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TURKISH JOURNAL OF OPHTHALMOLOGY

E-ISSN: 2149-8709

TURKISH JOURNAL OF OPHTHALMOLOGY TJO

Research Articles

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January
February
2026
56 Volume
Issue 1

galenos

TURKISH JOURNAL OF OPHTHALMOLOGY

TJO

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Publishing House
Molla Gürani Mah. Kaçamak Sokak No: 21, 34093 Fındıkzade-İstanbul-Türkiye
Publisher Certificate Number: 14521
Phone: +90 (530) 177 30 97
E-mail: info@galenos.com.tr
Online Publication Date: February 2026
Publication Type: Local Periodical
International scientific journal published bimonthly.
E-ISSN: 2149-8709

The Turkish Journal of Ophthalmology is an official journal of the Turkish Ophthalmological Association.

On Behalf of the Turkish Ophthalmological Association Owner

Kıvanç GÜNGÖR
Gaziantep University Faculty of Medicine, Department of Ophthalmology, Gaziantep, Türkiye

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The editorial and publication process of the Turkish Journal of Ophthalmology are shaped in accordance with the guidelines of ICMJE, WAME, CSE, COPE, EASE, and NISO. The journal adheres to the Principles of Transparency and Best Practice in Scholarly Publishing.

The Turkish Journal of Ophthalmology is indexed in **PubMed/MEDLINE, PubMed Central (PMC), Web of Science-Emerging Sources Citation Index (ESCI), Scopus, TÜBİTAK/ULAKBİM, Directory of Open Access Journals (DOAJ), EBSCO Database, Gale, CINAHL, Proquest, Embase, British Library, Index Copernicus, J-Gate, IdealOnline, Türk Medline, Hinari, GOALI, ARDI, OARE, AGORA,** and **Turkish Citation Index**.

Issues are published electronically six times a year.

Owner: Kıvanç GÜNGÖR on Behalf of the Turkish Ophthalmological Association Owner

Responsible Manager: Banu BOZKURT

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AT A GLANCE

2026 Issue 1 at a Glance:

Esteemed colleagues,

In our first issue of 2026, the Turkish Journal of Ophthalmology features six original research articles, one review, one case report, and four letters to the editor. This issue brings together articles dealing with current and compelling topics such as artificial learning in ophthalmology education, myopia control in children, the effect of contact lens surface moisturizing technologies on comfort, and sustainable ophthalmology.

In the original research section, a study by Balcı et al. titled "Evolving Minds: Natural Learning vs. Artificial Learning in Ophthalmology Training" compares the year-over-year performance of ChatGPT in Turkish nationwide ophthalmology resident training exams with changes in performance among residents during the same period (See pages 1-7).

In a study titled "Real-World Comparison of the Effectiveness of Defocus Incorporated Multiple Segments and Myopi-X Spectacle Lenses for Myopia Control in Turkish Children: A Retrospective Study", Akagün and Altıparmak compared the effectiveness of defocus incorporated multiple segments (DIMS), Myopi-X progressive addition spectacles, and single-vision spectacles in controlling myopia progression in children (See pages 8-15).

A study titled "The Impact of Advanced Surface Moisturizing Technologies on Contact Lens Comfort in Digital Platform Users" by Arslantürk Eren et al. evaluated the ocular surface performance of two lotrafilcon B contact lenses utilizing different surface moisturizing technologies in contact lens users with prolonged digital platform exposure (See pages 16-23).

The first study addressing diabetic macular edema (DME) in this issue is titled "Long-Term Intravitreal Dexamethasone Implant Monotherapy in Naive Patients with Diabetic Macular Edema" by Karataş et al. This study investigated the outcomes of repetitive dexamethasone implant injections in treatment-naïve eyes with DME over a follow-up period of at least 36 months, demonstrating that intravitreal dexamethasone monotherapy is a safe and effective long-term treatment modality (See pages 24-30).

The study by Özal et al. titled "Intravitreal Anti-Vascular Endothelial Growth Factor Therapy for Diabetic Macular Edema in Türkiye: 48-Month Data, BOSPHORUS-DME Study Group Report No. 1" is a multicenter study evaluating visual and anatomical outcomes and numbers of visits and injections over a 48-month follow-up period under real-life conditions in patients who received three consecutive loading doses of intravitreal anti-vascular endothelial growth factor therapy for DME (See pages 31-40).

In their study titled "Detection of Occult Retinal Breaks Using Subretinal Dye in Recurrent Retinal Detachment Surgery", Sül et al. evaluated the results and effectiveness of the intraoperative subretinal dual dye-assisted technique in cases operated for rhegmatogenous retinal detachment where small occult retinal tears could not be detected preoperatively or intraoperatively (See pages 41-46).

The review of this issue, titled "Sustainable Ophthalmology Applications: From the Perspective of Strabismus and Pediatric Ophthalmology" by Akgün et al., emphasizes that although pediatric ophthalmology and strabismus are generally considered eco-friendly subspecialties, there remain numerous steps that can be taken toward sustainable ophthalmology, ranging from anesthesia and outpatient services to amblyopia treatment (See pages 47-53).

In the sole case report in this issue, titled "Superior Segmental Optic Nerve Hypoplasia: A Rare Mimicker of Normal-Tension Glaucoma–A Case Series from Türkiye", Yüksel Elgin et al. present the characteristic features of superior segmental optic nerve hypoplasia seen in four patients diagnosed with normal-tension glaucoma, aiming to raise awareness of this rare condition (See pages 54-60).

Finally, the letters to the editor section includes articles by Dönmez Gün et al. titled "Partial Graft Detachment During Gonioscopy-Assisted Transluminal Trabeculotomy in a Patient Who Underwent Descemet Membrane Endothelial Keratoplasty" (See pages 61-64) and Ünal et al. titled "A Rare Corneal Scenario: Concurrent Diagnosis of Epithelial Basement Membrane Dystrophy and Crocodile Shagreen" (See pages 65-68).

We hope the articles featured in this first issue of the year will be engaging and provide guidance in your clinical practice.

Respectfully on behalf of the Editorial Board,

Hakan Özdemir, MD

Original Article

Evolving Minds: Natural Learning vs. Artificial Learning in Ophthalmology Training

Ali Safa Balcı[1], Zeliha Yazar[2], Banu Turgut Öztürk[3], Çiğdem Altan[4]

[1]University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
[2]Ankara Bilkent City Hospital, Clinic of Ophthalmology, Ankara, Türkiye
[3]Selçuk University Faculty of Medicine, Department of Ophthalmology, Konya, Türkiye
[4]University of Health Sciences Türkiye, Beyoğlu Eye Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Türkiye

Abstract

Objectives: This study aimed to compare year-over-year change in ChatGPT's performance on nationwide ophthalmology exams with the performance change among residents over the same period.

Materials and Methods: This observational study included ophthalmology residents in Türkiye who participated in both the 2023 and 2024 Resident Training Development Exams organized by the Turkish Ophthalmological Association Qualifications Committee. The 2023 examination consisted of 69 single-best-answer multiple-choice questions and was administered to ChatGPT-3.5. The 2024 version, containing 72 questions, was administered to ChatGPT-4o. The success rates of ChatGPT and the residents who participated in both exams were compared.

Results: ChatGPT's accuracy improved from 53.6% in 2023 to 84.7% in 2024. Among the 501 residents who participated in both years, the average score increased from 48.2% to 53.1%. ChatGPT ranked 292nd among residents in 2023 but achieved the top score in 2024. Based on percentage improvement in scores, ChatGPT-4o ranked 8th overall. The most notable performance gains for ChatGPT were seen in the areas of strabismus (+75%), neuro-ophthalmology (+40%), and optics (+40%). Among residents, the largest improvement occurred in oculoplastics (+33.5%), while a decrease was observed in cornea and ocular surface (-4.1%).

Conclusion: ChatGPT-4o showed a marked improvement in answering ophthalmology questions compared to its predecessor, whereas resident learning progressed more gradually. This rapid advancement in ChatGPT highlights the potential speed with which artificial learning can progress within defined boundaries. In contrast, human learning remains a deeper and more time-intensive process. Results suggest that evolving large language models will play an increasingly significant role in medical education and clinical support.

Keywords: Education, generative artificial intelligence, resident training

Cite this article as: Balcı AS, Yazar Z, Turgut Öztürk B, Altan Ç. Evolving Minds: Natural Learning vs. Artificial Learning in Ophthalmology Training. Turk J Ophthalmol. 2026;56:1-7

Address for Correspondence: Ali Safa Balcı, University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
E-mail: alisafabalci@gmail.com
ORCID-ID: orcid.org/0000-0001-9161-7839

Received: 02.08.2025
Revision Requested: 25.09.2025
Last Revision Received: 27.10.2025
Accepted: 11.12.2025
Publication Date: 18.02.2026

DOI: 10.4274/tjo.galenos.2025.16517

Introduction

Large language models such as OpenAI's ChatGPT are advanced artificial intelligence systems that operate based on natural language processing techniques and are capable of generating human-like responses. Built on the Generative Pre-trained Transformer (GPT) architecture, these models have reached the capacity to produce contextually consistent and meaningful responses by training on vast and diverse text datasets. While earlier versions such as ChatGPT-3.5 and ChatGPT-4.0 made significant advances in natural language comprehension, ChatGPT-4o (released on May 13, 2024) showed marked improvement over previous versions in terms of linguistic accuracy and interactional performance.[1] With increasing competencies in medical, educational, and academic contexts, ChatGPT exhibits high levels of accuracy and responsiveness.[2] Nevertheless, in the medical field especially, their responses must be

continuously evaluated to ensure clinical reliability for both healthcare professionals and patients.

The rapidly increasing popularity of ChatGPT in the medical field has led to growing interest in assessing its functionality in various health-related tasks. Research in ophthalmology has examined the accuracy of ChatGPT's responses to questions about various subspecialties, providing evidence that this AI model can be used as a complementary educational tool.[3,4,5] Furthermore, the ability to interpret and manage ocular conditions in clinical scenarios such as corneal ulcer, cataract management, and retinal pathologies has also been explored.[6,7,8] ChatGPT has emerged as a tool that can be helpful not only in diagnosis, but also in documentation processes such as the preparation of medical reports, as well as turning complex ophthalmological information into more understandable and accessible educational content.[9]

In this study, we aimed to evaluate the performance of both the ophthalmology residents who took a national resident training exam in two consecutive years and the ChatGPT models current in those years, and compare their year-over-year changes in performance.

Materials and Methods

The Turkish Ophthalmological Association Qualifications Committee held the third annual Resident Training Development Exam on May 26, 2023. In our previous study, we posed the questions from this exam to ChatGPT-3.5, the previous version of ChatGPT, and compared its performance with the results of the ophthalmology residents who took the exam nationwide.[10] The following year, on May 31, 2024, a total of 1,013 ophthalmology residents from 80 training centers across Türkiye took the fourth Resident Training Development Exam. In the present study, we administered the questions from this exam to ChatGPT-4o, the most current version of ChatGPT. Only residents who took the exam in both years were included in the study to allow a year-over-year analysis. The residents were grouped according to their year of training as of the 2024 exam date.

Both exams were prepared by the Turkish Ophthalmological Association Qualifications Committee to cover the same subspecialties, at a similar difficulty level. Each exam included a total of 75 questions. However, questions in a format other than single-best-answer multiple-choice questions were excluded from the study. Therefore, the analysis included 69 eligible questions from 2023 and 72 eligible questions from 2024. Distributions of the questions asked in 2023 and 2024 by subspecialty are given in Table 1 and Table 2, respectively.

After translating into English, the 2024 exam questions were posed to ChatGPT-4o (model identifier: gpt-4o-2024-05-13) using the official web interface on the website (https://chat.openai.com) in separate chat sessions on March 21, 2025. The system history was cleared before each question. As none of the questions contained visual or graphic content, no additional transcription or image description was required. To avoid the impact of subsequent updates to the language model, each question was accompanied by the prompt, "Answer the following question using the knowledge available as of May 31, 2024." The answers and explanations given by ChatGPT-4o for each question were recorded, and each response was evaluated as correct or incorrect according to the predetermined answer key.

Residents and ChatGPT-4o were scored out of 100 based on the number of correct answers. Additionally, a ranking was created based on these scores, calculated according to the number of examinees in the relevant year. Changes in performance were analyzed overall and by subspecialty for both the residents and ChatGPT. Year-over-year change in resident performance was determined from the average accuracy rates of the 501 residents who participated in both exams.

Ethics committee approval was not required because participant information was anonymized and no personal data were used.

Statistical Analysis

Statistical analyses were performed using SPSS version 26 (IBM, Armonk, NY, USA). The Kolmogorov-Smirnov test was used to evaluate the normality of data distributions. Resident data were not evaluated individually but averaged across the 501 residents in the sample. Comparisons between ChatGPT and the resident group were made descriptively, not with statistical tests. As ChatGPT provides a single model output, variation was not calculated and differences were compared using accuracy rates alone. Continuous variables were presented as mean ± standard deviation and range. The Wilcoxon signed rank test was used to analyze the change in resident accuracy rate overall and by subspecialty between the 2023 and 2024 exams. The 95% confidence intervals (CI) were calculated for the accuracy rates of the resident participant group and ChatGPT models. For comparisons of subspecialty, Bonferroni correction was performed to reduce the probability of type I error and the significance level was determined as $p<0.005$.

Table 1. Mean number of correct answers by residents and ChatGPT-3.5 on the 2023 exam, by subspecialty					
Subspecialty (number of questions)	**All residents (n=501)**	**First-year residents (n=249)**	**Second-year residents (n=132)**	**Third-year residents (n=120)**	**ChatGPT-3.5**
Lens and cataract (n=9)	3.82±1.64	3.16±1.36	4.21±1.63	4.77±1.61	7
Cornea/ocular surface/anterior segment (n=9)	4.55±1.24	4.4±1.29	4.57±1.24	4.83±1.09	4
Glaucoma (n=8)	3.34±1.41	2.92±1.34	3.54±1.4	4.01±1.29	4
Neuro-ophthalmology (n=5)	2.21±0.946	2.12±0.93	2.2±0.94	2.41±0.97	3
Oculoplasty (n=4)	1.30±0.83	1.11±0.78	1.35±0.76	1.63±0.89	2
Pediatric ophthalmology and strabismus (n=8)	3.96±1.51	3.62±1.46	4.27±1.49	4.32±1.52	0
Optics (n=5)	2.07±1.13	1.91±1.06	2.12±1.16	2.36±1.19	3
Retina (n=16)	8.98±2.53	7.85±2.27	9.68±2.33	10.56±2.15	11
Uveitis (n=5)	3.0±1.14	2.79±1.11	3.01±1.16	3.45±1.08	3
Total (n=69)	33.24±7.32	29.88±6.31	34.95±6.34	38.33±6.74	37

Table 2. Mean number of correct answers by residents and ChatGPT-4o on the 2024 exam, by subspecialty					
Subspecialty (number of questions)	**All residents (n=501)**	**Second-year residents (n=249)**	**Third-year residents (n=132)**	**≥Fourth-year residents (n=120)**	**ChatGPT-4o**
Lens and cataract (n=9)	4.14±1.59	3.81±1.50	4.21±1.46	4.73±1.71	8
Cornea/ocular surface/anterior segment (n=11)	5.11±1.90	4.59±1.81	5.39±1.89	5.87±1.76	9
Glaucoma (n=7)	3.34±1.28	3.11±1.21	3.47±1.25	3.66±1.36	5
Neuro-ophthalmology (n=4)	1.84±1.05	1.78±1.05	1.87±1.06	1.95±1.03	4
Oculoplasty (n=7)	4.61±1.32	4.20±1.28	4.74±1.30	5.32±1.07	6
Pediatric ophthalmology and strabismus (n=8)	4.34±1.59	3.96±1.49	4.52±1.64	4.93±1.52	6
Optics (n=5)	2.21±0.98	2.04±0.92	2.26±0.97	2.49±1.06	5
Retina (n=16)	9.30±2.46	8.62±2.33	9.52±2.52	10.45±2.20	14
Uveitis (n=5)	3.20±1.17	2.96±1.07	3.24±1.21	3.66±1.16	4
Total (n=72)	38.20±8.47	35.12±7.07	39.42±8.99	43.25±7.82	61

Results

A total of 501 ophthalmology residents took the exam in both years. When categorized by months of training in 2024, there were 249 second-year residents (12-23 months of experience), 132 third-year residents (24-35 months of experience), and 120 fourth-year or higher residents (≥36 months of experience). The mean training duration of the residents was 28.4±10.6 months (range, 13-64 months). Residents who took the exam in both years correctly answered a mean of 38.2±8.5 of the 72 questions in the 2024 exam, achieving a success rate of 53.1% (95% CI: 52.2%-54.0%). Second-year residents achieved a success rate of 48.8% (95% CI: 47.5%-50.1%), with a mean of 35.1±7.1 correct answers; third-year residents had a success rate of 54.8% (95% CI: 53.3%-56.3%), with a mean of 39.4±8.9 correct answers; and fourth-year or higher residents reached a success rate of 60.1% (95% CI: 58.7%-61.5%), with a mean of 43.3±7.8 correct answers. In contrast, ChatGPT-4o answered 61 of the 72 questions correctly, for an accuracy rate of 84.7% (95% CI: 74.7%-91.3%). ChatGPT-3.5 ranked 292nd among residents in the 2023 exam, whereas ChatGPT-4o achieved the top score in 2024. The mean numbers of questions (overall and by subspecialty) answered correctly by residents and ChatGPT-3.5 in 2023 are presented in Table 1, and the means of the same residents and ChatGPT-4o for 2024 are presented in Table 2.

Overall, the residents' accuracy rates in most subspecialties improved compared to the previous year, although this increase did not reach statistical significance in the field of neuro-ophthalmology (p=0.655). Corneal and ocular surface diseases was the only subspecialty in which residents' performance declined, and this decrease

was statistically significant (p<0.001). In contrast, ChatGPT showed major improvements across all subspecialties, with a 30.4% increase in overall accuracy rate. When the residents and ChatGPT were ranked according to the percentage increase in accuracy rate, ChatGPT-4o ranked 8th. Changes in accuracy rates between the two exams are summarized in Table 3.

Discussion

This study aimed to evaluate the year-over-year change in performance of Turkish ophthalmology residents and a large language model based on a nationwide resident training exam held over two consecutive years, thereby presenting a comparison of natural versus artificial learning. Our findings revealed that residents' average performance in most subspecialties improved between 2023 and 2024, whereas ChatGPT-4o showed consistent improvement over its predecessor ChatGPT-3.5 in all areas and outperformed all human examinees in 2024.

The widespread adoption of AI in the healthcare field has led to an increasing trend among both patients and healthcare professionals toward using these tools to obtain medical information and provide educational support.[11,12] As their use becomes increasingly widespread, particularly through advanced large language models like ChatGPT-4o, it is becoming more important than ever to evaluate the reliability and scientific accuracy of the responses produced by these systems. Despite the advantage of providing rapid and accessible information, their potential impact on clinical decision-making processes and medical education makes it imperative to rigorously assess their responses to domain-specific, evidence-based questions.

Artificial intelligence systems are constantly evolving and learning. ChatGPT-4.0 was reported to show improved accuracy when asked the same questions about intraocular lenses six months apart.[13] In another study, when medical questions initially answered incorrectly by ChatGPT were re-asked a short time later (8-17 days), the model answered most of the questions correctly.[14]

While human learning is a gradual process shaped by experience, cognition, and context, large language models such as ChatGPT acquire knowledge through periodic large-scale retraining cycles.[15] Each new release, such as ChatGPT-4o, reflects a gradual progression, enhanced by insights from increasingly diverse, current, and domain-specific datasets. This process enables rapid

Table 3. Mean change in the percentage of correct answers between the two exams for residents and ChatGPT

Subspecialty	Percentage change, all residents (%) (n=501)	Percentage change, ChatGPT (%)	p*
Lens and cataract	3.48±21.38 (-66.67 to 66.67)	11.11	**<0.001**
Cornea/ocular surface/anterior segment	-4.06±20.78 (-57.58 to 72.73)	37.37	**<0.001**
Glaucoma	5.85±23.36 (-50.0 to 73.21)	21.43	**<0.001**
Neuro-ophthalmology	1.82±29.73 (-80.0 to 80.0)	40.0	0.655
Oculoplasty	33.46±26.34 (-50.0 to 100.0)	35.71	**<0.001**
Pediatric ophthalmology and strabismus	4.74±22.63 (-62.50 to 75.0)	75.0	**<0.001**
Optics	2.67±27.91 (-80.0 to 80.0)	40.0	0.029
Retina	1.95±17.17 (-50.0 to 62.50)	18.75	0.011
Uveitis	3.91±28.18 (-80.0 to 80.0)	20.0	**0.002**
Total	4.31±9.97 (-39.81 to 56.75)	30.38	**<0.001**

*Change in the percentage of correct answers between the two exams for residents who took both; Wilcoxon signed rank test

and effective improvements in information accuracy and functional performance. However, this development lacks the continuity, ethical reasoning, and experiential depth involved in human learning.[16] In contrast, humans experience a slower but more holistic learning process. Knowledge is not only acquired through formal education, but is also shaped through trial and error, emotional context, and social interaction.[17] Especially in medical education, this type of learning process enhances qualities such as clinical judgment, empathy, and adaptability, which current artificial intelligence systems have yet to attain.[18]

The performance of large language models and humans on ophthalmology-related questions has also been compared in previous studies.[19,20] In another study using ophthalmology residency exam questions from 2020 to 2023, large language models did not show a significant change in accuracy over the four years.[21] However, it was not specified exactly when the questions were posed to the large language models; if all the questions were asked at approximately the same time, accuracy rates would be expected to remain similar even if the test years were different.[21] In a study by Taloni et al.[22] using 1,023 questions from the BCSC (Basic and Clinical Science Course) question set of the American Academy of Ophthalmology, ChatGPT-4.0 outperformed its predecessor ChatGPT-3.5. Human participants ranked second in overall performance. Similarly, Maino et al.[23] evaluated 440 previously administered multiple-choice questions on the European Board of Ophthalmology Diploma Examination and reported that ophthalmology residents performed better than ChatGPT-3.5 but were less accurate than ChatGPT-4o.

Although our findings are generally consistent with these studies, there is an important difference in study design. While previous studies adopted a cross-sectional approach, our study involved two similar national exams administered to the same group of residents one year apart, thereby enabling the observation of longitudinal changes. Moreover, we assessed not only human learning, but also the change in performance between successive versions of the same large language model. To the best of our knowledge, our study is the first to provide a parallel view of the progress of both human and machine learning over time.

The overall increase in resident scores is a positive indicator of the effectiveness of training over time, suggesting that structured training programs together with clinical experience contribute to knowledge retention. Interestingly, the only subspecialty with no statistically significant improvement was neuro-ophthalmology. This area is known for its multidisciplinary nature and limited clinical exposure in many training centers.[24] The only area in which resident performance declined significantly was corneal and ocular surface diseases. This may point to factors such as insufficient emphasis on this subspecialty in the training curriculum or a scarcity of clinical cases. These findings may guide future modifications to residency training programs, especially in terms of identifying areas that need strengthening. In contrast, ChatGPT-4o performed strongly in all subspecialties and showed significant improvement over ChatGPT-3.5. ChatGPT-4o had an overall accuracy rate of 84.7%, exhibiting greater accuracy and consistency than the resident group, although it ranked 8th in terms of year-over-year performance improvement. This reinforces the increasing potential of large language models as educational tools in medical education, especially in terms of exam preparation and theoretical knowledge support. However, it should be noted that these models do not include elements important to medical practice such as contextual nuance, clinical judgment, and practical skills. Therefore, such AI tools should be considered a supportive and complementary component of traditional medical education rather than a replacement.

Study Limitations

Our study has some limitations that should be noted. First, although a longitudinal comparison was made, the effect of variables such as individual learning environments, level of clinical experience, and work-related habits is unknown. Second, although both exams were similar in content and structure, their psychometric equivalence has not been assessed at the item level. Therefore, the study evaluates year-over-year differences not as absolute values, but as relative change in performance under similar conditions. Regarding the AI methodology, the web-based interface offers limited control over response length and context memory compared to the application versions of ChatGPT. This may lead to minor differences in responses, which we consider a methodological limitation. Furthermore, the selection of residents who participated in both exams may have introduced selection bias, as this approach could select for individuals who are more motivated or academically inclined. Finally, the limited number of questions and the fact that the study is based on the national exam of a single country may limit the generalizability of the findings to different education systems.

Conclusion

ChatGPT-4o demonstrated improved accuracy over the previous version (ChatGPT-3.5) and outperformed the resident group in the 2024 national ophthalmology

resident training exam. While residents showed more modest improvement, the dramatic progress made by ChatGPT-4o underscores the evolving capabilities of large language models. However, it is important to note that despite their high accuracy, these models can occasionally generate erroneous or misleading responses. Therefore, their role in medical education should be complementary, regarded as a supportive tool rather than a substitute for the critical thinking and experience-based knowledge that develops in humans through training.

Ethics

Ethics Committee Approval: Not required.

Informed Consent: Not required.

Declarations

Authorship Contributions

Concept: A.S.B., Z.Y., B.T.Ö., Ç.A., Design: A.S.B., Z.Y., B.T.Ö., Ç.A., Data Collection or Processing: A.S.B., Z.Y., Analysis or Interpretation: A.S.B., Literature Search: A.S.B., Writing: A.S.B., Z.Y., B.T.Ö., Ç.A.

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

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

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Original Article

Real-World Comparison of the Effectiveness of Defocus Incorporated Multiple Segments and Myopi-X Spectacle Lenses for Myopia Control in Turkish Children: A Retrospective Study

Nilay Akagün, Uğur Emrah Altıparmak

Acıbadem Ankara Hospital, Clinic of Ophthalmology, Ankara, Türkiye

Abstract

Objectives: This study compared the 12-month real-world effectiveness of defocus incorporated multiple segments (DIMS) spectacle lenses, Myopi-X progressive addition lenses, and single-vision (SV) lenses in slowing myopia progression in children.

Materials and Methods: This retrospective observational study included 385 eyes using one of the three spectacle types. Baseline age, spherical equivalent refraction (SER), and axial length (AL) were recorded. Twelve-month changes in SER and AL were analyzed using the Kruskal-Wallis test with Bonferroni-adjusted pairwise comparisons. Generalized estimating equations (GEE) were used to assess the effects of treatment group, age group, sex, and baseline AL group on SER and AL changes.

Results: The study population consisted of 118 Myopi-X eyes (32.4%), 107 SV eyes (29.4%), and 139 DIMS eyes (38.2%). Baseline demographic and ocular characteristics (including age, sex, SER, AL, age group, and baseline AL group) were comparable among the groups (all $p>0.05$). After 12 months, mean SER progression was -0.35±0.34 diopters (D) in the Myopi-X group, -0.46±0.37 D in the SV group, and -0.24±0.33 D in the DIMS group ($p<0.001$). Mean AL elongation was 0.21±0.12 mm, 0.24±0.17 mm, and 0.17±0.16 mm, respectively ($p=0.004$). GEE analyses demonstrated a significant treatment effect for both SER and AL change ($p<0.001$ for both). The least progression occurred in the DIMS group, followed by Myopi-X, while the SV group showed the highest progression. Baseline AL group was the only significant predictor of AL elongation ($\beta=0.210$, 95% confidence interval: 0.189-0.231, $p<0.001$), with greater elongation in eyes with high baseline AL. Age group and sex did not significantly influence SER or AL outcomes.

Conclusion: DIMS spectacle lenses were more effective than Myopi-X and SV lenses in reducing both refractive progression and axial elongation over 12 months. Baseline AL was a key determinant of axial growth, supporting the use of individualized risk assessment in pediatric myopia management.

Keywords: Myopia, spectacle lenses, axial length, refractive errors, child

Cite this article as: Akagün N, Altıparmak UE. Real-World Comparison of the Effectiveness of Defocus Incorporated Multiple Segments and Myopi-X Spectacle Lenses for Myopia Control in Turkish Children: A Retrospective Study. Turk J Ophthalmol. 2026;56:8-15

Address for Correspondence: Nilay Akagün, Acıbadem Ankara Hospital, Clinic of Ophthalmology, Ankara, Türkiye
E-mail: nildnd@yahoo.com
ORCID-ID: orcid.org/0000-0002-1522-3034

Received: 11.09.2025
Revision Requested: 06.12.2025
Last Revision Received: 16.12.2025
Accepted: 02.01.2026
Publication Date: 18.02.2026

DOI: 10.4274/tjo.galenos.2026.23529

Introduction

The global prevalence of myopia continues to increase at an alarming rate; projections suggest that nearly half of the world's population may be affected by 2050.[1,2] This is a major public health concern, especially due to the rising incidence of high myopia, which is strongly associated with complications such as glaucoma, retinal detachment, myopic maculopathy, and choroidal neovascularization.[3] Greater axial length (AL) and higher degrees of myopia are recognized as major risk factors for these sight-threatening outcomes.[4,5] The prevalence of myopia is rising not only in East Asian countries but also across Europe, with younger populations exhibiting the most marked increases.[6,7,8]

Myopia management in children generally involves three main strategies: pharmacological therapy, advanced optical designs, and behavioral or lifestyle modifications.[9,10] Among pharmacological options, low-dose atropine has consistently been demonstrated to slow myopia progression

while limiting the adverse effects typically associated with higher concentrations.[11] However, practical challenges such as monthly compounding, long-term compliance, and mild side effects may restrict its routine use. As alternatives, novel optical treatments, including defocus incorporated multiple segments (DIMS) lenses, highly aspherical lenslets (HALs), and orthokeratology, induce peripheral myopic defocus while preserving central visual clarity, thereby reducing axial elongation and slowing progression.[12,13] Evidence from clinical trials has confirmed that these lenses are more effective than single-vision (SV) lenses in controlling myopia progression.

