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AT A GLANCE

2026 Issue 5 at a Glance:

Esteemed colleagues,

The fifth issue of the Turkish Journal of Ophthalmology for 2026 comprises four original research articles, one review, one editorial, one case report, and three letters to the editor. Spanning a broad range of topics from glaucoma and retinopathy of prematurity to optic neuropathy and ptosis, this issue brings together articles on current topics and novel surgical techniques that may contribute to our clinical practice.

The editorial in this issue, titled "Competent Gonioscopy in the Age of Advanced Imaging," was written by Bayer and Spaeth. In this insightful article, the authors emphasize that competently performed gonioscopy remains indispensable in the current era of microinvasive glaucoma surgery and cannot be replaced by more technologically advanced methods of angle assessment. They also argue that the main reason gonioscopy does not receive the attention it deserves is that it is often taught as a technical ritual rather than as a method of clinical reasoning (See pages 294-296).

In the original research section, the article titled "Long-Term Ocular and Neurodevelopmental Outcomes of Retinopathy of Prematurity: A Bibliometric and Thematic Evolution Analysis" by Karataş et al. maps global research trends on the long-term outcomes of retinopathy of prematurity and evaluates the representation of four clinical outcome domains (visual and refractive outcomes, structural retinal and macular sequelae, late post-treatment complications, and neurodevelopmental and quality-of-life outcomes) in the literature, highlighting the need for greater focus on neurodevelopmental and quality-of-life outcomes (See pages 297-307).

The study titled "Comparison of Optical Coherence Tomography Biomarkers in Nonproliferative and Proliferative Diabetic Retinopathy: Marmasia Study Group Report No. 2" used real-life data to investigate whether structural optical coherence tomography biomarkers and visual acuity differ between eyes with nonproliferative and proliferative diabetic retinopathy (See pages 308-316).

In their original study titled "Evaluation of Plasma Spermine and Spermidine Levels in Primary Open-Angle Glaucoma and Exfoliation Glaucoma," Aygün et al. found that spermine levels were significantly higher in both the primary open-angle glaucoma (POAG) and exfoliation glaucoma groups than in the control group, whereas spermidine levels were significantly higher only in the POAG group. The authors interpreted these alterations in plasma spermine and spermidine levels as suggesting a possible association between systemic polyamine metabolism and glaucoma (See pages 317-324).

In the article by Orman et al. titled "Evaluation of Peripapillary Vitreous Dynamics in Patients with Acute Nonarteritic Anterior Ischemic Optic Neuropathy," peripapillary and vitreomacular interface characteristics were evaluated using spectral-domain optical coherence tomography in patients with acute nonarteritic anterior ischemic optic neuropathy (NAION). The study identified structural differences in vitreoretinal interface configuration in acute NAION, although the authors emphasize that the temporal relationship of these changes to ischemic injury remains uncertain (See pages 325-331).

In the review section, the article by Tekiner et al. titled "Eponymous Pupillary and Ocular Sensory Signs of Neurosyphilis: A Historical Review" examines the pupillary and ocular sensory signs associated with neurosyphilis from a historical perspective and describes in detail the eponyms that have been used most traceably and consistently in the literature (See pages 332-338).

In the case report section, the article titled "Anatomopathological Aspects and Clinical Correlation of Conjunctival Bleb Fibrosis Following Encapsulation of a Biodegradable Collagen Matrix Implant in Glaucoma Surgery" by Castro-Roger et al. presents the clinical characteristics and histopathological findings of four glaucoma patients in whom a biodegradable collagen-glycosaminoglycan implant (Ologen®) failed to prevent fibrosis after non-penetrating deep sclerectomy (See pages 339-350).

The first letter to the editor, written by Kaynak et al., is titled "PUAWS: 'Pelin's Up and Away' Suture (a Variation of the Brassiere Suture) as an Adjunct to Upper Blepharoplasty." The authors describe a new modification of the brassiere suture used in upper blepharoplasty and evaluate the outcomes of three patients treated with this technique (See pages 351-354).

In their letter titled "A Novel Reversible Tube Ligation Technique for Managing Hypotony After Paul Glaucoma Implant Surgery in Uveitic Glaucoma," Üçgül et al. describe the successful management of severe hypotony maculopathy after glaucoma drainage device implantation in a 21-year-old monocular patient with uveitic glaucoma, using temporary tube occlusion and anti-inflammatory therapy (See pages 355-359).

In the final letter to the editor in this issue, titled "Extension of a Severed Paul Glaucoma Implant Tube Using the Crawford Lacrimal Tube: A Novel Surgical Technique," Cabezas Vicente et al. describe a new surgical technique in which a segment of a Crawford lacrimal tube was used to extend a severed Paul Glaucoma Implant tube in a 76-year-old man. The authors state that the technique is simple, reproducible, and cost-effective (See pages 360-362).

We hope that the articles in this fifth issue of the year will interest you and serve as a useful guide in your clinical practice. We thank all our authors, reviewers, and colleagues for their contributions, and we wish you enjoyable and productive reading.

Respectfully on behalf of the Editorial Board,

Hakan Özdemir, MD

Editorial

Competent Gonioscopy in the Age of Advanced Imaging

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Gonioscopy is one of the most frequently neglected or poorly performed examinations in routine ophthalmology practice.[1] However, the equipment for gonioscopy is available in all ophthalmology clinics, the examination can usually be completed within a few minutes, and the information obtained may directly alter diagnosis and management.

The problem is not merely whether gonioscopy is performed. What matters is whether it is performed competently and interpreted correctly. Placing a goniolens on the cornea and assigning a single-digit number to the angle does not necessarily produce useful information.

The consequences of an incorrect angle assessment are not theoretical. A patient at risk of acute angle closure may lose vision because a necessary laser peripheral iridotomy (PI) was not performed.[2] Another patient with advanced chronic angle-closure glaucoma may undergo an unnecessary PI when the real problem is extensive synechial closure and established glaucomatous damage. A patient with plateau iris configuration may be treated as though relative pupillary block is the only mechanism. An eye with lens-related angle closure, aqueous misdirection, angle neovascularization, trauma, or abnormal pigmentation may be placed under an imprecise label such as "narrow angle" or "open angle."

The gonioscopic appearance of the normal anterior chamber angle varies with age, race, refractive status, iris configuration, lens position, and pigmentation.[3,4] These normal variations in the angle must be understood before abnormality can be recognized. The examiner must understand which angle elements are being observed, where the iris inserts, what the configuration of the peripheral iris is, how wide the angular approach is, how much pigment is present, and whether the angle changes during indentation.

The Shaffer system has historical value and remains familiar to generations of ophthalmologists, but it must be recognized that no single figure can adequately describe the complex three-dimensional structure of the angle. A Shaffer grade 4 angle, for example, may be entirely healthy, but it may also contain 4+ pigment, exfoliative material, abnormal vessels, blood, silicone oil, or evidence of trauma. Similarly, a Shaffer grade 1 angle may represent uncomplicated age-related narrowing, relative pupillary block, plateau iris configuration, lens-induced narrowing, aqueous misdirection, or chronic synechial closure.

Calling an angle "narrow" is often no more informative than describing a patient as "unwell." The description may be true, but it does not explain the cause, severity, or mechanism of narrowing, or the action required. Clinically useful documentation should define the features, including the level of iris insertion, the configuration of the iris, the most posterior visible angle element, and the amount and distribution of pigmentation. Other findings such as peripheral anterior synechiae, neovascularization, angle recession, foreign material, or abnormal vessels should also be recorded.[5,6] Gonioscopy helps physicians determine whether the angle is capable of closing, whether there is closure at the time of examination, and whether previous

Keywords: Gonioscopy, anterior chamber angle, glaucoma, anterior segment optical coherence tomography

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iridotrabecular contact has produced any adhesions. It can clarify whether the mechanism is primarily pupillary block, plateau iris, lens-related crowding, or another process. These findings influence whether the patient should be observed, undergo PI, lens extraction, or another glaucoma procedure, or be managed differently.

Anterior segment optical coherence tomography (AS-OCT) has provided clinicians with certain tools to quantify, document, and analyze anterior segment structures. However, AS-OCT does not provide the same direct, dynamic, and circumferential assessment of the angle.[7] It cannot reproduce the information obtained through indentation, nor can it reliably demonstrate all clinically relevant findings mentioned above involving pigmentation, fine vessels, subtle synechiae, angle recession, or foreign material. It commonly samples selected meridians, whereas gonioscopy permits examination of the entire angle circumferentially. Additionally, imaging systems such as AS-OCT are associated with substantial costs.

The description of imaging as "objective" and gonioscopy as "subjective" has also created confusion. Objective is not interchangeable with accurate, relevant, or clinically sufficient. A highly reproducible measurement can still be inaccurate or irrelevant to the clinical decision at hand. Every image in ophthalmology requires acquisition, selection, interpretation, and clinical judgment. Gonioscopy depends on examiner skill, but so does every other examination method, including slit-lamp biomicroscopy, optic disc evaluation, and visual field interpretation. The correct response to a skill-dependent examination is to teach it properly and practice it until it becomes reliable, not to abandon it.

Competent gonioscopy is also essential in the era of microinvasive glaucoma surgery (MIGS). MIGS procedures depend on accurate identification of the angle structures. The surgeon must understand the individual anatomy preoperatively, identify the target tissue, and maintain a clear gonioscopic view intraoperatively. A surgeon who is not comfortable with diagnostic gonioscopy is unlikely to become consistently competent in operative gonioscopy. MIGS has made mastery of the examination even more necessary.

Why, then, is gonioscopy underused? The most common reason is that it is often taught as a technical ritual rather than as a method of clinical reasoning. Trainees may learn how to place the goniolens on the eye but not how to identify angle structures, control illumination, avoid corneal folds, and perform dynamic gonioscopy.[8] They may be asked to record only a single-digit Shaffer grade. When such an examination fails to guide management, the clinician may conclude that gonioscopy itself has little value. The conclusion should not be that gonioscopy is useless. Poorly performed and poorly interpreted gonioscopy is useless.

Competent gonioscopy can be learned.[2] It requires a knowledgeable teacher, repeated examination of normal and abnormal angles, careful comparison of findings, and honest recognition of uncertainty. Residents should be taught to characterize what they actually see during gonioscopy rather than what they expect to see. Ophthalmologists should regard gonioscopy as a mandatory component of routine examination, particularly when glaucoma, ocular hypertension, angle closure, trauma, inflammation, or angle surgery is being considered. Glaucoma specialists should set a high standard by routinely documenting gonioscopic findings in a manner that supports diagnosis and management.

Once mastered, a careful gonioscopic evaluation of both eyes, including appropriate documentation, usually requires only a few minutes. Those minutes may prevent an attack of acute angle closure, reveal chronic synechial damage, explain an unexplained rise in intraocular pressure, identify a secondary mechanism, or prevent an inappropriate procedure. Few ophthalmology examinations provide so much clinically relevant information at such a low cost.

The anterior chamber angle should not remain uncharted territory. We should move beyond the question of whether gonioscopy was performed and ask whether it was performed well enough to help the patient. Anterior segment imaging must remain an adjunct. It should never be accepted as a substitute for direct clinical examination of the angle. The responsibility for understanding the angle remains with the clinician. When gonioscopy is skillfully performed, thoughtfully interpreted, and accurately recorded, it becomes what it has always had the potential to be: an essential examination for preserving vision.

Declarations

Authorship Contributions

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References

1. Skuta GL, Ding K, Lum F, Coleman AL. An IRIS registry-based assessment of primary open-angle glaucoma practice patterns in academic versus nonacademic settings. Am J Ophthalmol. 2022;242:228-242.

2. Wu AM, Stein JD, Shah M. Potentially missed opportunities in prevention of acute angle-closure crisis. JAMA Ophthalmol. 2022;140:598-603.
3. Oh YG, Minelli S, Spaeth GL, Steinman WC. The anterior chamber angle is different in different racial groups: a gonioscopic study. Eye (Lond). 1994;8:104-108.
4. Congdon NG, Youlin Q, Quigley H, Hung PT, Wang TH, Ho TC, Tielsch JM. Biometry and primary angle-closure glaucoma among Chinese, white, and black populations. Ophthalmology. 1997;104:1489-1495.
5. Spaeth GL. The normal development of the human anterior chamber angle: a new system of descriptive grading. Trans Ophthalmol Soc U K (1962). 1971;91:709-739.
6. Bayer A, Spaeth GL, editors. Gonioscopy: Microinvasive Glaucoma Surgery Era. 1st ed. Cham: Springer; 2026. doi:10.1007/978-3-032-13516-2.
7. Kim SH, Park KH. Anterior segment optical coherence tomography (AS-OCT) cannot be a substitution of gonioscopy. Jpn J Ophthalmol. 2013;57:493-494.
8. Forbes M. Gonioscopy with corneal indentation. A method for distinguishing between appositional closure and synechial closure. Arch Ophthalmol. 1966;76:488-492.

Original Article

Long-Term Ocular and Neurodevelopmental Outcomes of Retinopathy of Prematurity: A Bibliometric and Thematic Evolution Analysis

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Abstract

Objectives: To map the global research landscape on the long-term outcomes of retinopathy of prematurity (ROP) and quantify the representation of four clinically relevant outcome domains: visual and refractive outcomes, structural retinal and macular sequelae, late post-treatment complications, and neurodevelopmental and quality-of-life outcomes.

Materials and Methods: Two Web of Science Core Collection datasets were created on July 21, 2026 and limited to English-language original articles: Dataset A (general long-term ROP outcomes) and Dataset B (long-term outcomes after ROP treatment). Bibliometric analyses were performed in R using the bibliometrix package. A predefined 108-term outcome lexicon was applied to merged Author Keywords and Keywords Plus. Domain distributions were compared using the chi-square test, and representation ratios were calculated with 95% confidence intervals (CI).

Results: Dataset A included 6,946 articles from 1,035 sources, whereas Dataset B included 1,296 articles from 238 sources. The United States was the leading contributor in both datasets. Türkiye ranked third and fourth in publication output but showed the lowest international collaboration rate (0.9%) among leading countries. Visual and refractive outcomes were the most frequently represented domain (1.95% and 4.07% of keyword occurrences), whereas neurodevelopmental and quality-of-life outcomes were the least represented and the only domain underrepresented in the treatment literature (0.60% vs. 0.35%; representation ratio 0.59, 95% CI 0.43-0.83; p=0.003).

Conclusion: Research on long-term ROP outcomes is expanding rapidly, but the transition from acute treatment to survivorship remains incomplete. Greater emphasis on neurodevelopmental and quality-of-life outcomes and stronger international collaboration are needed.

Keywords: Bibliometrics, retinopathy of prematurity, treatment outcome, refractive errors, neurodevelopmental disorders

Introduction

Retinopathy of prematurity (ROP) is a vaso-proliferative disorder of the immature retina and remains a leading cause of preventable childhood blindness worldwide.[1,2] Advances in neonatal intensive care have increased the survival of extremely preterm infants, expanding the population at risk despite established screening and treatment programmes.[2,3] The third edition of the International Classification of Retinopathy of Prematurity (ICROP3) introduced longitudinal concepts such as reactivation, persistent avascular retina, and long-term sequelae, shifting attention from acute disease management toward lifelong outcomes.[1]

Although acute ROP may regress, affected children remain at risk of lifelong ocular complications, including high myopia, strabismus, amblyopia, retinal detachment, and glaucoma.[4,5,6,7] While long-term follow-up data from anti-vascular endothelial growth factor (anti-VEGF) and laser trials have become available, reported outcomes

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remain predominantly structural and refractive.[8,9] However, severe ROP has also been associated with adverse cognitive, motor, and behavioural outcomes, as well as reduced quality of life, raising the question of whether these dimensions have received comparable research attention.[10,11]

Bibliometric analysis provides a quantitative approach to mapping the intellectual structure and evolution of a research field.[12,13] Previous bibliometric studies have examined overall ROP research, artificial intelligence, or anti-VEGF therapy, but none has specifically focused on long-term outcomes, compared general and post-treatment literature, or quantified clinically relevant outcome domains.[14,15,16]

We therefore conducted a dual-corpus bibliometric analysis to characterise global research on long-term ROP outcomes and to quantify the representation of four predefined clinical outcome domains using a structured outcome lexicon.

Materials and Methods

Data source and search strategy

The Web of Science Core Collection was employed as the sole data source, as it supplies the structured Author Keywords, Keywords Plus, affiliation, and cited-reference fields essential for bibliometric mapping. Combining databases with divergent indexing rules would compromise keyword-level analysis. Both searches were conducted on 21 July 2026. Dataset A (general long-term outcomes) combined a topic search (TS) for ROP and its synonyms (retinopathy of prematurity, retrolental fibroplasia, retinopathy of prematurity survivor*, regressed or treated retinopathy of prematurity) with a second TS block of 48 long-term outcome terms covering follow-up duration, visual and refractive function, structural and imaging endpoints, reactivation, and neurodevelopmental and quality-of-life endpoints.

Dataset B (post-treatment long-term outcomes) combined a TS search for "retinopathy of prematurity" with a TS block of treatment modalities (bevacizumab, ranibizumab, aflibercept, anti-VEGF, laser, cryotherapy, vitrectomy, scleral buckle) and a third TS block of outcome terms (long-term, follow-up, outcome*, recurrence, reactivation, persistent avascular retina, neurodevelopment*, cognitive, motor, refractive, myopia, visual acuity). The full Boolean strings are given in Supplementary Appendix 1.

Inclusion and Exclusion Criteria

Both result sets were restricted to the document type "Article", with review articles excluded and the language limited to English, so that the two corpora would be composed of comparable primary research reports. No time restriction was applied; the retrieved records spanned 1980 to 2026, with 2026 necessarily incomplete. Of 7,193 records retrieved for Dataset A, 6,946 met the inclusion criteria; Dataset B comprised 1,296 records. Full records with cited references were exported in tab-delimited format. Two investigators independently verified the search strings and the refinement steps, and discrepancies were resolved by discussion.

Bibliometric Analysis

Bibliometric analyses were performed using R software (version 4.6.0; R Foundation for Statistical Computing, Vienna, Austria) together with the bibliometrix package (version 5.4.1) and its Biblioshiny web interface (Massimo Aria and Corrado Cuccurullo, University of Naples Federico II, Naples, Italy).[13] The following indicators were extracted for each corpus: annual production and growth rate; average document age; citations per document; numbers of sources, authors, single-authored documents, and co-authors per document; international co-authorship rate; most relevant and most locally cited sources; core journal stratification via Bradford's law; most relevant and most locally cited authors; author productivity distribution via Lotka's law; h-, g- and m-indices; most relevant affiliations; corresponding-author countries with single-country and multiple-country counts; most globally and locally cited documents; keyword co-occurrence; thematic mapping; and trend topics. Because the corpora overlap by design, they are described in parallel and never pooled.

Outcome Domain Lexicon

To move from generic keyword frequencies to clinically interpretable quantities, we constructed a predefined lexicon of 108 entries across four mutually exclusive domains: visual and refractive outcomes (31 entries), structural retinal and macular sequelae (31 entries), late post-treatment complications (20 entries), and neurodevelopmental and quality-of-life outcomes (26 entries). The lexicon was drafted from ICROP3 terminology and major ROP treatment trials and cohort studies. The original list of 108 entries was independently reviewed by two ophthalmologists with expertise in ROP before being finalized (Supplementary Appendix 2).[1,4,8,9,10] Each expert evaluated the relevance of each entry to its assigned outcome domain using a four-point Likert scale. The two reviewers demonstrated high agreement in the assignment of entries to the predefined outcome domains (mean agreement score: 0.90). For the final analysis, variant forms of the same terms were merged to yield 95 unique terms (26/27/18/24 terms in each domain, respectively).

Ethics

This study analysed publicly available bibliographic metadata and involved no human participants, human tissue or animals. Therefore, institutional review board approval and informed consent were not required.

Statistical Analysis

This is a descriptive bibliometric study, and most results are presented as counts, percentages and standard bibliometric indices. The full counting method was used for affiliations and countries, so category percentages may exceed 100%. Annual growth rate is the compound annual growth rate of publication counts. For the outcome lexicon, the distribution of domain-tagged keyword occurrences was compared between corpora with the Pearson chi-square test. For each domain, a representation ratio (share in Dataset B divided by share in Dataset A) was calculated with a 95% confidence interval (CI) from the standard error of the log ratio, and each domain was tested against the remainder of the corpus with the chi-square test. A two-sided $p<0.05$ was considered significant. No individual patient data were analysed and no imputation was required.

Results

Characteristics of the two corpora

Dataset A comprised 6,946 articles published in 1,035 sources between 1980 and 2026 by 24,298 authors, with 6.89 co-authors per document, 16.48% international co-authorships, and 92,252 cited references. Dataset B comprised 1,296 articles in 238 sources by 5,557 authors, with 7.29 co-authors per document, 12.19% international co-authorships, and 12,982 cited references. The annual growth rate was higher in the post-treatment corpus (9.15% vs. 6.87%) and its documents were more recent (mean age 10.9 vs. 12.1 years). Total citations were 201,451 for Dataset A (mean 29.0, median 11 citations per document; h-index 153, g-index 268) and 37,976 for Dataset B (mean 29.3, median 11 citations per document; h-index 85, g-index 148), while 9.6% and 10.3% of documents in the respective datasets were uncited (Table 1).

Annual output rose slowly until the early 2000s and then accelerated in both corpora, peaking in 2022 at 436 and 103 articles, respectively (Figure 1). More than half of all articles were published after 2014.

Sources

The *Journal of AAPOS* (n=252), *Investigative Ophthalmology & Visual Science* (n=242), and the *British Journal of Ophthalmology* (n=195) led Dataset A, whereas *Ophthalmology* and *Retina* (n=79 each) led Dataset B (Table 2). Bradford's law identified a core zone of 16 journals in Dataset A but only 8 in Dataset B, indicating that post-treatment research is published in a more concentrated set of journals. *Pediatrics* had the highest source h-index in Dataset A (h=77; 17,346 citations from 164 articles) and *Ophthalmology* in Dataset B (h=47). The most locally co-cited sources were *Pediatrics* and *Archives of Ophthalmology* in Dataset A and *Ophthalmology* and *Archives of Ophthalmology* in Dataset B, confirming the dual paediatric-ophthalmic identity of the general literature and the strictly ophthalmic identity of the treatment literature.

Authors and Institutions

Quinn GE was the most productive author in both corpora (123 and 50 articles) and had the highest author h-index in Dataset A (h=45; 11,116 citations), followed by Chiang MF (n=121), Hellström A (n=106), Chan RVP (n=91), and Campbell JP (n=88), the last having by far the highest m-index (2.50). Wu WC (n=47), Palmer EA (n=44), Tung B (n=43), and Dobson V (n=42) followed in Dataset

Table 1. Main bibliometric characteristics of the two datasets

Indicator	Dataset A (general)	Dataset B (post-treatment)
Timespan	1980-2026	1980-2026
Documents (original articles)	6,946	1,296
Sources (journals)	1,035	238
Annual growth rate (%)	6.87	9.15
Average document age (years)	12.1	10.9
Cited references	92,252	12,982
Keywords Plus (ID)	5,857	1,257
Author Keywords (DE)	6,832	1,255
Authors	24,298	5,557
Single-authored documents	271	48
Co-authors per document	6.89	7.29
International co-authorships (%)	16.48	12.19
Total citations	201,451	37,976
Mean citations per document	29.0	29.3
Median citations per document	11	11
Uncited documents, n (%)	664 (9.6)	134 (10.3)
h-index	153	85
g-index	268	148

Dataset A: general long-term outcomes of retinopathy of prematurity. Dataset B: long-term outcomes after treatment for retinopathy of prematurity. Citation metrics were computed from the exported Web of Science records

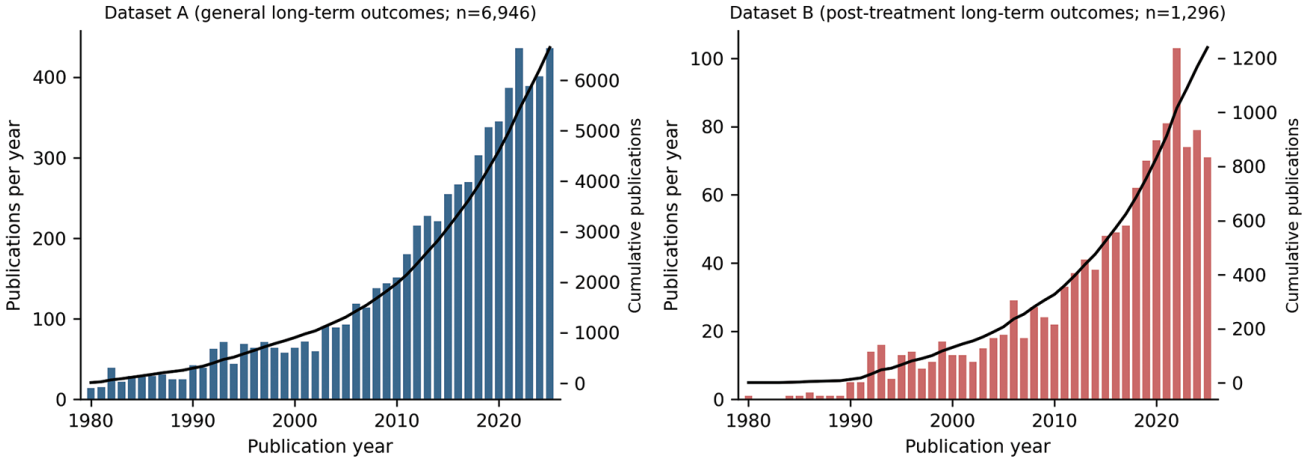


Figure 1. Annual and cumulative scientific production in the two datasets, 1980-2025. Bars show publications per year (left axis) and the black line shows cumulative output (right axis). 2026 is omitted because indexing for that year was incomplete at the time of the search

Table 2. Ten most productive sources in each dataset

Rank	Dataset A - source	n	Dataset B - source	n
1	*Journal of AAPOS*	252	*Ophthalmology*	79
2	*Investigative Ophthalmology & Visual Science*	242	*Retina*	79
3	*British Journal of Ophthalmology*	195	*Archives of Ophthalmology*	58
4	*Ophthalmology*	173	*Journal of AAPOS*	58
5	*Pediatrics*	164	*American Journal of Ophthalmology*	52
6	*Journal of Pediatric Ophthalmology & Strabismus*	158	*British Journal of Ophthalmology*	51
7	*Retina*	150	*Indian Journal of Ophthalmology*	44
8	*Eye*	142	*Eye*	42
9	*Archives of Ophthalmology*	139	*Journal of Pediatric Ophthalmology & Strabismus*	41
10	*American Journal of Ophthalmology*	130	*Graefe's Archive for Clinical and Experimental Ophthalmology*	39

Bradford zone 1 comprised 16 journals in Dataset A and 8 journals in Dataset B

B. Lotka's law was satisfied in both corpora, with 69.5% and 72.6% of authors contributing a single document. Harvard University (n=631) and the University of Pennsylvania (n=424) led the affiliations in Dataset A, while Chang Gung Memorial Hospital (n=118) led Dataset B. The University of Health Sciences Türkiye, with 164 articles, was the most productive Turkish institution and ranked twentieth overall in Dataset A.

Countries and Collaboration

The United States led both corpora as the corresponding-author country (2,235 articles, 32.2% of Dataset A; 407 articles, 31.4% of Dataset B), followed by China. Türkiye ranked third in Dataset A (426 articles, 6.1%) and fourth in Dataset B (116 articles, 9.0%), reflecting a higher relative share in the post-treatment corpus than in the general corpus (Table 3). However, Türkiye exhibited the lowest multiple-country publication rate of any leading country in both corpora (0.9% for both), compared with 15.3% for the United States, 24.8% for the United Kingdom, and 38.5% for Sweden in Dataset A (Figure 2). Türkiye's mean respective citation rates were 10.5 and 10.7 per article, versus 40.6 and 48.0 for the United States and 52.8 and 59.6 for the United Kingdom.

