the circadian system. While there are many external stimuli involved the regulation of circadian rhythm, the most powerful environmental stimulus is the daily light-dark cycle. Blind individuals with no light perception develop circadian desynchrony. This leads to non-24-hour sleep-wake rhythm disorder, which is associated with sleep-wake disorders, as well as mood disorders and loss of appetite and gastrointestinal disturbances due to disrupted circadian hormone regulation. As the diagnosis is often delayed because of under-recognition in clinical practice, patients must cope with varying degrees of social and academic dysfunction. Most blind individuals report that non-24-hour sleep-wake rhythm disorder affects them more than blindness. In the treatment of totally blind patients suffering from non-24-hour sleep-wake rhythm disorder, the first-line management is behavioral approaches. Drug therapy includes melatonin and the melatonin agonist tasimelteon. Diagnosing blind individuals' sleep disorders is also relevant to treatment because they can be improved with the use of melatonin and its analogues or by phototherapy if they have residual vision. Therefore, assessing sleep problems and planning treatment accordingly for individuals presenting with blindness is an important issue for ophthalmologists to keep in mind.

Keywords: Biological rhythms, circadian rhythm, blindness, light, melatonin

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Introduction

All living things have a multitude of biological rhythms occurring at different frequencies and periods, ranging from the cellular level to the physiological and social behavioral levels.[1] In humans, biological rhythm frequencies spanning nearly all segments of time have been described, such as electroencephalogram waves that oscillate by the second, 24-hour sleep-wake rhythms, the weekly pattern of urinary 17-ketosteroid excretion, and other rhythms that occur monthly, annually, or even every 10 years, like the appearance of some sunspots.[2] Among these biological rhythms, circadian rhythms (referring to a 24-hour period) are perhaps the most well studied. Human physiology and behavior are governed by a 24-hour circadian rhythm. The sleep-wake cycle, attention, behavior patterns, and hormone secretion are just a few examples of biological systems regulated by the circadian cycle. This rhythm is spontaneously adjusted by the suprachiasmatic nucleus in the anterior hypothalamus, which is an internal rhythm regulator.[3] In most people, this circadian rhythm is slightly longer than 24 hours and is adjusted daily to the solar rhythm of 24 hours according to environmental cues. The most important environmental cue for synchronization is light. Daily retinal exposure to light is needed to adjust the circadian rhythm to 24 hours.[4] Except for those with jetlag or shift work, this daily synchronization occurs with no problem in people with good eyesight. However, people with bilateral vision loss or blindness become desynchronized due to the lack of light input to the suprachiasmatic nucleus.[5]

In this review, we aimed to examine the changes in circadian rhythm associated with the lack of light input in blind individuals, as well as the physical and mental consequences of and treatment approaches to these changes, in light of the current literature. To better understand the physiopathology, we first examine the relationship between light, melatonin, and circadian rhythm.

Light, Melatonin, and Circadian Rhythm

Circadian rhythm refers to biological, physiological, and behavioral changes in an organism over a period of approximately one day. In this sense, the sleep-wake cycle is the most basic and definitive circadian rhythm in the human body.[6] The mammalian circadian system also includes the retina, the retinohypothalamic pathway, the pineal gland, and the suprachiasmatic nucleus. However, the structure responsible for regulating the circadian rhythm is the suprachiasmatic nucleus in the anterior hypothalamus.[3] The main purpose of this region is to ensure that the physiological functioning and internal equilibrium of the organism work in harmony with the external environment and that rhythmic functions are carried out regularly by maintaining that harmony in different conditions. The suprachiasmatic nucleus receives many external stimuli (zeitgeber) to adjust circadian rhythm and diurnal rhythm. Light is the most important rhythm regulator among these external stimuli.[7] The environmental light-dark cycle is a key factor in the regulation of circadian rhythm. Light is detected by melanopsin-containing photosensitive retinal ganglion cells, which project via the retinohypothalamic pathway to the suprachiasmatic nucleus. The light stimulus is transmitted through the superior cervical ganglion to the pineal gland via complex neural networks.[8] In this way, light suppresses the synthesis of melatonin, a pineal hormone. The synthesis and release of melatonin is stimulated at night in the dark and suppressed by light during the day.[9] Exposure to light at night causes a decrease in plasma melatonin levels through this mechanism. Melatonin suppresses neuronal firing in the suprachiasmatic nucleus, resulting in sleep induction and maintenance. Exogenous melatonin intake produces a hypnotic effect.[10] Depending on the timing of light exposure and melatonin administration, the phase of the endogenous rhythm can be delayed or advanced. Administering melatonin in the evening shifts the phase to earlier in the evening, while administering it in the morning causes the phase to be delayed.[11] The opposite is also true for light exposure. Intense light exposure in the evening delays the phase, while light exposure in the early morning advances the phase. Thus, phase changes in circadian rhythm disorders can be regulated through the use of bright light and melatonin at appropriate times.[12]

Initial data from various studies have shown that the eyes are essential for circadian photoreception. Individuals who do not have eyes because of bilateral enucleation or developmental disorders cannot entrain their circadian rhythm to the 24-hour light-dark cycle.[13] The same applies to most individuals whose eyes are preserved but have no light perception due to total blindness. Most legally blind individuals who still have some degree of light perception, even with little functional vision, have normal circadian rhythms.[13]

Blindness and its Effect on Circadian Systems

Definition and Prevalence of Blindness

The legal definition of blindness is having a corrected visual acuity 1/10 of normal (i.e., 20/200) or worse despite correction, or a visual field of 20 degrees or less. People with corrected visual acuity between 20/70 and 20/200 are described as having "low vision."[14,15]

The exact prevalence of blindness is difficult to estimate. According to World Health Organization data for 2000, there were approximately 45 million visually impaired people worldwide. This number was expected to increase by 1-2 million each year to reach 75 million by 2020.[16] The 2010 Global Burden of Disease Study estimated that there were 32.4 million blind individuals.[17] In 2000, it was determined that there were approximately 937,000 blind people in the United States of America (approximate prevalence of 0.78%).[18] It was also estimated in 2000 that approximately 120,000 people in Europe were totally blind. According to a study conducted in 2011 by Boğaziçi University Visually Impaired Technology Laboratory, which is one of the most recent studies conducted in Türkiye, there are approximately 400,000 visually impaired individuals in our country.[16]

Relationship Between Circadian Rhythm and Blindness According to its Timing and Etiology

One of the most curious issues related to blindness and circadian rhythm is how differences in its time of occurrence and underlying cause affect circadian rhythm. Blindness can be classified as congenital or acquired according to when it occurs. Congenital blindness refers to a group of diseases and conditions that occur in childhood or early adolescence (before the age of 16) and which, if left untreated, cause blindness or severe visual impairment that is likely to lead to permanent blindness.[19] Acquired blindness occurs later in life in association with various factors.

The World Health Organization uses two methods to classify blindness and low vision in children. The first method, which is a descriptive classification, refers to the anatomical region most affected. These are grouped as globe (e.g., anophthalmia, microphthalmia), cornea (e.g., corneal scar, keratoconus), lens (e.g., cataract, aphakia), uvea (e.g., aniridia), retina (e.g., retinal dystrophies), optic nerve (e.g., optic nerve atrophy), glaucoma, and conditions in which the eye appears normal (e.g., refractive errors, cortical blindness, amblyopia). The second method, which is an etiological classification, classifies blindness according to the underlying cause. This method uses categories based on the time of onset, which is classified as hereditary (during conception; e.g., genetic diseases, chromosomal abnormalities), intrauterine (during pregnancy; e.g., rubella or thalidomide), perinatal (e.g., retinopathy of prematurity, birth injury, neonatal conjunctivitis/ophthalmic neonatorum), childhood (e.g., vitamin A deficiency disorders, measles, trauma), and unknown (e.g., congenital abnormalities).[20] Acquired blindness can also be classified anatomically as in childhood and may occur due to causes such as cataract, glaucoma, age-related macular degeneration, and diabetic retinopathy.

Ophthalmologists' recognition of impaired circadian rhythms in blind patients is important because an irregular sleep cycle can exacerbate the challenges of life. However, not all individuals with total blindness develop circadian rhythm disorder, and identifying circadian rhythm disorder in blind patients can be complex. It is also extremely important to determine whether the patient has any residual light perception and to obtain a clinical history from the patient. The patient should be asked about unusual sleeping and waking hours, periodic insomnia, and daytime sleepiness.[21]

There are a few studies examining the timing and rate of onset of blindness and the effect of the circadian rhythm on sleep disorder. For example, one study investigated the relationship between sleep disturbance and duration of blindness, rate of vision loss, and type of visual field defect, and no significant correlation was observed. There was also no significant difference between those with congenital blindness and those with acquired blindness.[22] Similarly, Leger et al.[23] determined that sleep difficulties in blind subjects were not associated with factors such as congenital blindness or the number of prosthetic eyes. The etiology and affected anatomical structures are more important than the time of occurrence.

As is known, photic entrainment of circadian rhythms stems from the eye and involves a direct axonal pathway from a small portion of the retinal ganglion cells to the suprachiasmatic nucleus. The remarkable feature of this neural circuit is its apparent independence from conventional retinal phototransduction.[24] In animal studies, mice lacking rods and cones were still able to synchronize their activity to the external lighting cycle, and photic entrainment persisted with undiminished sensitivity, suggesting the presence of a different internal retinal (non-rod or cone) photoreceptor.[25,26]

Different studies have shown that circadian rhythms in blind individuals may be normal, abnormal, or non-entrained. Why does circadian rhythm entrainment differ among these individuals, all of whom have vision loss? One determining factor is an individual's degree of vision loss. In fact, the presence or absence of light perception is more important than the extent of vision loss, as individuals will most likely have a normal circadian rhythm if they have some degree of light perception. In one study, individuals with visual acuity of 3/60 Snellen or better, counting fingers, hand movements, or only light perception were found to have normally entrained and similar rhythms.[21]

Another factor is the etiology of blindness. While normal entrainment of the circadian rhythm cannot occur in pathologies involving ganglion cell damage, the circadian rhythm may be normal in pathologies of the outer retinal photoreceptor layer. In one study, 56% of the participants with eye pathologies suspected of damaging the ganglion cell photoreceptor layer (e.g., retinopathy of prematurity, diabetic retinopathy) were classified as non-entrained or abnormal phase entrained, regardless of vision status. Conversely, 85% of participants with conditions affecting retinal layers other than the retinal ganglion cell layer (e.g., retinitis pigmentosa, other retinal dystrophies, macular degeneration, Leber's congenital amaurosis) were classified as normally entrained, regardless of vision status. Among those with eye pathologies affecting the optic nerve (e.g., glaucoma, optic atrophy), 57% had normally entrained circadian rhythm.[27] However, as in many other studies, several eye pathology categories in this study included a small number of participants ($n<5$). Therefore, it was not possible to associate certain eye pathologies with the type of circadian rhythm. In the categories with more participants ($n>5$), the ocular conditions with the highest proportion of abnormal phase entrainment and/or non-entrainment were enucleation for any reason (67%) and retinopathy of prematurity (57%).[27]

Individuals with anterior segment disease (including diseases affecting the anterior third of the eye, the cornea, iris, ciliary body, and lens) are more likely to have normal circadian rhythm. Association with abnormal circadian rhythm was found to be stronger in patients with total anterior segment pathology compared to other anterior segment pathologies (e.g., albinism, aniridia). However, in individuals with anterior segment pathology that completely obscures posterior segment examination, retinal disease is more likely to be missed and this may be associated with abnormal phase entrainment.[27] In a different study, sleep disturbances were found to be more

common in low vision conditions caused by uveitis compared to other pathologies.[22]

These potential associations warrant further investigation because diseases associated with progressive degeneration in certain areas of the eye may increase the patient's risk of developing a circadian rhythm sleep disorder. Such studies will also be relevant in decision making before elective enucleation if the eyes still have functional light perception.[27] Therefore, studies with more participants are needed to elucidate these potential relationships.

