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**Hüban ATİLLA**
Ankara University Faculty of Medicine, Department of Ophthalmology, Ankara, Türkiye

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## AT A GLANCE

**2024 Issue 6 at a Glance:**

**Esteemed colleagues,**

In its sixth and final issue of 2024, the Turkish Journal of Ophthalmology features five original research articles, a review, three case reports, and a letter to the editor with the authors' response.

This issue includes two studies on large language models (LLM), which represent an important development in artificial intelligence technology. Although using these chat models as a source of medical information is becoming increasingly common, the accuracy and comprehensibility of their answers to medical questions are a cause of controversy. In fact, there has been an increase in research in this field in recent years. In their study on this topic, Aydın et al. posed 40 frequently asked questions in refractive surgery to four different language models (ChatGPT 3.5, ChatGPT 4.0, Gemini, and Microsoft Copilot chatbots), and the answers were evaluated in terms of suitability and readability by two experienced refractive surgeons. The Gemini chatbot had the highest response accuracy rate (87.5%), followed by Copilot (60%), ChatGPT 4.0 (52.5%), and ChatGPT 3.5 (45%). In terms of readability, it was reported that all LLM responses were very difficult to read and at a university reading level. The authors concluded that the Gemini chatbot was the best in terms of accuracy and had relatively better readability, and that patients should be warned that LLM chatbots can occasionally give inappropriate answers (See pages 313-317).

In their prospective study titled "Effects of Lotrafilcon A and Senofilcon A Bandage Contact Lenses on Visual Outcome and Ocular Comfort After Photorefractive Keratectomy", Yakar and Alaçamlı compared the effect of two different silicone hydrogel bandage contact lenses (BCL) on visual rehabilitation and ocular comfort after photorefractive keratectomy. The study included 30 patients who received a lotrafilcon A BCL in one eye and senafilcon A BCL in the other eye postoperatively. The lenses were removed on postoperative day 5, and subjective symptoms of ocular discomfort during this period were evaluated. The eyes were also compared in terms of spherical equivalent (SE) at postoperative 15 days and 1 month. While there was no difference between the BCLs in terms of ocular discomfort scores ($p>0.05$), a difference was noted in terms of SE values at postoperative day 15 and 1 month ($p<0.05$), with better visual rehabilitation in eyes that received senofilcon A lenses (See pages 318-323).

Erdoğdu and Yüksel investigated the publication rates of abstracts related to oculoplastic surgery and the orbit presented at Turkish Ophthalmology Association (TOA) national congresses between 2013 and 2022. Of 802 abstracts evaluated, 24% of the 233 studies presented orally were published, whereas only 11.6% of the 569 studies presented as posters were published ($p<0.05$). When the presentations were evaluated in terms of content, it was found that the publication rate was higher for clinical studies than case reports (21.8% vs. 6.3%) ($p<0.05$). The researchers pointed out that only 15.2% of studies presented over the 10-year period became publications, and emphasized that in order to increase the scientific publication potential in Türkiye, negative factors should be identified, problems should be eliminated, and clinicians should be supported in this regard (See pages 324-329).

The second study on LLM featured in this issue was conducted by Postacı and Dal. Retinopathy of prematurity (ROP) is among the main causes of childhood blindness and can be prevented with early diagnosis, continuous follow-up, and rapid appropriate treatment. It is essential for families to be aware of the importance of their infants' follow-up and treatment. In fact, the TOA prepared an ROP information guide on this subject. However, patients' families must be able to read and understand the information in the guide. In this study, the researchers compared the responses of the LLMs GPT-4.0, GPT-4o mini, and Gemini to 30 questions from the ROP guide prepared by the TOA. The readability of the TOA ROP guide and the chatbots' responses were analyzed using the Ateşman and Bezirci-Yılmaz formulas, and their comprehensiveness and accuracy were evaluated by ROP experts. The reading level of the TOA brochure was above the 6th-grade reading level recommended in the literature, while the reading levels of the materials produced by GPT-4.0 and Gemini were found to be significantly lower ($p<0.05$). In terms of accuracy and scope, GPT-4.0 had the highest scores and Gemini had the lowest scores. As a result, the authors pointed out that GPT-4.0 has the potential to provide more readable, accurate, and comprehensive content in the production of patient information materials, but regional medical differences may also be important and influential in the use of LLMs in the field of health (See pages 330-336).

In their study titled "The Efficacy of Adalimumab Treatment in Pediatric Non-Infectious Uveitis: A Retrospective Cohort Study", Yalçınsoy et al. retrospectively reviewed the records of 91 patients under the age of 16 years diagnosed with pediatric non-infectious uveitis (NIU) and evaluated the efficacy of adalimumab (ADA) treatment in 103 eyes of 53 patients who were unresponsive to conventional immunosuppressive therapy. The patients used ADA for at least one year, and their best-corrected visual acuity (BCVA), intraocular inflammation severity, uveitis attack frequency, topical and systemic corticosteroid use, and central macular thickness were evaluated before and after ADA treatment. Most patients (49%) had anterior uveitis, 41.5% had intermediate uveitis, and 9.4% had panuveitis. Follow-up times ranged from 18-120 months and the duration of ADA use was 18-60 months. Uveitis

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## AT A GLANCE

attack frequency, intraocular inflammation severity, topical and systemic corticosteroid dose, and mean CMT values were found to be significantly lower after ADA treatment ($p<0.05$), while BCVA was increased. The authors stated that ADA was generally used at the standard dose, but 22% of the patients were treated weekly. Intraocular inflammation was controlled in 83% of the patients with weekly administration. Noting the difficulties in the diagnosis and management of pediatric uveitis and stating that management is challenging due to the high risk of complications and vision loss, the authors emphasized that ADA is effective in improving visual outcomes and controlling intraocular inflammation in pediatric NIU and reduces the need for systemic and topical corticosteroids (See pages 337-343).

The review of this issue, penned by Şimşek et al., is titled "The Role of In Vivo Confocal Microscopy in Ocular Allergies" and addresses the ocular surface changes that occur in atopic keratoconjunctivitis (AKK) and vernal keratoconjunctivitis (VKK) with rich visuals obtained using in vivo confocal microscopy (IVCM), an imaging technique that enables noninvasive, real-time imaging of the corneal and conjunctival layers. The authors examined in detail the use of IVCM in determining the pathogenesis, facilitating diagnosis, and monitoring treatment response in AKK and VKK (See pages 344-353).

Özen and İnal Özen present the case of a patient who presented to the emergency department after noticing a decrease in vision and enlarged pupil in one eye. An eye consultation was requested after neurological evaluation and magnetic resonance imaging (MRI). On ophthalmologic examination, a metallic foreign body was detected in the eye, and it was determined that the patient had a history of ocular trauma two months earlier. The authors highlighted the importance of ophthalmology consultation before neurological examination in anisochoric patients, pointing out the risks associated with MRI in these cases due to the possibility of foreign bodies (See pages 354-357).

Oklar et al. report on a 63-year-old male patient diagnosed with granulomatous polyangiitis (GPA) who presented with lacrimal gland involvement, describing the different ocular pathologies that developed later and discussing the differential diagnosis and treatment approaches. They emphasized that early diagnosis and aggressive treatment are vital in GPA, a rare autoimmune disease characterized by necrotizing granulomas and vasculitis involving the respiratory tract and kidneys (See pages 358-363).

Lens remnants can be seen in the anterior chamber in the early or late period after cataract surgery can cause inflammation, high intraocular pressure, and corneal edema. Koçer et al. present two patients in which they used neodymium-doped yttrium aluminum garnet (Nd:YAG) laser to eliminate lens fragments and reported resorbtion of the lens fragments within the first day after the procedure, with no complications (See pages 364-368).

In their letter to the editor, Daungsupawong and Wiwanitkit expressed their views on an article by Korkmaz et al. titled "Evaluation of Medically Reversible Limbal Stem Cell Deficiency", stating that the article presented important information about the medical treatment of limbal stem cell deficiency (LSCD) but that some aspects should be critically examined. They noted that the study sample was small and heterogeneous in terms of age and LSCD etiology and that a single treatment strategy was not sufficient to generalize, and they desired a more detailed explanation of the treatment applied. The authors raised several questions regarding the effect of LSCD etiology on treatment response, which features of patients with complete LSCD regression can be used to guide future treatment decisions, and what long-term results can be expected from various medical treatments, especially for ocular rosacea and blepharitis, emphasizing the need for randomized controlled studies evaluating LSCD at the molecular level, planning targeted treatment, and including patients' long-term outcomes (See pages 369-370).

In response, Korkmaz et al. stated that the low case number was a result of including only patients with reliable data due to the retrospective nature of their study. They stated that LSCD can have different etiologies and that implementing a personalized and step-wise treatment protocol is preferable over a single strategy for all patients, but noted that their article aimed to highlight that restoring limbal homeostasis may allow the LSCD to be treated without the need for further surgical intervention, especially in certain etiologies. They stated that in their study, anti-inflammatory and lubrication therapy were accepted as the most appropriate medical approach and that data analysis was conducted accordingly. The authors noted that although this study was meant to draw clinicians' attention to reversible LSCD with a limited number of cases, they aimed to conduct more comprehensive studies focusing on molecular mechanisms, as suggested by Daungsupawong and Wiwanitkit in their letter. They concurred that prospective randomized controlled trials would help answer questions about the medical treatment approach to LSCD (See pages 370-371).

As we bid farewell to the year 2024 with these valuable scientific articles including original research, review, case reports, and letter to the editor, we hope that the new year brings health, happiness, and peace to the world.

**Respectfully on behalf of the Editorial Board,**

**Nilgün Yıldırım, MD**

Original Article

# Readability and Appropriateness of Responses Generated by ChatGPT 3.5, ChatGPT 4.0, Gemini, and Microsoft Copilot for FAQs in Refractive Surgery

Fahri Onur Aydın, Burakhan Kürşat Aksoy, Ali Ceylan, Yusuf Berk Akbaş, Serhat Ermiş, Burçin Kepez Yıldız, Yusuf Yıldırım

University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Ophthalmology, İstanbul, Türkiye

## Abstract

**Objectives:** To assess the appropriateness and readability of large language model (LLM) chatbots' answers to frequently asked questions about refractive surgery.

**Materials and Methods:** Four commonly used LLM chatbots were asked 40 questions frequently asked by patients about refractive surgery. The appropriateness of the answers was evaluated by 2 experienced refractive surgeons. Readability was evaluated with 5 different indexes.

**Results:** Based on the responses generated by the LLM chatbots, 45% (n=18) of the answers given by ChatGPT 3.5 were correct, while this rate was 52.5% (n=21) for ChatGPT 4.0, 87.5% (n=35) for Gemini, and 60% (n=24) for Copilot. In terms of readability, it was observed that all LLM chatbots were very difficult to read and required a university degree.

**Conclusion:** These LLM chatbots, which are finding a place in our daily lives, can occasionally provide inappropriate answers. Although all were difficult to read, Gemini was the most successful LLM chatbot in terms of generating appropriate answers and was relatively better in terms of readability.

**Keywords:** Artificial intelligence, chatbots, refractive surgery FAQs, ChatGPT, Gemini, Copilot

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**Address for Correspondence:** Fahri Onur Aydın, University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Ophthalmology, İstanbul, Türkiye

**E-mail:** onuraydin90@hotmail.com **ORCID-ID:** orcid.org/0000-0001-9414-6788

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## Introduction

The rapid integration of artificial intelligence (AI) into healthcare has transformed patient engagement and information dissemination. As AI models increasingly become a primary source of medical information, it is essential to evaluate the feasibility and accuracy of their responses to medical queries.[1,2] The rise of conversational robots, driven by advancements in natural language processing, marks a promising new era in the healthcare industry. These robots show remarkable potential in various medical fields, including disease prevention, diagnosis, treatment, monitoring, and patient support.[3]

Large language model (LLM) chatbots, such as OpenAI's ChatGPT, Google's Gemini, and Microsoft's Copilot, represent a significant leap forward in AI technology. These models are designed to generate human-like responses to a variety of text-based queries, leveraging extensive training data and sophisticated algorithms.[4] The evolution of LLM chatbots, characterized by self-supervised learning and training on vast textual data, has enabled them to produce responses that closely mimic human interactions. Their ability to provide detailed and relevant information makes them particularly valuable for medical applications.[5,6]

In the field of ophthalmology, especially in refractive surgery, patients often turn to the internet to obtain information about their conditions and treatment options. The quality and readability of this information are crucial, as they directly impact patient comprehension and decision-making. Despite the potential benefits of LLM chatbots in providing medical advice, their effectiveness in delivering accurate and understandable information still requires a thorough assessment.

This study aimed to explore the strengths and limitations of different LLM chatbots in providing reliable and accessible information about refractive surgery. By evaluating the relevance and readability of their responses, this research seeks to enhance

AI-driven patient education, thereby ensuring that patients receive accurate and comprehensible information to make informed decisions about their eye health.

## Materials and Methods

Approval from the ethics committee was not required since no patients were involved in our study.

This study was designed to investigate the appropriateness and readability of the information provided by LLM chatbots. Four newly developed and frequently used LLM chatbots were selected: ChatGPT 3.5, ChatGPT 4.0, Google Gemini, and Microsoft Copilot. Refractive surgeons were encouraged to compile a list of 40 questions about refractive surgery that patients frequently ask either through the patient portal or in the clinic. These questions were then answered by the LLM chatbots on July 3, 2024. The answers were evaluated for appropriateness and adequacy by two experienced refractive surgeons (Y.Y., B.K.Y.). The answers were categorized as "appropriate", "incomplete", and "inappropriate". An appropriate response was defined as a correct answer that was similar to the recommendations that the reviewer would give patients. An inappropriate response was either inaccurate or differed from the reviewer's recommendation in a clinical setting. An incomplete response was relevant and accurate but did not provide enough information.

To assess the ease of reading each answer for the average person, we entered the answers into an online readability application called Readable (https://app.readable.com/text/).[7] The readability and understandability criteria and standardization we used in the study were based on English. In our study, we formulated the questions in English and received answers in English. Five different indices were used to evaluate the readability of each response: the Gunning Fog Index, Coleman-Liau Index, Flesch Reading Ease Score, Flesch-Kincaid Grade Level, and Simple Measure of Gobbledygook (SMOG) Index.[8] The mathematical formulae used in Flesch reading tests are based on word complexity and sentence length. The Flesch Reading Ease score is a numerical value between 1 and 100. Higher numbers indicate more readability, and a score between 70 and 80 corresponds to an 8$^{th}$-grade level.[7] The Gunning Fog Index evaluates the frequency of polysyllabic words along with the average sentence length.[9] This index score, which ranges from 0 to 20, rates simplicity and clarity.[7] The Coleman-Liau Index helps assess medical data and is typically used in conjunction with other indices.[1] It focuses on the mean length of sentences and the mean number of letters per hundred words.[9] The SMOG Index uses the frequency of polysyllabic words in a sample of sentences.[9] Although widely used, SMOG is most frequently applied in healthcare.[10] The results of the latter three indices correspond to the grade level at which a student must be studying in the United States in order to comprehend the written material. Thus, texts with lower Gunning Fog, Coleman-Liau, and SMOG index values should be easier to read and understand.[11]

### Statistical Analysis

Statistical analysis was performed using the SPSS program (IBM SPSS Statistics, version 25; IBM Corp., Armonk, NY, USA). Descriptive analysis and normality distribution test (Shapiro-Wilk) were performed. Considering the abnormal distribution of the data, a non-parametric Kruskal-Wallis test and Bonferroni correction were performed to compare mean scores across the four LLM chatbots. An adjusted p value less than 0.05 was considered statistically significant.

## Results

### Appropriateness

Based on the responses generated by the LLM chatbots, 45% (n=18) of the answers given by ChatGPT 3.5 were correct, while 52.5% (n=21) of ChatGPT 4.0, 87.5% (n=35) of Gemini, and 60% (n=24) of Copilot answers were correct. ChatGPT 3.5, ChatGPT 4.0, and Copilot gave inappropriate answers to one question each, while Gemini did not give inappropriate answers to any question (Figure 1).

The LLM chatbots showed a statistically significant difference when compared in terms of appropriateness (p=0.001). When subgroup analysis was performed, this difference was observed between Gemini and ChatGPT 3.5 and 4.0 (p=0.001, p=0.008 respectively) (Table 1).

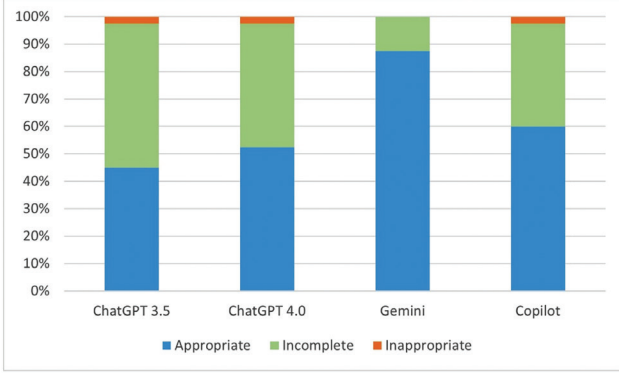


**Figure 1.** Consensus-based accuracy ratings of large language model chatbot responses to questions about refractive surgery, as determined by two experienced refractive surgeons

**Table 1. Overview of the appropriateness and length of large language model chatbots' responses to questions about refractive surgery**

| | ChatGPT 3.5 | ChatGPT 4.0 | Gemini | Copilot | p value |
|---|---|---|---|---|---|
| **Appropriateness** | 2.42±0.54 | 2.50±0.55 | 2.87±0.33 | 2.57±0.54 | 0.001 |
| **Word count** | 21.15±4.40 | 21.67±6.24 | 318.62±73.98 | 103.90±46.44 | <0.001 |
| **Character count** | 115.00±24.33 | 118.65±32.97 | 1767.02±450.00 | 587.15±260.76 | <0.001 |

### Readability

Readability indices are summarized in Table 2. A significant difference among the LLM chatbots was observed when compared according to Flesch-Kincaid Grade Level (p=0.003). Pairwise evaluations revealed this difference to be between ChatGPT 3.5 and Gemini and between ChatGPT 3.5 and Copilot, with ChatGPT 3.5 having significantly higher values (p=0.017 and p=0.008, respectively; Figure 2a). No significant difference was observed between the other chatbots. There were no significant differences among the chatbots in terms of Flesch Reading Ease scores (p=0.534; Figure 2b) or Coleman-Liau score (p=0.867; Figure 2c). When the SMOG index was compared, a significant difference was observed between the chatbots (p=0.012). This was found to be a result of a significantly lower SMOG value for Copilot compared to ChatGPT 3.5 (Figure 2d). A significant difference was again observed between the groups when Gunning Fog scores were evaluated (p=0.001). Pairwise comparisons showed that Copilot had a significantly lower score than both ChatGPT 3.5 and ChatGPT 4.0 (p=0.003 and 0.021, respectively) (Figure 2e).

**Table 2. Readability indices for large language model chatbots' responses to frequently asked questions about refractive surgery**

| | ChatGPT 3.5 | ChatGPT 4.0 | Gemini | Copilot | p value |
|---|---|---|---|---|---|
| **Coleman-Liau** | 14.86±3.90 | 14.99±5.11 | 14.60±1.58 | 14.88±2.51 | 0.867 |
| **Flesch Reading Ease score** | 30.97±22.49 | 31.79±26.72 | 37. 39±7.98 | 32.76±12.88 | 0.534 |
| **Flesch-Kincaid Grade Level** | 13.95±3.38 | 13.49±3.92 | 11.76±1.35 | 11.71±1.89 | 0.003 |
| **SMOG Index** | 15.03±2.80 | 14.50±3.07 | 13.93±1.35 | 13.34±1.28 | 0.012 |
| **Gunning Fog** | 16.30±3.96 | 15.74±4.73 | 14.09±1.65 | 13.48±2.08 | 0.001 |

SMOG: Simple Measure of Gobbledygook

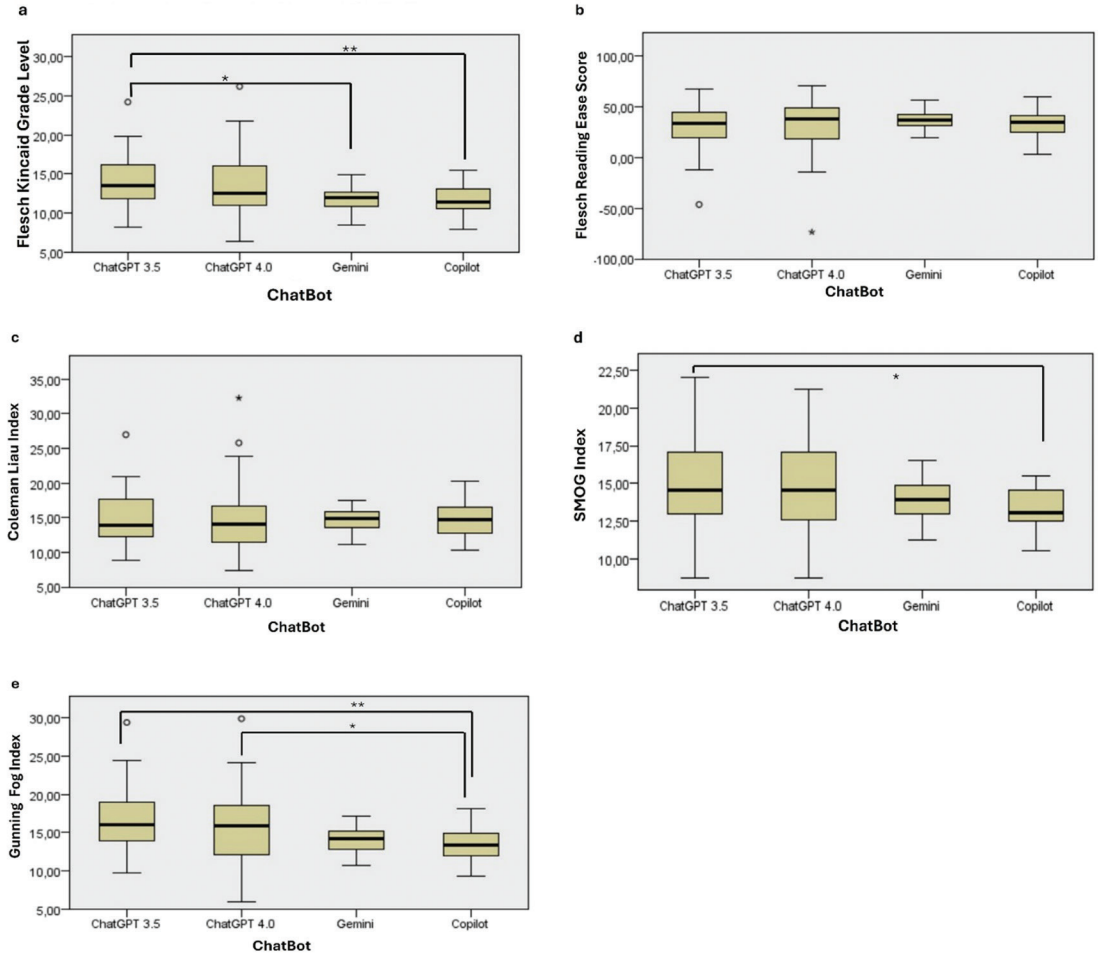


**Figure 2.** The scores of large language model chatbots in terms of readability shown on a boxplot. a) Flesch-Kincaid Grade Level, b) Flesch Reading Ease score, c) Coleman-Liau Index, d) Simple Measure of Gobbledygook (SMOG) Index, e) Gunning Fog Index

A comparison of word and character counts showed that Gemini had significantly higher values than the other LLM chatbots ($p<0.001$ for both). Word and character counts were significantly higher for Gemini compared to Copilot ($p=0.001$ for both) and both ChatGPT 3.5 and 4.0 ($p<0.001$ for all). The ChatGPT versions had comparable word and character counts (Table 1).

## Discussion

The use of AI is becoming increasingly widespread worldwide. With its increasing use, many new AI models are being developed. These include language models trained to use learned data to browse the internet and produce immediate responses in chatbot conversations.[12] This article presents an in-depth analysis of how this variation affects LLM chatbot performance and response quality, highlighting that differences between the responses of different LLM chatbots are mainly due to differences in the algorithms used.

Today, many people use LLM chatbots for various purposes. One of them is to get answers to their questions in the field of health. However, using AI to get health-related information can cause several problems. These include obtaining outdated or inaccurate information and misunderstanding correct information that is presented in a complex way. Therefore, it is very important that this information is both accurate and understandable by everyone.

In our study, when the appropriateness of the chatbots' responses was evaluated, it was observed that Gemini answered the questions correctly at a significantly higher rate than the other LLM chatbots. In contrast to our findings, Tepe and Emekli[13] reported in a study comparing ChatGPT 4.0, Gemini, and Copilot that ChatGPT 4.0 gave the most appropriate answers to questions about breast imaging. In another study, Lee et al.[14] compared Gemini and ChatGPT 3.5 as sources for hypertension education and determined that they provided similar results.

In our study, five different recognized readability indices were used to provide comprehensive results. According to these indices, the responses generated by the LLM chatbots had low readability scores. Flesch Reading Ease scores ranged from 30 to 50, with Gemini having the highest score (i.e., the most readable answers). This suggests that the texts could be understood by university students and the level of difficulty was suitable for only 33% of adults.[15] In terms of Flesch-Kincaid Grade Level, ChatGPT responses were found to be suitable for people in grade 14 and above, while Gemini and Copilot were appropriate for those in grade 12 and above, suggesting that Gemini and Copilot had slightly better readability.[16] The Gunning Fog Index also indicated a university level for all of the LLM chatbots. However, it was observed that ChatGPT responses were at the level of senior undergraduate students, while Gemini and Copilot were at the freshman level. The Coleman-Liau Index was similar for all LLM chatbots, indicating an undergraduate level that was difficult to read.[17] Similarly, SMOG Index values for all LLM chatbots showed their responses were at the undergraduate level and difficult to read for the general majority.[10]

In a study conducted with ChatGPT 4.0, the results of readability analyses were similar to those in our study, indicating an undergraduate or graduate level that was fairly difficult to read.[18] In the study conducted by Tepe and Emekli[13], comparison of ChatGPT 4.0, Gemini, and Copilot in terms of readability revealed that ChatGPT 4.0 was the most difficult and Gemini was relatively easier, but all had low readability.

When the number of words and characters were evaluated, it was observed that both ChatGPT versions used a significantly lower number of words and characters than the other LLM chatbots. Gemini used the highest number of words and characters. Despite being significantly longer, Gemini responses showed better readability and accuracy.

Although similar methodology has been used in other studies on LLM chatbots in the literature, a more holistic evaluation may be possible if a patient cohort is used. This idea may guide future research.

As the results show, LLM chatbots may provide incomplete or occasionally incorrect information. In addition, even if the information they provide is correct, there is also the possibility of misleading patients due to its relatively low readability. This poses a potential risk for patients. To reduce these possibilities, new LLM chatbots developed in collaboration with healthcare professionals specifically for health-related information may be beneficial in improving accuracy and accessibility.

### Study Limitations

This study has several limitations. First, the search was limited to 40 questions, which may limit the generalizability of the findings. In addition, the formulation of inputs when interacting with LLM chatbots can significantly affect the quality and nature of the responses produced. The repeatability of LLM chatbots is also questionable. In this study, each question was sent to the LLM chatbots only once. Furthermore, when assessing the readability of the answers, the absence of real patients as evaluators is another limitation of the study.

## Conclusion

In conclusion, we observed that Gemini was better than other LLM chatbots in giving appropriate answers to questions about refractive surgery. In terms of readability, we found that all chatbot responses were difficult to read, but Gemini and Copilot were relatively more readable. As a result, when the responses of the LLM chatbots were compared, it was seen that Gemini was the best in terms of both relevance and readability, while ChatGPT 3.5 was the worst. It is worth reminding our patients that these LLM chatbots can give inappropriate answers, albeit rarely.

### Ethics

**Ethics Committee Approval:** Not required.

**Informed Consent:** Not required.

### Declarations

#### Authorship Contributions

Concept: F.O.A., S.E., Y.B.A., B.K.Y., Design: F.O.A., A.C., Y.B.A., Y.Y., Data Collection or Processing: B.K.A., A.C., S.E., Analysis or Interpretation: A.C., B.K.Y., Y.Y., Literature Search: F.O.A., B.K.A., B.K.Y., Writing: F.O.A., B.K.A., A.C., Y.B.A., S.E., B.K.Y., Y.Y.

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Original Article

# Effects of Lotrafilcon A and Senofilcon A Bandage Contact Lenses on Visual Outcome and Ocular Comfort After Photorefractive Keratectomy

Konuralp Yakar[1], Göksu Alaçamlı[2]

[1]Atılım University Faculty of Medicine, Department of Ophthalmology, Ankara, Türkiye
[2]Muğla Sıtkı Koçman University Faculty of Medicine, Department of Ophthalmology, Muğla, Türkiye

## Abstract

**Objectives:** To compare the efficacy of two different silicone hydrogel bandage contact lenses (BCLs) in terms of visual rehabilitation and ocular discomfort following photorefractive keratectomy (PRK).

**Materials and Methods:** This prospective study included 60 eyes of 30 patients who underwent bilateral PRK surgery to correct myopia and/or astigmatism refractive errors. Following surgery, lotrafilcon A BCLs were applied to the right eye and senofilcon A BCLs were applied to the left eye. When the BCLs were removed on postoperative day 5, subjective ocular symptoms of discomfort were evaluated on a scale of 0 to 10, where 0 indicated no discomfort and 10 indicated maximum discomfort. The postoperative spherical equivalents (SE) of both eyes were compared at 15 days and 1 month. Postoperative SE ≤ ±0.50 diopters was accepted as emmetropia. The number of patients who achieved emmetropia was also compared at 15 days and 1 month postoperatively.