Most Cited Documents

The most globally cited document in Dataset A was the revised ICROP of 2005 (2,444 citations), followed by the 2015 Neonatal Research Network trends report (2,221 citations) and the original oxygen-induced retinopathy model description (1,570 citations). The Early Treatment for ROP (ETROP) trial (1,502 citations), BEAT-ROP (1,160

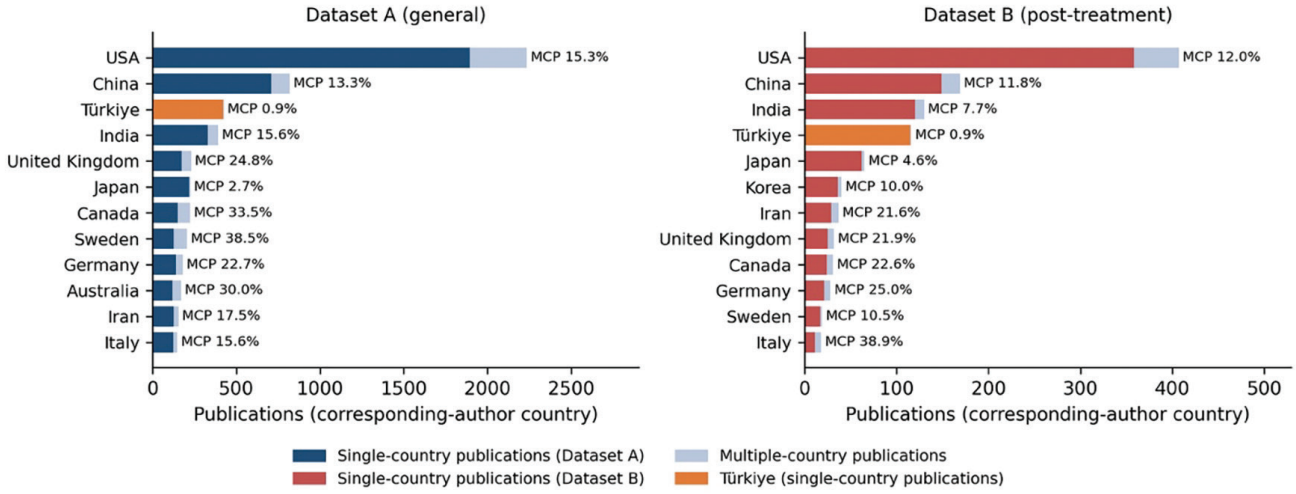


Figure 2. Twelve most productive corresponding-author countries in each dataset, partitioned into single-country and multiple-country publications. Türkiye is highlighted in orange
MCP: Multiple-country publications

Table 3. Ten most productive corresponding-author countries and their collaboration patterns and citation impact

Country	Dataset A			Dataset B		
	Articles (%)	MCP (%)	Citations/article	Articles (%)	MCP (%)	Citations/article
USA	2,235 (32.2)	15.3	40.6	407 (31.4)	12.0	48.0
China	818 (11.8)	13.3	14.6	169 (13.0)	11.8	18.0
Türkiye	426 (6.1)	0.9	10.5	116 (9.0)	0.9	10.7
India	391 (5.6)	15.6	11.6	130 (10.0)	7.7	11.2
United Kingdom	230 (3.3)	24.8	52.8	32 (2.5)	21.9	59.6
Japan	225 (3.2)	2.7	17.3	65 (5.0)	4.6	17.8
Canada	224 (3.2)	33.5	43.3	31 (2.4)	22.6	35.5
Sweden	205 (3.0)	38.5	40.3	19 (1.5)	10.5	18.3
Germany	181 (2.6)	22.7	31.8	28 (2.2)	25.0	33.1
Korea	144 (2.1)	9.0	21.6	40 (3.1)	10.0	23.9

MCP: Multiple-country publications, expressed as a percentage of that country's corresponding-author output

citations), the SUPPORT oxygen-saturation trial (766 citations), and the 2018 American Academy of Pediatrics screening statement (539 citations) headed Dataset B (Table 4).[17,18,19,20,21,22,23,24,25] Local citation analysis reordered these documents: ICROP-2005 and ETROP dominated Dataset A, whereas BEAT-ROP was the most locally cited document in Dataset B, confirming that the post-treatment literature is organised around anti-VEGF therapy.

Conceptual Structure

Keyword co-occurrence analysis identified four clusters in Dataset A and five in Dataset B. In Dataset A, these were labelled "retinopathy of prematurity" (66 terms; 11,792 occurrences), "preterm infants" (89 terms; 10,008 occurrences), "endothelial growth factor" (57 terms; 6,279 occurrences), and "bevacizumab" (38 terms; 4,453 occurrences). In Dataset B, the clusters were "retinopathy of prematurity" (80 terms; 3,694 occurrences), "infants" (57 terms; 1,911 occurrences), "outcomes" (50 terms; 1,009 occurrences), "retinal detachment" (32 terms; 696 occurrences), and "prematurity" (27 terms; 583 occurrences). On the thematic map (Figure 3), no cluster in Dataset B reached the motor-theme quadrant, whereas the outcome-related clusters "retinal detachment" and "outcomes" occupied the low-centrality, high-density quadrant characteristic of niche themes. In Dataset A, the "bevacizumab" cluster fell in the low-centrality, low-density quadrant of emerging or declining themes.

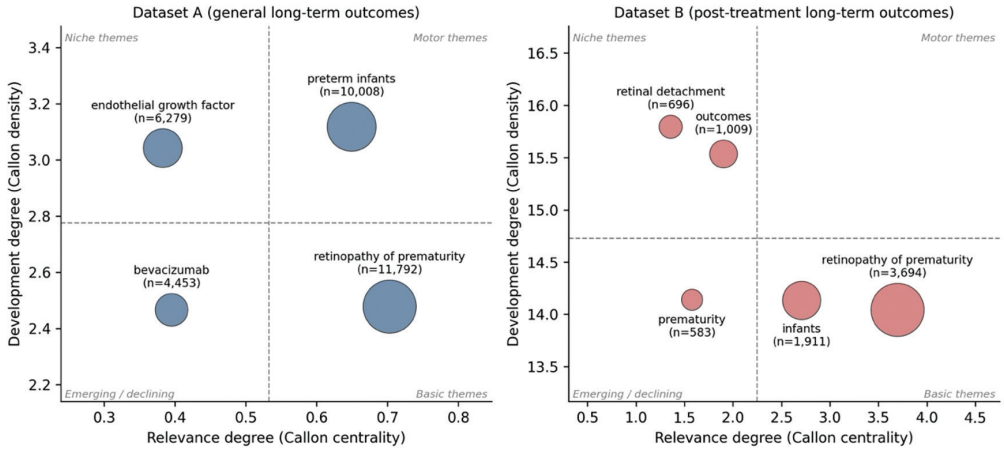


Figure 3. Thematic map of keyword co-occurrence clusters. The horizontal axis is Callon centrality (relevance degree) and the vertical axis is Callon density (development degree); dashed lines mark the corpus means and bubble size is proportional to cluster frequency

Table 4. Five most globally cited documents in each dataset

Dataset	First author, year, journal	Total citations	Citations/year
A	Gole GA, 2005, *Arch Ophthalmol* (ICROP revisited)[17]	2,444	111.1
	Stoll BJ, 2015, *JAMA*[18]	2,221	185.1
	Smith LEH, 1994, *Invest Ophthalmol Vis Sci*[19]	1,570	47.6
	Good WV, 2003, *Arch Ophthalmol* (ETROP)[20]	1,502	62.6
	Alon T, 1995, *Nat Med*[21]	1,330	41.6
B	Good WV, 2003, *Arch Ophthalmol* (ETROP)[20]	1,502	62.6
	Mintz-Hittner HA, 2011, *N Engl J Med* (BEAT-ROP)[22]	1,160	72.5
	Carlo WA, 2010, *N Engl J Med* (SUPPORT)[23]	766	45.1
	Fierson WM, 2018, *Pediatrics*[24]	539	59.9
	Costeloe KL, 2012, *BMJ* (EPICure-2)[25]	532	35.5

Citation counts are those recorded in the Web of Science Core Collection on July 21, 2026

Representation of the Four Outcome Domains

The lexicon matched 2,514 keyword occurrences in Dataset A (4.32% of 58,218) and 952 in Dataset B (8.87% of 10,734). Visual and refractive outcomes formed the best-represented domain in both corpora (1.95% and 4.07%), primarily attributable to myopia, blindness, visual acuity, and visual impairment. Structural retinal and macular sequelae accounted for 0.89% and 1.88%, led by optical coherence tomography, retinal detachment, and choroidal thickness. Late post-treatment complications accounted for 0.88% and 2.56%, led by follow-up, reactivation, complication, and cataract. Neurodevelopmental and quality-of-life outcomes were the least represented in both corpora (0.60% and 0.35%) (Table 5, Figures 4 and 5).

Compared with the general corpus, the post-treatment corpus more prominently featured late complications (representation ratio 2.91), visual and refractive outcomes (2.08), and structural retinal and macular sequelae (2.12). Conversely, neurodevelopmental and quality-of-life outcomes showed reduced representation in the post-treatment literature (0.59), constituting the domain with the lowest proportion of predefined lexicon terms appearing (13 of 24).

Thematic Evolution

Trend topic analysis showed the temporal distribution of terms with a median publication year of 2010 or later (Figure 6). Recent terms included anti-VEGF and reactivation (median year 2022), deep learning (2023), angiography and artificial intelligence (2024), and extremely low gestational age neonates (2026) in Dataset

A and anti-VEGF, reactivation, and type 1 retinopathy (2022), angiography (2023), and persistent avascular retina (2024) in Dataset B. Neither corpus contained recent trend terms explicitly denoting neurodevelopmental outcomes or quality of life. This finding was consistent with the outcome domain analysis, in which neurodevelopmental and quality-of-life outcomes were the least represented domain.

Discussion

This dual-corpus analysis of 6,946 general and 1,296 post-treatment articles shows a field that is growing quickly, is concentrated in a small number of journals and institutions, and is organised around anti-VEGF therapy. Our principal original finding is quantitative: when analysed using a predefined clinical outcome lexicon, research encompassing the transition from acute-phase treatment to survivorship proves selective rather than general. Three of four domains were enriched two- to three-fold in the post-treatment corpus, as would be expected if treatment trials had begun to report longer follow-up. The fourth—neurodevelopmental and quality-of-life outcomes—moved in the opposite direction.

This asymmetry has a plausible explanation and an uncomfortable implication. The explanation is disciplinary: post-treatment outcome research is published in a narrower, more strictly ophthalmic set of journals (8 core journals according to Bradford's law, against 16 in the general corpus), whereas neurodevelopmental endpoints belong to the paediatric and neonatal literature that dominates

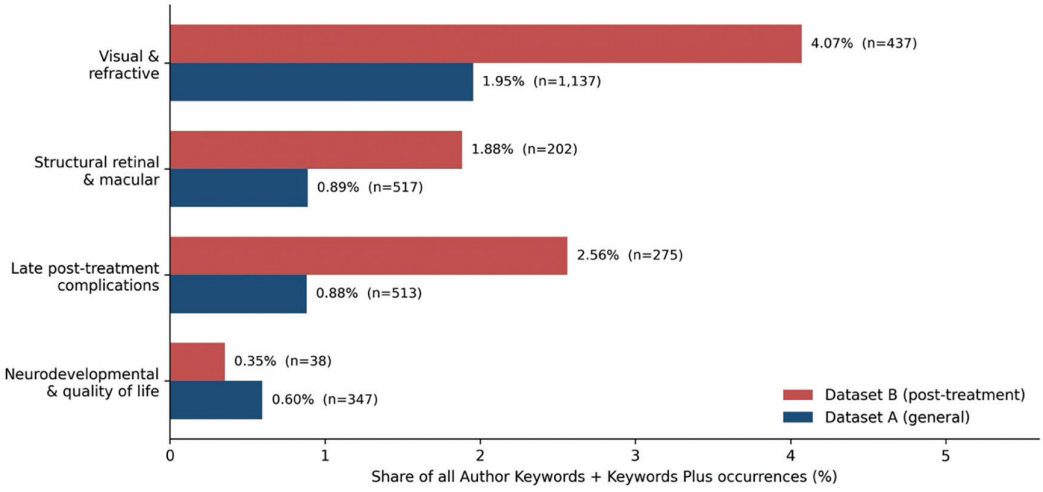


Figure 4. Representation of the four long-term outcome domains, expressed as the percentage of all merged Author Keywords and Keywords Plus occurrences in each dataset. Absolute occurrence counts are shown in parentheses. Three domains are enriched in the post-treatment dataset; neurodevelopmental and quality-of-life outcomes are not

Table 5. Representation of the four long-term outcome domains across the two datasets

Outcome domain	Lexicon terms (n)	Dataset A	Dataset B	Representation ratio (95% CI)	p
		matched terms/occurrences/share			
Visual and refractive outcomes	26	25/1,137/1.95%	25/437/4.07%	2.08 (1.87-2.32)	<0.001
Structural retinal and macular sequelae	27	22/517/0.89%	21/202/1.88%	2.12 (1.80-2.49)	<0.001
Late post-treatment complications	18	17/513/0.88%	16/275/2.56%	2.91 (2.51-3.36)	<0.001
Neurodevelopmental and quality-of-life outcomes	24	23/347/0.60%	13/38/0.35%	0.59 (0.43-0.83)	0.003
All domains combined	95	87/2,514/4.32%	75/952/8.87%	-	-

Share is the percentage of all merged Author Keywords and Keywords Plus occurrences in that dataset (58,218 in Dataset A; 10,734 in Dataset B). The representation ratio is the share in Dataset B divided by the share in Dataset A. p values are from the chi-square test comparing each domain against the remainder of the corpus. The overall distribution of domain-tagged occurrences differed between datasets (chi-square 81.89, df 3, p<0.001)
CI: Confidence interval

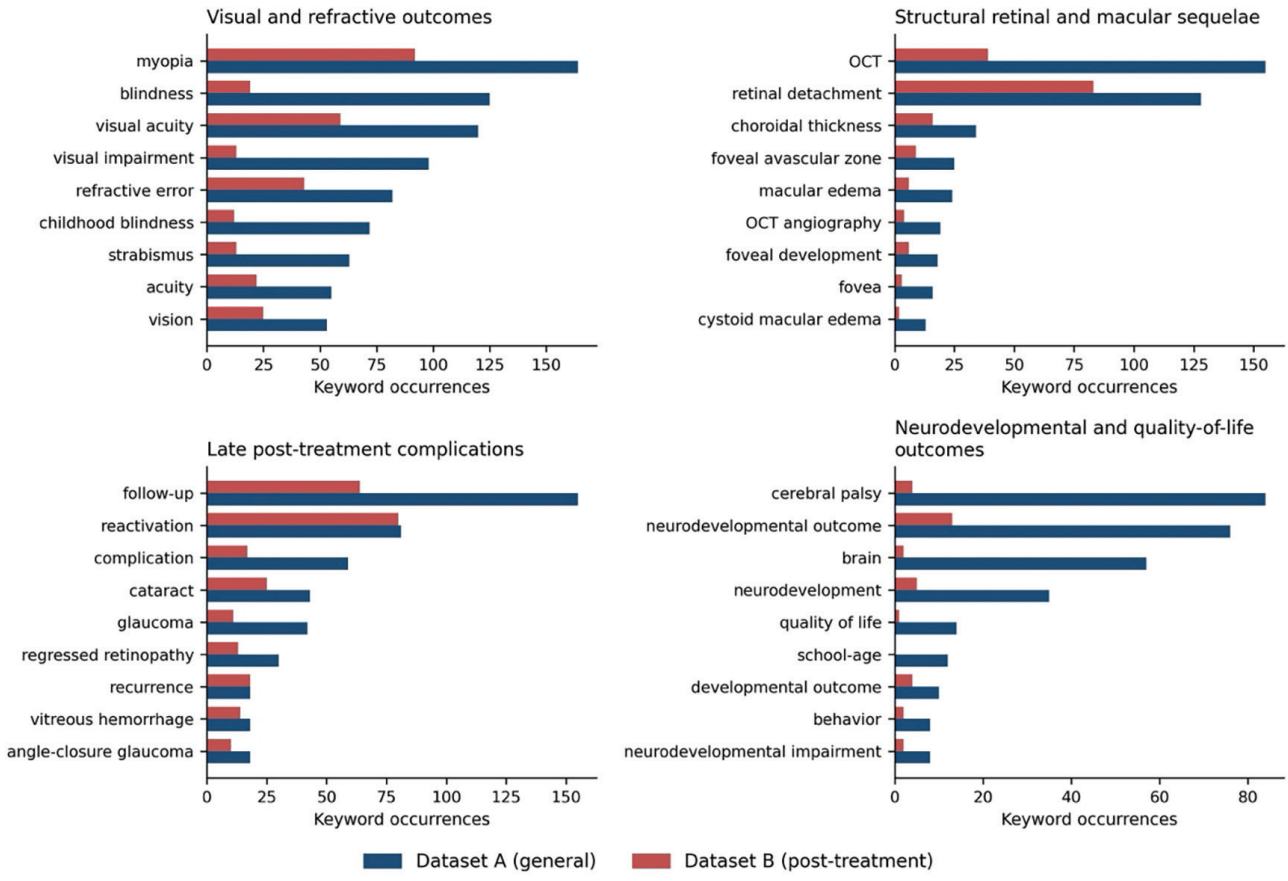


Figure 5. Most frequent lexicon terms within each of the four outcome domains
OCT: Optical coherence tomography

the general corpus, where *Pediatrics* has the highest source h-index. The implication is that the very studies best positioned to answer whether anti-VEGF agents affect the developing brain (those following the treated cohorts) are the least likely to report neurodevelopmental endpoints. Given the documented systemic escape of bevacizumab[26] and the association between severe ROP and adverse cognitive, motor, and behavioural outcomes,[10,11,27] this is a substantive evidence gap rather than a bibliometric artefact. RAINBOW and FIREFLEYE show that long follow-up in ROP trials is feasible.[8,9] Adding validated developmental instruments to their outcome sets would be a small incremental cost.

The temporal analysis reinforces this interpretation. Recent trend topics include anti-VEGF, reactivation, persistent avascular retina, and artificial intelligence. Reactivation and persistent avascular retina are concepts formalised by ICROP3 that are relevant to long-term follow-up.[1] Their presence among recent research themes suggests increasing attention to long-term anatomical monitoring. However, this attention has not been accompanied by a comparable increase in the assessment of visual function and neurodevelopmental outcomes. Long-term anatomical monitoring may therefore not be matched by equally comprehensive functional and neurodevelopmental assessment. The absence of recent trend terms explicitly denoting neurodevelopmental outcomes or quality of life in either corpus suggests that this evidence gap persists despite the growing emphasis on long-term follow-up after ROP treatment.

The findings also carry a specific message for Turkish ophthalmology. Türkiye is the third most productive country in the general corpus and the fourth in the post-treatment corpus, and its relative share is higher in the post-treatment literature. This is a creditable position for a middle-income setting with a large preterm population, and consistent with the national infrastructure demonstrated by the TR-ROP study across 69 neonatal intensive care units.[28] Turkish groups have

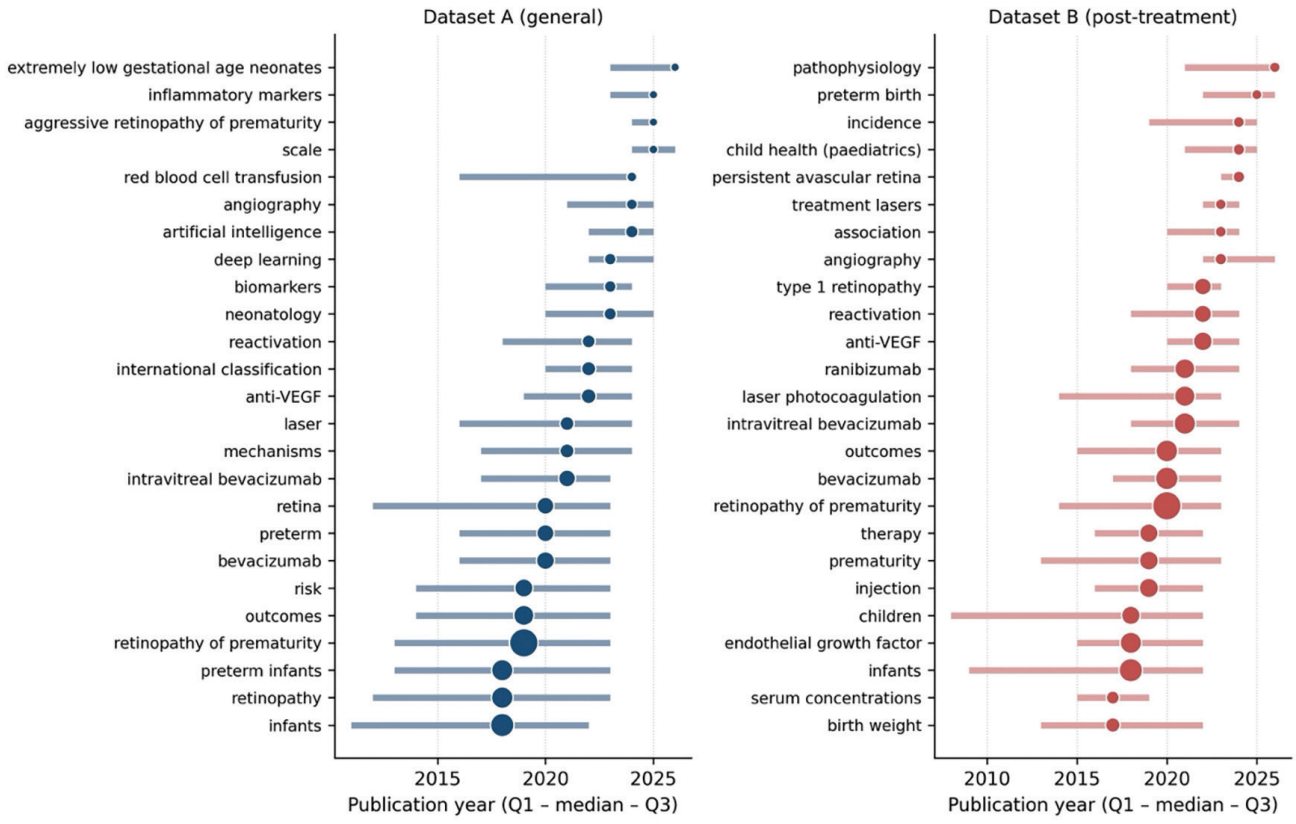


Figure 6. Trend topics with a median publication year of 2010 or later. Horizontal bars span the first to third quartile of the year distribution for each term and the marker denotes the median year; marker size is proportional to term frequency

contributed directly to the domains examined here, including work on macular ectopia and strabismus, on rhegmatogenous detachment in regressed ROP, on foveal hypoplasia and peripheral vitreoretinal interface abnormalities, and on the long-term refractive consequences of different treatment approaches.[5,6,29,30,31] Yet Türkiye's multiple-country publication rate of below 1% is the lowest among all leading countries, and its citation rate per article is one-fifth that of the United Kingdom. The same pattern of high productivity with low international collaboration and low citation impact has been reported for Turkish retinoblastoma and uveal melanoma research.[32,33] Because long-term outcome studies require large samples and prolonged follow-up, they are precisely the studies for which cross-border collaboration yields the greatest return. Embedding Turkish cohorts in international consortia and adding neurodevelopmental and quality-of-life instruments to follow-up protocols already in place would raise both the impact and the clinical value of this substantial national output.

Our results align with the three previous ROP bibliometric studies in identifying the United States as the leading country, anti-VEGF therapy and artificial intelligence as the dominant recent themes, and a small group of authors as central to the field.[14,15,16] They extend those studies by taking long-term outcomes as the unit of analysis, by contrasting a general with a treatment-specific corpus, and by replacing qualitative cluster labelling with a predefined, reproducible lexicon applicable to any future corpus.

Study Limitations

Several limitations should be acknowledged. First, only the Web of Science Core Collection was searched; Scopus, PubMed, and the Turkish TR Dizin database were not included. Although this approach preserved the consistency of the keyword-level analysis, it may have excluded some relevant studies, particularly those published in Turkish. Second, the analysis was restricted to English-language original research articles, excluding reviews, editorials, and non-English publications. As a result, the scientific contributions of countries that predominantly publish in their native languages may be underrepresented. Third, keyword-based analyses depend on the quality and consistency of indexing. Consequently, some studies may

have reported neurodevelopmental outcomes without including the relevant lexicon terms as keywords, leading to their underrepresentation in the analysis. Therefore, the reported proportions should be interpreted as indicators of the relative representation of outcome domains rather than estimates of their true prevalence. Fourth, because the two datasets overlapped by design, comparisons were descriptive in nature, and the chi-square tests should be interpreted as summaries of the observed differences in domain composition rather than as inferential analyses of a broader population of articles. Fifth, as the literature search was conducted before the completion of indexing for 2026, analyses of the most recent research trends were based on a smaller number of publications. Sixth, although the predefined lexicon demonstrated a high level of agreement between two independent ROP experts during its development, its evaluation was limited to two reviewers and did not involve a formal Delphi consensus process. Therefore, future studies using larger multidisciplinary expert panels may further refine and validate the proposed classification. Finally, bibliometric indicators reflect the visibility and research attention devoted to a topic rather than its methodological quality. Accordingly, a well-represented domain should not be assumed to have a correspondingly strong evidence base.

Conclusion

Incorporating validated developmental and quality-of-life instruments into ROP treatment cohort studies and embedding the substantial Turkish output in international collaborative networks are the two changes most likely to improve both the impact and the clinical usefulness of this literature.

Ethics

Ethics Committee Approval: Not required, as this study analysed publicly available bibliographic metadata and involved no human participants or animals.

Informed Consent: Not required, as this study analysed publicly available bibliographic metadata and involved no human participants or animals.

Declarations

Authorship Contributions:

Concept: E.K., Design: E.K., Y.O., Data Collection or Processing: E.K., M.N.G., Analysis or Interpretation: E.K., S.N.P., Literature Search: E.K., Y.O., Writing: E.K.

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

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

Declaration on the use of Artificial Intelligence (AI): During the preparation of this work, the authors used AI-based tools for bibliometric data processing, figure preparation and language editing. All analyses, interpretations and references were verified by the authors, who reviewed and edited the content and take full responsibility for it.

References

1. Chiang MF, Quinn GE, Fielder AR, Ostmo SR, Paul Chan RV, Berrocal A, Binenbaum G, Blair M, Peter Campbell J, Capone A Jr, Chen Y, Dai S, Ells A, Fleck BW, Good WV, Elizabeth Hartnett M, Holmstrom G, Kusaka S, Kychenthal A, Lepore D, Lorenz B, Martinez-Castellanos MA, Özdek Ş, Ademola-Popoola D, Reynolds JD, Shah PK, Shapiro M, Stahl A, Toth C, Vinekar A, Visser L, Wallace DK, Wu WC, Zhao P, Zin A. International Classification of Retinopathy of Prematurity, Third Edition. Ophthalmology. 2021;128:e51-e68.
2. Blencowe H, Lawn JE, Vazquez T, Fielder A, Gilbert C. Preterm-associated visual impairment and estimates of retinopathy of prematurity at regional and global levels for 2010. Pediatr Res. 2013;74(Suppl 1):35-49.
3. Wong ES, Choy RW, Zhang Y, Chan HY, Chen LJ, Pang CP, Tham CC, Yam JC. Global and regional trends in retinopathy of prematurity. JAMA Ophthalmol. 2026;144:139-147.
4. Hamad AE, Moinuddin O, Blair MP, Schechet SA, Shapiro MJ, Quiram PA, Mammo DA, Berrocal AM, Prakhunhungsit S, Cernichiaro-Espinosa LA, Mukai S, Yonekawa Y, Ung C, Holz ER, Harper CA 3rd, Young RC, Besirli CG, Nagiel A, Lee TC, Gupta MP, Walsh MK, Khawly JA, Campbell JP, Kychenthal A, Nudleman ED, Robinson JE, Hartnett ME, Calvo CM, Chang EY. Late-onset retinal findings and complications in untreated retinopathy of prematurity. Ophthalmol Retina. 2020;4:602-612.
5. Özdemir HB, Özdek S. Late sequelae of retinopathy of prematurity in adolescence and adulthood. Saudi J Ophthalmol. 2022;36:270-277.
6. Şahin Karamert S, Atalay HT, Özdek Ş. Strabismus in retinopathy of prematurity: risk factors and the effect of macular ectopia. Turk J Ophthalmol. 2023;53:241-246.
7. Hsu HT, Yu-Chuan Kang E, Blair MP, Shapiro M, Komati R, Hubbard BG, Price KW, Capone A Jr, Drenser KA, Trese MT, Shields R, Kondo H, Matsushita I, Yonekawa Y, Patel SN, Kusaka S, Mano F, Olsen KR, Ells A, Amphornphruet A, Walsh MK, Besirli CG, Moinuddin O, Baumal CR, Enriquez AB, Hwang YS, Lai CC, Wu WC. Late vitreoretinal complications of regressed retinopathy of prematurity: retinal break, vitreous hemorrhage, and retinal detachment. Ophthalmol Retina. 2023;7:72-80.
8. Stahl A, Lepore D, Fielder A, Fleck B, Reynolds JD, Chiang MF, Li J, Liew M, Maier R, Zhu Q, Marlow N. Ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW): an open-label randomised controlled trial. Lancet. 2019;394:1551-1559.
9. Stahl A, Sukgen EA, Wu WC, Lepore D, Nakanishi H, Mazela J, Moshfeghi DM, Vitti R, Athanikar A, Chu K, Iveli P, Zhao F, Schmelter T, Leal S, Köfüncü E, Azuma N; FIREFLEYE Study Group. Effect of intravitreal aflibercept vs laser photocoagulation on treatment success of retinopathy of prematurity: the FIREFLEYE randomized clinical trial. JAMA. 2022;328:348-359.