In summary, while studies point to a significant relationship between the etiology of blindness and circadian rhythm disorders, it has been shown that congenital and acquired blindness do not differ in their effect on sleep problems.[23]

Relationship Between Blindness and Circadian Rhythm Sleep-wake Disorders

Total or partial vision loss leads to structural and functional changes in the visual cortex and various other parts of the brain. Numerous studies have demonstrated these changes using neuroimaging techniques and electrophysiological methods. Individuals with total or partial blindness were found to have changes in the cortex and other brain regions because of reduced vision.[28,29] A study by Noebels et al.[30] showed that blind people had reduced resting occipital alpha oscillations when their eyes were closed. Studies by Kriegseis et al.[31] in 2006 and Schubert et al.[32] in 2015 demonstrated decreased parieto-occipital alpha activity indicating changes in the thalamo-cortical pathway in blind people. In addition to such anatomical and physiological changes, the decrease or absence of light input in blind people can also bring about significant changes in circadian rhythm.

There are also limited data on sleep structure and electrophysiological changes in blind people. These limited studies have yielded inconsistent information regarding rapid eye movement (REM) and the non-REM (NREM) stages. Some studies with small samples of blind individuals (n=5) indicated a decrease or absence in deep sleep (N3, formerly NREM stages 3 and 4), characterized by slow sleep wave.[33] These findings were confirmed in another study with a larger sample (n=10).[34] However, none of these studies showed any difference in REM sleep and NREM stage 2 between blind people and those with normal visual function. In a larger study (n=26) by Leger et al.,[23] all of the blind individuals were shown to have free-running circadian rhythms and shorter sleep duration, lower sleep efficiency, shorter REM duration, and longer REM latency compared to healthy controls. A prevalence study also conducted by Leger et al.[35] showed that approximately 83% of blind individuals had at least one sleep problem. Miles[36] reported that 76% of blind people in their study (n=50) had sleep-wake disorder and 40% of those people had a cyclical course of symptoms. In another study of 388 blind individuals, 48.7% of the blind group and 9% of the placebo group reported a sleep disorder.[22] In a study conducted with 794 individuals with blindness in France, 83% of the participants with blindness and 57% of the control group had at least one sleep problem (difficulty falling asleep, disrupted nighttime sleep, waking early in the morning, non-restful sleep, and poor sleep quality), while 18% of the blind group and 8% of the control group met the diagnostic criteria for non-24-hour sleep-wake disorder.[35] In another observational study conducted in New Zealand, there was a high frequency of sleep disorders. In particular, sleep timing problems associated with decreased light input were seen in 55% of blind individuals, while this rate was 4% in the matched general population.[37]

Data from studies conducted with blind individuals are very limited because they were obtained from small samples and generally did not include a circadian marker.[38] However, it is known that most individuals without light stimuli have a circadian rhythm sleep-wake disorder called non-24-hour sleep-wake disorder, also known as free-running sleep phase disorder.[27] Because it is uncommon in the general population, this disorder is inadequately understood and diagnosis is delayed considerably in some cases. Although non-24-hour sleep-wake disorder can be partially explained by decreased light input, it is not yet fully understood what causes other sleep disturbances in blind people.

Non-24-Hour Sleep-Wake Disorder (Free-running Sleep Phase Disorder)

In non-24-hour sleep-wake disorder, which is rare in individuals with normal visual function but common in total blindness, people experience desynchronization of the circadian rhythm because they cannot receive the light input that enables the circadian rhythm to be entrained to a 24-hour period. This results in progressive sleep-wake phase delay, characterized by a progressive delay in sleep onset.[39] In other words, they have a sleep-wake cycle in which nearly every day they fall asleep a few hours later and wake up later than the previous day. As a result, they experience insomnia at night and prolonged daytime sleepiness during the day.[40] In addition to sleep-wake problems, the disrupted circadian release of hormones such as melatonin and cortisol leads to appetite and digestive problems.[41] All of these symptoms are reflected in people's vigilance, mood, and performance during the day, causing disruptions in their social, academic, and professional lives. Most individuals with vision loss report that non-24-hour sleep-wake disorder affects them more than blindness.[41]

According to the International Classification of Sleep Disorders-third edition (ICSD-3), criteria A, B, C, and D are required for the diagnosis of non-24-hour sleep-wake disorder (**Figure 1**).[37]

The high frequency of non-circadian sleep disorders (e.g., insomnia, excessive sleepiness) and clinical manifestations such as depression and anxiety that cause various sleep problems in blind people often make it difficult to establish a diagnosis. In this sense, it is diagnostically valuable to demonstrate the daily shift in the sleep-wake cycle by keeping an actigraphy record for at least 2 weeks, as recommended in the ICSD-3 guideline for the diagnosis of non-24-hour sleep-wake disorder. Actigraphy is a noninvasive, watch-like measurement device worn on the wrist or ankle to measure sleep-wake cycles and motor activity.

This allows periods of rest and movement to be recorded and saved. Biochemical measurements are also recommended when necessary. Analysis of 24-hour urine, saliva, or blood samples two or three times over a period of 2-4 weeks are recommended to measure levels of 6-sulfatoxymelatonin, the main metabolite of melatonin.[42] Urine samples are typically collected every 4 hours during the day and over 8-10 hours at night. In people with non-24-hour sleep-wake disorder, repeated sampling will show abnormal circadian clock periodicity (<23.8 or >24.2 hours) and a gradual shift in the melatonin secretion profile. However, repeated measurement of 6-sulfatoxymelatonin is expensive and should be reserved for individuals at high risk for non-24-hour sleep-wake disorder. Measurement of other biomarkers, such as cortisol, can be used in complex cases or in cases of abnormal melatonin release, such as pineal resection.

Clinical Implications of Circadian Rhythm Disruption Associated with Blindness

Disruption of the circadian rhythm results in desynchronization of internal physiological processes such as cortisol, melatonin, and body temperature regulation, and these recurrent disruptions in the circadian system have negative effects on the endocrine, gastrointestinal, cardiovascular, and reproductive systems, as well as on mood. Alterations in these systems also lead to adverse effects on the immune system and increase the incidence of cancer. For example, the International Agency for Research on Cancer has classified shift work that causes circadian disruption as a possible carcinogen in humans.[43,44] A study by McHill et al.[45] showed that under laboratory conditions, circadian desynchrony led to reduced daily energy consumption and, if not compensated for by increased activity and reduced calorie intake, resulted in weight gain and adverse health outcomes. Circadian disruption due to shift work was reported to disrupt behavioral rhythms such as meal timing and lead to significant cardiac and general health consequences.[46,47] Night shift work has been shown to be associated with increased cardiometabolic disease, metabolic syndrome, type 2 diabetes, and cardiovascular heart disease due to its disruption of circadian synchronization.[48,49,50,51,52,53] Other studies have reported various gastrointestinal complaints and difficulties such as menstrual irregularities, dysmenorrhea, and gestational hypertension.[54,55] Boivin et al.[56] reported that circadian disruption due to shift work led to impairments in cognitive functions and performance. Other studies have also supported that impairment of circadian rhythm will lead to impairment of cognitive functions, severe sleepiness, and attention errors.[57,58]

Disturbances in circadian rhythm and melatonin release are thought to play a role in ocular diseases such as dry eye, corneal wound healing, glaucoma, myopia, cataract, and retinal diseases.[59] Tear osmolarity is known to show a circadian pattern. Inverse to tear volume, tear osmolarity is low in the morning and increases at night as sleep approaches.[60] In sleep-wake disorders associated with impaired circadian rhythm, dry eye disease may develop because the tear production pattern is disrupted. Corneal epithelial healing is also believed to be regulated by a circadian cycle, and mitotic activity peaks in the evening hours.[61] Some experimental studies have indicated that topical melatonin and its derivatives accelerate corneal wound healing.[62] Additionally, aqueous humor production in humans is influenced by circadian rhythm.[63] While the rate of aqueous humor production is high during the day, it decreases at night.[64] The aqueous humor outflow rate is also lower at night than during the day.[65] In glaucoma patients, the disruption of this equilibrium leads to increased intraocular pressure. Melatonin, which plays an important role in regulating circadian rhythm, reduces aqueous humor production. A comparison of melatonin concentrations in the aqueous humor and blood of glaucoma patients and normal individuals revealed significantly higher melatonin levels in the glaucoma patients.[66] Therefore, some studies have linked daytime changes in intraocular pressure to fluctuations in melatonin levels, and it has been suggested that some melatoninergic mechanisms play a role in the circadian rhythm of intraocular pressure.

Considering all of these data, it is apparent that circadian rhythm disturbance is associated with many negative health outcomes. In blind individuals, non-24-hour sleep-wake disorder caused by disrupted circadian alignment may not only lead to disruption in the sleep-wake cycle, but may also cause serious physical and mental conditions. The paucity of literature data on this subject indicates that new studies should be conducted.

Treatment Approaches in Non-24-Hour Sleep-Wake Disorder

Treatment for non-24-hour sleep-wake disorder is effective. People treated with various approaches show synchronization of the circadian rhythm to 24 hours and improvement in symptoms of insomnia and prolonged daytime sleepiness.[67]

Behavioral approaches such as regularizing sleeping, waking, and meal times and physical activity in the morning are recommended as first-line treatment. If partial light perception is present, daytime light exposure or morning bright-light therapy is recommended. Intellectual activities that increase alertness, a cold shower, or intense physical activity in the morning may be beneficial (**Figure 2**).

Pharmaceutical treatment consists of fast- and prolonged-release melatonin preparations and melatonin agonists. As the goal of therapy is to prevent further circadian drift, initiating treatments when the patient is in phase with the solar cycle may be most effective. This may require waiting for the patient's sleeping and waking hours to return to approximately normal, but that is not always possible.

Melatonin has a short half-life of 20-45 minutes because of the first-pass effect in the liver.[68] Given the role of melatonin on circadian rhythms, it is necessary to distinguish its acute sedative effects from its phase regulatory effect, also called the "chronobiotic effect."[69] Exogenous melatonin therapy has an acute sedative effect, a phase regulatory effect, as well as an effect on endogenous circadian rhythms such as body temperature.[70] Its phase regulation activity is related to the timing of administration.[12] Melatonin given early in the evening

advances the circadian clock, leading to earlier sleep onset and waking time, while melatonin given early in the morning leads to later sleep onset and waking time. However, the delaying effect of morning melatonin on circadian rhythm is less potent than the advancing effect of evening melatonin, leading to the risk of napping during the day.[71] Exogenous melatonin given in the late afternoon is often effective in helping patients with delayed sleep phase syndrome fall asleep and wake up earlier, but early morning melatonin has little to no effect in this group of patients.[72] Melatonin given mid-day also has no phase-corrective effect. The effect of melatonin on non-24-hour sleep-wake disorder depends on the person's circadian phase when treatment is started. If the circadian phase is already synchronized or is mildly delayed, evening melatonin administration advances the circadian phase and ensures proper alignment of the circadian rhythm.

In non-24-hour sleep-wake disorder, recommended treatment is 3-5 mg of melatonin at night 1 hour before sleep for the first month, continuing with 0.5 mg for maintenance after synchronization. Melatonin is also widely sold as a dietary supplement in Türkiye and the United States in addition to its sale as a pharmaceutical agent. However, the melatonin preparations sold as supplements are usually well above the dose needed to regulate circadian rhythm. In addition, they are often sold in combination with other preparations such as vitamin B_{12}.[73] Slow-release melatonin preparations are not as effective as normal-release preparations in regulating the circadian rhythm.