Despite the increasing use of Myopi-X and DIMS lenses in Türkiye, real-world evidence comparing their effectiveness with that of conventional SV lenses is limited. Moreover, the influence of baseline parameters such as age, sex, and AL on treatment response remains inadequately explored, although previous studies suggest that these may act as significant predictors.[14,15,16] This retrospective study aimed to evaluate the 1-year effectiveness of Myopi-X and DIMS lenses compared with SV lenses in slowing myopia progression in a Turkish pediatric cohort. Subgroup analyses were conducted to assess the effects of baseline AL (moderate vs. high), age (<10 vs. ≥10 years), and sex on treatment outcomes.

Materials and Methods

Study Design

This retrospective observational study was conducted between May 2023 and May 2024 in the Department of Ophthalmology of Acıbadem Hospital in Ankara, Türkiye. The study adhered to the tenets of the Declaration of Helsinki and was approved by the Acıbadem University Institutional Ethics Committee (date: 08.05.2025; decision no: 2025-07/295). Written informed consent was obtained from the parents or legal guardians of all participants.

Inclusion and Exclusion Criteria

Eligible participants were children aged 6-16 years diagnosed with myopia, defined as cycloplegic spherical equivalent refraction (SER) ≤-0.50 diopters (D). Additional inclusion criteria were anisometropia <1.50 D and astigmatism <2.00 D. The exclusion criteria were a history of ocular pathologies such as glaucoma, cataract, keratopathy, amblyopia, or strabismus, as well as systemic or ocular conditions that could interfere with measurement accuracy or adherence to treatment.

Intervention Protocols

The participants were divided into three groups: Myopi-X progressive addition spectacle lenses, DIMS spectacle lenses, and SV spectacle lenses (control). All lenses were prescribed for full-time wear, excluding sleep and bathing. Both eyes of each patient were included in the analysis. However, eyes not meeting the inclusion criteria were excluded from the study.

Cycloplegic autorefraction was performed 30 min after administering two drops of 1% tropicamide (Tropamid, Bilim İlaç, İstanbul, Türkiye) at 5-min intervals. This agent was selected due to its rapid onset, shorter recovery time, and proven cycloplegic efficacy in non-strabismic pediatric populations.[17] Measurements were taken using a Topcon CKR-8900 autorefractometer (Topcon Corp., Tokyo, Japan). Cycloplegic refraction was repeated until three consecutive readings demonstrated a standard deviation <0.05 D. AL was measured with the Zeiss IOL Master 700 (Carl Zeiss Meditec AG, Jena, Germany) until the standard deviation was <0.05 mm. These procedures followed published recommendations for measurement feasibility and repeatability in ophthalmology.[18]

Outcome Measures

The primary outcomes were changes in SER and AL after 12 months of follow-up.

Subgroup Classifications

The participants were stratified by sex (male or female), age (<10 years and ≥10 years), and baseline AL.

Baseline AL was categorized as moderate or high using age-specific normative percentile curves, based on the reference values reported by Tideman et al.[19] For age, 10 years was selected as the cut-off because children initiating spectacle wear before this age have been shown to demonstrate faster myopia progression and a greater likelihood of developing high myopia in adulthood.[20]

Statistical Analysis

All analyses were performed using IBM SPSS Statistics for Windows, version 29.0 (IBM Corp., NY, USA). Descriptive statistics were reported as mean ± standard deviation for continuous variables and as frequency (percentage) for categorical variables. The Shapiro-Wilk test was applied to assess normality. Group differences at baseline were evaluated using the Kruskal-Wallis test for continuous variables and the chi-square test for categorical variables.

For the primary outcomes (12-month SER and AL changes), generalized estimating equations (GEEs) were applied to account for within-participant correlations, as both eyes of each patient were included. Treatment group, sex, age group, and baseline AL group were entered as predictors. Regression coefficients (β) with 95% confidence

intervals (CI) and Wald χ^2 statistics were reported. Statistical significance was set at a two-sided $p<0.05$.

Power Analysis

Because of the retrospective design, the sample size was determined by the available eligible records. However, a priori sample size estimation was performed using G*Power (Version 3.1.9.7; Universität Düsseldorf, Düsseldorf, Germany) with a two-tailed alpha level of 0.05 and a statistical power of 80%.[21] Effect sizes were derived from our previously published study evaluating the 1-year effectiveness of DIMS spectacle lenses in a Turkish pediatric cohort.[22] Based on these effect sizes, the minimum required sample size was estimated to be 159 eyes (approximately 53 per group) for SER change and 260-270 eyes (approximately 85-90 per group) for AL change. The present study included 364 eyes (107-139 per group), exceeding the estimated sample size requirements.

Results

Baseline Characteristics

A total of 385 eyes were included in the analysis: 118 eyes (32.4%) in the Myopi-X group, 107 eyes (29.4%) in the SV group, and 139 eyes (38.2%) in the DIMS group. Baseline demographic and ocular characteristics are presented in Table 1 for continuous variables and Table 2 for categorical variables.

At baseline, there were no statistically significant differences among the groups in mean age, SER, or AL ($p>0.05$) based on the Kruskal-Wallis test (Table 1). Although pairwise comparisons suggested a trend toward older age and longer baseline AL in the SV group, these differences did not remain significant after Bonferroni correction.

Sex distribution was similar across the three treatment groups ($p=0.682$). Overall, 164 eyes (45.1%) belonged to children aged <10 years and 200 eyes (54.9%) to those aged ≥10 years. In total, 179 eyes (49.2%) were classified

Table 1. Baseline demographic and ocular characteristics

Variable	Myopi-X (n=118)	SV (n=107)	DIMS (n=139)	p value
Age (years)	9.07±2.15 (5-13)	9.57±1.77 (5-12)	9.19±2.53 (4-15)	0.061
SER (D)	-2.47±1.62 (-10.62 to -0.12)	-2.46±1.80 (-7.63 to +0.25)	-2.65±1.25 (-5.50 to -0.25)	0.073
AL (mm)	24.39±0.87 (22.95-26.58)	24.54±1.05 (22.26-27.60)	24.27±1.04 (22.48-26.90)	0.066

Values are presented as mean ± standard deviation (range). P values are based on the Kruskal-Wallis test
SV: Single-vision, DIMS: Defocus incorporated multiple segments, SER: Spherical equivalent refraction, expressed in diopters (D); AL, axial length, expressed in millimeters (mm)

Table 2. Baseline categorical characteristics

Variable	Myopi-X (n=118)	SV (n=107)	DIMS (n=139)	p value
Sex Female Male	 50 (42.4%) 68 (57.6%)	 49 (45.8%) 58 (54.2%)	 74 (53.2%) 65 (46.8%)	0.682
Age group <10 years ≥10 years	 65 (55.1%) 53 (44.9%)	 25 (23.4%) 82 (76.6%)	 74 (53.2%) 65 (46.8%)	0.415
Baseline AL group Moderate High	 56 (47.5%) 62 (52.5%)	 45 (42.1%) 62 (57.9%)	 78 (56.1%) 61 (43.9%)	0.732

Values are shown as n (%). Percentages are calculated per column based on the number of eyes in each treatment group. Between-group comparisons were performed using the chi-square test
SV: Single-vision, DIMS: Defocus incorporated multiple segments, AL: Axial length

as having moderate baseline AL and 185 eyes (50.8%) as having high baseline AL. Distributions of age and baseline AL category were also comparable among the treatment groups (both p>0.05).

SER and AL Changes After 12 Months

The mean change in SER after 12 months was -0.35±0.34 D in the Myopi-X group, -0.46±0.37 D in the SV group, and -0.24±0.33 D in the DIMS group. The Kruskal-Wallis test revealed a significant difference among the three groups (p<0.001). The distribution of SER changes by treatment group is illustrated in Figure 1.

Similarly, the mean AL elongation was 0.21±0.12 mm in the Myopi-X group, 0.24±0.17 mm in the SV group, and 0.17±0.16 mm in the DIMS group, with overall differences reaching statistical significance (p=0.004). Group differences stratified by baseline AL subgroups are presented in Figure 2, whereas further subgroup comparisons are illustrated in Figure 3. Detailed group comparisons are summarized in Table 3.

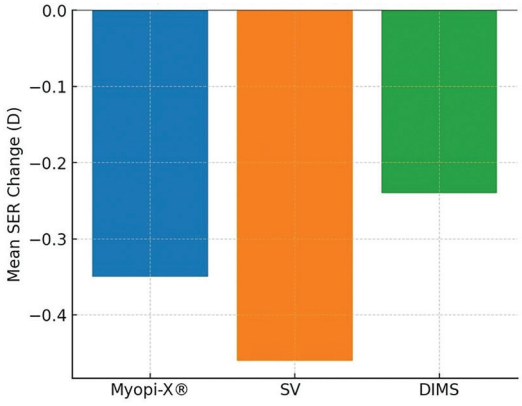

Figure 1. Twelve-month change in spherical equivalent refraction (SER) among the treatment groups. The bar chart illustrates the mean change in 12 months in the Myopi-X, single-vision (SV), and defocus incorporated multiple segments (DIMS) lens groups

GEE Analysis

The GEE analysis for 12-month SER change showed that the treatment group had a statistically significant effect (Wald χ^2=24.692, p<0.001). The least myopia progression was observed in the DIMS group (reference), followed by the Myopi-X group (β=-0.116, 95% CI: -0.197 to -0.034, p=0.005), with the highest progression in the SV group (β=-0.224, 95% CI: -0.314 to -0.135, p<0.001). SER change was not significantly associated with age group, baseline AL group, or sex (all p>0.05).

For AL change, treatment group also showed a statistically significant effect (Wald χ^2=407.742, p<0.001). The lowest elongation occurred in the DIMS group, followed by the Myopi-X group, whereas the SV group had the highest elongation (all p<0.001). The baseline AL group was a significant predictor (Wald χ^2=377.974, p<0.001), with eyes in the high baseline AL group showing greater elongation (β=0.210, 95% CI: 0.189-0.231, p<0.001). In contrast, age group and sex had no significant effect on AL change.

The predictors of SER and AL changes are summarized in Table 4. The GEE analysis showed that among the categorical variables (sex, age group, baseline SER group, and baseline AL group), only the baseline AL group was a significant predictor of 12-month AL change (p<0.001). As this variable comprised two categories (moderate vs. high), no further pairwise analyses were necessary.

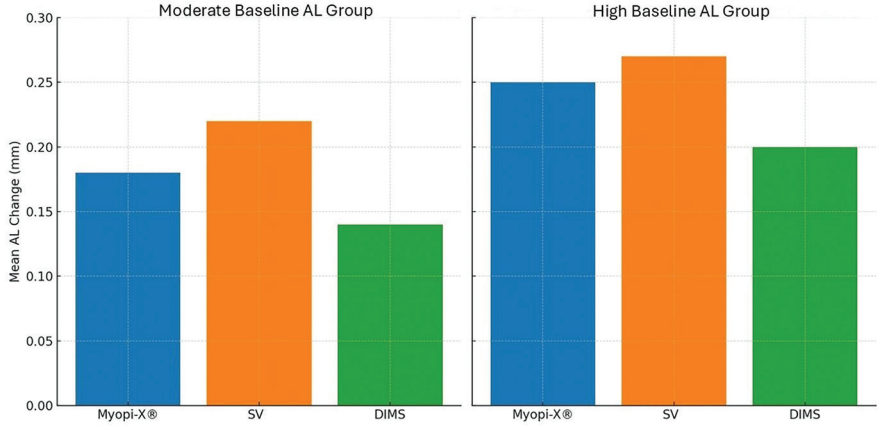

Figure 2. Twelve-month axial length (AL) changes according to baseline AL group. The bar charts illustrate the mean AL change in 12 months stratified by baseline AL group (moderate vs. high). Comparisons are shown for the Myopi-X, single-vision (SV), and defocus incorporated multiple segments (DIMS) lens groups

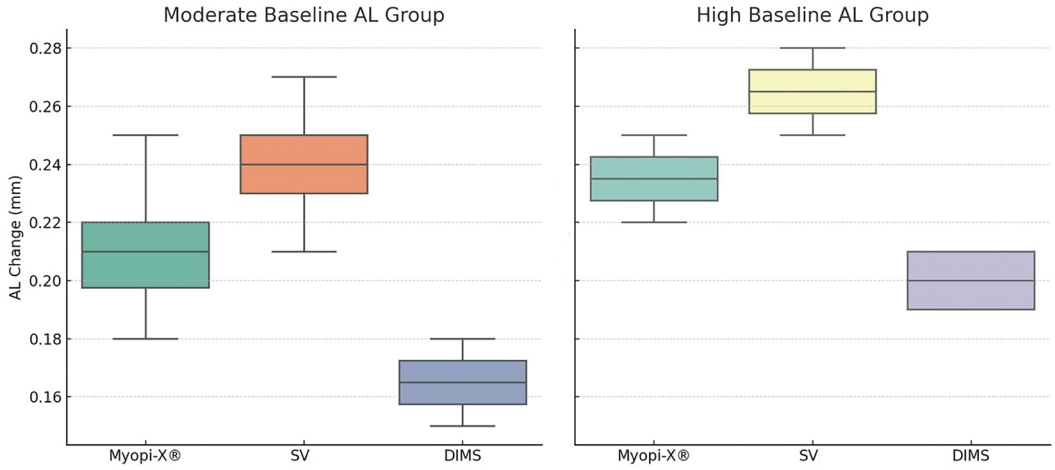

Figure 3. Twelve-month axial length (AL) change stratified by baseline AL group. The boxplots show the distribution of AL change in 12 months in the moderate and high baseline AL groups. Comparisons are presented for the Myopi-X, single-vision (SV), and defocus incorporated multiple segments (DIMS) lens groups. Boxes represent interquartile ranges; the horizontal line inside the box indicates the median, and whiskers denote the minimum and maximum values

Table 3. Twelve-month changes in spherical equivalent refraction (SER) and axial length (AL)

Variable	Myopi-X (n=118)	SV (n=107)	DIMS (n=139)	p values
SER change (D)	-0.35±0.34	-0.46±0.37	-0.24±0.33	Overall: <0.001
				DIMS vs. Myopi-X: 0.005
				DIMS vs. SV: <0.001
				Myopi-X vs. SV: 0.214
AL change (mm)	0.21±0.12	0.24±0.17	0.17±0.16	Overall: 0.004
				DIMS vs. Myopi-X: <0.001
				DIMS vs. SV: <0.001
				Myopi-X vs. SV: 0.326

Values are presented as mean ± standard deviation. Overall group differences were assessed using the Kruskal-Wallis test. Pairwise comparisons were performed with generalized estimating equations to account for the inclusion of both eyes
SV: Single-vision, DIMS: Defocus incorporated multiple segments

Table 4. Predictors of spherical equivalent refraction (SER) and axial length (AL) changes in 12 months (GEE analysis)

Outcome	Treatment group	Age group (<10 vs. ≥10 years)	Baseline AL group (moderate vs. high)	Sex (female vs. male)
SER change	<0.001	0.694	0.460	0.865
AL change	<0.001	0.950	<0.001	0.077

P values are derived from generalized estimating equation (GEE) models including both eyes

Discussion

This retrospective study including 364 eyes demonstrated that DIMS spectacle lenses were more effective in slowing myopia progression compared with both Myopi-X progressive addition lenses and conventional SV lenses. Eyes in the DIMS group showed the least SER progression (-0.24±0.33 D) and axial elongation (0.17±0.16 mm), whereas the SV group exhibited the highest progression (-0.46±0.37 D and 0.24±0.17 mm, respectively) after 12 months. Subgroup analyses identified higher baseline AL as a significant predictor of greater axial elongation, while age and sex did not significantly influence SER progression or axial elongation, highlighting baseline AL as a key determinant of treatment response.

Our findings are consistent with pivotal randomized controlled trials by Lam et al.[23,24,25] In their 2-year study,[23] children wearing DIMS lenses showed a 52% reduction in myopia progression and a 62% reduction in axial elongation compared with SV lenses, with sustained effects confirmed in 3- and 6-year follow-up studies.[24,25] Compared with these Asian cohorts, our real-world study in Turkish children demonstrated similar benefits, indicating that the effectiveness of DIMS lenses may extend beyond East Asian populations to other clinical settings.

Nucci et al.[26] reported comparable outcomes in Italian children wearing DIMS lenses, with significantly lower SER progression and axial elongation than with SV lenses at 12 months. While they adjusted for baseline age, SER, and AL, these variables were not identified as independent predictors. In contrast, our analyses demonstrated baseline AL as a significant predictor of axial elongation, with no association observed for age or sex.

Neller et al.[27] evaluated DIMS treatment response using age-specific physiological growth curves and reported greater axial elongation and lower treatment success in children with high baseline AL, as well as faster ocular growth in younger children. In line with these observations, our study confirmed baseline AL as a key predictor of axial elongation, although age did not reach statistical significance.

Our previously published study represents one of the few investigations of Myopi-X lenses.[28] In that analysis, Myopi-X lenses significantly reduced myopia progression and axial elongation compared with SV lenses but remained less effective than DIMS lenses. The present findings are consistent, confirming that Myopi-X lenses provide measurable control benefits, although DIMS lenses remain superior. These results emphasize the importance of evaluating locally available optical interventions in specific populations.

Earlier spectacle-based approaches, including bifocals and progressive addition lenses, demonstrated limited or modest efficacy in slowing myopia progression.[29,30] Subsequent designs such as MyoVision, Myopilux, Perifocal, and the experimental Apollo lens yielded only modest treatment effects.[31] Unlike these experimental prototypes, our real-world data showed that Myopi-X lenses achieved significantly lower SER progression and axial elongation than SV lenses, although their effect remained less pronounced than that of DIMS lenses.

Increasing attention has focused on baseline predictors of response to myopia control. Nucci et al.[26] confirmed the robustness of DIMS treatment effects after adjusting for baseline factors, whereas Neller et al.[27] highlighted the influence of baseline AL and age. Tideman et al.[19] introduced age-specific AL growth curves to support individualized treatment evaluation, and Brennan et al.[32] emphasized age and AL as major determinants of myopia progression. Consistent with this framework, baseline AL emerged as the strongest predictor of axial elongation in our cohort.

Retrospective orthokeratology studies have shown that baseline age and refractive error significantly influence treatment efficacy.[33] Zhong et al.[34] reported slower progression in older children, with additional effects of lens design and optical aberrations, whereas Sarkar et al.[35] demonstrated the influence of baseline age, SER, and AL on treatment outcomes. These differences likely reflect distinct mechanisms of action: orthokeratology induces corneal reshaping influenced by corneal biomechanics and age-related ocular growth, whereas DIMS and Myopi-X lenses act through peripheral myopic defocus without structural corneal changes, potentially explaining the lack of age dependence in our cohort.

Weise et al.[36] and Lee et al.[37] reported greater progression in younger children and those with higher baseline myopia. Lu et al.[38] observed slower elongation in eyes with higher baseline AL, whereas our study demonstrated greater elongation in such eyes, possibly due to differences in ethnicity, treatment modality, and baseline ocular characteristics. European cohorts comparing DIMS lenses and HALs reported inconsistent associations between age, sex, and axial elongation.[39,40] Overall, our findings align with European data, suggesting that baseline AL may exert a stronger influence on ocular growth dynamics than chronological age.

Strengths and Limitations

This study benefited from a relatively large sample size, inclusion of both eyes with appropriate statistical adjustment, and a real-world clinical setting. Subgroup and predictor analyses further strengthened the evaluation of treatment response.

Limitations include the retrospective design, 1-year follow-up duration, and lack of randomization. In addition, Myopi-X lenses are primarily prescribed in Türkiye, which may limit generalizability.

Conclusion

DIMS lenses were superior to Myopi-X and SV lenses in limiting both refractive progression and axial elongation. Myopi-X lenses, while not widely adopted internationally, are commonly prescribed in Türkiye and provide measurable benefits compared with SV lenses, although their effect remains less pronounced than that of DIMS lenses. Among all evaluated factors, baseline AL was

the only consistent predictor of axial elongation, whereas age and sex showed no significant influence.

Ethics

Ethics Committee Approval: Acıbadem University Institutional Ethics Committee (date: 08.05.2025; decision no: 2025-07/295).

Informed Consent: Written informed consent was obtained from the parents or legal guardians of all participants.

Declarations

Authorship Contributions

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

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

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

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Original Article

The Impact of Advanced Surface Moisturizing Technologies on Contact Lens Comfort in Digital Platform Users

Mehtap Arslantürk Eren[1], Tuna Çelik Büyüktepe[2], Ömür Ö. Uçakhan-Gündüz[3]

[1]University of Health Sciences Türkiye, Kanuni Training and Research Hospital, Clinic of Ophthalmology, Trabzon, Türkiye
[2]Ünye State Hospital, Clinic of Ophthalmology, Ordu, Türkiye
[3]Ankara University Faculty of Medicine, Department of Ophthalmology, Ankara, Türkiye

Abstract

Objectives: To evaluate and compare the on-eye performance and comfort of two lotrafilcon B contact lenses, each manufactured using different surface moisturizing technologies, in individuals who use digital platforms for more than 3 hours daily.

Materials and Methods: Twenty-nine asymptomatic habitual contact lens wearers participated in a randomized, double-masked crossover study. Each subject wore either Air Optix Aqua or Air Optix Plus HydraGlyde contact lenses for a month before switching to the other lens type for another month. Contact Lens Dry Eye Questionnaire 8 (CLDEQ-8) scores, biomicroscopic examination, tear function tests, and blink rates were recorded at baseline and at the end of each month. The patients were asked to complete a Likert-type questionnaire evaluating vision and comfort, along with first-impression ratings for visual clarity, comfort, and dryness with each lens.

Results: The mean age of patients was 25.5±7.2 years. Tarsal papillary grade was significantly lower, and tear-film break up time was higher with Air Optix Plus HydraGlyde lenses compared to Air Optix Aqua lenses ($p<0.05$). There were no significant differences between the two lenses in terms of slit-lamp findings, Schirmer's test, blink rate, or CLDEQ-8 scores ($p>0.05$). Air Optix Plus HydraGlyde lenses provided significantly better end-of-day comfort and less blurred vision, dryness, and eye tiredness ($p<0.05$).

Conclusion: Air Optix Plus HydraGlyde lenses with advanced surface moisturizing technology were superior in terms of end-of-day comfort, end-of-month comfort, and visual clarity. Technological advances in silicone hydrogel lens surface treatments seem to be helpful in improving contact lens comfort in lens wearers with moderate daily exposure to digital devices.

Keywords: Surface moisturizing technologies, contact lens comfort, lens surface modification, silicone hydrogel, digital eye strain

Cite this article as: Arslantürk Eren M, Çelik Büyüktepe T, Uçakhan-Gündüz ÖÖ. The Impact of Advanced Surface Moisturizing Technologies on Contact Lens Comfort in Digital Platform Users. Turk J Ophthalmol. 2026;56:16-23

This study was partially presented as an e-poster at the European Society of Ophthalmology Congress (SOE 2023); June 15-17, 2023; Prague, Czech Republic.

Address for Correspondence: Ömür Ö. Uçakhan-Gündüz, Ankara University Faculty of Medicine, Department of Ophthalmology, Ankara, Türkiye
E-mail: omuru@yahoo.com
ORCID-ID: orcid.org/0000-0002-3447-7785

Received: 25.12.2024
Revision Requested: 06.04.2025
Last Revision Received: 26.10.2025
Accepted: 11.11.2025
Publication Date: 18.02.2026

DOI: 10.4274/tjo.galenos.2025.68984

Introduction

Contact lenses (CLs) are effective and reliable optical devices for correcting refractive errors. They have been widely used since the introduction of soft lens materials. Despite the increase in the global population, the number of CL wearers has remained more or less stable over the years because of constant CL discontinuation reported in the range of 12% to 51% globally.[1] One of the leading causes for discontinuation is CL discomfort, which accounts for 30% to 50% of all discontinuations.[2,3,4]

For years, CL practitioners and scientists have questioned the influence of polymer chemistry, design, and other quantifiable material attributes as possible determinants of CL discomfort.[5] These attributes include the bulk (e.g., water content, dehydration, ionicity, oxygen transmissibility, modulus, and mechanical factors) and surface properties (e.g., friction, wettability, surface modification) of CL materials. Although the exact cause

of CL discomfort remains unclear, it is known to be multifactorial and complex.[6] In 2013, the Contact Lens Materials, Design, and Care Subcommittee of TFOS International Workshop on Contact Lens Discomfort[7] classified the factors underlying CL discomfort as CL-related and environmental factors. Among CL-related factors, lens material and design, lens care, and/or wear pattern have been extensively evaluated from the available literature. However, the specific parameters influencing CL discomfort could not be determined, as existing studies could not isolate other confounding factors.[1] Nevertheless, considering the relevance of pre-lens tear film stability in CL discomfort, the workshop recommended that future studies focus on developing novel materials or surface treatments to resist tear evaporation during CL wear.[1] The surface characteristics of CLs include friction, wettability, lubricity, and surface water contact.[5] Wettability and lubricity are two important predeterminants of the frictional forces between the lens and the ocular/palpebral surfaces.[5] Among the material properties of CLs, only friction was correlated with *in vivo* comfort scores according to previous studies.[1,8,9] Frictional forces have also been linked to CL discomfort-related conditions such as lid-wiper epitheliopathy.[7,10]

While silicone hydrogel soft CL materials effectively reduce hypoxia-related adverse events, the wettability/lubricity issues of these CLs still present challenges for the CL industry. Recognizing the impact of frictional forces on comfort, the CL industry has made significant efforts to enhance surface properties through intrinsic wettability agents, surface modifications, or water-gradient technologies. This study aims to evaluate and compare the impact of advanced moisturizing technology with lotrafilcon B lenses on patient comfort.

Materials and Methods

The study was approved by the Ethics Committee of Ankara University Faculty of Medicine Clinical Research Ethics Committee (number: 07-362-17; date: 10 April 2017) and was conducted according to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

Twenty-nine consecutive participants with myopic refractive errors (from -0.75 to -5.00 diopters [D]) who reported more than 3 hours of daily digital device use (desktop, laptop, tablet, or smartphone) and wore CLs for at least 8 hours per day, 6 days a week were included in the study. Habitual CL wearers who had signs of ocular disease, were using systemic or topical medication that could affect the ocular surface, or had CL-related discomfort were excluded. Following a 1-week washout period, participants were randomly assigned to wear either Air Optix Aqua (lotrafilcon B, Alcon, Fort Worth, TX, USA) or Air Optix Plus HydraGlyde (lotrafilcon B, Alcon, Fort Worth, TX, USA) lenses (Table 1). Randomization was performed by simple random sampling using a random number list from Excel. Both participants and observers were blinded to the lens allocation, and all CLs were applied by a CL nurse. CL fitting characteristics including centration, movement, and tightness were evaluated using slit-lamp biomicroscopy. Participants wore the assigned lens type on a daily wear basis for one month. At the end of the first month, the lenses were removed by the participants one day before the follow-up visit. At the follow-up visit, participants were assigned the alternate lens type. CL fit was reassessed at the slit-lamp, and the participants continued wearing the second lens type for another month. Throughout the study, all participants used the same lens solution (OptiFree Express, Alcon, Fort Worth, TX, USA).