**Results:** Scores for ocular discomfort in the first 5 days postoperatively did not differ significantly between the BCLs ($p>0.05$). However, a statistically significant difference was observed between the two lenses in terms of SE values at postoperative 15 days and 1 month ($p<0.05$). Eyes fitted with the senofilcon A BCL demonstrated better postoperative visual rehabilitation.

**Conclusion:** Although post-PRK ocular discomfort scores did not differ significantly between the two BCLs, the senofilcon A lenses performed better in terms of achieving the target SE postoperatively.

**Keywords:** Lotrafilcon A, senofilcon A, bandage contact lens, photorefractive keratectomy, refractive errors

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**Address for Correspondence:** Konuralp Yakar, Atılım University Faculty of Medicine, Department of Ophthalmology, Ankara, Türkiye
**E-mail:** alpyakar@yahoo.com **ORCID-ID:** orcid.org/0000-0002-3839-5699
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## Introduction

Refractive surgery is often preferred by individuals who seek an alternative to glasses or contact lenses, and outcomes have improved significantly over the past decade. Laser in situ keratomileusis (LASIK) has become the most widely used procedure, although reports of side effects such as corneal ectasia, epithelial ingrowth, and flap-related complications have been documented.[1] In contrast, photorefractive keratectomy (PRK) is a well-established flapless procedure with a low risk of complications and has been used for over two decades.[2] Additionally, individuals susceptible to flap instability issues, such as those in the military, participating in contact sports, or having thin corneas, may not be suitable for LASIK procedures but are good candidates for PRK.[3]

Appropriate corneal re-epithelialization is a critical factor in achieving optimal visual recovery in patients undergoing PRK.[4] Bandage contact lenses (BCLs) are used to shield the epithelium from the eyelid, promote rapid epithelial healing, minimize haze development, reduce postoperative pain, and restore the corneal epithelial barrier to prevent postoperative infection.[5] The use of silicone hydrogel BCLs after PRK is a common practice because they have higher oxygen permeability (Dk/t) compared to conventional lenses.[6] Various BCLs made of silicone hydrogel materials such as lotrafilcon A-B, senofilcon A, balafilcon A, and omafilcon A are used to obtain the best corneal epithelial healing.[7,8] The United States Food and Drug Administration has authorized senofilcon A for continuous use for 1 week and lotrafilcon B for 6 days, while lotrafilcon A is approved for both therapeutic use and extended wear up to 30 days.[9,10,11,12] Despite extensive investigation of the therapeutic effectiveness of different silicone hydrogel materials on pain, discomfort, and epithelial healing following PRK, their performance in terms of postoperative visual rehabilitation has not been extensively discussed.

The objective of the present study was to investigate the effects of two different silicone hydrogel BCLs materials, lotrafilcon A (Air Optix Night and Day Aqua®, Alcon) and senofilcon A (Acuvue Oasys with Hydraclear Plus®, Johnson & Johnson), on visual rehabilitation at postoperative 15 days and 1 month after PRK. Additionally, the study aimed to evaluate the role of these two materials in patient comfort during the first 5 days postoperatively.

## Materials and Methods

This study received ethical approval from the Ondokuz Mayıs University Ethics Committee (no: B.30.2.ODM.0.20.08/454-136, date: 18.03.2024) and adhered to the principles outlined in the Declaration of Helsinki. Informed consent was obtained from the participants after explaining the nature and possible consequences of the study. A total of 30 patients between the ages of 18 and 39 years who were admitted to our clinic seeking independence from glasses or contact lenses for myopic and/or astigmatic refractive errors were included in the study. These patients underwent PRK after completing a thorough ophthalmological examination, including corneal topography, pachymetry, intraocular pressure measurement, and fundoscopy. Prior to the laser procedure, a 1% cyclopentolate drop was applied 3 times at 5-minute intervals, and the refractive errors of the patients were measured 45 minutes later. Individuals with a preoperative cycloplegic spherical equivalent (SE) difference of ≤0.50 diopters (D) between their eyes were included in the study. PRK was performed with a target value of 0 D, considering the cycloplegic refractions.

The study excluded patients who underwent laser treatment for hyperopia, lost or removed their BCLs within the first 5 days postoperatively, did not present for follow-up at postoperative 15 days and 1 month, had a history of previous ocular surgery (e.g., cataract, pterygium, vitrectomy, radial keratotomy, LASIK, small incision lenticule extraction), had a history of corneal dystrophy, recurrent epithelial erosion, or keratoconus, had any systemic disease associated with delayed wound healing (e.g., collagen tissue disease, autoimmune disease), or underwent PRK for the second time.

### Surgical Protocol

All PRK procedures were performed by the same surgeon (K.Y.) using an Alcon WaveLight® Allegretto Eye-Q device (Alcon Inc., Fort Worth, Texas, USA). Prior to the excimer laser procedure, local anesthetic topical 0.5% proparacaine (Alcaine®, Alcon Laboratories, Puurs, Belgium) drops were administered twice in each eye. The surgical field was disinfected and draped, and a blepharostat was placed. A 20% alcohol solution was then applied to the central cornea (8.5-mm diameter) and left for 15 seconds before being washed with 30 mL of balanced salt solution (BSS). The corneal epithelium was mechanically removed using a standard hockey stick-shaped blade. Following excimer laser PRK, 0.02% mitomycin C was applied to the corneal stroma for 30 seconds and the eye was washed with 30 mL BSS. Then, a drop of 0.5% moxifloxacin (Vigamox®; Alcon Laboratories, Texas, USA) was instilled directly onto the cornea. During the procedure, an Air Optix Night and Day Aqua® lotrafilcon A lens (Alcon) was applied to the right eye, while an Acuvue Oasys with Hydraclear Plus® senofilcon A lens (Johnson & Johnson) was applied to the left eye. The properties of the two silicone hydrogel plano BCLs used in this study are presented in Table 1.

### Postoperative Clinical Assessment

The postoperative medication regimen for both eyes was standardized and comprised of 0.1% fluorometholone (Flarex®; Alcon Laboratories, Puurs, Belgium) and 0.5% moxifloxacin (Vigamox®; Alcon Laboratories, Texas, USA) administered 5 times daily and preservative-free artificial tear (VisuXL®; VISUfarma, Rome, Italy) drops administered 8 times per day. The BCLs were removed by the physician who performed the procedure (K.Y.) on day 5. Cycloplegic refractive errors were evaluated at postoperative day 15 and 1 month. The difference between both eyes in terms of SE at postoperative day 15 and 1 month was also assessed. Patients with an SE of ±0.50 D or less at both postoperative time points were considered emmetropic. The differences in residual refractive error between eyes with different BCLs and numbers of emmetropic eyes in the two groups was investigated.

On postoperative day 5, a thorough examination was conducted and the patients were evaluated by means of a questionnaire pertaining to their subjective ocular symptoms. The patients were asked to rate the burning, stinging, foreign body, and dryness they experienced in each eye during the first 5 days after surgery on a scale of 0 (no discomfort) to 10 (highest level of discomfort). These four symptom scores were averaged to yield the ocular discomfort score. The subjective ocular discomfort scores of the patients' paired eyes were also compared.

### Statistical Analysis

The data obtained were analyzed in SPSS (version 15.0; SPSS, Inc., Chicago, IL, USA). Initially, the distribution of the data was evaluated using the Kolmogorov-Smirnov test. Quantitative data were presented as mean ± standard deviation if normally distributed or median and range if non-normally distributed, while categorical data were expressed as numbers and percentages. The results from paired eyes were analyzed using the paired t-test or Wilcoxon paired test as appropriate. Categorical data were compared using Fisher's exact test according to appropriate criteria. A value of $p<0.05$ was considered statistically significant in all tests.

## Results

In this study, 60 eyes of 30 patients (50% female and 50% male) were evaluated. The mean age of participants was 24.7±5.97 years (range: 18-39 years). Preoperative median SE was -3.25 D (range: -1.50 to -7.00) for the right eyes fitted with lotrafilcon A lenses and -3.69 D (range: -1.25 to -7.25) for the left eyes fitted with senofilcon A lenses. There was no statistically significant difference in preoperative SE values between eyes fitted with lotrafilcon A and senofilcon

A lenses (p=0.09). There was also no statistically significant difference between the preoperative flattest keratometric measurement (K1) of the eyes with lotrafilcon A compared to senofilcon A lenses (43.05±1.45 D vs. 43.02±1.43 D, p=0.54). The mean value of the steepest keratometric measurement (K2) was also similar between the participants' paired eyes (44.10±1.24 D vs. 44.15±1.28 D, respectively, p=0.44). In the preoperative assessment, pachymetry measurements for the right eye were found to be 535.60±23.80 µm, while the corresponding measurements for the left eye were 537.40±23.56 µm. A statistically significant difference in preoperative corneal thickness was observed between the eyes (p<0.001). Preoperative patient data is summarized in Table 2.

The mean ocular discomfort score of patients on postoperative day 5 was 3.57±1.71 for the right eyes fitted with lotrafilcon A and 3.89±1.71 for the left eyes fitted with senofilcon A (p=0.17). On postoperative day 15, the median SE for the eyes fitted with lotrafilcon A lenses was significantly higher compared to the eyes fitted with senofilcon A (-0.50 D vs. -0.25 D, p=0.001). At postoperative 1 month, the median SE was -0.25 D (range: -0.75 to 0.50) in the eyes with lotrafilcon A lenses and 0 D (range: -0.50 to 1.25) in the eyes with senofilcon A lenses. There was a statistically significant difference between the two contact lenses in terms of SE at 1 month postoperatively (p=0.005). Upon adopting the criteria of a postoperative SE ≤ ±0.50 D as indicative of emmetropia, there was no statistically significant disparity between the lotrafilcon A and senofilcon A lenses in terms of the number of eyes achieving emmetropia at postoperative 15 days (60% vs. 73.3%, p=0.210). At the postoperative 1-month assessment, both groups had the same emmetropia ratio (93%). Postoperative outcomes with the two different BCLs are summarized in Table 3.

## Discussion

The current study compared the efficacy of two silicone hydrogel BCLs made of different materials, senofilcon A

**Table 1. Contact lens features**

| Parameter | Air Optix Night and Day Aqua® | Acuvue Oasys with Hydraclear Plus® |
|---|---|---|
| **Material** | Lotrafilcon A | Senofilcon A |
| **Manufacturer** | Alcon | Johnson & Johnson |
| **Base curve (mm)** | 8.6 | 8.4 |
| **Diameter (mm)** | 13.8 | 14 |
| **Dk** | 140 | 103 |
| **Dk/t** | 175 | 147 |
| **Water content** | 24% | 38% |
| **Modulus (MPa)** | 1.4 | 0.72 |
| **UV filter** | No | Yes |

Dk: Oxygen permeability ($x10^{-11}$), Dk/t: oxygen transmissibility ($x10^{-9}$), UV: Ultraviolet

**Table 2. Preoperative patient data**

| | Lotrafilcon A | Senofilcon A | p |
|---|---|---|---|
| **Preoperative SE (D), median (min, max)** | -3.25 (-1.50, -7.00) | -3.69 (-1.25, -7.25) | 0.09* |
| **Pachymetry (µm), mean ± SD** | 535.60±23.80 | 537.40±23.56 | <0.001** |
| **Preoperative K1 (D), mean ± SD** | 43.05±1.45 | 43.02±1.43 | 0.54** |
| **Preoperative K2 (D), mean ± SD** | 44.10±1.24 | 44.15±1.28 | 0.44** |

*Wilcoxon test, **Paired t-test, SE: Spherical equivalent, D: Diopter, min: Minimum, max: Maximum, SD: Standard deviation, K: Keratometric

**Table 3. Postoperative outcomes of two different bandage contact lenses**

| | Lotrafilcon A | Senofilcon A | p |
|---|---|---|---|
| **Ocular discomfort score, mean ± SD** | 3.57±1.71 | 3.89±1.71 | 0.17** |
| **SE day 15 (D), median (min, max)** | -0.50 (-1.50, 0.75) | -0.25 (-1.37, 2.25) | 0.001* |
| **SE 1 month (D), median (min, max)** | -0.25 (-0.75, 0.50) | 0 (-0.50, 1.25) | 0.005* |
| **Emmetropic eyes day 15 (n, %)** | 18 (60) | 22 (73.3) | 0.231*** |
| **Emmetropic eyes 1 month (n, %)** | 28 (93.3) | 28 (93.3) | 1*** |

*Wilcoxon, **Paired t-test, ***Fisher's exact test, SD: Standard deviation, SE: Spherical equivalent, D: Diopter, min: Minimum, max: Maximum

(Acuvue Oasys with Hydraclear Plus®) and lotrafilcon A (Air Optix Night and Day Aqua®) in terms of visual rehabilitation and ocular comfort following PRK to correct myopia and/or astigmatism. No significant difference in ocular discomfort scores for the first 5 postoperative days was detected between the eyes that received lotrafilcon A or senofilcon A lenses. However, a significant difference was observed between the two lenses in SE values at postoperative 15 days and 1 month. Although the senofilcon A lens showed better visual rehabilitation than the lotrafilcon A lens, the number of patients considered emmetropic (SE ≤ ±0.50 D) was not statistically different at either time point.

During the PRK procedure, the corneal epithelium is removed mechanically or with the laser itself (known as transepithelial ablation) to allow stromal ablation.[13] Epithelial cells are the first to regenerate corneal layers and trigger corneal repair. Delays in this process can result in increased subepithelial haze.[14,15] The use of appropriate BCLs after surgery helps in epithelial healing, reduces pain, and improves visual acuity.[16] BCLs are worn for 3 to 5 days post-surgery and are the gold standard for protecting the epithelium from the eyelid, reducing haze formation, and preventing erosion. Several silicone hydrogel contact lenses are available for therapeutic use, including lotrafilcon A-B, senofilcon A, balafilcon A, omafilcon A, and samfilcon A.[17] Lotrafilcon A is a first-generation silicone hydrogel contact lens with high oxygen transmissibility (Dk), low water content, and relatively high lens modulus or stiffness. It requires a plasma coating surface treatment to provide wettability. Senofilcon A is a second-generation silicone hydrogel contact lens having a fairly good Dk (103), lower than lotrafilcon A (140), but higher water content and lower modulus. The utilization of polyvinyl pyrrolidone (PVP) as an internal wetting agent in senofilcon A obviates the need for any surface treatment.[18] The modulus of elasticity is a constant value that quantifies the capacity of a material to maintain its shape and resist deformation under stress. A material with a high modulus exhibits stiffness, resists deformation, and maintains its shape more effectively, which facilitates manipulation (insertion and removal) and enhances visual acuity. Conversely, a high-modulus material may increase the incidence of mechanical complications of the lens (e.g., superior epithelial arcuate lesions, giant papillary conjunctivitis, corneal staining, conjunctival flap formation) and reduce lens comfort. As the modulus increases, the water content decreases and the lenses do not readily conform to the shape of the eye, which may contribute to mechanical irritation and a subsequent local inflammatory response. A high modulus was also associated with an increased risk of keratitis in prolonged contact lens wear.[18] Although it did not affect our ocular comfort scoring, we posit that the high modulus of lotrafilcon A (1.4 vs. 0.72 in senofilcon A) and low water content (24% vs. 38% in senofilcon A) are among the factors influencing visual rehabilitation.

There are numerous investigations on the influence of silicone hydrogel BCLs differing in material composition on the healing process of corneal epithelial wounds, as well as on postoperative pain and ocular discomfort following PRK. However, there is a paucity of research on the impact of these lenses on visual rehabilitation.[19,20] Razmjoo et al.[20] reported that patients who received senofilcon A contact lenses demonstrated significantly lower levels of pain than those who were fitted with lotrafilcon A lenses across all three visit days (days 1, 3, and 5) following PRK with alcohol-assisted epithelial debridement. However, there were no significant differences in visual acuity and epithelial defect size between the two groups. The present study diverges from the findings suggested by Razmjoo et al.[20] in terms of ocular discomfort. This discrepancy may be attributed to the subjective nature of ocular discomfort or to inter-racial differences. In terms of visual rehabilitation, Razmjoo et al.[20] compared uncorrected visual acuity on postoperative day 3 and found no difference between the two BCLs. In the present study, visual rehabilitation was objectively measured at postoperative 15 days and 1 month. Our findings that senofilcon A led to better results in visual rehabilitation than lotrafilcon A may be due to the fact that we measured refractive status with an objective method and evaluated it at a later time point.

Duru et al.[21] compared senofilcon A and lotrafilcon B in terms of epithelial healing and ocular discomfort for the first 3 days after PRK. They reported that there was no significant difference in the duration of corneal re-epithelialization between the two BCLs. However, senofilcon A lenses were found to cause significantly less pain and epiphora compared to lotrafilcon B. They investigated ocular discomfort only for the first 3 days, while the current study extended the investigation to the first 5 days and used lotrafilcon A instead of lotrafilcon B. The difference in water content and DK/t values between lotrafilcon A and lotrafilcon B may have also played a role in the different ocular discomfort outcomes.

In a study of pain management in eyes that underwent PRK with alcohol-assisted epithelial debridement, Taylor et al.[7] observed that eyes fitted with senofilcon A lenses displayed the lowest pain scores on postoperative days 1 and 4, followed by eyes fitted with lotrafilcon A lenses, and then eyes fitted with balafilcon A lenses. In the current investigation, the intensity of postoperative ocular discomfort was evaluated using an ocular discomfort score, which was calculated by averaging scores assigned for burning, stinging, foreign body sensation, and dryness, rather than relying on a single pain parameter. The reason for the difference in results between the two studies may be attributed to this methodological difference. Their study did not examine the effect of BCLs on visual rehabilitation. Another study conducted by Li et al.[22] found no significant differences between the senofilcon A and balafilcon A contact lenses in terms of corneal epithelial healing speed, tear film parameters, SE, or uncorrected visual acuity at postoperative 4 days, 10 days, and 1 month. However, senofilcon A BCLs were associated with less pain in the first few days after surgery and were more comfortable to use after transepithelial PRK (T-PRK). They speculated that the edge design of BCLs and the mobility of the lens on the

de-epithelized cornea may play a role in early postoperative pain outcomes. A possible reason for the lack of a difference in visual rehabilitation between their study and the present study could be that they preferred T-PRK instead of alcohol-assisted epithelial debridement, which may have influenced the outcomes.

Mukherjee et al.[23] conducted a study comparing the effectiveness of senofilcon A and comfilcon A BCLs following T-PRK. The researchers expected lower pain scores with comfilcon A due to its higher water content and oxygen permeability, but their results showed the opposite. They attributed this to the comfilcon A lens having increased mobility during blinking due to a higher base curve. The impact of BCLs on postoperative pain management appears to be influenced by several factors, including but not limited to oxygen permeability and water content. Additionally, the researchers found similar results in terms of uncorrected visual acuity at 1 month between the two BCLs.[23] In contrast, the present study demonstrated better visual rehabilitation outcomes with senofilcon A compared to lotrafilcon A, which may be attributed to the use of objective rather than subjective methods for evaluating postoperative refractive status.

### Study Limitations

Limitations of the present study are the small sample size and short 1-month postoperative follow-up. Another limitation is the consistent preference for one contact lens for the right eye and another for the left. Further studies with larger sample sizes and longer follow-up period are warranted to validate the results of the current study.

## Conclusion

Both senofilcon A and lotrafilcon A contact lenses were found to be effective in providing relief from ocular discomfort and serving as BCLs following PRK surgery. Nevertheless, it was observed that using a senofilcon A contact lens after PRK surgery had a more pronounced and beneficial effect on visual rehabilitation in the first month after the procedure compared to lotrafilcon A contact lens. Senofilcon A appears to be the superior choice for early visual rehabilitation following PRK, and should therefore be favored more often in daily clinical practice.

### Ethics

**Ethics Committee Approval:** This study received ethical approval from the Ondokuz Mayıs University Ethics Committee (no: B.30.2.ODM.0.20.08/454-136, date: 18.03.2024) and adhered to the principles outlined in the Declaration of Helsinki.

**Informed Consent:** Informed consent was obtained.

### Declarations

### Authorship Contributions

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

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Original Article

# Publication Rates of Oculoplastic Surgery and Orbit Abstracts Presented at Turkish Ophthalmological Association National Congresses: 10-Year Analysis

Yusuf İkbal Erdoğdu, Nilay Yüksel

Ankara Bilkent City Hospital, Clinic of Ophthalmology, Ankara, Türkiye

## Abstract

**Objectives:** This study aimed to examine the publication rates of abstracts related to oculoplastic surgery and orbital diseases presented at the Turkish Ophthalmological Association National Congresses (TOA-NCs) in 2013-2022.

**Materials and Methods:** The study included abstracts in the field of oculoplastic surgery and orbital diseases accepted for presentation at TOA-NCs between 2013 and 2022. These abstracts were reviewed in terms of presentation type (oral, poster), number of authors, study setting (university, training and research, private, public, or abroad hospital), study type (case, clinical, or basic science), study topic (eyelid, lacrimal system, orbit, or thyroid eye disease), journal publication status, time to publication (months), publishing journal (national, international), and journal impact factor.

**Results:** A total of 802 presentations (233 [29.1%] oral, 569 [70.9%] poster) were included in the study. Of these, 122 abstracts (15.2%) were published (56 [45.9%] oral, 66 [54.1%] poster presentations). The publication rate for oral presentations was higher than for poster presentations (24.0% vs. 11.6%, $p<0.05$). The median publication time and journal impact factor were 18 months (range, 1-88) and 1.3 (range, 0.1-5.17), respectively. Case abstracts had a publication rate of 6.3%, while clinical studies had a higher rate of 21.8% ($p<0.05$). Publication time was negatively correlated with journal impact factor ($r=-0.211$, $p=0.039$).

**Conclusion:** The 10-year publication rate (15.2%) of abstracts presented in the field of oculoplastic surgery and orbit at TOA-NCs was found to be lower than that of other international ophthalmology meetings. It is noteworthy that the publication rate of oral abstracts and clinical studies was significantly higher. To enhance the scientific publication potential in Türkiye, which has many active ophthalmologists and ophthalmology clinics, it would be beneficial to identify and address negative factors, support clinicians, and strengthen their connections with the basic medical sciences.

**Keywords:** Abstract, congress, oculoplastic surgery, publication rate

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**Address for Correspondence:** Nilay Yüksel, Ankara Bilkent City Hospital, Clinic of Ophthalmology, Ankara, Türkiye
**E-mail:** ozturk.nilay@gmail.com **ORCID-ID:** orcid.org/0000-0003-4336-7438
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## Introduction

National congresses are important scientific meetings where the latest issues in a field are discussed and new emerging technologies are introduced. They contribute to the academic development and clinical approaches of physicians and educators in scientific and social fields. Abstracts are submitted to present studies at national congresses. The preparation and presentation of abstracts are crucial steps in the life cycle of research projects. Abstracts convey the study's purpose, methods used, results obtained, and their implications. Following the review processes, successful abstracts are accepted for oral or poster presentation in the meetings. These review processes are generally different from peer-reviewed journals. The presented studies can influence physicians' decisions regarding the management of their patients and serve as a guide for planning new research. Therefore, the quality of abstracts presented at national congresses is important.[1,2] Publishing a study in a peer-reviewed journal is one of the highest indicators of the academic value of the study and its implications.[3]

There are an increasing number of studies on the publication rates of abstracts presented at national and international meetings in various fields, including ophthalmology. However, there has not yet been a study that evaluates national congress publication data in the field of ophthalmology in Türkiye. This study aimed to evaluate the general characteristics and publication rates of abstracts presented in the field of oculoplastic surgery and orbital

diseases at the Turkish Ophthalmological Association National Congresses (TOA-NCs) between 2013 and 2022.

## Materials and Methods

Ethics committee approval for this retrospective cross-sectional study was obtained from Ankara Bilkent City Hospital Ethics Committee No. 1 (E1/4358/2023, date: 29.11.2023). The study was conducted in accordance with the Declaration of Helsinki. Abstracts were accessed online at (https://www.todnet.org/html/todnet.asp?a=ulusal-kongreler). Papers accepted as oral or poster presentations in the field of oculoplastic surgery and orbital diseases at TOA-NCs between 2013 and 2022 were included in the study. These abstracts were reviewed in terms of presentation type (oral, poster), number of authors, hospital where the study was conducted (university, training and research, private, public, and abroad), type of study (case, clinic, and basic science), topic of study (eyelid, lacrimal system, orbit, and thyroid eye disease), publication status in journals, time until publication of the paper (months), journal in which it was published (national, international), and the impact factor of the journal.

The publication status of each study was evaluated between October 1 and 10, 2024, by two independent observers (Y.İ.E., N.Y.) according to the author names and study topics using Google Scholar, PubMed, and TR Index online databases. When searching for the abstracts in PubMed, (Title)/(Keywords of the abstract) AND (First author name) were used. If no publications were found, the names of the first three authors were searched separately. Studies were considered published if the title, purpose, methods, and author list matched those of the abstract. Journal impact factors for the published studies were obtained from Thomson Reuters Journal Citation Reports 2020. Twelve papers published before the congress date were excluded from the study.

### Statistical Analysis

The statistical analysis of the data was performed using SPSS (Statistical Package for Social Sciences) version 26.0. Publication rates and categorical variables are presented as percentages. Statistical significance between variables with non-parametric distribution was assessed using the Mann-Whitney U test. Statistical significance value was accepted as $p<0.05$.

## Results

A total of 802 presentations (233 [29.1%] oral, 569 [70.9%] poster) in the field of oculoplastic surgery and orbital diseases were included in the study. Of all abstracts, 44.5% were from university hospitals, 43.5% from training and research hospitals, 7.2% from private hospitals, 4.4% from public hospitals, and 0.4% from abroad. Case reports constituted 41.6%, clinical studies 57.9%, and basic science 0.5% of the studies. Eyelid represented the largest topic (38.1%), followed by the lacrimal system (29.1%), orbit (27.9%), and thyroid eye disease (4.9%). General characteristics and distribution of the abstracts are shown in Table 1.

A total of 122 (15.2%) abstracts were published; 56 (45.9%) of them were oral presentations and 66 (54.1%) were poster presentations. The publication rate for oral presentations was 24.0%, significantly higher than the 11.6% publication rate for poster presentations ($p<0.001$). The median publication time of published abstracts was 18 months (range: 1-88 months). The median impact factor of the journals in which published studies were found was 1.3 (range: 0.1-5.17). Forty-two journals (34.4%) were national, while 80 (65.6%) were international journals. The median number of authors per study was 3 (range: 1-11).

When examined according to the hospital where the study was conducted, publication rates were 15.7% for university hospitals, 16.0% for training and research hospitals, 8.6% for private hospitals, and 14.3% for public hospitals. There was no significant difference based on hospital type ($p>0.05$). None of the abstracts submitted from abroad were published. Case abstracts had a publication rate of 6.3%, while clinical studies had a significantly higher rate of 21.8% ($p<0.001$). The four studies categorized as basic science were not published. Publication rates for studies related to orbit, eyelid, lacrimal system, and thyroid eye diseases were 9.4%, 13.7%, 21.0%, and 25.6%, respectively. The publication rates for lacrimal system and thyroid eye disease studies were significantly higher than for orbit studies ($p<0.001$ and $p<0.01$, respectively). Additionally, the publication rate for lacrimal system studies was significantly higher than for eyelid studies ($p<0.05$). Publication rates and statistical significance within categories are shown in Table 2.

The publication rates of the abstracts varied from year to year, but the difference was statistically insignificant ($p>0.05$). The publication rates and the number of abstracts per year are shown in Figure 1. A negative correlation was found between the publication time of the study and the impact factor of the journal in which it was published ($r=-0.211$, $p=0.039$) (Figure 2). No significant correlation was observed between the number of authors and impact factor, publication time, or publication status (Table 3). It was also observed that clinical studies had a significantly higher rate of oral presentations compared to case presentations (48.3% vs. 2.4%; $p<0.001$). The oral presentation rates of clinical and case abstracts are shown in Table 4.

## Discussion

In this study, a 10-year analysis revealed a publication rate of 15.2% for abstracts presented in the field of oculoplastic surgery and orbit at TOA-NC, Türkiye's largest ophthalmology meeting. This rate is comparable to the 13% publication rate of oculoplastic surgery and orbit abstracts presented at the All India Ophthalmic Conference in 2010.[4] However, it is important to note that the latter rate is based on one year's meeting data, unlike this comprehensive 10-year analysis. The publication rate of abstracts presented at Saudi ophthalmology congresses between 2015 and 2018 was reported to be 45.7%. In that study, oculoplastic surgery abstracts ranked third with a publication rate of 50.9%.[5] For American Academy of Ophthalmology (AAO) meetings, which are the most widely attended in the field, the publication rate in 2012 and 2013 was 32.7% (304/929

abstracts).[6] Glaucoma studies had the highest publication rate at 47.1%, followed by retina (32.9%), cornea (32.8%), and cataract studies (25.2%). Oculoplastic surgery abstracts ranked fifth with a rate of 20.8% (5/24).[6] At Canadian Ophthalmological Society (COS) meetings between 2010 and 2015, 42.9% of the 874 abstracts were published.[7] Oculoplastic surgery had one of the lowest publication rates among subspecialties, at 35%. Zloto et al.[8] analyzed publication trends in ophthalmology journals from 2010 to 2019 and reported a significant decrease in articles published in the field of oculoplastic surgery. In a study by von Elm et al.,[9] the most commonly cited reasons for low publication rates were lack of time (31%), low priority (21%), previous rejection (10%), problems with co-authors (9%), expected rejection (8%), and negative study outcomes (3%). While we cannot fully explain the low publication rate in our study, it is plausible that one of the major obstacles to journal publication is the rigorous evaluation process employed by journals. Additionally, studies on oculoplastic and orbital surgery are generally published in more specialized journals, and due to the limited number of such journals, publication rates may be lower.