Although generally not the first to come to mind in the treatment of circadian rhythm sleep disorders, caffeine has been shown to alter the circadian phase in animals and plant models.[74,75] Caffeine has been shown to delay melatonin release in blind people.[76] In a study including the largest sample of blind individuals with circadian desynchronization, caffeine administration in the morning was reported to be beneficial in alleviating symptoms associated with desynchronized rhythms, such as decreased alertness and low mood, but not effective in regulating circadian rhythm.[77]

Melatonin agonists other than tasimelteon may be useful in regulating circadian rhythm, but these agonists have different pharmacological and pharmacokinetic effects and have not been studied in non-24-hour sleep-wake disorder.

In the SET and RESET studies conducted in 2015, Lockley et al.[78] reported that the melatonin agonist tasimelteon may be effective in the resynchronization of circadian rhythm in people with total blindness. In the first of these two large-scale studies (SET), participants were randomized to receive either 20 mg tasimelteon or a placebo 1 hour before the target sleep time. After approximately 1 month, circadian rhythm synchronization was observed in 8 (20%) of the 40 participants in the tasimelteon group and only 1 (3%) of the 38 participants in the placebo group (17% difference, 95% confidence interval: 3.2-31.6). In the exploratory analysis of 17 patients who continued to use tasimelteon for about 7 months, the rate of circadian rhythm synchrony reached nearly 60%. When tasimelteon treatment was discontinued, patients were observed to return to free-running circadian rhythm. In the RESET study, it was determined that daily use of tasimelteon was necessary to maintain circadian rhythm entrainment, as predicted from the results of the previous study.[78]

Although there are many melatonin agonists, only tasimelteon has been approved by the FDA (United States Food and Drug Administration) and EMA (European Medicines Agency) as a treatment with proven efficacy and safety. Tasimelteon is a potent and specific melatonin 1 (MT1) and 2 (MT2) receptor agonist. It has 2-4 times greater affinity for the MT2 receptor. Its half-life is 1.3 hours and peak plasma concentration is reached between 0.5 and 3 hours after intake. A daily dose of 20 mg in the evening is recommended. Although tasimelteon is well tolerated in the short term, the most common side effects are reported to be headache, elevated liver enzymes, nightmares or abnormal dreams, upper respiratory tract infection, and urinary tract infection. Long-term use has been reported to be safe and well tolerated.[79]

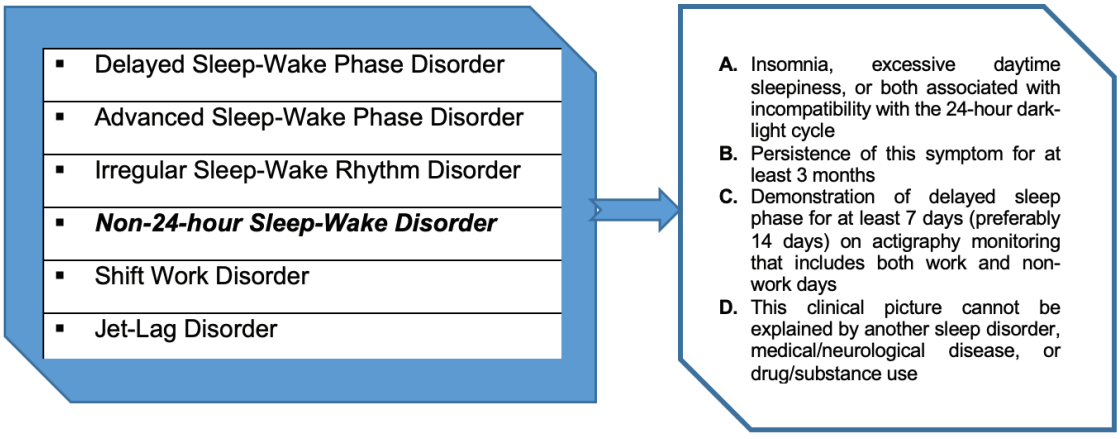

Figure 1. Circadian rhythm sleep-wake disorders (according to the International Classification of Sleep Disorders-3)

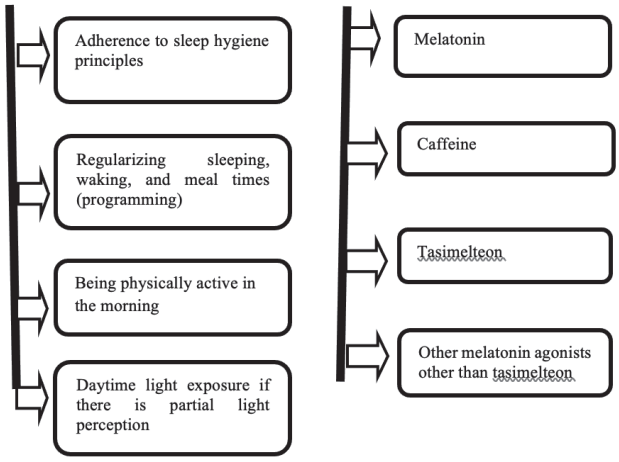

Figure 2. Treatment approaches for non-24-hour sleep-wake disorders

Cost is another important factor in the selection of treatment for circadian rhythm synchronization, as patients need to take the drug daily to maintain this synchronization. The annual cost of using melatonin is approximately $50, while the annual cost of using tasimelteon is around $60,000.[73]

Conclusion

Blind people who cannot receive light input experience symptoms such as insomnia and excessive daytime sleepiness due to disruption of and inability to re-entrain the circadian rhythm. In addition, disruptions in physiological functions and hormone release regulated by the circadian rhythm lead to various adverse consequences in their social, academic, and professional lives. Keeping a sleep diary, obtaining actigraphy measurements, and when necessary, analyzing biochemical parameters are beneficial when diagnosing non-24-hour sleep-wake disorder, which is very rare in the sighted population but common in the blind. Behavioral and pharmacological methods are often effective in the treatment of this disorder. The need to continuously use the drugs that prevent circadian drift is important in terms of considering effectiveness and cost when selecting pharmacological treatment. The diagnosis is often delayed, causing considerable functional losses for blind people, who already face obstacles in many areas of daily life. Diagnosis is also relevant to treatment, as the sleep patterns of blind people can be made more normal through the use of melatonin and its analogues, or phototherapy if they have residual vision. Therefore, assessing sleep problems and planning treatment accordingly for individuals presenting with blindness is an important issue for ophthalmologists to keep in mind.

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Case Report

Coincident Acute Macular Neuroretinopathy and Paracentral Acute Middle Maculopathy in COVID-19

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Abstract

An ophthalmology consultation was requested for a 29-year-old woman complaining of visual field defects. The patient had presented to the emergency department with cough and high fever one day earlier. Chest computed tomography demonstrated pneumonia and two severe acute respiratory syndrome coronavirus 2 polymerase chain reaction tests were positive. The patient had undergone renal transplantation 11 years ago due to glomerulonephritis. Best-corrected visual acuity (BCVA) was 20/40 in the right eye and 20/30 in the left eye. Fluorescein angiography showed macular hypoperfusion, and optical coherence tomography (OCT) showed hyperreflectivity in the inner nuclear, outer plexiform, and outer nuclear layers, as well as discontinuity of the ellipsoid zone. Perimetry confirmed bilateral central scotoma. Levels of D-dimer and fibrinogen were 0.86 g/mL and 435.6 g/mL, respectively. The patient was diagnosed as having concurrent acute macular neuroretinopathy and paracentral acute middle maculopathy and was given low-molecular-weight heparin treatment for one month. Her BCVA improved to 20/20 in both eyes, and regression was observed in the retinal findings, hyperreflectivity and ellipsoid zone disruption on OCT, and scotoma in perimetry. Inflammation, thrombosis, and glial involvement may play a role in the pathogenesis of retinal microvascular impairment in COVID-19.

Keywords: COVID-19, retinal ischemia, paracentral acute middle maculopathy, acute macular neuroretinopathy, central scotoma

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Introduction

Acute macular neuropathy (AMN) and paracentral acute middle maculopathy (PAMM) are manifestations of retinal microvascular ischemia. AMN presents with central/paracentral scotoma, photopsia, and mild visual acuity loss. Infections, vasoconstrictor drugs, oral contraceptive drugs, hypotension/shock, preeclampsia, and caffeine consumption are suspected risk factors. Optical coherence tomography (OCT) shows abnormalities in the deep retinal layers especially.[1] During the Coronavirus disease 2019 (COVID-19) pandemic, researchers noticed an upsurge in AMN cases.[2,3] PAMM, a variant of AMN, presents with central/paracentral scotoma and a mild reduction in visual acuity, and is described as related to ischemia of the middle retinal layers. The inner nuclear layer (INL) is a watershed zone and is therefore sensitive to hypoperfusion.[4] OCT shows hyperreflective bands in the INL and outer plexiform layer (OPL). Fluorescein angiography (FA) and OCT angiography (OCTA) can demonstrate ischemia, enlargement of the foveal avascular zone, and capillary drop-out areas. Scotoma can be confirmed with perimetry.

Herein we report a case of bilateral AMN and PAMM findings in a patient with active severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. This study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient.

Case Report

Our clinic was consulted regarding a 29-year-old woman with bilateral visual field loss. Her description was consistent with a central scotoma. Medical history was negative for ocular diseases. The patient had presented to the emergency department one day earlier with cough and high fever. Chest computed tomography findings were consistent with COVID-19 pneumonia and polymerase chain reaction test for SARS-CoV-2 resulted positive twice. The patient had undergone renal transplantation 11 years earlier because of glomerulonephritis. She was receiving favipiravir (Favira®, Novel, Türkiye), low-molecular-weight heparin (LMWH; (Oksapar®, Koçak, Türkiye) at a prophylactic dose (40 mg once a day), everolimus (Afinitor®, Novartis, Switzerland), tacrolimus (Prograf®,