At baseline and follow-up visits (at month 1 and month 2), a detailed slit-lamp biomicroscopic examination of the cornea and adnexa was performed, including blink rates, Schirmer-I test, fluorescein staining of the ocular surface, and tear break-up time (TBUT). The blink rate was recorded through direct observation of the participants. This observation was conducted while participants were calmly awaiting the examination to ensure natural blinking behavior. The Schirmer-I test was performed without topical anesthesia. On slit-lamp biomicroscopy, the tarsal papillary reaction was assessed using the grading system of Bonini et al.[11]: grade 0 (no papillary reaction), grade 1 (few papillae, 0.2 mm widespread over the tarsal conjunctiva or around the limbus), grade 2 (papillae of 0.3-1 mm over the tarsal conjunctiva or at the limbus), grade 3 (papillae of 1-3 mm all over the tarsal conjunctiva or for 360° around the limbus), and grade 4 (papillae of more than 3

Table 1. Physical properties of the contact lenses studied

	Air Optix Aqua	Air Optix Plus HydraGlyde
Material	Lotrafilcon B	Lotrafilcon B
Lens design	Aspherical	Aspherical
Water content (%)	33	33
Diameter (mm)	14.2	14.2
Base curve (mm)	8.6	8.6
Dk/t (@-3.00D)	138	138
Center thickness (mm)	0.08	0.08
Modulus (MPa)	1.0	1.0
Surface	SmartShield Technology	SmartShield Technology Moisture Matrix Technology

mm over the tarsal conjunctiva or gelatinous appearance at the limbus covering the peripheral cornea). Superficial punctate keratitis was graded based on corneal staining as grade 0 (no staining), grade 1 (mild staining with a few disseminated dots and limited to less than one third of the cornea), grade 2 (moderate staining with severity between 1 and 3), or grade 3 (severe confluent staining and occupying half or more of the cornea).[12] Both the tarsal papillary reaction and superficial punctate staining were graded by the same examiner (M.A.E.). TBUT was measured three times after fluorescein application and the mean value was recorded.

Following routine ophthalmic examination, all participants were asked to complete the Contact Lens Dry Eye Questionnaire 8 (CLDEQ-8), which has been validated in the Turkish language (Supplementary File 1).[13,14]

At follow-up visits, the participants were asked to report their CL experience in the past month. Firstly, they were asked to score each question regarding visual clarity, comfort, dryness, weariness, etc. on a scale from 1 (very poor) to 10 (excellent). Additionally, they responded to seven statements regarding their vision and comfort with the CL on a 5-point Likert-type scale (strongly agree, agree, undecided, disagree, strongly disagree) (Supplementary File 2). Lastly, the participants were asked if they would continue wearing this CL and requested to pick from the options of "definitely wear", "wear", "not wear", "probably not wear", or "definitely never wear".

Statistical Analysis

The sample size was calculated based on a two-tailed paired t-test, assuming an alpha level of 0.05, a power of 80%, and an expected effect size (Cohen's d) of 0.67. This yielded a required sample size of 24 participants. To account for potential dropouts, we planned to include a total of 29 participants. Data were described as mean and standard deviation for numerical variables and frequency and percentage for categorical variables. Normality of the data was tested using the Kolmogorov-Smirnov test/Shapiro-Wilk test and histogram and probability graphs. Nominal variables were compared with chi-square or Fisher's exact test, whereas numerical variables were compared with independent samples t-test or Mann-Whitney U test as appropriate. Responses to the Likert-type items were converted to binary format (strongly agree/agree: favorable [1], undecided/disagree/strongly disagree: unfavorable [0]) and compared using a binomial generalized linear mixed model. Statistical analyses were performed with SPSS version 26.0 (IBM Corp., Armonk, NY, USA). The level of statistical significance was set at $p<0.05$.

Results

Twenty-nine consecutive asymptomatic CL wearers were included in this study. The mean age was 25.5±7.2 years (range, 16-45 years) and 24% of them were male. The mean spherical refractive error was -3.01±1.80 D (range, -0.75 to -5.00 D). Among the participants, 65% wore their CLs for over 10 hours a day, and 52% wore their CLs 7 days a week. The mean daily duration of digital device use was 4.9±2.3 hours (range, 3-10 hours). Baseline clinical data of the participants are presented in Table 2.

Functional Parameters

The clinical characteristics of the eyes in each CL group are presented in Table 3. There were no statistically significant differences between the two groups in terms of mean CLDEQ-8 score, superficial punctate keratitis grade, blink rate, or Schirmer-I test score ($p>0.05$). The mean TBUT was significantly higher ($p=0.02$) and tarsal papillary grade ($p=0.003$) was lower with the Air Optix Plus HydraGlyde compared to the Air Optix Aqua.

Table 2. Demographic and clinical data of the participants

Age (years)		25.5±7.2
Sex (female:male)		22:7
BCVA (logMAR)		0.0±0.0
MR spherical (D)		-3.0±1.8
Schirmer I test (mm)		24.6±8.0
TBUT (s)	<10 ≥10	0 (0%) 57 (100%)
SPK grade	0 1 2 3 4	56 (98.2%) 1 (1.8%) 0 (0%) 0 (0%) 0 (0%)
Tarsal papillary grade	0 1 2 3 4	20 (35.1%) 29 (50.9%) 8 (14.0%) 0 (0%) 0 (0%)
Blink rate (blinks/min)		12.0±4.5
Digital platform use (hours/day)		4.9±2.3
Lens wear (hours/day)	8-10 10-12 12-14 ≥14	10 (17.5%) 10 (17.5%) 19 (33.4%) 18 (31.6 %)
CLDEQ-8 score		14.1±6.5

Numerical variables are presented as mean ± standard deviation, categorical variables as frequency and percentage
BCVA: Best corrected visual acuity, logMAR: Logarithm of the minimum angle of resolution, MR: Manifest refraction, D: Diopter, TBUT: Tear break-up time, SPK: Superficial punctate keratitis, CLDEQ-8: Contact Lens Dry Eye Questionnaire

Subjective Parameters

Out of 12 questions rated on a scale of 1 to 10, the Air Optix Plus HydraGlyde showed significantly better performance in alleviating blurred vision, dryness, and tiredness during the day, and provided better end-of-day comfort ($p<0.05$) (Table 4). Regarding Likert-type questionnaire responses, more than 80% of the participants agreed or strongly agreed that both lenses provided excellent visual acuity and handling (Figure 1). Most of the participants (>60%) agreed or strongly agreed that the Air Optix Plus HydraGlyde provided greater comfort and less tiredness, dryness, visual fluctuations, and lens awareness. However, according to the binomial generalized linear mixed model, there was no statistically significant difference between the two lenses (odds ratio: 1.27, 95% confidence interval: 0.64-2.51, p=0.488).

Overall, 79.3% of participants reported they would "definitely wear" or "probably wear" the Air Optix Plus HydraGlyde, while 76% expressed the same preference for the Air Optix Aqua.

Discussion

In this study, the Air Optix Plus HydraGlyde CL with advanced surface moisturizing technology was statistically significantly superior to the Air Optix Aqua CL in terms of end-of-day and end-of-month comfort and lower frequency of tiredness, dryness, and blurred vision, which are the common symptoms of CL discomfort. In addition to subjective outcomes, TBUT was significantly longer, and tarsal papillary grade was significantly lower with the Air Optix Plus HydraGlyde lens compared to the Air Optix Aqua. Outcomes of this preliminary study indicate that the incorporation of surface modifications to improve lubrication or decrease friction over silicone hydrogel CL surfaces does translate to improved patient comfort.

Despite developments in lens designs, material properties, and care regimens, CL discomfort remains a challenge for CL wearers, eye care practitioners, and the industry. Typically, ocular discomfort is minimal or absent immediately after lens insertion but tends to increase as the day progresses.[15,16,17] Management strategies often include rewetting drops, switching to lenses with alternative designs or materials, changing care solutions, altering the replacement schedules, or in more severe cases, prescribing topical medications.[18] Nevertheless, the prevalence of discomfort among CL wearers is as high as 75%, and it is one of the leading causes of CL discontinuation.[6,19]

CL-related factors influencing discomfort include lens material, fit, design, surface characteristics, and care solutions.[20] To date, studies investigating comfort with silicone hydrogel CLs have yielded controversial results,[20] with some studies reporting improved comfort with silicone hydrogel lenses compared to traditional hydrogel lenses[13,15,21,22,23] and others reporting no added benefit.[5,24,25,26] These discrepancies may be due to methodological variations, differences in outcome measures, and/or limited follow-up durations. Moreover, comfort also varies between different silicone hydrogel CL materials, indicating the influence of additional confounding variables. In addition to lens material, other CL-related factors associated with greater comfort include a tighter fit, steeper base curve, lower CL power,

Table 3. Subjective and objective ocular surface measurements

	Air Optix Aqua	Air Optix Plus HydraGlyde	p
CLDEQ-8 score	12.9±6.6	11.6±6.7	0.42
Blink rate (blinks/min)	14.0±4.9	13.2±4.5	0.91
SPK grade	0.15±0.3	0.03±0.1	0.050
TBUT (s)	8.8±2.0	9.4±1.2	0.02
Tarsal papillary grade	0.8±0.6	0.6±0.5	0.003
Schirmer I test (mm)	25.2±8.1	23.8±6.5	0.42

Values are presented as mean ± standard deviation. p: Independent samples t-test or Mann-Whitney U test
CLDEQ-8: Contact Lens Dry Eye Questionnaire, SPK: Superficial punctate keratitis, TBUT: Tear break-up time

Table 4. Comparison of participants' subjective scores on the questionnaire

	Air Optix Aqua	Air Optix Plus HydraGlyde	p
Initial visual clarity	8.3±1.2	8.6±1.4	0.18
Day-long visual clarity	8.3±1.2	8.4±1.3	0.19
End-of-day visual clarity	7.6±1.7	8.0±1.5	0.16
Initial comfort	8.2±1.6	8.3±1.5	0.14
Day-long comfort	8.0±1.5	8.2±1.2	0.42
End-of-day comfort	7.0±2.3	7.7±1.7	**0.02**
Blurred vision	7.4±2.1	8.1±2.1	**0.03**
Fluctuation in vision	8.1±1.6	8.2±1.6	0.59
End-of-day dryness	7.3±2.5	7.9±2.1	**0.04**
End-of-day tiredness	7.1±2.1	7.8±2.3	**0.04**
Lens awareness	8.1±1.9	8.6±1.6	0.09
Lens handling	8.4±1.7	8.7±1.5	0.25

Values are presented as mean ± standard deviation. p: Independent samples t-test or Mann-Whitney U test

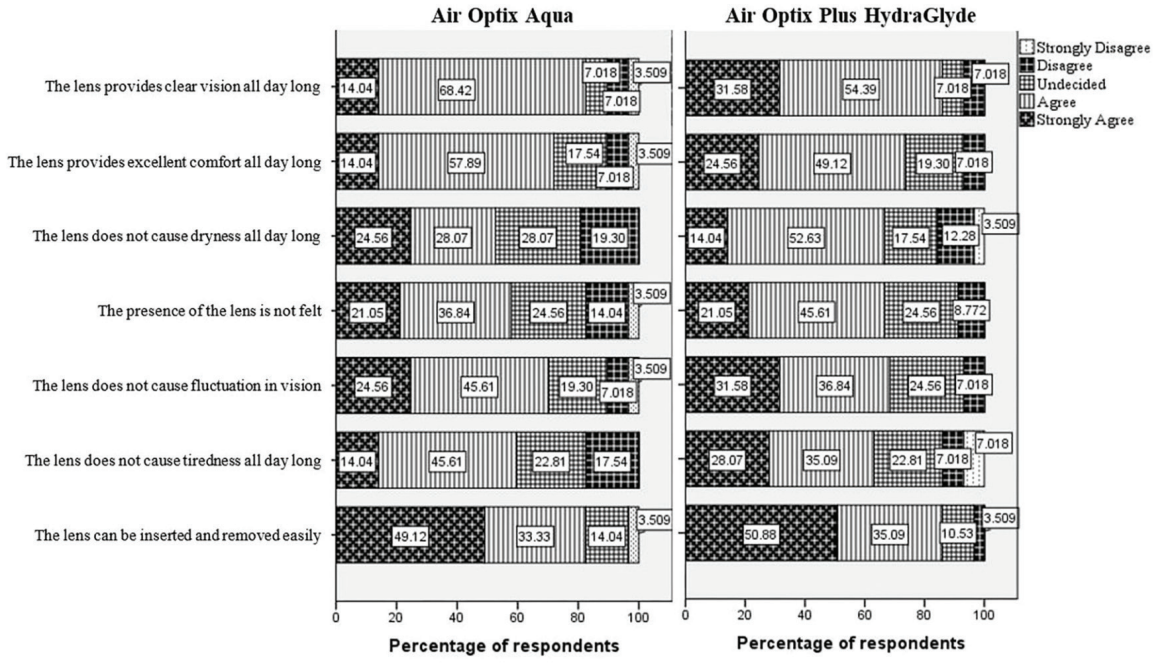

Figure 1. Likert-type responses regarding vision and comfort for the Air Optix Aqua and Air Optix Plus HydraGlyde contact lenses

knife-edge design, as well as a smooth and wettable lens surface with minimal deposits.[20]

In the present study, both types of lenses were covered with SmartShield® technology, a consistent protective plasma layer covering the outer surface of the lens which improves smoothness, wettability, and resistance to deposits.[27] Air Optix Plus HydraGlyde lenses also incorporate an additional surface modification, the HydraGlyde® Moisture Matrix. This technology utilizes a block copolymer (polyoxyethylene-polyoxybutylene, EOBO) that integrates into the lens surface, creating a long-lasting moisture envelope around the lens.[28,29] The EOBO moisture matrix acts as a surfactant that helps reduce frictional forces on the CL by maintaining extra hydration throughout the day, emphasizing the role of surface treatments in enhancing wearer comfort.[29,30] Recently, a prospective, contralateral eye study conducted with 30 novice CL users compared two CLs with different materials and surface treatments: the Bausch&Lomb ULTRA (samfilcon A with MoistureSeal® technology, Bausch&Lomb Inc., Rochester, NY, USA) and Air Optix Plus HydraGlyde (lotrafilcon B with HydraGlyde® Moisture Matrix and SmartShield® technology, Alcon, Fort Worth, TX, USA).[31] The authors reported good compliance with both lenses and similar CLDEQ-8 scores (5.1 and 6.8, respectively), which highlights the importance of surface treatment in providing patient comfort. However, despite their shared emphasis on surface treatment technologies, these lenses differ in other critical parameters that may influence comfort levels, such as water content, oxygen transmission, lens thickness, and design.[31] Another study seeking to eliminate these differences used a randomized cross-over design with 19 habitual CL wearers to evaluate the impact of an ultrathin surface coating on the comfort and wettability of a standard silicone hydrogel CL.[32] The patients wore formofilcon B monthly disposable soft CLs with and without a surface-modifying coating (Bettervision Pty, Keller, TX, USA) for one month each. The coated lenses provided superior subjective lens comfort, improved perceived visual quality, and reduced CL-related dry eye symptoms, as assessed by CLDEQ-8. The authors concluded that changing the physical properties (lubricity) of the surface of a soft CL positively impacts subjectively rated comfort.[32] Similarly, the present study compared two commercially available CLs from the same manufacturer, both made from identical bulk material, with the same water content, design, oxygen transmissibility, and modulus. The only variable between the two lenses was the addition of the surface moisturizing technology in the Air Optix Plus HydraGlyde lens. The results of this study support the findings of aforementioned study, with statistically significant improvements in end-of-day comfort ratings, as well as other subjective parameters such as blurred vision, end-of-day dryness, and end-of-day tiredness. Although CLDEQ-8 scores were also better

with the Air Optix Plus HydraGlyde lenses compared to their predecessor, the difference did not reach statistical significance in this study.

Enhanced surface wettability through surface modifications (coatings or moisturizing agents) is expected to decrease frictional forces over the CL and thereby improve wearer comfort.[8] Today, improved comfort is particularly important for CL wearers due to the increased daily exposure to digital platforms such as computers, tablets, and smartphones. Digital device use is associated with decreased blink rate and increased percentage of incomplete blinks, which lead to adverse ocular sensations and reductions in TBUT, mucin expression, and Schirmer scores—a.k.a., "digital eye strain" (DES) or "computer vision syndrome".[33,34,35] Studies have demonstrated that CL wearers using video display terminals for more than 4-6 hours per day are more likely to suffer from DES compared to non-wearers.[36,37,38] In a prospective comparative study conducted with 232 intensive digital device users with myopia, Uçakhan et al.[39] evaluated a samfilcon A lens with surface treatment (Bausch&Lomb ULTRA, MoistureSeal® Technology, Bausch&Lomb Inc., Rochester, NY, USA) compared to a senofilcon A lens (Acuvue Oasys, HydraClear® Plus, Vistakon, Jacksonville, FL, USA) and lotrafilcon B lens (Air Optix Aqua, SmartShield® Technology, Alcon, Fort Worth, TX, USA). The authors reported high overall ratings from both patients and clinicians for samfilcon A lenses. Among habitual wearers of lotrafilcon B or senofilcon A lenses, samfilcon A was rated significantly higher for comfort and visual performance than their habitual CLs.[39] In the present study, both lotrafilcon B lenses provided high levels of comfort, with Air Optix HydraGlyde outperforming Air Optix Aqua. These differing outcomes may be attributed to variations in study design and differences in daily screen time exposure. The mean duration of digital device use was not mentioned in the previous study. However, in the current study, participants reported a mean usage of 5 hours per day, during which the Air Optix Aqua still yielded satisfactory performance. Still, DES remains a challenge for the CL industry, highlighting the need to meet increased patient requirements and provide better CL material and surface technologies to overcome end-of-day comfort issues.

The effect of lens care solutions on ocular signs and symptoms has been previously evaluated in the literature.[20] Vidal-Rohr et al.[32] observed a low incidence of bulbar and limbal redness regardless of whether the lenses were coated or uncoated. They attributed the lack of a difference to the use of hydrogen peroxide disinfection systems, arguing that this might have masked any possible consequence of the frictional forces between the lens surface and lid margin.[32] In the present study, all participants used Polyquad/Aldox-preserved OptiFree Express, yet similarly low rates of objective signs were observed with both lens types. Even ocular surface staining, which is commonly cited as a frequent CL-related adverse event,[40] was minimal with both lens types in this study, despite previous findings that it occurs least often with peroxide-based care systems.[41]

Study Limitations

This study has some limitations. Firstly, the small sample size and limited follow-up duration reduce the generalizability of our results. Secondly, the absence of a wash-out period between lens switches could influence clinical outcomes by allowing residual effects from the first lens to carry over, potentially confounding the results. However, our study design was consistent with the existing literature, where similar crossover designs have been employed without the inclusion of a wash-out period between different lens types.[42,43,44] Additionally, our study employed randomization of lens wear sequence to minimize systematic bias. This random allocation ensures that any potential residual effects are evenly distributed across the study groups, thereby reducing the risk of confounding. Lastly, using different questionnaires to assess CL comfort might lead to confusion and redundancy. However, this approach allowed participants to more fully express their perceived comfort and symptom burden in a way that a single questionnaire may not have captured as effectively. Besides, based on our previous clinical experience, certain questions within each questionnaire were particularly effective to assess CL comfort. Rather than fragmenting the questionnaires, we opted to administer them together in a unified format.

Conclusion

In conclusion, the incorporation of a surfactant-based surface technology to enhance wettability and lubricity led to improved comfort scores in this study. Therefore, the efforts made by the CL industry to improve silicone hydrogel CL material, design, and surface characteristics may help alleviate CL discomfort and reduce discontinuation rates. However, larger-scale, longitudinal studies are necessary to confirm the long-term benefits of surface modifications on CL tolerance and dropout.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Ankara University Faculty of Medicine Clinical Research Ethics Committee (number: 07-362-17; date: 10 April 2017) and was conducted according to the tenets of the Declaration of Helsinki.

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

Declarations

Authorship Contributions

Surgical and Medical Practices: M.A.E., Ö.Ö.U-G., Concept: M.A.E., Ö.Ö.U-G., Design: M.A.E., Ö.Ö.U-G., Data Collection or Processing: M.A.E., T.Ç.B., Analysis or Interpretation: M.A.E., T.Ç.B., Literature Search: T.Ç.B., Writing: M.A.E., T.Ç.B., Ö.Ö.U-G.

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

Financial Disclosure: This study was supported in part by a grant from Ankara University.

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Original Article

Long-Term Intravitreal Dexamethasone Implant Monotherapy in Naïve Patients with Diabetic Macular Edema

Gamze Karataş[1], Akın Çakır[1], Öznur Aday[1], Tahsin Uzundede[1], Furkan Kırık[2], Ahmet Melih Özoğuz[1], Hakan Özdemir[2], Mustafa Nuri Elçioğlu[1]

[1]University of Health Sciences Türkiye, İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
[2]Bezmialem Vakıf University Faculty of Medicine, Department of Ophthalmology, İstanbul, Türkiye

Abstract

Objectives: To demonstrate the efficacy and safety of repeated dexamethasone (DEX) implants in eyes with naïve diabetic macular edema (DME) using real-life data over a minimum of 36 months follow-up.

Materials and Methods: This retrospective cohort study included treatment-naïve DME patients treated with intravitreal DEX monotherapy and followed for at least 36 months. Main outcomes were best corrected visual acuity (BCVA) and central macular thickness (CMT) change. Secondary outcomes were optical coherence tomography findings, including serous macular detachment, hard exudate, hyperreflective foci, cystoid degeneration, pearl necklace sign, epiretinal membrane (ERM), disorganization of the retinal inner layers (DRIL), ellipsoid zone and external limiting membrane (EZ-ELM) integrity, and intra-cystic hyperreflective material, as well as intraocular pressures and lens status.

Results: The study included 74 eyes of 52 patients. The mean follow-up period and number of injections were 49.24±13.51 months and 6.83±2.76, respectively. Both BCVA and CMT improved significantly throughout follow-up (p=0.009; p<0.001). The mean BCVA increased by 7.9±2.1 letters, and 38 patients (51.3%) gained ≥10 letters. Hyperreflective foci (p<0.001), pearl necklace sign (p=0.012), and intra-cystic hyperreflective material (p=0.042) decreased significantly, while ERM (p=0.006), DRIL (p<0.001), and EZ-ELM defects (p<0.001) increased significantly.

Conclusion: Intravitreal DEX monotherapy is a safe and effective treatment option for treatment-naïve DME patients in long-term follow-up.

Keywords: Dexamethasone, diabetic macular edema, diabetic retinopathy, steroid

Cite this article as: Karataş G, Çakır A, Aday Ö, Uzundede T, Kırık F, Özoğuz AM, Özdemir H, Elçioğlu MN. Long-Term Intravitreal Dexamethasone Implant Monotherapy in Naïve Patients with Diabetic Macular Edema.
Turk J Ophthalmol. 2026;56:24-30

Address for Correspondence: Gamze Karataş, University of Health Sciences Türkiye, İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
E-mail: madengamze14@gmail.com
ORCID-ID: orcid.org/0000-0003-4125-4819

Received: 29.08.2025
Revision Requested: 20.10.2025
Last Revision Received: 24.10.2025
Accepted: 06.12.2025
Publication Date: 18.02.2026

DOI: 10.4274/tjo.galenos.2025.77246

Introduction

Diabetic retinopathy (DRP) is one of the most prevalent microvascular complications of diabetes mellitus, and diabetic macular edema (DME) represents the leading cause of visual impairment in affected individuals.[1,2] Although substantial evidence has demonstrated the efficacy of anti-vascular endothelial growth factor (VEGF) therapy in the management of DME,[3,4] both inflammation and VEGF play key roles in DME pathogenesis.[5] Current guidelines state that anti-VEGF injections are the first-choice treatment of DME.[6,7] However, according to the EURORETINA guidelines, steroids may be a preferable first-line therapy in patients with a history of major cardiovascular events and those who do not want to travel for monthly injections (and/or monitoring) within the first 6 months of treatment.[6] The risk of cataract and glaucoma as side effects is the main reason steroids are the second choice. According to the MEAD study on the dexamethasone (DEX) implant, increases in intraocular pressure (IOP) were usually controlled with medical therapy or observation, and glaucoma surgery was necessary in only

two patients, corresponding to 0.6% of those in the 0.7-mg implant group.[8] Cataracts have also become relatively easy to manage owing to improvement of surgical instruments.

In the Protocol T study, approximately 30-40% of patients had intraretinal and/or subretinal fluid despite anti-VEGF therapy, illustrating the importance of combination therapy.[9]

There are a few case series of DME treated with only DEX implants in the literature, but they had a maximum follow-up of two years and included both resistant and naïve patients, with relatively small treatment-naïve groups.[10,11,12] Because the visual gains of non-naïve cases are lower than those of naïve cases due to chronicity, larger naïve samples are essential. Moreover, longitudinal studies are needed because the long-term side effects of intravitreal steroids remain unclear. Several multicenter studies have been conducted to evaluate anatomical and functional success with DEX implants in DME using current ancillary testing.[13,14] However, comparing results by different researchers using different devices and optical coherence tomography (OCT) modalities may lead to misinterpretations.

This study aimed to evaluate the long-term efficacy of repeated DEX implant monotherapy in treatment-naïve eyes with DME, utilizing real-world data from up to six years of follow-up.

Materials and Methods

This retrospective cohort study was performed in accordance with the ethical principles of the Declaration of Helsinki. Approval was granted by the Institutional Review Board of University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital (approval ID: 02.05.2023/3905), and all individuals provided written informed consent prior to participation.

The medical records of 1042 consecutive DME patients treated with intravitreal DEX implants in the retina department of the University of Health Sciences Türkiye, Prof. Dr. Cemil Taşcıoğlu City Hospital since 2015, when DEX implants were approved in Türkiye, were reviewed. Of these,143 were treatment-naïve at baseline, and 52 patients had at least 36 months' follow-up. For patients who received bilateral intravitreal DEX implants, both eyes were included. The final cohort comprised 74 eyes of 52 patients with DME who met these criteria.

Patients with prior grid laser or intravitreal anti-VEGF therapy were excluded. Additional exclusion criteria were vitreomacular adhesion or traction, glaucoma, retinal vascular occlusion, tractional detachment, complicated cataract surgery, ocular trauma, poor-quality OCT images, and incomplete medical documentation or consent.

Each follow-up visit included assessment of best-corrected visual acuity (BCVA), anterior segment biomicroscopy, IOP measurement with a Goldmann applanation tonometer, indirect ophthalmoscopy, and spectral-domain OCT (SD-OCT). Baseline and follow-up data also included a history of cerebrovascular or cardiovascular events and other comorbidities. Any initiation of anti-glaucoma therapy or performance of trabeculectomy during follow-up was documented. Additionally, the total follow-up duration (in months) and the cumulative number of DEX implant injections were recorded.

All patients were managed using a pro re nata (PRN) regimen. Patients were generally reassessed at intervals of approximately 45-60 days under this protocol. Criteria for retreatment included the presence of intraretinal or subretinal fluid with a central macular thickness (CMT) exceeding 300 μm, residual intra- or subretinal fluid, or a decrease in BCVA of more than 5 letters on the Early Treatment Diabetic Retinopathy Study scale, provided there was no cataract progression. Eyes with visually significant cataract development underwent surgical removal.

Patients with epiretinal membrane (ERM) causing tangential traction were included in the study, although none underwent ERM surgery. Eyes with vitreomacular interface abnormalities causing anteroposterior traction were excluded. At each follow-up visit, SD-OCT imaging was performed using the Spectralis system (Heidelberg Engineering, Heidelberg, Germany), which automatically provided CMT measurements for quantitative assessment of DME. CMT values were documented at baseline and all subsequent visits. Two independent investigators blinded to the clinical data (G.K. and A.Ç.) evaluated OCT biomarkers at baseline and the final visit. Assessed features included serous macular detachment (SMD), hard exudates, hyperreflective foci (HRF), cystoid degeneration, pearl necklace sign, ERM, disorganization of the retinal inner layers (DRIL), integrity of the ellipsoid zone and external limiting membrane (EZ-ELM), and intra-cystic hyperreflective material.

Cystoid degeneration was defined as cystoid spaces with a horizontal diameter of 600 μm or greater. SMD was considered present if the posterior retinal surface was raised above a hyporeflective cavity. EZ and ELM integrity were analyzed together; eyes showing continuous EZ-ELM within 1 mm of the foveal center were classified as intact, while any disruption was noted as a defect.[14] HRF were quantified in three ranges (1-10, 11-20, ≥21).[15] When HRF were arranged along the inner wall of cystoid cavities in a ring-like pattern, this was termed the pearl necklace sign.[16] DRIL was defined as the inability to clearly delineate the boundaries between the ganglion cell layer, inner plexiform layer, inner nuclear layer, and outer plexiform

layer.[17] Hyperreflective material present within cystoid spaces, without shadowing and distinct from HRF or hard exudates, was classified as intra-cystic hyperreflective material.[18]

The primary outcomes assessed were changes in visual acuity and anatomical parameters over the course of follow-up. Secondary outcomes included the percentage of eyes showing a change of 10 letters or more in BCVA, the evolution of OCT biomarkers and their influence on treatment efficacy, as well as the rates of cataract surgery and interventions for IOP control during the study period.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS software version 21.0. The distribution of variables was assessed both visually (histograms) and analytically using the Kolmogorov-Smirnov test. For normally distributed variables, descriptive statistics were reported as mean ± standard deviation. Comparisons between baseline and final measurements were performed using the paired Student's t-test or the Wilcoxon signed-rank test, as appropriate. Categorical variables were compared using either the chi-square test or Fisher's exact test. Correlation coefficients were calculated using Spearman's or Pearson's tests. A multiple linear regression analysis was employed to determine independent predictors of BCVA and CMT, with model fit evaluated through residual analysis and goodness-of-fit statistics. A p value less than 0.05 was considered statistically significant.