The aforementioned studies generally discussed annual ophthalmology meetings that encompass all subspecialties. A 10-year review of 2,161 studies presented at the North American Neuro-Ophthalmology Society meetings, which focus only on neuro-ophthalmology, revealed a publication rate of 31.5%.[10] This rate was similar to other ophthalmology and neurology conferences, where approximately two-thirds of the studies remained unpublished. Since there is no scientific meeting specifically dedicated to oculoplastic surgery and the orbit in Türkiye, it is not possible to directly compare our results to those of other studies.

According to a study examining 1,742 abstracts presented at the most widely attended international ophthalmology meetings in 2010, the publication rates at 2 and 5 years after the meetings were 33.3% and 47.2%, respectively.[11] von Elm et al.[9] reported that 27% of 19,123 papers from 234 medical meetings held between 1957 and 1999 were published after 2 years, 41% after 4 years, and 44% after 6 years. It is evident that studies continue to be published as long as 6 years after meetings.

Yu et al.[12] analyzed 685 articles from 58 ophthalmology journals and found that the median time from submission to publication was 161 days (interquartile range: 111-232), with a maximum of 594.5 days. The median publication times for abstracts were reported as 12 months (range: 0-60) for Saudi ophthalmology congresses, 40 months (range: 18-54) for AAO meetings and 16 months (range: 0-78) for COS meetings.[5,6,7] In the current study, the median publication time was 18 months (range: 1-88).

Yuan et al.[10] reported that studies with 3 or more authors, basic science studies, and those with over 100 samples were more likely to be published. Mullen et al.[7] also found a significant

**Table 1. General characteristics and distribution of the abstracts**

| | | Published (n=122) | Not published (n=680) | Total (n=802) |
|---|---|---|---|---|
| Presentation type | Oral | 56 (24.0%) | 177 (76.0%) | 233 |
| | Poster | 66 (11.6%) | 503 (88.4%) | 569 |
| Hospital | University | 56 (15.7%) | 301 (84.3%) | 357 |
| | Training and research | 56 (16.0%) | 293 (84.0%) | 349 |
| | Private | 5 (8.6%) | 53 (91.4%) | 58 |
| | Public | 5 (14.3%) | 30 (85.7%) | 35 |
| | Abroad | - | 3 (100%) | 3 |
| Study type | Case | 21 (6.3%) | 313 (93.7%) | 334 |
| | Clinical | 101 (21.8%) | 363 (78.2%) | 464 |
| | Basic science | - | 4 (100%) | 4 |
| Study topic | Eyelid | 42 (13.7%) | 264 (86.3%) | 306 |
| | Lacrimal system | 49 (21.0%) | 184 (79.0%) | 233 |
| | Orbit | 21 (9.4%) | 203 (90.6%) | 224 |
| | Thyroid eye disease | 10 (25.6%) | 29 (74.4%) | 39 |
| | | Median (range) | | |
| Number of authors | | 3 (1-11) | | |
| Publication time (months) | | 18 (1-88) | | |
| Median impact factor | | 1.3 (0.1-5.17) | | |
| Journal nationality, n (%)<br>National<br>International | | <br>42 (34.4%)<br>80 (65.6%) | | |

Row percentages given; n: Total number of abstracts for each category by column


**Figure 1.** Abstract numbers and publication rates by year

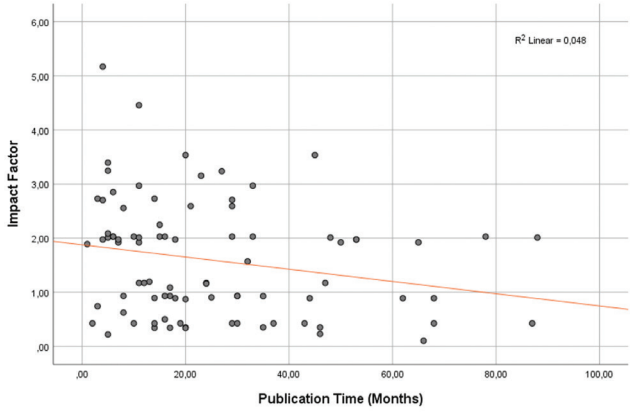


**Figure 2.** Correlation between impact factor and publication time (r=-0.211, p<0.05)

increase in the publication rate for papers with 5 or more authors. In the current study, the median number of authors was 3 (range: 1-11). However, no significant relationship was found between the number of authors and publication rate, publication time, or impact factor.

In widely attended ophthalmology meetings held at different times, the median impact factors of published abstracts were reported to range between 1.9 and 2.9.[6,13,14] The median impact factor in this study was 1.3 (range: 0.1-5.17), which appears low compared to other studies.

Previous studies have shown that higher journal impact factor was associated with faster acceptance after submission and shorter time from presentation to publication.[12,15] Similarly, the current study also revealed that an increase in the impact factor shortened the publication time (r=-0.211, p<0.05).

A systematic review and meta-analysis of 12,261 abstracts from 11 ophthalmology conferences found that oral presentations and basic science studies had higher publication rates.[16] In a study examining 1,742 abstracts, 44% of studies published at 2 years and 60.5% of studies published at 5 years after presentation were basic science studies.[11] The publication rate of poster presentations was about half that of oral presentations. A study of 8 years of annual congresses of the Royal College of Ophthalmologists between 2005 and 2012 found that randomized controlled trials, basic science studies, and oral presentations were more likely to be published.[15] Similarly, in the current study, oral presentations had a higher publication rate than poster presentations. The high publication rate of oral presentations suggests that higher quality studies are more likely to be accepted as oral presentations at meetings. It was also noteworthy that basic science studies, which other analyses showed are a positive factor for publication, were very underrepresented in this study.

Publication rates may vary depending on subspecialties. Dray et al.[17] reported a significant decline in the publication trend of studies on orbital diseases. They noted that among 465 oculoplastic articles published in general ophthalmology journals, 38.5% focused on the eyelid, 34.4% on the orbit, 19.8% on the lacrimal system, and 7.3% on thyroid eye disease. In the current study, the distribution of abstracts among these topics was 36.1%, 16.7%, 39.8%, and 7.4%, respectively. Studies on the lacrimal system (21.0%) and thyroid eye diseases (25.6%) showed relatively higher publication rates compared to studies on orbital diseases (9.4%). Additionally, the publication rate of lacrimal system studies (21.0%) was higher than that of eyelid studies (13.7%). This might indicate greater expertise and confidence among ophthalmologists in lacrimal system and eyelid diseases compared to the more technically demanding field of orbital diseases. Moreover, the higher prevalence of lacrimal system diseases in society could encourage more research in these areas.

Few studies have evaluated the effect of study setting on publication rates. Alsarhani et al.[5] reported that publication rates were higher for studies conducted in tertiary eye hospitals (54.3%) than general hospitals (32.4%) and in public hospitals (49.2%) than private hospitals (20.8%). In our study, the publication rates of studies from university, training and research, private, and public hospitals did not differ significantly.

In similar studies conducted in medical branches other than ophthalmology in Türkiye, the publication rate generally varied between 8% and 28%, which is lower than that of international counterparts.[18,19,20,21] Considering these similar rates, it can be concluded that the publication success of Turkish physicians is likely affected by common factors such as insufficient scientific value, lack of novelty, and authors' lack of time due to clinical commitments. We believe that providing clinicians with at least half a day of research time per week will increase publication rates.

### Study Limitations

Our study has several limitations. Although nearly two years have passed since the last congress evaluated, the wide publication window of 1-88 months suggests that some studies may still be awaiting publication. Since only studies in the field of oculoplastic surgery and orbit were assessed, the findings

| Table 2. Publication rates and statistical significance within categories | | | |
|---|---|---|---|
| | **Total number** | **Publication rate** | **p*** |
| **Presentation type** | | | |
| Oral vs. poster | 233 vs. 569 | 24.0% vs. 11.6% | **<0.001** |
| Hospital | | | |
| University vs. training and research | 357 vs. 349 | 15.7% vs. 16.0% | 0.896 |
| University vs. private | 357 vs. 58 | 15.7% vs. 8.6% | 0.159 |
| University vs. public | 357 vs. 357 | 15.7% vs. 14.3% | 0.828 |
| University vs. abroad | 357 vs. 3 | 15.7% vs. 0% | 0.456 |
| Training and research vs. private | 349 vs. 58 | 16.0% vs. 8.6% | 0.143 |
| Training and research vs. public | 349 vs. 35 | 16.0% vs. 14.3% | 0.786 |
| Training and research vs. abroad | 349 vs. 3 | 16.0% vs. 0% | 0.450 |
| Private vs. public | 58 vs. 35 | 8.6% vs. 14.3% | 0.395 |
| Private vs. abroad | 58 vs. 3 | 8.6% vs. 0% | 0.599 |
| Public vs. abroad | 35 vs. 3 | 14.3% vs. 0% | 0.488 |
| **Study type** | | | |
| Case vs. clinical | 334 vs. 464 | 6.3% vs. 21.8% | **<0.001** |
| Case vs. basic science | 334 vs. 4 | 6.3% vs. 0% | 0.605 |
| Clinical vs. basic science | 464 vs. 4 | 21.8% vs. 0% | 0.293 |
| **Study topic** | | | |
| Eyelid vs. lacrimal system | 306 vs. 23 | 13.7% vs. 21.0% | **0.025** |
| Eyelid vs. orbit | 306 vs. 224 | 13.7% vs. 9.4% | 0.127 |
| Eyelid vs. thyroid eye disease | 306 vs. 39 | 13.7% vs. 25.6% | 0.051 |
| Lacrimal system vs. orbit | 233 vs. 224 | 21.0% vs. 9.4% | **<0.001** |
| Lacrimal system vs. thyroid eye disease | 233 vs. 39 | 21.0% vs. 25.6% | 0.519 |
| Orbit vs. thyroid eye disease | 224 vs. 39 | 9.4% vs. 25.6% | **0.004** |
| *Mann-Whitney U test | | | |

| Table 3. Correlation values between selected variables | | |
|---|---|---|
| | **r** | **p** |
| Publication time and impact factor | -0.211* | **0.039** |
| Number of authors and impact factor | 0.067* | 0.520 |
| Number of authors and publication time | 0.061* | 0.504 |
| Number of authors and publication status | -0.064** | 0.070 |
| *Pearson correlation coefficient, **Spearman's correlation coefficient | | |

| Table 4. Oral and poster presentation rates for study types | | | | |
|---|---|---|---|---|
| | | **Study type** | | |
| | | **Case (n=334)** | **Clinical (n=464)** | **Basic science (n=4)** |
| Presentation type | Oral | 8 (2.4%)* | 224 (48.3%)* | 1 (25.0%) |
| | Poster | 326 (97.6%) | 240 (51.7%) | 3 (75.0%) |
| Column percentages given, n: Total number of abstracts in each column, *p<0.05, Mann-Whitney U test | | | | |

cannot be generalized to all fields of ophthalmology due to potential variations in publication rates among different subspecialties presented at the congress. Furthermore, there is a possibility that some studies might be indexed in databases other than those searched (PubMed, TR Index, and Google Scholar), although it is rare.

## Conclusion

The 10-year publication rate (15.2%) of abstracts presented in the field of oculoplastic surgery and orbit at TOA-NCs was found to be lower than that of other international ophthalmology meetings. It is noteworthy that publication rates were significantly higher for oral abstracts and clinical studies. To enhance the scientific publication potential in Türkiye, which hosts many active ophthalmologists and ophthalmology clinics, it would be beneficial to identify and address negative factors, support clinicians and strengthen their connections with basic medical sciences.

### Ethics

**Ethics Committee Approval:** Ethics committee approval for this retrospective cross-sectional study was obtained from Ankara Bilkent City Hospital Ethics Committee No. 1 (E1/4358/2023, date: 29.11.2023).

**Informed Consent:** Retrospective study.

### Declarations

#### Authorship Contributions

Concept: N.Y., Y.İ.E., Design: N.Y., Y.İ.E., Data Collection or Processing: Y.İ.E., N.Y., Analysis or Interpretation: N.Y., Y.İ.E., Literature Search: Y.İ.E., N.Y., Writing: Y.İ.E., N.Y.

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

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Original Article

# The Ability of Large Language Models to Generate Patient Information Materials for Retinopathy of Prematurity: Evaluation of Readability, Accuracy, and Comprehensiveness

Sevinç Arzu Postacı, Ali Dal

Mustafa Kemal University, Tayfur Sökmen Faculty of Medicine, Department of Ophthalmology, Hatay, Türkiye

## Abstract

**Objectives:** This study compared the readability of patient education materials from the Turkish Ophthalmological Association (TOA) retinopathy of prematurity (ROP) guidelines with those generated by large language models (LLMs). The ability of GPT-4.0, GPT-4o mini, and Gemini to produce patient education materials was evaluated in terms of accuracy and comprehensiveness.

**Materials and Methods:** Thirty questions from the TOA ROP guidelines were posed to GPT-4.0, GPT-4o mini, and Gemini. Their responses were then reformulated using the prompts "Can you revise this text to be understandable at a 6$^{th}$-grade reading level?" (P1 format) and "Can you make this text easier to understand?" (P2 format). The readability of the TOA ROP guidelines and the LLM-generated responses was analyzed using the Ateşman and Bezirci-Yılmaz formulas. Additionally, ROP specialists evaluated the comprehensiveness and accuracy of the responses.

**Results:** The TOA brochure was found to have a reading level above the 6$^{th}$-grade level recommended in the literature. Materials generated by GPT-4.0 and Gemini had significantly greater readability than the TOA brochure ($p<0.05$). Adjustments made in the P1 and P2 formats improved readability for GPT-4.0, while no significant change was observed for GPT-4o mini and Gemini. GPT-4.0 had the highest scores for accuracy and comprehensiveness, while Gemini had the lowest.

**Conclusion:** GPT-4.0 appeared to have greater potential for generating more readable, accurate, and comprehensive patient education materials. However, when integrating LLMs into the healthcare field, regional medical differences and the accuracy of the provided information must be carefully assessed.

**Keywords:** Retinopathy of prematurity, large language models, readability, patient education

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**Address for Correspondence:** Ali Dal, Mustafa Kemal University, Tayfur Sökmen Faculty of Medicine, Department of Ophthalmology, Hatay, Türkiye
**E-mail:** alidal19@hotmail.com **ORCID-ID:** orcid.org/0000-0002-0748-6416
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## Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative and multifactorial disease of the retina. It is primarily observed in preterm infants but can also occur in full-term infants who have received high levels of oxygen therapy.[1] Advances in neonatal care have increased survival rates for preterm infants, which has resulted in more frequent encounters with conditions such as ROP. Annually, approximately 15 million babies worldwide are born prematurely (before 37 completed weeks of gestation).[2] Each year, between 23,800 and 45,600 infants are reported to suffer from irreversible vision loss as a result of ROP.[3] Particularly in low- and middle-income countries, up to 40% of childhood blindness is attributed to preventable ROP cases, and Türkiye is one of these countries.[4] A multicenter study conducted in Türkiye revealed that among 6,115 preterm infants, 27% were diagnosed with some stage of ROP, and 6.7% developed severe ROP.[5]

ROP can be effectively managed with consistent monitoring and prompt therapy.[6,7] Monitoring commences soon after delivery and continues until retinal vascularization is fully established. The follow-up frequency is modified according to the severity of the disease; infants with severe ROP are followed on a weekly basis, while others are seen at extended intervals. However, delays in follow-up might lead to lost treatment opportunities and ultimately result in complete blindness.[8]

The dissemination of comprehensive information regarding the disease and treatment process to families is of utmost importance, as it greatly enhances their compliance with follow-up and treatment. Previous research has demonstrated that increased levels of knowledge within families are correlated with less anxiety and improved adherence to treatment regimens.[9,10]

In Türkiye, the Turkish Ophthalmological Association (TOA) offers patient education resources and informed consent forms for a range of disorders on its official website. It is crucial to ensure that these materials are comprehensible to facilitate patients' information-gathering process.[11] Per the guidelines of the American Medical Association and the National Institutes of Health, patient education materials should be produced at a reading level equivalent to that of a 6$^{th}$-grade student.[12] Various formulas which analyze factors such as sentence length and word structure are frequently employed to evaluate readability.[13] For Turkish texts, readability is commonly determined using the Ateşman[14] and Bezirci and Yılmaz[15] readability formulas.

Over the past few years, online information sources have emerged as readily available tools that patients often favor greatly. A survey conducted by the Pew Center reveals that 61% of persons in the United States actively access health information through internet platforms.[16] Nevertheless, it is widely recognized that the comprehensibility of online health information generally necessitates a greater degree of education.[17,18,19] Large language models (LLMs) are artificial intelligence systems trained using content available on the internet to generate texts in natural language.[20] Machine-learning models such as OpenAI's ChatGPT and Google's Gemini are being employed in the medical domain to provide patient education and create informative content.[21,22] Nevertheless, the dependability of these models is still a topic of contention, and further investigation is now being conducted.[23]

This research examined the readability levels of ROP patient education materials, structured in a question-and-answer format, available on the TOA website using the Ateşman and Bezirci-Yılmaz formulas. Thirty questions from these materials were posed to the advanced language models GPT-4.0, GPT-4o mini, and Gemini, and the responses were used to generate patient brochures. The readability, accuracy, and comprehensiveness of these brochures were then evaluated to assess the models' effectiveness in producing patient education materials.

## Materials and Methods

The main data source for this study consisted of informational brochures created for families regarding the treatment guidelines for ROP, which can be obtained from the TOA website (https://www.todnet.org/tod-rehber/rop-tedavi-rehberi-2021.pdf, available in Turkish: Appendix 1: Informational Brochure for Families: Retinopathy of Prematurity Screening, Appendix 2: Informational Brochure for Families: Retinopathy of Prematurity Treatment).[24] The guidelines comprise 30 questions pertaining to ROP, such as "What is ROP?" and "How is ROP treated?", along with their accompanying responses. An independent analysis was conducted on each response from the guidelines using the Ateşman and Bezirci-Yılmaz readability formulas. Since our study used only publicly available data and literature and did not entail the use of any animal or human data, ethics committee approval and patient consent were not required.

### Use of Large Language Models

In this study, 30 questions from the TOA ROP guidelines were posed to the ChatGPT-4.0, ChatGPT-4o mini, and Gemini models. Table 1 presents sample questions directed to the artificial intelligence tools used in this study. Each question was asked in a new chat session, and the responses were recorded. Additionally, the ability of LLMs to simplify texts for lower educational levels was evaluated. To assess this, the models were given their initial responses (initial format) with prompts to generate two new responses:[25]

Prompt 1: "Can you revise the following text to make it understandable at a 6$^{th}$-grade reading level?" (P1 format).

Prompt 2: "Can you revise the following text to make it easier to understand?" (P2 format).

Each response was analyzed individually using the Ateşman and Bezirci-Yılmaz readability formulas.

### Readability Criteria

**Ateşman Readability Formula:** The Ateşman formula provides a score between 0 and 100 based on average sentence and word length. We conducted the Ateşman analysis using an online program. The scoring system is categorized as follows: 90-100 points correspond to a 4$^{th}$-grade level or below, 80-89 points to a 5$^{th}$- or 6$^{th}$-grade level, 70-79 points to a 7$^{th}$- or 8$^{th}$-grade level, 60-69 points to a 9$^{th}$- or 10$^{th}$-grade level, 50-59 points to an 11$^{th}$- or 12$^{th}$-grade level, 40-49 points to an associate-degree level, 30-39 points to an undergraduate-degree level, and 29 points or below to a postgraduate-degree level.[14]

**Bezirci-Yılmaz Readability Formula:** The Bezirci-Yılmaz formula evaluates readability based on average sentence length and the number of syllables in words. The Bezirci-Yılmaz analysis was conducted using a specialized software tool. The scoring system is as follows: 1-8 points correspond to the primary-school level, 9-12 points to the high-school level, and

**Table 1. Sample questions directed to artificial intelligence tools in the study**

| Questions |
|---|
| What is ROP? |
| How common is ROP? |
| What is screening for ROP? |
| What causes ROP? |
| When should screening be done? |
| What happens during screening? |
| Is the examination painful? |
| What happens if my baby is sick when it's time for the eye exam? |
| What happens if ROP is found? |
| Will the screenings be finished before my baby goes home? |

ROP: Retinopathy of prematurity

12-16 points to the undergraduate level; scores above 16 indicate readability appropriate for academic-level texts.[15]

### Comprehensiveness and Accuracy of Patient-Targeted Information Produced by Large Language Models

The responses generated by LLMs were evaluated for comprehensiveness and accuracy based on the TOA ROP guidelines. Experts specialized in ROP and experienced in its clinical management (S.A.P. and A.D.) assessed the accuracy and comprehensiveness of the responses. The comprehensiveness of the answers was rated as follows:[26]

- 1 point: Insufficiently comprehensive (misses crucial information)
- 2 points: Somewhat comprehensive (contains minimal but necessary information)
- 3 points: Moderately comprehensive (provides a reasonable level of detail)
- 4 points: Comprehensive (includes critical information)
- 5 points: Very comprehensive (provides detailed and complete information)

The responses were evaluated for accuracy as follows:[27]

- 1 point: Poor (includes substantial inaccuracies and may be detrimental to patients)
- 2 points: Moderate (some inaccuracies but not likely to pose adverse effects for patients)
- 3 points: Excellent (free of errors)

### Statistical Analysis

In the data analysis, one-way analysis of variance (ANOVA) was used for comparison of multiple means, followed by post-hoc Tukey's honestly significant difference test to identify significant pairwise differences. Statistical analyses were conducted using SPSS software (IBM SPSS Statistics, Version 26.0). A p value of $<0.05$ was considered statistically significant.

## Results

### Bezirci-Yılmaz Readability Scores

The Bezirci-Yılmaz readability analysis revealed that the texts initially produced by GPT-4.0 and Gemini had a notably lower reading level than those in the TOA brochure (p=0.010 and p=0.039, respectively). No statistically significant difference was found between the materials generated by GPT-4o mini and the TOA brochure (p=0.325). No statistically significant differences were found in the comparisons among the other groups (Table 2).

When comparing the initial responses of the LLMs (GPT-4.0, Gemini, and GPT-4o mini) with their responses in the P1 and P2 formats, a statistically significant increase in readability was observed only in the responses of GPT-4.0 (p=0.005 and p=0.012, respectively). No significant differences were found in the other groups. Additionally, no statistically significant differences were observed between the responses in the P1 and P2 formats within any of the LLM groups (p>0.05) (Table 3).

### Ateşman Readability Scores

When examining the Ateşman readability scores, the initial responses generated by GPT-4.0 and Gemini were found to have significantly lower reading levels compared to the TOA brochure (p=0.016 and p=0.006, respectively). No significant difference was found between GPT-4o mini and the TOA brochure (p=0.910). Additionally, GPT-4.0 and Gemini showed significantly lower reading levels compared to GPT-4o mini (p=0.042 and p=0.035, respectively). However, no significant difference was observed between GPT-4.0 and Gemini (Table 2).

None of the LLMs' initial responses showed any statistically significant difference in Ateşman readability score when compared to their responses in the P1 and P2 formats. Furthermore, there were no notable disparities noted between the P1 and P2 formats for any of the models (Table 4). The reading level of the other LLMs groups was assessed to be at the 9$^{th}$- to 10$^{th}$-grade level, whereas the responses produced by GPT-4o mini were determined to be at the 11$^{th}$- to 12$^{th}$-grade level.

### Comprehensiveness Scores

When comparing the comprehensiveness scores of the initial responses from the LLMs, the responses generated by GPT-4.0 were found to have a significantly higher level of comprehensiveness compared to those from GPT-4o mini

**Table 2. Comparison of Bezirci-Yılmaz and Ateşman readability scores between the TOA brochure and LLM initial responses**

| | TOA | GPT-4.0 | Gemini | GPT-4o mini | p value | |
|---|---|---|---|---|---|---|
| **Bezirci-Yılmaz readability score, mean (SD)** | 12.30 (7.58) | 8.30 (2.50) | 9.17 (2.40) | 10.72 (4.20) | TOA vs. GPT 4.0:<br>TOA vs. Gemini:<br>TOA vs. GPT 4o mini:<br>GPT 4.0 vs. Gemini:<br>GPT 4.0 vs. GPT 4o mini:<br>Gemini vs. GPT 4o mini: | **0.010**<br>**0.039**<br>0.325<br>0.838<br>0.209<br>0.525 |
| **Ateşman readability score, mean (SD)** | 51.57 (21.74) | 62.06 (6.86) | 63.61 (7.94) | 51.07 (10.57) | TOA vs. GPT 4.0:<br>TOA vs. Gemini:<br>TOA vs. GPT 4o mini:<br>GPT 4.0 vs. Gemini:<br>GPT 4.0 vs. GPT 4o mini:<br>Gemini vs. GPT 4o mini: | **0.016**<br>**0.006**<br>0.910<br>0.682<br>**0.042**<br>**0.035** |

Significant results (p<0.05) shown in bold. TOA: Turkish Ophthalmological Association, LLM: Large language model, SD: Standard deviation

and Gemini (p=0.045 and p=0.001, respectively). However, no significant difference in comprehensiveness was observed between GPT-4o mini and Gemini. The comprehensiveness scores of GPT-4.0's responses in the P1 and P2 formats were higher than those of GPT-4o mini and Gemini (Table 5).

### Accuracy Scores

When comparing the accuracy scores of the initial responses from the LLMs, GPT-4.0's accuracy scores were found to be statistically significantly higher than those of Gemini (p=0.001). However, no significant difference in accuracy was observed between GPT-4o mini and Gemini or GPT-4.0. When comparing the accuracy scores of responses in the P1 and P2 formats, GPT-4.0 was significantly more accurate than Gemini (p=0.039 and p=0.034, respectively). No other statistically significant differences were observed (Table 5).