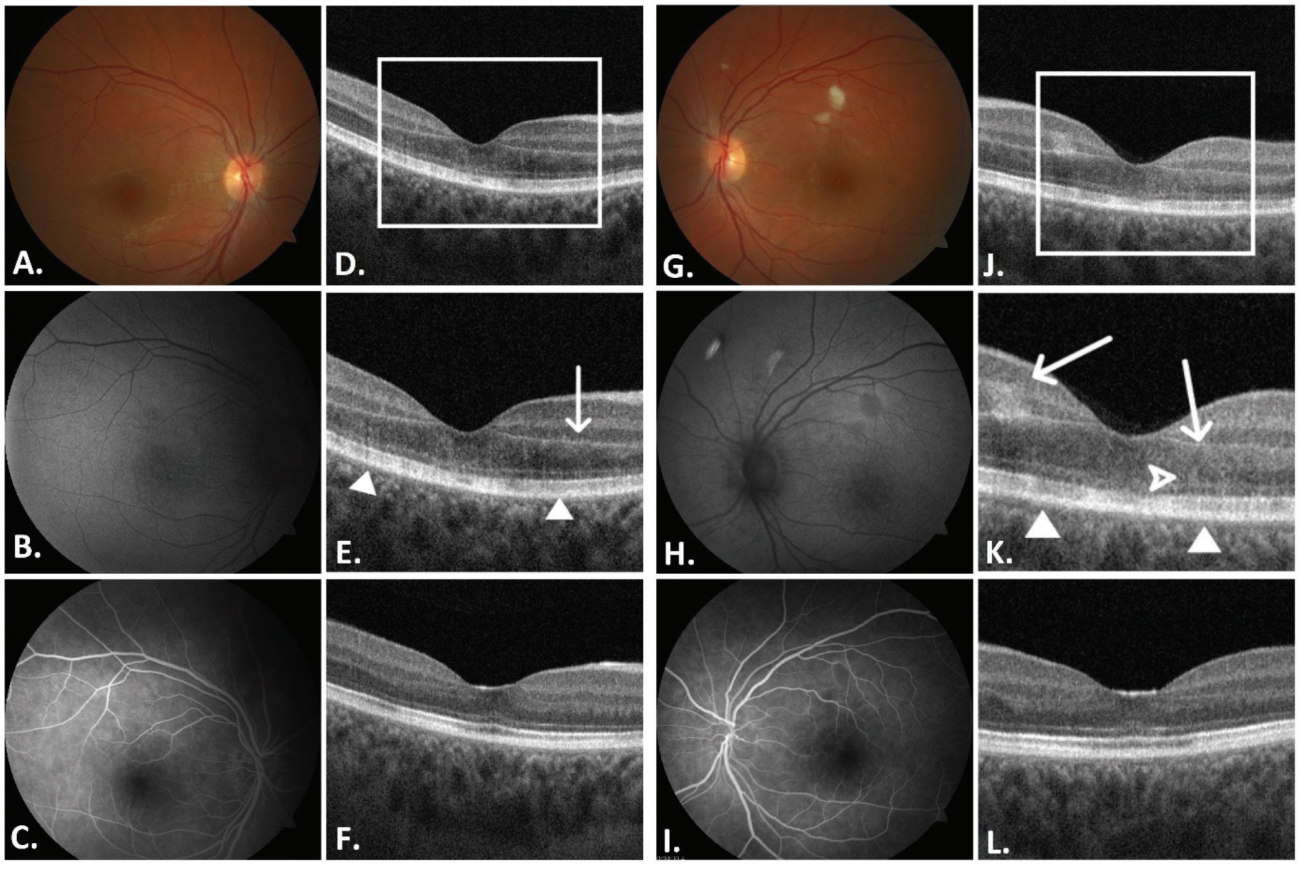

Figure 1. A) Fundus image of the right eye shows subtle retinal whitening. B) Autofluorescence image of the right eye shows a spotted appearance in the superior perifovea. C) Fluorescein angiography of the right eye shows hypoperfusion in the perifovea. D-E) Initial optical coherence tomography (OCT) images of the right eye show hyperreflectivity at the inner nuclear layer (INL) and outer plexiform layer (OPL) junction (white arrow) and disruption of the ellipsoid zone (white arrowheads). F) OCT image of the right eye after 6 months of follow-up. G). Fundus image of the left eye shows cotton wool spots and subtle retinal whitening. H) Autofluorescence image of the left eye shows hypofluorescence at the location of the cotton wool spots and a spotted appearance in the superior perifovea. I) Fluorescein angiography of the left eye shows hypoperfusion in the perifovea. J-K) Initial OCT images of the left eye show hyperreflectivity in the INL and INL-OPL junction (white arrows), disruption of the ellipsoid zone (white arrowheads), and Z-shaped hyperreflectivity in the Henle fiber layer (white empty arrowhead). L) OCT image of the left eye after 6 months of follow-up

Astellas, Ireland), prednisolone (Deltacortril®, Pfizer, Türkiye), valsartan (Diovan®, Novartis, Switzerland), and benidipine (Benipin®, Deva, Türkiye) as systemic treatment at the onset of ocular symptoms. She had no history of oral contraceptive treatment. Best corrected visual acuity was 20/40 in the right eye and 20/30 in the left eye. Biomicroscopy was normal. Intraocular pressure was 15 mmHg in both eyes. Fundoscopy revealed ill-defined patches of subtle retinal whitening in both eyes and cotton wool spots in the left eye (**Figure 1A, 1G**). D-dimer and fibrinogen levels were 0.86 µg/mL and 435.6 µg/mL, respectively. Horizontal OCT (Optovue RTVue XR Avanti; Optovue, Inc, Fremont, CA) scans over the fovea showed hyperreflectivity in the INL and OPL, consistent with PAMM, and discontinuity of the ellipsoid zone and interdigitation zone, which is consistent with AMN (**Figure 1E, 1K**). Z-shaped reflectivity in the Henle fiber layer due to extension of the hyperreflective bands defined by Iovino et al.[5] was observed in the OCT images (**Figure 1K**). FA demonstrated areas of macular hypoperfusion corresponding to the retinal whitening. Perimetry with standard 30-2 program of Humphrey Field Analyzer confirmed bilateral central scotoma. Due to the presence of chronic immunosuppression, further investigations with cranial magnetic resonance imaging and lumbar puncture were conducted by the neurology department but revealed no other pathological findings. The patient was diagnosed with AMN and PAMM. In cooperation with the nephrology and infectious diseases departments, LMWH was increased to treatment dosage (1 mg/kg, twice a day) for one month. A month later, visual acuity increased to 20/20 in both eyes and retinal findings diminished. There was partial regression in the ellipsoid zone disruption on OCT (**Figure 1F, 1L**) and scotoma in perimetry. Her clinical findings were the same at the one-year visit.

Discussion

COVID-19-related vascular complications were found to be associated with D-dimer levels higher than 0.5 µg/mL.[6] COVID-19-related cytokine storm and hyperinflammatory state may contribute to the risk for microvascular alterations.[7]

There are other reports of PAMM or AMN lesions in patients with active or recent SARS-CoV-2 infection. Padhy et al.[8] hypothesized that high D-dimer level was an indicator and risk factor for capillary ischemia. Capuano et al.[3] described an AMN case in a COVID-19 patient with protein S deficiency, which is consistent with the thrombosis hypothesis. Our patient's D-dimer level was 0.86 µg/mL at presentation. Hypotension is a suspected risk factor for AMN.[1] Although valsartan and benidipine are antihypertensive drugs, the patient's medical history was negative for hypotension and she was never hypotensive during the treatment period. In addition, valsartan inhibits vasoconstriction. Ozsaygılı et al.[9] suggested inflammation as a possible mechanism. However, in our patient, microvascular complications occurred while under anti-inflammatory treatment with prednisolone, tacrolimus, and everolimus. Therefore, thrombosis in micro-vessels may better explain the pathogenesis. Gascon et al.[10] stated that post-viral retinal damage may occur through the immune-mediated mechanisms. Given that our patient is immunocompromised, immunological pathways may also play a role in the pathogenesis.

IIovino et al.[5] reported coincident AMN and PAMM in patients with Purtscher retinopathy, retinal vein occlusion, central retinal artery occlusion, and retinal vasculitis. They suggested Müller cell impairment as the shared pathology. Vargas et al.[11] discussed the possibility that glial cell involvement in COVID-19 may be associated with neurological damage. Therefore, our case may represent a form of COVID-19-related Müller cell dysfunction that led to concurrent AMN and PAMM lesions in the same eye.[11]

Our study has some limitations. Firstly, the findings were analyzed retrospectively. The patient's comorbidities and state of chronic immunosuppression can be considered risk factors for ischemia, but the systemic treatment the patient was receiving had no known ischemic ocular complications. Retinal findings in the left eye resembled Purtscher-like retinopathy. However, in Purtscher-like retinopathy we would expect the periarteriolar retina to be spared from whitening.[12] The simultaneous occurrence of AMN and PAMM in the same eye differs from previous reports.

Involvement of the retinal microvasculature in COVID-19 is important because its circulation is an end-artery system. Hence, COVID-19-related retinal microvascular impairment is a potentially vision-threatening clinical manifestation. Further research has to be done to confirm the association between SARS-CoV-2 infection and PAMM/AMN lesions and to elucidate the exact pathogenesis of this involvement.

Ethics

Informed Consent: Oral and written informed consent was obtained from the patient.

Peer-review: Internally and externally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Y.C., O.K., D.U., Concept: A.Y.C., O.K., D.U., Design: A.Y.C., O.K., D.U., Data Collection or Processing: A.Y.C., O.K.,

Analysis or Interpretation: A.Y.C., O.K., D.U., Literature Search: A.Y.C., O.K., Writing: A.Y.C., O.K., D.U.

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Case Report

Different Cases, Different Manifestations of Post-COVID-19 Retinal Artery Occlusion: A Case Series

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Abstract

Coronavirus disease 2019 (COVID-19) is a procoagulant disease that increases the risk of clinically evident thrombotic complications. Herein we present 3 cases with different retinal artery occlusions that emerged soon after the diagnosis of COVID-19. The first patient had central retinal artery occlusion (CRAO) that resulted in visual loss in one eye. The second patient had inflammatory peripheral retinal artery occlusion, vasculitis, and uveitis which did not affect vision. The third patient presented with CRAO following the progression from orbital cellulitis to orbital apex syndrome. Interestingly, CRAO progressed to internal carotid artery occlusion in this case within days and resulted in monocular visual loss. Variations in the underlying pathophysiology and the characteristics of individual immune responses in patients with COVID-19 may be factors that determine differences in clinical manifestations. This article aims to describe different presentations of COVID-19-related retinal artery occlusions and discuss possible pathophysiological aspects.

Keywords: COVID-19, retinal artery occlusion, SARS-CoV-2

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel member of the human coronaviruses and causes coronavirus disease 2019 (COVID-19).[1] It has the potential to affect various organs and systems within the body. Ocular involvement of the disease is potentially possible, though it is not known when, why, in whom, how, and to what extent SARS-CoV-2 will affect the ocular tissues.[2]

COVID-19 is known to be a procoagulant disease that increases the risk of clinically evident thrombotic complications.[3,4] Recently, it has been published that 42.7% of cases with SARS-CoV-2-associated neurological complications presented with ischemic stroke.[5,6] By definition, retinal artery occlusion represents end-organ ischemia and is analogous to terminal branch occlusion in cerebral stroke.[7] Although the overall incidence of arterial thrombosis in COVID-19 has been reported to be lower than that of venous thrombosis (3.7% vs. 25%), the number of retinal artery occlusion cases in the literature is close to that of retinal vein occlusions.[8,9]

However, the components involved in the ocular thromboembolism process, the mechanism of interaction, and the clinical findings have not yet been adequately defined. Herein we aim to report three cases with different types of retinal artery occlusions secondary to COVID-19 and to discuss possible pathophysiological aspects. Written informed consent for publication of the clinical details and/or clinical images have been obtained from all patients in this study.

Case Reports

Case 1

A 48-year-old woman presented with blurry vision in the right eye that started the day before. The patient had been diagnosed with COVID-19 fifteen days earlier and treated with favipiravir according to the Ministry of Health policy at that time. As in all cases in this series, COVID-19 was diagnosed by a real-time reverse transcription polymerase chain reaction (RT-PCR) swab test upon the presence of related symptoms. Her past medical history was insignificant. Pulmonary involvement of SARS-CoV-2 was not found. Outpatient treatment was deemed sufficient for the patient and hospitalization was not required during or after the quarantine period. The patient reported that she had no severe side effects of the disease or treatment and her symptoms of fatigue and fever resolved within a week. Fourteen days after the initial diagnosis of COVID-19, her vision diminished in the right eye.

At presentation, best corrected visual acuity (BCVA) was hand motion in the right eye and 20/20 in the left eye. Anterior segment examination and intraocular pressure were within normal limits in both eyes. Fundus fluorescein angiography (FFA) showed signs of delayed arterial perfusion, poor perfusion in the retinal artery, and prolonged arteriovenous transit time, while optical coherence tomography (OCT) (Heidelberg Engineering Gmbh, Heidelberg, Germany) demonstrated increased reflectivity and thickness of the inner retina suggesting central retinal artery occlusion (CRAO) in the right eye. However, the left eye was quite normal. Systemic workup showed elevated levels of D-dimer, fibrinogen, factor VIII, and von Willebrand factor, while antithrombin was decreased (**Figure 1**).

Anterior chamber paracentesis was performed on the day of presentation and the patient was referred to hyperbaric oxygen treatment for 21 days. However, at 10 months after presentation, her BCVA is still hand motion in the right eye and 20/20 in the left eye. OCT shows significant inner retinal atrophy in the right eye. There is no sign of neovascular glaucoma. The patient did not have any systemic complications related to COVID-19 during follow-up.