Results

A total of 74 eyes of 52 naïve patients (23 female [44.2%] and 29 male [55.8%]) treated with repeated intravitreal DEX implants and followed for at least 3 years were included. The mean age, follow-up period, and number of injections were 68.16±9.06 years, 49.24±13.51 months (median: 45, interquartile range [IQR]: 21), and 6.83±2.76, respectively. The annual mean number of injections in years 1-6 was 2.47±0.57, 2.16±0.70, 1.35±0.95, 0.82±0.84, 0.62±0.77, and 0.50±0.65, respectively (Figure 1).

The minimum and maximum follow-up times were 36 and 80 months, respectively. Thirty-four of the 74 eyes were followed up for ≥4 years, and 11 were followed up for ≥6 years. Thirteen patients (17.5%) were followed up for a mean of 28.8±21.9 months without treatment. The mean initial HbA1c value was 8.2±1.4%, and 26 (50%) patients had a diagnosis of systemic hypertension.

Mean BCVA improved significantly between baseline (0.81±0.50 logarithm of the minimum angle of resolution [logMAR] [20/125]; median: 0.7, IQR: 0.6) and the final visit (0.65±0.54 logMAR [20/80]; median: 0.6, IQR: 0.83; p=0.009). The mean change in BCVA was +7.9±2.1 letters (median: 10, IQR: 26.25), which was significant (p=0.009), and 38 patients (51.3%) gained ≥10 letters.

The change from mean baseline to final CMT was 540.05±161.27 µm to 351.78±123.49 µm, respectively, which was significant (p<0.001). Cystoid degeneration was present in 20 eyes (27%) at baseline, which was reduced to 9/20 (45%) at last follow-up.

The mean baseline and final IOP was 14.40±2.50 mmHg and 15.48±3.36 mmHg, respectively (p=0.009). Sixty-two (83.8%), 7, 4, and 1 eyes were followed up with no, one, two, and three anti-glaucomatous agents, respectively. None of the patients underwent glaucoma surgery.

There were 41 phakic eyes at baseline, 40 (97%) of which underwent phacoemulsification surgery during the follow-up period (p<0.001).

Thirty-nine eyes (52.7%) had prior panretinal photocoagulation (PRP) at baseline. During follow-up, PRP was performed in another 9 eyes (25.7%) (p=0.012).

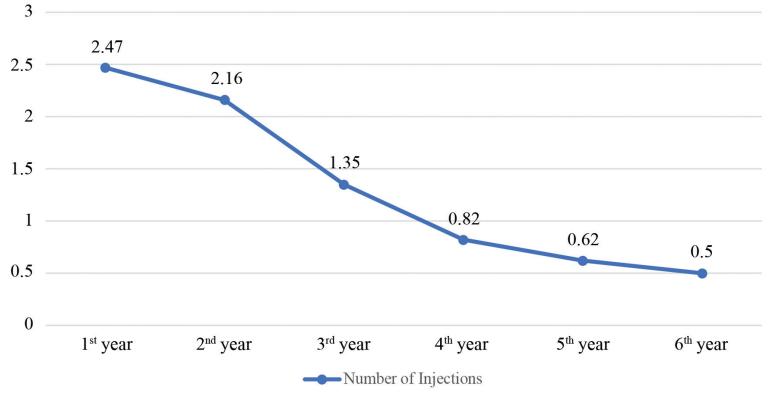

Figure 1. Number of dexamethasone implant injections per year

In those cases specifically, the mean follow-up time and injection number were 59.1±18.7 and 7.3±1.9, respectively.

Eight eyes (10.8%) were vitrectomized at baseline and 3 eyes (4.5%) underwent vitrectomy because of newly developed vitreous hemorrhage secondary to proliferative DRP during follow-up (p=0.508).

At baseline, 9 patients (17.3%) had experienced cerebrovascular or cardiovascular events within the preceding 6 months. During the treatment and follow-up periods, no new cerebrovascular or cardiovascular events were observed in any patient.

There were 27 eyes (36.5%) with SMD at baseline. At the end of follow-up, no SMD was observed in any patient (p<0.001). Initially, 52 eyes had hard exudates, which completely disappeared in 8 (15.3%) of them. However, new hard exudate formation was observed in 5 of the 22 eyes initially free of hard exudate. HRF at final follow-up was significantly decreased compared to baseline (p<0.001). From baseline to last follow-up, the prevalence of pearl necklace sign decreased from 21 eyes (28.4%) to 8 eyes (10.8%) (p=0.012), whereas the presence of ERM increased from 54 eyes (73%) to 64 eyes (86.5%) (p=0.006) and DRIL increased from 29 eyes (39.2%) to 43 eyes (58.1%) (p<0.001).

Additionally, the number of eyes with disrupted EZ-ELM increased from 14 eyes (18.9%) to 35 eyes (47.3%) (p<0.001) while intra-cystic hyperreflective material decreased from 19 eyes (25.6%) to 8 eyes (10.8%) (p=0.042) from baseline to final follow-up. The participants' baseline and final clinical characteristics are summarized in Table 1.

Multiple linear regression analysis showed a significant negative correlation between BCVA improvement and baseline BCVA in logMAR units (B=-0.524, p<0.001), the presence of EZ-ELM defects (B=-16.1 p=0.015), and the presence of HRF (B=-8.32 p=0.040). CMT improvement was positively correlated with baseline CMT (B=0.560, p<0.001), and final CMT was positively correlated with baseline CMT (B=231.5, p=0.014).

Discussion

This retrospective cohort study evaluated treatment-naïve DME patients who received intravitreal DEX implants, representing the longest single-center follow-up reported in the literature to date (36-80 months). Intravitreal DEX implant therapy alone was associated with both functional and anatomical improvements in these patients over long-term follow-up. Additionally, the study included the largest cohort of treatment-naïve eyes currently described in the literature (74 eyes). Only 9 patients (17.3%) had a prior history of cerebrovascular or cardiovascular events; therefore, intravitreal DEX implant therapy was administered to the remaining patients based on the clinician's decision.

An Australian prospective multicenter study included 200 patients from 25 ophthalmology clinics, of whom 57 (28.5%) were treatment-naïve and 41 (71.9% of 57) completed the study.[10] The IRGREL-DEX study was a retrospective, 10-center study of 71 naïve DME eyes followed up for 24 months using 4 different OCT devices (Cirrus, Spectralis, Topcon, and Optovue).[11] In contrast, the single-center and single-device nature of our study ensures standardization of results.

In the MEAD study, non-naïve patients received an average of 5 intravitreal DEX implants over 3 years.[8] In the IRGREL-DEX study, the mean number of intravitreal DEX implants was 3.5±1.0 over 24 months.[11] Adjusting for the difference in follow-up times, the number of injections in our study is consistent with these studies.

Considering that 97% of our patients underwent cataract surgery during the study period, lens status did not affect the increase in vision. Our results are in line with other studies reporting that intravitreal DEX implants provided significant long-term improvement in visual acuity in patients with naïve DME. In the IRGREL-DEX study, the BCVA gain at 24 months was 11.3±10.0 letters.[11] Kodjikian et al.[19] reported that the best response in patients with DME unresponsive to anti-VEGF treatment was in the early switch group. This supports the idea that there may be better visual improvement in cases where the retinal architecture is not impaired, such as in naïve patients. Similarly, Akıncıoğlu et al.[20] reported favorable anatomical and functional outcomes of intravitreal DEX implant therapy in patients with recalcitrant DME in a Turkish real-world setting, supporting the broader efficacy of DEX implants across different DME subgroups.

Numerous studies of DEX implants reported high IOP, which in most cases was controlled with antiglaucoma medication and rarely required surgical treatment.[8,10,11,12,21] Although we found a significant increase in IOP, only a few patients required antiglaucoma treatment, and none required surgery. If these patients had previously had glaucoma, an increase of approximately 1 mmHg would have led to a deviation from the target IOP.[22] However, this increase is not clinically significant because the patients did not have glaucoma.

Phacoemulsification surgery was performed in 40/41 (97%) eyes during the follow-up period. The IRGREL-DEX study reported that 15 of 16 phakic eyes in the treatment-

Table 1. Baseline and final clinical characteristics of patients			
	Baseline	**Final**	**p**
Age, years	68.16±9.06	-	
HbA1c, %	8.2±1.4	-	
Duration of DM, years	-	16.8±8.4	
Follow-up time, months	-	49.24±13.51	
Total DEX implants	-	6.83±2.76	
BCVA, logMAR, mean ± SD	0.81±0.50	0.65±0.54	**0.009**
CMT, µm, mean ± SD	540.05±161.27	351.78±123.49	**<0.001**
IOP, mmHg, mean ± SD	14.40±2.50	15.48±3.36	**0.009**
Lens status (pseudophakia), n (%)	33 (44.5)	73 (98.6)	**<0.001**
PRP, n (%)	39 (52.7)	48 (64.8)	**0.012**
PPV, n (%)	8 (10.8)	11 (14.8)	0.508
CVA/CVE, n (%)	9 (17.3)	9 (17.3)	1
SMD, n (%)	27 (36.4)	0	**<0.001**
Hard exudate, n (%)	52 (70.2)	49 (66.2)	0.268
Pearl necklace sign, n (%)	21 (28.3)	8 (10.8)	**0.012**
HRF, n (%) Grade 1 (1-10) Grade 2 (11-20) Grade 3 (≥21)	 48 (64.9) 13 (17.6) 8 (10.8)	 47 (63.5) 9 (12.2) 1 (1.4)	**<0.001**
ERM, n (%)	54 (72.9)	64 (86.4)	**0.006**
DRIL, n (%)	29 (39.1)	43 (58.1)	**<0.001**
EZ-ELM, n (%)	14 (18.9)	35 (47.2)	**<0.001**
Intra-cystic hyperreflective material, n (%)	19 (25.6)	8 (10.8)	**0.042**

HbA1c: Glycosylated hemoglobin, DM: Diabetes mellitus, DEX: Dexamethasone, BCVA: Best corrected visual acuity, logMAR: Logarithm of the minimum angle of resolution, SD: Standard deviation, CMT: Central macular thickness, IOP: Intraocular pressure, PRP: Panretinal photocoagulation, PPV: Pars plana vitrectomy, CVA/CVE: Cerebrovascular accident/cardiovascular event, SMD: Serous macular detachment, HRF: Hyperreflective foci, ERM: Epiretinal membrane, DRIL: Disorganization of the retinal inner layers, EZ-ELM: Ellipsoid zone-external limiting membrane

naïve DME group underwent cataract surgery by the 24-month follow-up.[11] Cataract formation is a recognized long-term complication of DEX implant therapy and occurs in the majority of patients over time.

At final follow-up, SMD had disappeared in all our patients. The number of HRF and presence of both the pearl necklace sign and intra-cystic hyperreflective material also decreased significantly. In contrast, ERM, DRIL, and EZ-ELM defects increased significantly. Similarly, Horozoglu et al.[23] reported that intravitreal DEX implant therapy provided significant short-term efficacy for SMD and HRF in patients with treatment-resistant DME but noted increases in EZ-ELM defects, ERM, and DRIL at final follow-up. DRIL is commonly observed in patients with proliferative DRP.[24] In contrast to our results, Zur et al.[25] reported that DEX implants could potentially ameliorate DRIL based on their multicenter, retrospective, 12-month study including eyes with DME. In our study, however, DRIL increased with DEX implant monotherapy in naïve DME over much longer follow-up.

We propose that the observed increase in DRIL, EZ–ELM defects, and ERM is driven by a combination of natural disease progression and real-world treatment dynamics. The literature supports an association between EZ-ELM changes and DRP severity.[26,27] Hui et al.[28] also reported a correlation between ERM and DME duration. Since proliferative and severe non-proliferative DRP predominated at baseline in our study, high initial rates of structural alterations are unsurprising. The long follow-up period of this study is also suitable for evaluating DRP progression. However, it is likely that the PRN exacerbated this process. Under a PRN regimen, patients may not always receive retreatment at optimal intervals, resulting in recurrent episodes of macular edema. These cycles of edema and resolution could induce repeated fluctuations

in retinal thickness, thereby contributing to progressive structural alterations over time. As a result of these factors, 13.5% of our naïve DME patients developed ERM, 18.9% developed DRIL, and 28.4% developed EZ-ELM defects over follow-up of 3-6 years. With DEX monotherapy, more successful results may be obtained by opting for a treat-and-extend regimen instead of PRN.

Notably, this anatomical progression did not appear to compromise overall functional gains. The final BCVA was significantly higher than at baseline.

BCVA gain was negatively correlated with baseline BCVA, whereas CMT gain was positively correlated with baseline and final CMT. In other words, patients with lower baseline BCVA had larger BCVA gains, while an increase in CMT was more common in patients with high CMT. However, even with greater increases, the final BCVA and CMT remained lower than those in patients with better baseline values. These results can be explained by the ceiling effect.[29]

A total of 13 eyes (17.5%) in the study cohort were followed without treatment for a mean duration of 28.8±21.9 months, which represents a relatively long observation period. These findings suggest that following DEX implant therapy, patients may require fewer injections over time and treatment can be discontinued in some cases. The resulting reduction in visit frequency and injection burden may substantially decrease the overall treatment load.

No serious ocular/systemic (thromboembolic events) side effects were observed in any patient during the study period.

Study Limitations

The main limitation of this study was its retrospective design. However, real-life studies can be valuable for reflecting real-life data. Our study has the following advantages: its single-center nature, long follow-up time, largest naïve cohort group studied to date, and standardization of data. Notably, as the same OCT device was used in all patients, our results contribute valuable information to the current literature.

Conclusion

In summary, intravitreal DEX monotherapy demonstrates long-term efficacy and acceptable tolerability in the management of treatment-naïve DME patients. Over extended follow-up periods without concomitant anti-VEGF therapy, both the number of injections and the frequency of visits may be reduced. With careful patient selection, DEX monotherapy could serve as a first-line option alongside current standard treatments for DME. Potential complications, such as cataract formation and elevated IOP, are generally manageable with appropriate clinical intervention. Further prospective, randomized studies are warranted to strengthen the evidence base and confirm these findings.

Ethics

Ethics Committee Approval: Approval was granted by the Institutional Review Board of University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital (approval ID: 02.05.2023/3905).

Informed Consent: All individuals provided written informed consent prior to participation.

Declarations

Authorship Contributions

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

Conflict of Interest: Hakan Özdemir, MD, is an Associate Editor of the Turkish Journal of Ophthalmology. He was not involved in the peer review of this article and had no access to information regarding its peer review. The other authors has no disclosures.

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

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Original Article

Intravitreal Anti-Vascular Endothelial Growth Factor Therapy for Diabetic Macular Edema in Türkiye: 48-Month Data, BOSPHORUS-DME Study Group Report No. 1

Ece Özal[1], Abdullah Özkaya[2], Murat Arıcı[3], Anıl Korkmaz[3], Serhat Ermiş[1], Şerife Çiloğlu Hayat[1], Murat Karapapak[1], Sadık Altan Özal[1], Akın Çakır[4], Gamze Karataş[4], Dilan Yıldız[4], Mehmet Erdoğan[5], İbrahim Koçak[5], Nihat Sayın[5], Veysel Levent Karabaş[6], Ecem Önder Tokuç[6], Semra Tiryaki Demir[7], Mehmet Egemen Karataş[7], Turgay Uçak[7], Mine Öztürk[8], Bengi Demirayak[9], İsmail Umut Onur[10], Mustafa Hepokur[11]

[1]University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
[2]Memorial Şişli Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
[3]University of Health Sciences Türkiye, Beyoğlu Eye Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
[4]University of Health Sciences Türkiye, İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
[5]University of Health Sciences Türkiye, Kanuni Sultan Süleyman Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
[6]Kocaeli University Faculty of Medicine, Department of Ophthalmology, Kocaeli, Türkiye
[7]University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
[8]University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
[9]University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
[10]Tekirdağ Namık Kemal University Faculty of Medicine, Department of Ophthalmology, Tekirdağ, Türkiye
[11]İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Ophthalmology, İstanbul, Türkiye

Cite this article as: Özal E, Özkaya A, Arıcı M, Korkmaz A, Ermiş S, Çiloğlu Hayat Ş, Karapapak M, Özal SA, Çakır A, Karataş G, Yıldız D, Erdoğan M, Koçak İ, Sayın N, Karabaş VL, Önder Tokuç E, Tiryaki Demir S, Karataş ME, Uçak T, Öztürk M, Demirayak B, Onur İU, Hepokur M. Intravitreal Anti-Vascular Endothelial Growth Factor Therapy for Diabetic Macular Edema in Türkiye: 48-Month Data, BOSPHORUS-DME Study Group Report No. 1. Turk J Ophthalmol. 2026;56:31-40

Address for Correspondence: Ece Özal, University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
E-mail: ecemansuroglu@hotmail.com
ORCID-ID: orcid.org/0000-0002-4251-9308
Received: 08.08.2025
Revision Requested: 05.10.2025
Last Revision Received: 12.12.2025
Accepted: 02.01.2026
Publication Date: 18.02.2026

DOI: 10.4274/tjo.galenos.2026.67863

Abstract

Objectives: This study aimed to evaluate the 48-month visual and anatomical outcomes, as well as the number of clinic visits and intravitreal injections, in patients treated with three consecutive loading doses of intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy for diabetic macular edema (DME) under real-world conditions in Türkiye.

Materials and Methods: In this retrospective, multicenter study conducted by the BOSPHORUS-DME Study Group, the medical records of 2,424 eyes of 1,696 patients who experienced vision loss due to DME and were treated with intravitreal anti-VEGF injections between January 2019 and January 2023 were reviewed. The study was carried out across eight tertiary referral hospitals located on the European side of İstanbul and in the province of Kocaeli. Seven cohort groups were created based on follow-up at baseline and months 3, 6, 12, 18, 24, 36, and 48. Best-corrected visual acuity (BCVA), central macular thickness (CMT), the number of clinic visits and injections, and the rates of anti-VEGF or dexamethasone switching were analyzed.

Results: The study included a total of 2,424 eyes of 1,696 patients (mean age: 60.6±10.0 years; 46.4% female). The mean baseline BCVA and CMT were 0.34±0.24 (decimal) and 400±134 μm, respectively. At month 48, these values improved to 0.49±0.29 ($p<0.0001$) and 324±115 μm ($p<0.0001$). The mean cumulative number of injections at years 1,

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2, 3, and 4 were 6.5, 9.6, 12.2, and 15.7, respectively. A switch in anti-VEGF therapy occurred between month 3 and 6 in 43.5% of eyes, mostly due to mandatory transition to on-label agents.

Conclusion: This is the largest and longest real-world study on DME treatment conducted in Türkiye. It demonstrates that visual and anatomical gains can be sustained over a 48-month period. While the overall trend aligns with previous real-world studies, the higher injection frequency in our cohort appears to have contributed to more favorable outcomes. These findings underscore the importance of early intensive therapy and sustained treatment adherence in the real-world management of DME.

Keywords: Aflibercept, anti-VEGF, bevacizumab, diabetic macular edema, intravitreal injection, long-term outcomes, ranibizumab, real-world evidence

Introduction

Diabetic macular edema (DME) is a vision-threatening complication of diabetes and remains one of the leading causes of preventable blindness in the working-age population.[1] The efficacy and safety of anti-vascular endothelial growth factor (anti-VEGF) agents in the treatment of DME have been well established through randomized controlled trials (RCTs),[2,3] and these agents are recommended as first-line therapy in clinical guidelines.[4] The Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T study compared the efficacy of intravitreal ranibizumab (Lucentis®, Novartis, Genentech, South San Francisco, CA, USA), aflibercept (Eylea®, Regeneron Pharmaceuticals, Tarrytown, NY, USA), and bevacizumab (Avastin®, Genentech, Roche Group, South San Francisco, CA, USA) for the treatment of DME. When administered according to a structured protocol, all three agents demonstrated comparable visual gains at two years (+12.3, +12.8, and +10.0 ETDRS letters for ranibizumab, aflibercept, and bevacizumab, respectively).[5] However, a five-year extension of the study showed that when patients transitioned to physician-discretion-based treatment in routine clinical practice, best-corrected visual acuity (BCVA) declined between years two and five despite ongoing care.[6]

In recent years, real-world studies derived from diverse clinical settings have gained increasing significance, particularly for chronic diseases like DME that require individualized treatment approaches.[7] However, outcomes in real-world studies often fall short of RCT results due to undertreatment, infrequent monitoring, and suboptimal patient adherence.[8,9,10]

Durukan et al.[11] reported the first large-scale real-world study on DME treatment conducted in the Central Anatolia region of Türkiye, demonstrating lower injection frequencies and modest visual improvements consistent with previous real-world findings. Similarly, Yayla et al.[12] conducted the MARMASIA Study across eight tertiary referral centers on the Asian side of the Marmara region and reported comparable outcomes. Although both studies provided valuable data, they reflected treatment practices prior to 2018 and included follow-up results of up to 36 months.

Building on this foundation, we initiated a multicenter study across eight tertiary referral centers located on the European side of Istanbul and in the Kocaeli province of Türkiye to comprehensively evaluate the real-world outcomes of intravitreal anti-VEGF therapy for DME. The BOSPHORUS-DME study represents the post-2018 treatment era following the reimbursement policy implemented by the Turkish Social Security Institution, which mandated three consecutive loading doses of bevacizumab as the initial therapy and expanded access to on-label anti-VEGF agents.[13] With follow-up data extending up to 48 months, this large and contemporary multicenter cohort provides the most comprehensive assessment to date of visual and anatomical outcomes, injection burden, and patient adherence under real-world clinical conditions in Türkiye. Given the absence of a centralized national ophthalmology database, such multicenter collaborations are crucial for generating reliable real-world data that accurately reflect nationwide clinical practices and long-term treatment outcomes.

Materials and Methods

Study Design

This retrospective, observational, multicenter study included patients with DME who received three consecutive monthly intravitreal anti-VEGF injections between January 2019 and January 2023, with at least three months of follow-up. The BOSPHORUS-DME Study Group comprised 23 retina specialists from eight tertiary centers on the European side of Istanbul and in Kocaeli, Türkiye. Ethics approval was obtained from Kocaeli University Faculty of Medicine Ethics Committee (decision no: KÜ GOKAEK-2025/06/18; date: 13.03.2025; project: 2025/115). The study adhered to the Declaration of Helsinki, and written informed consent was obtained from all participants.

Study Population

The medical records of patients diagnosed with DME, either treatment-naïve or previously treated with intravitreal anti-VEGF injections, were retrospectively reviewed. Patients who had not received any intravitreal injections for DME within the six months prior to inclusion were considered treatment-naïve.

Following the reimbursement regulation issued by the Turkish Social Security Institution on December 28, 2018 (published in the Official Gazette), patients initiating anti-VEGF therapy for DME were required to receive three consecutive intravitreal bevacizumab (IVB) injections as a prerequisite for reimbursement.[13] According to this regulation, alternative anti-VEGF agents (ranibizumab or aflibercept) were permitted only in cases demonstrating non-response or resistance to IVB. Therefore, eyes that had begun treatment prior to this regulation were excluded from the study.

In treatment-naïve eyes, three consecutive monthly IVB (1.25 mg/0.05 mL) injections were administered as the initial loading phase, followed by a pro re nata (PRN) treatment regimen based on anatomical and functional response. In eyes that had received three loading doses of IVB at other centers within the preceding six months, an additional loading phase was performed at the discretion of the treating physician, consisting of three consecutive monthly injections of either IVB or an on-label anti-VEGF agent (ranibizumab 0.5 mg/0.05 mL or aflibercept 2 mg/0.05 mL). Following completion of this loading phase, patients transitioned to PRN therapy and continued to receive additional anti-VEGF injections or adjunctive treatments as clinically indicated throughout the follow-up period. Thus, all eyes included in the study completed a full loading course of three consecutive injections before entering the PRN phase at our centers.

The inclusion criteria were as follows: (1) age ≥18 years, (2) receiving three consecutive loading doses of intravitreal anti-VEGF injections as the initial treatment for DME, and (3) having a minimum follow-up period of three months after the injections. Patients with a history of vitreoretinal surgery or secondary macular edema resulting from other retinal or systemic diseases were excluded from the study. No restrictions were imposed regarding additional procedures performed during follow-up, which could include phacoemulsification, pars plana vitrectomy, panretinal, focal, or grid laser photocoagulation, micropulse laser treatment, or intravitreal dexamethasone implant (IDI; Ozurdex®, AbbVie-Allergan, CA, USA) administration. In cases where both eyes met the inclusion criteria, each eye was analyzed separately.

Data Collection

Medical data were retrospectively collected at baseline and during each follow-up visit up to month 48. Baseline demographic and clinical characteristics included age, sex, stage of diabetic retinopathy (non-proliferative [NPDR] or proliferative [PDR]), and, when applicable, details of intravitreal injections administered within the preceding six months, including the type of agent and the number of injections.

The patients' eyes were divided into seven cohorts according to follow-up duration. Follow-up data were extracted from examinations conducted at months 3, 6, 12, 18, 24, 36, and 48, allowing for a ±2-week window. Because patients with longer follow-up durations also contributed to earlier time points, the cohorts were not independent.

All patients underwent a comprehensive ophthalmologic examination at baseline and during each follow-up visit. The examinations included BCVA assessment using a Snellen chart, intraocular pressure (IOP) measurement with Goldmann applanation tonometry, anterior segment evaluation with slit-lamp biomicroscopy, dilated fundus examination, and optical coherence tomography (OCT) imaging. OCT scans were obtained using one of the following devices, depending on the center: Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany), Cirrus OCT (Zeiss, Dublin, CA, USA), RTVue-100 OCT (Optovue Inc., Fremont, CA, USA), DRI OCT Triton Plus swept-source OCT (Topcon Inc., Tokyo, Japan), or Xephilio WF-OCT S1 (Canon Inc., Tokyo, Japan).

At each visit, BCVA, lens status (phakic or pseudophakic), and OCT parameters were recorded, along with the type of intravitreal agent administered, cumulative number of injections and visits, and the presence of ocular adverse events associated with injection therapy or other procedure-related complications.

All OCT images were centered on the foveola, and central macular thickness (CMT, μm) was automatically calculated using the software of each device. OCT features were classified according to the criteria of the European School for Advanced Studies in Ophthalmology, as follows:[14]

1. Cystic changes: absent (0), mild (1), moderate (2), severe (3);
2. Subretinal fluid: absent (0), present (1);
3. Disorganization of retinal inner layers (DRIL): absent (0), present (1);
4. Integrity of the ellipsoid zone (EZ) and external limiting membrane: intact (0), disrupted (1), absent (2);
5. Hyperreflective foci: <30 (0), ≥30 (1);

6. Vitreoretinal interface: no pathology (0), incomplete posterior vitreous detachment (PVD) (1), complete PVD (2), vitreomacular traction (3), or epiretinal membrane (4);
7. Cyst content: hyporeflective or hyperreflective;
8. Subfoveal hard exudates: present or absent;
9. Foveal depression: present or absent.

Statistical Analysis

Statistical analyses were performed using SPSS version 22.0 for Windows (IBM Corp., Armonk, NY, USA). Data distribution was assessed using histogram plots, Shapiro-Wilk, and Kolmogorov-Smirnov tests. Continuous variables were expressed as mean ± standard deviation or median (interquartile range [IQR]: Q1-Q3), while categorical variables were presented as counts (n) and percentages (%). Snellen BCVA values were converted to logarithm of the minimum angle of resolution for statistical analyses.

Depending on data distribution and variable count, dependent variables were analyzed using paired samples t-test or repeated measures analysis of variance (ANOVA), and Wilcoxon signed-rank test or Friedman test. For comparisons involving more than two time points, post-hoc analyses were conducted using Dunn–Bonferroni or SPSS-provided pairwise comparisons for ANOVA and Friedman test, respectively. Bonferroni-adjusted p values are reported as "adj. p" where applicable. Since patients with longer follow-up contributed to multiple cohorts, appropriate dependent tests were used. A two-sided p value <0.05 was considered statistically significant.

Results

Baseline Characteristics

This study included 2,424 eyes of 1,696 patients (mean age: 60.6±10.0 years; range: 19-93), of whom 787 (46.4%) were female. All eyes with at least three months of follow-up were included in the 3-month cohort. As follow-up duration increased, the number of eyes declined across the 6-, 12-, 18-, 24-, 36-, and 48-month cohorts, with 1,878, 1,321, 697, 427, 204, and 86 included, respectively. Cohort-specific baseline characteristics are summarized in Table 1.