## Discussion

In this study, the readability of patient education materials in the TOA ROP treatment guidelines was assessed. According to the Bezirci-Yılmaz readability formula, the materials were at an average high-school level, whereas the Ateşman readability formula placed them at 11$^{th}$ or 12$^{th}$ grade. Research conducted in Türkiye revealed the average education level to be 6.51 years.[28] When creating patient education materials, it is important to consider the average education level of each country.[29] In the literature, the recommended reading level for patient education materials is often at the 6$^{th}$-grade level.[12] Materials that exceed this level may be difficult to interpret for patient populations with limited health literacy, potentially reducing treatment adherence. Therefore, the reading level of the TOA ROP guidelines is higher than suggested for patient education materials, indicating that they should be simplified. A similar problem occurred with the materials produced by ChatGPT-4.0, ChatGPT-4o mini, and Gemini. The reading levels of these materials were determined to be above the recommended level, not aligned with the norms stated in the literature.[30,31]

Delays in the treatment of ROP can lead to irreversible vision loss as well as significant medicolegal issues for healthcare professionals.[32] The most common issue in malpractice cases related to ROP is the failure to perform timely screening or follow-up.[33] One of the main reasons for this is that families do not have sufficient knowledge about ROP and the screening process. Studies in the literature have shown that when parents

**Table 3. Comparison of Bezirci-Yılmaz readability scores and education levels between the initial (IF), P1, and P2 format responses from GPT-4.0, Gemini, and GPT-4o mini**

| | | Bezirci-Yılmaz readability score, mean (SD) | Education level | p value |
|---|---|---|---|---|
| **GPT-4.0** | IF | 8.30 (2.50) | Primary school | IF vs. P1: **0.005**<br>IF vs. P2: **0.012**<br>P1 vs. P2: 0.974 |
| | P1 | 7.04 (3.04) | Primary school | |
| | P2 | 6.74 (3.62) | Primary school | |
| **Gemini** | IF | 9.17 (2.40) | High school | IF vs. P1: 0.970<br>IF vs. P2: 0.942<br>P1 vs. P2: 0.907 |
| | P1 | 8.53 (1.58) | Primary school | |
| | P2 | 8.22 (1.46) | Primary school | |
| **GPT-4o mini** | IF | 10.72 (4.20) | High school | IF vs. P1: 0.879<br>IF vs. P2: 0.971<br>P1 vs. P2: 0.990 |
| | P1 | 9.78 (3.04) | High school | |
| | P2 | 10.16 (3.62) | High school | |

Significant results (p<0.05) shown in bold. SD: Standard deviation

**Table 4. Comparison of Ateşman readability scores and education levels between the initial (IF), P1, and P2 format responses from GPT-4.0, Gemini, and GPT-4o mini**

| | | Ateşman readability score, mean (SD) | Education level | p value |
|---|---|---|---|---|
| **GPT-4.0** | IF | 62.06 (6.86) | 9$^{th}$-10$^{th}$ grade | IF vs. P1: 0.256<br>IF vs. P2: 0.312<br>P1 vs. P2: 0.999 |
| | P1 | 68.03 (7.56) | 9$^{th}$-10$^{th}$ grade | |
| | P2 | 67.65 (6.90) | 9$^{th}$-10$^{th}$ grade | |
| **Gemini** | IF | 63.61 (7.94) | 9$^{th}$-10$^{th}$ grade | IF vs. P1: 0.484<br>IF vs. P2: 0.219<br>P1 vs. P2: 0.901 |
| | P1 | 65.54 (6.65) | 9$^{th}$-10$^{th}$ grade | |
| | P2 | 67.84 (6.85) | 9$^{th}$-10$^{th}$ grade | |
| **GPT-4o mini** | IF | 51.07 (10.57) | 11$^{th}$-12$^{th}$ grade | IF vs. P1: 0.904<br>IF vs. P2: 0.684<br>P1 vs. P2: 0.793 |
| | P1 | 58.12 (9.52) | 11$^{th}$-12$^{th}$ grade | |
| | P2 | 56.02 (9.39) | 11$^{th}$-12$^{th}$ grade | |

SD: Standard deviation

**Table 5. Comparison of comprehensiveness and accuracy scores of GPT-4.0, Gemini, and GPT-4o mini**

| | | GPT-4.0 | Gemini | GPT-4o mini | p value | |
|---|---|---|---|---|---|---|
| Comprehensiveness score, mean (SD) | IF | 3.83 (0.91) | 2.80 (1.16) | 2.83 (1.26) | GPT 4.0 vs. Gemini:<br>GPT 4.0 vs. GPT 4o mini:<br>GPT 4o mini vs. Gemini: | **0.001**<br>**0.045**<br>0.078 |
| | P1 | 3.57 (0.90) | 2.57 (0.97) | 2.70 (1.18) | GPT 4.0 vs. Gemini:<br>GPT 4.0 vs. GPT 4o mini:<br>GPT 4o mini vs. Gemini: | 0.004<br>**0.002**<br>0.093 |
| | P2 | 3.53 (0.90) | 2.50 (1.01) | 2.43 (1.14) | GPT 4.0 vs. Gemini:<br>GPT 4.0 vs. GPT 4o mini:<br>GPT 4o mini vs. Gemini: | **0.030**<br>**0.013**<br>0.061 |
| Accuracy score, mean (SD) | IF | 2.90 (0.31) | 2.10 (0.76) | 2.50 (0.57) | GPT 4.0 vs. Gemini:<br>GPT 4.0 vs. GPT 4o mini:<br>GPT 4o mini vs. Gemini: | **0.001**<br>0.058<br>0.345 |
| | P1 | 2.90 (0.31) | 2.13 (0.73) | 2.50 (0.57) | GPT 4.0 vs. Gemini:<br>GPT 4.0 vs. GPT 4o mini:<br>GPT 4o mini vs. Gemini: | **0.039**<br>0.159<br>0.397 |
| | P2 | 2.90 (0.31) | 2.13 (0.73) | 2.50 (0.57) | GPT 4.0 vs. Gemini:<br>GPT 4.0 vs. GPT 4o mini:<br>GPT 4o mini vs. Gemini: | **0.034**<br>0.217<br>0.231 |

Significant results ($p<0.05$) shown in bold. SD: Standard deviation

are informed and made aware, adherence to treatment improves and their infants have better outcomes.[9,10] In one study, it was reported that the parents of very low birth weight infants, especially those with limited English proficiency and poor health literacy, were not adequately informed about ROP, which negatively impacted treatment.[34] The study showed that more than half of parents did not receive adequate information about their infant's ROP condition upon discharge. One reason for this information gap is that 1 in 10 adults in the United States has low health literacy.[2]

An analysis conducted in the domain of pediatric ophthalmology revealed that online patient education materials were suitable for an audience with an average educational attainment of 11.75±2.72 years.[34] Insufficient comprehensibility of this educational material may result in inadequate compliance with therapy among persons with limited health literacy. Hence, it is imperative to provide patient education materials that are easily understandable for individuals with lower knowledge levels. According to the data collected in our study, the TOA guidelines for ROP are written at an unacceptably high reading level. Therefore, it is necessary to enhance the comprehensibility of these materials.

In this study, when comparing the readability levels of the brochures generated by GPT-4.0, GPT-4o mini, and Gemini with the TOA brochure, GPT-4.0 and Gemini were found to have lower readability levels compared to the TOA brochure. Additionally, in the P1 and P2 formats, which were designed to improve comprehensibility, an increase in readability (as assessed by Bezirci-Yılmaz score) was observed for the brochure created by GPT-4.0, while no significant changes were observed for Gemini or GPT-4o mini. These findings are consistent with the literature.[27,35,36] In terms of readability, these findings indicate that GPT-4.0 may be a more appropriate choice for creating a Turkish ROP guide.

LLMs are developing as new and intriguing instruments in the healthcare sector. They show potential particularly in patient consultation, medical triage, and providing information. LLMs can enhance access to healthcare by answering common medical questions from patients and improving care for individuals in remote or underserved areas.[22,37] Furthermore, these models have been observed to take on administrative tasks, allowing healthcare professionals to dedicate more time to patient care.[38] However, the use of LLMs presents certain challenges. LLMs may provide inaccurate information, posing a risk to patients and their families, particularly in medical settings.[39] These models have limited capacity for self-checking their responses and correcting errors. Misleading or incomplete information could lead to medical errors, posing serious risks to patient safety.[40] In order to fully integrate LLMs into clinical practice, further improvements in validation processes and stricter oversight of these models are essential.

Patient education materials must not just be easy to read, they must also be thorough and accurate. In our study, we also looked at the accuracy and comprehensiveness of the LLM-generated brochures. The results showed that the GPT-4.0 materials were more complete than the GPT-4o mini and Gemini materials. In terms of accuracy, GPT-4.0 scored highest, while Gemini received the lowest scores. These data indicate that GPT-4.0 could be a more trustworthy model for creating patient education materials. Similarly, Pushpanathan et al.[26] found that GPT-4.0 outperformed both GPT-3.5 and Google Bard in terms of accuracy and comprehensiveness when answering complex ocular symptom queries, highlighting its potential in patient education. Antaki et al.[21] also reported that GPT-4.0 provided

more consistent and relevant medical information compared to other LLMs in ophthalmology, underscoring its utility in generating reliable educational materials.

Another concern about the medical information offered by LLMs is the possibility of geographic variations in the data. Screening criteria for ROP may differ by country.[2] While some criteria may not be met in developed nations, the risk of severe ROP is higher in less developed countries.[39] The TOA ROP guidelines recommend screening all newborns delivered before 34 weeks of gestation or weighing less than 1,700 grams.[5] GPT-4.0's response for this question ("infants born before 30 weeks or weighing less than 1,500 grams") was comparable to the screening criteria employed in the United Kingdom but not with the TOA standards for Türkiye.[41] This disparity may generate uncertainty among patient relatives, potentially leading to misinformation and lower adherence to therapy.

### Study Limitations

One of the major limitations of our study is the variability in the performance of language models across different languages. In our study, we asked questions in Turkish and requested that the responses be provided in Turkish as well. Additionally, we asked the language models to produce responses that were more understandable than those from Turkish sources. However, since LLMs are typically trained on English data, they may not perform as effectively in languages like Turkish. This discrepancy can be attributed to differences in linguistic structures and the limited availability of Turkish datasets.[20] It has also been noted in the literature that LLMs tend to show reduced performance when generating medical information in less-represented languages, which can increase the risk of errors in clinical applications.[42] Furthermore, the questions were posed as they appear in the TOA brochure, without the additional context of being asked from the perspective of a user in Türkiye. As such, the potential impact of including a phrase like "I am asking for Türkiye" on the model's responses was not evaluated. Therefore, the use of these models in languages such as Turkish requires careful consideration and should be supported by validation processes conducted by local experts.

## Conclusion

Educating patients and their families is critical in the management of ROP. The reading level of TOA patient information pamphlets was determined to be higher than the acceptable level. In terms of readability, comprehensiveness, and accuracy, GPT-4.0 brochures outperformed GPT-4o mini and Gemini brochures. While LLMs are a promising tool in healthcare, it has been discovered that some information may be misleading, and there is a risk of misdirection owing to geographical variations. As a result, the integration of LLMs into healthcare should be thoroughly tested and supported by relevant recommendations. It has been determined that the accuracy of information generated by LLMs, particularly essential medical information, must be carefully assessed.

### Ethics

**Ethics Committee Approval:** Not required.
**Informed Consent:** Not required.

### Declarations

### Authorship Contributions

Concept: S.A.P., Design: A.D., Data Collection or Processing: S.A.P., Analysis or Interpretation: A.D., Literature Search: S.A.P., Writing: S.A.P., A.D.

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Original Article

# The Efficacy of Adalimumab Treatment in Pediatric Non-Infectious Uveitis: A Retrospective Cohort Study

Kübra Özdemir Yalçınsoy[1], Osman Özen[2], Yasemin Özdamar Erol[3], Pınar Çakar Özdal[4]

[1]University of Health Sciences Türkiye, Ulucanlar Eye Training and Research Hospital, Clinic of Ophthalmology, Ankara, Türkiye
[2]Kastamonu Training and Research Hospital, Clinic of Ophthalmology, Kastamonu, Türkiye
[3]University of Health Sciences Türkiye, Ankara Etlik City Hospital, Clinic of Ophthalmology, Ankara, Türkiye
[4]Uvea Academy Eye Clinic, Ankara, Türkiye

## Abstract

**Objectives:** To evaluate the clinical features of pediatric non-infectious uveitis (NIU) patients treated with adalimumab (ADA) and the efficacy of ADA in patients unresponsive to conventional immunosuppressive therapy.

**Materials and Methods:** The records of 91 NIU patients aged ≤16 years who received ADA therapy were evaluated retrospectively. The patients' demographic and clinical characteristics and treatment approaches were recorded. The efficacy of ADA in patients treated for at least 1 year after failure of conventional immunosuppressive treatment was evaluated by comparing the best corrected visual acuity (BCVA), severity of intraocular inflammation, uveitis flare-ups, topical and systemic corticosteroid (CS) use, and central macular thickness (CMT) values before and after ADA treatment.

**Results:** The study included 103 eyes of 53 patients, of whom 29 (54.7%) were female. The mean age at presentation was 8.2±3.4 (range: 3-16) years. The mean follow-up period was 41.6±28.2 (range: 18-120) months. Twenty-six patients (49.0%) had anterior uveitis, 22 (41.5%) had intermediate uveitis, and 5 (9.4%) had panuveitis. The mean duration of ADA treatment was 23.0±13.7 (range: 12-60) months. Uveitis flare-ups developed in only 13 patients (24.5%) while on ADA treatment. When pre- and post-treatment periods were compared, the mean number of uveitis flare-ups, intraocular inflammation severity, mean dose of topical and systemic CS, and mean CMT values were significantly lower in the post-treatment period ($p<0.05$). The mean BCVA was significantly improved after 6 and 12 months of ADA treatment compared to the pre-treatment visual acuity ($p<0.05$).

**Conclusion:** ADA effectively controlled intraocular inflammation, reducing the need for systemic and topical CS and improving visual outcomes in pediatric NIU.

**Keywords:** Pediatric uveitis, non-infectious uveitis, treatment, adalimumab, tumor necrosis factor alpha

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**Address for Correspondence:** Kübra Özdemir Yalçınsoy, University of Health Sciences Türkiye, Ulucanlar Eye Training and Research Hospital, Clinic of Ophthalmology, Ankara, Türkiye
**E-mail:** kubraozdemir250@gmail.com
**ORCID-ID:** orcid.org/0000-0002-3352-9547
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## Introduction

Pediatric uveitis is less common than uveitis in adults, accounting for 5-10% of all uveitis cases.[1] According to data from the Behçet's Uveitis Frequency Screening (BUST) study, children represent approximately 9% of the uveitis patients in our country.[2] Although pediatric uveitis is less common, it is often diagnosed late due to its asymptomatic, insidious course and examination difficulties. In addition, prognosis is quite poor in pediatric uveitis due to chronic recurrent inflammation and the high rate of vision-threatening complications.[1,3] Etiologically, pediatric uveitis is mostly non-infectious, with studies reporting varying rates of pediatric non-infectious uveitis (NIU) ranging from 75% to 95%.[1,4]

A stepwise treatment approach is recommended in pediatric NIU to effectively suppress inflammation and prevent ocular complications.[3,5,6] Topical and systemic corticosteroids (CSs) provide rapid inflammation suppression and are a first-line treatment. However, due to the high side effect profile of systemic CSs, particularly their adverse effects on the growth and development of children, they should only be used in the short term to suppress acute attacks.[3,5] In patients with refractory or CS-dependent chronic uveitis, second-line treatment includes steroid-sparing immunosuppressive agents.[1,6] Biologic therapy

consists primarily of tumor necrosis factor alpha (TNF-α) inhibitors and is used in cases of severe NIU that does not respond to conventional immunosuppressives or threatens vision.[3] Studies show that in pediatric NIU, early and aggressive treatment with conventional immunosuppressives and biologic agents markedly improves the prognosis.[5,6] Therefore, in current practice, these treatment steps are tailored to each individual patient's ocular and systemic condition.[3]

Adalimumab (ADA), a fully human monoclonal TNF-α antibody, is now the only biologic agent approved for use in the treatment of NIU in adults and children.[7,8] Studies have shown ADA to be a safe and effective biologic agent for controlling intraocular inflammation and reducing relapses in the treatment of pediatric NIU.[7,8,9,10,11,12] Experiences with the use and outcomes of ADA in pediatric NIU are steadily increasing. This study aimed to evaluate the clinical characteristics of patients using ADA for pediatric NIU in a tertiary reference center and the effectiveness of ADA in cases refractory to conventional immunosuppressives.

## Materials and Methods

This was a retrospective observational study evaluating the records of patients followed up for pediatric NIU and treated with ADA in the uvea department of a tertiary eye hospital between 2010 and 2024. The study was conducted in accordance with the principles of the Declaration of Helsinki and ethics committee approval was obtained from the Ankara Training and Research Hospital Ethics Committee (decision no: 522/2020, approval date: 30.12.2020).

We retrospectively analyzed data from 91 patients with NIU aged ≤16 years who received ADA therapy. The patients' demographic and clinical characteristics and treatment approaches were recorded. Patients with pediatric NIU who used ADA for at least 1 year after non-response to conventional immunosuppressive therapy were included in the study, and the effectiveness of ADA therapy in these patients was evaluated. All patients were diagnosed based on the clinical features of uveitis, ocular examination, and imaging findings, by the same ophthalmologists experienced in the field of uveitis. Infectious causes were excluded with laboratory tests. Systemic investigations and assessments performed during diagnosis and follow-up were carried out in cooperation with pediatric rheumatology specialists.

Demographic data, best corrected visual acuity (BCVA) according to Snellen chart, intraocular pressure (IOP) measured by pneumotonometry, slit-lamp anterior and posterior segment examination findings, follow-up time, and systemic and topical treatment approaches were analyzed. BCVA values were converted to logarithm of the minimum angle of resolution (LogMAR) for analysis. Assessment and classification of ocular inflammation was performed according to the Standardization of Uveitis Nomenclature (SUN) Working Group guideline.[13] Pars planitis was diagnosed using the diagnostic criteria of the SUN Working Group and defined as non-infectious intermediate uveitis not associated with systemic disease, accompanied by vitreous inflammation and snowball and snowbank opacities. For the diagnosis of sarcoidosis-associated uveitis, patients were evaluated in conjunction with pediatric rheumatology based on the SUN criteria and the revised International Ocular Sarcoidosis Workshop criteria for ocular sarcoidosis.[14,15,16] A uveitis attack was defined as a two-grade increase in inflammation (anterior chamber cells and/or vitreous haze) or an increase from grade 3+ to 4+.[13,17] In intermediate and panuveitis patients who had fundus fluorescein angiography data, these findings were taken into account when evaluating the progression of intraocular inflammation and response to treatment.

Indications for initiating ADA (AbbVie Inc., Chicago, USA) included refractory, sight-threatening severe uveitis despite conventional immunosuppressive therapy, CS-dependent recurrent uveitis, and CS-related complications. ADA therapy was initiated subcutaneously at a dose of 20 mg for patients weighing less than 30 kg and 40 mg in those weighing ≥30 kg. It was administered at 2-week intervals from the beginning or after a loading dose consisting of two doses (40 or 80 mg by weight) in week 0 and a single dose (20 or 40 mg) in week 1. Patients who did not respond to the standard dose were switched to a weekly regimen, whereas the frequency of ADA doses was extended to intervals of 3 to 4 weeks for patients with intraocular inflammation control and no new attacks for 2 years. Before treatment, all patients underwent interferon gamma release (Quantiferon) test and chest radiography to exclude tuberculosis, and hepatitis and HIV serology were examined. During treatment, blood biochemistry analyses including regular blood count and liver and kidney function tests were performed every 2 months.

Systemic immunosuppressive treatment approaches before and after initiating ADA and the frequency and duration of ADA use were recorded. The number of uveitis attacks, severity of intraocular inflammation, and topical/systemic CS doses in the 6-month period before ADA therapy, after 6 months of ADA therapy, and between 6 and 12 months of ADA therapy. The severity of intraocular inflammation was determined based on the highest grade (between 0 and 4+) of anterior chamber cells in eyes with anterior uveitis or vitreous haze in eyes with intermediate and panuveitis during the relevant time period. Similarly, topical and systemic CS doses were calculated according to the highest dose used in the relevant time period. The patients' central macular thickness (CMT) on optical coherence tomography and BCVA values were recorded before ADA therapy and at 6 months and 12 months of ADA therapy. The patients' ocular complications at admission and follow-up and the ocular surgeries performed were also noted.

### Statistical Analysis

The data were analyzed using IBM SPSS Statistics 22.0 (IBM, Armonk, NY, USA). Descriptive statistics were presented as mean, standard deviation, median, frequency, and percentage. Categorical variables (frequencies and percentages) were compared between dependent groups using the McNemar test.

Normality of the data was evaluated using visual (histogram and probability) and analytical methods (Shapiro-Wilk test). Friedman test was used to compare repeated measures in dependent groups. For variables with significant results, Bonferroni-corrected Wilcoxon's signed-rank test was used in post-hoc pairwise comparisons to determine the sources of the differences. P<0.05 was set as the level of statistical significance.

## Results

Of 91 pediatric NIU patients who received ADA therapy during the study period, 53 patients (103 eyes) treated with ADA for at least 1 year after non-response to conventional immunosuppressive therapy were included in the study. Thirty-eight patients (41.8%) who received biologic agents as first-line treatment were excluded. The demographic and clinical characteristics of all pediatric NIU patients evaluated within the scope of the study are summarized in Table 1. Of the 53 patients included in the study, 29 (54.7%) were female and 24 (45.3%) were male. The mean age at admission was 8.2±3.4 years (range, 3-16 years) and the mean follow-up period was 41.6±28.2 months (range, 18-120 months). The mean LogMAR visual acuity of the patients at admission was 0.22±0.28 (range, 0.0-1.51) (Table 2).

For systemic treatment, all patients received systemic CS and/or conventional immunosuppressive therapy, followed by ADA therapy. ADA was administered at the standard dose every 2 weeks in 50 patients (94.3%), while 3 patients (5.7%) started with a weekly regimen. The mean duration of ADA use in all patients was 23.0±13.7 months (range, 12-60 months). Only 13 patients (24.5%) developed new uveitis attacks while receiving ADA therapy; the mean time to the first attack in these patients was 4.9±2.4 months (range, 1-9 months). Nine patients (16.9%) received ADA every 2 weeks for a mean of 12.6±10.6 months (range, 4-48 months) before switching to a weekly regimen. The mean duration of use in patients using ADA weekly was 9.4±2.9 months (range, 6-13 months). In 4 patients (7.5%) receiving ADA every 2 weeks for a mean of 12.5±5.0 months (range, 6-18 months), the dosing schedule was extended to 3-week intervals for a mean of 7.7±3.3 months (range, 4-12 months), then to 4-week intervals. The systemic CS and immunosuppressive therapy received by the patients before ADA initiation and at the last visit after ADA treatment are summarized in Table 3.

Systemic CS was used by 50 patients (94.3%) before ADA therapy and 11 patients (20.7%) after ADA therapy (p<0.001). The systemic CS dose was reduced (<5 mg/day) in 8 (72.7%) of the patients receiving CS therapy. After ADA treatment, the dose of methotrexate (MTX) (Koçak Pharmaceuticals, İstanbul, Türkiye) was reduced in 27 patients (50.9%), and cyclosporine-A (Novartis, Basel, Switzerland) was discontinued in 2 patients (3.7%). Tocilizumab (Roche, Basel, Switzerland) and infliximab (Shering-Plough Pharma, Berlin, Germany) were each initiated in 1 patient (1.9% each) who had refractory uveitis despite weekly ADA (after 10 months and 15 months of use, respectively). In addition, 1 patient (1.9%) received mycophenolate mofetil (Roche, Basel, Switzerland) due to elevated liver enzymes secondary to MTX therapy, and 1 patient (1.9%) received azathioprine (Aspen Farma, Durban, South Africa) due to MTX-related gastrointestinal adverse effects. In all 4 patients whose ADA treatment was extended to 4-week intervals, MTX was tapered and discontinued, and ADA was also discontinued in 2 (50.0%) of these patients after a mean of 5.0±1.4 months (range, 4-6 months) (Table 3). None of the patients developed serious adverse effects due to ADA use during follow-up.

When the severity of intraocular inflammation before and after ADA therapy was evaluated, the mean anterior chamber reaction severity was significantly lower after 6 months and 6-12 months of ADA treatment than before treatment in eyes with anterior and panuveitis (p<0.05 for all). In the eyes with intermediate and panuveitis, the mean vitreous haze severity was also significantly lower after 6 months and 6-12 months of ADA treatment compared to before ADA treatment (p<0.05 for all) (Table 4).

When uveitis attacks before and after ADA therapy were evaluated, the number of uveitis attacks observed after 6

**Table 1. Demographic and clinical characteristics of all patients with pediatric non-infectious uveitis treated with adalimumab**

| **Sex** | **Patients, n (%)** |
|---|---|
| Female | 41 (45.1) |
| Male | 50 (54.9) |
| **Age,** years, mean±SD (range) | 9.3±3.6 (3-16) |
| **Ocular involvement** | |
| Unilateral | 6 (6.6) |
| Bilateral | 85 (93.4) |
| **Anatomical and etiological uveitis classification** | |
| **Anterior uveitis** | 44 (48.3) |
| JIA-associated anterior uveitis | 24 (26.4) |
| Chronic anterior uveitis | 18 (19.7) |
| Sarcoidosis-associated anterior uveitis | 1 (1.1) |
| FMF-associated anterior uveitis | 1 (1.1) |
| **Intermediate uveitis** | 34 (37.4) |
| Pars planitis | 34 (37.4) |
| **Panuveitis** | 13 (14.3) |
| Chronic (late-stage) VKH | 6 (6.6) |
| Idiopathic | 5 (5.5) |
| Acute (early-stage) VKH | 1 (1.1) |
| Sarcoidosis-associated panuveitis | 1 (1.1) |
| **First-line systemic therapy** | |
| Conventional immunosuppressive followed by ADA | 53 (58.2) |
| Conventional immunosuppressive with ADA | 38 (41.8) |

SD: Standard deviation, JIA: Juvenile idiopathic arthritis, FMF: Familial Mediterranean fever, VKH: Vogt-Koyanagi-Harada disease, ADA: Adalimumab

months and 6-12 months of ADA treatment was found to be significantly lower than before ADA treatment (p<0.001 for all). However, no difference was observed between the number of uveitis attacks after 6 months and 6-12 months of ADA treatment (p=0.842) (Table 4). Comparison of mean topical and systemic CS doses before and after ADA therapy showed that CS doses were significantly lower after 6 months and 6-12 months of ADA treatment compared to before ADA treatment (p<0.01 for all). There was no difference in topical or systemic CS doses after 6 months and 6-12 months of ADA treatment (p=1.0 for all) (Table 4).

When CMT was evaluated before and after ADA treatment, the mean CMT values after 6 months and 12 months of ADA treatment were significantly lower than before treatment (p<0.05 for all) (Table 5). Comparison of mean LogMAR BCVA values before and after ADA therapy revealed a significant increase in BCVA after 6 and 12 months of ADA treatment (p=0.003 and p=0.002, respectively). Mean LogMAR BCVA values at 6 and 12 months were similar (p=1.0) (Table 5).

At least one ocular complication was observed at admission in 53 eyes (51.4%). The most common ocular complications at admission were posterior synechiae (25 eyes, 24.2%), cataract (12 eyes, 11.6%), and cystoid macular edema (CME) (11 eyes, 10.6%). The most common ocular complications observed during follow-up were steroid-induced IOP elevation (20 eyes, 19.4%), cataract (18 eyes, 17.4%), and posterior synechiae (14 eyes, 13.5%) (Figure 1). IOP was controlled with antiglaucoma therapy in 19 (79.1%) of the 24 eyes with IOP elevation. Antiglaucoma therapy was discontinued in 14 eyes (58.3%) after ADA treatment. However, the other 5 eyes (20.8%) required glaucoma surgery, with trabeculectomy performed in 3 eyes (12.5%) and Ahmed valve tube implantation surgery in 2 eyes (8.3%). Phacoemulsification and intraocular lens implantation surgery were performed in 8 eyes (7.7%) with cataract during follow-up. The mean LogMAR BCVA of the patients at the last examination was 0.08±0.2 (range, 0.0-1.0), which was a significant improvement compared to BCVA at admission (p<0.001).

**Table 2. Demographic and clinical characteristics of study group patients who started adalimumab after conventional treatment**

| **Sex** | **Patients, n (%)** |
|---|---|
| Female | 29 (54.7) |
| Male | 24 (45.3) |
| **Age,** years, mean±SD (range) | 8.2±3.4 (3-16) |
| **Follow-up time,** months, mean±SD (range) | 41.6±28.2 (18-120) |
| **Ocular involvement** | |
| Unilateral | 3 (5.7) |
| Bilateral | 50 (94.3) |
| **Anatomical and etiological uveitis classification** | |
| **Anterior uveitis** | 26 (49.0) |
| JIA-associated anterior uveitis | 16 (30.2) |
| Chronic anterior uveitis | 9 (16.9) |
| Sarcoidosis-associated anterior uveitis | 1 (1.9) |
| **Intermediate uveitis** | 22 (41.5) |
| Pars planitis | 22 (41.5) |
| **Panuveitis** | 5 (9.4) |
| Late-stage VKH | 2 (3.7) |
| Idiopathic | 2 (3.7) |
| Sarcoidosis-associated panuveitis | 1 (1.9) |
| **Visual acuity, LogMAR, mean±SD (range)** | 0.22±0.28 (0.0-1.51) |

SD: Standard deviation, JIA: Juvenile idiopathic arthritis, VKH; Vogt-Koyanagi-Harada disease, LogMAR: Logarithm of the minimum angle of resolution

**Table 3. Systemic treatment received by study patients before and after adalimumab therapy**

| **Systemic therapies before ADA initiation** | **Patients, n (%)** |
|---|---|
| Systemic CS+MTX | 45 (84.9) |
| Systemic CS+MTX+CSA | 3 (5.7) |
| MTX | 3 (5.7) |
| Systemic CS | 2 (3.7) |
| **Systemic therapies at the last visit after ADA treatment** | |
| ADA+MTX | 35 (66.0) |
| ADA+MTX+systemic CS | 10 (18.9) |
| ADA | 2 (3.7) |
| ADA+MTX+CSA+systemic CS | 1 (1.9) |
| ADA+AZA | 1 (1.9) |
| TCZ+MMF | 1 (1.9) |
| IFX+MTX | 1 (1.9) |

ADA: Adalimumab, CS: Corticosteroid, MTX: Methotrexate, CSA: Cyclosporine A, AZA: Azathioprine, TCZ: Tocilizumab, MMF: Mycophenolate mofetil, IFX: Infliximab

## Discussion

This study evaluated the effectiveness of ADA therapy in pediatric patients with NIU and showed that ADA use in children was effective in improving visual acuity as well as controlling intraocular inflammation, which reduced the need for topical and systemic steroids.