Case 2

A 46-year-old woman presented with sudden-onset concentric visual field loss in both eyes. She had been diagnosed with COVID-19 ten days earlier and received favipiravir treatment. Pulmonary involvement of SARS-CoV-2 was not detected at that time. Her BCVA was 20/20 in both eyes. Biomicroscopy showed that there were 1+ cells in the anterior chamber and vitreous of both eyes. Intraocular pressures were within normal limits. Funduscopic examination revealed a partial macular star in the right eye and bilateral peripheral vascular sheathing suggesting retinal vasculitis (**Figure 2**). Multiple areas of arterial

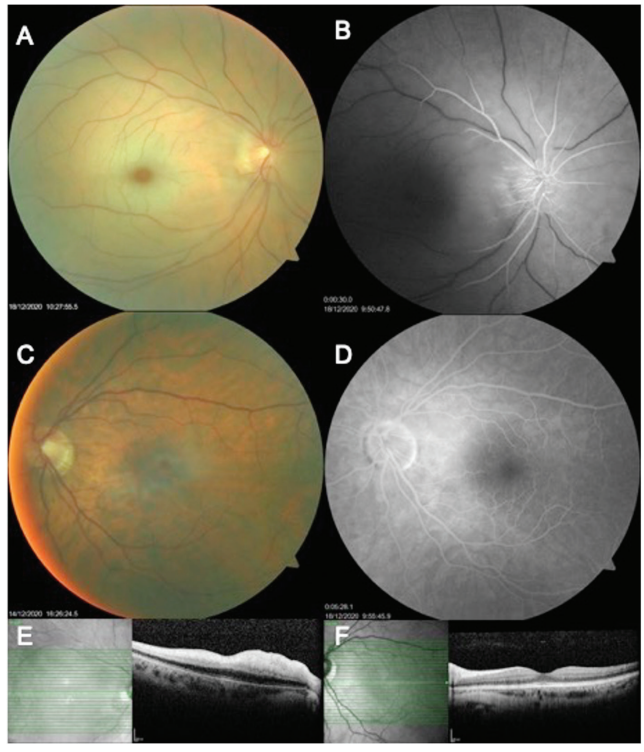

Figure 1. Fundus photography, fundus fluorescein angiography (FFA), and optical coherence tomography (OCT) of patient 1 (48-year-old female). FFA showed signs of longer arterial perfusion time, poor perfusion in the retinal artery, and delayed arteriovenous transit time, while OCT demonstrated increased reflectivity and thickness of the inner retina suggesting central retinal artery occlusion in the right eye

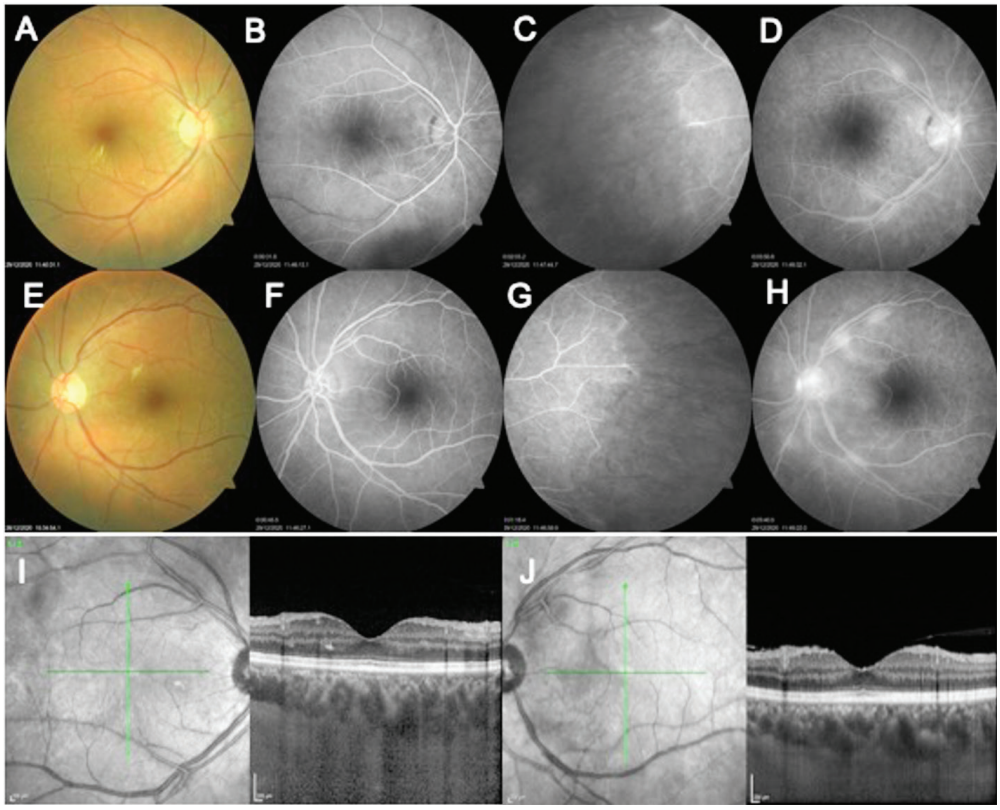

Figure 2. Fundus photography, fundus fluorescein angiography, and optical coherence tomography images from patient 2 (46-year-old female). She had mild uveitis, retinal vasculitis in the posterior pole, and peripheral retinal artery occlusion in both eyes. A-D and I show the right eye while E-H and J show the left eye

wall hyperfluorescence were present in the posterior pole and peripheral retina in both eyes, while capillary dropout extending from the equator to the ora serrata was visible on FFA bilaterally (**Figure 2**). There were no signs of retinitis.

Her past medical history was unremarkable for systemic diseases. Systemic and ocular workup was initiated for further investigation. She had no complaints other than intermittent non-specific mechanical back pain. No recent or past hearing loss or central nerve system dysfunction were present. The patient had no history of oral or genital aphthae. Diagnostic work-up for retinal vasculitis and/or vascular occlusion including hypertension, systemic lupus erythematosus, Susac's syndrome, granulomatosis with polyangiitis, Behçet's disease, tuberculosis, and thrombophilia all resulted negative. Flow parameters of the carotid arteries and the ophthalmic arteries were normal on Doppler ultrasonography. Levels of D-dimer and fibrinogen were also found to be within normal limits.

The patient was started on high-dose methylprednisolone, with azathioprine added in the second week of steroid therapy. Due to the persistence of peripheral retinal ischemia, panretinal laser was applied to the ischemic areas two months after the onset of symptoms. The patient is in the ninth month of follow-up and her BCVA is still 20/20 in both eyes. Optic disc hyperfluorescence is present in both eyes on FFA. Reportedly, the patient had no health-related quality of life challenges after COVID-19.

Case 3

Consultation was requested for a 66-year-old man in the emergency department complaining of vision loss in his left eye. He had a history of positive COVID-19 PCR test 22 days prior to presentation and was hospitalized for 15 days due to bilateral peripheral ground glass and consolidative pulmonary opacities suggestive of pulmonary involvement. No signs or symptoms of pulmonary embolism were detected and intensive care was not needed during hospitalization. In accordance with Ministry of Health policy, he was discharged after treatment.

Within the week following his discharge, the patient developed pain and proptosis of the left eye with eyelid edema and ptosis. At 1 week after discharge, he presented with complaints of decreased vision for 2 days. On ophthalmological examination, his BCVA was 20/20 in the right eye and light perception (LP) in the left eye. Ocular motility, lid function, and corneal reflexes were normal in the right eye, but features of orbital cellulitis including ophthalmoplegia and relative afferent pupillary defect were noted in the left eye (**Figure 3**). The anterior segments were normal in both eyes, whereas CRAO was present in the left fundus. OCT revealed hyperreflectivity in the inner retinal layers. Consistent with non-perfusion, FFA displayed impaired chorioretinal filling even after 5 minutes (**Figure 4**).

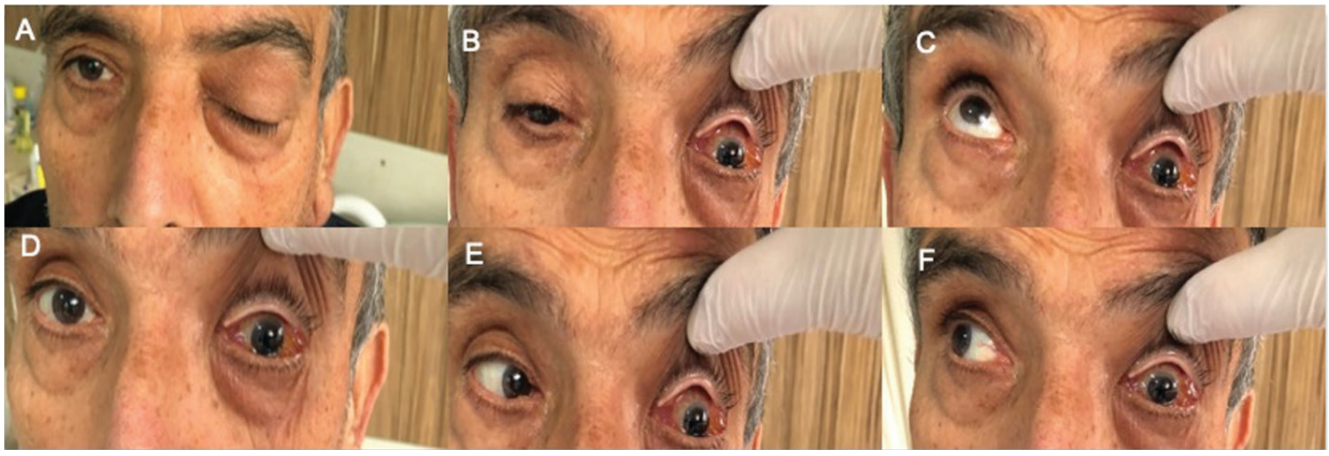

Figure 3. Patient 3 exhibited eyelid edema (A), ptosis (A), and ophthalmoplegia (B-F) of the left eye

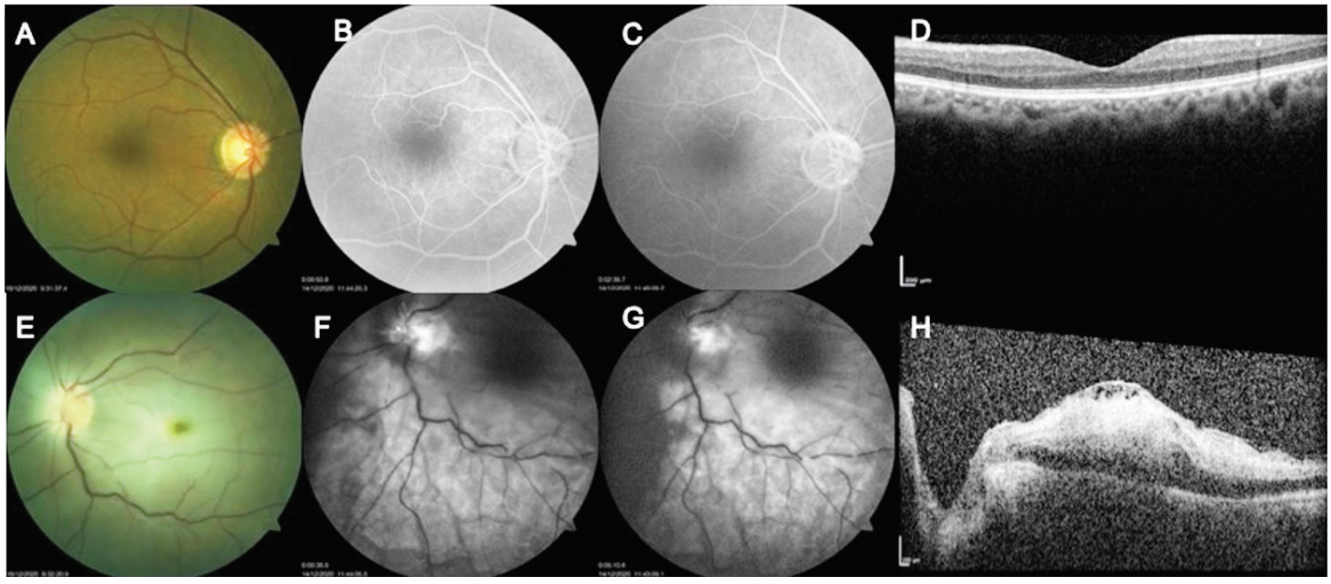

Figure 4. Fundus fluorescein angiography and optical coherence tomography findings in patient 3 (66-year-old male) indicated the presence of central retinal artery occlusion. A-D show the right eye while E-H show the left eye