10. Quinn GE, Dobson V, Saigal S, Phelps DL, Hardy RJ, Tung B, Summers CG, Palmer EA; CRYO-ROP Cooperative Group. Health-related quality of life at age 10 years in very low-birth-weight children with and without threshold retinopathy of prematurity. Arch Ophthalmol. 2004;122:1659-1666.
11. Lundgren P, Olsson HBK, Pivodic A, Jacobson L, Vallin L, Smith LE, Sävman K, Hellström A. Increased risk of autism in extremely preterm children with a history of retinopathy of prematurity. Acta Paediatr. 2025;114:1161-1168.
12. Donthu N, Kumar S, Mukherjee D, Pandey N, Lim WM. How to conduct a bibliometric analysis: an overview and guidelines. J Bus Res. 2021;133:285-296.
13. Aria M, Cuccurullo C. Bibliometrix: an R-tool for comprehensive science mapping analysis. J Informetr. 2017;11:959-975.
14. Zhang Y, Chai X, Fan Z, Zhang S, Zhang G. Research hotspots and trends in retinopathy of prematurity from 2003 to 2022: a bibliometric analysis. Front Pediatr. 2023;11:1273413.
15. Gao J, Fang N, Xu Y. Application of artificial intelligence in retinopathy of prematurity from 2010 to 2023: a bibliometric analysis. Health Sci Rep. 2025;8:e70718.
16. Pirdankar OH, Nene AS, Thakur R, Shah S, Shenoy P, Badole P. Intravitreal anti-vascular endothelial growth factor in retinopathy of prematurity: a bibliometric analysis. J Pediatr Ophthalmol Strabismus. 2026:1-10.
17. International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol. 2005;123:991-999.
18. Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, Laptook AR, Sánchez PJ, Van Meurs KP, Wyckoff M, Das A, Hale EC, Ball MB, Newman NS, Schibler K, Poindexter BB, Kennedy KA, Cotten CM, Watterberg KL, D'Angio CT, DeMauro SB, Truog WE, Devaskar U, Higgins RD; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. JAMA. 2015;314:1039-1051.
19. Smith LE, Wesolowski E, McLellan A, Kostyk SK, D'Amato R, Sullivan R, D'Amore PA. Oxygen-induced retinopathy in the mouse. Invest Ophthalmol Vis Sci. 1994;35:101-111.
20. Early Treatment For Retinopathy of Prematurity Cooperative Group. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. Arch Ophthalmol. 2003;121:1684-1694.
21. Alon T, Hemo I, Itin A, Pe'er J, Stone J, Keshet E. Vascular endothelial growth factor acts as a survival factor for newly formed retinal vessels and has implications for retinopathy of prematurity. Nat Med. 1995;1:1024-1028.
22. Mintz-Hittner HA, Kennedy KA, Chuang AZ; BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med. 2011;364:603-615.
23. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network; Carlo WA, Finer NN, Walsh MC, Rich W, Gantz MG, Laptook AR, Yoder BA, Faix RG, Das A, Poole WK, Schibler K, Newman NS, Ambalavanan N, Frantz ID 3rd, Piazza AJ, Sánchez PJ, Morris BH, Laroia N, Phelps DL, Poindexter BB, Cotten CM, Van Meurs KP, Duara S, Narendran V, Sood BG, O'Shea TM, Bell EF, Ehrenkranz RA, Watterberg KL, Higgins RD. Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med. 2010;362:1959-1969.
24. Fierson WM; American Academy of Pediatrics Section on Ophthalmology; American Academy of Ophthalmology; American Association for Pediatric Ophthalmology and Strabismus; American Association of Certified Orthoptists. Screening examination of premature infants for retinopathy of prematurity. Pediatrics. 2018;142:e20183061. Erratum in: Pediatrics. 2019;143:e20183810.
25. Costeloe KL, Hennessy EM, Haider S, Stacey F, Marlow N, Draper ES. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). BMJ. 2012;345:e7976.
26. Sato T, Wada K, Arahori H, Kuno N, Imoto K, Iwahashi-Shima C, Kusaka S. Serum concentrations of bevacizumab (Avastin) and vascular endothelial growth factor in infants with retinopathy of prematurity. Am J Ophthalmol. 2012;153:327-333.e1.
27. Tan H, Blasco P, Lewis T, Ostmo S, Chiang MF, Campbell JP. Neurodevelopmental outcomes in preterm infants with retinopathy of prematurity. Surv Ophthalmol. 2021;66:877-891.
28. Bas AY, Demirel N, Koc E, Ulubas Isik D, Hirfanoglu İM, Tunc T; TR-ROP Study Group. Incidence, risk factors and severity of retinopathy of prematurity in Turkey (TR-ROP study): a prospective, multicentre study in 69 neonatal intensive care units. Br J Ophthalmol. 2018;102:1711-1716.
29. Özdemir Zeydanlı E, Özdek Ş, Küçükbalcı T. Surgical outcomes of rhegmatogenous retinal detachment associated with regressed retinopathy of prematurity. Turk J Ophthalmol. 2024;54:223-227.
30. Kizilay O, Kunbaz A, Akarsu Acar OP, Gunay M, Celik G. Impact of different treatment approaches on long-term refractive and visual outcomes in retinopathy of prematurity. Int J Ophthalmol. 2026;19:1107-1116.
31. Çelik G, Oto BB, Kizilay O, Gunay M. Evaluation of foveal hypoplasia in children with a history of retinopathy of prematurity. Retina. 2025;45:660-666.
32. Aykut A, Sarıgül Sezenöz A. Turkish retinoblastoma research: a bibliometric analysis (1966-2024). Turk J Ophthalmol. 2024;54:282-290.
33. Aykut A, Sezenoz AS. Turkish uveal melanoma research: a bibliometric analysis (1987-2024). European Eye Research. 2024;4:141-149.

Original Article

Comparison of Optical Coherence Tomography Biomarkers in Nonproliferative and Proliferative Diabetic Retinopathy: Marmasia Study Group Report No. 2

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Abstract

Objectives: To compare structural optical coherence tomography (OCT) biomarkers and visual acuity between eyes with nonproliferative (NPDR) and proliferative diabetic retinopathy (PDR) in real-life clinical settings.

Materials and Methods: This retrospective, cross-sectional, multicentre study included 818 eyes of 534 patients with treatment-naive diabetic macular oedema (DMO) from nine tertiary clinics. Evaluated parameters included central macular thickness (CMT), DMO morphology, disorganisation of the retinal inner layers, ellipsoid zone (EZ) integrity, vitreoretinal interface abnormality (VRIA), and posterior hyaloid status. Analyses used eye-level data with patient-clustered robust standard errors and study-centre fixed effects. A joint multivariable logistic model mutually adjusted EZ integrity, posterior hyaloid status and VRIA together with clinical covariates, with Holm correction across six structural-domain tests.

Results: Of the 818 eyes, 646 had NPDR and 172 PDR. Mean best-corrected visual acuity (BCVA) was worse in PDR (0.74±0.54 versus 0.57±0.42 logarithm of the minimum angle of resolution; p<0.001). In univariable clustered comparisons, no biomarker survived false

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Abstract

discovery rate correction across ten comparisons (lowest q=0.095, VRIA). In the joint model (636 eyes, 431 clusters), none survived Holm correction: posterior hyaloid detachment was nominally associated with PDR (odds ratio [OR] 2.03, 95% confidence interval [CI] 1.05-3.92; Holm p=0.208), the global EZ term was not significant (p=0.221), and VRIA was not significant after adjustment for posterior hyaloid status (OR 1.36, 95% CI 0.67-2.75; p=0.388). Centre-adjusted CMT did not differ (p=0.890). Secondarily, PDR, disrupted EZ, higher CMT and VRIA were each associated with worse BCVA.

Conclusion: In treatment-naive DMO, no structural OCT biomarker was independently associated with proliferative disease after accounting for fellow-eye correlation, centre effects, mutual adjustment, and multiplicity. Posterior hyaloid detachment gave the most consistent nominal signal, and the vitreoretinal interface variables carried overlapping rather than independent information. These findings do not establish prognosis.

Keywords: Diabetic retinopathy, diabetic macular oedema, ellipsoid zone, OCT biomarkers, vitreoretinal interface

Introduction

Diabetes mellitus affects about 460 million people worldwide, and diabetic retinopathy (DR) is its most common microvascular complication.[1] DR is classified as either nonproliferative (NPDR) or proliferative (PDR). PDR is characterised by new blood vessel growth caused by severe retinal ischaemia.[2] Vision loss in DR most frequently results from diabetic maculopathy, including diabetic macular oedema (DMO) and ischaemic maculopathy, as well as PDR-related complications such as vitreous haemorrhage and tractional retinal detachment.[3] DMO can develop at any stage of DR, with the risk increasing as disease duration and severity increase.[3,4]

The main imaging methods for DR are colour fundus photography, fundus fluorescein angiography (FFA), and optical coherence tomography (OCT). FFA shows leakage and blood flow, while OCT provides detailed cross-sectional images and retinal thickness measurements, which are important for making treatment decisions and monitoring progress.[5]

Studies of macular oedema structural features have shown links between DR stage and vision impairment.[6,7,8] This has led to different DMO classification systems incorporating features such as diffuse retinal thickening, cystoid macular oedema, subretinal fluid (SRF), and disorganisation of the retinal inner layers (DRIL).[6,9,10,11] Advances in technology have also improved our understanding of vitreoretinal interface disorders and the importance of the ellipsoid zone (EZ) and external limiting membrane (ELM) for prognosis.[12] In this study, we compared structural OCT biomarkers between NPDR and PDR eyes with untreated DMO in a large multicentre group, using methods that consider correlations between eyes, differences between centres, and adjustments for multiple biomarkers and comparisons.

Materials and Methods

This retrospective, cross-sectional, multicentre study was conducted within the MARMASIA Study Group, a network of retina specialists at nine tertiary ophthalmology departments in İstanbul, Kocaeli, and Sakarya, Türkiye. The Institutional Review Board of Kocaeli University Faculty of Medicine approved the study protocol (no: GOKAEK-2022/07.19, date: 14.04.2022), which followed the ethical principles of the 1964 Declaration of Helsinki and later amendments. Written informed consent for the use of their medical data for research purposes was obtained from all patients at their initial presentation. The study is registered on ClinicalTrials.gov (number: NCT05472376).

Eligible patients were aged 18 years or older with type 1 or type 2 diabetes mellitus and treatment-naive DMO at the index examination, defined as no previous intravitreal injection and no previous macular (focal, grid, or micropulse) laser. Panretinal photocoagulation (PRP) performed more than four months before the index visit was permitted. Of the included eyes, 115 (75 with NPDR and 40 with PDR) had previously received PRP. Therefore, the cohort was treatment-naive for macular oedema but not globally naive to photocoagulation. We excluded eyes with phacoemulsification within 1 month, any laser within 4 months of the index visit, or a history of intravitreal injection or vitrectomy.

Eyes with a coexisting ocular condition capable of affecting macular architecture or visual acuity, such as retinal vein occlusion, age-related macular degeneration, uveitis, advanced glaucoma, or high myopia (spherical equivalent worse than -6.00 dioptres) were also excluded. Other exclusion criteria were media opacity precluding adequate imaging, scans below the recommended signal strength, haemodialysis, and pregnancy. Both eyes were included when eligible; within-patient correlation was accounted for in the statistical analyses.

Baseline data comprised age, sex, and diabetes duration. In addition, each participant underwent a standardised assessment including best-corrected visual acuity (BCVA) with an electronic Snellen chart, slit-lamp biomicroscopy, dilated fundoscopy, and OCT. Retinopathy

stage was assigned by the treating retina specialist on the basis of dilated fundus examination and colour fundus imaging, in accordance with the International Clinical Diabetic Retinopathy Disease Severity Scale.[2] FFA was obtained at the clinician's discretion during routine care, usually when neovascularisation was suspected, and, when available, was used to support staging. However, angiographic findings were not systematically recorded in the study dataset and were therefore unavailable for analysis.

Optical Coherence Tomography Assessment

OCT was performed using Spectralis (Heidelberg Engineering, Heidelberg, Germany), RS-3000 (Nidek, Gamagori, Japan), RTVue-100 (Optovue Inc., Fremont, CA, USA), or Triton (Topcon Corporation, Tokyo, Japan), depending on availability at each centre, with the macular cube or raster protocols on each device. We checked image quality and foveal centration before grading. Although acquisition protocols differed across devices, we graded biomarkers using shared predefined definitions.

The device software automatically calculated central macular thickness (CMT) after confirming foveal centration. Since platforms differ in the outer segmentation boundary—Spectralis measures from the internal limiting membrane to Bruch's membrane, others to the retinal pigment epithelium—absolute CMT values are not interchangeable. The platform used was determined solely by the equipment at each centre and was unrelated to retinopathy stage, ensuring device allocation was independent of group assignment.

Before study initiation, investigators met to standardise the assessment procedures. They jointly reviewed sample images and resolved any uncertain cases by reaching a consensus with the coordinating investigators. Cases were graded at each centre by retina specialists or experienced ophthalmologists. Graders were aware of retinopathy stage, as this information was available in the clinical records.

DMO was classified into four types according to Panozzo et al.[13] and the EURETINA guideline:[14] diffuse/spongious oedema, defined as sponge-like retinal swelling with reduced intraretinal reflectivity; cystoid oedema, defined as low-reflective intraretinal cystoid spaces separated by highly reflective septa; and each of these with SRF, defined as an optically clear space between the retina and the retinal pigment epithelium (Figure 1). Where both patterns coexisted, the predominant one was selected. Largest cyst

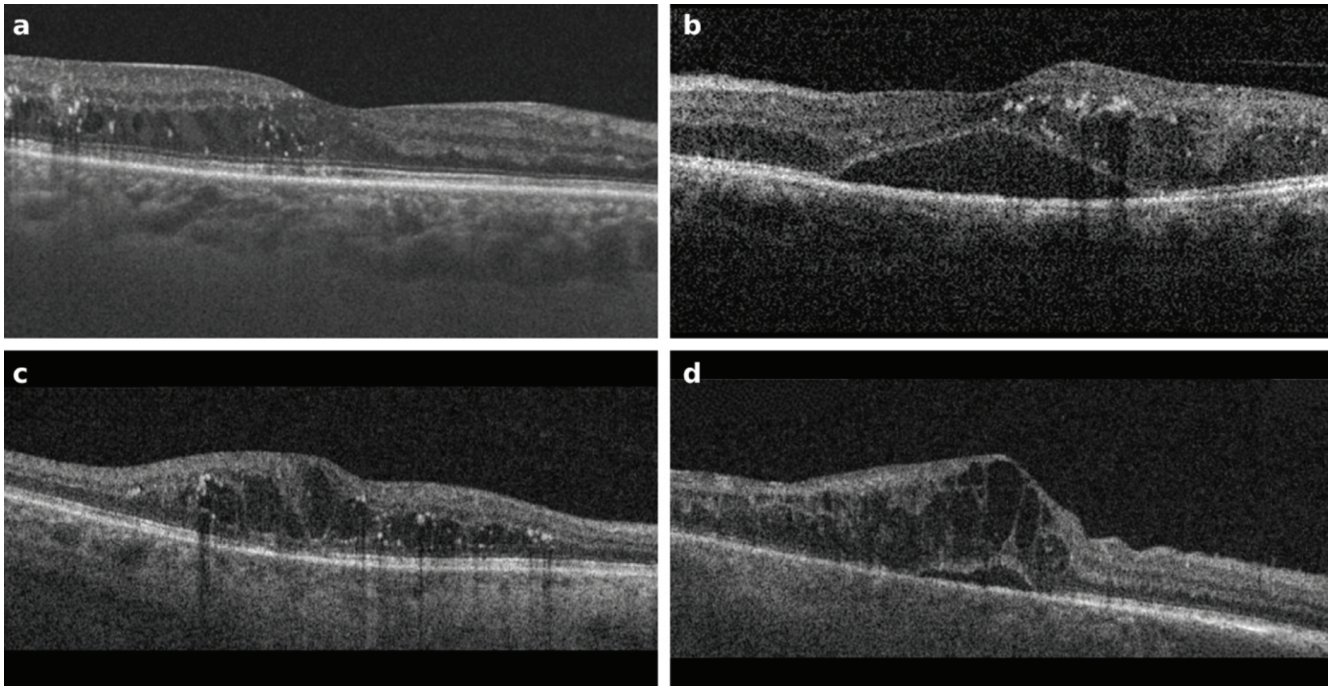


Figure 1. Representative spectral-domain optical coherence tomography B-scans of the four morphological types of diabetic macular oedema, obtained from eyes included in the present study. a) Diffuse/spongious oedema: sponge-like retinal swelling of the macula with reduced intraretinal reflectivity. b) Diffuse/spongious oedema with subretinal fluid: spongiform thickening accompanied by an optically clear space between the retina and the retinal pigment epithelium. c) Cystoid oedema: low-reflective intraretinal cystoid spaces with highly reflective septa. d) Cystoid oedema with subretinal fluid: cystoid oedema accompanied by an optically clear space between the retina and the retinal pigment epithelium

diameter and maximum vertical SRF height were measured with the calliper tool in the OCT software.

EZ and ELM integrity was assessed within a 500-µm fovea-centred region on the central scan and graded as disrupted (complete loss of the band), partially intact (continuous but attenuated or irregular), or intact. Scans with shadowing that prevented band assessment were classified as not evaluable and excluded from analysis.

DRIL was defined, in accordance with Sun et al.[15], as the inability to identify the boundaries between the ganglion cell–inner plexiform and inner nuclear-outer plexiform layer complexes over a minimum width of 500 µm in the central foveal region. Areas in which these layers were displaced, thinned, or compressed by cystoid spaces but whose boundaries remained identifiable were not graded as DRIL.

Vitreoretinal interface abnormalities (VRIA) comprised epiretinal membrane, vitreomacular adhesion, vitreomacular traction, and other tractional abnormalities of the macula. Posterior hyaloid status was classified as attached or detached where reliably visualised, and as not evaluable otherwise.

Statistical Analysis

We used SPSS version 26.0 (IBM Corp., Armonk, NY, USA) for descriptive statistics and R version 4.6.0 for all inferential analyses. Continuous data are shown as mean ± standard deviation, and categorical data as counts and percentages. Snellen BCVA was converted to logarithm of the minimum angle of resolution (logMAR) following standard testing protocols,[16] using 2.10 and 3.10 as equivalents for counting fingers and hand motions, respectively.

We analysed 818 eyes of 534 patients, including both eyes for 284 patients and one eye for the other 250. All eye-level comparisons and regression models used patient-clustered robust (sandwich) standard errors to account for correlation between fellow eyes. Retinopathy stage was concordant between fellow eyes in 93.7% of bilateral pairs (κ=0.814). For variables with more than two categories, we report a single global Wald test. Eyes where ELM integrity, EZ integrity, or posterior hyaloid status could not be graded were excluded from those comparisons. Differences in gradability between groups are discussed in the Study Limitations.

We compared ten OCT biomarkers between groups: CMT, SRF presence, SRF height, largest cyst diameter, DMO morphology, DRIL, ELM integrity, EZ integrity, posterior hyaloid status, and VRIA. These biomarkers were treated as one multiplicity family and adjusted using the Benjamini-Hochberg false discovery rate procedure, with q values shown in Table 1. Age, sex, BCVA, and lens status were not included in this analysis.

We used multivariable logistic regression with the same clustering to examine factors linked to proliferative disease. The joint model included age, sex, diabetes duration, within-centre standardised CMT, DMO morphology, DRIL, EZ integrity, posterior hyaloid status, VRIA, lens status, and study centre. This analysis included only eyes evaluable for both EZ integrity and posterior hyaloid status, allowing mutual adjustment. ELM was only examined in a substitution model because EZ and ELM grades were highly collinear (Spearman ρ=0.932). We controlled family-wise error using the Holm correction across the six structural-domain terms. These analyses were not prespecified and are reported as secondary.

Since imaging was done on four platforms and protocols could vary by site, we included study centre as a fixed effect in all multivariable models and standardised CMT within each centre. We examined centre-related variability in CMT using a linear model with retinopathy group, centre, and their interaction. Because the dataset does not include an eye-level device field, we could not estimate device effects. We used the same multivariable linear regression structure to estimate associations with BCVA in secondary analyses. To test robustness, we refitted the models using only one eye per patient and after excluding eyes with previous PRP. We considered p values < 0.05 significant.

Results

We analysed 818 eyes of 534 patients with treatment-naive DMO, of which 646 eyes had NPDR and 172 had PDR (Table 1). Mean BCVA was significantly worse in PDR than NPDR eyes (0.74±0.54 versus 0.57±0.42 logMAR; p<0.001). Age was slightly lower in the PDR group (p=0.035).

In univariable clustered comparisons, VRIA and posterior hyaloid detachment were more common in the PDR group (21.5% and 35.7%, respectively) compared to the NPDR group (12.5% and 25.2%; p=0.010 and p=0.047, respectively). However, after false discovery rate correction across the ten comparisons, no biomarker remained significant. The lowest adjusted values were q=0.095 for VRIA and q=0.235 for posterior hyaloid status. All other results were non-significant before and after adjustment (Table 1).

The joint multivariable model included 636 eyes from 431 patient clusters that could be evaluated for both EZ integrity and posterior hyaloid status (Table 2). No structural term remained significant after Holm correction. Posterior hyaloid detachment showed a nominal association with PDR (odds ratio [OR] 2.03, 95% confidence interval

Table 1. Demographic, clinical, and OCT characteristics of eyes with NPDR and PDR				
Variable	**NPDR (n=646 eyes)**	**PDR (n=172 eyes)**	**p***	**q†**
Age, years	62.36±8.90	60.43±8.55	0.035	
Sex			0.139	
Female	320 (49.5%)	99 (57.6%)		
Male	326 (50.5%)	73 (42.4%)		
BCVA, logMAR	0.57±0.42	0.74±0.54	<0.001	
Lens status			0.462	
Phakic	544 (84.2%)	140 (81.4%)		
Pseudophakic	102 (15.8%)	32 (18.6%)		
CMT, µm	470.60±171.02	472.54±171.84	0.912	0.912
SRF height, µm	145.50±82.87 (n=206)	152.36±92.54 (n=50)	0.662	0.827
Largest cyst diameter, µm	299.95±177.36 (n=420)	325.20±161.10 (n=113)	0.208	0.482
DMO morphology			0.759	0.844
Diffuse/spongious	100 (15.5%)	32 (18.6%)		
Cystoid	306 (47.4%)	84 (48.8%)		
Diffuse/spongious + SRF	75 (11.6%)	18 (10.5%)		
Cystoid + SRF	165 (25.5%)	38 (22.1%)		
SRF present	240 (37.2%)	56 (32.6%)	0.351	0.584
DRIL present	326 (50.5%)	82 (47.7%)	0.585	0.827
ELM integrity			0.241	0.482
Disrupted	87 (14.5%)	21 (14.8%)		
Partially intact	198 (33.1%)	58 (40.8%)		
Intact	314 (52.4%)	63 (44.4%)		
Not evaluable, n	47	30		
EZ integrity			0.142	0.473
Disrupted	97 (16.4%)	24 (17.1%)		
Partially intact	205 (34.7%)	61 (43.6%)		
Intact	289 (48.9%)	55 (39.3%)		
Not evaluable, n	55	32		
Posterior hyaloid status			0.047	0.235
Detached	139 (25.2%)	45 (35.7%)		
Attached	412 (74.8%)	81 (64.3%)		
Not evaluable, n	95	46		
VRIA present	81 (12.5%)	37 (21.5%)	0.010	0.095

Values are presented as mean ± SD or n (%) unless otherwise indicated. Percentages for ELM integrity, EZ integrity, and posterior hyaloid status are calculated among gradable eyes; numbers of non-evaluable eyes are shown separately. *p values from comparisons with patient-clustered robust (sandwich) standard errors; for variables with more than two categories, a single global Wald test is reported. †q values: Benjamini-Hochberg false discovery rate-adjusted p values across the ten OCT biomarker comparisons; not calculated for demographic and clinical variables

BCVA: Best-corrected visual acuity, CMT: Central macular thickness, DMO: Diabetic macular oedema, DRIL: Disorganisation of the retinal inner layers, ELM: External limiting membrane, EZ: Ellipsoid zone, NPDR: Nonproliferative diabetic retinopathy, OCT: Optical coherence tomography, PDR: Proliferative diabetic retinopathy, SD: Standard deviation, SRF: Subretinal fluid, VRIA: Vitreoretinal interface abnormality, logMAR: Logarithm of the minimum angle of resolution

Table 2. Joint multivariable model of structural OCT biomarkers associated with proliferative diabetic retinopathy			
Variable	**Adjusted OR (95% CI)**	**p**	**Holm-adjusted p**
Posterior hyaloid status		0.035	0.208
Attached	Reference		
Detached	2.03 (1.05-3.92)		
Ellipsoid zone integrity (global test)		0.221	0.884
Intact	Reference		
Partially intact	1.62 (0.90-2.94)		
Disrupted	1.10 (0.43-2.82)		
Vitreoretinal interface abnormality		0.388	1.000
Absent	Reference		
Present	1.36 (0.67-2.75)		
DMO morphology (global test)	-	0.045	0.224
DRIL, present vs absent	1.02 (0.48-2.17)	0.966	1.000
CMT, per within-centre SD	1.02 (0.78-1.35)	0.862	1.000
CI: Confidence interval, CMT: Central macular thickness, DMO: Diabetic macular oedema, DRIL: Disorganisation of the retinal inner layers, OCT: Optical coherence tomography, OR: Odds ratio, SD: Standard deviation			

[CI] 1.05-3.92; p=0.035; Holm-adjusted p=0.208), as did DMO morphology (global p=0.045; Holm p=0.224). The global EZ term was not associated with PDR (p=0.221), and the association for VRIA became weaker after adjusting for posterior hyaloid status (OR 1.36, 95% CI 0.67-2.75; p=0.388). These two factors were strongly related (OR 8.56, 95% CI 5.14-14.26). In a secondary model that did not include posterior hyaloid status, VRIA was associated with PDR (OR 2.19, 95% CI 1.27-3.78; p=0.005), but this is not considered an independent effect. CMT (p=0.862) and DRIL (p=0.966) were not associated with proliferative disease.

After adjusting for study centre, mean CMT was 1.99 µm greater in PDR than in NPDR eyes (95% CI -26.23 to 30.22; p=0.890), and the group-by-centre interaction was not significant (p=0.250). Imaging was more often ungradable in PDR eyes than in NPDR eyes for ELM integrity (17.4% compared to 7.3%; OR 2.45, 95% CI 1.16–5.16), EZ integrity (18.6% compared to 8.5%; OR 2.19, 95% CI 1.07-4.47), and posterior hyaloid status (26.7% compared to 14.7%; OR 2.13, 95% CI 1.22-3.72). All three differences remained significant after Holm correction.

In the secondary analysis of visual acuity, worse BCVA was linked to PDR (0.137 logMAR, 95% CI 0.037-0.237; p=0.007), higher within-centre standardised CMT (0.160 logMAR per standard deviation, 95% CI 0.115-0.205; p<0.001), complete EZ disruption versus an intact EZ (0.285 logMAR, 95% CI 0.121-0.450; p<0.001), and VRIA (0.168 logMAR, 95% CI 0.043-0.292; p=0.008). There was no association with partially intact EZ (p=0.293) or posterior hyaloid detachment (p=0.581).

Two sensitivity analyses supported these results. In the first, one eye per patient was analysed, using the index-eye designation recorded in the study database. After excluding 109 eyes with ungradable EZ integrity and/or posterior hyaloid status from the 523 index eyes, this analysis included 414 eyes of 414 patients. Posterior hyaloid detachment again showed a nominal association with PDR (OR 2.22, 95% CI 1.04-4.70; p=0.038), whereas VRIA (OR 1.35, 95% CI 0.55-3.31) and the global EZ term (p=0.129) did not. In the second, the 95 eyes with previous PRP within the 636-eye evaluable subset were excluded, leaving 541 eyes of 365 patients, and the pattern was unchanged: posterior hyaloid detachment (OR 2.50, 95% CI 1.18-5.28, p=0.017); VRIA (OR 1.68, 95% CI 0.75-3.78); EZ (p=0.220). All sensitivity p values are nominal.

Discussion

Interest in using OCT-based biomarkers for staging and predicting DR is increasing. Many studies now support OCT as a reliable way to assess both DR and DMO. New OCT biomarkers and oedema classification methods are expected to become more common in daily clinical practice.[6,7,8,17,18]

We studied 818 eyes from 534 patients with untreated DMO, comparing key structural OCT biomarkers between nonproliferative and proliferative disease. Our analysis accounted for inter-eye correlations, centre effects, and multiple comparisons. No biomarker showed a clear independent association with PDR after adjusting for these factors. Posterior hyaloid detachment showed the most consistent association, but group differences involving

vitreoretinal interface observed in simpler analyses did not maintain their significance.