Many studies in the literature have demonstrated the effectiveness of ADA therapy in children with chronic NIU refractory to conventional immunosuppressive therapy.[7,8,9,10,11,12,18,19] In the SYCAMORE randomized controlled trial, the addition of ADA to MTX therapy in children and adolescents with juvenile idiopathic arthritis (JIA)-associated uveitis was reported to reduce treatment failure.[7] In ADJUVITE, another important randomized controlled trial conducted in children with JIA-associated uveitis, successful outcomes were reported with ADA therapy in patients with chronic uveitis who showed an inadequate response to topical therapy and MTX.[8] In addition to non-infectious anterior uveitis, ADA therapy has also been shown to be effective in the treatment of intermediate uveitis, posterior uveitis, and panuveitis in children.[12,18,19] Based on these studies, ADA is now accepted as the first choice of

**Table 4. Comparison of intraocular inflammation severity and corticosteroid doses of the study patients before and after adalimumab therapy**

| | Before ADA Mean±SD Median (range) | | After ADA Mean±SD Median (min-max) | | | | $p^a$ |
|---|---|---|---|---|---|---|---|
| | | $p^b$ | 6 months | $p^c$ | 6-12 months | $p^d$ | |
| **Anterior chamber cells** (31 patients/59 eyes) | 2.1±0.9<br>0.5 (1-4) | | 0.89±0.7<br>0.5 (0-3) | | 0.42±0.7<br>0 (0-3) | | <0.001 |
| | | <0.001 | | 0.023 | | <0.001 | |
| **Vitreous haze** (26 patients/52 eyes) | 2.16±0.7<br>2.0 (1-3) | | 0.55±0.4<br>0.5 (0-2) | | 0.14±0.22<br>0 (0-1) | | <0.001 |
| | | <0.001 | | 0.024 | | <0.001 | |
| **Systemic steroid dose (mg/day)** | 13.4±11.3<br>10.0 (0-40) | | 1.0±2.0<br>0 (0-10) | | 0.68±1.5<br>0 (0-8) | | <0.001 |
| | | <0.001 | | 1.00 | | <0.001 | |
| **Topical steroid** (drops/day) | 3.5±4.2<br>3.0 (0-16) | | 0.67±1.5<br>0 (0-8) | | 0.62±1.58<br>0 (0-8) | | <0.001 |
| | | 0.003 | | 1.00 | 0.016 | 0.001 | |
| **Uveitis attack** (53 patients/103 eyes) | 1.5±0.7<br>1.0 (0-3) | | 0.23±0.4<br>0 (0-1) | | 0.05±0.2<br>0 (0-1) | | <0.001 |
| | | <0.001 | | 0.842 | | <0.001 | |

$p^a$: Friedman test, three-group comparison (before, 6 months after, 12 months after ADA initiation), $p^b$: Wilcoxon signed-rank test, two group comparison (before and 6 months after ADA initiation), $p^c$: Wilcoxon signed-rank test, two-group comparison (6 months and 12 months after ADA initiation), $p^d$: Wilcoxon signed-rank test, two-group comparison (before and 6-12 months after ADA initiation), ADA: Adalimumab, SD: Standard deviation, min: Minimum, max: Maximum

**Table 5. Comparison of central macular thickness and visual acuity results of study patients before and after adalimumab therapy**

| | Before ADA Mean±SD Median (range) | | After ADA Mean±SD Median (range) | | | | $p^a$ |
|---|---|---|---|---|---|---|---|
| | | $p^b$ | 6 months | $p^c$ | 12 months | $p^d$ | |
| **CMT (µm)** | 307.1±47.5<br>311 (223-437) | | 282.8±37.7<br>281 (214-358) | | 273.3±39.2<br>270 (224-339) | | <0.001 |
| | | <0.001 | | 0.034 | | <0.001 | |
| **BCVA (LogMAR)** | 0.16±0.27<br>0.1 (0.0-1.51) | | 0.11±0.25<br>0.0 (0.0-1.40) | | 0.11±0.26<br>0.0 (0.0-1.0) | | <0.001 |
| | | 0.003 | | 1.00 | | 0.002 | |

$p^a$: Friedman test, three-group comparison (before, 6 months after, 12 months after ADA initiation), $p^b$: Wilcoxon signed-rank test, two-group comparison (before and 6 months after ADA initiation), $p^c$: Wilcoxon signed-rank test, two-group comparison (6 months and 12 months after ADA initiation), $p^d$: Wilcoxon signed-rank test, two-group comparison (before and 12 months after ADA initiation), ADA: Adalimumab, SD: Standard deviation, CMT: Central macular thickness, BCVA: Best corrected visual acuity

biologic agent for children with chronic NIU. In our study, we evaluated the outcomes of ADA treatment in patients with recurrent non-infectious anterior, intermediate, and panuveitis refractory to conventional immunosuppressive therapy and determined that only a quarter of the patients developed a new uveitis attack after starting ADA therapy. The standard dosing regimen for ADA is every 2 weeks. Studies have shown that weekly ADA administration is effective in children with severe uveitis that cannot be controlled with the standard dose.[3,9,10] In our study, the majority of patients received ADA at the standard dose, while 22% received ADA weekly. ADA was found to be effective in controlling intraocular inflammation in 83% of patients on a weekly regimen.

In a study by Sonmez et al.[20] including pediatric patients with NIU of varying etiology, ADA therapy was found to be effective in the control of anterior and posterior segment inflammation and there was a significant reduction in CMT values from the second week, but the decrease leveled off after 12 weeks. In our study, CMT values decreased significantly after 6 and 12 months of treatment. Tao et al.[18] found that ADA improved visual acuity in the long term and was effective in controlling ocular inflammation in children with non-infectious posterior and panuveitis. The authors reported a significant reduction in uveitis attacks in children using ADA compared to those using conventional therapy, but the use of ADA had no superior advantage in terms of systemic CS cessation.[18]

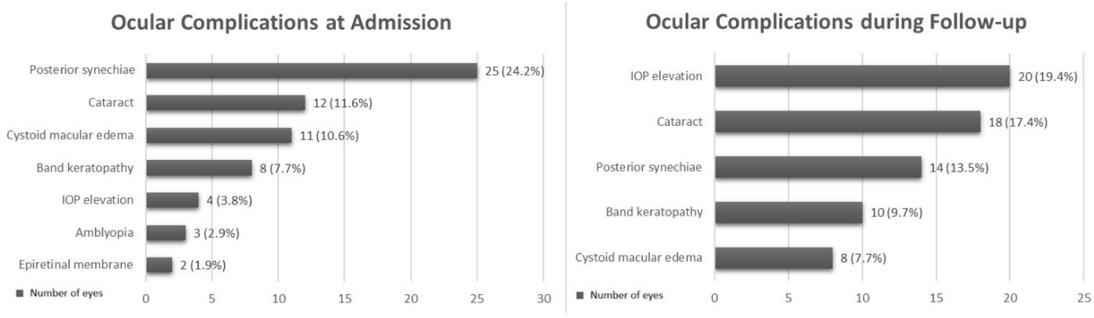


**Figure 1.** Distribution of the study patients' ocular complications at presentation and during follow-up
IOP: Intraocular pressure

In another study evaluating 59 patients with pars planitis, most (87%) of whom were children, ADA was found to be highly effective in cases refractory to conventional immunosuppressive therapy, with ADA use enabling discontinuation of systemic CS therapy in 70% of patients.[12] In our study, there was a reduction in uveitis attacks with ADA use in children with non-infectious anterior, intermediate, and panuveitis, and the need for topical and systemic CS use also decreased substantially. In addition, a significant improvement in BCVA was observed in our patients after ADA treatment.

There is still insufficient evidence in the literature on how long biologic therapy should be used and when it should be discontinued in children with NIU.[1,21] In a recent study, ADA dose reduction and discontinuation was associated with a high risk of relapse in children with NIU.[21] Another study indicated that gradual tapering of ADA treatment in pediatric NIU was linked to a low relapse rate.[22] In our study, the ADA dose was reduced in only 4 patients (8%) by extending to 3-week and then 4-week intervals, and discontinuation of ADA was possible in 2 (50%) of these patients.

Serious, sight-threatening ocular complications are common in pediatric uveitis, both at the time of diagnosis and during follow-up.[3,5,20,21,22,23,24,25] Ekici Tekin et al.[26] reported that 74% of pediatric NIU patients had ocular complications at the time of admission. Numerous studies have demonstrated posterior synechiae, CME, and cataract as the most common complications at diagnosis in pediatric uveitis.[12,18,19,24,25,26] In our study, at least ocular complication was detected in 51% of patients at admission. Consistent with the literature, the most common complications in our study included posterior synechiae (22%), cataract (11%), and CME (10%). Pediatric patients are more susceptible than adults to ocular complications secondary to topical CS use, with high doses and long-term use of topical CSs shown to increase the risk of cataract development and IOP elevation.[3,27,28] In our study, the main complications seen during follow-up were steroid-induced IOP elevation (19%) and cataract development (17%). After ADA treatment, antiglaucoma therapy was discontinued in more than half (58%) of the eyes with IOP elevation, and IOP control was achieved without medication. This shows the importance of steroid-sparing systemic immunomodulatory therapy for children with chronic NIU. ADA therapy is highly effective in the management of steroid-related ocular complications in pediatric NIU.

### Study Limitations

The main limitations of our study include the retrospective design, limited sample size, heterogeneity of our patient group, and varying follow-up times. Due to the differences in follow-up periods, ocular complications at admission and during follow-up were evaluated separately, so the effect of ADA use on the development of ocular complications could not be evaluated. In this regard, comparative and prospective studies with larger and homogeneous patient groups and standard follow-up periods may be beneficial.

## Conclusion

Pediatric uveitis is a difficult disease group to manage due to challenges in its diagnosis and treatment, as well as the high complication rates and risk of vision loss. ADA is effective in improving visual outcomes and controlling intraocular inflammation in pediatric NIU, as well as reducing the need for systemic and topical CS treatment.

### Acknowledgements

We thank Dr. Damla Sebhan Bozbay for assisting with statistical analyses.

### 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 the Ankara Training and Research Hospital Ethics Committee (decision no: 522/2020, approval date: 30.12.2020).

**Informed Consent:** Retrospective study.

### Declarations

### Authorship Contributions

Surgical and Medical Practices: P.Ç.Ö., Y.Ö.E., K.Ö.Y., Concept: K.Ö.Y., P.Ç.Ö., Y.Ö.E., Design: K.Ö.Y., P.Ç.Ö., O.Ö., Data Collection or Processing: K.Ö.Y., P.Ç.Ö., Y.Ö.E., Analysis

or Interpretation: K.Ö.Y., P.Ç.Ö., Literature Search: K.Ö.Y., P.Ç.Ö., Writing: K.Ö.Y., P.Ç.Ö.

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Review

# The Role of In Vivo Confocal Microscopy in Ocular Allergies

Cem Şimşek[1], Takashi Kojima[2], Murat Doğru[2]

[1]Muğla Sıtkı Koçman University Faculty of Medicine, Department of Ophthalmology, Muğla, Türkiye
[2]Keio University Faculty of Medicine, Department of Ophthalmology, Tokyo, Japan

## Abstract

In vivo confocal microscopy (IVCM) is a non-invasive imaging technique used to visualize the layers of the cornea and conjunctiva in real time. In patients with atopic keratoconjunctivitis (AKC) and vernal keratoconjunctivitis (VKC), this technology can be useful in diagnosing and monitoring the disease, as well as evaluating the efficacy of treatments. IVCM can reveal subclinical abnormalities in the corneal and conjunctival epithelium such as inflammatory cell infiltrates and tissue damage, which can provide insight into the pathogenesis of AKC. In AKC, IVCM reveals changes around the conjunctival papillae, inflammatory cells around punctate defects in the corneal epithelium, changes in subbasal nerve morphology, and deteriorations in the goblet cells in the meibomian gland are observed. In VKC, alterations can be observed in the diameter, brightness and nucleus/cytoplasm ratio of the superficial epithelial cells in the cornea. The use of IVCM in AKC and VKC can therefore aid in the early detection and management of the disease, as well as contribute to a better understanding of its underlying mechanisms.

**Keywords:** Atopic keratoconjunctivitis, vernal keratoconjunctivitis, in vivo confocal microscopy, cornea, conjunctiva, meibomian glands

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**Address for Correspondence:** Murat Doğru, Keio University Faculty of Medicine, Department of Ophthalmology, Tokyo, Japan
**E-mail:** muratodooru2005@yahoo.co.jp
**ORCID-ID:** orcid.org/0000-0003-1487-2435
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## Introduction

The word atopy describes hypersensitivity to common household or environmental allergens in individuals with a history of hereditary allergic disease. Atopic diseases affect 5% to 20% of the general population.[1] Bronchial asthma, allergic rhinitis, atopic dermatitis, and ocular allergic disorders are among the most common conditions encountered by allergic individuals. Recent research shows that the lifetime prevalence of these atopic diseases in children and adolescents ranges from 24% to 45%.[2] Atopic dermatitis alone affects about 3% of the population in the United States, while in Japan it is seen at a higher rate of about 8%.[3]

Between 25% and 40% of patients with atopic dermatitis have ocular involvement. The most severe ocular surface involvement in this disease is atopic keratoconjunctivitis (AKC). Patients with AKC present with findings ranging from typical eczema and keratinization of the eyelids to cicatricial conjunctivitis, severe superficial punctate keratopathy, and corneal neovascularization, thinning, ulceration, and perforation (Table 1).[4,5,6,7]

Ocular allergy is defined as an inflammatory reaction that occurs on the surface of the eye as a result of a hypersensitivity reaction of the ocular adnexa to environmental allergens. Seasonal and perennial allergic conjunctivitis is the most common form, observed at a rate of 6%-30%.[8] Understanding the pathophysiology of allergy is necessary to enable diagnosis and optimize treatment, and corneal and conjunctival dendritic cells are critical in understanding the pathophysiology of ocular allergy.[8] It is thought that increasing our knowledge of the function of dendritic cells in ocular allergic inflammation will facilitate the development of novel therapeutic approaches. In vivo confocal microscopy (IVCM) studies showed that patients with allergic conjunctivitis had higher dendritic cell density in the cornea and conjunctiva compared to control groups.[8,9] These patients were also shown to have larger dendritic cell bodies as well as cells with longer dendrites, suggesting that the corneal dendritic cells had greater antigen capture capacity.[9] In summary,

alterations in corneal and conjunctival dendritic cell density and morphology have been observed in allergic conjunctivitis.[8,9] These findings indicate that the ocular surface immunological response is heightened in allergic conjunctivitis (Table 2).[8,9]

AKC is a bilateral chronic hypersensitivity disease of the ocular surface associated with systemic atopic dermatitis. The ocular inflammation process and release of allergic mediators into the ocular surface and tear film is thought to be responsible for a wide range of clinical corneal findings including keratoconus, herpetic keratitis, superficial punctate keratitis, macroerosions, corneal ulceration, plaque formation, dry eye disease, corneal neovascularization, and lipid infiltration.[10] In a previous study, it was reported that ocular surface disorder in patients with atopic dermatitis was characterized by marked tear film imbalance, goblet cell loss, conjunctival squamous metaplasia, and reduced corneal sensitivity.[10]

**Table 1. Ocular findings in patients with atopic dermatitis**

| Clinical findings | Number of eyes | % |
|---|---|---|
| **Eyelids** | | |
| Eczema | 476 | 65.7 |
| Trichiasis | 14 | 1.9 |
| Ectropion | 2 | 0.2 |
| **Conjunctiva** | | |
| Atopic keratoconjunctivitis | 489 | 65.7 |
| **Conjunctival papillary reaction** | | |
| Upper tarsus | 179 | 24.7 |
| Lower tarsus | 310 | 42.8 |
| Chemosis | 489 | 65.7 |
| Hyperemia | 489 | 65.7 |
| Symblepharon | 2 | 0.2 |
| **Limbus** | | |
| Trantas dots | 2 | 0.2 |
| **Cornea** | | |
| Superficial punctate keratopathy | 489 | 65.7 |
| Epithelial defect | 9 | 1.2 |
| Keratoconus | 24 | 3.3 |
| Peripheral neovascularization | 16 | 2.2 |
| **Tear film abnormalities** | | |
| TBUT <10 s | 452 | 62.4 |
| Schirmer test <5 mm | 407 | 56.2 |
| TBUT time <10 s and Schirmer test <5 mm | 242 | 33.4 |

TBUT: Tear film break-up time

IVCM is a non-invasive imaging method that allows the examination of the cornea at the cellular level and is frequently used both in healthy corneas and in the differential diagnosis and follow-up of many diseases. IVCM enables the evaluation of pathological changes in dry eye disease, diabetes, *Acanthamoeba* keratitis, infectious corneal ulcers, herpetic keratitis, keratoconus, aging, contact lens use, and refractive surgical procedures.[11,12,13,14,15,16,17,18,19,20] With the increased clinical use of IVCM, high-resolution images of the corneal subbasal nerves and immune/inflammatory (dendritic) cells can be obtained in the healthy and pathological cornea.[12]

**Evaluating Corneal Changes in Atopic Keratoconjunctivitis Patients with In Vivo Confocal Microscopy**

AKC is reported to be associated with herpetic keratitis, keratoconus, and dry eye.[15,21,22,23] A previous study of AKC patients showed that despite the absence of concomitant keratoconus, some similar morphological changes were observed, such as a decrease in basal epithelial cells and subbasal nerve density.[24]

AKC has been shown to be associated with short tear film break-up time (TBUT)-type dry eye.[10] Patients with severe active atopic dermatitis in childhood are more likely to have the aqueous-deficient type of dry eye disease as adults if active skin disease persists in adulthood.[25] The IVCM findings reported in keratoconjunctivitis sicca are an increase or decrease in superficial epithelial cell density, depending on the condition, a decrease in basal epithelial cell density, reduced subbasal nerve fiber number and density, and an increase in nerve tortuosity compared to healthy controls.[26,27,28,29]

In a study of AKC patients, although dry eye was not of the aqueous-deficient type, a similar decrease in subbasal nerve density and increase in nerve tortuosity (compared to control subjects) were observed.[24] As none of the patients in that study had keratoconus, history of contact lens use, history of herpetic eye disease, keratoconjunctivitis sicca, previous ocular surgery, or

**Table 2. Confocal microscopy findings associated with allergic (seasonal and vernal) conjunctivitis**

| Findings | Description |
|---|---|
| Changes in corneal epithelium thickness | In allergic reactions, the corneal epithelium may increase in thickness |
| Cell infiltration | Epithelial and subepithelial cell infiltration (especially eosinophils and lymphocytes) may be observed |
| Superficial keratopathy | Findings of corneal surface irregularity, erosion, and keratopathy |
| Meibomian gland status | Enlargement or atrophic changes in the meibomian glands |
| Papillary hyperplasia | Swelling and hyperplasia of the conjunctival papillae may be seen |
| Subepithelial cystic formations | Small cystic lesions may be observed under the corneal epithelium |
| Changes in stromal thickness | Stromal changes such as edema or thickening may be seen |
| Connection and cell irregularity | Abnormal epithelial cell connections and disorganization |

any other ocular disease, the abnormalities observed in subbasal nerve structure were attributed primarily to AKC and its associated pathophysiological mechanisms (Figure 1).[24]

Confocal microscopy in patients with AKC reveals abrupt termination of the subbasal nerves, which may represent perforation sites of nerve fibers through the Bowman layer or sites of nerve degeneration.[24] As previously reported in dry eye and diabetic patients, a higher rate of looping and coiling patterns as well as high metabolic activity or nerve regeneration may be seen in AKC patients. It is thought this high metabolic activity is likely intended to repair the changes observed at the epithelial level (Figure 2).[24]

An abnormal architecture can be seen not only in the subbasal nerve plexus, but also the stromal nerves.[24] Thicker stromal nerves (likely due to edema and increased metabolic activity) with deviation and bifurcation abnormalities are observed, which are considered attempts to restore a healthy stromal environment. This regeneration process is thought to be the reason why the stromal nerves in patients with AKC are relatively thicker, less reflective, and more tortuous compared to those of healthy individuals.[24]

Corneal nerve fibers have trophic effects on the corneal epithelium and are important for the maintenance of a healthy ocular surface.[30,31,32] Corneal nerves have been shown to harbor neuropeptides and neurotransmitters with neurotrophic properties, such as calcitonin gene-related peptide and substance P, as demonstrated in previous experimental studies.[33,34] Corneal nerve fibers release dispersible factors that stimulate epithelial growth, proliferation, differentiation, and type VII collagen production.[12] Epithelial cells produce soluble factors with neurotrophic effect, such as neuronal growth factor and glial cell-derived neurotrophic factor.

Significant positive correlations have been demonstrated between corneal sensitivity and basal epithelial cell density and between subbasal nerve density and basal epithelial cell density, all of which support the theory that the corneal nerves exert a trophic effect on the corneal epithelium.[24] The loss of the trophic effect can lead to decreased basal epithelial cell density, higher ocular surface vital staining scores, and corneal ulceration.

Other important IVCM findings are the presence of inflammatory infiltrates around ulcer margins and near the subbasal and stromal nerves, especially in patients with diffuse superficial punctate keratopathy.[24] Moreover, there is strong evidence that corneal sensitivity is significantly reduced in eyes with higher inflammatory cell densities. The density of corneal long nerve fibers and nerve branches has been reported to be significantly lower in AKC patients compared to healthy control subjects on IVCM scans.[24] Previous studies using IVCM have revealed large numbers of inflammatory cells near or on the corneal subbasal and stromal nerves, which explains the lower corneal sensitivity scores and more severe ocular surface inflammation in patients with AKC.[35]

### Evaluation of Conjunctival Changes in Atopic Keratoconjunctivitis Patients with In Vivo Confocal Microscopy

Examining conjunctival changes in patients with AKC at the cellular level may help elucidate the pathogenesis and

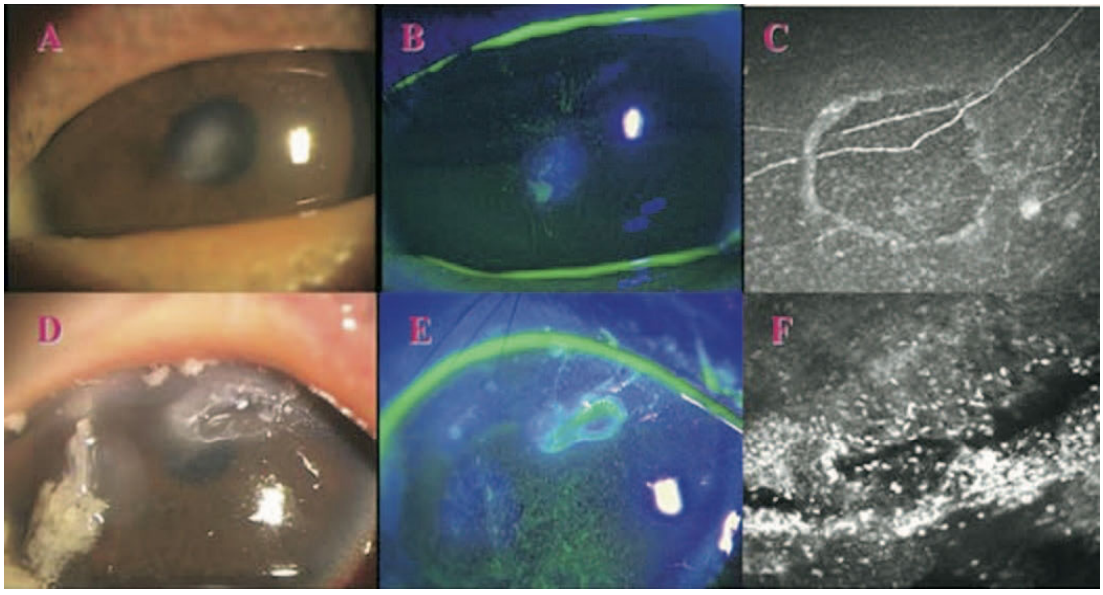


**Figure 1.** A-C) Anterior segment photographs and in vivo confocal scanning laser microscopy image of a 27-year-old male patient with atopic keratoconjunctivitis (AKC). The images show central corneal opacity (A), extensive superficial punctate keratopathy (B), and the highly reflective irregular borders of the epithelium surrounding the scar tissue with intraepithelial nerve fibers that become apparent on confocal microscopy (C). His Schirmer test value was 9 mm, tear film break-up time was 2 seconds, and corneal sensitivity was 40 mm. D-F) Anterior segment photographs and in vivo confocal scanning laser microscopy image of a 20-year-old male patient with AKC and corneal ulcer. Abundant mucus discharge on the ocular surface (D), positive fluorescent staining of the ulcer, and paracentral ulceration with impaired corneal epithelium (E) are observed. A confocal scanning image taken over the corneal ulcer showed diffuse, round, highly reflective inflammatory infiltrates (F). The patient's Schirmer test value was 7 mm, tear film break-up time was 0 seconds, and corneal sensitivity was 25 mm.[24]

subsequent clinical appearance of atopic ocular allergies, which can be sight-threatening. Histopathologically, tarsal conjunctival changes in AKC have been reported as hyperplasia of the connective tissue, proliferative and degenerative changes in the epithelium, pronounced infiltrations in the epithelium, and an increase in eosinophils, lymphocytes, mast cells, macrophages, basophils, plasma, and dendritic cells in the substantia propria.[36] One of the most important findings in AKC is the overgrowth of conjunctival connective tissue consisting of gelatinous, sessile papillae. In the deep layers of the conjunctiva, collagen fibers form a fibrous structure within the papilla. The proliferation of capillaries and vascular neoformations provides vascular support to the papilla (Figure 3).[36] Hyaline degeneration of the conjunctival stroma has also been observed in papillary lesions. Invasive techniques such as conjunctival biopsies have been the source of such valuable information in many studies. Significant positive correlations have been reported between conjunctival inflammatory cell density and ocular surface vital staining, as well as significant negative correlations between corneal sensitivity, tear stability, and inflammatory cell density, all of which support the assertion that conjunctival inflammation adversely affects tear functions and leads to ocular surface epithelial disease.[36,37] A previous study showed that TBUT was significantly associated with conjunctival goblet cell density in patients with AKC.[38] Goblet cells are known to be very sensitive to inflammation and decline in number at higher grades of inflammation.[39,40] It is thought that patients with higher inflammatory cell density may have lower goblet cell density, leading to lower TBUT.[40] Despite a weak correlation, patients with higher confocal inflammatory cell density were found to have significantly lower TBUT.[35]

In a previous study, diffuse ocular surface inflammatory cell infiltration in AKC was demonstrated with brush cytology samples, and inflammatory cell counts in brush cytology samples were also reported to be associated with the severity of corneal lesions.[41,42,43] IVCM observations have confirmed the role of conjunctival inflammation in the ocular surface disease process and were shown to aid evaluation and comparison of the effects of different treatment protocols on the ocular surface in AKC (Figure 4).[36]

Remarkable observations of the architecture and inflammatory state of tarsal conjunctival papillae have been made with IVCM.[36] AKC patients not using topical cyclosporine were found to have stromal edema along with much more extensive inflammatory cell infiltrates on the surface of the papillae and in the lacunar spaces within the papillae.[36] In patients using topical cyclosporine, a marked reduction of infiltrates in the papillae,

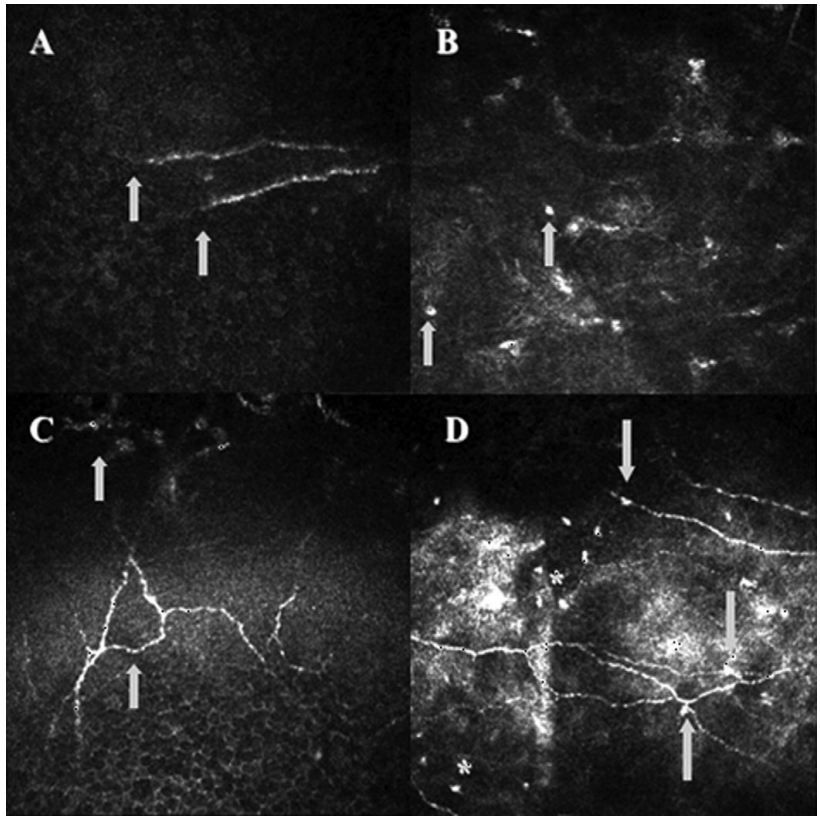


**Figure 2.** In vivo confocal scanning laser microscopy images of the subbasal nerve plexus in patients with atopic keratoconjunctivitis (AKC). A) White arrows indicate a decrease in the number of long nerve fibers that terminate abruptly. B) Subbasal nerve plexus could not be observed in some patients with AKC. White arrows indicate inflammatory cells. C) Nerve fibers are randomly oriented, wavy, and show frequent looping. D) Inflammatory cells with increased reflectivity on the subbasal nerves (arrows) and numerous inflammatory cells near the subbasal nerves (white asterisks) are seen.[24]

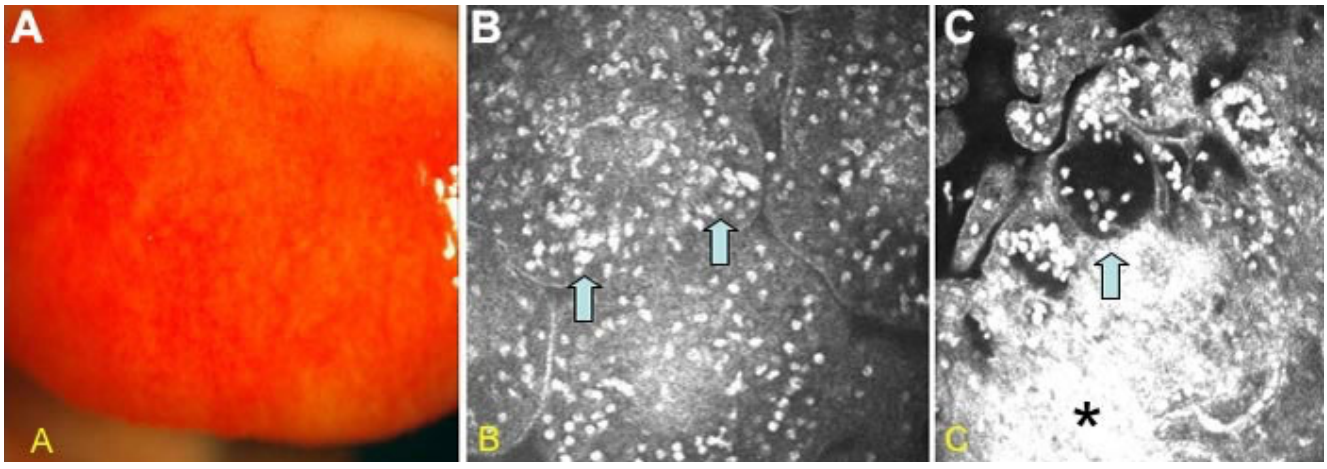


**Figure 3.** Conjunctival slit-lamp and in vivo confocal microscopy (IVCM) scan images from a patient with atopic keratoconjunctivitis using only topical steroids and topical anti-allergic. A) The slit lamp photo shows cherry red injection of the tarsal conjunctiva. B) IVCM images of intense inflammation on the surface of papillary formations (blue arrows). C) Deeper in the papilla formation, hyperreflective edematous areas (black asterisk) and cavitations (lacunae) surrounded by inflammatory infiltrates (blue arrow) were seen.[36]

dendritic cells, vascular loops, and around lacunar spaces with a fibrotic response were observed.[36] The lacunar morphology in the papillae shows areas of collagen resorption during the remodeling processes or areas of stromal degeneration (Figure 5).[36]

The effects of topical cyclosporine therapy on the corneal microstructure are also being investigated in patients with vernal keratoconjunctivitis (VKC).[38] The conjunctiva and cornea are among the main ocular components affected by VKC, and observations made during the treatment process can provide valuable information about changes in these important structures.[38] Changes in the corneal microstructure observed in patients treated with topical cyclosporine may serve as an important indicator in assessing the response to treatment and the course of the disease. The compilation of such findings will contribute to our understanding of the pathophysiology of VKC and the development of treatment approaches, enabling it to become a focal point of research. In particular, understanding the mechanism of these microstructural changes and integrating this knowledge into the treatment process may pave the way for the development of more effective VKC management strategies in the future.[38]

### Evaluation of Meibomian Gland Dysfunction with In Vivo Confocal Microscopy in Atopic Keratoconjunctivitis and Vernal Keratoconjunctivitis Patients

The meibomian glands (MG) secrete lipids on the ocular surface, and these lipids form the outer layer of the tear film. MG secretions prevent rapid evaporation of the tear film, act as a barrier to prevent contamination, and lubricate to reduce friction on the ocular surface from blinking.[45]

With the increase in the clinical use of IVCM, pathophysiological changes on the ocular surface have been investigated in more detail. Studies have reported that IVCM parameters such as acinar unit density and diameter are valuable in understanding histopathological changes such as glandular atrophy and acinar/ductal dilation in obstructive meibomian gland dysfunction (MGD).[46,47] However, periglandular inflammatory cell density has been identified as another IVCM parameter that can distinguish inflammatory obstructive MGD from non-inflammatory subtypes.[46] These parameters were characterized by high sensitivity and specificity in the diagnosis of MGD and showed a good correlation with ocular surface condition.