The patient had type 2 diabetes mellitus and underwent coronary artery bypass surgery in 2004. The decision was made to hospitalize the patient for further investigation. There was no systemic abnormality in his physical examination, and no signs of necrotic lesions were observed in the oral examination. Consistent with left orbital apex syndrome, orbital magnetic resonance imaging (MRI) revealed preseptal and postseptal inflammation, prominent optic nerve edema, and severe restriction findings on diffusion MRI (**Figure 5A**). The appearance and intensity of brain parenchyma were normal on cranial MRI. Laboratory tests showed elevated levels of D-dimer, fibrinogen, factor VIII, and von Willebrand factor and attenuated levels of antithrombin. The patient was started on amoxicillin-clavulanic acid and 1 mg/kg prednisolone with tight blood sugar control. Anticoagulants were not administered at that time. One week after the onset of ocular symptoms, the patient experienced sudden-onset weakness, numbness, and difficulty with speech and understanding which resolved within 24 hours.

Two days later, the patient exhibited right hemiparesis involving the arm. On cranial MRI, newly developed distinct diffusion-restricting areas suggesting acute-subacute infarction were observed in the left frontal and parietal lobes (**Figure 5B**). Computer tomography angiography showed complete occlusion of the left internal carotid artery (ICA) (**Figure 5C**). No further endovascular intervention was considered as the left middle cerebral artery was recanalized with collaterals. The patient started physical rehabilitation for the paresis. At the time of writing, he is in the tenth month of follow-up and still has limited upper limb mobility and LP vision in the left eye. Ptosis of the left eyelid improved while ocular motility returned to normal.

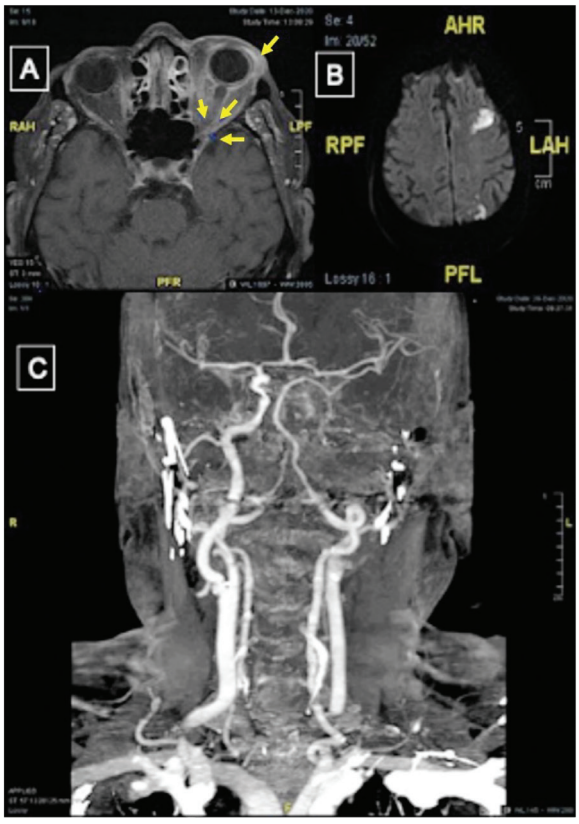

Figure 5. A) Preseptal and postseptal inflammation and prominent optic nerve edema in patient 3 at presentation are marked with arrows on orbital magnetic resonance imaging (MRI). B) On the ninth day of hospitalization newly developed distinct diffusion-restricting areas suggesting acute-subacute infarction were observed in the left frontal and parietal lobes on cranial MRI. C) Computed tomography angiography shows complete occlusion of left internal carotid artery on after the onset of right hemiparesis

Discussion

Growing evidence shows that macrovascular and microvascular thrombotic diseases may occur in the venous and arterial circulation of both hospitalized and ambulatory patients with COVID-19.[10,11,12] The question of whether thrombosis is specific to SARS-CoV-2 or is a pathway of the thromboinflammatory response to viral infection remains uncertain.[13] A recent autopsy study revealed that almost no organ within the body is spared of thrombosis.[14]

This case series highlights that retinal artery occlusions associated with SARS-CoV-2 may present with different features. Herein, isolated microvascular occlusion was observed in the first two cases. The first case was a routine case of CRAO which seems to be of thromboembolic origin. However, the second patient had inflammatory peripheral retinal artery occlusion, vasculitis, and uveitis. The third case featured CRAO originating from the progression of orbital cellulitis to orbital apex syndrome. Interestingly, this microvascular occlusion progressed to macrovascular (ICA) occlusion within days.

In COVID-19, variations in the underlying pathophysiology and characteristics of individual immune responses may be factors that determine differences in clinical manifestations.[15] Although the pathophysiological mechanism of thromboembolic complications in the ocular vasculature has not been clearly established, the coagulopathy mechanisms proposed in SARS-CoV-2 infection may be relevant.[16,17] Evidence from the literature shows that SARS-CoV-2 infects vascular endothelial cells via ACE2, which is highly expressed in endothelial cells and pneumocytes. Basically, destruction of ACE2 receptors has been associated with increased levels of reactive oxygen species, induction of fibrosis, hypertrophy, and inflammation.[18] The resulting endothelial dysfunction and subsequent potentiation of the renin-angiotensin system reduces anticoagulation and fibrinolytic activity. The emergence of extensive hypercoagulation, diffuse intravascular thrombosis, and secondary fibrinolysis may lead to microvascular and macrovascular complications in COVID-19.[19] Hypothetically, the clinical picture may progress to retinal artery occlusion, as in the first case, when the pathology is limited to the ocular microvasculature.

On the other hand, SARS-CoV-2 can also stimulate the innate immune system to participate in thrombosis. Essentially, immune cells, inflammatory cytokines, and pathogen-associated molecular patterns induce the formation of thrombi consisting of fibrin, monocytes, neutrophils, and platelets.[20,21,22] Although immunothrombi initially promote pathogen recognition and serve as a protective barrier against pathogen invasion, they may become maladaptive and injurious to tissue and organ perfusion in time.[20,23,24] Alveolar immunothrombosis has been proposed as a mechanism to limit dissemination of SARS-CoV-2 outside the alveoli.[14] The peripheral retinal artery occlusion in our second case may have been caused by a similar mechanism or from occlusive retinal vasculitis which may have been triggered by or as a response to COVID-19. Cases of COVID-19-related uveitis of varying severity have been reported in the literature, but the presence of mild uveitis, retinal vasculitis, and peripheral retinal artery occlusion has not been reported before.[25]

In the third case, the possible underlying pathophysiology seems somewhat complex. The arterial occlusion may have been caused by the direct thrombotic effect of COVID-19.[16,17] In this case, as in our first patient, the increase in D-dimer, fibrinogen, factor VIII, and von Willebrand factor and the decrease in antithrombin levels seem to support this suggestion. However, other mechanisms may have been involved as well. In this context, progression of orbital cellulitis to orbital apex syndrome may be the key factor. Progression of orbital cellulitis to orbital apex syndrome has been reported before in patients with COVID-19, which is congruent with our third case.[26] In our opinion, further invasion of inflammation may have triggered retrograde spread to the cavernous sinus and caused involvement of the vascular ICA wall. The resulting stenosis may have caused occlusion of the ICA in this third case.

In summary, all these different clinical courses depicted above emerged soon after the diagnosis of COVID-19 and had variable visual prognoses and possible mechanisms of action. In addition to one case without vision loss, two cases with devastating vision loss occurred in our series. There have been several recent reports of retinal artery occlusion associated with

SARS-CoV-2, ranging from isolated CRAO to ischemic stroke with CRAO and cilioretinal artery occlusion with paracentral acute middle maculopathy.[27,28,29] To our knowledge, this is the first case series to include cases of post-COVID-19 CRAO with different presentations. While the limited number of cases, the speculative nature of the available evidence, and the individual characteristics of patients preclude any firm conclusions, this study may help gain insight into a fairly new topic that is likely to have more facets and deeper connections.

Currently, the cause of microvascular or macrovascular thromboembolism in the ocular vasculature in patients with post-COVID-19, its mechanism of development, prognostic significance, and the necessity of prophylactic measures are still unclear. Prevention of irreversible visual loss depends mainly on suspicion and timely intervention. The importance of increasing awareness of ocular thromboembolic complications and reinforcing a multidisciplinary approach is obvious. Further studies on the propagation of ocular screening in patients with COVID-19 may help solve this inadvertent complication.

Ethics

Informed Consent: Each patient provided written informed consent for inclusion in this study.

Peer-review: Externally peer reviewed.

Authorship Contributions

Concept: Ö.Y., G.U.G., F.C., B.H., Design: Ö.Y., G.U.G., F.C., B.H., Data Collection or Processing: Ö.Y., G.U.G., B.H., S.D., Analysis or Interpretation: Ö.Y., G.U.G., F.C., B.H., S.D., Literature Search: Ö.Y., G.U.G., F.C., Writing: Ö.Y., G.U.G., F.C., B.H., S.D.

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Case Report

Flap-Related Complications Following Temporal Inverted Internal Limiting Membrane Flap for Macular Hole Repair

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Abstract

Here we report three cases of flap-related complications following temporal inverted internal limiting membrane (ILM) flap technique for the repair of macular holes (MH). The first case showed a flap closure pattern in which the MH completely closed at 2 months spontaneously. The second case showed early anatomical and functional improvement provided by an immediate closure of the MH but developed flap contracture and nasally located epiretinal membrane (ERM) at postoperative 18 months. There was no functional deterioration, thus no further intervention was required. In the third case, early postoperative flap dislocation was observed and an additional surgery to reposition the flap was needed. The flap closure pattern observed with inverted ILM flap techniques may represent the ongoing healing process of large MHs and may be related to delayed spontaneous anatomical closure. ILM flap contracture and ERM formation may be a harmless long-term complication. Dislocation of the ILM flap is an unexpected early postoperative complication that may necessitate a second surgery for flap repositioning.