Vitreoretinal interface problems are known to be part of advanced DR. Vitreomacular adhesion and traction are more common in proliferative disease, likely due to higher levels of inflammatory mediators and vascular endothelial growth factor in the vitreous.[19,20] Our findings are consistent with these reports, but our joint analysis shows that posterior hyaloid status and VRIA are closely linked. When we included posterior hyaloid status in the model, the link with VRIA mostly disappeared. This suggests that both markers reflect the same interface issue rather than separate problems. Studies on posterior vitreous detachment and DR stage have shown mixed results, with some finding it more common and others less common in advanced disease.[21,22,23,24,25]

Many studies have examined the importance of EZ disruption. Szeto et al.[17] found that when both the EZ and ELM are affected, visual outcomes in DMO are worse. Turkseven Kumral et al.[26] observed more EZ disruption in proliferative disease. In our simple analysis, EZ grade distributions differed descriptively between groups, but the global test was not significant. There are two possible explanations for this. First, we could not grade EZ integrity in more PDR eyes, often because of shadowing from bleeding or opacity. These eyes likely had more advanced disease, and their exclusion may have obscured a group difference. Second, both groups were restricted to eyes with DMO, making our results different from studies of all eyes. Importantly, disrupted EZ remained the strongest sign of worse vision in our secondary analysis, showing the importance of outer retinal health even without stage differences.[27]

Wang et al.[28] recently compared NPDR and PDR eyes using spectral-domain OCT and fundus autofluorescence. They found that posterior vitreous detachment and epiretinal membrane were more common in PDR, consistent with our descriptive results. However, these associations did not persist after adjusting for multiple factors. Their findings for the outer retina were the opposite of our unadjusted results, possibly because our study included only eyes with DMO and because sample size and image quality differed. They also found hyperreflective foci to be the biomarker most strongly associated with proliferative disease. We did not measure this in our study, but including it in future research would make sense.

The main strength of this study is its multicentre analysis of DMO-related OCT features, using methods that consider inter-eye correlations, mutual adjustment, image quality, and multiple comparisons. We do not claim that these biomarkers differ independently by retinopathy stage. Some associations reported in smaller studies, including ours, may not show true independent effects. DMO morphology, which has been associated with treatment response,[29] also did not distinguish between the two stages in our data, and reported subtypes vary widely between populations.[30] Our joint model was complex and used a smaller group of evaluable cases, so its accuracy is limited. The absence of multiplicity-adjusted significant associations means we did not show independent effects, but it does not prove they do not exist. For example, DMO morphology was not significant in simple analysis but was nominally significant in the joint model.

Study Limitations

This retrospective, cross-sectional study cannot determine causality or prognosis. The lack of standardised angiographic data and the optional use of FFA resulted in an inability to assess retinal ischaemia. This may have led to misclassification between severe NPDR and early PDR, which could have reduced observed differences. The role of ischaemia is only hypothesised and not tested. Furthermore, retinopathy stage was binary, limiting severity analysis.

Imaging was done on four platforms with different boundaries and resolutions. Devices were assigned without considering retinopathy stage, and missing eye-level identifiers prevented adjusting for device effects, risking confounding. Grading was performed at each centre without central review or duplicate grading, so interobserver agreement could not be assessed. Graders were also aware of the retinopathy stage, possibly causing bias and variability.

Image gradability varied across groups, meaning complete-case estimates reflect associations within a selected, fully evaluable subset. Assessing DRIL is more challenging with significant cystoid change, potentially leading to misclassification in eyes with severe oedema. Hyperreflective foci were not recorded. Finally, 115 eyes had prior PRP treatment over four months before the index examination, but excluding these eyes did not affect the results.

Conclusion

In this large multicentre cohort of eyes with treatment-naive DMO, we found no structural OCT biomarker that was independently associated with proliferative disease after accounting for fellow-eye correlation, study centre, clinical factors, and the influence of other biomarkers. Posterior hyaloid detachment had the most consistent association and showed a similar pattern in sensitivity analyses. However, the association between VRIA and PDR observed in univariable tests did not persist after

adjustment for posterior hyaloid status. EZ integrity was not significantly associated with PDR in either analysis. In the secondary analysis, proliferative disease, greater macular thickness, EZ disruption, and VRIA were each associated with worse visual acuity. Future longitudinal studies using standardised multimodal imaging and central grading are needed to determine whether any of these features have prognostic value.

Ethics

Ethics Committee Approval: The Institutional Review Board of Kocaeli University Faculty of Medicine approved the study protocol (no: GOKAEK-2022/07.19, date: 14.04.2022), which followed the ethical principles of the 1964 Declaration of Helsinki and later amendments.

Informed Consent: Written informed consent for the use of their medical data for research purposes was obtained from all patients at their initial presentation.

Declarations

Authorship Contributions

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

Conflict of Interest: Dr. Özlem Şahin is a member of the Advisory Board of the Turkish Journal of Ophthalmology. However, she did not participate in the peer-review process of this manuscript and had no access to any information related to the review process. The other authors declare that they have no conflicts of interest.

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References

1. Aschner P, Karuranga S, James S, Simmons D, Basit A, Shaw JE, Wild SH, Ogurtsova K, Saeedi P; International Diabetes Federation's Diabetes Epidemiological Guide Writing Group. The International Diabetes Federation's guide for diabetes epidemiological studies. Diabetes Res Clin Pract. 2021;172:108630.
2. Wilkinson CP, Ferris FL 3rd, Klein RE, Lee PP, Agardh CD, Davis M, Dills D, Kampik A, Pararajasegaram R, Verdaguer JT; Global Diabetic Retinopathy Project Group. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology. 2003;110:1677-1682.
3. Klein R, Klein BE, Moss SE. Visual impairment in diabetes. Ophthalmology. 1984;91:1-9.
4. Das A, McGuire PG, Rangasamy S. Diabetic macular edema: pathophysiology and novel therapeutic targets. Ophthalmology. 2015;122:1375-1394.
5. Badaró E, Novais E, Prodocimo LM, Sallum JM. Spectral-domain optical coherence tomography for macular edema. ScientificWorldJournal. 2014;2014:191847.
6. Endo H, Kase S, Tanaka H, Takahashi M, Katsuta S, Suzuki Y, Fujii M, Ishida S, Kase M. Factors based on optical coherence tomography correlated with vision impairment in diabetic patients. Sci Rep. 2021;11:3004.
7. Chatziralli I, Theodossiadis G, Dimitriou E, Theodossiadis P. Evaluation of morphological characteristics of diabetic macular edema in patients with non-proliferative versus proliferative diabetic retinopathy: a spectral-domain optical coherence tomography study. Int Ophthalmol. 2021;41:2417-2424.
8. Alkuraya H, Kangave D, Abu El-Asrar AM. The correlation between optical coherence tomographic features and severity of retinopathy, macular thickness and visual acuity in diabetic macular edema. Int Ophthalmol. 2005;26:93-99.
9. Arf S, Sayman Muslubas I, Hocaoglu M, Ersoz MG, Ozdemir H, Karacorlu M. Spectral domain optical coherence tomography classification of diabetic macular edema: a new proposal to clinical practice. Graefes Arch Clin Exp Ophthalmol. 2020;258:1165-1172.
10. Ruia S, Saxena S, Gemmy Cheung CM, Gilhotra JS, Lai TY. Spectral domain optical coherence tomography features and classification systems for diabetic macular edema: a review. Asia Pac J Ophthalmol (Phila). 2016;5:360-367.
11. Markan A, Agarwal A, Arora A, Bazgain K, Rana V, Gupta V. Novel imaging biomarkers in diabetic retinopathy and diabetic macular edema. Ther Adv Ophthalmol. 2020;12:2515841420950513.
12. Ota M, Nishijima K, Sakamoto A, Murakami T, Takayama K, Horii T, Yoshimura N. Optical coherence tomographic evaluation of foveal hard exudates in patients with diabetic maculopathy accompanying macular detachment. Ophthalmology. 2010;117:1996-2002.
13. Panozzo G, Cicinelli MV, Augustin AJ, Battaglia Parodi M, Cunha-Vaz J, Guarnaccia G, Kodjikian L, Jampol LM, Jünemann A, Lanzetta P, Löwenstein A, Midena E, Navarro R, Querques G, Ricci F, Schmidt-Erfurth U, Silva RMD, Sivaprasad S, Varano M, Virgili G, Bandello F. An optical coherence tomography-based grading of diabetic maculopathy proposed by an international expert panel: the European School for Advanced Studies in Ophthalmology classification. Eur J Ophthalmol. 2020;30:8-18.
14. Schmidt-Erfurth U, Garcia-Arumi J, Bandello F, Berg K, Chakravarthy U, Gerendas BS, Jonas J, Larsen M, Tadayoni R, Loewenstein A. Guidelines for the Management of Diabetic Macular Edema by the European Society of Retina Specialists (EURETINA). Ophthalmologica. 2017;237:185-222.
15. Sun JK, Lin MM, Lammer J, Prager S, Sarangi R, Silva PS, Aiello LP. Disorganization of the retinal inner layers as a predictor of visual acuity in eyes with center-involved diabetic macular edema. JAMA Ophthalmol. 2014;132:1309-1316.

16. Beck RW, Moke PS, Turpin AH, Ferris FL 3rd, SanGiovanni JP, Johnson CA, Birch EE, Chandler DL, Cox TA, Blair RC, Kraker RT. A computerized method of visual acuity testing: adaptation of the early treatment of diabetic retinopathy study testing protocol. Am J Ophthalmol. 2003;135:194-205.
17. Szeto SK, Hui VWK, Tang FY, Yang D, Sun ZH, Mohamed S, Chan CKM, Lai TYY, Cheung C. OCT-based biomarkers for predicting treatment response in eyes with centre-involved diabetic macular oedema treated with anti-VEGF injections: a real-life retina clinic-based study. Br J Ophthalmol. 2023;107:525-533.
18. Koc F, Güven YZ, Egrilmez D, Aydın E. Optical coherence tomography biomarkers in bilateral diabetic macular edema patients with asymmetric anti-VEGF response. Semin Ophthalmol. 2021;36:444-451.
19. Lin A, Xia H, Zhang A, Liu X, Chen H. Vitreomacular interface disorders in proliferative diabetic retinopathy: an optical coherence tomography study. J Clin Med. 2022;11:3266.
20. Agarwal D, Gelman R, Prospero Ponce C, Stevenson W, Christoforidis JB. The vitreomacular interface in diabetic retinopathy. J Ophthalmol. 2015;2015:392983.
21. Hayreh SS, Jonas JB. Posterior vitreous detachment: clinical correlations. Ophthalmologica. 2004;218:333-343.
22. Hayashi K, Sato T, Manabe SI, Hirata A, Yoshimura K. Posterior vitreous detachment in patients with diabetes mellitus. Jpn J Ophthalmol. 2020;64:187-195.
23. Gella L, Raman R, Kulothungan V, Sharma T. Prevalence of posterior vitreous detachment in the population with type II diabetes mellitus and its effect on diabetic retinopathy: Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetic Study SN-DREAMS report no. 23. Jpn J Ophthalmol. 2012;56:262-267.
24. Foos RY, Kreiger AE, Forsythe AB, Zakka KA. Posterior vitreous detachment in diabetic subjects. Ophthalmology. 1980;87:122-128.
25. Ono R, Kakehashi A, Yamagami H, Sugi N, Kinoshita N, Saito T, Tamemoto H, Kuroki M, Ishikawa SE, Kawakami M. Prospective assessment of proliferative diabetic retinopathy with observations of posterior vitreous detachment. Int Ophthalmol. 2005;26:15-19.
26. Turkseven Kumral E, Ercalık NY, Alpogan O, Yenerel NM, Ozcelik Kose A, Ozturk Y, Acar ZA. OCT biomarkers of treatment-naive diabetic macular edema in patients with non-proliferative and proliferative diabetic retinopathy. Eur J Ophthalmol. 2023;33:1061-1067.
27. Nadri G, Saxena S, Stefanickova J, Ziak P, Benacka J, Gilhotra JS, Kruzliak P. Disorganization of retinal inner layers correlates with ellipsoid zone disruption and retinal nerve fiber layer thinning in diabetic retinopathy. J Diabetes Complications. 2019;33:550-553.
28. Wang Z, Ji C, Hu X, Zhang T, Liu T, Zhang X, Wang Y, Li Z, Qin X, Sun M. Multimodal imaging features of non-proliferative and proliferative diabetic retinopathy based on SD-OCT and fundus autofluorescence. Front Med (Lausanne). 2026;13:1779259.
29. Limon DU, Kaplan FB, Saygın I, Önder Tokuç E, Kutlutürk Karagöz I, Kanar HS, Sevik MO, Yayla U, Çelik E, Sönmez A, Aykut A, Kumral Türkseven E, Erçalık NY, Oncu Aydın Ö, Bozkurt E, Aydoğan T, Emengen EB, Özkaya A, Açıkalın Öncel B, Yenerel NM, Şahin Ö, Karabaş L. One-year functional and morphological prognosis after intravitreal injection treatments according to different morphological patterns of diabetic macular edema in real-life: MARMASIA study group report no.13. Semin Ophthalmol. 2024;39:460-467.
30. Yassin SA, ALjohani SM, Alromaih AZ, Alrushood AA. Optical coherence tomography patterns of diabetic macular edema in a Saudi population. Clin Ophthalmol. 2019;13:707-714.

Original Article

Evaluation of Plasma Spermine and Spermidine Levels in Primary Open-Angle Glaucoma and Exfoliation Glaucoma

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Abstract

Objectives: This study aimed to compare plasma spermine and spermidine concentrations in patients with primary open-angle glaucoma (POAG), patients with exfoliation glaucoma (EG), and healthy individuals, and to explore their potential association with disease severity.

Materials and Methods: This prospective case-control study was conducted at a tertiary referral center and included patients with an established diagnosis of POAG or EG for more than two years. The control group consisted of age- and sex-matched healthy individuals. Participants with predefined systemic comorbidities or ocular conditions that could potentially confound the study findings were excluded. Plasma concentrations of spermine and spermidine were measured using enzyme-linked immunosorbent assay. Glaucoma severity was assessed using the modified Hodapp-Parrish-Anderson glaucoma staging system.

Results: Significant differences in spermine and spermidine concentrations were observed among the three study groups (p=0.005 and p=0.037, respectively). Post-hoc analyses showed that spermine levels were significantly elevated in both the POAG and EG groups relative to controls, whereas spermidine levels were significantly increased only in the POAG group. In the EG group, spermidine levels showed a weak inverse correlation with glaucoma severity (Kendall's tau-b=-0.317, p=0.037).

Conclusion: The observed alterations in plasma spermine and spermidine concentrations suggest a potential association between systemic polyamine metabolism and glaucoma. Given the proposed roles of polyamines in neurodegenerative processes, further studies are warranted to clarify the biological significance of these findings in glaucoma.

Keywords: Primary open-angle glaucoma, exfoliation glaucoma, spermine, spermidine, polyamines, neurodegeneration

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Introduction

Glaucoma is a leading cause of permanent vision impairment and is characterized by ongoing structural and functional deterioration of the optic nerve, particularly the optic nerve head and retinal nerve fiber layer.[1,2] As life expectancy increases, the incidence of glaucoma is expected to rise. However, the underlying mechanisms driving its onset and progression remain poorly understood. Elevated intraocular pressure (IOP) remains the only confirmed modifiable risk factor linked to retinal ganglion

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cell degeneration, making its regulation the cornerstone of glaucoma management. Nevertheless, vision loss may progress even in patients whose IOP has been normalized through medical or surgical interventions.[1,3] These findings support the multifactorial nature of glaucomatous optic nerve damage.[1] Emerging evidence links glaucomatous degeneration to neurodegenerative processes, leading to growing interest in neuroprotective strategies as a complementary approach to disease management.[3]

Polyamines are low-molecular-weight organic cations synthesized from ornithine, structurally defined by a terminal primary amino group and a chain of alternating secondary amino groups.[4,5] The principal members of the polyamine family include spermidine, spermine, putrescine, and cadaverine.[4,6] Polyamines are involved in a broad range of cellular activities, such as promoting cell proliferation, regulating programmed cell death, maintaining DNA structural stability, and influencing gene expression through transcriptional and translational control.[5,6,7] Furthermore, polyamine levels have been linked to key neurobiological processes, including neuritogenesis, brain development, and neuronal survival.[8] Although limited in number, studies examining the association between polyamines and neurodegenerative diseases have yielded inconsistent findings. Notably, polyamine levels have been shown to decline with age, while exogenous supplementation has been associated with lifespan extension in experimental models.[9] This age-related decline is particularly noteworthy given reports of markedly altered polyamine levels in the blood or tissues of individuals with age-related neurodegenerative disorders, including Alzheimer's[10] and Parkinson's disease.[11] Collectively, these findings—along with evidence supporting their therapeutic potential—suggest that polyamines may exert pleiotropic, adaptive, and pathogenic effects in neurodegenerative disorders.[9]

Despite increasing evidence supporting the involvement of polyamine metabolism in oxidative homeostasis, neurodegeneration, and neuronal survival, there are still limited clinical data regarding circulating spermine and spermidine levels in patients with glaucoma. Moreover, it remains unclear whether circulating polyamine profiles differ between primary open-angle glaucoma (POAG) and exfoliation glaucoma (EG), and whether these alterations are associated with glaucoma severity.

Given the neurodegenerative nature of glaucoma and the potential involvement of polyamines in neurodegenerative processes, we hypothesized that circulating polyamine levels would be altered in patients with glaucoma and might be associated with disease severity. Accordingly, this study aimed to compare plasma spermine and spermidine concentrations among patients with POAG, patients with EG, and healthy controls, and to evaluate the association between these concentrations and glaucoma severity.

Materials and Methods

Study Design

This prospective case-control study was conducted between February and July 2020 and included patients with an established diagnosis of glaucoma for more than two years prior to enrollment. The study was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (approval number: GO 18/933-14; project number: GO 18/933; date: 11 December 2018) and conducted in accordance with the principles of the Declaration of Helsinki and its subsequent amendments. Written informed consent was obtained from all participants.

A priori power analysis was performed to estimate the minimum sample size required. Based on previously reported spermine and spermidine levels in humans[5,12] and assuming an α error of 5% with a statistical power of 80-90%, it was estimated that 36 to 46 participants per group (totaling 108 to 138 subjects) would be necessary to achieve adequate power.

Glaucoma Diagnosis and Participant Selection

Patients with POAG or EG and a disease duration longer than two years were consecutively enrolled in the study.

The diagnosis of POAG was based on the following criteria: absence of exfoliation material in both eyes upon maximal pupillary dilation; IOP >21 mmHg; open anterior chamber angle confirmed by gonioscopy (Shaffer grade 3 or 4); characteristic glaucomatous changes in the optic nerve head (e.g., rim thinning or notching in the superior or inferior temporal quadrant, or total cupping); and corresponding glaucomatous visual field defects (e.g., paracentral, arcuate, or Seidel's scotoma, or a nasal step).

The diagnosis of EG was established based on the presence of characteristic exfoliative material deposits in the anterior segment structures (cornea, lens, and/or pupillary margin) in one or both eyes, along with fulfillment of the other POAG diagnostic criteria stated above. All patients with glaucoma were receiving topical combination therapy consisting of dorzolamide hydrochloride 2% and timolol maleate 0.5% (Cosopt; Merck Sharp & Dohme, Istanbul, Türkiye) and brimonidine tartrate 0.15% (Alphagan P; AbbVie, Istanbul, Türkiye) at the time of blood sampling. The control group included healthy individuals over the age of 50 who were matched for age and sex and had no ocular conditions other than refractive errors.

To prevent potential confounding effects, strict exclusion criteria were applied across all three groups. Individuals with a known or suspected history of systemic conditions, including diabetes mellitus, hypertension, coronary artery disease, obesity (body mass index [BMI] ≥30 kg/m^2), or neurodegenerative disorders such as Alzheimer's or Parkinson's disease, were not included in the study. Additionally, individuals with inflammatory ocular disease, a history of ocular trauma, or systemic medication use were excluded.

Data Collection and Clinical Examination

Detailed medical histories were obtained from all participants. Each participant underwent a comprehensive ophthalmic examination, including visual acuity testing, slit-lamp biomicroscopy of the anterior segment, IOP measurement using Goldmann applanation tonometry, dilated fundus examination, gonioscopy, and standard automated perimetry with the 24-2 threshold program (Humphrey Instruments; Carl Zeiss Meditec, Dublin, CA).

Glaucoma severity was classified into six stages (0-5) using the modified Hodapp-Parrish-Anderson (HPA) glaucoma staging system described by Mills et al.[13] HPA classification could not be determined for patients whose visual field examinations remained unreliable despite repeated testing.

After a 12-hour fast, venous blood samples were collected from all participants. The samples were then centrifuged at 1500 × g for 10 minutes to isolate plasma. The plasma was aliquoted and stored at -80°C until analysis. Plasma concentrations of spermine and spermidine were quantified in the Research Laboratory of the Department of Medical Biochemistry at Hacettepe University using commercially available enzyme-linked immunosorbent assay (ELISA) kits, in accordance with the manufacturers' protocols (Human Spermine ELISA Kit, Mybiosource, USA; Human Spermidine ELISA Kit, Cloud Clone Corp., USA).

Statistical Analysis

All statistical analyses were performed using SPSS software, version 25.0 for Windows (IBM Corp., Armonk, NY, USA). Quantitative variables were presented as mean ± standard deviation (SD). Normality of distribution was assessed using the Shapiro-Wilk test and evaluation of kurtosis and skewness values, with an absolute threshold of 0.5. Comparisons of quantitative variables among the three groups were conducted using one-way analysis of variance (ANOVA) or the Kruskal-Wallis test, based on the distribution of the data. Post-hoc pairwise comparisons were performed using Dunn's test with adjustment for multiple comparisons following the Kruskal–Wallis test, and Bonferroni-adjusted pairwise comparisons following one-way ANOVA. Categorical variables were presented as counts and percentages (n, %), and group comparisons were performed using Pearson's chi-squared test. Associations between quantitative variables were evaluated using Spearman's rank correlation coefficients (rho), while Kendall's tau-b was used to assess correlations between ordinal variables (HPA stage) and continuous measures. A p value ≤0.05 was considered indicative of statistical significance. Spermidine and spermine concentrations were graphically represented by group using median values and interquartile ranges, plotted with GraphPad Prism version 8.4.2 (GraphPad Software, San Diego, CA, USA).

Results

A total of 134 participants were included in the study. Sex distribution, age, and BMI were comparable across the three groups (p=0.425, p=0.067, and p=0.886, respectively) (Table 1).

Among patients with classifiable HPA stages, most had mild-to-moderate glaucoma, and relatively few had advanced disease. A significant difference in glaucoma severity was observed between the two glaucoma groups (p=0.019) (Table 1).

Significant differences in spermine and spermidine concentrations were observed among the three study groups (p=0.005 and p=0.037, respectively; Table 1, Figures 1 and 2). Post-hoc pairwise comparisons indicated that spermidine levels were significantly higher in the POAG group compared to the control group (p<0.05), whereas differences between the remaining group pairs did not reach statistical significance. Post-hoc analysis of spermine levels demonstrated no significant difference between the POAG and EG groups. However, both groups exhibited significantly elevated concentrations compared to controls (Table 1).

Correlation analysis revealed a weak positive association between age and spermine concentration in the POAG group (rho=0.324, p=0.020). In the EG group, spermine and spermidine concentrations were moderately and positively correlated (rho=0.463, p=0.002). Furthermore, HPA stage exhibited a weak positive correlation with age in the POAG group (tau-b=0.242, p=0.031) and a weak negative correlation with spermidine levels in the EG group (tau-b=-0.317, p=0.037). No other statistically significant correlations were identified, including those between age and spermidine or spermine levels in the control group. The statistically significant correlation analyses are summarized in Table 2.

Table 1. Comparison of the groups in terms of characteristics, glaucoma severity, and plasma spermine and spermidine concentrations

	POAG (n=51)	EG (n=44)	Control (n=39)	p value
Sex, n (%)				
Female	30 (58.8)	20 (45.5)	20 (51.3)	0.425*
Male	21 (41.2)	24 (54.5)	19 (48.7)	
Age (years), mean ± SD	66.7±9.2	67.0±6.6	63.9±7.6	0.067†
BMI (kg/m^2), mean ± SD	24.4±3.2	24.3±3.4	24.6±3.0	0.886‡
Modified Hodapp-Parrish-Anderson stage, n (%)				
Stage 0	6 (11.8)	1 (2.3)	39 (100)	POAG vs. EG **0.019***
Stage 1	22 (43.1)	5 (11.4)	0	
Stage 2	11 (21.6)	12 (27.3)	0	
Stage 3	10 (19.6)	4 (9.1)	0	
Stage 4	1 (2.0)	4 (9.1)	0	
Stage 5	1 (2.0)	2 (4.5)	0	
Unknown (no data)	0	16 (36.4)	0	
Spermine (ng/mL), mean ± SD	358.7±124.7[a]	354.3±131.8[a]	307.0±157.5	**0.005**†
Spermidine (ng/mL), mean ± SD	5.08±1.45[a]	4.86±1.38[a,b]	4.34±1.13 [b]	**0.037**‡

POAG: Primary open-angle glaucoma, EG: Exfoliation glaucoma, BMI: Body mass index, SD: Standard deviation. *Pearson chi-square, †Kruskal-Wallis, ‡One-way ANOVA. p values in bold indicate the presence of statistical significance. Same letters denote the lack of statistical significance in pairwise comparisons (Dunn's test with adjustment for multiple comparisons following Kruskal-Wallis; Bonferroni-adjusted pairwise comparisons following one-way ANOVA)

Discussion

Compared with healthy controls, patients with POAG and EG exhibited elevated circulating spermine levels, whereas spermidine concentrations were significantly increased only in the POAG group. Additionally, glaucoma severity classified using the modified HPA system showed a weak positive correlation with age in the POAG group and a weak negative correlation with spermidine levels in the EG group. Taken together, these findings indicate that circulating polyamine levels are altered in glaucoma, whereas their associations with disease severity appear to be limited.

Recent evidence increasingly characterizes glaucoma as a complex neurodegenerative disease in which retinal ganglion cell loss is associated not only with elevated IOP but also with mitochondrial dysfunction, metabolic stress, impaired axonal transport, oxidative stress, and neuroinflammation.[14,15,16,17] A recent review by Ekici and Moghimi[18] further highlighted the multifactorial nature of glaucomatous neurodegeneration, emphasizing the interconnected contributions of elevated IOP, impaired ocular blood flow, extracellular matrix remodeling, excitotoxicity, oxidative stress, and neuroinflammation to retinal ganglion cell dysfunction and loss. Although IOP remains the only established modifiable risk factor, disease progression may occur despite adequate IOP control,

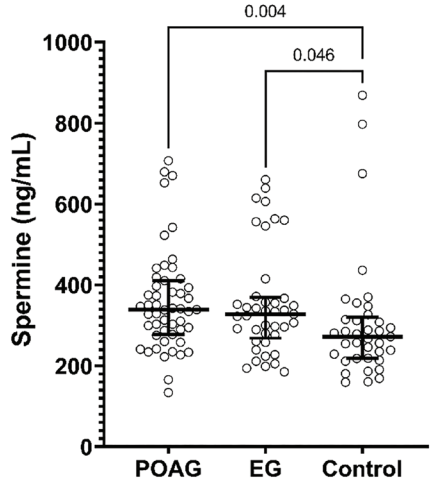


Figure 1. Scatterplot of plasma spermine concentrations in the glaucoma and control groups. Data are presented as individual values; horizontal lines indicate the median and error bars represent the interquartile range. Pairwise comparisons were performed using Dunn's test following the Kruskal-Wallis test. The comparison between POAG and EG was not statistically significant (p>0.999, not shown in the figure)
POAG: Primary open-angle glaucoma, EG: Exfoliation glaucoma

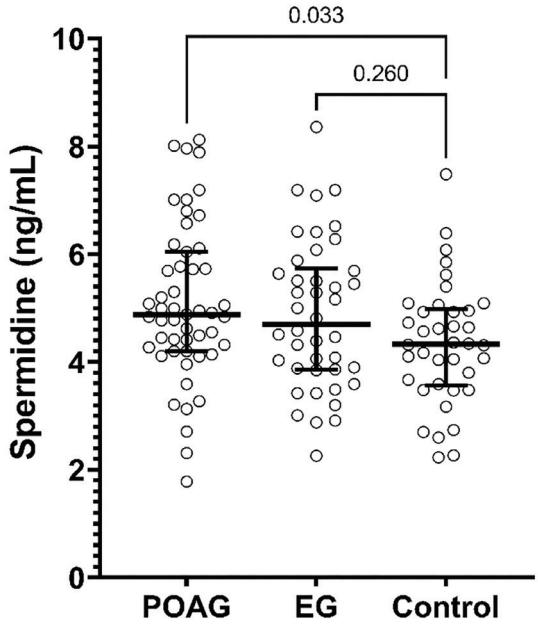


Figure 2. Scatterplot of plasma spermidine concentrations in the glaucoma and control groups. Data are presented as individual values; horizontal lines indicate the median and error bars represent the interquartile range. Pairwise comparisons were performed using Bonferroni correction following one-way ANOVA. The comparison between POAG and EG was not statistically significant (p>0.999, not shown in the figure)

POAG: Primary open-angle glaucoma, EG: Exfoliation glaucoma

underscoring the need for neuroprotective approaches targeting retinal ganglion cell survival. Experimental studies have demonstrated that spermidine exerts neuroprotective effects in models of retinal ganglion cell injury and optic nerve damage.[19] Given that clinical studies evaluating circulating spermine and spermidine concentrations in glaucoma remain scarce, these experimental findings provide a biological rationale for investigating circulating polyamines in patients with glaucoma. Furthermore, recent reviews indicate that neuroprotective strategies targeting retinal ganglion cell metabolism, mitochondrial function, and oxidative stress may complement conventional IOP-lowering therapy.[16,20]

Consistent with this biological framework, circulating spermine levels were elevated in both POAG and EG, whereas increased spermidine levels were observed only in patients with POAG. In light of the neuroprotective effects of spermidine reported in experimental models of neurodegeneration and optic nerve injury,[19] the observed increase in circulating spermidine may reflect an adaptive response to glaucomatous neurodegeneration. It may also represent altered systemic polyamine metabolism accompanying the disease process. Nevertheless, whether increased circulating spermidine represents a compensatory response, a marker of altered systemic polyamine metabolism, or an epiphenomenon of the disease process cannot be determined from the present cross-sectional study.