A decline in the conjunctival goblet cell population and deterioration in tear quality and quantity have been reported in AKC patients.[47] Tear film instability in these patients was attributed in part to disturbances in tear mucins resulting from decreased goblet cell density.[47] In another study, Ibrahim et al.[48] suggested that because AKC patients have greater MG damage and lid margin changes, deterioration in the lipid layer of the tear film leads to tear instability and consequently exacerbates ocular surface epithelial damage. In the same study, the results of IVCM examinations revealed severe fibrosis and atrophy in the MG, as well as a decrease in the size and density of MG acinar units (Figure 6).[48]

In addition, MG acinar unit atrophy is a novel IVCM parameter that can be used in the evaluation of MG damage.[48] MG acinar unit area values were found to be significantly lower in AKC patients compared to obstructive MGD and control subjects.[48] However, there was a significant increase in periglandular inflammatory cell density in AKC patients compared with obstructive MGD and normal controls.[48]

MG status in AKC patients requires careful attention, as it can lead to deterioration in the tear film structure and exacerbate the inflammatory status through a vicious cycle. There is a need for further studies investigating the differences in MG status in AKC and VKC patients using IVCM and infrared meibography technologies.

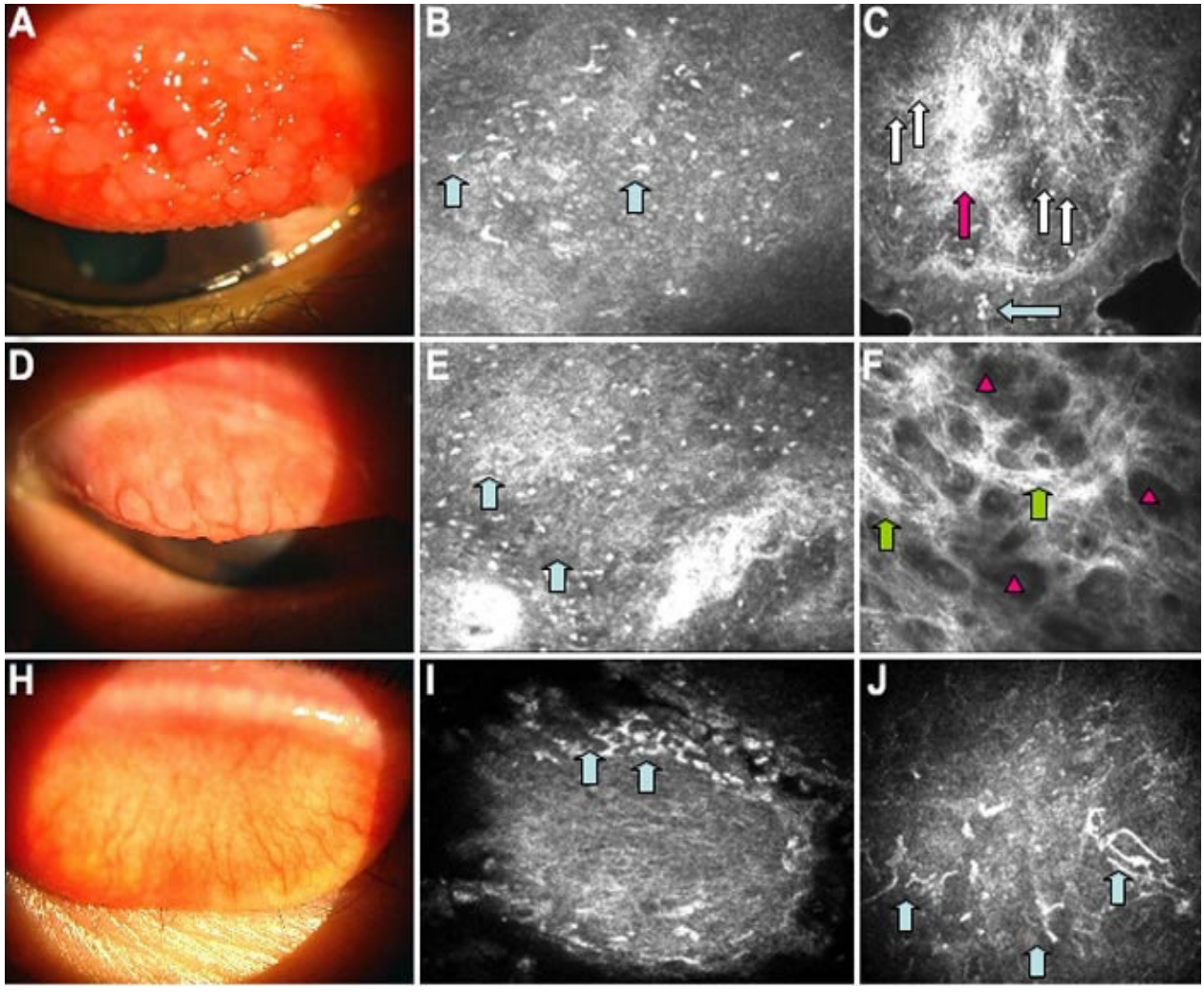


**Figure 4.** Conjunctival slit-lamp photo and in vivo confocal scan images from patients with atopic keratoconjunctivitis (AKC) using topical cyclosporine. Upper row: A) slit-lamp photo showing injection in the tarsal conjunctiva and papillary hypertrophy. B) Confocal images showed less inflammation on the surface of the papillary formations (blue arrows). C) Deeper images of the papillary formations show fibrosis (pink arrow) and vascular neoformations (white arrows) with inflammatory cells. Middle row: this row shows the conjunctival slit lamp photograph and in vivo confocal scan images of another patient with AKC using topical cyclosporine. D) The slit-lamp image shows papillary hypertrophy and conjunctival hyperemia. E) Confocal images showed less inflammation on the surface of the papillary formations (blue arrows). F) Deeper sections revealed extensive fibrosis (green arrows) with lacunar spaces showing no inflammatory infiltrates (pink triangles). Bottom row: conjunctival slit-lamp photograph and confocal scan images from another AKC patient are shown. H) Notice the conjunctival hyperemia in the slit-lamp photograph. Confocal scans showed less inflammation at the edges of the surface of the papillary formations (blue arrows; I) and dendritic cells (blue arrows; J).[36]

In VKC patients, although obstruction of the MG orifices and metaplasia were not observed, the presence of intraluminal hyperactive solid matter was shown in the MG lumen and contours.[49] In addition, extensive Langerhans cells have been observed surrounding MGs, especially in the tarsal regions. It is thought that these Langerhans cells are closely related to MG acinar unit density and that the immunological inflation initiated by these cells may damage and eliminate the MG.[49]

As a result, the IVCM used in these studies is a non-invasive and effective method that can be used to elucidate the structural and functional changes in the cornea, conjunctiva, and MG that occur in AKC patients (Table 3). IVCM can also provide information about decreased corneal nerve density and distribution in patients with AKC and can be used to evaluate disease severity and treatment response.

Studies have shown that IVCM can help identify infiltrative cells, dendritic cells, and subepithelial fibrosis in patients with AKC and VKC. In addition, they have shown that IVCM can be used to monitor the effects of topical and systemic therapies for AKC.[36,48] This has provided insight into the effectiveness of different approaches and enabled adjustments when necessary.

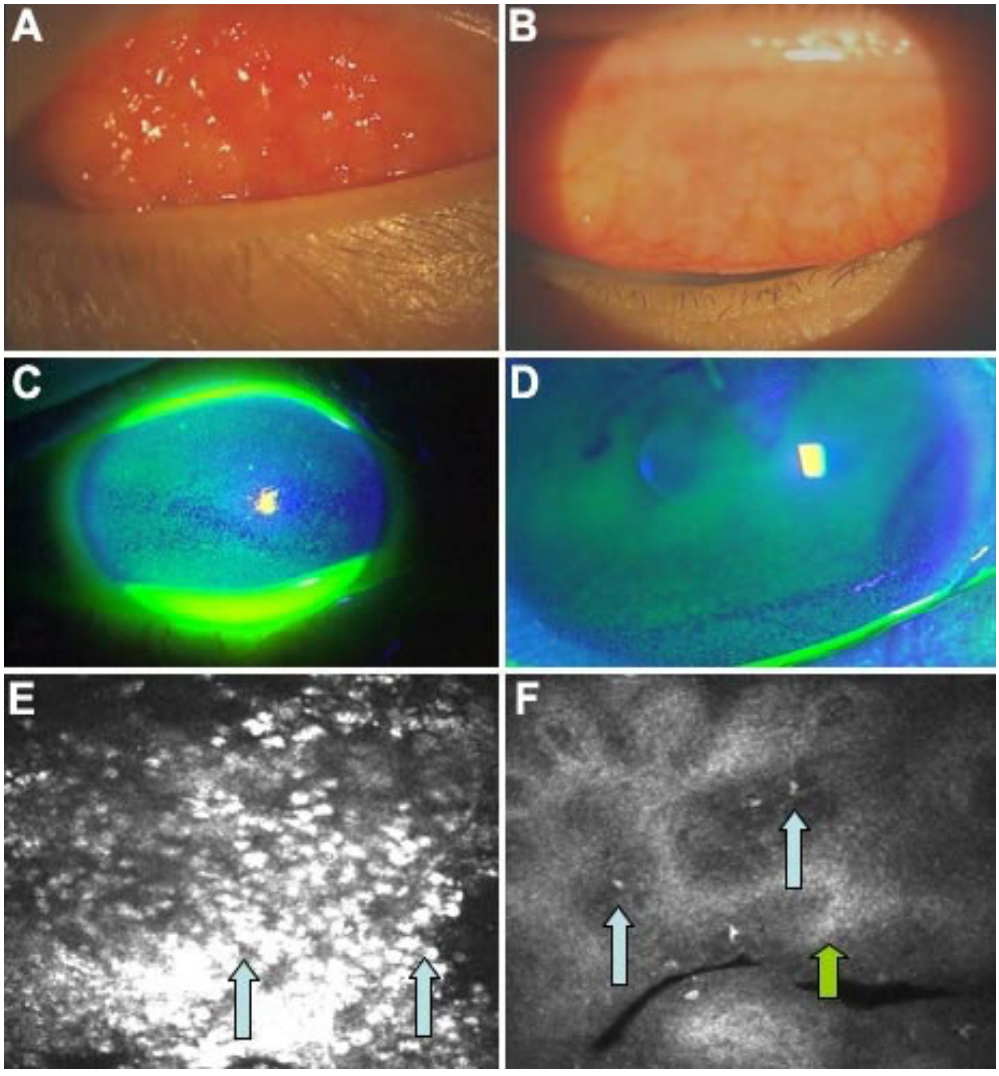


**Figure 5.** Anterior segment photographs and confocal scan images of a patient with atopic keratoconjunctivitis (refractory to 8 weeks of treatment with steroid and anti-allergic eye drops for eight weeks) before and after treatment with topical cyclosporine drops administered for 8 weeks in addition to the anti-allergic and steroid eye drops. A, B) There was a marked decrease in tarsal conjunctival injection and edema with regression of the papillary formations. C, D) Changes in corneal epithelial damage are observed with cyclosporine treatment. E, F) Dramatic reductions in conjunctival inflammatory cell infiltrates on the surface of the papillary formations (blue arrows) and the fibrotic response in papillary formations (green arrow) are seen.[36]

**Evaluation of Vernal Keratoconjunctivitis Patients with In Vivo Confocal Microscopy**

VKC is an inflammatory eye disease that particularly affects children and young adults. It is characterized by symptoms such as itching, redness, and excessive tearing.[50] In the context of VKC, corneal IVCM can provide important information when assessing the presence and severity of corneal involvement.[50] It can help visualize structural changes such as significantly increased diameter, reflectivity, and nucleus/cytoplasm ratio of the epithelial cells on the corneal surface; decreased basal epithelial cell density; decreased corneal subbasal nerve density and increased stromal nerve thickness, branching, and tortuosity; and decreased keratocyte density but significantly increased number of active keratocytes and inflammatory cells in the anterior stroma.[50,51,52,53] Csorba et al.[52] showed that Langerhans cells were present at high density and largely showing a mature phenotype in parallel with the severity of papillary hypertrophy, even when VKC was inactive. The alterations in Langerhans cells indicate a subclinical inflammatory process in the absence of ocular symptoms. The IVCM imaging technique is an important tool in establishing a diagnosis, assessing disease severity, and monitoring response to treatment.[53] It can also contribute to an understanding of the pathophysiology underlying VKC, and offers a non-invasive alternative to traditional invasive procedures such as corneal biopsy, which can be uncomfortable for patients.

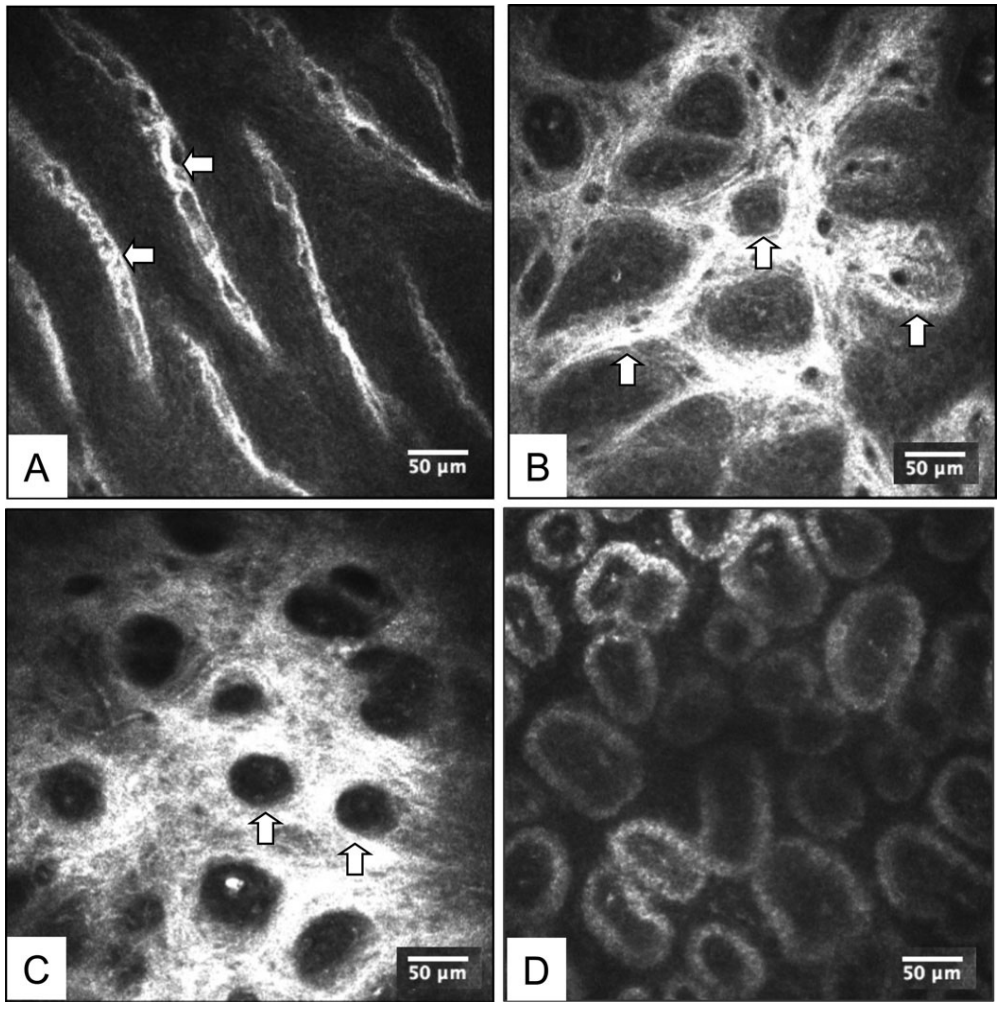


**Figure 6.** In vivo confocal microscopy images of meibomian gland (MG) changes in patients with atopic keratoconjunctivitis compared to a healthy subject. A) Linear streaks of MG fibrosis. B) Loss of MG architecture with extensive fibrotic tissue surrounding the atrophic remnants of the MG. C) Intense fibrotic changes in the MG and neighboring conjunctival tissues. White arrows indicate areas of fibrosis in the MG. D) Representative image of MG acinar units in a normal position.[48]

Based on the current literature, it is seen that confocal microscopy reveals in detail the effects of ocular allergic diseases, especially VKC. This imaging method provides the opportunity to clearly observe microstructural alterations in the corneal epithelium, cellular infiltration, and degenerative processes. Confocal microscopy has allowed a better understanding of important parameters such as morphological changes in corneal cells, immune responses, and treatment response during the course of allergic diseases, which has in turn provided new perspectives on clinical interventions. As a result, confocal microscopy is considered an important tool in understanding the mechanisms of allergic eye diseases and evaluating treatment processes.

## Conclusion

In conclusion, imaging methods, especially IVCM, guide clinicians' treatment approaches by providing more in-depth information about the pathology of AKC and VKC. These methods are regarded as a valuable tool in the diagnosis and treatment of AKC and VKC in particular, contributing to a better understanding of these diseases and allowing more effective care for patients.

### Declarations

#### Authorship Contributions

Concept: C.Ş., T.K., M.D., Design: C.Ş., T.K., M.D., Data Collection or Processing: C.Ş., T.K., M.D., Analysis or Interpretation: C.Ş., T.K., M.D., Literature Search: C.Ş., T.K., M.D., Writing: C.Ş., T.K., M.D.

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| **Table 3. Ocular surface in vivo confocal microscopy findings in patients with atopic keratoconjunctivitis** |
|---|
| **Conjunctival changes** |
| Stromal edema on the surface of the papillae and in the lacunar cavities within the papillae |
| Dense inflammatory cells on the surface of papillary formations |
| Hyperreflective edematous areas deep in the papillary formations |
| Cavitations (lacunes) surrounded by inflammatory infiltrates deep in the papillary formations |
| Fibrosis and neovascularizations in deeper images of the papillary formations |
| Decline in goblet cell population |
| **Corneal changes** |
| ***Epithelium*** |
| Presence of inflammatory cells around the ulcer margins in patients with punctate keratopathy |
| Exposed intraepithelial nerve fibers |
| Subepithelial fibrosis with epithelial irregularities |
| ***Nerves*** |
| Decrease in subbasal nerve density |
| Increased nerve tortuosity |
| Abrupt termination of subbasal nerves |
| High prevalence of looping and coiling patterns |
| Abnormal stromal nerve architecture |
| Thicker stromal nerves with deviation and bifurcation abnormalities |
| ***Stroma*** |
| Presence of inflammatory infiltrates adjacent to the stromal nerves |
| Stromal turbidity |
| Stromal fibrosis |
| **Meibomian gland (MB) changes** |
| Lid margin changes |
| Severe fibrosis and atrophy |
| Reduction in the size and density of MB acinar units |
| Increase in periglandular inflammatory cell density |

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Case Report

# An Unusual Case of Low Vision and Anisocoria Considered a Neurological Finding in the Emergency Department: Ocular Siderosis

Osman Özen, Menekşe İnal Özen

Kastamonu Training and Research Hospital, Clinic of Ophthalmology, Kastamonu, Türkiye

## Abstract

We present the case of a patient who came to the emergency department with a significant decrease in vision and dilated pupil in the left eye. Since neurological pathologies were primarily considered, diffusion brain magnetic resonance imaging (MRI) and brain computed tomography (CT) were requested. After the results were reported as normal, we were consulted. On examination, the anterior segment was normal but we detected shiny pearl-like formations in the anterior vitreous, condensation at the inferior of the posterior vitreous, and a scar in the macula. When we evaluated the orbital section of the current brain CT, we detected an intraocular foreign body (IOFB). On the brain MRI, we saw a large artifact that obscured the left orbit and surrounding anatomical structures. When we questioned again, we learned that he had been admitted to another emergency department two months prior due to an object hitting his left eye, where the eye was only washed with saline. Our case emphasizes that ocular siderosis caused by IOFBs should be kept in mind in the differential diagnosis of anisocoria, especially before MRI. Because metallic objects may move during MRI, undiagnosed IOFBs can cause serious ocular side effects.

**Keywords:** Anisocoria, iron mydriasis, intraocular foreign body, magnetic resonance imaging, ocular siderosis

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**Address for Correspondence:** Osman Özen, Kastamonu Training and Research Hospital, Clinic of Ophthalmology, Kastamonu, Türkiye
**E-mail:** dr.oozen16@gmail.com **ORCID-ID:** orcid.org/0000-0003-1685-6885
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## Introduction

Eye injuries are among the most common occupational accidents and reasons for emergency department admission. Studies report that patients presenting with eye trauma are 22-25 years of age on average and predominantly male.[1,2] Intraocular foreign bodies (IOFBs) account for 18-41% of all open-globe injuries.[3] IOFBs diagnosed after penetrating eye injuries cause severe intraocular toxic reactions of varying severity depending on their material composition, duration, shape, and size.[4]

In 1890, Bunge described a series of ocular changes that occurred as a result of iron-containing IOFBs, which he called ocular siderosis (OS).[3] OS may occur months or years after trauma and can affect all ocular tissues, from the cornea to the optic nerve. The most common findings are cataract formation, mydriasis, iris heterochromia, secondary glaucoma, iritis, vitreous opacities, diffuse pigment changes in the retinal pigment epithelium, macular edema, and attenuated responses on electroretinography.[5] Radiographs, orbital computed tomography (CT), and ultrasound are considered the gold standard for the early detection of IOFBs in patients presenting with eye injuries.[6] Magnetic resonance imaging (MRI) can also be used to detect non-metallic IOFBs. However, MRI is contraindicated for metallic IOFBs because of their potential to produce motion artifacts and even serious adverse ocular effects.[7]

In this case report, we present a patient with an overlooked IOFB whom we clinically diagnosed as having OS. This case highlights the importance of careful history-taking and a high suspicion of trauma when examining patients employed in industrial workplaces and presenting with visual impairment while working.

## Case Report

A 22-year-old man presented to the emergency department with complaints of mild left pupil dilation and a marked

decrease in vision in the left eye that he noticed upon waking in the morning. He had no other complaints, and the results of neurological examinations were normal. In the emergency department, diffusion brain MRI and brain CT examinations were first performed to rule out a neurological cause. However, when imaging was reported as normal, the ophthalmology department was consulted due to the absence of central nervous system pathology.

On ophthalmological examination, there was anisocoria with a larger pupil in the left eye (Figure 1). Direct and indirect light reflexes were normal on the right and weak but present on the left, with no relative afferent pupil defect detected in either eye. Color vision was normal on the right but could not be evaluated on the left because of low vision. Best corrected visual acuity (BCVA) in Snellen decimal units was 1.0 on the right and 0.1 on the left. Intraocular pressure was normal, corneas were clear, and the anterior chamber, iris, and lens appeared normal bilaterally. In the gonioscopic angle examination of the left eye, increased pigment was noticed at the angle. Shiny, pearl-like formations were observed in the anterior vitreous, while the posterior vitreous appeared condensed in the inferior periphery. Color fundus and fundus autofluorescence images (TRC-50DX, Topcon Corporation, Tokyo, Japan) revealed a macular scar in the inferior parafoveal area (Figure 2). Optical coherence tomography (OCT) (Cirrus HD-OCT 5000, Carl Zeiss Meditec AG, Jena, Germany) showed choroidal rupture in the area of the macular scar and irregularity of the retinal outer layers consistent with scarring (Figure 3). In the light of these findings, the images were examined with the suspicion of IOFB. On the orbital part of the brain CT scan, a metallic IOFB was noticed in the left eye (Figure 4). Moreover, brain MRI showed a large artifact obscuring the anatomical structures of the left orbit and surrounding regions (Figure 5). When we questioned the patient again in detail, he reported that two months earlier, he had presented to the emergency department of a different hospital because of a foreign body in his left eye. After examination, the eye had been washed with saline (Polyflex 0.9% isotonic sodium chloride solution, Polifarma Pharmaceuticals, Tekirdağ, Türkiye) and he was told there was no other pathology. We informed the patient of his condition and referred him to a more advanced center, where he underwent lens-sparing vitrectomy and IOFB removal surgery. At postoperative 1 month, the mydriasis had resolved and his BCVA remained unchanged at 0.1.

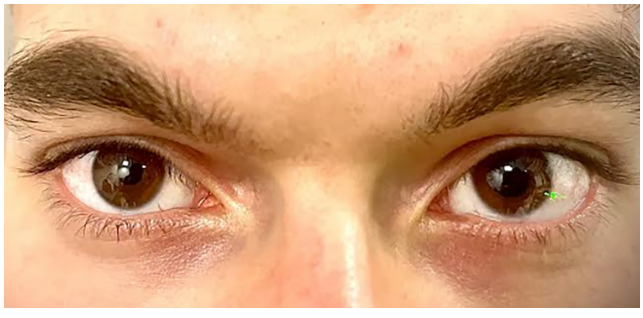

**Figure 1.** Anisocoria with a larger pupil in the left eye

## Discussion

This case of anisocoria accompanied by low vision demonstrates the potential clinical consequences that can arise because of an overlooked IOFB, even months later. There are a limited number of cases in the literature presenting the clinical findings of posttraumatic OS. The clinical manifestations in these cases include heterochromia, mydriasis, cataract, secondary glaucoma, anterior and posterior uveitis, retinal vessel sheathing, and retinal pigmentary changes.[8] In our case, there was no additional finding other than unilateral mydriasis and visual impairment associated with a parafoveal scar.