Keywords: Macular hole, vitrectomy, inverted internal limiting membrane flap, flap contracture, flap dislocation, flap closure

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Introduction

Macular hole (MH) is a full-thickness break in the foveal retina. The closure rate of MHs has greatly improved since the introduction of internal limiting membrane (ILM) peeling, which became important in MH surgery. However, failure rates remained high for large MHs. The inverted ILM flap technique, described by Michalewska et al.,[1] has shown superiority to the traditional ILM peeling technique for the surgical treatment of large MHs, with higher closure rates. The closure rate of large MHs with the inverted ILM flap was reported as 98%, compared with the 88% closure rate attained with conventional vitrectomy and ILM peeling. The temporal inverted flap technique, a modified form in which ILM peeling was limited to the temporal fovea, was later introduced by the same group in 2015 and found to be as effective as the original technique with less surgical trauma.[2]

As the popularity of inverted flap techniques increase, structural macular changes and complications associated with the technique have started to emerge. Besides the most common closure patterns described in the literature (U-shaped closure, V-shaped closure, and W-shaped closure),[2,3] a distinct "flap closure" pattern was noted in approximately 15% of cases.[2,3,4,5] In these cases, the MH was covered by a thin layer of inverted ILM that acted as a bridge between the edges, and anatomical closure was eventually achieved. It is believed that the ILM flap induces migration and proliferation of glial cells in the retinal layers. While this brings about closure of the defect, it may also result in long-term adverse morphologic changes in the retina. However, to our knowledge, there are only a few reports on postoperative structural changes that may lead to complications associated with inverted ILM flaps.[6,7,8,9,10]

Herein, we report three cases of inverted ILM flap-related complications: the first is late MH closure with flap closure pattern, the second is late flap contracture, and the third is early postoperative flap dislocation.

Case Reports

Case 1

A 61-year-old woman presented with blurry and distorted vision in her left eye. She noticed this by chance one month earlier after covering the fellow eye. Best corrected visual acuity (BCVA, decimal) was 0.15 and fundus examination revealed a MH in the left eye.

Spectral domain optical coherence tomography (SD-OCT; SPECTRALIS, Heidelberg, Germany) demonstrated a large MH, the diameter of which was 459 µm at its narrowest point and 943 µm at its base, with cystoid spaces at the edges (**Figure 1A**). Ocular examination of the right eye was normal. Pars plana vitrectomy (PPV) was performed in left eye with 360-degree ILM peeling around the macula and temporal ILM flap isolation and inversion over the hole. ILM forceps were used to peel the ILM off at the nasal side of the MH, which was removed completely. Then, the temporal ILM was peeled in an area of two disc diameters. During this peeling, the ILM was not removed completely from the retina and was left attached to the temporal edge of the MH, then inverted and placed over the MH. Fluid-air exchange was performed, which ensured the flap lay flat over the hole. Then air-gas exchange was performed with 20% sulfur hexafluoride (GOT Multi SF6;Alchimia, Beijing) gas. The patient was instructed to stay in face-down position for the next 3 days. She was prescribed dexamethasone and moxifloxacin drops for 2 weeks and then tapered within a month. Postoperative progress was monitored with serial visual acuity measurements and OCT images.

The patient was seen at postoperative 10 days, following partial resorption of the gas. OCT revealed a flap closure pattern, marked by persistence of the full-thickness MH with the ILM flap bridging the edges (**Figure 1B**). This pattern remained almost the same at the 1-month visit except for slight thickening of the flap (**Figure 1C**). Full closure with a regular foveal contour was observed 2 months after surgery (**Figure 1D**). Her vision improved to 0.6 with a small ellipsoid zone defect in the fovea. One year later, the patient returned with decreased vision due to nuclear sclerosis and underwent cataract surgery. Thereafter, her BCVA reached 1.0 and was maintained during 16-month follow-up. The outer retinal defect became smaller on OCT within this period (**Figure 1E**).

Case 2

A 63-year-old woman presented with floaters in the right eye. BCVA was 0.4 in the right eye and 1.0 in the left eye. Fundus examination and SD-OCT revealed a small MH with cystoid edges in the right eye and focal vitreomacular traction (VMT) in the left eye. The diameters of the MH were 213 µm at its narrowest point and 843 µm at the base (**Figure 2A**). While the patient was scheduled for surgery on the right eye, she returned a month later with photopsia and blurry and distorted vision in the left eye. BCVA had decreased to 0.5 and a small MH with a minimum diameter of 100 µm and a base diameter of 200 µm was detected in the left eye (**Figure 3A**). PPV combined with phacoemulsification and intraocular lens implantation was performed in the right and left eyes, respectively, 2 weeks apart. In both eyes, surgery included a large temporal inverted ILM flap while the nasal ILM was preserved. Fluid-air exchange followed by air-gas (20% SF6) exchange was performed as described in the first case.

At the postoperative 10-day visit, BCVA was 0.6 in the right eye, and SD-OCT showed closure of the inner layers of the MH with a gap in the outer layers (**Figure 2B**). The outer layer defect was healed and BCVA improved to 1.0 at the 2-month visit (**Figure 2C**), after which the findings remained stable over 2-year follow-up.

The left eye showed excellent closure of the MH with almost normal foveal contour and BCVA improvement to 1.0 at 10 days postoperatively. However, an ILM flap traversing the foveal contour, presumably bridging the edges of the previous MH, was noted on SD-OCT (**Figure 3B**). Vision and OCT findings remained stable within the first 6 months postoperatively.

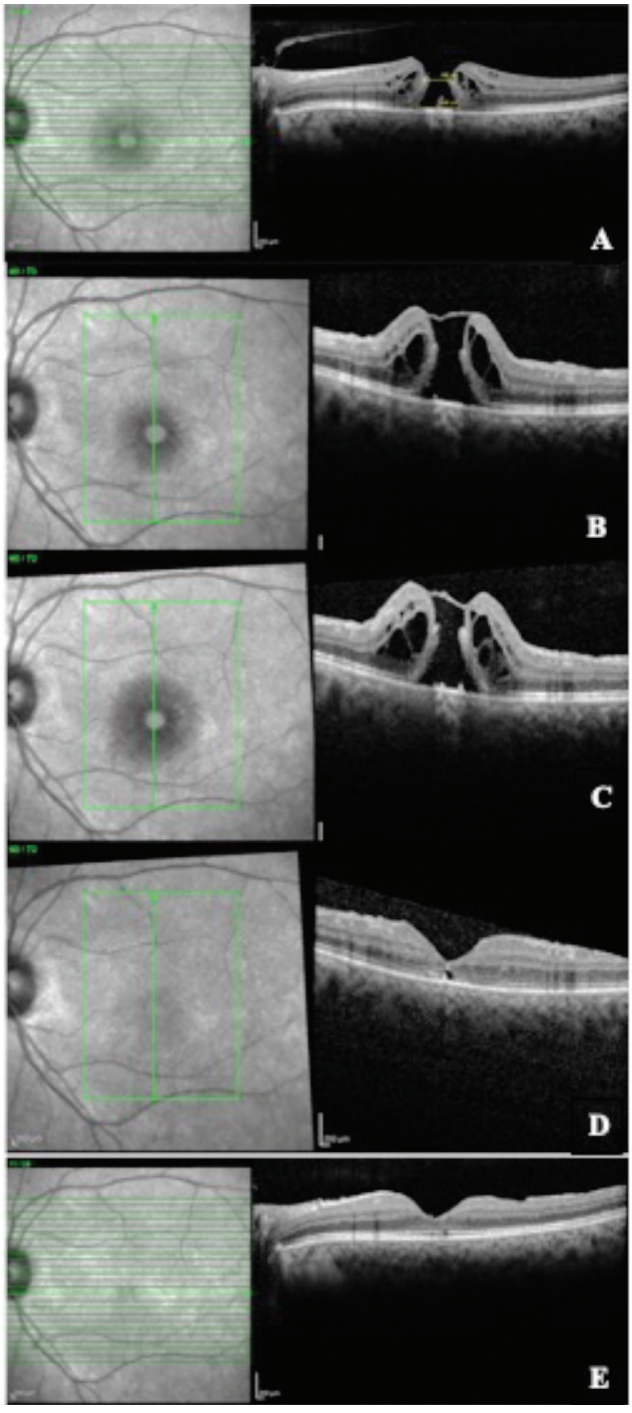

Figure 1. Case 1: A) Spectral domain optical coherence tomography (SD-OCT) shows a large full-thickness macular hole (MH) at baseline. B) SD-OCT showing the "flap closure" pattern with persistence of the MH with internal limiting membrane flap at the top bridging the cystic edges of the hole at postoperative 10 days. C) Persistent "flap closure" appearance with slightly thickened flap and outer retina at 1 month. D) Complete closure of the MH with a small defect in the ellipsoid zone at 2 months. Visual acuity improved to 0.6. E) SD-OCT at the 16-month follow-up demonstrating a smooth foveal contour and restoration of the outer retinal layers

At postoperative 18 months, SD-OCT revealed ILM flap contracture accompanied by a nasal epiretinal membrane (ERM) causing irregularity of the inner retinal layers (**Figure 3C**). However, BCVA remained 1.0 with mild metamorphopsia. The patient was observed without intervention, and her symptoms and OCT findings remained stable during the 2-year follow-up.

Case 3

A 76-year-old woman presented with a sudden loss of vision in the right eye. She stated that her vision had already been subnormal in both eyes for a long time. Her BCVA was 0.04 in the right eye and 0.2 in the left eye. Slit-lamp examination showed bilateral corticonuclear cataract. Fundus examination revealed yellowish flecks at the level of retinal pigment epithelium in both eyes and a MH in the right eye. The left eye had a focal VMT and subfoveal vitelliform material on SD-OCT, which showed corresponding hyperreflectance and hyperautofluorescence on the infrared and fundus autofluorescence imaging consistent with adult-onset foveomacular dystrophy (**Figure 4A,B**). SD-OCT of the right eye showed a large full-thickness MH with a minimum diameter of 800 µm, accompanied by VMT, cysts at the edges, and RPE atrophy leading to prominent choroidal hyper-transmission (**Figure 4C**). Fluorescein angiography showed no sign of neovascularization. PPV combined with phacoemulsification and intraocular lens implantation was performed in the right eye. PPV included a temporal inverted ILM flap over the MH while the nasal ILM was preserved. Fluid-air exchange followed by air-gas (20% SF6) exchange was performed. At the 10 days postoperatively, following partial resorption of the gas, SD-OCT revealed

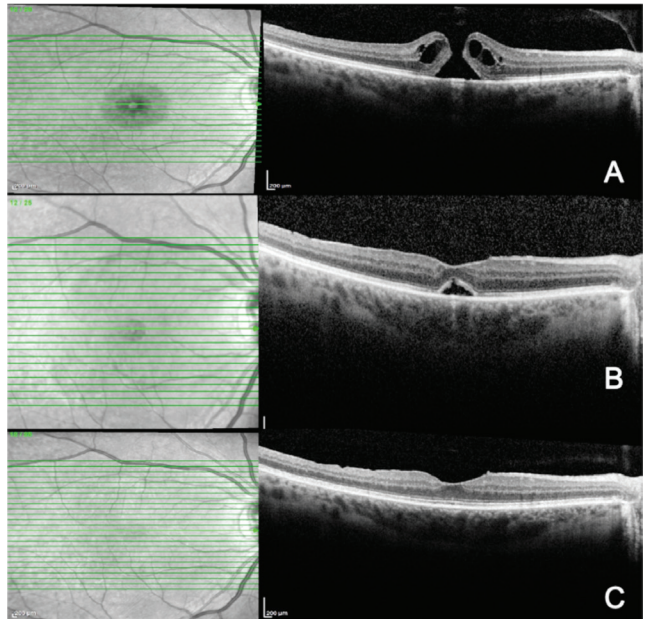

Figure 2. Case 2, right eye: A) Spectral domain optical coherence tomography (SD-OCT) shows a small full-thickness macular hole (MH) at baseline. B) SD-OCT on postoperative day 10 shows closure of the inner layers of the MH, with a large gap in the outer layers. C) MH was totally closed at postoperative 2 months and remained stable throughout 2-year follow-up