In addition to their experimentally demonstrated neuroprotective effects, polyamines are involved in oxidative homeostasis, mitochondrial function, autophagy, and cellular stress responses.[21,22] These biological properties provide a plausible mechanistic link between altered polyamine metabolism and glaucomatous neurodegeneration. Mitochondrial dysfunction and oxidative stress are also implicated in retinal ganglion cell degeneration, reinforcing interest in metabolic and neuroprotective therapeutic strategies.[15,16,23] Nevertheless, whether circulating polyamine levels directly reflect retinal oxidative stress or neuroprotective activity in human glaucoma remains uncertain.

Spermine and spermidine are naturally occurring polyamines that are abundant in the central nervous system and retina, where they are predominantly localized to astrocytes and contribute to neuronal homeostasis.[24] Polyamine metabolism is tightly regulated through coordinated biosynthetic and catabolic pathways, allowing dynamic interconversion among spermine, spermidine, and their metabolic precursors.[6,25] Consequently, changes in circulating polyamine levels may reflect tissue-specific disturbances in polyamine homeostasis associated with glaucomatous neurodegeneration rather than alterations in a single metabolic pathway.

Table 2. Summary of significant correlation analyses

Study group	Variables	Correlation method	Correlation coefficient	p value
POAG	Age - Spermine	Spearman's rho	0.324	**0.020**
EG	Spermine - Spermidine	Spearman's rho	0.463	**0.002**
POAG	HPA grade - Age	Kendall's tau-b	0.242	**0.031**
EG	HPA grade - Spermidine	Kendall's tau-b	-0.317	**0.037**

POAG: Primary open-angle glaucoma, EG: Exfoliation glaucoma, HPA: Hodapp-Parrish-Anderson; the modified grading system was used

Age-related changes in polyamine metabolism appear to be tissue-specific. Experimental studies have demonstrated declining spermidine levels with age in several animal tissues, whereas human studies have reported distinct age-related patterns for different organs.[26] These observations further suggest that circulating spermine and spermidine levels should be interpreted cautiously, as systemic concentrations may not directly reflect local retinal polyamine metabolism. In addition, previous studies have associated both spermine and spermidine with antioxidant and anti-inflammatory effects in neurodegenerative disorders, including Alzheimer's disease.[23] Collectively, this evidence supports the biological plausibility of altered circulating polyamine levels in glaucoma, although the underlying mechanisms remain incompletely understood.

The distinct polyamine profiles observed in POAG and EG may also reflect differences in their underlying pathophysiology. Although oxidative stress is implicated in both conditions, POAG is primarily characterized by progressive retinal ganglion cell degeneration and neuroaxonal dysfunction, whereas EG is additionally associated with exfoliative material deposition, extracellular matrix remodeling, and characteristic alterations in anterior segment tissues. However, the specific mechanisms linking these pathophysiological variations to systemic polyamine metabolism remain to be elucidated. Because the study did not assess polyamine-related enzyme activity or interconversion, the basis of the observed groupwise pattern remains uncertain.

The clinical significance of altered circulating polyamine levels remains uncertain, including whether these alterations reflect disease activity, progression, or treatment response. Taken together, the present findings support further investigation of polyamine metabolism as a potential mechanistic pathway and circulating polyamines as candidate biomarkers in glaucoma, rather than providing direct evidence for a neuroprotective role of circulating polyamines.

Study Limitations

Although patients with varying degrees of glaucoma severity were included, their uneven distribution across HPA categories may have influenced the strength of the observed correlations between disease severity and polyamine levels and might limit the generalizability of these findings across the full disease spectrum. Furthermore, HPA classification data were unavailable for a subset of patients with EG because reliable visual field examinations (required for HPA grading) could not be obtained despite repeated testing. Consequently, fewer patients were available for the severity-based analyses, potentially reducing their statistical power. However, the primary comparisons of circulating spermine and spermidine concentrations between study groups were independent of HPA stage.

Although overall disease severity was categorized using the modified HPA grading system, individual clinical parameters of glaucomatous damage, including baseline and current IOP, visual field indices (mean deviation, pattern SD, visual field index), and optical coherence tomography-derived retinal nerve fiber layer measurements, were not incorporated into the final analytical dataset. Consequently, the present study could not assess whether circulating spermine and spermidine concentrations were associated with these specific structural and functional clinical parameters beyond the HPA-based severity classification.

All patients with glaucoma received comparable topical combination therapy, but the potential influence of these medications on circulating polyamine concentrations cannot be excluded. In addition, the cross-sectional design of the study precludes the assessment of temporal changes in these concentrations across different stages of glaucoma and limits the interpretation of their relationship with disease progression.

The absence of additional parameters related to polyamine metabolism, including aqueous-humor polyamine concentrations and relevant enzyme activity and gene expression, represents another limitation that may have constrained a more comprehensive interpretation of the findings. Although age distributions did not differ significantly across the study groups, age-related alterations in spermine and spermidine metabolism may still have acted as a confounding factor. Despite these limitations, a strength of the present study is the inclusion of participants without clinically significant systemic comorbidities, thereby reducing the potential influence of systemic diseases on circulating spermine and spermidine levels.

Conclusion

This study demonstrated alterations in circulating polyamine levels in glaucoma when compared with controls, with elevated spermine concentrations in both POAG and EG but increased spermidine concentrations only in patients with POAG. These findings suggest that systemic polyamine metabolism may be altered in glaucoma. However, the biological and clinical significance of these changes remains uncertain. Although experimental evidence supports potential neuroprotective effects of polyamines, the present cross-sectional findings do not establish whether the observed alterations represent an adaptive response to glaucomatous neurodegeneration,

a consequence of the disease process, or other changes in systemic polyamine metabolism. Further prospective longitudinal studies that span the full spectrum of glaucoma severity and integrate circulating and ocular polyamine measurements with structural and functional clinical parameters are warranted to clarify the relationship between polyamine metabolism and glaucoma.

Ethics

Ethics Committee Approval: The study was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (approval number: GO 18/933-14; project number: GO 18/933; date: 11 December 2018) and conducted in accordance with the principles of the Declaration of Helsinki and its subsequent amendments.

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

Declarations

Authorship Contributions

Surgical and Medical Practices: O.A., Ö.D., S.K., M.İ., Concept: O.A., Ö.D., A.Y.G., M.İ., Design: O.A., Ö.D., A.Y.G., M.İ., Data Collection or Processing: O.A., Ö.D., A.Y.G., Analysis or Interpretation: O.A., A.Y., H.A.Ö., Literature Search: O.A., Ö.D., M.İ., Writing: O.A.

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

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References

1. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol. 2006;90:262-267.
2. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology. 2014;121:2081-2090.
3. Gauthier AC, Liu J. Neurodegeneration and neuroprotection in glaucoma. Yale J Biol Med. 2016;89:73-79.
4. Fischer M, Ruhnau J, Schulze J, Obst D, Flöel A, Vogelgesang A. Spermine and spermidine modulate T-cell function in older adults with and without cognitive decline ex vivo. Aging (Albany NY). 2020;12:13716-13739.
5. Pucciarelli S, Moreschini B, Micozzi D, De Fronzo GS, Carpi FM, Polzonetti V, Vincenzetti S, Mignini F, Napolioni V. Spermidine and spermine are enriched in whole blood of nona/centenarians. Rejuvenation Res. 2012;15:590-595.
6. Minois N, Carmona-Gutierrez D, Madeo F. Polyamines in aging and disease. Aging (Albany NY). 2011;3:716-732.
7. Pegg AE. Functions of polyamines in mammals. J Biol Chem. 2016;291:14904-14912.
8. Gilad GM, Gilad VH. Early polyamine treatment enhances survival of sympathetic neurons after postnatal axonal injury or immunosympathectomy. Brain Res. 1988;466:175-181.
9. Polis B, Karasik D, Samson AO. Alzheimer's disease as a chronic maladaptive polyamine stress response. Aging (Albany NY). 2021;13:10770-10795.
10. Morrison LD, Kish SJ. Brain polyamine levels are altered in Alzheimer's disease. Neurosci Lett. 1995;197:5-8.
11. Makletsova MG, Syatkin SP, Poleshchuk VV, Urazgildeeva GR, Chigaleychik LA, Sungrapova CY, Illarioshkin S. Polyamines in Parkinson's disease: their role in oxidative stress induction and protein aggregation. J Neurol Res. 2019;9:1-7.
12. Madeo F, Bauer MA, Carmona-Gutierrez D, Kroemer G. Spermidine: a physiological autophagy inducer acting as an anti-aging vitamin in humans? Autophagy. 2019;15:165-168.
13. Mills RP, Budenz DL, Lee PP, Noecker RJ, Walt JG, Siegartel LR, Evans SJ, Doyle JJ. Categorizing the stage of glaucoma from pre-diagnosis to end-stage disease. Am J Ophthalmol. 2006;141:24-30.
14. Tribble JR, Hui F, Quintero H, El Hajji S, Bell K, Di Polo A, Williams PA. Neuroprotection in glaucoma: mechanisms beyond intraocular pressure lowering. Mol Aspects Med. 2023;92:101193.
15. Ju WK, Perkins GA, Kim KY, Bastola T, Choi WY, Choi SH. Glaucomatous optic neuropathy: mitochondrial dynamics, dysfunction and protection in retinal ganglion cells. Prog Retin Eye Res. 2023;95:101136.
16. Wang LH, Huang CH, Lin IC. Advances in neuroprotection in glaucoma: pharmacological strategies and emerging technologies. Pharmaceuticals (Basel). 2024;17:1261.
17. Xu Y, Yu P, Xie Y, Yang J, Wu J, Ling L, Zhou W. Oxidative stress in glaucomatous retinal ganglion cell injury: mechanisms and neuroprotective strategies. Exp Eye Res. 2026;264:110837.
18. Ekici E, Moghimi S. Advances in understanding glaucoma pathogenesis: a multifaceted molecular approach for clinician scientists. Mol Aspects Med. 2023;94:101223.
19. Noro T, Namekata K, Kimura A, Guo X, Azuchi Y, Harada C, Nakano T, Tsuneoka H, Harada T. Spermidine promotes retinal ganglion cell survival and optic nerve regeneration in adult mice following optic nerve injury. Cell Death Dis. 2015;6:e1720.
20. Bou Ghanem GO, Wareham LK, Calkins DJ. Addressing neurodegeneration in glaucoma: Mechanisms, challenges, and treatments. Prog Retin Eye Res. 2024;100:101261.
21. Hofer SJ, Simon AK, Bergmann M, Eisenberg T, Kroemer G, Madeo F. Mechanisms of spermidine-induced autophagy and geroprotection. Nat Aging. 2022;2:1112-1129.
22. Jimenez Gutierrez GE, Borbolla Jiménez FV, Muñoz LG, Tapia Guerrero YS, Murillo Melo NM, Cristóbal-Luna JM, Leyva Garcia N, Cordero-Martínez J, Magaña JJ. The molecular role of polyamines in age-related diseases: an update. Int J Mol Sci. 2023;24:16469.

23. Xu TT, Li H, Dai Z, Lau GK, Li BY, Zhu WL, Liu XQ, Liu HF, Cai WW, Huang SQ, Wang Q, Zhang SJ. Spermidine and spermine delay brain aging by inducing autophagy in SAMP8 mice. Aging (Albany NY). 2020;12:6401-6414.

24. Laube G, Veh RW. Astrocytes, not neurons, show most prominent staining for spermidine/spermine-like immunoreactivity in adult rat brain. Glia. 1997;19:171-179.

25. Moriya SS, Miura T, Takao K, Sugita Y, Samejima K, Hiramatsu K, Kawakita M. Development of irreversible inactivators of spermine oxidase and N1-acetylpolyamine oxidase. Biol Pharm Bull. 2014;37:475-480.

26. Nakanishi S, Cleveland JL. Polyamine homeostasis in development and disease. Med Sci (Basel). 2021;9:28.

Original Article

Evaluation of Peripapillary Vitreous Dynamics in Patients with Acute Nonarteritic Anterior Ischemic Optic Neuropathy

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Abstract

Objectives: To evaluate peripapillary and vitreomacular interface configurations using spectral-domain optical coherence tomography (SD-OCT) in patients with acute nonarteritic anterior ischemic optic neuropathy (NAION) and to compare findings with age-matched controls.

Materials and Methods: This single-center, retrospective, observational study included 60 patients with acute NAION and 60 age- and sex-matched healthy controls. Circumpapillary retinal nerve fiber layer scans and macular SD-OCT images were analyzed. Assessed peripapillary vitreoretinal interface parameters included peripapillary vitreoretinal adhesion, vitreoretinal traction, complete peripapillary vitreous detachment, peripapillary folds, superficial vascular protrusions, and hyperreflective vitreous dots. Vitreomacular interface characteristics were also evaluated.

Results: Peripapillary vitreoretinal adhesion was more frequently observed in NAION eyes compared with controls (50% vs. 25%, p=0.04). Hyperreflective vitreous dots were significantly more common in NAION eyes (68.3% vs. 8.3%; p<0.001), with a higher mean count (5.31±6.05 vs. 0.50±1.54; p<0.001). Peripapillary folds were also more prevalent in NAION (41.7% vs. 1.7%; p<0.001). Although peripapillary superficial vascular protrusions were common in both groups, mean counts differed significantly (p<0.001). Among 34 NAION eyes with longitudinal follow-up, 29.4% demonstrated interval changes in vitreoretinal interface configuration.

Conclusion: Acute NAION is associated with distinct peripapillary vitreoretinal interface characteristics detectable by SD-OCT. These findings highlight structural differences in vitreoretinal interface configuration in acute NAION. However, their temporal relationship to ischemic injury remains uncertain.

Keywords: NAION, optical coherence tomography, vitreous detachment

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Introduction

Nonarteritic anterior ischemic optic neuropathy (NAION) typically presents with a history of sudden painless unilateral visual loss, visual field defects, and optic disc edema in people over 50 years of age.[1] NAION is generally attributed to impaired perfusion within the short posterior ciliary artery circulation.[2,3] Anatomically crowded optic discs appear particularly susceptible to perfusion imbalance, suggesting that structural and microenvironmental factors at the optic nerve head may influence disease expression.[1,2] Optic disc edema in NAION is primarily thought to result from axoplasmic flow stasis secondary to impaired perfusion of the anterior optic nerve.[4]

Age-related changes at the vitreoretinal interface, including posterior vitreous detachment (PVD), are common in older adults and are known to contribute to a spectrum of vitreoretinal disorders.[5] In certain configurations, persistent attachment of the posterior hyaloid at or near the optic nerve head has been described as vitreopapillary adhesion or traction.[6,7,8] Recent optical coherence tomography (OCT)-based observations have identified vitreoretinal interface variations in some eyes with NAION, raising the question of whether consistent

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peripapillary structural patterns coexist in the acute phase of the disease.[7,8,9] However, it remains unclear whether such findings represent incidental age-related changes, secondary alterations related to disc edema, or disease-associated interface characteristics.

The development of spectral-domain (SD) OCT has enabled high-resolution visualization of both macular and peripapillary vitreoretinal interface configurations.[10,11] Although the vitreomacular interface has been extensively studied in macular disease, the peripapillary interface in NAION has received comparatively limited and heterogeneous investigation.

Accordingly, the present study aimed to evaluate peripapillary vitreoretinal and vitreomacular interface characteristics using SD-OCT in patients with acute NAION and to compare these findings with age- and sex-matched controls.

Materials and Methods

Study Design and Participants

This retrospective observational study included newly diagnosed patients with acute NAION evaluated at the Neuro-ophthalmology Unit of the University of Health Sciences Türkiye, Ankara Training and Research Hospital between June 2016 and December 2024. The study adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board of the University of Health Sciences Türkiye, Ankara Training and Research Hospital (protocol number: E-24-330, decision no: 330/2024, decision date: 18.12.2024). Informed consent was obtained from all participants.

Acute NAION was diagnosed based on sudden, painless unilateral vision loss in individuals older than 50 years, accompanied by diffuse or sectoral optic disc edema and corresponding visual field defects, with no alternative ocular, neurologic, or systemic cause identified. Only patients presenting within 15 days of symptom onset were included to ensure assessment during the acute phase. Patients with previous NAION sequelae, optic disc edema attributable to etiologies other than NAION (e.g., papilledema or inflammatory optic neuropathy), prior intraocular surgery (except uncomplicated cataract surgery), ocular trauma, uveitis, or other retinal or optic nerve diseases were excluded. A small optic disc was defined clinically based on the funduscopic appearance of a crowded optic nerve head with a small or absent physiologic cup. No predefined quantitative optic disc area cutoff was used.

Age- and sex-matched control subjects were randomly selected from individuals undergoing routine ophthalmologic examination. Inclusion criteria were age greater than 50 years, spherical equivalent between +5 and -5 diopters, astigmatism less than 3 diopters, clear media, and the absence of retinal or optic nerve pathologies such as glaucoma, diabetic retinopathy, macular degeneration, and optic disc anomalies. Only one eye per control subject was included.

Collected data included age, sex, medical history, best-corrected visual acuity (BCVA), intraocular pressure measured by Goldmann applanation tonometry, slit-lamp biomicroscopy and dilated fundus examination findings, and SD-OCT imaging of the optic disc region and macula.

OCT Acquisition and Image Evaluation

All OCT images were obtained using the Heidelberg Spectralis system (Heidelberg Engineering, Heidelberg, Germany). Peripapillary retinal nerve fiber layer (RNFL) imaging was performed using a standardized 3.4-mm-diameter circular scan centered on the optic disc. Macular scans were acquired using the standard SD-OCT macular protocol.

All OCT scans were reviewed by a single experienced neuro-ophthalmologist (G.O.) masked to the study hypothesis. Image quality was assessed prior to review, and scans with insufficient quality to evaluate the vitreoretinal interface were excluded.

Evaluation of the Peripapillary Vitreoretinal Interface

Because circumpapillary RNFL scans do not directly image the optic nerve head surface, the study evaluated peripapillary vitreoretinal interface configurations rather than direct vitreopapillary attachment over the optic disc.

The following peripapillary parameters were assessed on circumpapillary RNFL scans: peripapillary vitreoretinal adhesion, peripapillary vitreoretinal traction, peripapillary vitreous detachment, peripapillary folds, peripapillary superficial vascular protrusions, and hyperreflective vitreous dots.

Peripapillary vitreoretinal adhesion was defined as visible contact between the posterior hyaloid and the inner retinal surface along the circumpapillary scan in at least one quadrant, without associated inner retinal deformation (Figure 1a). Peripapillary vitreous detachment was defined as the absence of visible posterior hyaloid attachment along the entire 360-degree circumpapillary scan ring. Peripapillary vitreoretinal traction was defined as visible peripapillary vitreoretinal adhesion accompanied by structural retinal deformation at the site of attachment, including focal elevation or tenting of the inner retinal surface (Figure 1b). In the absence of retinal deformation,

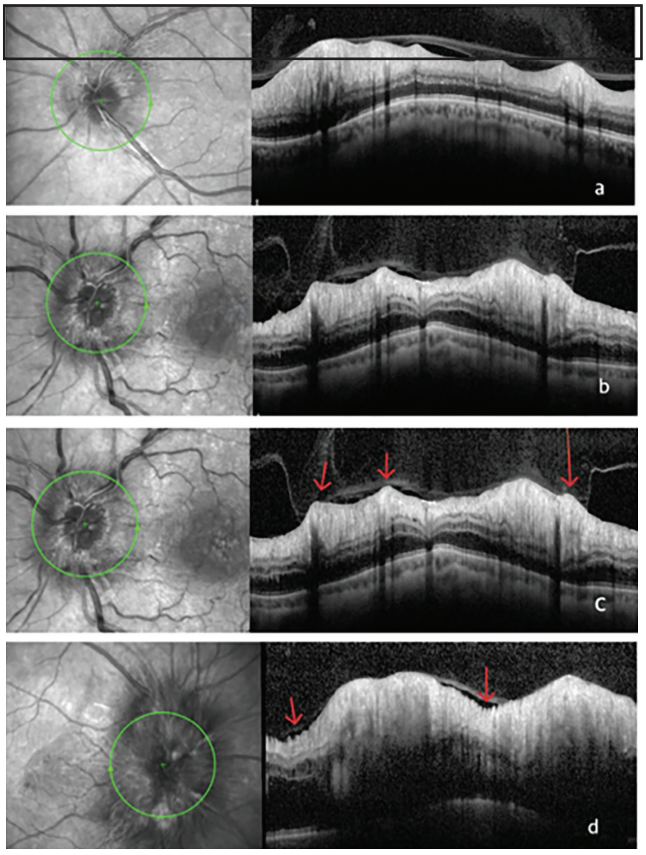


Figure 1. Spectral-domain optical coherence tomography circular circumpapillary retinal nerve fiber layer B-scans centered on the optic disc. a) Peripapillary vitreoretinal adhesion in the left eye of a patient with nonarteritic anterior ischemic optic neuropathy (NAION). b) Peripapillary vitreoretinal traction in the left eye of a patient with NAION. c) Red arrows indicate peripapillary superficial vessel protrusions in the left eye of a patient with NAION. d) Red arrows indicate peripapillary folds in the right eye of a patient with NAION

the finding was classified as adhesion rather than traction. Peripapillary superficial vascular protrusion was defined as focal anterior displacement of superficial retinal vessels above the RNFL contour (Figure 1c). Peripapillary folds were defined as concentric or spiral undulations of the inner retinal surface within the RNFL layer (Figure 1d). Hyperreflective vitreous dots were defined as discrete punctate hyperreflective foci within the peripapillary vitreous exceeding background speckle reflectivity. Dots were manually counted on the circumpapillary RNFL scan and recorded per eye.

Evaluation of the Vitreomacular Interface

Macular SD-OCT scans were used to evaluate vitreomacular interface features. Vitreomacular adhesion was defined as perifoveal vitreous detachment with persistent foveal attachment and the absence of retinal distortion. Vitreomacular traction required persistent vitreomacular attachment accompanied by structural retinal changes, including inner retinal deformation, pseudocyst formation, macular schisis, cystoid macular edema, or subretinal fluid. Epiretinal membrane (ERM) was defined as a hyperreflective membrane on the inner retinal surface. Lamellar macular hole was defined as a partial-thickness foveal defect with preservation of the outer retinal layers.

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to assess the normality of continuous variables. Continuous variables were expressed as mean±standard deviation, and comparisons between the NAION and control groups were performed using the Mann-Whitney U test. Categorical variables were expressed as frequencies and percentages and were compared using the chi-square test. All statistical tests were two-tailed, and a p-value <0.05 was considered statistically significant.

Results

Demographics and Ophthalmologic Examination

A total of 60 eyes from 60 patients with acute NAION and 60 eyes from 60 age- and sex-matched healthy controls were included. The mean age was 60.9±8.4 years in the NAION group and 61.3±9.7 years in the control group (p=0.912). Each group consisted of 27 females and 33 males. Mean BCVA was significantly lower in the NAION group (0.46±0.36) compared with controls (0.86±0.16; p=0.017). Thirty-four NAION patients (56.7%) had follow-up longer than six months and were included in the longitudinal analysis. Baseline demographic and clinical findings are summarized in Table 1.

Peripapillary Vitreoretinal Interface Findings

On circumpapillary RNFL scans at baseline, peripapillary vitreoretinal adhesion was identified in 30 NAION eyes (50%). Peripapillary vitreoretinal traction was observed in 12 eyes (20%). Complete peripapillary vitreous detachment was present in 2 eyes (3.3%). Compared with controls, NAION eyes showed a significantly higher frequency of peripapillary vitreoretinal adhesion (p=0.04). The distribution of peripapillary vitreoretinal interface configurations is summarized in Table 2.

Longitudinal Peripapillary Changes

Among the 34 NAION eyes with follow-up imaging, 10 (29.4%) demonstrated interval changes in peripapillary

Table 1. Demographic and clinical characteristics of patients with acute NAION and age-matched controls			
Variable	**NAION (n=60)**	**Controls (n=60)**	**p value**
Age, years	60.9±8.4	61.3±9.7	0.912
Female sex, n (%)	27 (45)	27 (45)	1.000
BCVA, Snellen decimal	0.46±0.36	0.86±0.16	0.017
IOP, mmHg	12.95±3.55	13.15±4.74	0.554
Mean RNFL thickness, µm	203.64±48.27	100.93±8.49	<0.001
NAION: Nonarteritic anterior ischemic optic neuropathy, BCVA: Best-corrected visual acuity, IOP: Intraocular pressure, RNFL: Retinal nerve fiber layer			

Table 2. Peripapillary vitreoretinal interface configuration and peripapillary structural features in acute NAION and controls			
Parameter	**NAION (n=60)**	**Controls (n=60)**	**p value**
Normal peripapillary vitreoretinal interface, n (%)	16 (26.7)	31 (51.7)	0.04
Peripapillary vitreoretinal adhesion, n (%)	30 (50.0)	15 (25.0)	0.04
Peripapillary vitreoretinal traction, n (%)	12 (20.0)	9 (15.0)	0.473
Peripapillary vitreous detachment, n (%)	2 (3.3)	5 (8.3)	0.245
Hyperreflective vitreous dots present, n (%)	41 (68.3)	5 (8.3)	<0.001
Hyperreflective dot count, mean ± SD	5.31±6.05	0.50±1.54	<0.001
Peripapillary superficial vascular protrusions present, n (%)	53 (88.3)	58 (96.7)	0.084
Number of vascular protrusions, mean ± SD	2.51±1.84	3.45±1.47	<0.001
Peripapillary folds present, n (%)	25 (41.7)	1 (1.7)	<0.001
Small optic disc, n (%)	56 (93.3)	10 (16.7)	<0.001
NAION: Nonarteritic anterior ischemic optic neuropathy, SD: Standard deviation			

vitreoretinal interface configuration. Eight eyes (23.5%) progressed from adhesion to traction, and two eyes (5.9%) developed complete peripapillary vitreous detachment.

Additional Peripapillary Structural Findings

Hyperreflective vitreous dots were detected significantly more frequently in NAION eyes (41 eyes, 68.3%) compared with controls (5 eyes, 8.3%) (p<0.001). The mean number of hyperreflective dots per eye was also higher in the NAION group (5.31±6.05 vs. 0.50±1.54; p<0.001). Peripapillary superficial vascular protrusions were common in both groups (88.3% in NAION vs. 96.7% in controls; p=0.084). However, the mean number of protrusions per eye differed significantly (2.51±1.84 vs. 3.45±1.47; p<0.001). Peripapillary folds were identified in 25 NAION eyes (41.7%) compared with 1 control eye (1.7%; p<0.001). These findings are summarized in Table 2.

Vitreomacular Interface Findings

At baseline, vitreomacular adhesion was present in 15 NAION eyes (25.0%), vitreomacular traction in 3 eyes (5.0%), ERM in 4 eyes (6.7%), complete PVD in 5 eyes (8.3%), and lamellar macular hole in 1 eye (1.7%). The overall prevalence of vitreomacular interface abnormalities was significantly higher in the NAION group compared with controls (p<0.001). A summary of vitreomacular interface findings is provided in Table 3.

Among NAION patients with follow-up imaging, 10 eyes (29.4%) developed ERM not present at baseline. Interval macular interface changes were observed in 12 eyes (35.3%), including progression to PVD (26.5%), vitreomacular traction (5.9%), and vitreomacular adhesion (2.9%). A summary of longitudinal vitreomacular interface changes is provided in Table 4.