Among all eyes, 2,190 (90.3%) were treatment-naïve and 234 (9.7%) had previously received anti-VEGF therapy. All eyes were treated with a PRN regimen following three consecutive monthly loading injections. The mean duration to complete the loading phase was 66±9.5 days (range, 47-90 days). Bevacizumab was the most commonly used initial agent (93.3%), followed by ranibizumab (3.9%) and aflibercept (2.8%). Eyes treated with ranibizumab or aflibercept had received three consecutive bevacizumab injections at other centers within the previous six months.

Most patients (69.9%) had NPDR at baseline. Detailed clinical characteristics per cohort are provided in Table 2, and OCT findings in Table 3. The most frequent cystic pattern was hyporeflective cysts (71.2%), followed by hyperreflective cysts (28.1%). In 0.7% of eyes with cysts, their content could not be assessed. Foveal depression was present in 50.7% and subfoveal hard exudates in 31.5% of the eyes. In addition to these anatomical characteristics, changes in lens status were also observed during follow-up. A total of 262 eyes underwent cataract surgery and were subsequently recorded as pseudophakic.

Functional and Anatomical Results

In the study sample, the mean baseline BCVA (Snellen, decimal) was 0.34±0.24, and the mean CMT was 400±134 µm. BCVA showed gradual, statistically significant improvement at all follow-up points ($p<0.0001$), reaching 0.37±0.25, 0.41±0.26, 0.44±0.27, 0.46±0.28, 0.48±0.28, 0.49±0.29, and 0.49±0.29 at months 3, 6, 12, 18, 24, 36, and 48, respectively. Although modest, these functional gains were largely sustained over time, despite potential undertreatment and compliance issues in routine practice.

CMT also declined consistently to 354±120, 334±112, 324±110, 327±112, 333±137, 324±120, and 324±115 µm at the same respective time points. Despite minor increases at months 18 and 24, all reductions from baseline were significant ($p<0.0001$). These results support the sustained anatomical benefits of anti-VEGF therapy in real-world settings, even with variability in retreatment and monitoring.

Changes in BCVA and CMT over time are illustrated in Figures 1 and 2, respectively.

Number of Visits and Intravitreal Anti-VEGF Injections

The cumulative numbers of intravitreal injections and clinical visits were assessed annually. The average number of visits in years 1 through 4 was 7.5±2.9, 11.2±3.7, 14.7±5.1, and 17.6±5.6, respectively; the corresponding mean number of injections was 6.5±1.7, 9.6±2.8, 12.2±3.9, and 15.7±5.5. Although both visit and injection counts increased over time, the rate of injections slowed notably after the first year. These findings suggest a tendency for reduced adherence to treatment intensity and monitoring over extended follow-up in real-world settings. Detailed data are provided in Table 4.

Anti-VEGF Switch

Between months 3 and 6 of follow-up (i.e., following the initial loading phase), anti-VEGF switching was performed in 813 eyes (43.5%). Among these, 68.1% were switched to an on-label agent, while 31.9% were switched due to poor response. Both the choice of agent and timing of the switch were determined at the discretion of the treating physician. The distribution of switching in the subsequent follow-up intervals was as follows: 255 eyes (19.3%) in months 6-12, 94 eyes (13.6%) in months 12-18, 49 eyes (11.3%) in months 18-24, 17 eyes (7.8%) in months 24-36, and 14 eyes (15.5%) in months 36-48. Detailed information on switch timing and rationale is presented in Table 5.

In selected cases, combination therapy with IDI or a switch to IDI monotherapy was implemented based on the treating physician's clinical assessment. The monthly distribution of IDI usage throughout the follow-up period is summarized in Table 6.

Adverse Events

During the 48-month follow-up period, recorded ocular adverse events included vitreous hemorrhage and elevated IOP. No ocular complications were reported beyond month 36. Importantly, no cases of retinal tear, retinal detachment, or endophthalmitis occurred at any time. The monthly distribution of observed adverse events is summarized in Table 7.

Discussion

This large-scale, multicenter, real-world study presents a comprehensive evaluation of intravitreal anti-VEGF therapy for DME in tertiary centers across the European side of İstanbul and the Kocaeli province of Türkiye. Our findings confirm that anti-VEGF agents are effective in improving visual acuity and reducing CMT. Mean visual acuity increased from 0.34±0.24 Snellen at baseline to 0.49±0.29 at month 48, while mean CMT decreased from 400±134 µm to 324±115 µm over the same period. However, as observed in other real-world studies, visual gains plateaued after the second year, likely due to undertreatment, disease chronicity, and patient adherence issues.[15,16] Treatment patterns varied considerably. Between months 3 and 6, 43.5% of eyes required a switch from the initial anti-VEGF agent, mostly due to a transition to on-label drugs (68.1%).

Table 1. Baseline characteristics of the patients and eyes in each cohort

	Baseline	3-month cohort (whole group)	6-month cohort	12-month cohort	18-month cohort	24-month cohort	36-month cohort	48-month cohort
Eyes, n	2424	2424	1878	1321	697	427	204	86
Age, years, mean ± SD	60.6±10.0	60.6±10.0	60.8±9.9	60.6±10.0	60.2±10.2	59.4±10.7	59.1±10.6	58.4±11.2
Sex, n of patients (%)								
Female	787 (46.4)	787 (46.4)	650 (47.3)	435 (44.2)	225 (42.8)	140 (44)	58 (43.4)	24 (40.0)
Male	909 (53.6)	909 (53.6)	728 (52.7)	549 (55.8)	300 (57.2)	178 (56)	89 (56.6)	36 (60.0)
BCVA, decimal, mean ± SD (range)	0.34±0.24 (0.01-1.0)	0.37±0.25 (0.01-1.0)	0.41±0.26 (0.01-1.0)	0.44±0.27 (0.01-1.0)	0.46±0.28 (0.01-1.0)	0.48±0.28 (0.01-1.0)	0.49±0.29 (0.01-1.0)	0.49±0.29 (0.01-1.0)
CMT, µm, mean ± SD	400±134	354±120	334±112	324±110	327±112	333±137	324±120	324±115

SD: Standard deviation, BCVA: Best corrected visual acuity, CMT: Central macular thickness

Table 2. Baseline clinical characteristics of all patients and eyes

Previous treatment status, n (%)	Treatment-naive	2190 (90.3)
	Previously treated	234 (9.7)
Baseline lens status, n (%)	Phakic	1883 (77.7)
	Pseudophakic	541 (22.3)
Baseline IOP, mmHg, mean ± SD (range)		15.9±3.4 (5-50)
Diabetic retinopathy stage, n (%)	NPDR	1694 (69.9)
	PDR	730 (30.1)
Initial treatment, n (%)	Bevacizumab	2261 (93.3)
	Ranibizumab	95 (3.9)
	Aflibercept	68 (2.8)

IOP: Intraocular pressure. SD: Standard deviation. NPDR: Non-proliferative diabetic retinopathy. PDR: Proliferative diabetic retinopathy

Table 3. Baseline OCT parameters of all patients and eyes		
Cysts, n (%)	Absent (0)	117 (4.7)
	Mild (1)	829 (34.2)
	Moderate (2)	787 (32.5)
	Severe (3)	691 (28.5)
Subretinal fluid, n (%)	Absent (0)	1794 (74.0)
	Present (1)	630 (26.0)
DRIL, n (%)	Absent (0)	1890 (78.0)
	Present (1)	442 (18.2)
	Not evaluated	92 (3.8)
Hyperreflective foci, n (%)	Less than 30 in number (0)	1166 (48.1)
	More than 30 in number (1)	1258 (51.9)
EZ and/or ELM status, n (%)	Intact (0)	1890 (78)
	Disrupted (1)	440 (18.2)
	Absent (2)	62 (2.6)
	Not evaluated	32 (1.3)
Vitreomacular interface disorders, n (%)	No (0)	1493 (61.5)
	Incomplete PVD (1)	403 (16.9)
	Complete PVD (2)	114 (4.7)
	VMT (3)	46 (1.9)
	ERM (4)	368 (15.1)

OCT: Optical coherence tomography. DRIL: Disorganization of the inner retinal layers. EZ: Ellipsoid zone. ELM: External limiting membrane. PVD: Posterior vitreous detachment. VMT: Vitreomacular traction. ERM: Epiretinal membrane

While 31.9% of eyes were switched due to poor response during this period, this rate climbed rapidly, reaching 75% in months 6–12 and 100% after month 24. Additionally, 18.8% of eyes received IDI within the first 6 months, and the cumulative requirement increased to 38.7% by month 48, indicating the need for alternative therapeutic strategies in refractory cases. Bevacizumab was initially administered in 93.3% of eyes, reflecting national reimbursement policies and highlighting the influence of healthcare regulations on clinical decision-making. Adverse events were rare: IOP elevation occurred in 0.4% and vitreous hemorrhage in 0.2% of eyes during the first 3 months, with no such events reported after month 36. Importantly, no cases of endophthalmitis or retinal detachment were detected throughout the study, reaffirming the overall safety of intravitreal therapy.

Intravitreal anti-VEGF injection is widely recognized as the first-line therapy for center-involved DME in most clinical settings.[4] However, in real-world practice, treatment regimens often diverge significantly from those employed in RCTs due to factors such as restricted access to healthcare, the presence of multiple comorbidities, and poor adherence, particularly among elderly patients. Consequently, patients

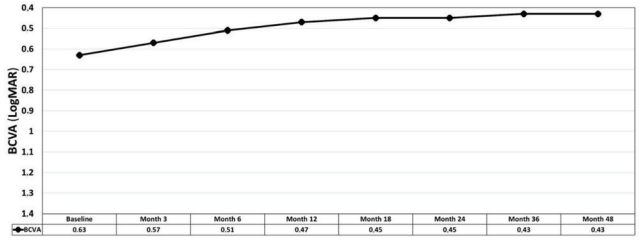

Figure 1. Mean best corrected visual acuity (BCVA) in logMAR over the 48-month follow-up period. Visual acuity improved from a baseline value of 0.63 to 0.43 at both months 36 and 48. All post-treatment time points demonstrated statistically significant improvements compared to baseline (all p<0.0001)
logMAR: Logarithm of the minimum angle of resolution

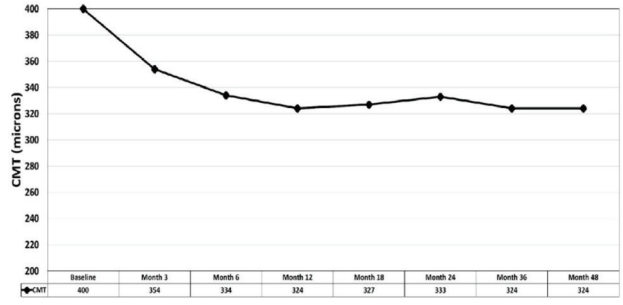

Figure 2. Mean central macular thickness (CMT) over the 48-month follow-up period. CMT decreased from a baseline value of 400 µm to 324 µm at month 48, with the most substantial reduction observed during the initial 6 months of treatment. Although a slight increase was noted at months 18 and 24, the overall reduction in CMT remained statistically significant at all follow-up visits compared to baseline (all p<0.0001)

tend to receive fewer injections and attend fewer follow-up visits than required by the more intensive regimens used in controlled studies. Previous studies have reported a wide range of visual outcomes with anti-VEGF therapy, largely influenced by follow-up duration and injection frequency. Over two years, visual gains of +3.36 letters with 12.4 to 13.1 injections, +3.0 letters with 8.6 injections, and +2.7 letters with 9.1 injections have been documented.[17,18,19] In shorter-term studies, outcomes included gains of +6.6 letters with 6.6 injections in one year and +4.3 to +4.9 letters with 2.6 to 3.8 injections over six months.[20,21] Conversely, in longer follow-up, a four-year study reported a mean gain of +6.6 letters with 7.7 injections.[22] These findings emphasize the heterogeneity of treatment outcomes across studies and underscore the importance of individualized treatment strategies in daily practice. In our study, mean BCVA improved from 0.34±0.24 at baseline to 0.49±0.29 Snellen at month 48, with patients receiving a mean of 15.7 injections during the entire follow-up

Table 4. Visit and intravitreal injection counts				
	12-month cohort (n=1321)	**24-month cohort (n=427)**	**36-month cohort (n=204)**	**48-month cohort (n=86)**
Number of visits, cumulative mean ± SD (range)	7.5±2.9 (2-12)	11.2±3.7 (3-25)	14.7±5.1 (6-35)	17.6±5.6 (7-31)
Number of injections, cumulative mean ± SD (range)	6.5±1.7 (3-12)	9.6±2.8 (3-20)	12.2±3.9 (3-27)	15.7±5.5 (3-36)
SD: Standard deviation				

Table 5. Intravitreal switch rates and reasons			
Time period (months)	**Total eyes switched, n (%)***	**Switched to an on-label agent, n (%)****	**Switched due to poor response, n (%)****
3-6	813 (43.5)	554 (68.1)	259 (31.9)
6-12	255 (19.3)	64 (25.0)	191 (75.0)
12-18	94 (13.6)	14 (13.8)	80 (85.2)
18-24	49 (11.3)	2 (4.0)	47 (96.0)
24-36	17 (7.8)	0 (0.0)	17 (100.0)
36-48	14 (15.5)	0 (0.0)	14 (100.0)
*Total number and percentage of eyes that underwent agent exchange among the eyes being followed within the specified time period; **Percentage of total eyes switched during the time period			

Table 6. Requirement and/or addition of dexamethasone implant	
Time period (months)	**DEX implant requirement/addition, n (%)***
Baseline-6	352 (18.8)
6-12	331 (24.9)
12-18	171 (24.5)
18-24	87 (20.9)
24-36	57 (26.1)
36-48	36 (38.7)
*Cumulative number and percentage of eyes that received a DEX implant during the specified follow-up interval	

Table 7. Ocular adverse effects		
Time period (months)	**VH, n (%)***	**Increase in IOP, n (%)***
Baseline-3	5 (0.2)	12 (0.4)
3-6	3 (0.1)	9 (0.5)
6-12	8 (0.4)	15 (0.7)
12-18	3 (0.1)	4 (0.1)
18-24	1 (<0.1)	4 (<0.1)
24-36	2 (<0.1)	3 (<0.1)
36-48	-	-
*Percentages are based on all eyes at baseline (n=2424). as adverse events could occur at any point during follow-up and might persist or recur across multiple follow-up intervals. Values are not cohort-specific VH: Vitreous hemorrhage. IOP: Intraocular pressure		

period. Notably, the average number of injections in the first year was 6.5, which is higher than those reported in previous large-scale real-world studies from Türkiye. Durukan et al.[11] reported a mean of 4.6 injections, while the MARMASIA Study Group[12] reported a median of 5 injections (IQR: 4-6) (Table 8). This relatively higher treatment intensity in our cohort likely contributed to the favorable early functional and anatomical outcomes. Furthermore, the injection frequency in our cohort surpassed that of international real-world studies, including the German OCEAN study[23] (mean of 4.4 injections) and IRIS Registry data from the United States (approximately 5 injections).[24] These findings highlight the importance of strict adherence to the initial loading phase and regular retreatment to sustain visual and anatomical gains under routine clinical conditions. Nevertheless, as in other real-world reports, the cumulative injection numbers in our study remained considerably lower than those in RCTs, where patients typically received 7-12 injections in the first year and over 20 across two years. In comparison, a recent four-year study by Epstein and Amrén[22] reported declining injection numbers, with patients receiving 4.7, 1.4, 0.7, and 0.9 injections in years 1 through 4, respectively. This treatment gap may stem from the burden of frequent healthcare visits required for DME management, resulting in missed appointments and delayed care. In our cohort, the average number of visits was 7.5, 11.2, 14.7, and 17.6 at

months 12, 24, 36, and 48, respectively, substantially fewer than those observed in tightly controlled clinical trials.[2,25]

The suboptimal treatment adherence observed in our study may be explained by several real-world barriers, such as the need for bilateral injections, limited patient awareness about the importance of intensive therapy, scheduling conflicts, and comorbidities that hinder regular hospital visits. The mean number of injections per patient over 48 months was 15.7, reflecting the difficulty of sustaining long-term, intensive treatment outside of clinical trial conditions. In our cohort, 43.5% of eyes required a switch in anti-VEGF agent between months 3 and 6 of follow-up, which corresponds to the period following the initial 3-month loading phase, and early switching was associated with better visual gains. This is consistent with Maggio et al.,[26] who reported that although switching agents does not always improve outcomes, early therapeutic modifications tend to be more effective. Moreover, dexamethasone implants were needed in some of our patients, particularly those with chronic DME and persistent intraretinal cysts.[18] In the same Maggio et al.[26] study, early steroid use led to greater CMT improvement. Similarly, 18.8% of our patients received dexamethasone implants in the first six months, increasing to 38.7% by month 48. Since inflammation plays a key role in chronic DME, anti-VEGF monotherapy may be insufficient for some patients.

In Türkiye, healthcare reimbursement policies require bevacizumab as the first-line anti-VEGF agent, significantly shaping treatment decisions. In our study, 93.3% of patients received bevacizumab initially. Maggio et al.[26] suggested that the choice of first-line agent influences treatment outcomes, with aflibercept and ranibizumab often producing better results. Similarly, Durukan et al.[11] and Yayla et al.[12] noted that reimbursement restrictions limited both injection frequency and agent selection, potentially compromising long-term visual outcomes.

In our study, mean CMT decreased from 400±134 μm at baseline to 324±115 μm at 48 months. However, BCVA improvement did not always parallel CMT reduction. This supports Maggio et al.,[26] who noted that CMT alone may not predict visual gains, emphasizing the importance of retinal structural integrity. Recent studies suggest that biomarkers like DRIL and EZ integrity are stronger predictors of long-term vision.[18]

Study Limitations

This study has several limitations inherent to its retrospective design. Treatment decisions were made based on the clinical judgment of physicians at each participating center. The analysis included all eyes with available follow-up data of varying durations up to 48 months. However, the number of patients decreased substantially over time, with only 86 eyes remaining under follow-up at month 48. This finding clearly demonstrates the challenges of maintaining long-term anti-VEGF therapy for DME, where the high injection burden, frequent visit requirements, and the chronic nature of the disease constitute major barriers to sustained treatment adherence in real-world

Table 8. Comparison of cumulative intravitreal anti-VEGF injection and clinical visit numbers in real-world studies from Türkiye

	Present study	Durukan et al.[11]	Yayla et al.[12]
Follow-up period (months)	**48**	**36**	**36**
Number of eyes			
Start of therapy	2424	1072	1372
Month 12	1321	495	1185
Month 24	427	293	972
Month 36	204	284	623
Month 48	86	-	-
Number of cumulative intravitreal injections			
Month 12	6.5±1.7	4.6±2.0	5 (4-6)
Month 24	9.6±2.8	7.1±3.1	7 (5-8)
Month 36	12.2±3.9	8.0±4.2	9 (7-10)
Month 48	15.7±5.5	-	-
Number of cumulative visits			
Month 12	7.5±2.9	7.4±2.1	7 (6-10)
Month 24	11.2±3.7	13.2±3.8	11 (9-14)
Month 36	14.7±5.1	18.7±5.7	16 (14-18)
Month 48	17.6±5.6	-	-

Injection and visit numbers reported as mean ± SD or median (range)
anti-VEGF: Anti-vascular endothelial growth factor. SD: Standard deviation

settings. In addition, eyes that showed rapid improvement after short-term treatment or failed to respond despite multiple injections may not have been fully represented in the long-term outcomes. The use of different OCT devices across centers may have introduced minor technical variations in retinal thickness measurements. Finally, systemic and ocular adverse events were not consistently documented throughout the 48-month period. While some were recorded, others were not systematically entered into clinical files.

Conclusion

This large-scale real-world study provides important insights into intravitreal anti-VEGF therapy for DME. Our results were generally consistent with previous real-world studies; however, the superior visual and anatomical outcomes observed in our cohort likely reflect a higher injection frequency. Nevertheless, the outcomes remained below RCT standards; this gap is primarily attributable to undertreatment and delays in routine clinical practice. Building on these findings, future BOSPHORUS-DME reports will explore clinical and anatomical subgroups to strengthen real-world evidence and support more personalized treatment strategies.

Ethics

Ethics Committee Approval: Ethics approval was obtained from Kocaeli University Faculty of Medicine Ethics Committee (decision no: KÜ GOKAEK-2025/06/18; date: 13.03.2025; project: 2025/115).

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

Declarations

Authorship Contributions

Surgical and Medical Practices: All authors, Concept: V.L.K., Design: V.L.K., A.Ö., A.Ç., Data Collection or Processing: All authors, Analysis or Interpretation: All authors, Literature Search: All authors, Writing: E.Ö., S.A.Ö., M.K.

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

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

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Original Article

Detection of Occult Retinal Breaks Using Subretinal Dye in Recurrent Retinal Detachment Surgery

Sabahattin Sül, Sema Tamer Kaderli, Elchin Osmanlı, Ahmet Kaderli

Muğla Sıtkı Koçman University Faculty of Medicine, Department of Ophthalmology, Muğla, Türkiye

Abstract

Objectives: To evaluate the results and effectiveness of the intraoperative subretinal dual dye-assisted technique in patients treated in our clinic for recurrent rhegmatogenous retinal detachment (RRD), where small hidden retinal tears could not be detected before or during surgery.

Materials and Methods: This retrospective observational study included 11 patients who underwent surgery in our clinic for recurrent RRD and in whom no retinal tears were detected during either preoperative or intraoperative examinations. Data from patients who underwent surgery using the modified subretinal MembraneBlue-Dual® (trypan blue 0.15% + Brilliant Blue G 0.025% + PEG 4%) dye method applied with a 41-gauge cannula were examined. Postoperative outcomes were analyzed.

Results: In 38.4% of patients, retinal tears were located at the posterior edge of a previous laser retinopexy scar. Dye leakage was seen from the edge of a previously lasered retinal tear in 30.7% and from a new tear in 30.7%. At 1-year follow-up, anatomical success and permanent retinal reattachment were achieved in all of the patients. At postoperative 1 year, best corrected visual acuity had increased from 2.0±0.3 logarithm of the minimum angle of resolution (logMAR) to 0.7±0.1 logMAR.

Conclusion: Occult small retinal tears that are undetectable in recurrent RRD can be successfully identified using the subretinal dye-assisted technique.

Keywords: Subretinal dye, retinal detachment, retinal tears, rhegmatogenous retinal detachment, vitrectomy

Cite this article as: Sül S, Tamer Kaderli S, Osmanlı E, Kaderli A. Detection of Occult Retinal Breaks Using Subretinal Dye in Recurrent Retinal Detachment Surgery. Turk J Ophthalmol. 2026;56:41-46

Address for Correspondence: Sema Tamer Kaderli, Muğla Sıtkı Koçman University Faculty of Medicine, Department of Ophthalmology, Muğla, Türkiye
E-mail: sematamerkaderli@hotmail.com
ORCID-ID: orcid.org/0000-0003-4851-6527

Received: 29.06.2025
Revision Requested: 18.09.2025
Last Revision Received: 22.09.2025
Accepted: 17.11.2025
Publication Date: 18.02.2026

DOI: 10.4274/tjo.galenos.2025.91043

Introduction

Pars plana vitrectomy (PPV) is a commonly performed surgery for rhegmatogenous retinal detachment (RRD).[1,2] To prevent fluid re-entry and ensure retinal adhesion, tamponades such as gas and silicone oil are often used.[1,3,4] Despite these interventions, retinal detachment surgeries sometimes fail due to factors such as new or missed retinal breaks, reopening of original tears, or proliferative vitreoretinopathy (PVR).[5,6] Hence, identifying and addressing these issues are crucial for successful surgical outcomes.

The detection of retinal holes or breaks is critical for a successful retinal detachment repair. However, this goal can be challenging during redo surgery due to modifications made during previous surgeries. The dye-assisted technique for detecting occult retinal breaks offers a promising solution, simplifying the identification of previously undetected retinal breaks and improving anatomical and functional success. Previous case reports in the literature have demonstrated the effectiveness of an injection of subretinal dye, such as trypan blue or MembraneBlue-Dual®, with or without 180° endolaser retinopexy.[7,8]

The current study aimed to evaluate the efficacy and safety of the MembraneBlue-Dual® subretinal dye-assisted technique for detecting occult retinal tears in patients with RRD in whom retinal breaks could not be identified during either preoperative or intraoperative examinations.

Materials and Methods

This retrospective study included patients admitted to our department for recurrent RRD, in whom retinal breaks were not detected during preoperative and initial intraoperative examinations, and who subsequently underwent subretinal dye injection. The study was conducted in accordance with the principles of the Declaration of Helsinki, and ethics committee approval was obtained from Muğla Sıtkı Koçman University Medical Sciences Ethics Committee (protocol number: 241048, decision number: 127, date: 22.11.2024). A waiver of consent was granted as the study involved a retrospective review.

The medical records of patients who underwent PPV for recurrent RRD with unidentified tears between January 2018 and January 2023 were analyzed. The following data were collected: age at the time of surgery, sex, laterality, previous surgeries, type of previous surgery, concomitant ocular disorders, best corrected visual acuity (BCVA), intraocular pressure values, biomicroscopic anterior segment and fundus examination findings, optical coherence tomography (OCT), and ultra-widefield imaging using the Optos 200Tx system (Optos plc, Dunfermline, UK) before and at 6 months and 1 year post-PPV follow-up, findings at the last visit, complications, and disease course.

The inclusion criterion was RRD with no retinal breaks identified preoperatively or intraoperatively through scleral indentation. Exclusion criteria were primary retinal detachment, history of encircling scleral buckle surgery combined with vitrectomy, and detection of preoperative or intraoperative retinal tears.

The surgical procedures were performed by the same expert vitreoretinal surgeon (S.S.) and were similar in all patients (Figure 1). They began with the injection of perfluorocarbon heavy liquid to protect the posterior pole of the retina and optic disc from potential dye toxicity. MembraneBlue-Dual® (Trypan Blue 0.15% + Brilliant Blue G 0.025% + 4% PEG) was then injected into the subretinal space using a 41-gauge cannula. Additional perfluorocarbon heavy liquid was added to displace subretinal fluid toward the retinal periphery. The eye was rotated, allowing the dye to exit through the tiny break, facilitating its identification. Surgical success for PPV was defined as postoperative reattachment of the neurosensory retina for at least 1 year.

Statistical Analysis

Data analysis was performed using descriptive statistics to summarize the patient demographics, surgical history, and outcomes. Continuous variables such as age and duration between surgeries were expressed as the mean ± standard deviation (SD). Categorical variables, including the sex distribution and type of tamponade used, were presented as frequencies and percentages. Visual acuity outcomes at three and six months postoperatively were expressed as mean ± SD. Given the small sample size, no inferential statistical tests were applied, and the results were interpreted descriptively.

Results

A total of 11 patient files were included in the study. The mean age was 52.6±12.5 years. Eight patients (72.7%) were female and 3 (27.3%) were male. The mean duration between PPV surgeries was 65±11.3 days. In terms of procedures, 3 eyes (27.3%) underwent pneumatic retinopexy, 7 eyes (63.6%) underwent PPV with gas tamponade, and 1 eye underwent PPV with silicone oil. A history of trauma was present in 6 eyes (54.5%), while 5 (45.5%) had peripheral

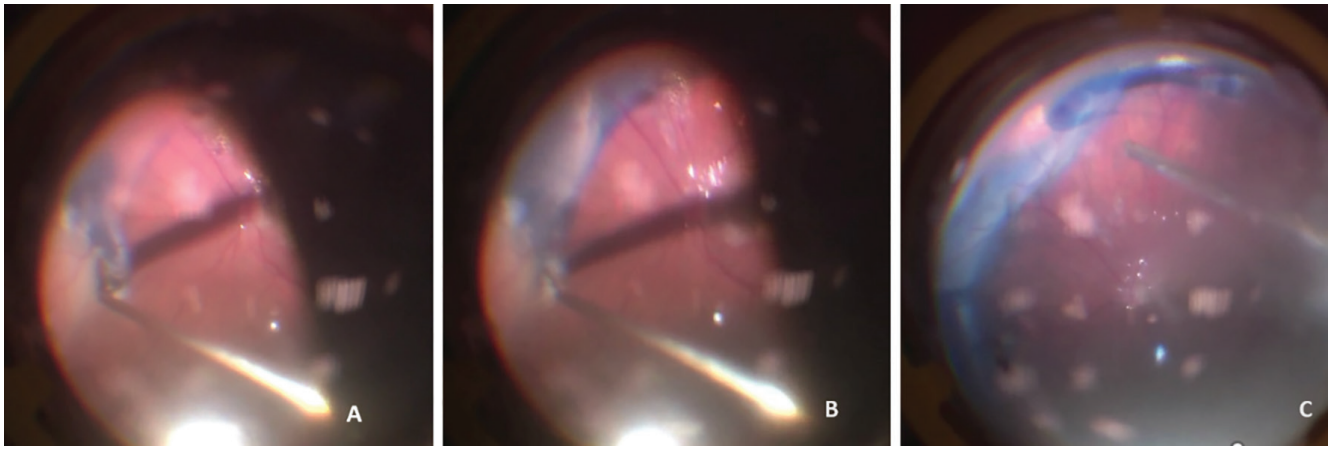

Figure 1. The surgical procedure: A) the dye was injected into the subretinal space using a 41-gauge cannula; B) the dye displaced the subretinal fluid toward the retina periphery; C) additional perfluorocarbon heavy liquid was then injected into the vitreous cavity until the dye was vented out of a very small break

degeneration. Only in one case, PVR was observed in the inferior quadrant around the remnant vitreous base. However, this area was attached and the previous laser spots were present in front of it, and the recurrent retinal tear was located away from that area. The new retinal tear, detected with dye, was located in a different quadrant, at the edge of previous laser retinopexy scar. There were no PVR-related detachments in our cohort, recurrent RRD was associated with occult tears in all cases. The demographic and baseline characteristics are summarized in Table 1.