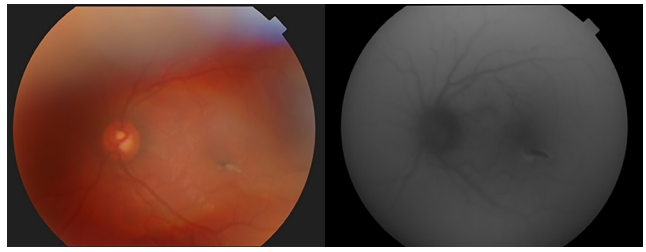

**Figure 2.** A scar in the lower parafoveal region

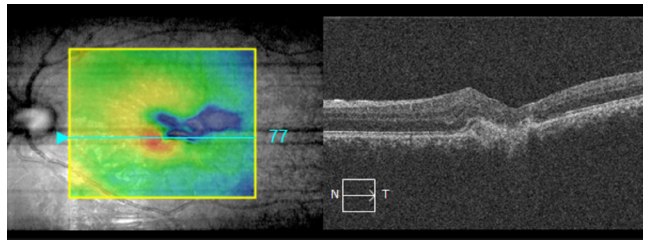


**Figure 3.** Optical coherence tomography image of the parafoveal scar

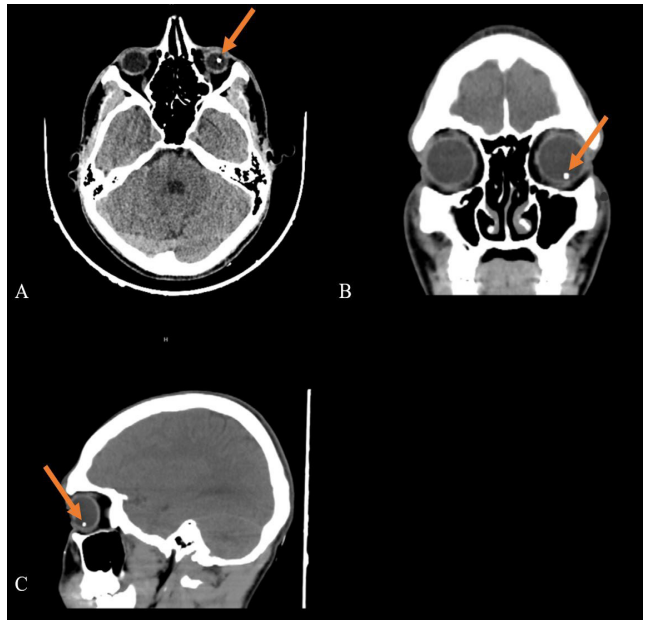


**Figure 4.** Computed tomography images of the metallic intraocular foreign body in the left eye (orange arrows): A) axial section, B) coronal section, C) sagittal section

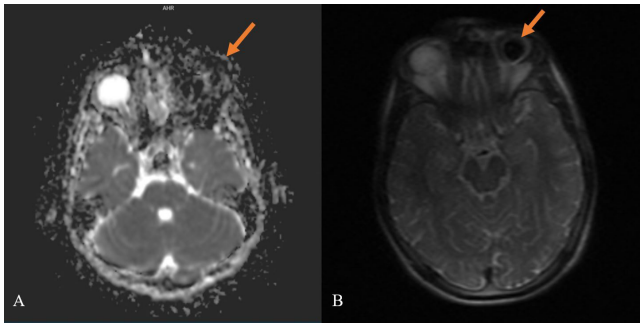


**Figure 5.** Diffusion magnetic resonance images in the axial plane showing typical magnetic susceptibility artifact (orange arrows) obscuring the anatomical structures of the left orbit and surrounding regions

An enlarged pupil may be the initial sign of OS, as in our case. New-onset anisocoria is an important condition that should always be investigated. Differential diagnoses for anisocoria include Horner syndrome, acute neurological anisocoria, physiological anisocoria, Argyll Robertson pupil, pharmacologically shrunken pupil, and Adie (tonic) pupil.[9,10] The term "iron mydriasis", on the other hand, has been used to characterize cases of mydriasis caused by OS after overlooking an IOFB, which is often not suspected, and should be included in the differential diagnosis.[11,12] Mydriasis is thought to occur as a result of OS-induced parasympathetic neuropathy, and the pupil shows a hypersensitive reaction to diluted pilocarpine, like Adie pupils.[11,13,14]

Various animal studies have shown that ferromagnetic bodies can move considerably during MRI, potentially leading to intraocular complications.[15,16] Gunenc et al.[17] showed that foreign bodies such as iron, chromium, and solder can move 7-10 mm within bovine eyes during MRI. As we did not have a comparative orbital CT scan obtained after MRI, we do not know whether the IOFB moved in our case. However, the fact that we were unable to detect an IOFB visible on CT in the mid-inferior vitreous during our fundus examination suggests that it may have shifted to a far-peripheral location. The large dark area observed on MRI in our case was a magnetic susceptibility artifact. Susceptibility artifacts appear on clinical MRI due to the presence of even a small amount of a metal-containing substance, which can cause signal loss and large geometric distortions of anatomical structures, as in our case.[7]

There are very few case reports in the literature showing MRI of a metallic IOFB in vivo.[16,17,18,19,20] A handful of case reports have documented ocular complications after MRI that were caused by overlooked IOFBs. Kelly et al.[21] first reported sudden unilateral vision loss due to vitreous hemorrhage after a brain MRI in 1986. In a similar case, a patient presented with sudden eye pain and loss of vision immediately after MRI. Ophthalmological examination revealed a small paracentral corneal scar and 50% hyphema.[18] In both cases, subsequent CT revealed the presence of an IOFB. Vote and Simpson[22] reported rapid progression of traumatic cataracts due to IOFB after MRI in 2001, and a more recent case report described a case of microhyphema after MRI resulting from the dislocation of an IOFB embedded in the iris.[23] In contrast, Platt et al.[20] reported that an orbital IOFB was detected in a 12-year-old child undergoing routine brain MRI examination without causing any ocular complications. Similarly, our patient seems to have another rare case of orbital IOFB that was noticed on brain MRI but caused no ocular adverse effects associated with MRI. The eye is considered one of the most vulnerable parts of the body in terms of metallic fragments. Therefore, to avoid surprises such as those seen in the present case or worse, it has been recommended that patients and other personnel be carefully questioned and screened for IOFBs before entering the controlled area of the MRI room.[24]

Despite clinical improvements, IOFBs can still be overlooked, and OS occurs mainly as a result of delayed admission or missed diagnosis. Our report highlights the importance of a detailed ophthalmologic examination prior to MRI in patients with unilateral fixed or poorly reactive dilated pupil, especially young male patients and even in the absence of a definitive trauma history, to prevent delaying or overlooking the diagnosis of OS. Despite having appropriate screening protocols prior to imaging, metallic IOFBs unnoticed before MRI can cause a number of adverse events from monocular blindness to other intraocular complications. Therefore, we believe this case demonstrating that "iron mydriasis" should be kept in mind during the differential diagnosis of anisocoria will be a good reminder for clinicians.

### Ethics

**Informed Consent:** Obtained.

### Declarations

### Authorship Contributions

Concept: O.Ö., M.İ.Ö., Design: O.Ö., M.İ.Ö., Data Collection or Processing: M.İ.Ö., Analysis or Interpretation: O.Ö., M.İ.Ö., Literature Search: O.Ö., M.İ.Ö., Writing: O.Ö.

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

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Case Report

# Management of Orbital Granulomatous Polyangiitis Presenting with Lacrimal Gland Involvement: Treatment of Subsequent Peripheral Ulcerative Keratitis, Anterior Uveitis, and Exudative Retinal Detachment in a Challenging Case

Murat Oklar[1], Elif Sarı[1], Hatice Selen Kanar[1], Hikmet Süslü[2], Tufan Çiftçi[3], Mehmet Engin Tezcan[4]

[1]University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Neurosurgery, İstanbul, Türkiye
[3]University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Pathology, İstanbul, Türkiye
[4]University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Rheumatology, İstanbul, Türkiye

## Abstract

This case report discusses a case of granulomatosis with polyangiitis (GPA) initially presenting with lacrimal gland involvement and subsequently developing additional features. GPA is a disease known for inflammation in the respiratory tract and kidneys. A 63-year-old male patient presented with a mass, swelling, and ptosis in the right upper eyelid. The patient was referred to us when his symptoms had persisted and worsened despite topical and oral antibiotic therapy administered at another center. Based on clinical and laboratory findings from evaluation and consultations, GPA was diagnosed and confirmed by biopsy. The patient initially presented with necrotizing scleritis and later developed peripheral ulcerative keratitis and anterior uveitis, which regressed under cyclophosphamide treatment but progressed to exudative retinal detachment due to orbital involvement. Clinical remission was achieved after adding rituximab therapy. Presentation with lacrimal gland involvement may serve as an initial manifestation of locally aggressive orbital and adnexal GPA, which can exhibit variable clinical features. Rapid diagnosis and aggressive treatment are critical for preserving vision and preventing complications in patients with GPA.

**Keywords:** Granulomatosis with polyangiitis, lacrimal gland, peripheral ulcerative keratitis, retinal detachment, necrotizing scleritis, uveitis

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**Address for Correspondence:** Murat Oklar, University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
**E-mail:** muratoklar@hotmail.com **ORCID-ID:** orcid.org/0000-0001-5254-0613
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## Introduction

Granulomatosis with polyangiitis (GPA) is a rare autoimmune condition characterized by vasculitis primarily affecting the respiratory tracts and kidneys.[1] Predominantly observed in Caucasians, GPA shows a peak incidence in the fifth decade of life and is less common in individuals under 19 years old.[2] Both sexes are equally affected, although in Europe the incidence is relatively higher among men.[3] Diagnostic markers such as serum cytoplasmic antineutrophil cytoplasm antibodies (c-ANCA) are crucial, and up to 80% of ANCA-positive GPA patients present with antibodies against proteinase 3 (PR3). Ophthalmic involvement is common, with over half of patients experiencing related symptoms, including vision loss in 8% of cases.[4] Orbital GPA occurs in 45% of patients and may be the initial symptom in 16% of cases.[5] In the present case, we report initial involvement of the lacrimal gland that subsequently progressed to an orbital mass and led to significant ocular complications.

## Case Report

In this case study, we present a 63-year-old male diagnosed with GPA initially affecting the lacrimal gland and adjacent sclera. Despite treatment, the condition rapidly progressed to peripheral ulcerative keratitis (PUK), leading to widespread orbital masses and exudative retinal detachment. This report offers an overview of the disease progression and medical management of ocular manifestations in this case. The study adhered to the principles of the Declaration of Helsinki and complied with the Health Insurance Portability and Accountability Act. The patient consented to the publication of his anterior segment photographs.

A 63-year-old Caucasian male who was initially seen at the neurosurgery clinic presented to the Ophthalmology Department of University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital with complaints of right upper eyelid swelling, ptosis, and eye redness. He reported that his symptoms had worsened despite three months of treatment with topical Maxidex eye drops (dexamethasone 0.1%, Alcon Laboratories, Inc., Fort Worth, TX, USA) and oral Monodoks antibiotic (doxycycline 100 mg, Deva Holding Co., İstanbul, Türkiye). Examination revealed a Snellen best-corrected visual acuity of 20/30 in the right eye (OD) and 20/20 in the left eye (OS), with intraocular pressures of 23 mmHg OD and 15 mmHg OS. The right upper eyelid exhibited ptosis and proptosis, with a palpable mass in the superotemporal quadrant of the orbit. Extraocular muscle movements were normal. Anterior segment examination showed ciliary injection, marked erosion, and necrosis in the superotemporal quadrant of the bulbar and forniceal conjunctiva (Figure 1a, b), along with necrotizing scleritis in the adjacent sclera (Figure 1c). The area of necrotizing scleritis measured approximately 2x4 mm. Fundoscopic examination revealed retinal pigment epithelium (RPE) changes in the bilateral macula consistent with age-related macular degeneration. A computed tomography (CT) scan revealed an intraorbital mass without bony destruction (Figure 1d) and magnetic resonance imaging (MRI) indicated a heterogeneously enhancing mass in the superotemporal orbit (Figure 1e). By joint decision with the neurosurgery department, excisional biopsy (Figure 1f) involving a superotemporal orbitotomy and right dacryoadenectomy was performed as a collaborative effort between the neurosurgery and ophthalmology departments. Three days after surgery, we noted persistent conjunctival necrosis and necrotizing scleritis, with the new development of PUK (Figure 2a). Additionally, +2 cells were observed in the anterior chamber, along with iris pigments on the anterior lens capsule (Figure 2b).

The patient, now medically stable, was transferred to an ophthalmology inpatient clinic for further evaluation and intervention. Potential infectious etiologies such as tuberculosis, syphilis, fungal infections, and viral causes were thoroughly considered and excluded through comprehensive laboratory tests. Blood tests revealed anti-PR3 antibodies at levels >200 RU/mL (relative units per milliliter) and positive c-ANCA. Anti-myeloperoxidase (anti-MPO) antibody levels were negative (<2 U/mL), with C3 and C4 levels within normal range (1.44 and 0.21 g/L, respectively). Inflammatory markers such as C-reactive protein (95.58 mg/L) and erythrocyte sedimentation rate (55 mm/h) were elevated. Due to the rapid progression of inflammatory signs such as PUK, anterior uveitis, and necrotizing scleritis, as well as consistent laboratory tests including positive c-ANCA, we suspected GPA and promptly initiated high-dose intravenous methylprednisolone (500 mg for 3 days; Prednol, Mustafa Nevzat Pharmaceutical Industry Co., Istanbul, Türkiye) followed by oral tapering to prevent vision loss and further tissue damage without waiting for the definitive pathology report.

The pathology report later confirmed geographic necrosis, granuloma formation, fibrosis, vasculitis, and giant cell formation (Figure 2c, d), suggesting necrotizing granulomatous disease consistent with GPA. Following clinical, serological, and radiological assessments confirming GPA, consultations with the rheumatology, pulmonary medicine, and otorhinolaryngology departments were initiated for systemic evaluation. Incidentally, two pulmonary nodules were detected on thoracic CT and were monitored. No renal impairment or upper respiratory tract manifestations were observed. As recommended by

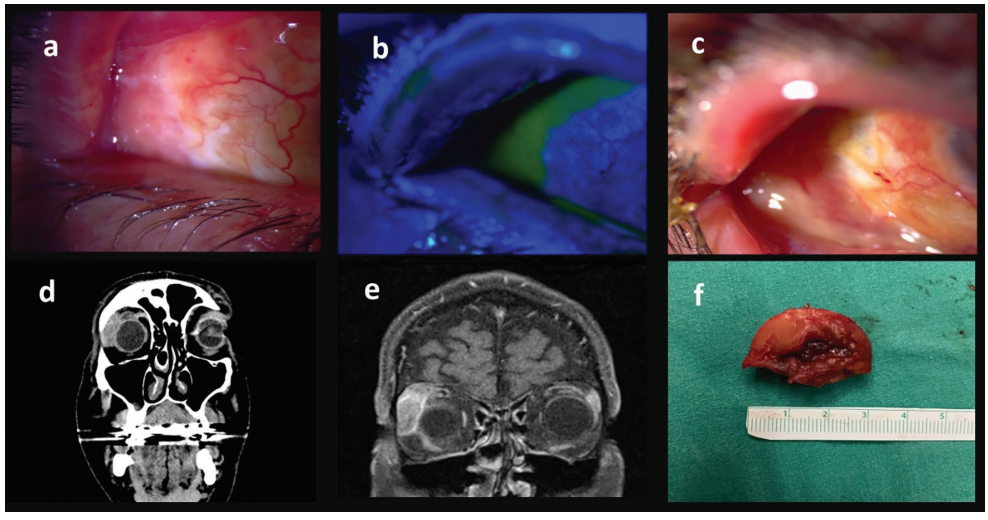


**Figure 1.** a) Slit-lamp anterior segment examination at presentation showed ciliary injection, marked erosion, and necrosis in the superotemporal quadrant of the bulbar and forniceal conjunctiva. b) After applying 1% fluorescein dye, the cobalt blue filter indicates necrosis in the superotemporal quadrant of the bulbar and forniceal conjunctiva. c) Hemorrhage, conjunctival necrosis, and scleral thinning in the region corresponding to the area where the enlarged palpebral lobe of the lacrimal gland makes contact, consistent with necrotizing scleritis. d) Coronal computed tomography scan of the orbit revealed an intraorbital mass located superotemporally, in the area corresponding to the lacrimal fossa, without any bony erosion. e) A coronal T1-weighted magnetic resonance image of the orbit showed a hyperintense orbital lesion in the lacrimal fossa. f) Excisional biopsy material measuring 30x20 mm was removed from the lacrimal fossa intraoperatively

the rheumatology department, the patient received 500 mg pulse cyclophosphamide (Endoxan, Baxter Oncology GmbH, Halle/Westfalen, Germany) intravenously every two weeks for induction therapy. During treatment, ciliary injection decreased, reconjunctivalization of necrotic areas occurred, scleral thinning improved, necrotizing scleritis regressed, and the PUK stabilized (Figure 2e, f). However, in the 8th week of treatment, the patient reported vision loss. Fundoscopic examination revealed a large exudative retinal detachment in the inferotemporal quadrant of the OD, extending to the macula with associated serous macular detachment (Figure 3a). Optical coherence tomography (OCT) also showed serous retinal detachment and choroidal thickening (Figure 4a). MRI revealed significant infiltration of granulomatous lesions in the right orbit (Figure 5a, b, c, d), indicating a relapse. Treatment involved 1 g pulse methylprednisolone (Prednol) for 3 days and increased intravenous cyclophosphamide (750 mg; Endoxan), with additional 1000 mg rituximab induction every 2 weeks, followed by maintenance therapy every 6 months (MabThera®, Roche Müstahzarları Sanayi A.Ş., İstanbul, Türkiye).

Five months after rituximab initiation, significant regression of the exudative detachment was observed (Figure 4b), and the serous detachment on OCT gradually resolved over time (Figure 4c). The exudative detachment affecting the inferotemporal quadrant of the retina regressed (Figure 3b) into formations resembling chorioretinal scars, with areas of RPE hyperplasia,

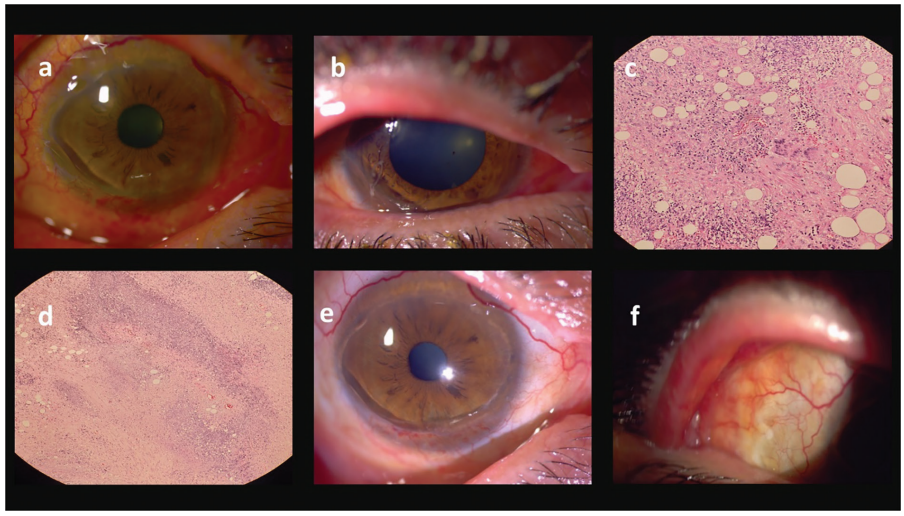


**Figure 2.** Anterior segment photographs showing (a) onset of peripheral ulcerative keratitis (PUK) and (b) anterior uveitis and iris pigments on the anterior lens capsule. c) On histopathological examination of the mass, high-magnification photomicrograph revealed an area characterized by vasculitis and the presence of giant cells (hematoxylin & eosin [H&E] staining). d) Medium magnification photomicrograph showed an area of geographic necrosis, granuloma formation, and fibrosis (H&E staining). e) Observations during treatment indicated that the PUK area had become demarcated, conjunctival hyperemia had decreased, and vascularization had begun. Healing with lipid degeneration was observed in the superior corneolimbal region. f) Post-treatment images showed the scleral thinning had regressed and the necrotic conjunctival area had reconjunctivalized

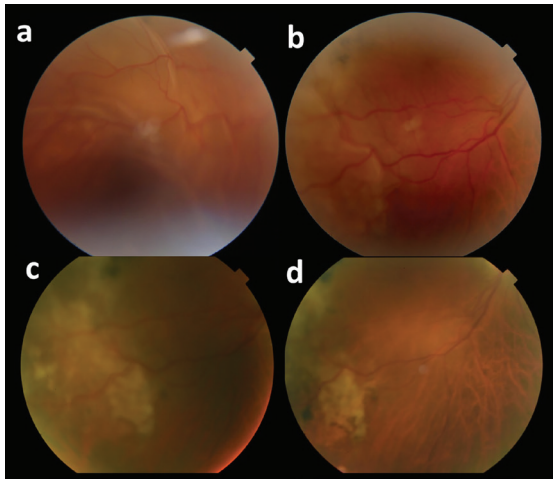


**Figure 3.** Digital color fundus photographs of the exudative retinal detachment. a) A large exudative retinal detachment was seen in the inferotemporal region of the right eye. b) The exudative retinal detachment appeared to be limited. c) Improvement in the exudative retinal detachment with residual exudation and retinal pigment epithelium (RPE) changes was noted. d) Regression of posterior segment findings with RPE hyperplasia, RPE atrophy, and choroidal alterations was observed

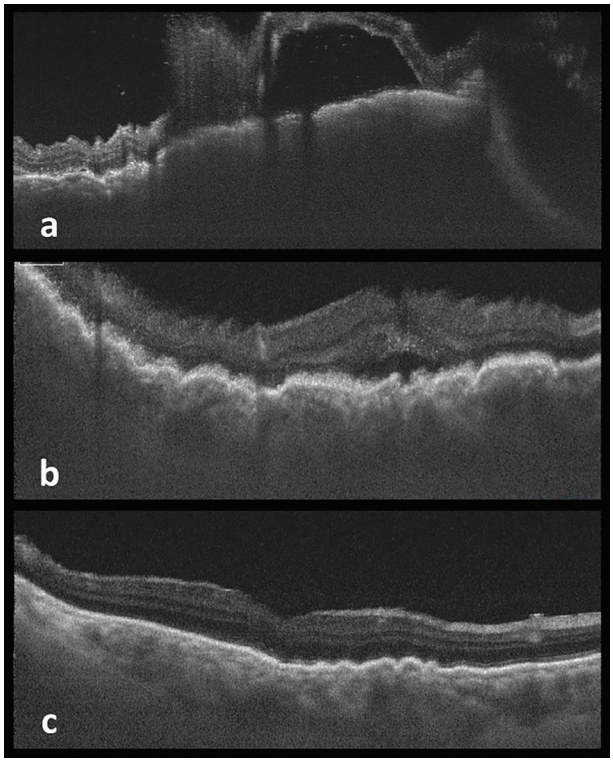


**Figure 4.** Optical coherence tomography (OCT) sections of the right eye. a) The OCT section passing through the area of exudative retinal detachment. b) The macular OCT section showed diffuse, bumpy choroidal thickening with serous macular detachment. c) The serous detachment on OCT gradually resolved over time

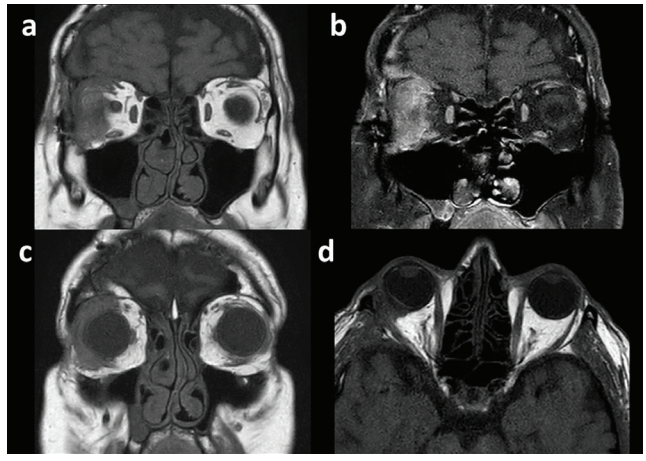


**Figure 5.** Imaging of the orbital structures using different magnetic resonance imaging (MRI) sequences. a) A coronal T1-weighted orbital MRI scan showed that the granuloma extended to the apex of the orbit, in proximity to the optic nerve. b) A coronal T1-weighted orbital MRI scan with contrast and fat suppression revealed contrast enhancement (hyperintensity) in the region corresponding to the orbital granuloma. c) A coronal T1-weighted orbital MRI scan revealed a presentation consistent with an intraorbital granuloma surrounding the globe circumferentially and involving the superior, inferior, and temporal aspects. d) An axial T1-weighted orbital MRI scan indicated relapse, with intraorbital infiltration and exudative retinal detachment in the right eye

RPE atrophy, and choroidal alterations (Figure 3c). Maintenance corticosteroids were gradually tapered to 8 mg/day and were supplemented by methotrexate (15 mg/week; Metoart®, Deva Holding Co., İstanbul, Türkiye) around the 7th month of treatment. Rituximab effectively controlled the recurrent orbital GPA episode, resulting in regression of posterior segment findings (Figure 3d). The final BCVA was 70/100 OD.

## Discussion

This case report describes a patient with GPA presenting with a lacrimal gland mass and necrotizing scleritis without systemic symptoms. GPA can affect various organs, and up to sixty percent of patients experience ocular symptoms.[6] Eye involvement can occur at any stage of the disease, either as a limited or systemic condition. However, Tan et al.[7] found that none of their patients with lacrimal gland involvement developed systemic symptoms, suggesting possible long-term localization. Despite this, they noted significant progression of orbital disease necessitating systemic immunosuppressive therapy in all cases, with high ocular morbidity. Similarly, our patient's orbital disease advanced without systemic involvement despite effective therapy.

In the differential diagnosis of a patient presenting with lacrimal gland enlargement, PUK, and necrotizing scleritis, it is crucial to consider a variety of conditions that mimic the clinical features of GPA. Sarcoidosis is a key consideration, as it can present with lacrimal gland masses and ocular inflammation.[8] However, it typically lacks the necrotizing vasculitis seen in GPA and is characterized by non-caseating granulomas. Infectious etiologies, such as tuberculosis or syphilis, should also be ruled out, particularly in the presence of orbital granulomas or necrotizing scleritis, as these infections require specific antimicrobial treatments.[9,10] Idiopathic orbital inflammation is another important differential diagnosis. It presents with orbital masses but lacks systemic vasculitis and is ANCA-negative.[11] Another neoplastic condition to consider is lymphoma, especially in cases involving lacrimal gland masses.[12] However, biopsy findings in lymphoma show monoclonal lymphoid proliferation rather than granulomatous inflammation and necrosis.

Immune cells and substances that cause inflammation often move to the peripheral cornea through chemotaxis from the nearby sclera and episcleral tissues. This process can result in the formation of PUK.[13] The patient in our case report developed conjunctival necrosis, scleral thinning, and PUK with anterior uveitis. Corneal involvement can be a primary manifestation of GPA as well as a secondary manifestation of orbital and conjunctival disease resulting in cicatrization, tear film deficiency, poor eyelid closure, and trichiasis.[14] Previous research has demonstrated that the existence of PUK and necrotizing scleritis are indicative of an unfavorable prognosis regarding the severity of systemic GPA.[15]

Orbital involvement has been identified as the first or second most prevalent ocular finding after conjunctivitis/episcleritis, accounting for 15% of all cases and 45% of all

ocular manifestations. In a retrospective study including 74 patients with orbital GPA, it was observed that 35.1% of patients presented with isolated lacrimal gland involvement, while orbital mass involvement (without primary lacrimal gland involvement) was seen in 60.8%. The group with orbital mass involvement was noted to have a more severe disease course compared to the group with isolated lacrimal gland involvement. Additionally, the orbital mass group exhibited significantly more anterior segment findings (e.g., necrotizing scleritis, PUK), ANCA-positivity, and visual loss, a higher incidence of systemic disease, and a greater association with relapses in comparison to the group with isolated lacrimal gland involvement.[16]

MRI is more effective than CT in detecting orbital granulomas and mucosal changes. On the other hand, CT is more useful for assessing the destruction of bones and the hardening of sinus walls in orbital GPA with sinonasal involvement. Orbital granulomas appear hypointense on T2 images and may show varying levels of contrast enhancement.[17] Orbital GPA can be difficult to distinguish from other orbital inflammatory conditions based solely on clinical features. However, the presence of sinonasal involvement and bony changes on imaging strongly indicate orbital GPA. Nevertheless, during our initial presentation, there were no signs of bone erosion or sinonasal manifestations. In suspected cases of GPA, biopsy of the orbital lesion is performed to obtain a definitive pathological diagnosis due to the unusual presentations and non-specific clinical findings. The biopsy often demonstrates the typical histological characteristics of GPA, including vasculitis, necrosis, and granulomatous inflammation. However, Kalina et al.[18] discovered that the traditional pathological triad was observed in only 54% of orbital biopsies, whereas it was identified in 91% of open lung biopsies. Thus, the lack of the typical histopathological findings does not exclude the diagnosis of orbital GPA.

Retinal and choroidal involvement in GPA is uncommon. Ismailova et al.[16] reported that retinal involvement was detected in 4.4% of all ophthalmic manifestations. Retinal disease manifestations may include retinal vasculitis, retinal vein occlusion, and rarely, exudative retinal detachment.[19] Posterior scleritis or chorioretinal granulomas can also lead to exudative retinal detachment. Furthermore, in patients presenting with widespread exudative detachment, Sugisawa et al.[19] suggested that GPA-associated necrotizing scleritis and inflammation spread may contribute to the development of exudative retinal detachment. In our case, the exudative detachment area was more limited, and it was postulated that the orbital granuloma caused choroidal compression, resulting in choriocapillaris ischemia and RPE pump dysfunction. Following rituximab therapy, as the granulomas diminished and compression symptoms improved, the exudative detachment regressed, leading to healing with the formation of chorioretinal scars. Similar to the case reported by Sugisawa et al.[19], the noteworthy development of exudative detachment under cyclophosphamide treatment in our case suggests that GPA presenting with exudative detachment may indicate resistance to initial treatment.