Discussion

In the present study, we evaluated peripapillary and macular vitreoretinal interface configurations in patients with acute NAION using SD-OCT. Compared with age-matched controls, NAION eyes demonstrated a higher prevalence of detectable peripapillary vitreoretinal adhesion, hyperreflective vitreous dots, and peripapillary folds. Nearly one-third of patients with longitudinal follow-up exhibited interval interface changes, further indicating that vitreoretinal interface alterations are frequently observed in acute NAION.

Table 3. Vitreomacular interface findings			
Parameter	**NAION (n=60), n (%)**	**Controls (n=60), n (%)**	**p value**
Normal vitreomacular interface	32 (53.3)	50 (83.3)	<0.001
Abnormal vitreomacular interface	28 (46.7)	10 (16.7)	<0.001
Epiretinal membrane	4 (6.7)	1 (1.7)	0.172
Lamellar macular hole	1 (1.7)	0 (0)	0.317
Vitreomacular traction	3 (5.0)	0 (0)	0.081
Vitreomacular adhesion	15 (25.0)	9 (15.0)	0.173
Posterior vitreous detachment	5 (8.3)	5 (8.3)	1.00
NAION: Nonarteritic anterior ischemic optic neuropathy			

Table 4. Longitudinal changes in the vitreomacular interface (NAION eyes, n=34)	
Parameter	**n (%)**
Any interval macular interface change	12 (35.3)
Development of epiretinal membrane	10 (29.4)
Progression to posterior vitreous detachment	9 (26.5)
Progression to vitreomacular traction	2 (5.9)
Progression to vitreomacular adhesion	1 (2.9)
NAION: Nonarteritic anterior ischemic optic neuropathy	

Age-related vitreous liquefaction leads to progressive syneresis and a reduction in gel volume, generating tractional stress at residual sites of vitreoretinal adhesion. Under physiological conditions, these forces are generally well tolerated. However, when PVD occurs anomalously, persistent peripapillary attachment may produce vitreopapillary adhesion or traction.[12] Clinical observations indicate that persistent vitreous adhesion can transmit mechanical forces to the optic nerve head.[13,14] Hayreh et al.[1,2] demonstrated that even minimal reductions in optic disc perfusion may precipitate ischemia in anatomically crowded discs, underscoring the intrinsic vulnerability of these eyes to circulatory imbalance. More recent work has suggested that vitreopapillary traction represents part of a broader spectrum of vitreopapillary interface abnormalities that can influence optic nerve head biomechanics, and in certain contexts may also affect local vascular dynamics.[14,15] In this setting, persistent vitreous adhesion may influence local peripapillary biomechanics. In our cohort, peripapillary interface differences were more frequently observed in acute NAION than in controls. These observations suggest that variations in peripapillary vitreoretinal interface configuration may coexist with acute NAION. However, whether such interface characteristics represent pre-existing structural features, secondary responses to disc edema, or epiphenomena of ischemic injury remains uncertain.

OCT-based studies have reported shallow adhesions, microfolds, and localized vitreous configuration changes as common accompanying features.[8] Li et al.[7] further demonstrated that incomplete papillary vitreous detachment is highly prevalent in NAION and can produce dynamic, intermittent traction on the optic disc, manifesting as peripapillary wrinkles, superficial vessel protrusions, and localized surface distortion-features that may mirror the interface abnormalities identified in our cohort. Hondur et al.[14] indicated that persistent or residual vitreous adhesion may influence prelaminar and peripapillary tissue biomechanics, contributing to localized vessel wall deformation and altered microvascular behavior in susceptible discs. The peripapillary folds observed in our cohort may reflect structural changes associated with acute disc edema rather than definite tractional deformation. Overall, our results indicate that peripapillary interface characteristics differ in NAION, although it is not possible to determine whether these findings precede ischemia or develop as a consequence of disc swelling.

The detection of hyperreflective dots within the peripapillary vitreous was a notable observation in our NAION cohort. To our knowledge, vitreous-based hyperreflective dots have not been systematically described in patients with NAION. Previous reports, including the recent case series by Santos et al.[16], described hyperreflective foci within the retinal layers, where they were interpreted as activated microglia, inflammatory cells, or proteinaceous debris following ischemic injury. In contrast, our observations demonstrated hyperreflective foci located within the vitreous compartment, suggesting that they may represent a different phenomenon from previously described intraretinal hyperreflective foci. Comparable vitreous hyperreflective dots have been reported in other inflammatory or ischemic retinal diseases, particularly uveitis and central retinal artery occlusion, where they are considered OCT correlates of inflammatory cell aggregates or reactive vitreous debris.[17,18] These observations raise the possibility that vitreous hyperreflective dots in NAION may

be related to local inflammatory or ischemia-associated changes; however, their origin remains uncertain. They may correspond to inflammatory cells, erythrocytes, or microhemorrhagic material. Alternatively, some may represent vitreous collagen condensations, age-related vitreous opacities, or imaging artifacts, and their exact nature cannot be determined based on OCT findings alone. Correlation with disc hemorrhage was not systematically evaluated in our cohort, which should be considered a limitation of this study.

We observed interval changes in vitreomacular interface configuration, including ERM formation and progression toward partial PVD or vitreomacular traction. These findings may reflect dynamic remodeling of the vitreoretinal interface in the setting of acute NAION; however, the underlying mechanisms cannot be determined from imaging data alone. Such alterations could represent structural remodeling occurring during the course of the disease rather than a direct effect of ischemia itself. Histopathologic and prospective imaging studies would be required to clarify the biological mechanisms involved. Similar post-ischemic remodeling phenomena have been reported in diabetic macular edema and retinal vein occlusion.[19,20] NAION is likely multifactorial, involving structural crowding, disc edema, and microvascular dysregulation. Peripapillary interface abnormalities should therefore be interpreted as accompanying structural findings within a multifactorial process rather than primary etiologic factors.

Study Limitations

This study has several limitations. Its retrospective design and modest sample size preclude causal inference. Not all patients underwent longitudinal OCT follow-up, limiting our ability to characterize the temporal evolution of vitreoretinal interface changes. In addition, the control group did not undergo longitudinal imaging and was not matched for systemic microvascular comorbidities. Conditions such as diabetes and hypertension may independently influence vitreoretinal interface characteristics and could partially account for some of the observed differences. The absence of a comorbidity-matched disease-control cohort should therefore be considered when interpreting these findings. Because the control group consisted of healthy eyes without optic disc edema, the present study cannot determine whether peripapillary folds, superficial vascular protrusions, or retinal contour alterations are specific to NAION or represent nonspecific structural consequences of optic disc swelling. Comparative studies including other causes of optic disc edema, such as papilledema or inflammatory optic neuropathy, are required to clarify the specificity of these findings.

Furthermore, the study did not directly assess vitreopapillary adhesion over the optic nerve head but rather evaluated peripapillary retinal surface configurations using circumpapillary scans. Additionally, the OCT acquisition protocol was not specifically designed for comprehensive staging of PVD. Although both peripapillary and macular vitreoretinal interface configurations were evaluated, complete PVD staging could not be reliably performed retrospectively. Therefore, peripapillary vitreous adhesion should be interpreted within the context of age-related vitreous attachment rather than as an inherently pathologic finding.

Finally, all OCT images were evaluated by a single observer, which may have introduced observer bias, particularly in the assessment of qualitative vitreoretinal interface features. Interobserver agreement was therefore not assessed, and future studies using masked independent graders would improve the reproducibility of these findings. Despite these limitations, the structural differences observed between NAION and control eyes suggest that vitreoretinal interface configuration warrants further investigation in this setting.

Conclusion

Acute NAION is associated with distinct peripapillary and vitreomacular interface characteristics detectable by SD-OCT. Hyperreflective vitreous dots and surface contour irregularities were observed more frequently in NAION eyes than in controls, and NAION eyes demonstrated changes in vitreoretinal configuration over follow-up. These findings highlight structural differences at the vitreoretinal interface in the setting of acute NAION, although their temporal sequence and clinical significance remain uncertain. Prospective studies incorporating standardized imaging protocols and appropriate disease-control cohorts are needed to further clarify the relevance of these interface characteristics in NAION.

Ethics

Ethics Committee Approval: The study adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board of the University of Health Sciences Türkiye, Ankara Training and Research Hospital (protocol number: E-24-330, decision no: 330/2024, decision date: 18.12.2024).

Informed Consent: Informed consent was obtained from all participants.

Declarations

Authorship Contributions

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

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References

1. Hayreh SS, Zimmerman MB. Incipient nonarteritic anterior ischemic optic neuropathy. Ophthalmology. 2007;114:1763-1772.
2. Hayreh SS, Joos KM, Podhajsky PA, Long CR. Systemic diseases associated with nonarteritic anterior ischemic optic neuropathy. Am J Ophthalmol. 1994;118:766-780.
3. Berry S, Lin WV, Sadaka A, Lee AG. Nonarteritic anterior ischemic optic neuropathy: cause, effect, and management. Eye Brain. 2017;9:23-28.
4. Parsa CF, Hoyt WF. Nonarteritic anterior ischemic optic neuropathy (NAION): a misnomer. Rearranging pieces of a puzzle to reveal a nonischemic papillopathy caused by vitreous separation. Ophthalmology. 2015;122:439-442.
5. Fincham GS, James S, Spickett C, Hollingshead M, Thrasivoulou C, Poulson AV, McNinch A, Richards A, Snead D, Limb GA, Snead MP. Posterior vitreous detachment and the posterior hyaloid membrane. Ophthalmology. 2018;125:227-236.
6. Martin-Gutierrez MP, Petzold A, Saihan Z. NAION or not NAION? A literature review of pathogenesis and differential diagnosis of anterior ischaemic optic neuropathies. Eye (Lond). 2024;38:418-425.
7. Li D, Sun S, Liang J, Yue Y, Yang J, Zhi Y, Zhang X, Yu R, Li X. Papillary vitreous detachment as a possible accomplice in non-arteritic anterior ischaemic optic neuropathy. Br J Ophthalmol. 2024;108:607-612.
8. Thompson AC, Bhatti MT, Gospe SM 3rd. Spectral-domain optical coherence tomography of the vitreopapillary interface in acute nonarteritic anterior ischemic optic neuropathy. Am J Ophthalmol. 2018;195:199-208.
9. Chan JW, Liu H, Ma EL, Sadun AA, Sadda SR. Peripapillary vitreous traction syndrome: expanding the spectrum of anterior optic neuropathies. J Neuroophthalmol. 2023;43:514-519.
10. Mikhail M, Stewart S, Seow F, Hogg R, Lois N. Vitreomacular interface abnormalities in patients with diabetic macular oedema and their implications on the response to anti-VEGF therapy. Graefes Arch Clin Exp Ophthalmol. 2018;256:1411-1418.
11. Cabrera S, Katz A, Margalit E. Vitreopapillary traction: cost-effective diagnosis by optical coherence tomography. Can J Ophthalmol. 2006;41:763-765.
12. Johnson MW. Posterior vitreous detachment: evolution and complications of its early stages. Am J Ophthalmol. 2010;149:371-382.e1.
13. Katz B, Hoyt WF. Intrapapillary and peripapillary hemorrhage in young patients with incomplete posterior vitreous detachment. Signs of vitreopapillary traction. Ophthalmology. 1995;102:349-354.
14. Hondur AM, Moazami G, Hondur G, Tezel TH. Vitreopapillary findings in nonarteritic ischemic optic neuropathy versus healthy eyes: a clinical and OCT comparison. Ophthalmology. 2025;132:327-334.
15. Gabriel RS, Boisvert CJ, Mehta MC. Review of vitreopapillary traction syndrome. Neuroophthalmology. 2020;44:213-218.
16. Santos E, Maloca PM, Kawasaki A. Hyperreflective dots (HRDs) in two patients with nonarteritic anterior ischemic optic neuropathy (NAION). Klin Monbl Augenheilkd. 2025;242:471-474.
17. Ganesh SK, Mistry S, Nair N. Role of swept source optical coherence tomography in management of acute Vogt-Koyanagi-Harada's disease. Indian J Ophthalmol. 2022;70:2458-2463.
18. Vujosevic S, Dellavalle A, Romano S, Vitale L, Moretti G, Lizzio RAU, Nucci P. Hyper-reflective vitreous spots in central retinal artery occlusion: an unusual finding in two cases. Eur J Ophthalmol. 2023;33:NP101-NP104.
19. Bringmann A, Wiedemann P. Involvement of Müller glial cells in epiretinal membrane formation. Graefes Arch Clin Exp Ophthalmol. 2009;247:865-883.
20. Chatziralli I, Agapitou C, Dimitriou E, Kapsis P, Kazantzis D, Risi-Koziona A, Theodossiadis G, Theodossiadis P. Vitreoretinal interface abnormalities in patients with retinal vein occlusion in a tertiary referral center. Cureus. 2024;16:e66638.

Review

Eponymous Pupillary and Ocular Sensory Signs of Neurosyphilis: A Historical Review

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Abstract

The objective of this study was to review pupillary and ocular sensory signs historically associated with neurosyphilis, focusing on eponymous findings because they are the most traceable and consistently cited descriptors in the historical neuro-ophthalmic literature. These signs were originally described between 1850 and 1910 by five clinicians whose observations later received eponymous recognition. This study was designed as a narrative historical review supported by a structured search to ensure completeness. Only eponymous signs with established and consistent usage in the medical literature were included; purely descriptive or ambiguous terms were excluded. Searches were conducted and last updated on January 1, 2026, using PubMed/MEDLINE, Google Scholar, and major digitized archives (Gallica, HathiTrust, Internet Archive, and the Wellcome Collection). Search strategies in English, German, and French combined syphilis-related terms with the names of the relevant clinicians (Baillarger, Berger, Gowers, Haenel, and Saenger). Two reviewers independently screened the sources and extracted data on the eponym, year of description, primary reference, clinical features, and biographical background. Disagreements were resolved by consensus. Three signs involved characteristic pupillary abnormalities: unilateral mydriasis (Baillarger sign), an oval or elliptical pupil (Berger sign), and absent light reaction with a sluggish near response (Saenger sign). Two additional signs reflected sensory or autonomic involvement: diminished deep ocular sensation to digital pressure on the globe (Haenel sign) and non-specific pupillary oscillation (hippus) described by Gowers. Taken together, these findings show how clinicians attempted to localize autonomic and sensory deficits in neurosyphilis in the era before serologic testing. Although current diagnosis depends largely on serologic testing, neuroimaging, and established treatment protocols, knowledge of these historical neuro-ophthalmic signs remains clinically relevant. They can assist in identifying atypical or delayed cases and help illuminate the development of diagnostic thinking in neurosyphilis.

Keywords: Syphilis, neurosyphilis, pupil, neuro-ophthalmology, history, eponym

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Introduction

The ocular manifestations of syphilis were noted early in the nineteenth century, at a time when ophthalmology was transitioning from a predominantly surgical craft into a clinically grounded discipline supported by systematic bedside observation—such as pupillary testing and crude visual field assessment—and later by instrument-based examination.[1] In 1801, Johann Adam Schmidt (1759-1809) published the first structured clinical account of iritis.[2] Georg Joseph Beer (1763-1821) provided the earliest clear description of what was later recognized as syphilitic iritis in 1813, documenting iris inflammation with nodules and condylomata.[3]

By the mid-nineteenth century, clinical neuro-ophthalmic methods had advanced considerably. These gains were accelerated by Hermann von Helmholtz (1821-1894) and his introduction of the ophthalmoscope in 1851, which made direct visualization of the fundus possible for the first time and inaugurated modern instrument-

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based ophthalmology.[4] This new diagnostic capability allowed clinicians to observe pupillary and oculomotor abnormalities with far greater accuracy. In 1869, Douglas Argyll Robertson (1837-1909) characterized the dissociation between light and near responses that later became strongly associated with neurosyphilis.[5] Sir Jonathan Hutchinson (1828-1913) subsequently identified the triad of interstitial keratitis, notched incisors, and deafness—findings highly suggestive of congenital syphilis—illustrating the systemic diagnostic value of ocular examination.[1,6]

Therapeutic innovations profoundly altered the natural history of ocular syphilis. Before penicillin, treatment relied on arsenicals, bismuth, iodides, and fever therapy. The introduction of penicillin in 1943 greatly reduced late neurosyphilitic complications, including ocular involvement.[7] Despite these advances, recent surveillance demonstrates a global resurgence of syphilis across multiple demographic groups, renewing clinical attention to its variable ocular manifestations.[7,8,9]

Within this broader historical trajectory, several late nineteenth- and early twentieth-century neurologists and ophthalmologists described distinctive pupillary and oculomotor abnormalities that later entered the medical lexicon as eponymous signs of neurosyphilis. These findings complement more widely known eponyms such as Hutchinson's triad.[10] Importantly, although rarely encountered in regions with reliable access to treatment, these historical signs remain conceptually valuable. These signs illustrate early clinical recognition of neurosyphilitic pathways, highlight patterns still relevant to modern pupillary assessment, and provide diagnostic insight into atypical, delayed, or multisystem presentations.

This review synthesizes these pupillary and ocular sensory eponymous signs chronologically, clarifying their original descriptions, clinical significance, and relevance for contemporary neuro-ophthalmic practice.

Materials and Methods

A historical-documentary narrative review was conducted to identify pupillary and ocular sensory signs historically associated with neurosyphilis. Only eponyms with clear usage in the medical literature were included; purely descriptive or ambiguous terms were excluded. No temporal, geographic, or linguistic restrictions were applied, and both European and non-European literature was eligible. Searches of non-European literature did not identify additional pupillary or ocular sensory eponyms meeting the inclusion criteria.

Searches were completed and last updated on January 1, 2026, using PubMed/MEDLINE, Google Scholar, and major digitized repositories (Gallica, HathiTrust, Internet Archive, Wellcome Collection). Search terms in English, German, and French combined syphilis-related terminology with the names of individual physicians (e.g., Baillarger, Berger, Gowers, Haenel, and Saenger). Two reviewers independently screened all sources and extracted data on the eponym, year of origin, primary reference, clinical description, and brief biographical details. Disagreements were resolved through discussion and consensus.

Results

Between 1850 and 1910, five clinicians described pupillary and ocular sensory findings of neurosyphilis that later became established as eponymous signs (Table 1). Their original accounts were verified through primary sources and supported by authoritative secondary literature. Three signs involve distinct pupillary abnormalities: unilateral mydriasis (Baillarger), an elliptical pupil (Berger), and a sluggish near reaction with absent light response (Saenger). The remaining two signs reflect sensory or autonomic dysfunction: reduced deep ocular sensation on globe pressure (Haenel) and non-specific pupillary instability or hippus (Gowers).

Table 1. Eponymous ocular signs of neurosyphilis (1850-1910)

Name	Nationality	Date	Description	Primary finding
Baillarger sign	French	1850	Unilateral mydriasis observed in a patient with general paralysis	Pupil
Berger sign	Austrian	1889	Elliptical or oval pupil, typically with the long axis directed superomedially	Pupil
Gowers sign	British	1895	Irregular alternating pupillary constriction and dilation, sometimes observed in tabes dorsalis	Pupil/iris motility
Saenger sign	German	1902	Absent light reaction with extremely sluggish accommodation and prolonged post-accommodative constriction	Pupil
Haenel sign	German	1910	Marked reduction or absence of deep ocular sensation during firm globe pressure in patients with tabes dorsalis	Ocular sensation

Discussion

Baillarger Sign

Jules Gabriel François Baillarger (1809-1890; Figure 1) was born in Montbazon, France, and studied medicine in Tours and Paris.[11] He began his career under Jean-Étienne Esquirol (1772-1840) at the Maison de Charenton and, from 1840 onward, served as a physician at the Salpêtrière Hospital, where he spent most of his professional life. He also collaborated with Jacques-Joseph Moreau (1804-1884) at the Maison de Santé d'Ivry, eventually helping direct the institution. His 1842 monograph on hallucinations earned recognition from the National Academy of Medicine in France.[11,12]

During his life, Baillarger was a well-known figure in French psychiatry. In 1843, he helped start *Annales Médico-Psychologiques (Annals of Medical Psychology)*. In 1847, he became a member of the National Academy of Medicine, and in 1878, he became its president.[13] His scientific work encompassed neuropathology and mental disease, including studies of cerebral cortex structure, automatisms, melancholia, and general paralysis. His collected writings were later assembled as *Recherches sur les maladies mentales (Studies on Mental Illnesses)*.[11,14]

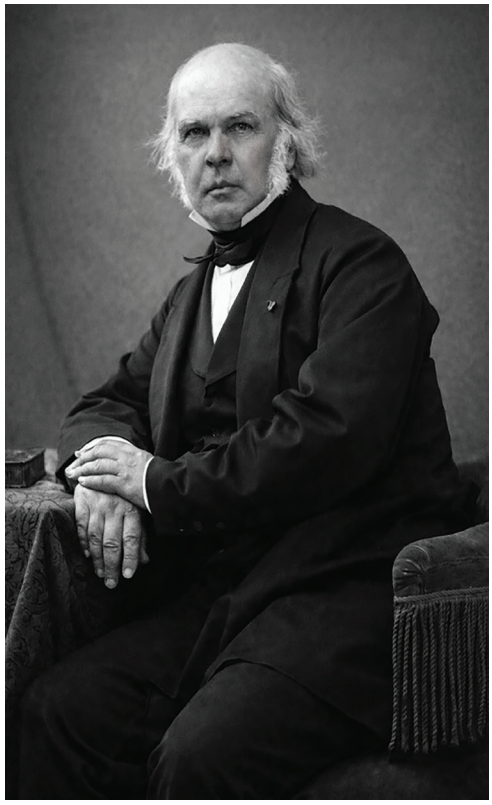


Figure 1. Jules Gabriel François Baillarger (1809-1890). Portrait recreated from an archival photograph, designed by H. Tekiner with digital-enhancement assistance

In 1850, Baillarger[15] briefly reported the case of a 59-year-old woman with general paralysis who exhibited a markedly dilated right pupil. He regarded unilateral mydriasis as an additional sign of the disease but provided no information on the light or near responses, leaving the mechanism uncertain (Table 1).

From a modern perspective, this finding may represent a tonic (Adie-type) pupil in the setting of neurosyphilis, a presentation later documented in both unilateral and bilateral forms.[16,17,18] Alternative explanations include pharmacologic dilation, partial oculomotor palsy, traumatic sphincter damage, or severe optic nerve or retinal pathology. Because pupillary reflex testing was not described, the etiology remains speculative. Baillarger sign refers to the earliest recorded description of unilateral mydriasis in general paralysis. It illustrates how clinicians closely observed pupillary abnormalities in neurosyphilis before systematic neurological examinations and serologic testing became established.

Berger Sign

Emil Berger (1855-1926) was an Austrian ophthalmologist born in Vienna. He received his medical education at the University of Vienna under Eduard von Jaeger (1818-1884), a key figure of the Vienna ophthalmological school. Berger continued his postgraduate training in Halle with Alfred Karl Graefe (1830-1899) and in Berlin under Julius Hirschberg (1843-1925), thereby gaining exposure to several leading German-speaking ophthalmic centers.[19] From 1883 to 1887, he served as an associate professor in ophthalmology at the University of Graz. He later moved to Paris, where he worked with Photinos Panas (1832-1903) and Édouard Meyer (1838-1902), completed his medical degree, and established a private eye clinic.[19,20]

Berger combined clinical practice with technical and scientific innovation. In 1883, he designed an ophthalmoscope equipped with an automatic lens-changing mechanism, reflecting his interest in improving fundus examination and increasing the reproducibility of ocular assessment. His research on ocular anatomy and on the systemic determinants of ocular pathology earned recognition from the medical faculty in Graz and from the Paris Academy of Sciences.[19]

In his 1889 study of visual disturbances in tabes dorsalis, Berger described a characteristic pupillary deformation: an elliptical or oval pupil in which the long axis typically lay obliquely upward and inward.[21] He also documented other atypical forms, such as pupils that

were longer vertically or had angular irregularities. Berger attributed these pupillary configurations to localized dysfunction of the iris sphincter, which made the aperture mechanically imbalanced.[21]

Berger sign denotes this characterization of an elliptical pupil in individuals with tabes dorsalis (Figure 2). Berger did not intend this observation as a diagnostic criterion; instead, he reported it as a recurring morphological pattern in a subset of tabetic individuals. Irregular pupils may arise from various conditions, including congenital iris anomalies, postoperative changes following corneal or cataract surgery, posterior synechiae from iritis, traumatic mydriasis, or even in association with Argyll Robertson pupil (ARP). Nonetheless, Berger's description represents one of the earliest systematic observations of iris deformities in neurosyphilis and illustrates the morphological diversity of pupillary changes encountered before the advent of serologic testing (Table 1).

Gowers Sign

Sir William Richard Gowers (1845-1915; Figure 3) was born in London and began his medical career through an apprenticeship in Essex before training at University College Hospital.[22] He became a Member of the Royal College of Surgeons in 1867, received his M.B. in 1869, and completed his M.D. with gold-medal distinction in 1870. Gowers later held senior appointments at the National Hospital for the Paralyzed and Epileptic and at University College Hospital, became a Fellow of the Royal College of Physicians in 1879, was elected to the Royal Society in 1887, and was knighted in 1897.[23]

A prolific neurologist, Gowers authored several influential texts—including *Medical Ophthalmoscopy* (1879), *The Diagnosis of Diseases of the Spinal Cord* (1880), and the two-volume *Manual of Diseases of the Nervous System* (1888)—which helped formalize the neurologic examination and emphasized the value of pupillary assessment.[24]

In his writings on the nervous system, Gowers noted that in most patients with tabes dorsalis there is a loss of the light reflex. He observed that the pupil may alternately constrict and dilate even when the light reflex appears absent, noting that this instability is seen in various neurological disorders, including neurosyphilis.[24,25] In cases where the pupillary reaction to light appears absent, using a binocular loupe may reveal delayed and passive contractions in response to light.

Within this historical context, Gowers emphasized that pupillary dynamics are shaped not only by basic light and near reflexes, but also by broader autonomic and central nervous system factors (Table 1). Although Gowers did not specifically use the term, "hippus" refers to a rhythmic, involuntary oscillation in pupillary diameter. Hippus is a non-specific finding that may accompany autonomic imbalance, metabolic disturbances, encephalopathy, or a range of other neurological disorders. This contrasts with ARP, which lacks a light response but retains constriction to near stimuli.



Figure 2. Berger sign and oval pupil

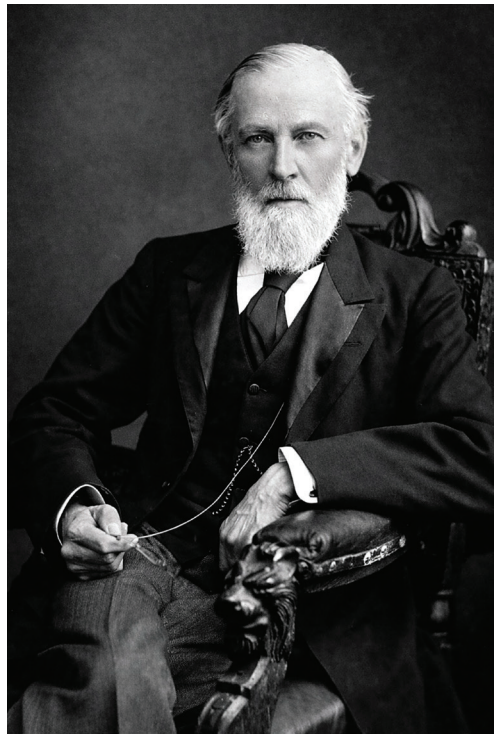


Figure 3. Sir William Richard Gowers (1845-1915). Portrait recreated from an archival photograph, designed by H. Tekiner with digital-enhancement assistance

In contemporary neurology, the term "Gowers' sign" is more commonly used for the maneuver observed in proximal myopathy, where patients use their hands to "climb up" their thighs when rising from the floor. In this review, the term is used in a more restricted historical sense, specifically referring to Gowers' observation of pupillary instability rather than the myopathic sign.

While hippus is rarely used as a diagnostic clue today, Gowers' description highlights the dynamic pupillary abnormalities seen in pre-penicillin neurosyphilis and contributes to the historical framework of neuro-ophthalmic examination.