At least one clinically unidentified retinal break was identified in each case using subretinal dye. Of these occult tears, 38.4% were located at the posterior edge of a previous laser retinopexy scar, 30.7% were at the edge of a previously lasered retinal tear, and 30.7% were new tears (Figure 2). Silicone oil was used in five cases, and C3F8 was used in six for tamponade. Persistent retinal attachment was achieved in all 11 patients.

After silicone oil removal and absorption of the gas tamponade, the retinas remained attached at the 1-year follow-up (Table 2). BCVA improved from 2.0±0.3 to 0.8±0.1 logarithm of the minimum angle of resolution (logMAR) at postoperative 3 months and 0.7±0.1 logMAR at postoperative 6 months.

At 6 months postoperatively, minimal cystoid macular edema (CME) was observed in two patients and we administered sub-Tenon triamcinolone acetonide. Three weeks after the sub-Tenon injection, CME had regressed in both patients. Only one patient had focal disruption of the external limiting membrane and ellipsoid zone in the temporal parafoveal area. The mean RNFL thickness was 94.2±9.7 and 91.9±7.6 µm, respectively, at 6 months and 1 year postoperatively. At the 1-year follow-up, the mean BCVA remained stable at 0.7±0.1 logMAR. No additional postoperative complications were observed.

Table 1. Baseline patient demographics and clinical findings (n=11)	
Age (years), mean ± SD	52.6±12.5
Sex (female/male), n	8/3
Laterality (R/L), n	7/4
IOP (mmHg), mean ± SD	7.2±1.2
Duration between PPV (days), mean ± SD	65.0±11.3
Previous treatment, n (%)	
Pneumatic retinopexy	3 (27.2)
PPV + gas tamponade	7 (63.6)
PPV + silicon oil	1 (9.1)
History of trauma, n (%)	6 (54.5)
Presence of peripheral degeneration, n (%)	5 (45.4)
Presence of PVR, n (%)	1 (9.1)
Location of RD (superior/inferior/total), n	3/4/4
Macula on/off RD, n	3/8
SD: Standard deviation, L: Left, R: Right, IOP: Intraocular pressure, PPV: Pars plana vitrectomy, PVR: Proliferative vitreoretinopathy, RD: Retinal detachment	

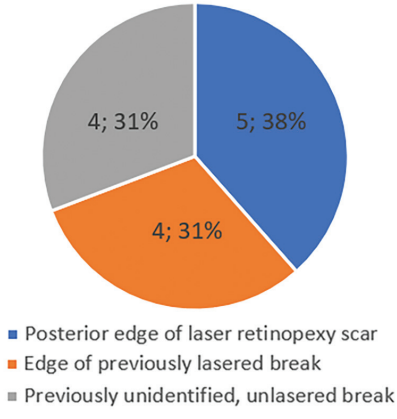

Figure 2. Locations of the detected occult breaks

Table 2. Postoperative clinical features (n=11)				
	Baseline	**Postoperative 3 months**	**Postoperative 6 months**	**Postoperative 1 year**
BCVA (logMAR), mean ± SD	2.0±0.3	0.8±0.1	0.7±0.1	0.7±0.1
IOP (mmHg), mean ± SD	7.2±1.2	14.0±3.2	13.5±2.3	12.5±1.8
CMT (μm), mean ± SD	-	342±45	321±52	311±48
RNFL (μm), mean ± SD	-	101.0±8.9	94.2±9.7	91.9±7.6
Presence of CME, n (%)	-	1 (9.1)	2 (18.1)	-
Presence of ELM disruption, n (%)	-	1 (9.1)	1 (9.1)	1 (9.1)
Presence of EZ disruption, n (%)	-	1 (9.1)	1 (9.1)	1 (9.1)

BCVA: Best corrected visual acuity, logMAR: Logarithm of the minimum angle of resolution, SD: Standard deviation, IOP: Intraocular pressure, CMT: Central macular thickness, RNFL: Retinal nerve fiber layer, CME: Cystoid macular edema, ELM: External limiting membrane, EZ: Ellipsoid zone

Discussion

This study evaluated the subretinal dye technique, as described in the literature, for identifying clinically undetectable retinal breaks and summarized the clinical results. This technique involves injecting dual blue dye under the retina, followed by the use of perfluorocarbon heavy liquids to reveal hidden retinal breaks. This approach successfully identified retinal breaks in all the patients.

The identification of retinal breaks is crucial in repairing RRD.[7,9] Typically, retinal breaks are identified using Lincoff's rules and careful examination before and during surgery. During surgery where liquid perfluorocarbon is used, the passage of subretinal fluid into the vitreous cavity may facilitate the detection of tears. However, small retinal breaks may still be overlooked despite thorough preoperative and intraoperative examination. If these tears are missed, they can lead to transretinal fluid flow into the subretinal space, causing redetachment and surgical failure.[7,8,9,10]

Previous studies have shown that undetected retinal tears can be identified using vital dyes, with various techniques showing high efficacy. Gupta et al.[9] utilized trans-scleral Vision Blue® injections targeting the site of greatest subretinal fluid depth. However, the use of this technique is limited because of potential complications such as hypotony and hemorrhage.[9,11] In case series by Jackson et al.[7] and Wong et al.,[12] MembraneBlue® successfully revealed hidden breaks in eyes with complex retinal detachment where traditional methods had failed. More recently, Khanduja et al.[13] reported that the modified subretinal dye extrusion technique (MORE-DETECH) (using trypan blue) effectively revealed occult retinal breaks in retinal detachment after silicone oil endotamponade removal. In their study, the technique achieved a success rate of 90.4% in detecting breaks, which were most commonly at the posterior edge of laser retinopexy scars. Berarducci et al.[14] similarly described chromophore-assisted detection (using MembraneBlue-Dual®) as a valuable surgical technique for detecting occult retinal breaks and managing challenging situations during retinal detachment surgery.

However, the use of dyes remains a topic of debate due to risks such as dye-related toxicity and the creation of iatrogenic retinal holes, and authors have emphasized the need for careful management to minimize these complications.[7,12,15,16,17,18] In the present study, perfluorocarbon heavy liquid was applied to protect the posterior pole before injecting the dual dye. Our findings aligned with reports supporting the effectiveness of subretinal dye,[7,17] and the lack of complications noted in earlier studies[7,12] suggests that this modified approach may offer a safer approach.

The choice of dye is important. Brilliant Blue is typically used to visualize the internal limiting membrane and appears safer due to lower toxicity.[18] However, we opted for MembraneBlue-Dual® in this research for improved visibility of any remaining vitreous or membrane. This decision was made despite research in rat models suggesting that trypan blue can cause dose-dependent neurotoxicity at concentrations above 0.04%.[18] Although we observed no retinal toxicity based on clinical findings and OCT data, definitive conclusions regarding subclinical toxicity could not be drawn, as we did not perform electrophysiological tests or microperimetry, which are effective in detecting subtle functional alterations following dye-assisted vitrectomy.[19,20,21]

Study Limitations

No serious adverse events were observed in the current study, and postoperative visual acuities improved as expected. However, the small sample size was a limitation, restricting the generalizability of the findings. Another limitation of our study is the absence of advanced assessments

such as electrophysiological testing and microperimetry. Additionally, collecting baseline data was challenging since the need for subretinal dye is often identified only during surgery. Future multicenter, prospective randomized controlled trials with larger patient populations are needed to provide more definitive outcomes on the efficacy and safety of subretinal dyes. Furthermore, animal studies are crucial to understanding potential long-term toxicity, which could aid in optimizing dye concentrations and application techniques.

Conclusion

The results herein demonstrate the benefit of using subretinal dye in challenging cases where retinal tears are undetectable during preoperative and intraoperative examinations. Although we do not recommend routine use, it may serve as a valuable tool for specific patient populations, such as those with recurrent retinal detachment or a history of failed retinal detachment surgeries. For patients at high risk of developing PVR, subretinal dye application could improve anatomical outcomes and should be considered in clinical decision-making. However, further research is needed to establish clear guidelines for its use in clinical practice.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the principles of the Declaration of Helsinki, and ethics committee approval was obtained from Muğla Sıtkı Koçman University Medical Sciences Ethics Committee (protocol number: 241048, decision number: 127, date: 22.11.2024).

Informed Consent: Retrospective study.

Declarations

Authorship Contributions

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

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

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

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Review

Sustainable Ophthalmology Applications: From the Perspective of Strabismus and Pediatric Ophthalmology

Zeynep Akgün, Elif Demirkılınç Biler, Melis Palamar

Ege University Faculty of Medicine, Department of Ophthalmology, İzmir, Türkiye

Abstract

Ophthalmology significantly contributes to the healthcare sector's carbon footprint. Despite recent increases in sustainability research in ophthalmology, there remains limited information on initiatives specific to pediatric ophthalmology and strabismus. This review aims to examine the existing literature and provide insights into sustainability and reducing carbon footprints in these areas. Although there has been no specific assessment of carbon emissions associated with congenital and developmental cataracts, measures related to cataract surgery and operating room practices remain relevant. Strabismus surgeries can be considered environmentally friendly, affordable, and energy-efficient procedures. Involving non-ophthalmologist personnel, expanding telemedicine applications, and restructuring outpatient services could reduce clinic congestion, lower costs, and improve sustainability. Some amblyopia examinations requiring long-term follow-up could be performed at local healthcare centers. While compliance and effectiveness are primary concerns in patching treatment, it is crucial to acknowledge that the patches generate significant waste and carbon footprints. Therefore, exploring alternative solutions is essential. Anesthesia poses an additional challenge for pediatric examinations, and various strategies have been suggested to reduce carbon dioxide emissions. Additionally, artificial intelligence is promising and its integration into pediatric ophthalmic examinations could further enhance sustainability. In brief, although pediatric ophthalmology and strabismus are considered environmentally friendly subspecialties of ophthalmology, especially in the operating room, there are many steps that can be taken for "sustainable ophthalmology," from anesthesia to amblyopia treatment and outpatient clinic services.

Keywords: Sustainability, carbon footprint, climate change, strabismus, pediatric ophthalmology

Introduction

Climate change and increased greenhouse gas emissions are among the greatest threats to health worldwide.[1] Healthcare services contribute significantly to the climate crisis due to their broad scope and specific requirements. World Bank and World Health Organization data indicate that as of 2020, the health sector was responsible for approximately 4%-5% of global carbon dioxide equivalent (CO_2eq) emissions.[2]

Sustainability has become a major priority in health care, with numerous initiatives being taken globally, most notably the United Nations Sustainable Development Goals.[3] Sustainability and "green" health care involve practices that minimize environmental impact through waste reduction, energy efficiency, and resource conservation with the aim of creating a sustainable environment for future generations. Numerous studies conducted in various fields have started to raise awareness of this important issue in recent years.[4]

Ophthalmology is one of the largest healthcare sectors, with millions of outpatient services and surgeries performed worldwide every year. As the world population and average life expectancy continue to increase, the demand for ophthalmological care is also growing. Important steps can be taken to achieve sustainability goals in this area, such as the widespread use of reusable instruments, reduction

Cite this article as: Akgün Z, Demirkılınç Biler E, Palamar M. Sustainable Ophthalmology Applications: From the Perspective of Strabismus and Pediatric Ophthalmology. Turk J Ophthalmol. 2026;56:47-53

Address for Correspondence: Ege University Faculty of Medicine, Department of Ophthalmology, İzmir, Türkiye
E-posta: melispalamar@hotmail.com
ORCID-ID: orcid.org/0000-0002-2494-0131

Received: 18.08.2025
Revision Requested: 05.10.2025
Last Revision Received: 08.10.2025
Accepted: 22.10.2025
Publication Date: 18.02.2026

DOI: 10.4274/tjo.galenos.2025.55562

of drug waste, and optimization of energy and resource use in operating rooms. Recently, there has been an increase in publications and studies on sustainability in ophthalmology practices.[5] A closer investigation of the literature demonstrates that current research has primarily focused on surgical procedures, especially cataract surgery. This is not surprising, as cataract surgery is one of the most commonly performed surgical procedures, not only in ophthalmology, but among all medical specialties.[6] In addition to cataract and cataract surgery, there are also a few reports concerning vitreoretinal, corneal, and glaucoma surgery and outpatient services.[7,8,9,10]

Pediatric ophthalmology and strabismus are subspecialties that encompass both the anterior and posterior segments of the eye, as well as central nervous system connections such as the afferent and efferent visual pathways. A wide range of diseases such as amblyopia, cataract, nystagmus, retinopathy of prematurity, and strabismus fall within this field of study. Both outpatient services and surgical procedures generate significant resource utilization.[11] However, research on sustainability in this area is limited. This review aims to analyze the existing literature and provide insight into sustainability and carbon footprint reduction in pediatric ophthalmology and strabismus.

Literature Review

A comprehensive literature review on sustainability and carbon footprint reduction in ophthalmology was conducted using the PubMed and Google Scholar databases. The initial screening was performed using the keywords sustainability, carbon footprint, greenhouse gas, CO_2eq emission, telemedical, teleophthalmology, climate change, eye health, ophthalmic surgery, cataract, travel, artificial intelligence, strabismus, amblyopia, and pediatric ophthalmology. No restrictions were imposed in terms of time, language, or geography. Article titles and abstracts were screened, and publications on pediatric ophthalmology and strabismus were selected for full-text review. Only English abstracts were used for articles that were not written in English or had no English translation available.

A Brief Review: The Core Principles of Sustainability

To facilitate applicability and understanding, the principles of sustainability can be summarized as the 5R rule: Reduce, Reuse, Recycle, Rethink, and Research.[12] In ophthalmology, these principles can be applied both in the operating room and in the outpatient clinic. The rest of this review will focus on actions specific to strabismus and pediatric ophthalmology.

Measures to Take in the Operating Room

The operating room is a large workspace where various sustainability measures can be implemented. Cataract surgery is responsible for a significant portion of ophthalmology's carbon footprint because of the high patient circulation, overuse of disposable instruments and equipment, and reliance on devices with high energy consumption.[13] Morris et al.[14] estimated that the total carbon footprint of 343,782 cataract surgeries performed in England in 2011, including building and energy use, travel, and supply factors, was approximately 63,000 tons of CO_2eq. The carbon footprint of a single cataract surgery was reported to be 151.9 kg CO_2eq in New Zealand, 86.62 kg in Spain, and 81.13 kg CO_2eq in France.[15,16,17]

Several strategies have been proposed to make these procedures more environmentally friendly without compromising patient safety. These strategies primarily include simple, practical solutions to reduce energy consumption in operating rooms, such as turning off lights and ventilation when the room is not in use, and powering down equipment when not needed.[18] Another strategy is to reuse equipment or choose equipment designed to be reusable. Kallay et al.[19] found that a phacoemulsification device with specially designed reusable cassettes provided a 75.3% reduction in plastic waste production compared to conventional devices with disposable cassettes, without posing any risk to patient safety. Noteworthy studies on equipment reuse have been conducted in 11 regional eye hospitals within the Aravind Eye Care System in South India. In this region, surgical gloves, gowns, irrigation/aspiration probes, irrigation bottles, scalpels, and cannulas are widely reused to reduce costs and minimize waste generation, with post-cataract endophthalmitis rates similar to or below global rates.[20,21] Another measure that can be taken is to improve waste management. Most operating room waste consists of recyclable materials such as paper, plastic packaging, metal, and glass.[14] Khor et al.[22] reported that approximately 57% of the waste generated in cataract surgery can be classified as clinical waste, 38% as general waste, and 6% as sharps waste. Fifty-one percent of the general waste produced can be recycled, which would reduce CO_2eq emissions from 0.421 kg to 0.282 kg per operation.

There are no studies in the current literature evaluating carbon emissions related to congenital and developmental cataracts specifically. However, the above-mentioned carbon emission sources and solutions also apply. Nevertheless, when implementing these measures, it should be kept in mind that pediatric patients may be more prone to infection and inflammatory conditions and can have different outcomes than adults.

We also found no study specifically examining measures that can be taken in strabismus surgery. However, economic analyses have shown that strabismus surgery is cost-effective.[23,24] Beauchamp et al.[24] conducted a cost-benefit analysis of adult strabismus surgeries and found that the estimated total cost per case was $4254 according to the model they developed. When evaluated according to quality-adjusted life year (QALY) gains, adult strabismus surgery costs $1632/QALY. This is very cost-effective compared to other ocular procedures such as cataract surgery ($2093/QALY for the first eye, $2863/QALY for the second eye), pars plana vitrectomy for diabetes-related vitreous hemorrhage ($2038/QALY), and amblyopia treatment ($2395/QALY).[25,26,27]

In a study on waste production in ophthalmic surgeries, Lever et al.[28] reported that intraocular procedures produced approximately 80% more waste than extraocular procedures. A very recent study conducted at Ann & Robert H. Lurie Children's Hospital in Chicago examined CO_2eq emissions produced during strabismus surgery. The CO_2eq emissions of the materials used were calculated using the Sustainability Index tool of the European Society for Cataract and Refractive Surgery, and the average total CO_2eq emission per case was determined as 4.80 kg. The largest component in this average was surgical drapes, which produced an average of 2.54 kg CO_2eq and represented 53% of the average emissions per case. This was followed by unused operating room towels (1.51 kg CO_2eq) and cotton-tipped applicators (0.33 kg CO_2eq).[29] Although it varies by country and the metrics used, strabismus surgery is an efficient and environmentally friendly procedure, considering that the CO_2eq emissions associated with a single cataract surgery range from 81.13 to 151.9 kg.

Reorganizing Polyclinic Services

Advances in telemedicine and the continuation of practices that originated as COVID-19 measures have led to increased usage of local health centers and virtual clinics as an alternative to traditional face-to-face visits.[30] These approaches are also time- and labor-efficient, making them an attractive option in the restructuring of outpatient clinic services. With the growing awareness of sustainability in ophthalmology, it is increasingly recognized that these methods not only save time and effort, but also support sustainability by reducing transport, building, and energy use and decreasing waste production. However, telemedicine services create their own carbon footprint, especially in terms of server and digital device use. Holmner et al.[31] compared CO_2eq emissions generated during telemedical appointments and routine services and determined that telemedicine services became carbon cost-effective when the transportation distance was more than 7.2 km.

Pediatric ophthalmology and strabismus practice involves a large team of pediatric ophthalmologists, strabismus specialists, opticians, nurses, and other staff.[32] Reorganizing outpatient clinic services to include non-physician personnel in the system can reduce clinical intensity, reduce costs, and increase sustainability. An interesting study on this topic was conducted by Francis et al.[33] at NHS Sheffield Teaching Hospitals in the United Kingdom. The study team has implemented virtual strabismus clinics since January 2015 and further developed these outpatient clinics during the COVID-19 pandemic. They provide an environmentally friendly and sustainable service that reduces travel, parking costs, energy consumption, and waste while ensuring that patients are served in a timely manner. Studies conducted in other countries have also reported favorably on the integration of non-physician personnel into the system. In Spain, 90% of 42 pediatric ophthalmologists and strabismus specialists supported the inclusion of orthoptists in the team because they believed it would alleviate the patient burden.[34]

Amblyopia Management: Another Major Challenge in Pediatric Ophthalmology

A 2020 meta-analysis evaluating a total of 16,385 cases from 60 studies indicated an amblyopia prevalence of 1.44%. In 2019, there were approximately 99.2 million amblyopes worldwide, with this number expected to increase to 175.2 million by 2030 and 221.9 million by 2040.[35] Amblyopia treatment usually requires repeated examinations over a long follow-up period. Considering the increasing prevalence of amblyopia, this suggests substantial carbon emissions from transportation.

Thomas et al.[36] compared the transportation distance, time in clinic, and treatment costs of amblyopic children followed up in a hospital versus local health centers and found that all three parameters were lower in local health centers (Table 1). Therefore, performing post-diagnosis follow-up and control examinations at local health centers can be considered as a safe, cost-effective, time-saving, and environmentally friendly option.

Table 1. Average transportation, waiting times, and treatment costs for amblyopic children treated in hospitals and local health centers

	Hospital	Local health center (n=71)
Mean transportation distance (miles)	(n=92)	3.7
Mean time in clinic (minutes)	(n=71)	20
Mean examination cost (pounds)	100	55

Another problem in amblyopia management is the waste produced by disposable patches. Although the literature on occlusion therapy mainly focuses on compliance and efficacy, the patches used are also thought to cause significant waste and carbon footprint production. Despite various alternative treatments such as penalization, pharmacotherapy, and levodopa, occlusion therapy still remains the gold standard for amblyopia.[37,38] Aside from patches, various products such as opaque spectacles, Doyne occluders, Bangerter filters, and contact lens occluders have been developed and marketed specifically to address compliance problems.[39] As an affordable and eco-friendly option, patches made of fabric and foam fixed to the head with an elastic strap may be a good alternative. Moreover, a study by the Pediatric Eye Disease Investigator Group (PEDIG) found that Bangerter filters provided vision gains equivalent to 2 hours of occlusion per day in children with moderate amblyopia (20/40-20/80).[40] PEDIG also reported that atropine and occlusion provided similar visual gains in children with moderate amblyopia.[41] These alternative treatment options can be considered in children with mild to moderate amblyopia especially, both to increase compliance and reduce the environmental impact of treatment. Furthermore, Abu-Ain and Watts[42] emphasized that occlusive contact lenses had an acceptable side effect profile and may offer an alternative treatment for amblyopia.

Ophthalmologists' Carbon Footprint: Analysis of the 2021 and 2022 AAPOS Annual Meetings

In addition to the known sources of greenhouse gas emissions in health care, the carbon footprint associated with professional conferences have also become a subject of research.[43] A noteworthy study conducted by West and Hunter[44] examined the carbon footprint of pediatric ophthalmology meetings. The authors compared the CO_2eq emissions of the 2021 and 2022 AAPOS Annual Meetings, which were held virtually due to the pandemic, with the CO_2eq emissions of face-to-face meetings. The study team found that in 2021, the virtual meeting format saved 1,282 tons of CO_2eq emissions, which is equivalent to the emissions of 264 vehicles used for a year. Although face-to-face meetings offer advantages such as facilitating interaction, business partnerships, and workshop and course participation, they create a significant transportation and accommodation burden worldwide, leading to a serious carbon footprint.

Anesthesia: An Added Problem in Pediatric Examinations

Datta et al.[45] randomized 50 children aged 1-5 years undergoing ophthalmological examination under anesthesia into two groups. Both groups received 8% sevoflurane in O_2:N_2O (40:60), followed by a standard 2% sevoflurane regimen with 1 L/min fresh gas flow (50:50) in one group (Group S), while in the other group (Group L), sevoflurane was discontinued and the fresh gas flow was reduced to 0.5 L/min. Effective anesthesia time showed no difference between the groups (median 14-15 minutes), whereas Group L used 2 mL less sevoflurane ($p<0.001$, 95% confidence interval: 0.96-3.04) and 3.75 mL less nitrous oxide per case. In addition, laryngeal mask removal time was shorter in Group L compared to Group S (86 s vs. 131 s; $p=0.002$, 95% confidence interval=19.85-70.15). This anesthesia approach produced an average of 11,327 L less carbon dioxide per day. The study team concluded that this method can reduce the negative environmental impact without affecting the duration and quality of anesthesia.[45]

Pediatric patients are a high-risk group for hypothermia due to the lower capacity of the central nervous system to regulate body temperature, the different body weight/surface area ratio than adults, and lower amount of subcutaneous adipose tissue.[46] Rather than addressing this by heating the entire operating room, forced-air heating has been recommended as a sustainable measure to maintain adequate body temperature throughout the procedure.[47]

Finally, the laryngeal airway mask (LMA) has been used for many years in ophthalmic surgery and offers advantages over tracheal intubation in terms of intraocular pressure and cardiovascular stability.[48] In a study of pediatric patients, the LMA was also found to be advantageous over conventional intubation in terms of both anesthesia time and awakening time.[49] This should be taken into account in terms of anesthesia efficiency, especially the efficiency of the operating room.

Artificial Intelligence in Pediatric Ophthalmology and Strabismus

Artificial intelligence has started to play a role in the diagnosis and management of various anterior and posterior segment pathologies, optic nerve diseases, strabismus, and pediatric diseases. With improvements in diagnostic accuracy, it has become particularly valuable in reducing workload and costs related to screening.[50] Chen et al.[51] introduced a deep learning-based screening method that can diagnose 16 common eye pathologies in children, including strabismus. In another study, Long et al.[52] developed a system that successfully identified abnormal patterns (area under the curve: 86.4%-93.0%) by analyzing the behavioral phenotypes of 4,196 infants. Shu et al.[53] reported that an artificial intelligence model they developed effectively detects myopia, strabismus, and ptosis (with 84%, 73%, and 85% sensitivity, respectively) using mobile phone photographs.

In addition, mobile photo-supported applications have been developed that can quantitatively measure strabismus deviation. These programs may be useful for both orthoptists and strabismus specialists in teleophthalmology examinations, diagnosis, and even surgical decision-making.[54,55] Several other studies report similarly successful results, and it is believed that artificial intelligence will become an important part of examinations once standardization is achieved.[56,57,58] Such advances will help conserve resources and promote sustainability in many areas such as transportation, waste management, and energy consumption.

In summary, although research on sustainability practices has increased in recent years, there is still limited information on what can be done in pediatric ophthalmology and strabismus. In addition to the general principles of sustainability that can be applied in outpatient clinics and operating rooms, certain measures related to the core areas of pediatric ophthalmology and strabismus can help reduce its carbon footprint, such as involving non-physician personnel (e.g., optometrists), performing amblyopia examinations in local health centers, integrating artificial intelligence, and modifying anesthesia protocols. However, it should be kept in mind that the existing literature stems from very different health systems, and results may vary in countries with different levels of development and different practice patterns.

Declarations

Authorship Contributions

Concept: M.P., E.D.B., Design: M.P., E.D.B., Literature Search: Z.A., Writing: Z.A., E.D.B., M.P.

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

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

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Case Report

Superior Segmental Optic Nerve Hypoplasia: A Rare Mimicker of Normal-Tension Glaucoma–A Case Series from Türkiye

Cansu Yüksel Elgin, İlayda Kaner Savcı, Özcan Ocakoğlu

İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Ophthalmology, İstanbul, Türkiye

Abstract

This retrospective case series presents the characteristic features of superior segmental optic nerve hypoplasia (SSONH) in four patients who were initially misdiagnosed with normal-tension glaucoma (NTG), aiming to raise awareness of this rare condition in Türkiye. Four patients (two females and two males) with a mean age of 38 years were included. All were initially diagnosed with NTG and treated with brimonidine drops for three years. Comprehensive ophthalmological examinations were performed, including optic disc photography, optical coherence tomography retinal nerve fiber layer (RNFL) analysis, and visual field testing, with follow-up evaluations conducted over at least one year. Bilateral involvement was observed in two cases, and unilateral involvement in the other two. History of maternal diabetes was noted in 50% of the patients. During medication-free follow-up, all patients demonstrated stable structural and functional parameters, supporting the diagnosis of SSONH. These findings suggest that SSONH should be considered in young patients presenting with superior RNFL thinning and corresponding inferior visual field defects. The non-progressive nature of the condition helps differentiate it from glaucomatous optic neuropathy. Recognizing unilateral cases is essential for avoiding misdiagnosis.

Keywords: Superior segmental optic nerve hypoplasia, normal tension glaucoma, Türkiye

Cite this article as: Yüksel Elgin C, Kaner Savcı İ, Ocakoğlu Ö. Superior Segmental Optic Nerve Hypoplasia: A Rare Mimicker of Normal- Tension Glaucoma–A Case Series from Türkiye. Turk J Ophthalmol. 2026;56:54-60

Address for Correspondence: Cansu Yüksel Elgin, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Ophthalmology, İstanbul, Türkiye
E-mail: cansu.elgin@iuc.edu.tr
ORCID-ID: orcid.org/0000-0002-3120-8782

Received: 17.06.2025
Revision Requested: 25.08.2025
Last Revision Received: 13.10.2025
Accepted: 17.11.2025
Publication Date: 18.02.2026

DOI: 10.4274/tjo.galenos.2025.89699

Introduction

Superior segmental optic nerve hypoplasia (SSONH) is a rare congenital developmental anomaly first described by Petersen and Walton[1] in 1977 as a distinct form of optic nerve hypoplasia. Unlike generalized optic nerve hypoplasia, SSONH is characterized by preserved visual acuity with sectoral visual field defects and has gained attention as a crucial differential diagnosis for glaucoma, particularly normal-tension glaucoma (NTG).