The primary goal of treating GPA is to induce and maintain remission of the disease. Cyclophosphamide and glucocorticoids form the cornerstone of GPA treatment, providing remission in 70-90% of patients. However, due to the potential side effects of cyclophosphamide, such as cytopenia and the risk of cancer, and the fact that 50% of those who achieve remission may experience relapse within 2 years, there is a clear necessity for alternative treatment options.[20] Rituximab, an anti-CD20 monoclonal antibody, recently emerged as an alternative to traditional treatments. A multicenter study on ANCA-associated vasculitis showed that rituximab was as effective as cyclophosphamide in treating the disease without significant adverse effects. Moreover, rituximab was found to be superior to cyclophosphamide in the treatment of relapsed disease.[21] There are also some studies in the literature showing the effectiveness of rituximab in treating orbital GPA.[22] In our case, rituximab therapy was chosen due to the recurrence of orbital disease under cyclophosphamide and maintenance corticosteroid treatment. Additionally, in GPA, there is a higher likelihood of orbital masses showing a refractory course. In one series, complete remission in orbital masses was observed in only 8.1% of 37 patients, with disease progression seen in 40% despite initial treatment.[23] These findings indicate the need for alternative treatment options in this group. Given that rituximab is a well-known systemic treatment for GPA, its intralesional or intraorbital application in refractory orbital masses could be similarly effective.[24] This emphasizes the need for further research in this area to explore the potential efficacy of intralesional rituximab in treating refractory orbital masses.

In conclusion, presenting with lacrimal gland involvement may be an initial manifestation of locally aggressive orbital and adnexal GPA, which displays variable clinical features. Despite the common belief in the literature that lacrimal gland involvement is associated with a favorable prognosis, our case highlights the potential coexistence of multiple ophthalmic conditions in the same individual but at different times, such as lacrimal gland enlargement, PUK, anterior uveitis, necrotizing scleritis, orbital mass, and exudative retinal detachment. Our aim was to contribute this perspective to the literature.

**Ethics**

**Informed Consent:** Obtained.

**Declarations**

**Authorship Contributions**

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

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Case Report

# Nd:YAG Laser Application for the Treatment of Retained Lens Fragment in the Anterior Chamber Following Cataract Surgery

Ali Mert Koçer, Bekir Eren Aksoy, Özge Uysal

University of Health Sciences Türkiye, Ulucanlar Eye Training and Research Hospital, Clinic of Ophthalmology, Ankara, Türkiye

## Abstract

Cataract surgery is the most frequently performed surgery worldwide. Although it is an effective surgical treatment option for improving patients' visual acuity, various complications can occur postoperatively. One such complication is the presence of retained lens material in the anterior chamber, which can lead to intraocular inflammation, increased intraocular pressure, corneal edema, and endothelial cell loss. Treatment options include observation and surgical removal of the retained lens material. Another notable treatment option is the use of neodymium-doped yttrium aluminum garnet (Nd:YAG) laser to fragment the retained lens material. In this paper, we aim to present two cases from our clinic where Nd:YAG laser treatment was applied to patients with retained small lens fragments in the anterior chamber following cataract surgery. It was observed that in both patients, the retained lens fragments were resorbed by the first day after Nd:YAG laser treatment, and no complications developed.

**Keywords:** Cataract surgery, retained lens fragment, Nd:YAG laser, anterior chamber

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**Address for Correspondence:** Ali Mert Koçer, University of Health Sciences Türkiye, Ulucanlar Eye Training and Research Hospital, Clinic of Ophthalmology, Ankara, Türkiye

**E-mail:** alimertkocer@gmail.com **ORCID-ID:** orcid.org/0000-0001-6847-1560

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## Introduction

Cataract surgery is a common and generally safe procedure aimed at restoring vision by removing the clouded lens of the eye and replacing it with an artificial lens.[1] Nevertheless, complications such as retained lens fragments may arise, potentially hindering recovery and requiring further medical intervention.[2,3] These fragments may lead to various ocular complications, including intraocular inflammation, increased intraocular pressure (IOP), corneal edema, and endothelial cell loss, potentially necessitating additional medical or surgical interventions.[4,5]

Various treatment strategies exist for managing retained lens fragments, ranging from observation to more invasive surgical removal. The application of neodymium-doped yttrium aluminum garnet (Nd:YAG) laser to fragment and facilitate the resorption of retained lens material represents an additional treatment option. This technique offers a minimally invasive approach that may help mitigate the complications associated with retained lens fragments. In this report, we present two patients from our clinic who developed retained lens fragments in the anterior chamber following cataract surgery and were treated with Nd:YAG laser.

## Case Reports

### Case 1

An 80-year-old male patient presented for a routine evaluation. The best corrected visual acuity (BCVA) was 0.3 Snellen decimal in the right eye and 0.6 in the left eye, with IOP measurements of 18 mmHg bilaterally. Anterior segment examination revealed bilateral pseudoexfoliation syndrome and posterior subcapsular cataracts, along with insufficient pupillary dilation. Fundus examination was normal. The anterior chamber depth (ACD), axial length (AL), and lens thickness (LT) were 2.85 mm, 22.48 mm, and 4.87 mm, respectively. Cataract surgery was recommended for the right eye, and following

informed consent, phacoemulsification with iris hooks was performed without complications.

On the first postoperative day, BCVA improved to 0.9. IOP measured 20 mmHg in the right eye. The cornea was clear, with a +1 anterior chamber reaction (ACR). However, a retained nuclear fragment measuring 1.0x1.0 mm was detected in the inferior anterior chamber (Figure 1A). Given the minimal size of the lens material and the absence of complications, a management strategy involving observation and topical therapy was selected. The patient was prescribed hourly topical steroids (0.1% dexamethasone; Maxidex, Alcon, Puurs, Belgium) and a topical non-steroidal anti-inflammatory drug (0.1% diclofenac sodium; Inflased, Bilim Pharmaceuticals, Istanbul, Türkiye). Despite two weeks of treatment, the retained lens fragment neither resolved nor decreased in size, and no complications were observed during this period.

After a thorough discussion of all available treatment options, the patient consented to Nd:YAG laser therapy (total energy: 13.0 mJ, number of shots: 5) to address the retained lens material. On the first day post-treatment, no residual lens material was observed in the anterior chamber, the cornea remained clear, and the BCVA was 0.9 in the right eye (Figure 1B). IOP measurement was 18 mmHg, and gonioscopic examination revealed no lens material (Figure 2A). At the six-month follow-up, the patient exhibited no complications, and optical coherence tomography (OCT) confirmed the absence of macular edema (Figure 2B).

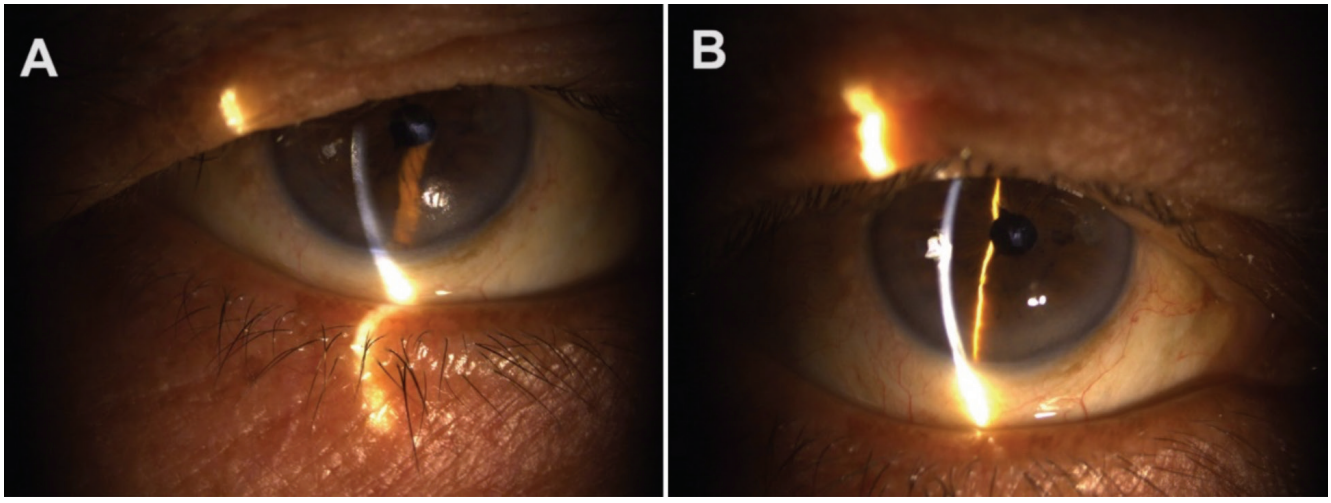


**Figure 1.** Anterior segment photography of an 80-year-old male patient reveals retained nuclear material in the inferior anterior chamber following cataract surgery (A). Anterior segment imaging of the same patient one day after Nd:YAG laser application shows the absence of lens material (B)

*Nd:YAG: Neodymium-doped yttrium aluminum garnet*

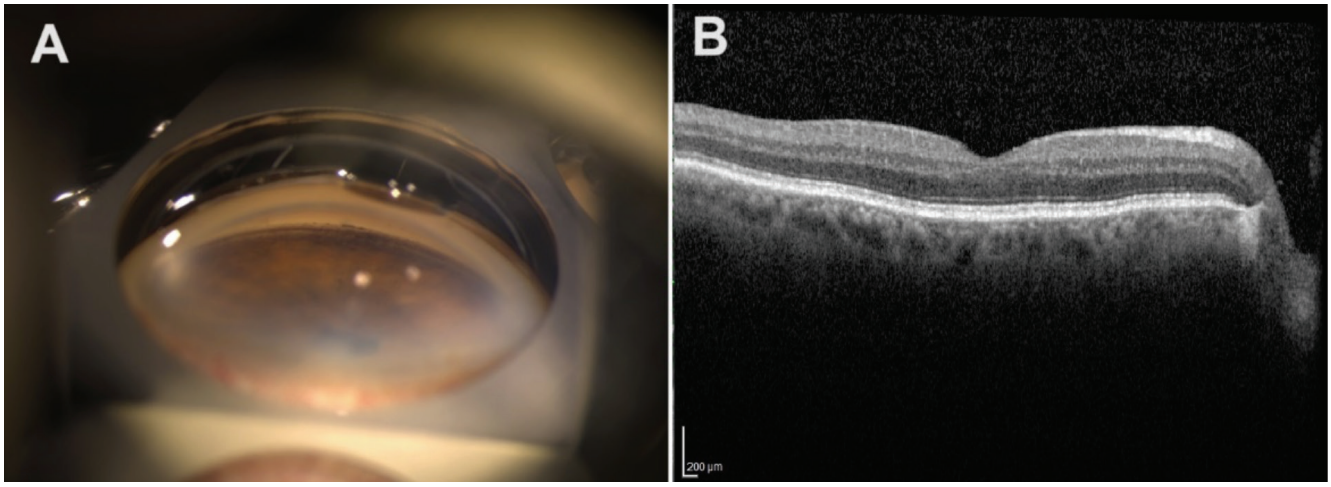


**Figure 2.** Gonioscopic evaluation of case 1 demonstrates the absence of retained material in the inferior angle following laser treatment (A). Optical coherence tomography reveals a normal macula appearance, with no evidence of cystoid macular edema after laser therapy (B)

**Case 2**

A 71-year-old female patient was admitted for a routine evaluation. The BCVA was 0.05 Snellen decimal in the right eye and 0.3 in the left eye. IOP measurements were 14 mmHg in both eyes. Anterior segment examination revealed bilateral corticonuclear cataracts. Fundus examination was normal. The ACD, AL, and LT were 2.68 mm, 23.19 mm, and 4.5 mm, respectively. Cataract surgery was recommended for the right eye, and following informed consent, phacoemulsification was performed without complications by an inexperienced surgeon.

On postoperative day one, a large retained cortical lens fragment measuring 3.0x4.0 mm was detected in the anterior chamber, accompanied by grade 1 inferior corneal edema and Descemet's membrane folds extending through the visual axis. The BCVA in the right eye was 0.5, and IOP measured 21 mmHg. Additionally, a +3 ACR with limbal injection was noted. Despite the large size of the retained lens material, a management approach involving observation with topical medications was initially preferred due to the cortical nature of the lens material. The retained material decreased in size to 2.0 x 2.0 mm, but intraocular inflammation remained uncontrolled, and persistent mild corneal edema was observed despite the intensification of topical steroid therapy (Maxidex, Alcon, Puurs, Belgium) and the absence of lens material touch to the cornea after one-week treatment (Figure 3A).

Treatment options were thoroughly discussed with the patient. The patient expressed reluctance to undergo a second surgical intervention. With her consent, Nd:YAG laser therapy (total energy: 20.1 mJ, number of shots: 9) was administered to fragment the retained lens material into smaller pieces, thereby increasing its surface area and promoting faster dissolution. On post-treatment day one, no residual lens material was observed in the anterior chamber, with a +1 ACR noted (Figure 3B). Improvement in corneal edema was also documented, and no lens material was detected during gonioscopic examination (Figure 4A). At the six-month follow-up, no complications were noted (Figure 4B). The final BCVA in the right eye was 1.0.

**Nd:YAG Laser Procedure**

The VISULAS YAG III laser (Carl Zeiss Meditec, Jena, Germany) was employed under topical anesthesia. An Abraham iridotomy lens was applied and the defocus was set to zero. Initial laser power was set at 2.5 mJ and adjusted as needed based on the fragmentation (0.2± mJ). Careful attention was given to prevent tissue damage such as corneal burns. Laser treatment continued until the prominent lens pieces were fully fragmented. Topical anti-inflammatory (Maxidex, Alcon, Puurs, Belgium) and IOP-lowering medications (0.15% brimonidine tartrate; Brimogut, Bilim Pharmaceuticals, Istanbul, Türkiye) were administered after laser treatment.

## Discussion

Retention of lens fragments following cataract surgery is an uncommon but significant complication of phacoemulsification that often requires additional treatment.[6,7] These fragments can lead to severe complications, such as corneal edema, which may progress to corneal decompensation.[7]

The presentation of retained lens fragments in the anterior chamber can vary significantly, with detection occurring from the acute postoperative period to several years later.[8,9] Tien et al.[9] reported a case in which retained lens fragments were identified 32 years after cataract surgery. Additionally, retained lens fragments have been identified after Nd:YAG laser capsulotomy, even when the initial cataract surgery occurred a year prior.[6] In contrast, we identified retained lens fragments acutely

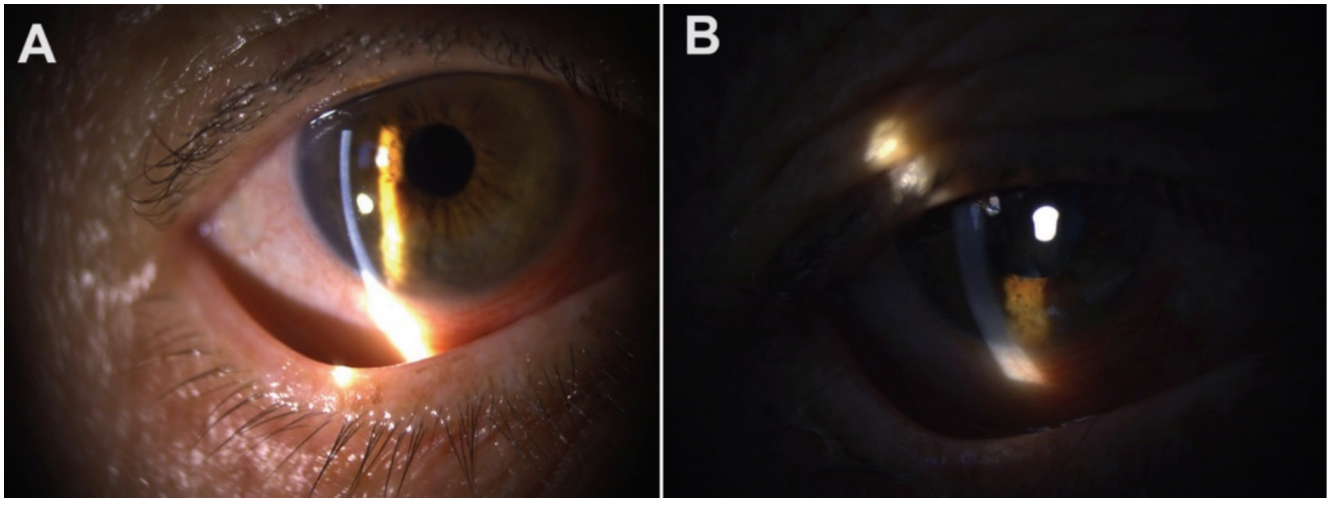


**Figure 3.** Anterior segment photography of a 71-year-old female patient demonstrates limbal injection, mild inferior corneal edema, and residual cortical material in the inferior anterior chamber following phacoemulsification (A). One day after Nd:YAG laser treatment, anterior segment imaging of the same patient reveals a clear anterior chamber, free of any lens material (B)

*Nd:YAG: Neodymium-doped yttrium aluminum garnet*

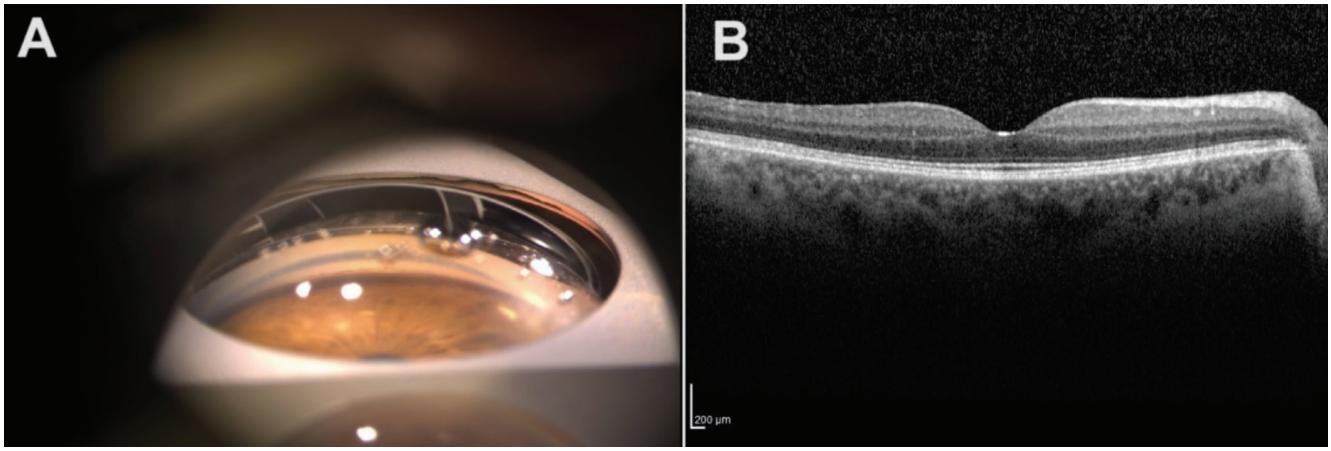


**Figure 4.** Gonioscopic assessment in case 2 shows no residual material in the inferior angle post-laser treatment (A). Optical coherence tomography depicts a normal macular profile, with no signs of cystoid macular edema after laser therapy (B)

after phacoemulsification, allowing for immediate treatment management.

Several risk factors can increase the likelihood of retained lens fragments following cataract surgery. These include advanced age, dense or mature cataracts, pseudoexfoliation syndrome, thick lenses, and posterior capsular rupture.[3] Although studies show conflicting results, variations in ADC may be an additional risk factor for lens fragment retention.[3,10] In our patients, the presence of pseudoexfoliation syndrome and mid-dilated pupils were significant risk factors for retained lens fragments. Additionally, a lower level of surgical experience may constitute an additional risk factor.

Based on a review of the literature, the primary treatment options for retained lens fragments in the anterior chamber include observation and surgical removal.[11] However, there is a notable lack of detailed descriptions regarding the use of Nd:YAG laser therapy in the management of retained lens fragments. Initially, we opted for observation with adjunctive topical medications, subsequently offering Nd:YAG laser treatment as a less invasive alternative to surgical removal. This approach was motivated by concerns that irrigation/aspiration of the residual material could potentially result in further corneal endothelial loss, endothelial decompensation, or endophthalmitis. Moreover, surgical removal may not always be definitive, particularly when lens material is inadequately visualized during irrigation/aspiration, leading to incomplete removal and possibly necessitating repeated surgeries. Therefore, the application of Nd:YAG laser can be recommended as a preliminary approach before considering surgical removal, given its less invasive nature and lower risk of severe complications compared to the surgery. In line with this view, Meduri et al.[12] stated in their multicenter retrospective case series that the Nd:YAG laser procedure may be a good option for treating retained lenticular fragments in the anterior chamber. The authors also indicated that the procedure offers advantages over repeat surgery, such as reducing endothelial damage, minimizing patient discomfort, and lowering healthcare expenses.[12]

However, Nd:YAG laser treatment may not be suitable for all patients. The procedure can induce intraocular inflammation and increase IOP, rendering patients with glaucoma, uveitis, or maculopathy ineligible for laser therapy. In one instance from our practice, a patient presented with uncontrolled intraocular inflammation. However, Nd:YAG laser treatment was performed nevertheless due to the patient's reluctance to undergo surgery and the cortical nature of the retained lens material, which is typically more amenable to resolution than nuclear fragments. Furthermore, surgical removal may be a more appropriate approach for patients presenting with large nuclear fragments in the anterior chamber.

Significant corneal edema can also be a limiting factor for Nd:YAG laser application, as it may obstruct laser focus and elevate the risk of corneal damage. Nd:YAG laser may induce endothelial loss due to the proximity of material to the cornea, but likely to a lesser degree than surgery. Descement's membrane detachment has been reported following Nd:YAG laser iridotomy.[13] Additionally, because the retained lens material is located inferiorly in the anterior chamber, possible iris damage during laser treatment may lead to dysphotopsia or pigment dispersion.[14] It is essential to discuss the risks and benefits of various treatment options with patients, allowing for a collaborative decision-making process to determine the most suitable treatment modality.

In conclusion, Nd:YAG laser treatment represents a viable option in the management of retained lens materials in the anterior chamber, potentially mitigating the need for surgical removal and thereby reducing the associated risks of surgical complications.

**Ethics**

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

## Declarations

### Authorship Contributions

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

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

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# Letter to the Editor Re: Evaluation of Medically Reversible Limbal Stem Cell Deficiency

Hinpetch Daungsupawong[1], Viroj Wiwanitkit[2]

[1]Private Academic Consultant, Phonhong, Lao People's Democratic Republic
[2]Saveetha University, Saveetha Institute of Medical and Technical Sciences, Saveetha Dental College and Hospitals, Department of Research Analytics, Chennai, India

## Keywords

Medical, reversible, limbal, stem cell, deficiency

## Dear Editor,

This is a response to a published article titled "Evaluation of Medically Reversible Limbal Stem Cell Deficiency" by Korkmaz et al.[1] This study describes the patients' demographics, etiology, and clinical results, providing important insights into the use of medication for limbal stem cell deficiency (LSCD). However, some aspects must be critically examined. First, the sample size of 29 eyes from 21 individuals is modest, potentially limiting the findings' generalizability. The variety of the underlying causes raises concerns regarding the suitability of a one-size-fits-all treatment strategy. Furthermore, the participants' ages (5 to 71 years) resulted in variations in their biological responses to therapy, implying that age-specific analyses may provide more nuanced insights.

The methodology utilized to assess the LSCD stage adhered to the requirements specified by the International LSCD Working Group and seemed to be effective. However, this study may have benefited from a more in-depth explanation of the medicinal therapy used. The absence of detail makes it difficult to duplicate the study and assess the efficacy of certain treatment techniques. Furthermore, while the results are promising, including a reduction in LSCD severity and an improvement in best-corrected visual acuity, the lack of a control group hinders an evaluation of the effectiveness of medical therapy compared to routine care or allows for limited observation to draw conclusions. Future research should include randomized controlled trials to increase the evidence base for the medical treatment of LSCD.

The reported data raise several questions. For example, how does LSCD's underlying etiology affect response to therapy? What characteristics of patients with complete LSCD regression can be used to guide future therapy decisions? Furthermore, what long-term results can we expect from various medical therapies, particularly for ocular rosacea and blepharitis? Exploring these questions can help us better understand LSCD management and make better therapeutic decisions.

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**Address for Correspondence:** Hinpetch Daungsupawong, Private Academic Consultant, Phonhong, Lao People's Democratic Republic
**E-mail:** hinpetchdaung@gmail.com **ORCID-ID:** orcid.org/0009-0002-5881-2709
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To promote new research and future approaches, studies should look into the molecular mechanisms driving LSCD and the possibility of targeted therapeutics. Furthermore, investigating the function of adjuvant therapy such as autologous serum ointments and anti-inflammatory medications could provide a more holistic approach to LSCD management. Long-term studies evaluating the durability of therapeutic effects and patient quality of life following therapy would also make valuable contributions to this research. Finally, including patient-reported outcomes in future research may ensure that therapies are more closely aligned with patients' actual experiences and expectations.

**Declarations**

**Authorship Contributions**

Concept: H.D., V.W., Design: H.D., V.W., Data Collection or Processing: H.D., V.W., Analysis or Interpretation: H.D., V.W., Literature Search: H.D., V.W., Writing: H.D., V.W.

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## Reply

We would like to address the concerns raised in the letter to the editor regarding our article, "Evaluation of Medically Reversible Limbal Stem Cell Deficiency", which was published in Turkish Journal of Ophthalmology.[1] We thank the authors for taking the time to read our article with interest and provide valuable feedback. We are grateful for their contribution to the scientific community.

It is evident that the sample size (29 eyes of 21 patients) of the study was limited. Given the retrospective nature of this study, we included patients with reliable data to assess disease reversal. We expect that prospective studies, ideally including larger numbers of participants, will provide more valuable contributions.

Limbal stem cell deficiency (LSCD) is a sight-threatening ocular surface disease, with underlying mechanisms that vary based on the primary etiology. Direct physical damage to the limbal region leads to LSCD through limbal stem cell aplasia. On the other hand, limbal stem cell dysfunction becomes prominent in LSCD cases where increased inflammation plays a primary role. Chronic ocular surface inflammation leads to limbal niche dysfunction characterized by abnormal microenvironment and inadequate stromal support, resulting in impaired limbal stem cell function.[2] In our previous study, although the numerous underlying causes and age differences, we assessed the etiologies of LSCD involving chronic ocular surface inflammation and disruption of limbal niche homeostasis. As emphasized by the authors in the letter, regardless of the etiology of LSCD, a personalized and stepwise treatment protocol should be adopted instead of a one-size-fits-all strategy. However, our article aimed to highlight that, particularly in certain etiologies, addressing the re-establishment of limbal homeostasis could enable the treatment of LSCD without the need for further surgical intervention. Restoring ocular surface health and controlling inflammation are essential to re-establish homeostasis. Furthermore, if it is possible to eliminate all pathological conditions that may cause LSCD, such as by discontinuing contact lens use or avoiding toxic agents, this constitutes the basic approach. In accordance with the recommendations of the global consensus on the treatment of LSCD, the aforementioned approach should be adopted in all LSCD patients, regardless of whether or not surgical intervention is required.[3,4] Consequently, in our study, eliminating the underlying pathology, which primarily entailed anti-inflammatory and lubrication therapies, was regarded as the optimal medical approach for the specific needs of the eyes in question. Data analysis was conducted in accordance with these considerations.

A review of the literature on best corrected visual acuity (BCVA) reveals that BCVA was previously considered a criterion for the evaluation of the disease, both in diagnosis and treatment, prior to the publication of the global consensus on the diagnosis and treatment of LSCD. However, there is now a global consensus that BCVA is no longer considered a criterion in the evaluation and classification LSCD severity.[3] Consequently, BCVA was not associated with LSCD in this study, given that stromal opacity or other factors that may reduce visual acuity may not be associated with disease severity.

It is of great importance in the field of medicine to conduct controlled studies in order to obtain high-quality evidence. However, LSCD is actually classified under the rare diseases. Therefore, even in pharmacological and related research, phase studies are constrained by the regulations pertaining to orphan diseases.[5] In this study, which involved dependent data, the results were analyzed within this context.

The objective of the study was to draw the attention of clinicians to reversible LSCD, which we aimed to emphasize with a limited number of cases. Furthermore, we aim to pioneer more comprehensive studies on this subject, which also focus on molecular mechanisms, as suggested in the author's letter. Prospective, randomized controlled trials in the future will help answer remaining questions regarding the medical treatment approach to LSCD.

**Declarations**

**Authorship Contributions**

Concept: M.P., Ö.B.S., Design: N.F.E., Ö.B.S., Data Collection or Processing: İ.K., N.F.E., Analysis or Interpretation: S.E., A.Y., Literature Search: İ.K., Writing: İ.K.

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**İlayda Korkmaz, Nihat Furkan Eratılgan, Melis Palamar, Sait Eğrilmez, Ayşe Yağcı, Özlem Barut Selver**

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

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**Address for Correspondence:** Özlem Barut Selver, Ege University Faculty of Medicine, Department of Ophthalmology, İzmir, Türkiye
**E-mail:** ozlembarutselver@yahoo.com **ORCID-ID:** orcid.org/0000-0003-3333-3349
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