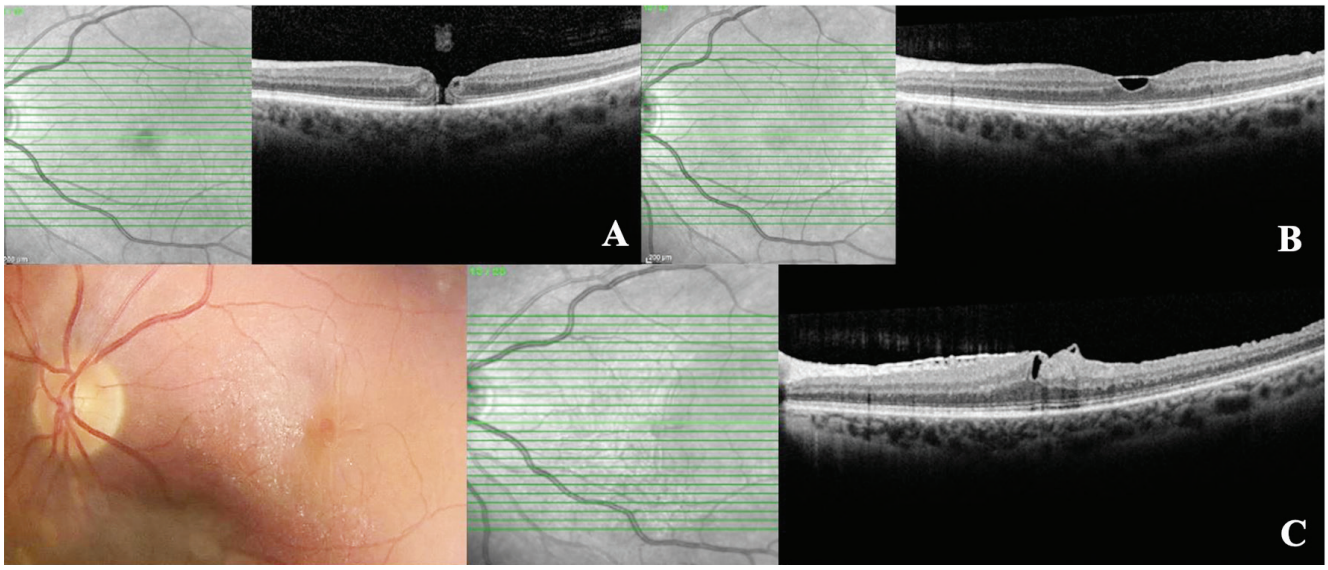

Figure 3. Case 2, left eye: A) Spectral domain optical coherence tomography (SD-OCT) shows a small full-thickness macular hole (MH) at baseline. B) SD-OCT on postoperative day 10 shows the internal limiting membrane flap bridging the edges of the closed MH. This appearance remained stable in the following 6 months. C) Color fundus image and the corresponding OCT at postoperative 18 months revealed contracture of the flap which caused inner layer irregularities and was accompanied by an epiretinal membrane on the nasal side

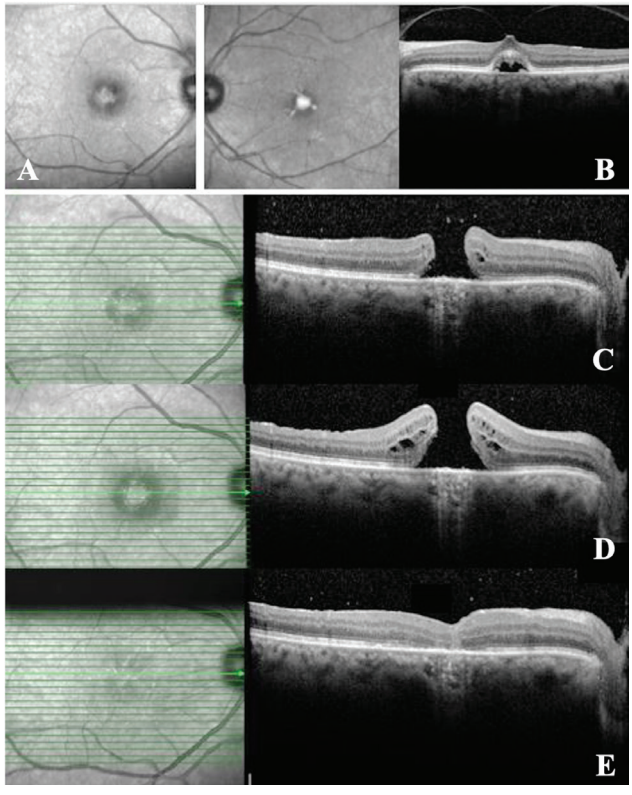

Figure 4. Case 3: A,B) Infrared retinal images and spectral domain optical coherence tomography (SD-OCT) of the left eye suggesting pattern dystrophy as a background pathology in this patient. C) In the right eye, SD-OCT shows a large full-thickness macular hole (MH) with a minimum diameter of 800 µm at baseline. D) The MH remained open at the postoperative 1 month. The underlying cause of persistence of the MH was the detached internal limiting membrane flap. E) MH closure was observed 2 weeks after repositioning surgery, and was stable throughout 18-month follow-up

persistence of the MH, which was confirmed to be still open at the postoperative 1-month (**Figure 4D**). Reoperation was performed at postoperative 3 months. During surgery, the ILM flap was found to have returned to its original temporal position. The nasal ILM was peeled, the previous temporal ILM flap was remobilized to form a temporal flap and repositioned over the MH, and 12% perfluoropropane (C3F8) gas tamponade was given. The patient was instructed to stay in face-down position for a week. At postoperative 2 weeks, OCT demonstrated closure of the MH, accompanied by ellipsoid zone atrophy (**Figure 4E**). The BCVA improved to 0.4 and was maintained during 18 months follow-up period. The MH remained closed and the outer layer defect has been stable within the follow-up period.

Discussion

In this report, we examined three MH patients who were treated with temporal inverted ILM flap technique and developed unexpected flap-related morphological changes and complications in the postoperative period.

The first case demonstrated late MH closure associated with the flap closure pattern, a newly described pattern after the emergence of inverted flap techniques.[2] This pattern, as occurred in case 1, was recognized as a thin hyperreflective band of ILM extending across the inner retina surface on both sides of the previous MH following surgery with inverted flap technique.[1,2] Reported rates of flap closure pattern range between 14% and 27% in the early postoperative period and decreases over time.[1,5,8,11] Boniṅska et al.[5] showed that flap closure persisted in only one-third of the eyes at the end of 1 month, and completely disappeared and turned into other closure patterns at the end of the 3 months. Tsui and Yang[12] reported the mean time to disappearance of the flap closure as 2 months, which was similar

to case 1 in this report. However, in some eyes, the ILM flap may persist much longer while MH closure takes place. Michalewska et al.[2] reported that flap closure remained at postoperative 6 months in 11% of the original inverted ILM flap group and 3% of the temporal inverted ILM flap group. By postoperative 12 months, 3% of original inverted ILM group still showed the flap closure pattern, but MH closure was eventually achieved in all cases.

The proposed mechanism of MH closure with the inverted ILM flap technique is that the ILM flap acts as a scaffold for glial cells to proliferate, as well as provides a barrier to the entrance of fluid from the vitreous cavity to the MH.[5] In this regard, the flap closure pattern represents an ongoing physiological healing process of large MHs that may remain open if standard ILM peeling were used. Closure of large MHs with postoperative flap closure pattern is very likely. However, full closure may take a longer time, and the decision to perform revision surgery should not be made hastily.

Our second patient also demonstrated bridging by the ILM flap, but this time over the closed MH. Following a long and stable persistence, the flap tissue showed contraction 18 months postoperatively. This was accompanied by a newly ERM in the nasal quadrant, where the ILM had been previously preserved. Contracture and thickening of the ILM flap is defined as the first step of the regeneration process, followed by formation of gliosis on the retinal side of the flap, which eventually fills the cavity and results in anatomical closure of the MH within 1-4 months postoperatively.[12] While the ILM flap forms a bridge and improves the integrity of the foveal structure, it may also persist as an additional tissue after hole closure. Previously, Boniṅska et al.[5] reported hyperreflective ILM remnants on the retinal surface in 44% of eyes with an inverted ILM flap. Later, Tsui and Yang[12] pointed out a higher incidence of persistent ILM tissue, showing a rate of 66% in their series. Both studies suggested that these remnants remained stable over time and had no influence on the vision. However, recently Hirata et al.[8] quantitatively demonstrated contracture of ILM flaps in 23% of eyes that underwent MH surgery with temporal inverted ILM flap. Of these, one required ILM peeling 12 months after the initial surgery due to severe flap contraction causing decreased vision and metamorphopsia. This case also had an ILM flap overlying a closed MH in the early postoperative period. At postoperative 6 months, the ILM flap integrated into the retinal layers and transformed into an epiretinal membrane.[9,10] Several other reports also showed ERM formation following inverted ILM techniques. In a case report by Kanda et al.,[9] histopathological examination of the surgically removed ERM showed cellular proliferation between overlapping ILMs. Authors proposed that cells and collagen remaining on the vitreous side of the ILM may have served as a scaffold for cell proliferation. In these reports, ERMs occurred 3-6 months postoperatively and coincided with the position of the ILM flaps. In contrast, the ERM in our patient originated from the nasal macula and formed later. This may indicate that a nasal ERM may be a long-term consequence of gliotic proliferation of the nasal retina where the ILM is left in place. Late contracture of the flap could be attributed to the tangential force applied by the nasal ERM and/or "reverse" gliosis developing on the vitreous side of the flap. Although vision was not affected except for mild metamorphopsia in our case, removal of the nasal ILM may be safer, especially if there is a suspicion of residual epiretinal membrane. Moreover, conventional ILM peeling would have been preferable for primary treatment in this particular case because the MH was small. Although our clinical experience suggests that the inverted flap technique provides a much smoother and better foveal contour, it may have some disadvantages in small MHs in the long term, as demonstrated in this case. Apart from removing the nasal ILM, the conventional technique would also eliminate the potential of any ILM flap tissue contributing to the formation of ERM in such small holes.

Our third case showed early postoperative dislocation of the ILM flap. This is a rather unexpected complication, because the temporal inverted flap technique provides a wider connection to retina, thereby decreasing the likelihood of spontaneous detachment or flipping of the flap during fluid-air exchange compared to the original inverted ILM flap technique. Previously, Kawamata et al.[7] described a case of partial flap detachment following a superior inverted flap technique, which recovered spontaneously within 3 months without any further intervention. Total dislocation in our case would have made the spontaneous recovery unlikely, if not impossible. Therefore, after discussing the options with the patient, we decided on a repeat surgery at 3 months. Dislocation of the flap could be attributed to inadequate postoperative head positioning of the patient, resulting in an insufficient tamponade effect. Although preservation of the nasal ILM provides a more stable flap and decreases the risk of flap loss and free flap formation, it might also contribute to persistence of the MH and the need for repeat surgery once a dislocation occurred. Some precautions may be taken to prevent early postoperative flap dislocation, such as efficient drying of the fluid in the posterior pole during fluid-air exchange, or using perfluorodecalin to stabilize and secure the flap tissue in place. Positioning of the head slightly nasally and waiting for some time may allow accumulation of residual fluid on the optic nerve. Also, local anesthesia may be preferred to general anesthesia to ensure appropriate head positioning immediately after surgery.

In conclusion, we addressed three different complication scenarios following use of temporal inverted ILM flaps and their related mechanisms. Flap closure pattern may be inherently associated with delayed closure of MHs. MH dimensions may have some effect on flap closure pattern, which needs to be further investigated. ILM flaps may show contraction in the long-term in association with secondary ERM formation, which may be prevented by peeling off the nasal ILM during temporal inverted flap surgery and creating a smaller overlapping area of ILM tissue. Finally, flap dislocation should be considered in MH

cases that fail to close following inverted ILM flap surgery, and may require reoperation for flap repositioning.

Ethics

Informed Consent: This case report was conducted in accordance with the Declaration of Helsinki. The collection and evaluation of all protected patient health information was performed in a Health Insurance Portability & Accountability Act (HIPAA)-compliant manner.

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Authorship Contributions

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