The four key diagnostic features of SSONH are relative superior entrance of the central retinal artery, pallor of the superior optic disc, superior peripapillary halo, and thinning of the superior peripapillary nerve fiber layer.[2] However, not all patients exhibit all of these characteristics, and the presence of at least two features with documented non-progressive disease course may be sufficient for diagnosis.[3] Figure 1 demonstrates characteristic fundoscopic appearances of SSONH, showing both unilateral and bilateral presentations with the classic "topless disc" appearance described by Landau et al.[4]

Maternal diabetes has been recognized as a significant risk factor, though recent studies suggest other factors may contribute to SSONH development.[3,5] The condition predominantly affects females and remains stable over time without progression, distinguishing it from glaucomatous optic neuropathy.[6]

Despite being well-documented in East Asian countries, SSONH remains underrecognized in Türkiye, where it is often misdiagnosed as glaucoma, leading to unnecessary treatments and interventions. To address this gap in awareness, we present a retrospective case series of four patients who were initially misdiagnosed with NTG but later identified as having SSONH.

Case Reports

All patients were evaluated at our glaucoma clinic and underwent comprehensive ophthalmological examinations including optic disc photography (Visucam 500; Carl Zeiss Meditec AG, Jena, Germany), retinal nerve fiber layer (RNFL) analysis (Cirrus HD-OCT 4000; Carl Zeiss Meditec, Inc., Dublin, CA, USA), and visual field testing (HFA-II 750; Carl Zeiss Meditec, Inc., Dublin, CA, USA). Detailed medical histories were reviewed, and follow-up assessments were carried out over a minimum of one year to evaluate the stability of structural and functional parameters. Table 1 summarizes the sociodemographic and clinical features of all four patients. The cohort included two females and two males with a mean age of 38 years (range 30-55). All patients had been treated with brimonidine drops for suspected NTG for at least three years before correct diagnosis.

Case 1

A 30-year-old female patient presented for glaucoma follow-up after relocating. Visual acuity was 20/20 bilaterally with intraocular pressure (IOP) of 16 mmHg. Figure 2 shows bilateral superior RNFL thinning on optical coherence tomography (OCT) analysis. Maternal type 1 diabetes was documented. No progression was observed during three years of external follow-up. Following SSONH diagnosis, brimonidine therapy was discontinued, and two-year medication-free follow-up showed stable parameters (IOP 16-18 mmHg) with resolution of ocular surface complaints.

Case 2

A 32-year-old female patient sought a tertiary opinion after receiving NTG diagnoses from two centers. Visual acuity was 20/20 in the right eye and 20/30 in the left (due to amblyopia from childhood ankyloblepharon surgery). Guided progression analysis showed stable RNFL parameters over time in right-sided unilateral SSONH (Figure 3). Maternal insulin-dependent diabetes

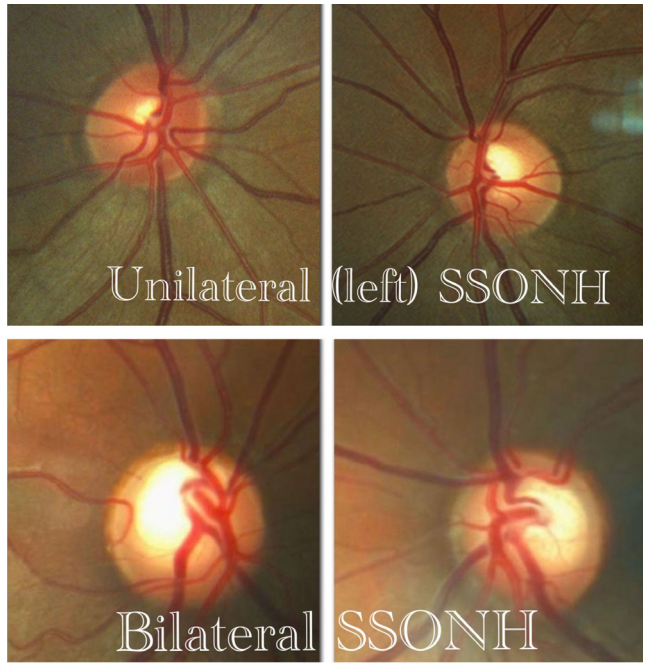

Figure 1. Appearance of the right and left optic disc in unilateral and bilateral cases of superior segmental optic nerve hypoplasia (SSONH)

Table 1. Sociodemographics and clinical features of the patients

	Case 1	Case 2	Case 3	Case 4
Age (years)	30	32	55	35
Sex	Female	Female	Male	Male
BCVA (Snellen feet) (R, L)	20/20, 20/20	20/20, 20/32	20/20, 20/20	20/20, 20/20
IOP (mmHg) (R, L)	16, 16	12, 13	17, 17	15, 16
CCT (µm) (R, L)	585, 580	530, 540	612, 618	585, 588
Average RNFL thickness (µm) (R, L)	75, 77	74, 89	76, 63	64, 82
Eye involvement	Bilateral	Unilateral	Unilateral	Bilateral
Maternal diabetes	Yes	Yes	Unknown	No
Systemic comorbidity	None	None	None	None
Ocular comorbidity	None	Unilateral congenital ankyloblepharon	Presbyopia	None
Mean follow-up in SSONH (months)	24	27	13	18

BCVA: Best corrected visual acuity, R: Right eye, L: Left eye, IOP: Intraocular pressure, CCT: Central corneal thickness, RNFL: Retinal nerve fiber layer, SSONH: Superior segmental optic nerve hypoplasia

was documented. Two-year follow-up without treatment confirmed stable IOP (11-14 mmHg) and no structural progression.

Case 3

A 55-year-old male patient initially presented with presbyopic complaints and was diagnosed with glaucoma. Despite irregular medication compliance, no progression was observed over two years. Visual acuity was 20/20 bilaterally with IOP of 17 mmHg. Maternal diabetes history was unavailable due to early maternal loss. The patient was diagnosed as having left unilateral SSONH and showed stable parameters (IOP 14-18 mmHg) over 13-month medication-free follow-up.

Case 4

A 35-year-old male patient sought a second opinion three years after receiving a diagnosis of asymptomatic NTG. Maternal gestational glucose intolerance was suspected. Visual field testing demonstrated characteristic

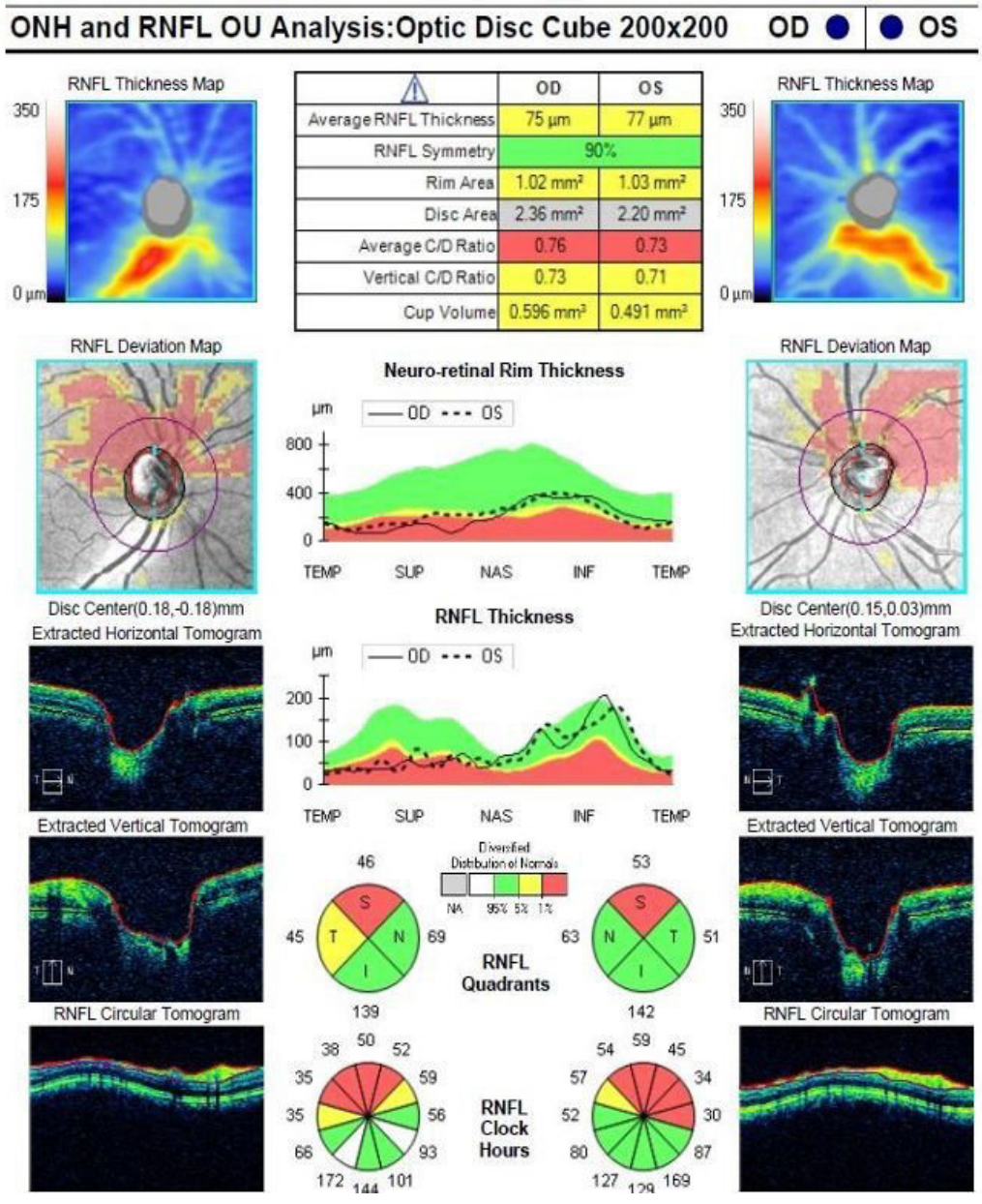

Figure 2. Representative optical coherence tomography (OCT) retinal nerve fiber layer (RNFL) findings in superior segmental optic nerve hypoplasia (SSONH)

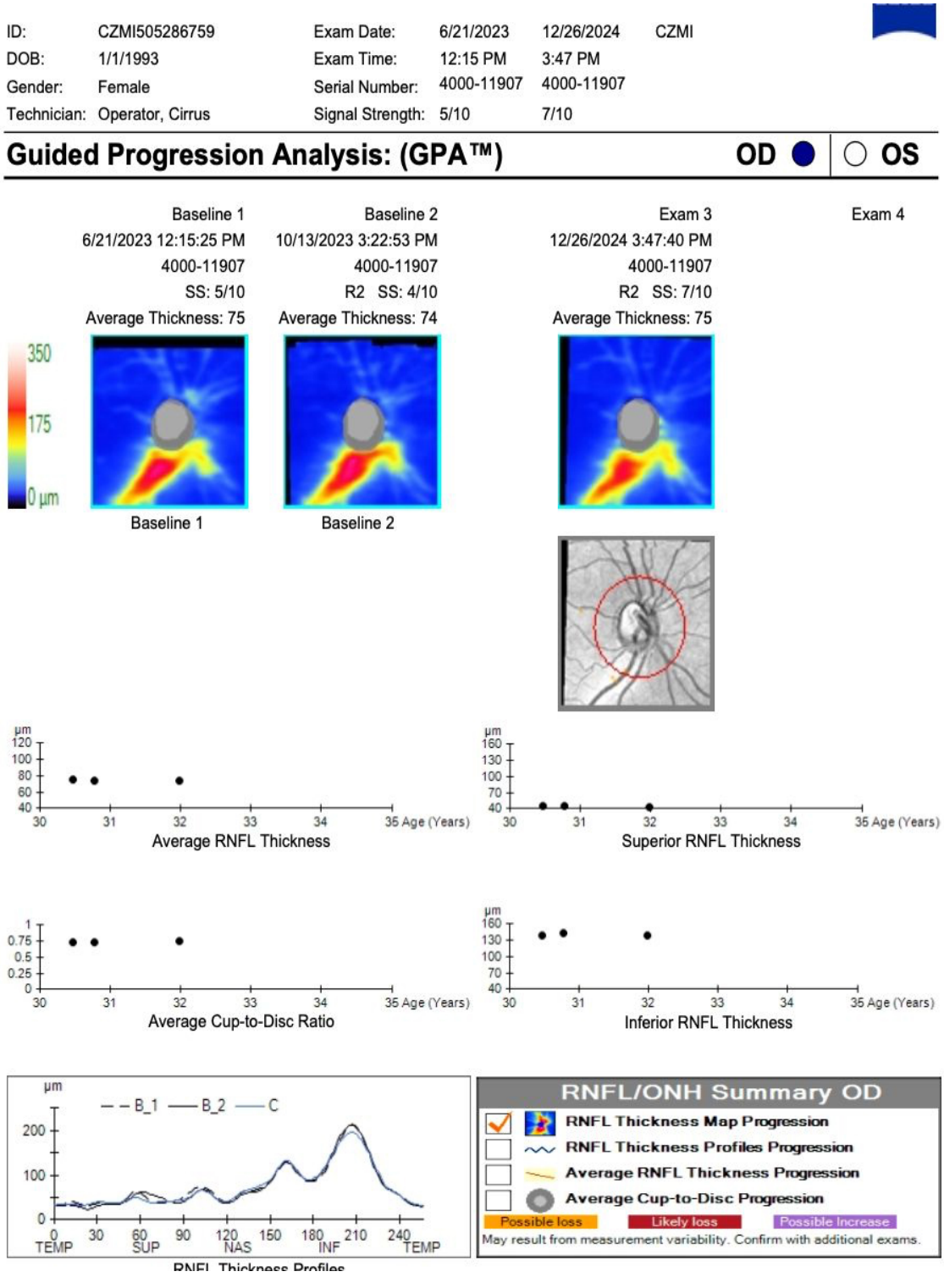

Figure 3. Longitudinal retinal nerve fiber layer (RNFL) imaging in superior segmental optic nerve hypoplasia (SSONH) demonstrating structural stability over time

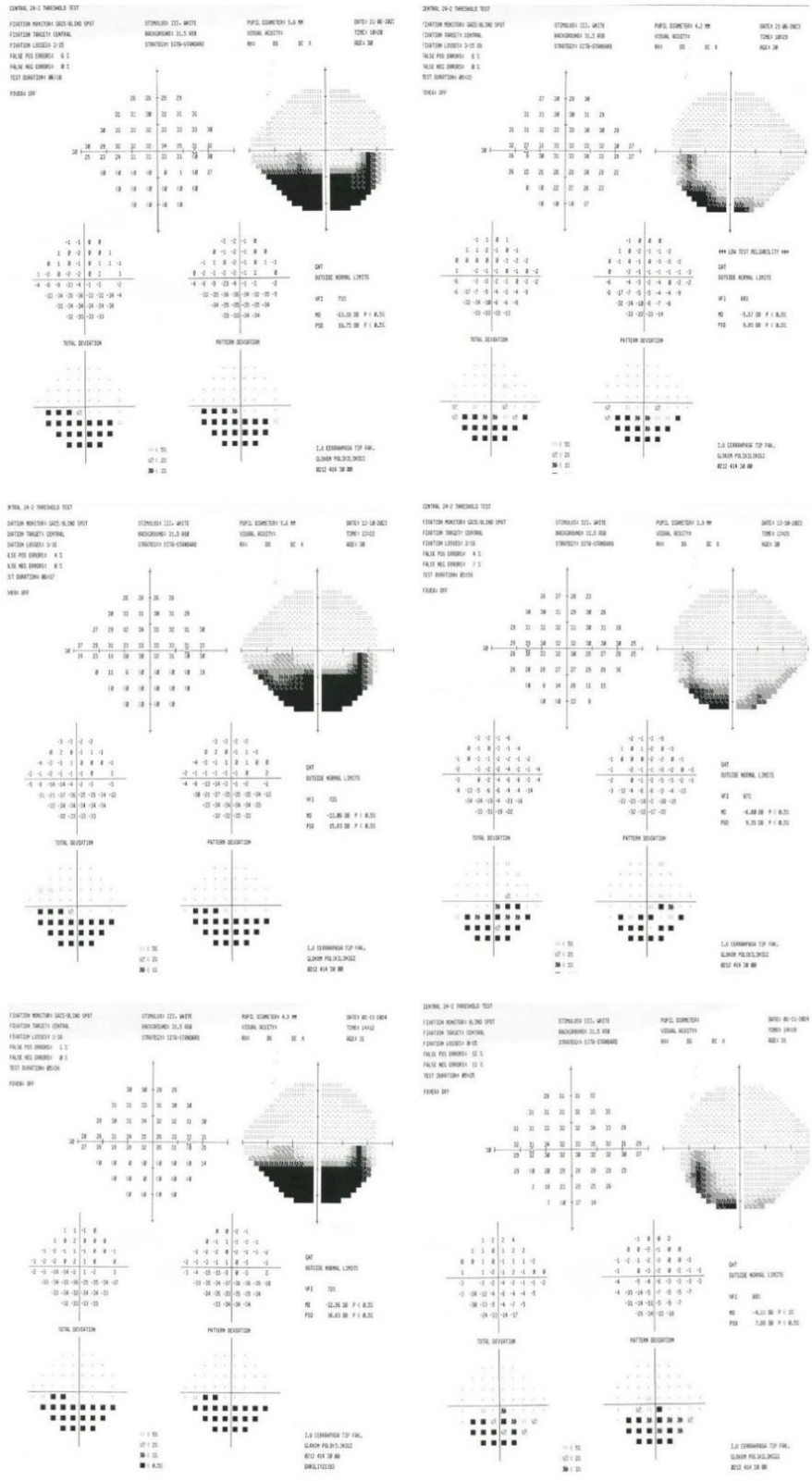

Figure 4. Long-term visual field stability in superior segmental optic nerve hypoplasia (SSONH)

inferior arcuate scotomas (Figure 4). The patient exhibited bilateral SSONH with more prominent findings in the right eye. Lack of structural or functional progression over time (18 months) supported a diagnosis of SSONH over glaucomatous optic neuropathy.

Discussion

This case series highlights the diagnostic challenges of SSONH, particularly its differentiation from NTG. All four patients were initially misdiagnosed and received unnecessary treatment, emphasizing the importance of awareness among ophthalmologists.

The demographic profile shows interesting patterns. While previous studies suggested female predominance,[3,4] our cohort included two males (50%), reinforcing that SSONH affects both genders.[7] Notably, two patients (50%) presented with unilateral involvement, which contrasts with typical bilateral presentations reported in the literature.[1,3] Unilateral SSONH, though less common, has been documented and should be recognized as a valid presentation pattern.[8] This finding is particularly important, as unilateral cases may be more easily misdiagnosed as glaucoma due to asymmetric presentation.

Maternal diabetes was documented in two cases (50%), consistent with established associations.[1,2] However, the fourth patient lacked a history of maternal diabetes, supporting recent findings that other factors may contribute to SSONH development beyond maternal diabetes.[9]

OCT RNFL analysis revealed characteristic superior RNFL thinning in all cases, differing from the inferotemporal thinning commonly observed in glaucoma. This pattern provides a valuable diagnostic distinction. Visual field defects predominantly affected inferior regions, further supporting the SSONH diagnosis.

The most significant diagnostic feature was stability of structural and functional parameters during long-term follow-up without treatment. This non-progressive nature distinguishes SSONH from glaucomatous optic neuropathy, which typically shows progression if untreated. Our cases demonstrated stable parameters over mean 20.5 months of medication-free follow-up.

Several conditions should be considered in the differential diagnosis of SSONH. NTG is the most common diagnostic challenge, as both disorders may present with superior RNFL thinning and inferior visual field defects. However, SSONH is a congenital and usually non-progressive anomaly observed in younger patients, whereas NTG typically appears later in life, often when systemic vascular disease is more prevalent.[10,11] Although our patients were younger than the typical age group for NTG, all underwent systemic internal medicine and neurology consultations, as well as magnetic resonance imaging (MRI), and no significant pathological findings were detected. Considering the age group in which SSONH is typically diagnosed, periventricular leukomalacia (PVL) should also be included in the differential diagnosis, as it may mimic both SSONH and NTG by demonstrating optic disc cupping and superior RNFL loss with corresponding inferior field defects.[12] Yet, PVL is usually associated with a history of prematurity and characteristic periventricular or subcortical white matter changes on MRI, which help to distinguish it from SSONH.[13] In addition, split RNFL variations, most often observed superiorly, may resemble SSONH in asymptomatic adults with IOP below 21 mmHg, but these represent benign anatomical variants without underlying congenital optic nerve anomalies.[14]

An important clinical implication is the unnecessary treatment burden. All patients had received brimonidine drops for 3 years, causing financial burden and, in one case, ocular surface complications. This underscores the importance of accurate differential diagnosis to prevent unnecessary interventions.

Limitations of this study include the retrospective nature and small sample size. However, given SSONH's rarity (prevalence <1%), case series remain valuable for understanding this condition. Recent advances in OCT angiography may provide additional diagnostic tools through peripapillary vessel density measurements, though this was not evaluated in our cases.[15]

SSONH should be considered in young patients with suspicious optic nerve appearance, superior RNFL thinning, and inferior visual field defects, especially with maternal diabetes history. However, the absence of maternal diabetes should not exclude the diagnosis. Importantly, both bilateral and unilateral presentations should be recognized, as unilateral cases may be more prone to misdiagnosis as glaucoma. The stability of structural and functional parameters over time, even without treatment, remains the key diagnostic feature distinguishing SSONH from NTG. Long-term follow-up is essential for accurate diagnosis. Raising awareness among Turkish ophthalmologists regarding this rare congenital anomaly is crucial for preventing misdiagnosis and unnecessary treatments, thereby improving patient care and reducing the healthcare burden.

Ethics

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

Declarations

Authorship Contributions

Surgical and Medical Practices: C.Y.E., Ö.O., Concept: C.Y.E., İ.K.S., Design: C.Y.E., İ.K.S., Data Collection or Processing: C.Y.E., İ.K.S., Analysis or Interpretation: C.Y.E., İ.K.S., Literature Search: C.Y.E., İ.K.S., Ö.O., Writing: C.Y.E., İ.K.S.

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

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

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Partial Graft Detachment During Gonioscopy-Assisted Transluminal Trabeculotomy in a Patient Who Underwent Descemet Membrane Endothelial Keratoplasty

Raziye Dönmez Gün[1], Burak Tanyıldız[2], Erdi Karadağ[1], Mustafa Talan[1]

[1]University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
[2]Kartal Acıbadem Hospital, Clinic of Ophthalmology, İstanbul, Türkiye

Dear Editor,

Microinvasive glaucoma surgeries (MIGS) are surgical techniques that utilize an ab-interno approach, cause minimal tissue disruption with little to no scleral dissection, involve limited conjunctival manipulation, and are characterized by a favorable safety profile and quick postoperative recovery.[1] Gonioscopy-assisted transluminal trabeculotomy (GATT) is a recently developed conjunctiva-sparing technique that enables circumferential trabeculotomy. It is considered an innovative MIGS method with a favorable safety profile and proven effectiveness in lowering intraocular pressure (IOP) in patients with open-angle glaucoma.[2] However, like all surgical procedures, GATT is associated with potential complications. Reported adverse events include transient hyphema, steroid-induced IOP elevation, cystoid macular edema, Descemet's membrane detachment (including hemorrhagic forms), corneal edema, inadvertent iridodialysis or cyclodialysis, partial separation of Schlemm's canal, trabecular meshwork, and Descemet's membrane, choroidal detachment, and hypotony maculopathy.[3,4]

GATT surgery has been reported to be safe and effective in eyes that have undergone various corneal procedures, including Descemet membrane endothelial keratoplasty (DMEK).[5] This study reports a newly identified complication of GATT surgery observed in a patient with a history of DMEK.

A 38-year-old male patient underwent cataract surgery in the left eye 18 years ago following a bullet injury. Due to subsequent persistent corneal edema despite medical treatment, he was referred to our clinic for corneal transplantation. The patient underwent DMEK in the left eye 2.5 years ago, followed by repeat DMEK 4 months later due to graft rejection. Following the second DMEK surgery, the patient was diagnosed with Irvine-Gass syndrome and received a sub-Tenon triamcinolone injection. The spherical equivalent was -1.00 diopter (D) in the right eye and -6.00 D in the left eye. The best corrected visual acuity (BCVA) in the right eye was 20/20, with unremarkable anterior and posterior segment examinations. The BCVA in his left eye was 20/40, and despite maximum topical medical therapy and oral acetazolamide, IOP remained uncontrolled at 24 mmHg. On slit-lamp biomicroscopy of the left eye, the corneal graft was well-apposed, the cornea was mildly edematous, and the eye was pseudophakic. Fundus

Keywords: Gonioscopy-assisted transluminal trabeculotomy, Descemet membrane endothelial keratoplasty, graft detachment, complication

Cite this article as: Dönmez Gün R, Tanyıldız B, Karadağ E, Talan M. Partial Graft Detachment During Gonioscopy-Assisted Transluminal Trabeculotomy in a Patient Who Underwent Descemet Membrane Endothelial Keratoplasty. Turk J Ophthalmol. 2026;56:61-64

This case presentation was available in the ESCRS Video Library as part of the 43rd Congress of the ESCRS.

Address for Correspondence: Raziye Dönmez Gün, University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
E-mail: rdmstf84@gmail.com
ORCID-ID: orcid.org/0000-0002-0785-5162

Received: 13.10.2025
Revision Requested: 12.12.2025
Last Revision Received: 16.12.2025
Accepted: 17.12.2025
Publication Date: 18.02.2026

DOI: 10.4274/tjo.galenos.2025.67672

examination revealed a cup-to-disc ratio of 0.3 in the right eye and 0.6 in the left eye. The retinal nerve fiber layer thickness was 103 µm in the right eye and 100 µm in the left eye. Central corneal thickness was 550 µm in the right eye and 610 µm in the left eye. As the angle structures were clearly identifiable on gonioscopic examination, GATT surgery was chosen to achieve IOP control. One year after re-DMEK, the patient underwent GATT surgery. Figure 1A shows the anterior segment image before GATT surgery.