Saenger (Pupillary) Sign

Alfred Saenger (1860-1921) was born in Mergentheim (now Bad Mergentheim) in the Kingdom of Württemberg. After completing his medical studies, he trained in Hamburg under Heinrich Eisenlohr at the Eppendorf Hospital and, from 1890, worked in the Eye Clinic at St. Georg's Hospital under Dr. Haase—an environment closely linked with the emerging academic clinics of Hamburg. This early dual exposure shaped his later neuro-ophthalmic work.[26] Working alongside Hermann Wilbrand (1851-1935), he contributed to the development of neuro-ophthalmology as a distinct field. Saenger later became associate professor of neurology at the University of Hamburg, and by 1910, chief of the Third Medical Clinic at St. Georg's Hospital. He was appointed extraordinary professor in 1919.[26] His major works include *Über Sehstörungen bei funktionellen Nervenleiden* (*On visual disturbances in functional nervous disorders*, 1892), the nine-volume *Die Neurologie des Auges* (*The Neurology of the Eye*, 1900-1922) co-authored with Wilbrand, and *Die Beurtheilung der Nervenerkrankungen nach Unfall* (*The assessment of nervous disorders following injury*, 1896).[27]

Saenger's eponymous contribution derives from his 1902 report of a patient with progressive tabes dorsalis and ARP. He observed marked pupillary asymmetry: the left pupil measured 6.2 mm, had an irregular angular contour, and showed no response to light.[28] During accommodation, however, it constricted extremely slowly and remained contracted for prolonged periods—sometimes up to five minutes—before re-dilating. The right pupil measured about 3 mm, also showed no reaction to light, and exhibited a slightly faster—though still delayed—response to near stimulation. Saenger regarded this pattern as indicative of marked disruption of the pupillary reflex pathways in tabes dorsalis (Table 1).[28]

Today, Saenger's sign denotes the triad of absent light reaction, markedly delayed accommodation, and unusually prolonged post-accommodative constriction. It represents a variant within the broader spectrum of pupillary abnormalities in late neurosyphilis, distinct from but related to the classical ARP. Although rarely encountered in modern practice, Saenger's detailed description remains an instructive example of early neuro-ophthalmic observation and of the careful bedside examination characteristic of the pre-penicillin era.

Haenel Sign

Hans Haenel (1874-1942) was born in Chemnitz, then part of the Kingdom of Saxony within the newly unified German Empire. He studied medicine at the University of Heidelberg and subsequently worked at the Psychiatric Clinic in Halle and the Municipal Hospital in Dresden-Friedrichstadt, both centers where neuropathological methods were increasingly integrated into psychiatric practice.[29] He later became chief psychiatrist at the Waldpark Sanatorium in Dresden-Blasewitz, a prominent early twentieth-century institution for mental and nervous diseases. His clinical work reflected the German neuropsychiatric tradition of careful bedside examination and close phenomenological observation.[29,30]

In 1909, at a meeting of the Central German Psychiatrists and Neurologists in Jena, Haenel presented the observation that came to be known as Haenel's sign. While examining patients with tabes dorsalis, he noted that firm pressure applied to the globe using one or two fingers against the orbital floor failed to provoke pain, discomfort, blinking, or defensive head movement. This marked reduction in deep ocular sensation occurred in roughly half of the tabetic patients he assessed and could be unilateral or bilateral.[30] Haenel attributed the finding to degenerative involvement of sensory and autonomic pathways affected in neurosyphilis, a conclusion consistent with the neuropathological understanding of the time (Table 1).

Although Haenel's sign is no longer used diagnostically, it illustrates the profound sensory deficits once seen in late neurosyphilis before the advent of effective antimicrobial therapy. In contemporary practice, pronounced ocular hypoesthesia more commonly suggests trigeminal neuropathy, neurotrophic keratopathy, or sensory impairment secondary to herpetic, diabetic, or surgical injury rather than tabes dorsalis. Nonetheless, Haenel's account remains a clear example of early neuro-ophthalmic bedside elicitation and of how clinicians sought subtle sensory changes to characterize neurosyphilitic involvement of the cranial nerves.

Study Limitations

Historical research presents certain constraints when performing a review. Digitization biases have primarily favored fully digitized journals in English, French, and

German, which has resulted in underrepresentation of sources in other languages or those with limited archival preservation. Moreover, unsuccessful or negative bedside signs were likely underreported, contributing to survivorship bias. Incomplete biographical information and variations in translation introduce further limitations.

Conclusion

Syphilis remains a substantial clinical and public health concern, particularly among individuals aged 18–49 years. Recent U.S. surveillance data indicate that between 2019 and 2023, syphilis cases in females increased by 112%, while congenital syphilis rose by 106%—a pattern echoed internationally.[7] This epidemiological revival coincides with increasing reports of syphilitic eye disease, highlighting the necessity for timely diagnosis, partner assessment, and suitable treatment. Intravenous aqueous crystalline penicillin G remains the recommended treatment for neurosyphilis and ocular involvement.

Importantly, while early ocular syphilis most commonly manifests as uveitis or optic neuropathy, the eponymous signs described by Baillarger, Berger, Saenger, Haenel, and Gowers predominantly represent late neurosyphilis—especially tabes dorsalis—and are now rarely seen where effective treatment is accessible. These historical observations clarify the diverse mechanisms through which *Treponema pallidum* can affect the visual system and demonstrate how detailed documentation of pupillary and ocular sensory findings once guided neurologic diagnosis. Although contemporary management relies chiefly on serologic testing, neuroimaging, and standardized treatment protocols, familiarity with these earlier signs—together with careful pupillary examination—may still aid in recognizing atypical, multisystem, or treatment-delayed presentations, and serves as an educational link between historical neuro-ophthalmic practice and modern clinical reasoning.

Declarations

Authorship Contributions

Concept: H.T., S.H.Y., E.S.Y., Design: H.T., S.H.Y., E.S.Y., Data Collection or Processing: H.T., S.H.Y., E.S.Y., Analysis or Interpretation: H.T., S.H.Y., E.S.Y., Literature Search: H.T., S.H.Y., E.S.Y., Writing: H.T., S.H.Y., E.S.Y.

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References

1. Wilhelmus KR. The history of ocular syphilis. In: Bialasiewicz AA, Schaal KP, eds. Infectious Diseases of the Eye. Boston: Butterworth & Heinemann; 1994:494-498.
2. Schmidt JA. Ueber Nachstaar und Iritis nach Staaroperationen [On After-Cataract and Iritis Following Cataract Operations]. Wien: Camesina; 1801.
3. Beer GJ. Lehre von den Augenkrankheiten [Textbook of Eye Diseases]. Wien: Camesinische Buchhandlung; 1813.
4. Helmholtz H. Beschreibung eines Augen-Spiegels zur Untersuchung der Netzhaut im lebenden Auge [Description of an Eye-Mirror for Examining the Retina in the Living Eye]. Berlin: A. Förstner; 1851.
5. Robertson DA. On an Interesting Series of Eye-Symptoms in a Case of Spinal Disease, with Remarks on the Action of Belladonna on the Iris, Etc. Edinb Med J. 1869;14:696-708.
6. Hutchinson J. Syphilis. London: Cassell & Co.; 1887.
7. Chevalier FJ, Bacon O, Johnson KA, Cohen SE. Syphilis: a review. JAMA. 2025;334:1927-1940.
8. Chauhan K, Fonollosa A, Giralt L, Artaraz J, Randerson EL, Goldstein DA, Furtado JM, Smith JR, Sudharshan S, Ahmed AS, Nair N, Joseph J, Pavesio C, Westcott M, Trepatchayakorn S, Sallam AB, Elhusseiny AM, Tyagi M. Demystifying ocular syphilis - a major review. Ocul Immunol Inflamm. 2023;31:1425-1439.
9. Furtado JM, Simões M, Vasconcelos-Santos D, Oliver GF, Tyagi M, Nascimento H, Gordon DL, Smith JR. Ocular syphilis. Surv Ophthalmol. 2022;67:440-462.
10. van Ruth S, Toonstra J. Eponyms of Sir Jonathan Hutchinson. Int J Dermatol. 2008;47:754-758.
11. Ritti A. Mort de M. le Dr Baillarger [Death of Dr Baillarger]. Ann Med Psychol. 1891;13:161-168.
12. No author list. Obituary: M. Baillarger. J Ment Sc. 1891;37:333.
13. Baillarger. In: Gilman DC, Peck HT, Colby FM, eds. The New International Encyclopaedia. Vol. 2. New York: Dodd, Mead & Co.; 1902:363.
14. Magnan V. A eulogy on Baillarger. J Ment Pathol. 1903;4:136-138.
15. Baillarger J. Paralysie générale: nouveau symptôme [General paralysis: new symptom]. Gaz Hosp Civ Milit. 1850;2:225.
16. Camoriano GD, Kassab J, Suchak A, Gimbel HV. Neurosyphilis Masquerading as an Acute Adie's Tonic Pupil: Report of a Case. Case Rep Ophthalmol. 2011;2:205-210.
17. Jivraj I, Johnson M. A rare presentation of neurosyphilis mimicking a unilateral Adie's tonic pupil. Semin Ophthalmol. 2014;29:189-191.
18. Sakai T, Shikishima K, Mizobuchi T, Yoshida M, Kitahara K. Bilateral tonic pupils associated with neurosyphilis. Jpn J Ophthalmol. 2003;47:368-371.
19. Schett A. Emile Berger (1855-1926). In: The Ophthalmoscope: Textbook. Vol. 2. Oostende: J.-P. Wayenborgh; 1996:218-221.
20. Koren N. Jewish Physicians: A Biographical Index. Jerusalem: Israel Universities Press; 1973.
21. Berger E. Die Sehstörungen bei Tabes dorsalis und Versuch einer einheitlichen Erklärung des Symptomencomplexes der Tabes [Visual disturbances in tabes dorsalis and an attempt at a unified explanation of the symptom complex of tabes]. Arch Augenheilkd. 1889;19:391-454.
22. Critchley M. Neurological biographies: Sir William Gowers (1845-1915). Cent Afr J Med. 1958;4:212-215.

23. [No author]. Obituary: Sir William Richard Gowers. Lancet. 1915;185:1055-1056.
24. Gowers WR. A Manual of Diseases of the Nervous System. Vol. 1. Philadelphia: P. Blakiston, Son & Co.; 1895:407.
25. Leftwich RW. An Index of Symptoms with Diagnostic Methods. London: Smith, Elder & Co.; 1915.
26. No author list. Alfred Saenger. Z Gesamte Neurol Psychiatr. 1921;69:364.
27. No author list. Reviews and notice of books. Lancet. 1907;170:230-232.
28. Saenger A. Ueber myotonische Pupillenbewegung [On myotonic pupillary movement]. Neurol Zentralbl. 1902;21:837-839.
29. No author list. Hänel, Hans. Katalog der Deutschen Nationalbibliothek [Catalogue of the German National Library]. https://d-nb.info/gnd/136755739. Accessed April 13, 2026.
30. Haenel H. Ein neues Symptom bei Tabes dorsalis [A new symptom in tabes dorsalis]. Neurol Zentralbl. 1910;29:459-461.

Case Report

Anatomopathological Aspects and Clinical Correlation of Conjunctival Bleb Fibrosis Following Encapsulation of a Biodegradable Collagen Matrix Implant in Glaucoma Surgery

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Abstract

This study reports a case series of glaucoma patients in whom a biodegradable collagen-glycosaminoglycan implant (Ologen®) failed to prevent fibrosis after non-penetrating deep sclerectomy (NPDS) and describes the associated histopathological findings. This single-centre retrospective study included four patients with progressive glaucoma and inadequate intraocular pressure (IOP) control despite maximal medical therapy. All underwent NPDS with implantation of a collagen-glycosaminoglycan matrix and adjunctive mitomycin C. Postoperative follow-up included IOP monitoring, slit-lamp examination, and photographic documentation. Patients with bleb failure required surgical revision, and excised tissue, including the implant and surrounding Tenon's capsule, was analysed histologically. All cases developed progressive bleb fibrosis. The implants remained intact, encapsulated by dense fibrotic tissue ("ring-of-steel" appearance), with minimal fibroblast infiltration, extensive collagen deposition, and no significant degradation for up to three years. These findings highlight variability in tissue response and suggest a potential role of patient-specific fibrotic predisposition in surgical outcomes.

Keywords: Biodegradable collagen-glycosaminoglycan implant, glaucoma surgery, fibrosis, wound modulation, biodegradation

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Introduction

Filtering surgery remains the most widely used surgical intervention for glaucoma.[1] These procedures aim to create a fistulous tract between the anterior chamber and the subconjunctival space to facilitate the drainage of aqueous humour and reduce intraocular pressure (IOP). As a result, aqueous humour accumulates in a subconjunctival reservoir known as the filtration bleb. The primary cause of surgical failure is excessive formation of fibrotic tissue around the new drainage pathway,[2,3] which compromises proper functioning of the bleb.

Glaucoma surgery is intrinsically pro-fibrotic[2] due to a chronic pro-inflammatory conjunctival environment that often results from prolonged use of topical medications, preservative agents in eye drops, hypersensitivity to active compounds, and a high prevalence of dry eye disease. Furthermore, postoperative tissue exposure to aqueous humour, which is rich in pro-inflammatory cytokines, promotes fibroblast activation.[4]

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Fibrotic scarring involves the excessive synthesis of extracellular matrix (mainly consisting of dense, organised collagen fibres[3]) and the persistence of myofibroblasts that should normally undergo apoptosis.[2] Effectively modulating this fibrotic response is crucial for improving surgical outcomes.

Advances in tissue engineering have provided alternative strategies to modulate wound healing and reduce scar formation after glaucoma surgery, such as biodegradable implants. Unlike antimetabolites, whose non-specific inhibition of cell proliferation may lead to significant ocular toxicity, these implants promote the formation of functionally effective filtering blebs while degrading into non-toxic byproducts, thereby eliminating the need for surgical removal.[5]

Ologen® (Aeon Astron Europe B.V., Leiden, the Netherlands) is a biocompatible, biodegradable implant composed of collagen (90%) and glycosaminoglycan (10%).[5,6] These components are organised in a three-dimensional system, creating a 95% porous structure that acts as a biological scaffold for the healing process,[7,8,9] facilitating fibroblast growth inside the implant and guiding their migration to create a loose, randomly organised deposition of connective tissue similar to physiological conditions.[6,7,8,9] This is the mechanism underlying the implant's modulation of wound healing.[8,10,11,12] However, it is important to highlight that the implant itself does not have antifibrotic properties and could therefore hypothetically cause a secondary tissue reaction in the subconjunctival space.[13] To avoid this reaction and modulate its immunogenicity, the collagen is purified with pepsins that eliminate telopeptides, which are the N- and C-terminal amino acid sequences responsible for the antigenicity of the collagen molecule.[10,11,14,15]

Various published surgical series comparing patients undergoing surgery with and without the implant have yielded inconclusive results regarding its potential to enhance the antifibrotic effect of other techniques (summarised in Tables 1[3,7,8,9,16-27] and 2[12,13,14,15,28-41]). In this case series, we present four cases of glaucoma surgery in which this biodegradable collagen-glycosaminoglycan implant failed to prevent fibrosis and was associated with an encapsulating fibrotic response surrounding the implant, which ultimately compromised surgical success.

Case Reports

Case 1

A 56-year-old female patient with moderate primary open-angle glaucoma (POAG) underwent non-penetrating deep sclerectomy (NPDS) with an intrascleral Esnoper V Clip implant, subconjunctival Ologen® implantation (6 mm×2 mm), and a subconjunctival injection of 0.1 mL 0.01% mitomycin C (MMC). The patient exhibited progressive bleb flattening during the postoperative follow-up, causing a rise in IOP and requiring additional hypotensive medical therapy. One year after the initial surgery, the patient underwent surgical bleb revision. Intraoperatively, fibrotic conjunctiva and Tenon's capsule were observed encasing the intact Ologen® implant. Histopathological analysis revealed focal areas of dense fibrosis within the collagen matrix (Figure 1), with disorganised collagen bundles and scattered inflammatory cell infiltration, indicating a chronic foreign body reaction. Additionally, no significant degradation of the implant was observed.

Case 2

An 85-year-old female patient diagnosed with advanced POAG presented with inadequately controlled IOP despite maximally tolerated topical treatment. She underwent NPDS with a subconjunctival MMC injection and Ologen® implantation (6 mm×2 mm). During the postoperative course, the bleb developed an avascular appearance with cystic spaces and fluorescein leakage (Figure 2A). The patient was therefore scheduled for surgical bleb revision. Intraoperatively, the Ologen® implant was found to be intact 18 months after implantation, surrounded by a dense fibrotic capsule resembling a "ring-of-steel" reaction. This caused retraction of Tenon's capsule, leaving an area of thin, avascular limbal conjunctiva. Histopathological analysis (Figure 2B) confirmed the absence of Ologen® degradation,

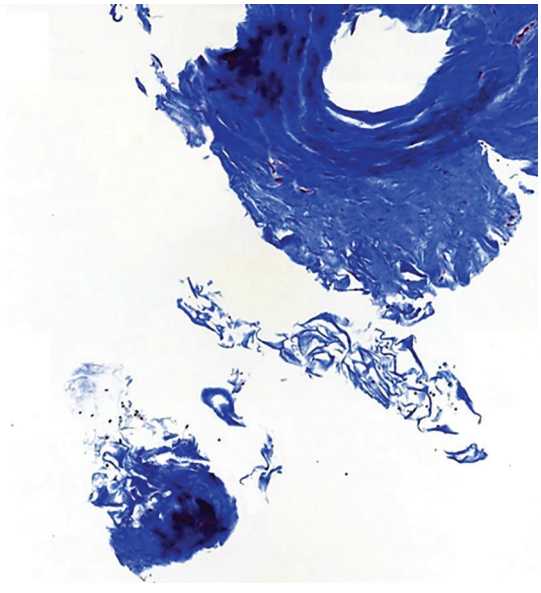


Figure 1. Masson's trichrome-stained sections showing fibrosis associated with exogenous mesh-like material (Ologen®)

Table 1. Published studies evaluating the safety and efficacy of Ologen® and MMC as adjuvants in trabeculectomy surgery for glaucoma

		Study	Type of study	Groups	N	Follow-up (months)	Outcomes	MMC dose	Complications
Compared to MMC-enhanced trabeculectomy	OLO > MMC	Yuan et al. 2015[16]	Prospective randomised	Trab + OLO	31	60	Higher success rates (complete and qualified) in OLO group Lower IOP in OLO group	0.2 mg/mL 2 min	No significant differences between groups
				Trab + MMC	32				
		El-Sayyad et al. 2017[17]	Prospective randomised *(JOAG)*	Trab + OLO	20	12	Lower IOP at end point in OLO group Better MBGS scoring of blebs in OLO group	0.4 mg/mL 2 min	Higher rate of hypotony in MMC group Less needling and suture lysis in OLO
				Trab + MMC	20				
	OLO = MMC	Cillino et al. 2011[18]	Prospective randomised	Trab + OLO	20	24	No differences in mean IOP and IOP reduction at end point. No differences in complete and qualified success at any target IOP Higher bleb height in OLO group	0.2 mg/mL 2 min	Higher incidence of early hypotony in MMC, although not statistically significant Higher incidence of early bleb leak in OLO group
				Trab + MMC	20				
		Chelerkar et al. 2021[19]	Prospective non-randomised	Phaco + Trab + OLO	40	12	No statistically significant differences in IOP or bleb height, area, and vascularity	0.2 mg/mL 2 min	No significant differences between groups
				Phaco + Trab + MMC	53				
		Glandorf et al. 2020[20]	Retrospective	Trab + MMC	43	12	No differences in IOP reduction, complications, or need for additional medical treatment Greater success with MMC alone, although not statistically significant	0.2 mg/mL 1 min	No significant differences between groups
				Trab + MMC + OLO + BVZ	46				
				Trab + MMC + OLO + intracameral BVZ	41				
		Paul et al. 2022[21]	Prospective non-randomised	Phaco + Trab + OLO	18	12	No differences in IOP reduction or need for additional medical treatment Better bleb morphology in OLO group	0.2 mg/mL 1 min	No significant differences between groups
				Phaco + Trab + MMC	16				
		Navero-Rodríguez et al. 2024[22]	Retrospective non-randomised	Trab + MMC	44	36	No differences in IOP reduction, use of topical medications, or complete and qualified success rates More suture release and bleb needling with MMC alone	0.2 mg/mL 2 min	No significant differences between groups
				Trab + OLO	34				
				Trab + OLO + MMC	41				

Table 1. Continued

		Study	Type of study	Groups	N	Follow-up (months)	Outcomes	MMC dose	Complications
Compared to MMC-enhanced trabeculectomy	OLO < MMC	Rosentreter et al. 2010[23]	Prospective randomised	Trab + OLO	10	12	Lower IOP at end point in MMC group Higher complete success rate in MMC group More avascularity in MMC group	0.2 mg/mL 3 min	No significant differences between groups
				Trab + MMC	10				
		Senthil et al. 2013[7]	Prospective randomised	Trab + OLO	19	24	Lower mean IOP reduction at 6 months in OLO group No differences at 12 and 24 months	0.4 mg/mL 2 min	More hyphaema in OLO group
				Trab + MMC	20				
		Rosentreter et al. 2014[24]	Prospective randomised	Trab + OLO	15	12	Lower IOP at end point in MMC group Higher success rate in MMC group	0.2 mg/mL 3 min	No significant differences between groups
				Trab + MMC	15				
		Narayanaswamy et al. 2013[8]	Prospective non-randomised	Phaco + Trab + OLO	33	12	Lower IOP in MMC group Greater bleb area in MMC group OLO blebs were more vascular Needling required more frequently in OLO group	0.4 mg/mL 2 min	No significant differences between groups
				Phaco + Trab + MMC	33				
		Sen et al. 2018[25]	Prospective randomised	Trab + MMC	25	12	Greater IOP reduction in MMC group Blebs more diffuse in MMC group More avascular blebs in MMC group	0.1 mg/mL 1 min	More hypotony in MMC group
				Trab + MMC + OLO	25				
Compared to standalone Trab		Papaconstantinou et al. 2010[3]	Prospective randomised	Trab + OLO	20	6	No significant differences between groups in IOP or topical medication use	-	No significant differences between groups
				Trab standalone	20				
Compared to standalone and enhanced Trab		Khairy et al. 2023[26]	Prospective randomised *(PCG)*	CTT without augmentation	21	12	No differences in IOP at end point No differences in success rates, failure rates, or survival rates between groups	0.2 mg/mL 3 min	No significant differences between groups No report of hypotony or shallow AC in OLO group
				CTT + MMC	21				
				CTT + OLO	21				
Non-comparative		Angmo et al. 2017[27]	Retrospective	Trab + OLO + MMC	23	24	Significant reduction in IOP and use of hypotensive medications Complete success in 92.6% Failure in 3.7%	0.1 mg/mL 1 min	Shallow AC in 14.8% Encapsulated blebs requiring needling in 11.1%
		Dada et al. 2013[9]	Retrospective	Trab + OLO+MMC	33	12	Significant reduction in IOP and use of hypotensive medications	0.1 mg/mL 1 min	2 cases of shallow AC 2 cases of encapsulated blebs requiring needling

MMC: Mitomycin C, OLO: Ologen, Trab: Trabeculectomy, IOP: Intraocular pressure, JOAG: Juvenile open-angle glaucoma, MBGS: Moorfields Bleb Grading System, CTT: Combined trabeculotomy and trabeculectomy, Phaco: Phacoemulsification, BVZ: Bevacizumab, PCG: Primary congenital glaucoma, AC: Anterior chamber

Table 2. Studies evaluating the safety and efficacy profile of Ologen® in other types of glaucoma surgery								
Surgery	**Study**	**Type of study**	**Groups**	**N**	**Follow-up (months)**	**Outcomes**	**MMC dose**	**Complications**
GDD	Rosentreter et al. 2010[28]	Retrospective	Excision of GDD capsule + MMC + OLO	10	8-12	Adding OLO to capsule excision + MMC yielded higher success rate when revising GDD No significant differences in IOP	0.2 mg/mL 2 min	-
			Excision of GDD capsule + MMC	9				
	Salimi et al. 2019[29]	Retrospective	Excision of GDD capsule + MMC + OLO	12	36	No significant differences between groups in IOP reduction, hypotensive medications or success rate Valid strategy for GDD revision, successful in reducing IOP in both groups	0.5 mg/mL 2 min	Significantly lower rate of complications in OLO group – no report of erosion of GDD, although MMC group had an erosion rate of 25%
			Excision of GDD capsule + MMC	11				
	Song et al. 2017[30]	Retrospective	Conventional GDD	24	6	Same IOP reduction, no differences in success. Enzymatic degradation rate of OLO-7 was slower	-	Lower hypotony rates in OLO groups than in conventional surgery, and less hyphaema or choroidal effusion.
			GDD + OLO-6	20				
			GDD + OLO-7	24				
	Stephens et al. 2016[12]	Retrospective	Report of erosion rates when using OLO over GDD tube	43	12-45	95.4% required no intervention for tube erosion	-	-
	Kim et al. 2018[31]	Retrospective	GDD + OLO over plate	8	12	No differences between groups in overall IOP reduction, complete or qualified success. Number of IOP-lowering medications was significantly lower in OLO group during the early hypertensive phase	-	No differences in complication rates.
			Conventional GDD	12				
	Sastre-Ibáñez et al. 2019[32]	Prospective randomised	GDD + OLO over plate	27	12	No differences between groups in IOP reduction, complete or qualified success or survival rates.	-	No differences in complication rates.
			Conventional GDD	31				
	Suzuki Junior et al. 2023[33]	Retrospective multicentre case-control	GDD + OLO over plate	25	6	No significant differences between groups in IOP reduction, hypotensive medication use, or complete success rate Better outcomes in OLO group for qualified success	-	No differences in complication rates.
			Conventional GDD	100				

Table 2. Continued

Surgery	Study	Type of study	Groups	N	Follow-up (months)	Outcomes	MMC dose	Complications
NPDS	Guedes et al. 2019[34]	Retrospective	Phaco-NPDS + MMC + OLO	51	12	Significantly lower IOP and greater IOP reduction in OLO group Lower rate of medication use in OLO group	0.2 mg/mL subconjunctival injection	Higher rate of needling in group without OLO
			Phaco-NPDS + MMC	49				
	Aptel et al. 2009[35]	Prospective	NPDS enhanced with OLO in scleral bed	15	3	Significant reduction in IOP Large fluid-filled spaces on AS-OCT, lower reflectivity in OLO group	-	-
	Elmekawey et al. 2020[36]	Retrospective	NPDS + OLO	20	6	Significant reduction in IOP and better bleb morphology in OLO group	-	-
			NPDS	20				
XEN	Park et al. 2022[37]	Retrospective	XEN (± Phaco) + OLO	61	6	No significant differences in IOP reduction or antiglaucoma medication	0.4 mg/mL 2 min	Hypotony reported in OLO-augmented group, possibly related to increased filtration facilitated by aqueous humour absorption by OLO No significant differences between groups
			XEN (± Phaco)	42				
	Navero-Rodríguez et al. 2020[38]	Case-control	XEN + OLO + MMC	74	Not reported	No differences between groups in IOP reduction or glaucoma medication use	0.1 mg/mL subconjunctival injection	More late bleb fibrosis with XEN standalone - more needling or 5-FU needed in this group
			XEN + MMC	75				
	Jin et al. 2025[39]	Retrospective	XEN ab externo + OLO + MMC	47	12	Significantly lower rate of medication use and bleb revisions in OLO group Greater cumulative surgical success in OLO group	0.2-0.4 mg/mL subconjunctival injection	Lower rate of complications in OLO group
			XEN ab interno + MMC	29				
PRESERFLO	Vastardis et al. 2021[40]	Retrospective	PRESERFLO + MMC + OLO	25	6	Comparable results in terms of IOP reduction and medication usage	0.2 mg/mL 3 min	Bleb fibrosis more frequent in OLO group
			PRESERFLO + MMC	25				

Table 2. Continued

Surgery	Study	Type of study	Groups	N	Follow-up (months)	Outcomes	MMC dose	Complications
Ex-PRESS	Johnson & Sarkisian 2014[15]	Retrospective	Ex-PRESS + OLO	49	12	Significant reduction with no differences between groups. OLO is an effective alternative, but not superior to MMC	0.4 mg/mL 2 min	Similar rate of complications in both groups
			Ex-PRESS + MMC	50				
	Menda et al. 2015[41]	Retrospective	Ex-PRESS + OLO	7	12	Higher IOP and reoperation rate in OLO-only group	0.5 mg/mL 3-4 min	Higher rate of bleb leak in OLO-only group
			Ex-PRESS + MMC	34				
			Ex-PRESS + OLO + 5-FU	14				

MMC: Mitomycin C, GDD: Glaucoma drainage device, OLO: Ologen, IOP: Intraocular pressure, NPDS: Non-penetrating deep sclerectomy, Phaco: Phacoemulsification of cataract, AS-OCT: Anterior segment optical coherence tomography, 5-FU: 5-fluorouracil

minimal fibroblast migration into the scaffold, and a thick wall of organised collagen deposition surrounding the implant.