During GATT, a partial graft detachment was noted after completing the 360-degree procedure, when a semi-transparent horizontal line appeared on the superior cornea (Figure 2) during viscoelastic removal via irrigation/aspiration (I/A). The graft was successfully repositioned by injecting air into the anterior chamber through an inferior corneal incision. Postoperative management included topical moxifloxacin (Moxai® 0.5%; Abdi İbrahim Pharmaceuticals, İstanbul, Türkiye) administered five times daily for ten days. Dexamethasone drops (Maxidex® 0.1%; Alcon Laboratories, Inc., Fort Worth, TX, USA) were prescribed every two hours and tapered according to the level of inflammation observed during follow-up, with complete discontinuation within 14 days. At the two-week postoperative visit, the corticosteroid regimen was transitioned to loteprednol drops (Lotemax® 0.5%; Bausch & Lomb Incorporated, Rochester, NY, USA), administered twice daily. Nepafenac (Apfecto® 0.3%; World Medicine Pharmaceuticals, İstanbul, Türkiye) was also given once daily for one month. Early postoperative evaluation with clinical examination and anterior segment optical coherence tomography confirmed proper graft adherence. Figure 1B presents the anterior segment image on postoperative day 2, while Figure 3 demonstrates anterior segment optical

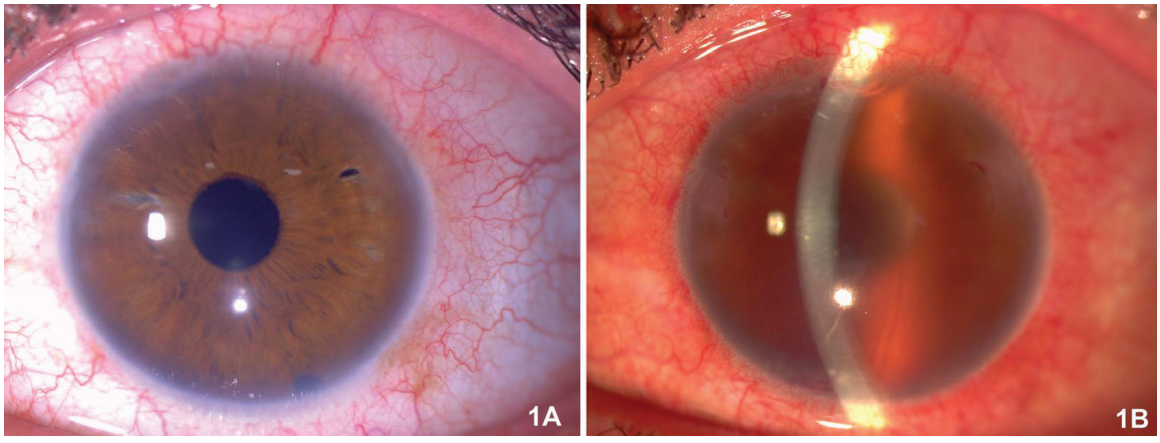

Figure 1. A) Preoperative anterior segment image before gonioscopy-assisted transluminal trabeculotomy (GATT) surgery. B) Postoperative day-2 anterior segment image after GATT

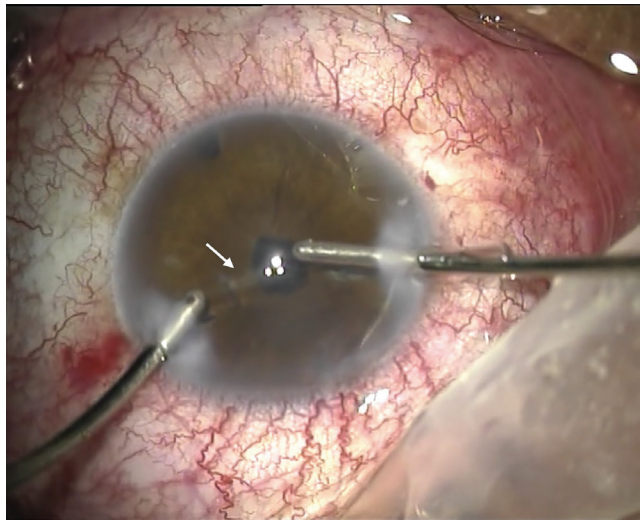

Figure 2. Partial graft detachment (arrow)

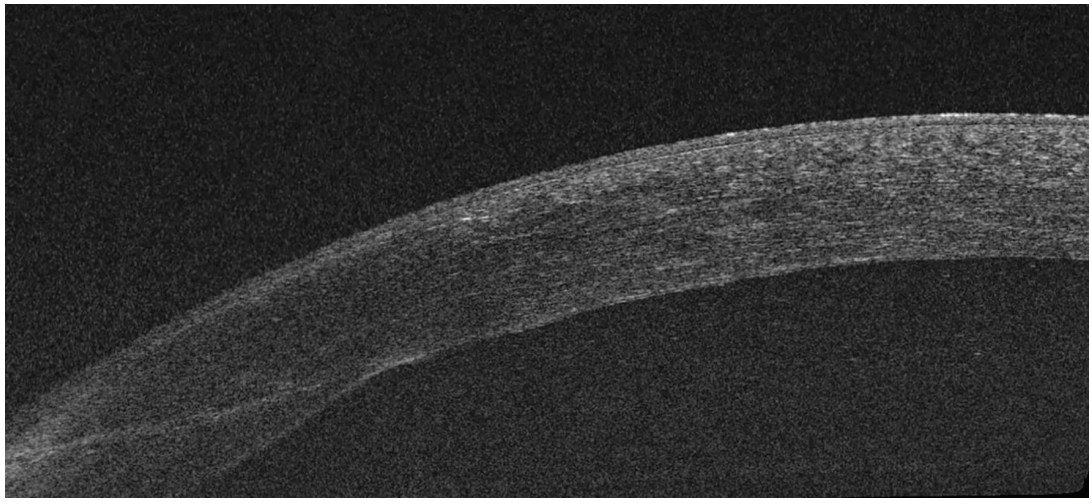

Figure 3. Anterior segment optical coherence tomography confirming graft reattachment in the area of intraoperative detachment

coherence tomography confirming graft reattachment in the region of intraoperative detachment. At postoperative week 1, the patient's IOP was well-controlled at 15 mmHg without medication. However, on postoperative day 19, routine follow-up revealed an IOP spike (31 mmHg), prompting initiation of antiglaucoma therapy, which successfully stabilized the pressure. Dorzolamide hydrochloride + timolol maleate (Tomec® eye drops; Abdi İbrahim Pharmaceuticals, İstanbul, Türkiye) and brimonidine tartrate (Alphagan P® eye drops; AbbVie, North Chicago, IL, USA) were administered twice daily. In addition, oral acetazolamide (Diazomid® tablets; Sanofi, Türkiye) were prescribed at a dose of half a tablet four times daily, together with potassium citrate (Kalinor® tablets; Farma-Tek Pharmaceuticals, Türkiye) once daily. At 6 months after GATT surgery, the patient's IOP was 17 mmHg with medical treatment. The patient remains under follow-up.

Glaucoma develops in approximately 30% of patients following endothelial or penetrating keratoplasty, making it a serious postoperative complication that can adversely affect graft survival and long-term visual outcomes.[6,7] Patients may have pre-existing glaucoma prior to DMEK; however, *de novo* IOP elevation can also occur postoperatively. This postoperative IOP rise may result from air bubble-induced mechanical angle closure, steroid response, peripheral anterior synechiae, or sometimes without identifiable cause.[8] In our patient, the likely mechanism was steroid-induced response following sub-Tenon triamcinolone injection for Irvine-Gass syndrome after DMEK surgery. The patient was already receiving topical corticosteroid therapy following DMEK.

Reports of GATT surgery in patients with DMEK history are limited. Smith et al.[5] performed GATT surgery in patients with corneal transplantation history. In their study of 39 eyes, only one patient (2.6%) had previously undergone DMEK before GATT. They reported no intraoperative complications. In our case, two prior DMEK procedures may have led to weak graft attachment, while factors such as a potentially long temporal incision or the I/A cannula could have contributed to graft detachment during I/A. Although anterior segment OCT confirmed proper graft attachment before GATT surgery, distinguishing pathologically weak adhesion may not always be possible. Moreover, although we noticed the graft detachment during I/A, we cannot be certain exactly when it began. Considering both GATT and DMEK are ab interno procedures, all potential complications related to previous intraocular surgeries should be anticipated when planning GATT in eyes with such history. As demonstrated in our case, graft detachment risk may be higher in patients who have undergone repeated DMEK procedures, warranting greater caution during surgery. Another precaution when planning GATT surgery in patients with DMEK history is avoiding excessively long incisions. However, despite all precautions, if graft detachment occurs during GATT surgery in an eye with DMEK history, it can be successfully managed, as in our case, by injecting an air bubble into the anterior chamber to reposition the graft.

In conclusion, in eyes with a history of DMEK surgery, GATT can successfully achieve IOP control. However, there is a risk of graft detachment. Keeping this risk in mind throughout the procedure and monitoring the graft during surgery is advisable. In the event of detachment, the graft can be repositioned by injecting air into the anterior chamber.

Ethics

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

Declarations

Authorship Contributions

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

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

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

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Letter to the Editor

A Rare Corneal Scenario: Concurrent Diagnosis of Epithelial Basement Membrane Dystrophy and Crocodile Shagreen

Serap Ünal, Ayşe Bozkurt Oflaz, Şaban Gönül, Banu Bozkurt

Selçuk University Faculty of Medicine, Department of Ophthalmology, Konya, Türkiye

Dear Editor,

Epithelial basement membrane dystrophy (EBMD), also known as "map-dot-fingerprint dystrophy", is the most common form of corneal dystrophy and is frequently encountered in clinical practice. Although asymptomatic in many patients, recurrent epithelial erosions occur in approximately 10% of cases.[1] On clinical examination, it is characterized by subepithelial map-like patterns, fingerprint-like lines, and microcystic opacities on the epithelial surface. It usually appears between the ages of 20 and 40 years.[1]

Corneal degenerations are common clinical manifestations in ophthalmology and can be classified as age-related changes, deposits, and marginal degenerations.[2] Crocodile shagreen is an asymptomatic corneal degeneration characterized by bilateral grayish-white, polygonal corneal stromal opacities reminiscent of crocodile skin, seen especially in older patients.[2,3,4] There are two subtypes: anterior and posterior. In the anterior form (shagreen of Vogt), mosaic patterns and calcium deposits are seen at the level of Bowman's layer, while the posterior form crocodile shagreen is characterized by a "sawtooth" configuration of the stromal collagen lamellae.[2,4] In most cases, it does not affect visual acuity, is detected incidentally, and requires no treatment.[2,3]

In this case report, we discuss the clinical, anterior segment optical coherence tomography (AS-OCT), and *in vivo* confocal microscopy (IVCM) findings of a patient who presented with low vision in his left eye and was diagnosed with EBMD and crocodile shagreen, a previously unreported co-occurrence.

A 52-year-old man presented with a 6-year history of declining vision in the left eye. He had a history of phacoemulsification and intraocular lens (IOL) implantation surgery in the right eye 13 years earlier. Best corrected visual acuity was 0.8 Snellen decimal in the right eye and hand movements in the left eye. On biomicroscopic examination, both corneas were hazy and exhibited map-like structures consistent with EBMD in the epithelium and mosaic opacities characteristic of crocodile shagreen in the stroma (Figure 1A, B). The right eye was pseudophakic and the left eye had posterior polar cataract. On fundus examination, the optic disc and visible retinal areas in the right eye appeared normal, while the retina of the left eye could not be examined due to lens opacity. The retina appeared attached on ultrasound examination. Intraocular pressures were measured as 15 mmHg and 13 mmHg in the right and left eye, respectively. The patient had no systemic disease, regular medication use, or family history of similar ocular disease.

On AS-OCT (DRI OCT Triton, Topcon, Tokyo, Japan), central corneal thickness was 505 µm on the right and 511 µm on the left. Basement membrane irregularities,

Keywords: Epithelial basement membrane dystrophy, crocodile shagreen, *in vivo* confocal microscopy, corneal degeneration, optical coherence tomography

Cite this article as: Ünal S, Bozkurt Oflaz A, Gönül Ş, Bozkurt B. A Rare Corneal Scenario: Concurrent Diagnosis of Epithelial Basement Membrane Dystrophy and Crocodile Shagreen. Turk J Ophthalmol. 2026;56:65-68

Address for Correspondence: Ayşe Bozkurt Oflaz, Selçuk University Faculty of Medicine, Department of Ophthalmology, Konya, Türkiye
E-mail: draysebozkurtoflaz@yahoo.com
ORCID-ID: orcid.org/0000-0001-5894-0220

Received: 29.08.2025
Revision Requested: 10.10.2025
Last Revision Received: 11.11.2025
Accepted: 08.12.2025
Publication Date: 18.02.2026

DOI: 10.4274/tjo.galenos.2025.61254

hyperreflective epithelial incursions, and increased reflectivity in the anterior stroma were observed. Epithelial thickness was measured as 71 µm on the right and 73 µm on the left (Figure 2A, B). IVCM (Heidelberg Retina Tomograph II–Rostock Cornea Module, Heidelberg Engineering GmbH, Heidelberg, Germany) imaging revealed hyperreflective lines in the epithelium, an irregular, thickened basement membrane with sporadic lace-like appearance, and hyperreflective spots (Figure 3A, B). In addition, there were numerous dendritic cells situated around the basement membrane and penetrating into the epithelium (Figure 3B). A mosaic pattern of hyperreflective polygonal areas 50-200 µm in diameter, separated by black streaks, was observed in the stroma (Figure 3C). There were scattered guttae and a single hyperreflective opacity in the endothelium (Figure 3D). Endothelial cell counts were 2014 and 2107 cells/mm^2 in the right and left eyes, respectively. Phacoemulsification and posterior chamber IOL implantation were performed in the left eye. The surgery was uncomplicated, and visual acuity increased to 0.8 postoperatively.

IVCM enables histological examination of the cornea and is widely used in the diagnosis of corneal infections,

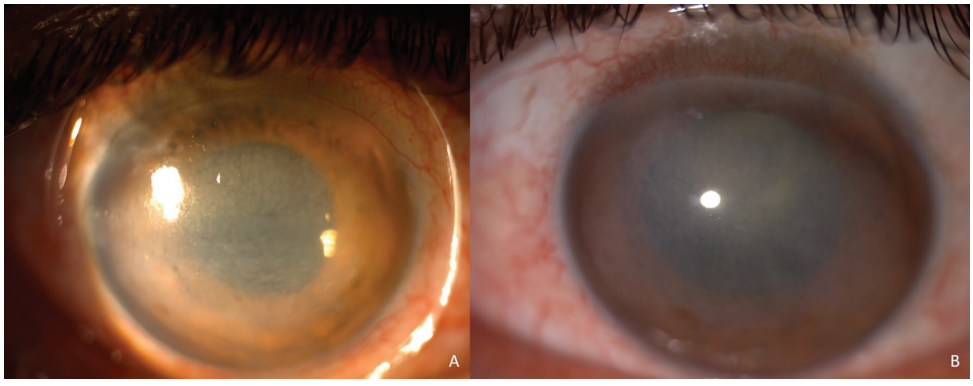

Figure 1. Anterior segment images of a patient with epithelial basement membrane dystrophy and crocodile shagreen. A) A therapeutic contact lens was applied to the right eye because of corneal haze and recurrent epithelial erosions; B) Corneal haze and the characteristic polygonal pattern of crocodile shagreen are seen in the left eye (×16 magnification)

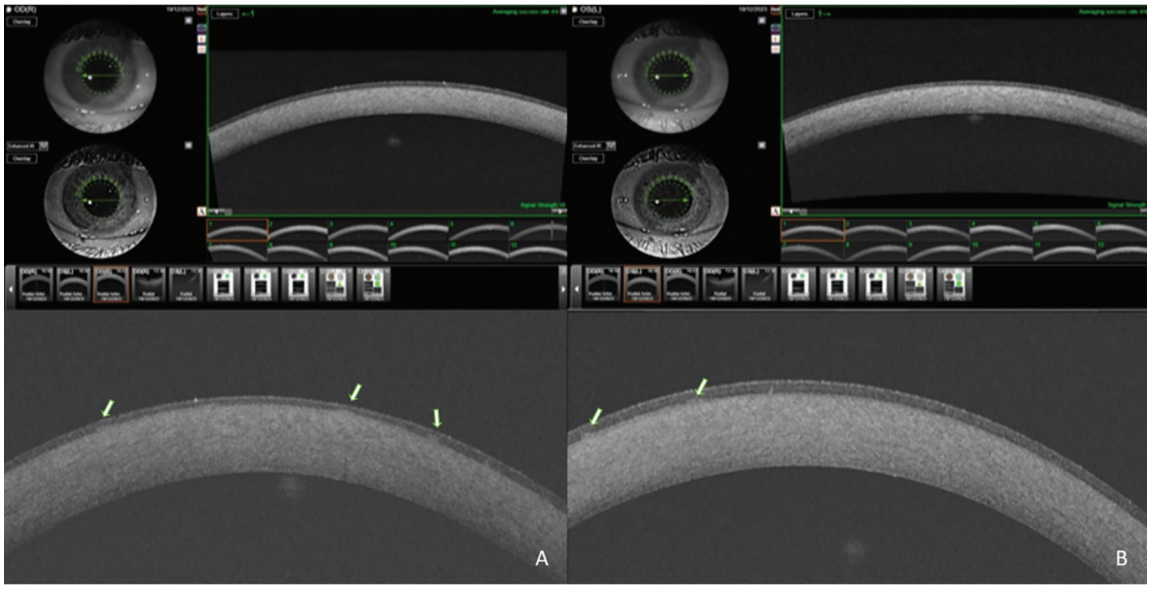

Figure 2. Anterior segment optical coherence tomography images (AS-OCT, DRI OCT Triton, Topcon, Tokyo, Japan). The right (A) and left (B) eyes show irregularities in the basement membrane, hyperreflective protrusions into the epithelium (arrows), and increased reflectivity in the anterior stroma

degeneration, and dystrophies.[5] Consistent with the literature, IVCM imaging in our patient demonstrated an irregular basement membrane with a thickened, lace-like appearance penetrating into the epithelium, round hyperreflective deposits in the epithelium, and irregular epithelial cells and structural defects in these regions, which are characteristic findings of EBMD.[6,7] In a study including 3 patients with crocodile shagreen and polymorphic amyloid degeneration, Woodward et al.[8] observed areas of acellular, hyperreflective opacity separated by linear black areas in the stroma on IVCM imaging in a patient with isolated posterior crocodile shagreen. In the patient with combined polymorphic amyloid degeneration and posterior crocodile shagreen, hyperreflective punctate lesions were observed in the stroma in addition to these findings. Similarly, our patient exhibited a mosaic pattern in the stroma consisting of hyperreflective polygonal areas with a diameter of 50-200 μm, separated by black streaks.

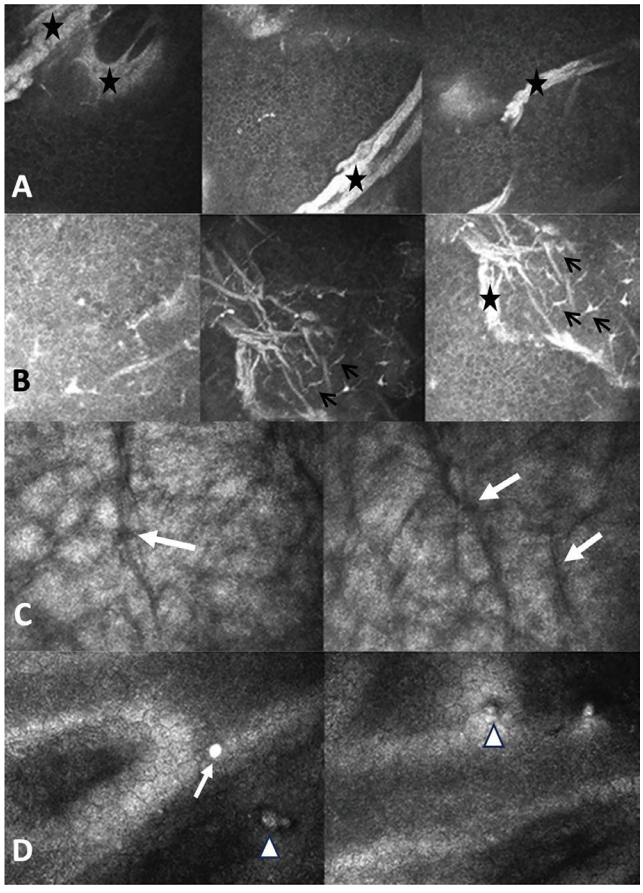

Figure 3. *In vivo* confocal microscopy images (IVCM, Heidelberg Retinal Tomograph 3/Rostock Cornea Module, Heidelberg Engineering). A, B) Hyperreflective lines in the epithelium, a sporadically lace-like, irregular, thickened basement membrane penetrating into the epithelium (black stars), and hyperreflective dots. B) Numerous dendritic cells (black arrows) around the thickened basement membrane. C) A mosaic pattern of hyperreflective polygonal areas 50-200 μm in diameter separated by black streaks (white arrows) in the stroma. D) Scattered guttae (white triangles) and a hyperreflective opacity (white arrow) in the endothelium

We found no AS-OCT study on crocodile shagreen in the literature. In this case report, images obtained with swept-source AS-OCT reveal irregularities in the epithelial basement membrane at high magnification, consistent with EBMD, with protrusion of the basement membrane into the epithelium. Although not very pronounced, there was increased reflectivity in the anterior stroma.

Belliveau et al.[4] used electron microscopy to examine corneal specimens from 3 patients with crocodile shagreen who underwent keratoplasty and demonstrated that the stromal collagen lamellae lost their parallel arrangement assuming a sawtooth-like irregular, wavy appearance. They also detected vacuoles in the stroma, particularly in the region adjacent to the banded anterior part of Descemet's membrane. The fibrillogranular electron-dense material in these vacuoles is thought to be caused by degenerative collagen products and mucopolysaccharide accumulation in the stroma. As vacuoles detected by electron microscopy are probably very small in diameter, they could not be detected on IVCM imaging in our study. Krachmer et al.[9] examined the cornea of a 75-year-old patient with posterior crocodile shagreen and polymorphic amyloid degeneration by postmortem transmission electron microscopy and showed the presence of sawtooth-like stromal collagen lamellae corresponding to central fuzzy opacities seen on clinical examination. They also confirmed the amyloid nature of the punctate and filamentous hyperreflective structures seen on clinical examination by histochemical staining and electron microscopy.

This case makes an important contribution to the literature as the first detailed documentation of EBMD and crocodile shagreen co-occurrence using both IVCM and AS-OCT. EBMD and crocodile shagreen are two separate clinical entities with pathophysiologically distinct etiologies and affect the epithelial and stromal layers of the cornea, respectively. While EBMD mostly causes structural disorders in the epithelial basement membrane, crocodile shagreen is characterized by degenerative changes in stromal collagen organization. These differences suggest that their coexistence may be a coincidental association.

Ethics

Informed Consent: Written informed consent was obtained from the patient to publish their clinical data and images for scientific purposes.

Declarations

Authorship Contributions

Surgical and Medical Practices: B.B., Ş.G., Concept: S.Ü., B.B., Ş.G., A.B.O., Design: S.Ü., B.B., Ş.G., A.B.O., Data Collection or Processing: S.Ü., B.B., Ş.G., A.B.O., Analysis or Interpretation: B.B., Ş.G., A.B.O., Literature Search: S.Ü., B.B., Ş.G., A.B.O., Writing: S.Ü., B.B., Ş.G., A.B.O.

Conflict of Interest: Banu Bozkurt, MD, is an Editor-in-Chief of the Turkish Journal of Ophthalmology. She was not involved in the peer review of this article and had no access to information regarding its peer review. The other authors has no disclosures.

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

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

Erum Habib

Dow University of Health Sciences, Department of Ophthalmology and Visual Sciences, Karachi, Pakistan

Dear Editor,

We read with great interest the study by Erbezci et al.[1] evaluating preferred retinal locus (PRL) characteristics in juvenile macular dystrophy (JMD). The authors are to be commended for addressing an important clinical question and for employing scanning laser ophthalmoscope/optical coherence tomography to characterize fixation behavior. While the findings are valuable, several methodological limitations not discussed in the article warrant consideration.

First, the study did not report genetic or phenotypic stratification of JMD patients. JMDs encompass heterogeneous entities, including ABCA4-related Stargardt disease and cone-rod dystrophies, with differing lesion morphology and progression, which may confound PRL patterns.[2] Second, prior exposure to low-vision rehabilitation or eccentric viewing training was not documented. Such interventions can influence PRL location and stability, making it difficult to distinguish spontaneous adaptation from training effects.[3]

Third, fixation stability was quantified using maximum dispersion of fixation points rather than standardized metrics such as the bivariate contour ellipse area. This methodological choice may limit comparability with other studies and underestimate subtle instability.[4] Fourth, the absence of a control group (e.g., age-matched individuals with other macular diseases) restricts the ability to contextualize whether observed PRL behaviors are unique to JMD or reflect broader adaptation mechanisms.[5] Finally, the modest sample size precluded subgroup analyses by disease severity or lesion morphology, which could have provided more nuanced insights into PRL adaptation.[2]

Despite these limitations, the study contributes meaningfully to our understanding of PRL behavior in JMD. Future prospective, longitudinal studies with larger, genetically characterized cohorts and standardized fixation metrics will be essential to fully elucidate PRL adaptation and optimize rehabilitation strategies for young patients with central vision loss.

Keywords: Juvenile macular dystrophy, preferred retinal locus, fixation stability, low vision rehabilitation, methodological critique

Cite this article as: Habib E. Letter to the Editor Re: "Preferred Retinal Locus in Juvenile Macular Dystrophy". Turk J Ophthalmol. 2026;56:69-70

Address for Correspondence: Erum Habib, Dow University of Health Sciences, Department of Ophthalmology and Visual Sciences, Karachi, Pakistan

E-mail: erumhabib131@gmail.com

ORCID-ID: orcid.org/0009-0003-7072-6560

Received: 07.12.2025

Accepted: 08.01.2026

Publication Date: 18.02.2026

DOI: 10.4274/tjo.galenos.2026.89021

Declarations

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

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

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Reply

We thank the author for their interest in our study[1] and their constructive comments.[2] We appreciate the opportunity to clarify several methodological aspects of our retrospective analysis evaluating preferred retinal locus (PRL) characteristics in patients with juvenile macular dystrophy (JMD).[1]

First, we acknowledge that JMD comprises a heterogeneous group of inherited retinal disorders with diverse genetic and phenotypic backgrounds. Genetic testing was not systematically available for the majority of patients during the study period. All patients were diagnosed and referred by experienced retina specialists based on clinical examination and multimodal retinal imaging, reflecting routine real-world clinical practice. The primary objective was to characterize functional fixation behavior in a clinically defined cohort of young patients with central macular involvement. Retrospective genetic stratification would have substantially reduced the sample size and introduced selection bias.

Second, regarding prior low-vision rehabilitation or eccentric viewing training, we would like to explicitly clarify that all patients were evaluated at their first referral to the low-vision rehabilitation unit. As stated in the Methods section, "JMD-related lesions and PRLs were assessed at the beginning of their low-vision clinical evaluation." Accordingly, none of the patients had previously undergone structured low-vision rehabilitation or formal eccentric viewing training. Therefore, the PRL characteristics described in this study reflect spontaneous neurovisual adaptation to central vision loss rather than rehabilitation-induced effects. While informal compensatory strategies cannot be entirely excluded, no patient had received supervised rehabilitation prior to assessment.

Third, fixation stability was quantified using maximum dispersion of fixation points rather than the bivariate contour ellipse area (BCEA). While BCEA is a widely accepted metric, fixation data were acquired using an Optos SLO/OCT-based microperimetry system, whose software versions available during the study period did not consistently compute BCEA or export raw fixation coordinates. Post-hoc BCEA calculation from the summary reports was not feasible, and raw coordinate export was not supported by the legacy software configuration. However, maximum dispersion provides a clinically interpretable measure of fixation instability and has been applied in previous clinical studies.[3] Moreover, dispersion and BCEA are strongly correlated measures of the same underlying fixation instability, and the observed clinical associations would be expected to remain consistent regardless of the metric used.[4]

Fourth, with respect to control groups, age-matched controls with other macular diseases are epidemiologically difficult to identify, as most macular disorders occur later in life. Comparisons with healthy controls yield limited insight into eccentric fixation mechanisms, as healthy subjects invariably use the fovea. Accordingly, the most relevant comparisons are internal correlations with disease-related parameters, supported by comparisons with established PRL patterns in age-related macular degeneration reported in the literature.[5]

Finally, the modest sample size and absence of a control group are acknowledged limitations and should be interpreted in the context of the epidemiology of JMD. As JMD is a rare disorder, assembling a cohort of young patients (mean age 19.8 years) with complete fixation and microperimetric data at a single center is inherently challenging. Many foundational PRL studies have relied on similarly sized cohorts, whereas larger datasets (e.g., ProgSTAR) required multicenter collaboration.[6] Despite the limited number of cases, the sample size allowed detection of strong main associations, including a significant correlation between age and PRL location ($r=0.541$, $p=0.002$).

Despite these limitations, we believe that our study provides clinically relevant real-world data on PRL behavior in young patients with central macular disease—an underrepresented population in the literature. We agree that future prospective, longitudinal studies incorporating genetic characterization and standardized fixation metrics will be essential to further elucidate PRL adaptation mechanisms.

Declarations

Authorship Contributions

Surgical and Medical Practices: M.E., Concept: M.E., Z.Ö.T., T.Ö., Design: M.E., Z.Ö.T., T.Ö., Data Collection or Processing: M.E., Z.Ö.T., T.Ö., Analysis or Interpretation: M.E., Z.Ö.T., T.Ö., Literature Search: M.E., Z.Ö.T., T.Ö., Writing: M.E., Z.Ö.T.

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

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

Murat Erbezci[1], Zühal Özen Tunay[2], Taylan Öztürk[3]

[1]Private Practice, İzmir, Türkiye
[2]TOBB University of Economics and Technology Faculty of Medicine, Department of Ophthalmology, Ankara, Türkiye
[3]İzmir Tınaztepe University Faculty of Medicine, Department of Ophthalmology, İzmir, Türkiye

Cite this article as: Erbezci M, Özen Tunay Z, Öztürk T. Reply to Letter to the Editor Re: "Preferred Retinal Locus in Juvenile Macular Dystrophy". Turk J Ophthalmol. 2026;56:70-71

Address for Correspondence: Murat Erbezci, Private Practice, İzmir, Türkiye
E-mail: muraterbezci@gmail.com
ORCID-ID: orcid.org/0000-0003-2163-2157

Received: 04.01.2026
Accepted: 08.01.2026
Publication Date: 18.02.2026

DOI: 10.4274/tjo.galenos.2026.66806

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