Case 3

A 56-year-old female patient with a history of diabetic retinopathy was referred for primary angle-closure glaucoma. The patient developed toxicity associated with hypotensive treatment, and glaucoma progression was noted in the left eye. Therefore, NPDS with MMC injection and Ologen® implantation (6 mm×2 mm) was performed. Postoperatively, the bleb progressively became fibrotic, necessitating an escalation in hypotensive treatment. Bleb revision was performed three years after the initial procedure. Intraoperative findings revealed a highly retracted Tenon's capsule that had contracted the bleb around the Ologen® matrix, which had remained intact for three years (Figure 3A). Histopathological assessment

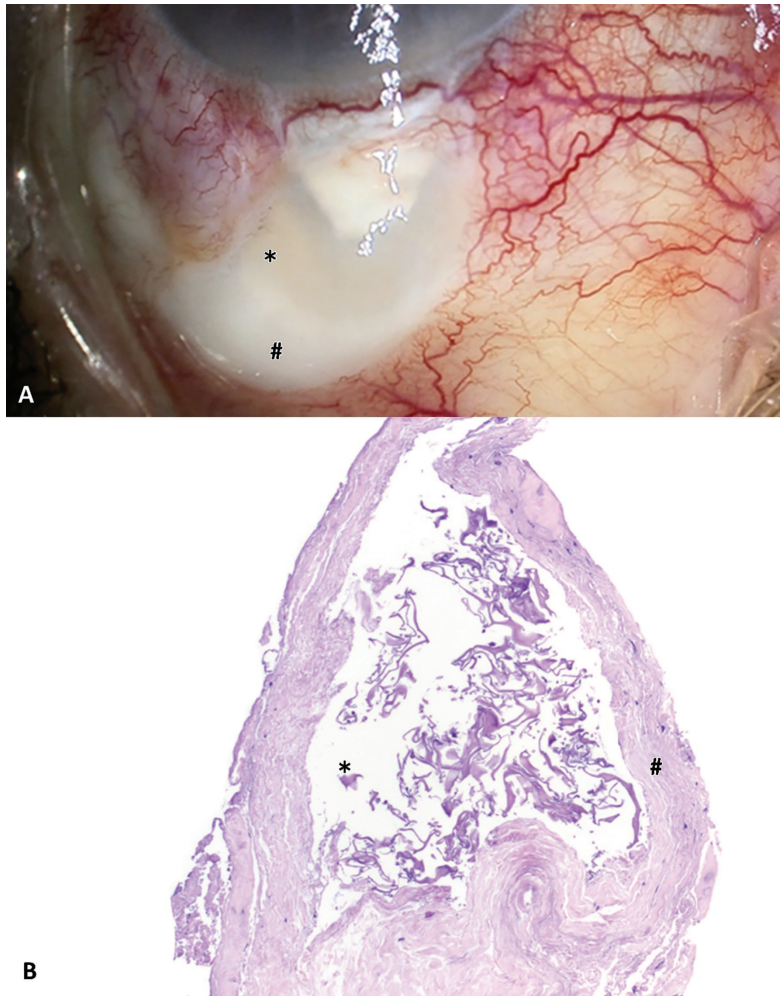


Figure 2. A) Intraoperative image showing the presence of Ologen® (*) surrounded by a fibrotic wall (#). B) Histopathological examination of haematoxylin- and eosin-stained sections of the resected bleb demonstrated that the Ologen® matrix (*) remained intact with very little fibroblast migration and a fibrotic wall encapsulating it (#)

(Figure 3B) revealed dense fibrotic tissue surrounding exogenous mesh-like material (Ologen®).

Case 4

A 53-year-old female patient diagnosed with pigmentary glaucoma presented with a long history of topical antiglaucoma therapy. Visual field progression warranted a combined phacoemulsification and NPDS procedure enhanced with MMC and Ologen® implantation (6 mm×2 mm). IOP control remained inadequate a year after the procedure, with a fibrotic bleb that required needling on two separate occasions to reach target IOP. During surgical bleb revision, an intense scarring reaction was observed around the scleral flap and Ologen® implant. The implant was encapsulated in a manner similar to a foreign body reaction. After debridement of the fibrous tissue and removal of the residual Ologen® matrix, a single-layer pericardial graft was placed to reinforce the scleral flap. Histological examination revealed the Ologen® material embedded within a hyalinised collagenous matrix with minimal fibroblast presence (Figure 4).

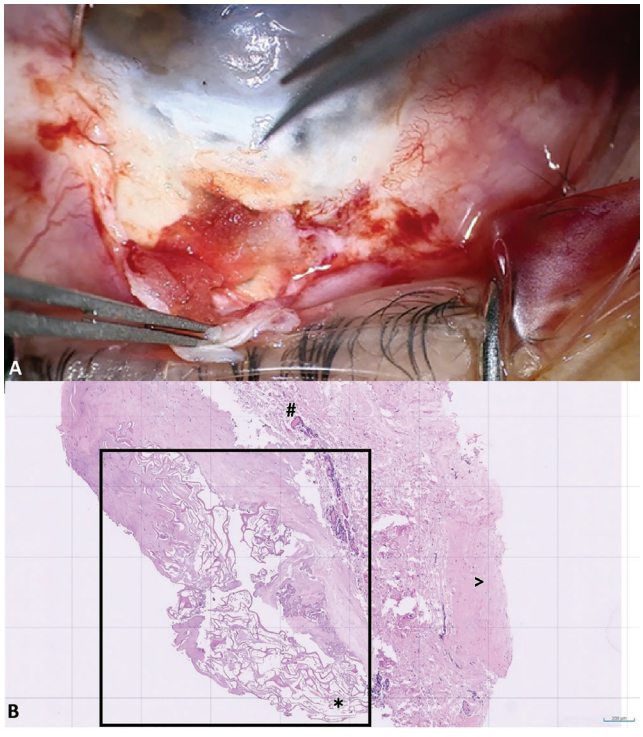


Figure 3. A) Intraoperative image of intact Ologen® trapped in fibrotic tissue. B) Severe fibrosis and dense collagen deposition in a haematoxylin and eosin-stained sample from Case 3. Exogenous mesh-like material (Ologen) is surrounded by dense fibrotic tissue (*), fibroblasts (#) and blood vessels (>)

Following bleb revision, all patients demonstrated improved bleb function and better IOP control. No additional surgical procedures were required during follow-up, and IOP remained stable with or without adjunctive medical therapy depending on the case.

Discussion

Numerous studies have examined the effectiveness of Ologen® across several types of glaucoma surgery (summarised in Tables 1[3,7,8,9,16-27] and 2[12,15,28-41]). However, interpretation is challenging due to variability in study design, limited sample sizes, and differences in surgical technique, including MMC timing and dosage. The heterogeneity of methodologies, from randomised trials to retrospective studies, further limits generalisability, resulting in inconsistent and sometimes contradictory findings.

Most literature focuses on comparisons with MMC in trabeculectomy. Meta-analyses report no significant differences in IOP control or success rates at 12-24 months.[6,13] This implant is generally considered a safe and viable alternative to MMC; the absence of avascular blebs in the treatment groups, alongside a low incidence of postoperative complications, has been consistently reported.[18,25] Additionally, this matrix promotes physiological bleb vascularisation[23] and serves as a mechanical buffer that mitigates overfiltration during the early postoperative period, potentially reducing the risk of hypotony.[35] In contrast, MMC is often associated with diffuse bleb formation, which may contribute to sustained long-term IOP reduction,[25] albeit at the cost of an increased risk of early hypotony and avascular bleb development.[18,25]

Beyond trabeculectomy, studies on Ologen® use with glaucoma drainage devices (GDD) indicate that the implant may improve success rates when used as a patch graft over the tube.[28,29] While no significant differences in IOP reduction were observed,[29,30,31,32,33] it appears to lower the risk of tube exposure.[28]

The biodegradable collagen-glycosaminoglycan implant modulates the deposition of connective tissue in a manner that more closely replicates physiological wound healing. It prevents direct contact between the conjunctiva and sclera, thereby acting as a biological spacer.[12,42] Regarding the physical characteristics of filtering blebs, studies have reported mixed findings on the height and volume occupied by the collagen matrix. Some investigations indicate that the matrix can fill the entire subconjunctival space of the bleb, whereas others suggest that it occupies only a limited volume and gradually resorbs. Early postoperative observations consistently show that blebs in eyes receiving this implant appear more prominent than those in eyes

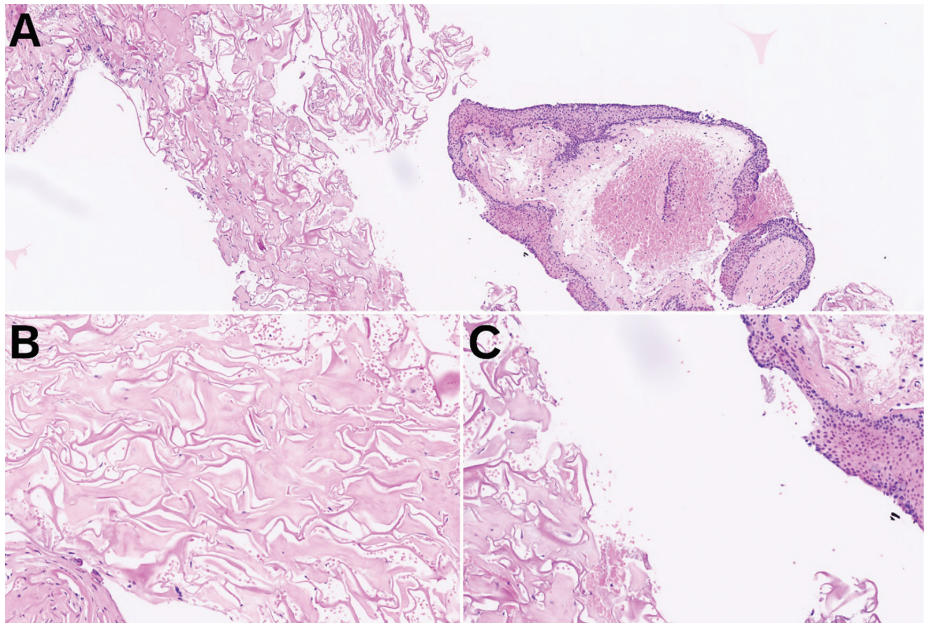


Figure 4. Histological sections of a surgical sample from Case 4, stained with haematoxylin and eosin. A) Fibrotic scar tissue around the Ologen® material (left) alongside a fragment of normal conjunctival mucosa. B) Detail of the fibrotic tissue showing sparse fibroblasts in a hyalinised collagenous matrix with entrapped mesh-like exogenous material. C) Close-up of the normal-appearing conjunctival mucosa (right) adjacent to the scar tissue (left)

treated with MMC, likely reflecting the immediate space-occupying effect of the subconjunctival implant.

Nevertheless, several studies report a higher incidence of encapsulated blebs and an increased need for postoperative needling.[8,9,27] In a study by Min et al.[43], encapsulated blebs developed more frequently and more rapidly in eyes receiving this matrix compared to those undergoing conventional trabeculectomy. Most encapsulated blebs were observed between the second week and the first month postoperatively. The authors proposed that non-contractile, collagen-producing fibroblasts play a key role in this process. Because this implant is biodegradable, it may facilitate migration of fibroblasts into the bleb, contributing to early encapsulation. To mitigate this, the authors suggested strategies such as soaking it in relatively high concentrations of antimetabolites, applying antimetabolite eye drops in the early postoperative period, or injecting antimetabolites directly into the bleb during the first one to two weeks after surgery.

In a case reported by Voykov and Rohrbach[11], the implant remained in place one month after surgery, but no filtering bleb was observed. Histopathology showed no foreign body reaction or inflammatory infiltrate, with early fibrosis and vascularisation confined to the implant margins. These findings align with those of Rosentreter et al.[23], who reported fibroblast infiltration of the Ologen implant, encasement by a collagenous pseudocapsule, accumulation of α-smooth muscle actin-positive myofibroblasts, collagen III deposition at the implant borders and within the pseudocapsule, strong fibronectin expression, and positive prolyl-4-hydroxylase staining in both the implant and overlying epithelium.

Studies on NPDS have demonstrated substantial reductions in IOP and the need for glaucoma medications.[34,35,36] These observations are consistent with our own clinical findings. Similarly, subconjunctival devices such as XEN, PRESERFLO, and Ex-PRESS demonstrate comparable IOP reductions and medication usage between eyes treated with antimetabolites and those receiving this biodegradable collagen-glycosaminoglycan implant.[15,37,38,40,41] Although late bleb fibrosis requiring subsequent needling or 5-fluorouracil was more frequently reported in the XEN group without Ologen,[38] the incidence of fibrosis was higher in the PRESERFLO group when Ologen was used.[40] In fact, individual genetic predisposition to a fibrotic response may also contribute to surgical outcomes. A hyper-fibrotic gene expression profile has recently been identified in patients experiencing surgical failure (with conjunctival overexpression of genes such as *VEGFA* or *CXCL8*).[44] We hypothesise that patients with this hyper-fibrotic profile may be inherently more prone to exaggerated scarring responses in general,

and specifically to Ologen®, undermining its intended modulatory function.

This collagen matrix is designed for complete degradation within 90 to 180 days.[19,35] However, factors such as the degree of cross-linking, type of collagen preparation, and enzymatic processing can influence this timeline.[30] In our clinical experience, degradation timelines deviated markedly from expectations: in Case 2, Ologen® remained intact for 18 months after implantation, and in Case 3, it persisted for 3 years. This phenomenon may be attributable to an encapsulating immunological reaction surrounding the implant, which prevents enzymatic degradation by tissue proteases. Similar histopathological findings have been reported by Selvan et al.[45], who described a "ring-of-steel" reaction encasing the intact implant in both eyes of the same patient. This phenomenon was observed following the use of MMC-soaked Ologen® and was thought to result from the prolonged localised effect of MMC and the resultant excessive fibroblast proliferation in the surrounding tissue. The observations with GDD and NPDS support the hypothesis of Stephens and Sarkisian[12] that this implant could become encapsulated when not directly exposed to aqueous humour, potentially hindering its biodegradation. In addition, other possible complications associated with Ologen® include implant migration and the development of symptomatic blebs, which may reflect an altered subconjunctival wound-healing response. These potential adverse events should be considered when interpreting the overall clinical performance of the implant.[46]

In summary, Ologen® and MMC demonstrate comparable efficacy across various glaucoma surgical modalities. Although MMC may achieve marginally lower IOP in selected contexts, it carries an increased risk profile. Our findings do not challenge the overall safety of this biodegradable collagen-glycosaminoglycan implant but rather highlight that its biological behaviour may be unpredictable in selected patients. The matrix appears to reduce severe complications such as hypotony and tube erosion. However, as observed in our series, it may also be associated with encapsulation, delayed degradation, and bleb fibrosis, even when used in conjunction with MMC. These findings highlight the considerable variability in tissue response to biodegradable implants and suggest a potential role of patient-specific fibrotic predisposition. Emerging evidence indicating distinct conjunctival gene expression profiles associated with early surgical failure supports the concept that a hyper-fibrotic molecular phenotype may influence wound-healing responses to collagen-based implants. Consequently, careful patient selection, meticulous ocular surface preparation, and the future integration of genetic or molecular profiling of hyper-fibrotic phenotypes may help to optimise surgical outcomes and refine the role of collagen-based implants in glaucoma surgery.

Ethics

Informed Consent: Informed consent was obtained from the patients included in the study.

Declarations

Authorship Contributions

Surgical and Medical Practices: E.M., Concept: E.M., Design: E.M., Data Collection or Processing: X.S., J.L.G., Analysis or Interpretation: L.C-R., S.L-T., X.S., J.L.G., E.M., Literature Search: L.C-R., S.L-T., Writing: L.C-R., S.L-T., E.M.

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

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References

1. Allingham RR, Damji KF, Freedman S, Moroi SE, Rhee DJ, Shields MB. Shields' Textbook of Glaucoma. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2011.
2. Yamanaka O, Kitano-Izutani A, Tomoyose K, Reinach PS. Pathobiology of wound healing after glaucoma filtration surgery. BMC Ophthalmol. 2015;15(Suppl 1):157.
3. Papaconstantinou D, Georgalas I, Karmiris E, Diagourtas A, Koutsandrea C, Ladas I, Apostolopoulos M, Georgopoulos G. Trabeculectomy with OloGen versus trabeculectomy for the treatment of glaucoma: a pilot study. Acta Ophthalmol. 2010;88:80-85.
4. Schlunck G, Meyer-ter-Vehn T, Klink T, Grehn F. Conjunctival fibrosis following filtering glaucoma surgery. Exp Eye Res. 2016;142:76-82.
5. Ichhpujani P, Dada T, Bhartiya S. Biodegradable collagen implants in trabeculectomy. J Curr Glaucoma Pract. 2015;9:24-27.
6. Ji Q, Qi B, Liu L, Guo X, Zhong J. Efficacy and safety of Ologen implant versus mitomycin C in primary trabeculectomy: a meta-analysis of randomized clinical trials. J Glaucoma. 2015;24:e88-e94.
7. Senthil S, Rao HL, Babu JG, Mandal AK, Garudadri CS. Comparison of outcomes of trabeculectomy with mitomycin C vs. Ologen implant in primary glaucoma. Indian J Ophthalmol. 2013;61:338-342.
8. Narayanaswamy A, Perera SA, Htoon HM, Hoh ST, Seah SK, Wong TT, Aung T. Efficacy and safety of collagen matrix implants in phacotrabeculectomy and comparison with mitomycin C augmented phacotrabeculectomy at 1 year. Clin Exp Ophthalmol. 2013;41:552-560.
9. Dada T, Kusumesh R, Bali SJ, Sharma S, Sobti A, Arora V, Panda A. Trabeculectomy with combined use of subconjunctival collagen implant and low-dose mitomycin C. J Glaucoma. 2013;22:659-662.
10. Classen L, Kivelä T, Tarkkanen A. Histopathologic and immunohistochemical analysis of the filtration bleb after unsuccessful glaucoma seton implantation. Am J Ophthalmol. 1996;122:205-212.
11. Voykov B, Rohrbach JM. Histopathological findings of a 1-month-old Ologen implant. Clin Exp Ophthalmol. 2015;43:604-605.

12. Stephens JD, Sarkisian SR Jr. The use of collagen matrix (Ologen) as a patch graft in glaucoma tube shunt surgery, a retrospective chart review. F1000Res. 2016;5:1898.
13. Song DS, Qian J, Chen ZJ. Ologen implant versus mitomycin-C for trabeculectomy: a meta-analysis. Medicine (Baltimore). 2019;98:e16094.
14. Hsu WC, Ritch R, Krupin T, Chen HS. Tissue bioengineering for surgical bleb defects: an animal study. Graefes Arch Clin Exp Ophthalmol. 2008;246:709-717.
15. Johnson MS, Sarkisian SR Jr. Using a collagen matrix implant (Ologen) versus mitomycin-C as a wound healing modulator in trabeculectomy with the Ex-PRESS mini glaucoma device: a 12-month retrospective review. J Glaucoma. 2014;23:649-652.
16. Yuan F, Li L, Chen X, Yan X, Wang L. Biodegradable 3D-porous collagen matrix (Ologen) compared with mitomycin C for treatment of primary open-angle glaucoma: results at 5 years. J Ophthalmol. 2015;2015:637537.
17. El-Sayyad F, El-Saied HMA, Abdelhakim MASE. Trabeculectomy with Ologen versus mitomycin C in juvenile open-angle glaucoma: a 1-year study. Ophthalmic Res. 2017;57:230-238.
18. Cillino S, Di Pace F, Cillino G, Casuccio A. Biodegradable collagen matrix implant vs mitomycin-C as an adjuvant in trabeculectomy: a 24-month, randomized clinical trial. Eye (Lond). 2011;25:1598-1606.
19. Chelerkar VJ, Agrawal D, S Kalyani VK, Deshpande M. Comparison of bleb morphology by anterior segment optical coherence tomography and clinical outcome after phacotrabeculectomy with mitomycin C or Ologen implant. Indian J Ophthalmol. 2021;69:2734-2739.
20. Glandorf K, Lommatzsch C, Heinz C, Koch JM. Trabekulektomie mit Ologen®-implantat und bevacizumab [trabeculectomy with Ologen® implant and bevacizumab]. Ophthalmologe. 2020;117:445-451.
21. Paul C, Divya J, Kamal R, Paul A. Ologen implant versus mitomycin C in combined trabeculectomy and phacoemulsification. Indian J Ophthalmol. 2022;70:1248-1252.
22. Navero-Rodríguez JM, Boldú-Roig J, Pinilla L, Vidal-Martí M, Antón A. Clinical Impact of the Use of Ologen in filtering surgery performed in uncontrolled glaucoma. J Clin Med. 2024;13:4463.
23. Rosentreter A, Schild AM, Jordan JF, Krieglstein GK, Dietlein TS. A prospective randomised trial of trabeculectomy using mitomycin C vs an Ologen implant in open angle glaucoma. Eye (Lond). 2010;24:1449-1457.
24. Rosentreter A, Gaki S, Cursiefen C, Dietlein TS. Trabeculectomy using mitomycin C versus an atelocollagen implant: clinical results of a randomized trial and histopathologic findings. Ophthalmologica. 2014;231:133-140.
25. Sen M, Midha N, Sidhu T, Angmo D, Sihota R, Dada T. Prospective randomized trial comparing mitomycin C combined with Ologen Implant versus Mitomycin C alone as adjuvants in trabeculectomy. Ophthalmol Glaucoma. 2018;1:88-98.
26. Khairy MA, Kenawy S, Fawzi KM, Al-Nashar HY. Combined trabeculotomy-trabeculectomy with and without augmentation in primary congenital glaucoma: triple-armed randomized controlled trial. Int Ophthalmol. 2023;43:1591-1600.
27. Angmo D, Wadhwani M, Upadhyay AD, Temkar S, Dada T. Outcomes of trabeculectomy augmented with subconjunctival and subscleral Ologen implantation in primary advanced glaucoma. J Glaucoma. 2017;26:8-14.
28. Rosentreter A, Mellein AC, Konen WW, Dietlein TS. Capsule excision and Ologen implantation for revision after glaucoma drainage device surgery. Graefes Arch Clin Exp Ophthalmol. 2010;248:1319-1324.
29. Salimi A, Kovalyuk N, Harasymowycz PJ. Tube shunt revision with excision of fibrotic capsule using mitomycin C with and without Ologen-a collagen matrix implant: a 3-year follow-up study. J Glaucoma. 2019;28:989-996.
30. Song M, Lee S, Choe D, Kim S, Roh YH, Rho S. Clinical and biological evaluations of biodegradable collagen matrices for glaucoma drainage device implantation. Invest Ophthalmol Vis Sci. 2017;58:5329-5335.
31. Kim TJ, Kang S, Jeoung JW, Kim YK, Park KH. Comparison of 1-year outcomes after Ahmed glaucoma valve implantation with and without Ologen adjuvant. BMC Ophthalmol. 2018;18:45.
32. Sastre-Ibáñez M, Cabarga C, Canut MI, Pérez-Bartolomé F, Urcelay-Segura JL, Cordero-Ros R, García-Feijóo J, Martínez-de-la-Casa JM. Efficacy of Ologen matrix implant in Ahmed glaucoma valve implantation. Sci Rep. 2019;9:3178.
33. Suzuki Junior ER, Maestrini HA, Ruppert ADP, Seixas RCS, Belfort AF, de Miranda Santos HD, Basile Neto A, Balbino M, Lopes da Silva MJ. A Retrospective comparison of Ahmed glaucoma valve implants with or without Ologen collagen matrix. Clin Ophthalmol. 2023;17:15-23.
34. Paletta Guedes RA, Gravina DM, Paletta Guedes VM, Chaoubah A. Use of a collagen matrix implant as an adjuvant in combined surgery involving phacoemulsification and nonpenetrating deep sclerectomy. J Glaucoma. 2019;28:363-366.
35. Aptel F, Dumas S, Denis P. Ultrasound biomicroscopy and optical coherence tomography imaging of filtering blebs after deep sclerectomy with new collagen implant. Eur J Ophthalmol. 2009;19:223-230.
36. Elmekawey H, Abdelrahman A, Kotb MS, Mostafa DA. Effect of filtering bleb dimensions on postoperative intraocular pressure in deep sclerectomy with collagen implant: a comparative study. Int Ophthalmol. 2020;40:7-12.
37. Park J, Shin JW, Sung KR. Comparison of surgical outcomes with and without Ologen collagen matrix augmentation during XEN gel stent implantation. BMC Ophthalmol. 2022;22:426.
38. Navero-Rodríguez JM, Espinosa-Barberi G, Morilla-Grasa A, Anton A. Efficacy of the Ologen collagen matrix in combination with the XEN gel stent implantation in the treatment of open-angle glaucoma: a case-control study. Clin Exp Ophthalmol. 2020;48:1003-1005.
39. Jin SJ, Kim SY, Tallo J, Rana HS, Raiciulescu S, Oguntoye-Ouma MO, Kim WI. Comparison of XEN45 gel stent outcomes in glaucoma: Ab externo open-conjunctiva approach with Ologen vs. Ab interno closed-conjunctiva approach. J Clin Med. 2025;14:4426.
40. Vastardis I, Fili S, Perdikakis G, Kontopoulou K, Balidis M, Gatzioufas Z, Kohlhaas M. Preliminary results of preserflo microshunt versus preserflo microshunt and Ologen implantation. Eye Vis (Lond). 2021;8:33.
41. Menda SA, Lowry EA, Porco TC, Stamper RL, Rubin MR, Han Y. Ex-PRESS outcomes using mitomycin-C, Ologen alone, Ologen with 5-fluorouracil. Int Ophthalmol. 2015;35:357-363.
42. He M, Wang W, Zhang X, Huang W. Ologen implant versus mitomycin C for trabeculectomy: a systematic review and meta-analysis. PLoS One. 2014;9:e85782.

43. Min JK, Kee CW, Sohn SW, Lee HJ, Woo JM, Yim JH. Surgical outcome of mitomycin C-soaked collagen matrix implant in trabeculectomy. J Glaucoma. 2013;22:456-462.

44. Millá E, Ventura-Abreu N, Vendrell C, Muniesa MJ, Pazos M, Gasull X, Comes N. Differential gene and protein expression of conjunctival bleb hyperfibrosis in early failure of glaucoma surgery. Int J Mol Sci. 2023;24:11949.

45. Selvan H, Gupta S, Puri P, Sen S, Gupta V. The immortal Ologen: persisting 10 years after trabeculectomy. Can J Ophthalmol. 2019;54:e305-e308.

46. Phogat J, Rathi M, Sachdeva S, Takkar B, Khanduja S. Intracameral migration of collagen matrix implant. Indian J Ophthalmol. 2019;67:395-396.

PUAWS: "Pelin's Up and Away" Suture (a Variation of the Brassiere Suture) as an Adjunct to Upper Blepharoplasty

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Dear Editor,

Traditional upper eyelid blepharoplasty focuses on excising redundant skin and fat; however, it does not consistently ensure long-term contour stability or symmetric eyelid positioning.[1] The brassiere suture technique was introduced as an adjunct to upper blepharoplasty to support the upper eyelid contour and prevent and manage postoperative upper eyelid temporal hooding by anchoring the orbicularis oculi muscle to the superior lateral orbital rim periosteum.[2] In the current report, we present a modified version of the brassiere suture in which the orbicularis oculi muscle at the upper edge of the blepharoplasty incision is fixed to a more superior and temporal (up and away) periosteal point above the superotemporal orbital rim to provide enhanced temporal support. This study evaluated the outcomes of upper blepharoplasty using this method in three patients and was conducted in accordance with the Declaration of Helsinki.

Standardized preoperative and postoperative photographs of three patients (two female, one male) who underwent upper blepharoplasty with our modified brassiere suture were evaluated. Their ages were 38, 49, and 56 years, resulting in a mean age of 47.7 years. The exclusion criteria were a history of thyroid eye disease, ptosis, blepharospasm, facial nerve paresis, previous upper facial surgery, or trauma. Measurements were performed using ImageJ software (U.S. National Institutes of Health, Bethesda, Maryland, USA). Two authors independently evaluated the ImageJ results and the mean values were recorded. No discordance occurred between the observers. For each patient, tarsal platform show (TPS) and brow fat span (BFS) were quantified at three standardized anatomic landmarks: the mid-pupillary point, the lateral corneal limbus, and the lateral canthus. TPS was measured as the distance between the upper eyelid margin and the crease, and BFS was measured as the distance from the superior brow hairs to the crease.

All participants provided informed consent before undergoing the procedure. The edges for placing suspension sutures between the lateral eyebrow region and the temporal region of the upper eyelid were identified and marked. Local anesthesia was achieved by the subcutaneous administration of 3-4 mL of 2% lidocaine with epinephrine (1:80,000) (Jetokain, Adeka, Türkiye) into the upper eyelid. An upper blepharoplasty was performed with the excision of the redundant skin. Fat pad excision was performed if necessary. The pretarsal orbicularis oculi muscle was largely preserved, excluding the lateral third of the eyelid. Blunt dissection was carried out beneath the orbicularis muscle

Keywords: Brassiere suture, dermatochalasis, upper blepharoplasty

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This study was presented at WSOPRAS, held in İstanbul, Türkiye, on April 11-13, 2025.

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and continued beyond the superior orbital rim to where the orbicularis fibers would be attached to the periosteum. The dissection plane was safe, with no major blood vessels or nerves in close proximity. Suspensory sutures were adjusted individually and applied to the region between the lateral limbus and the lateral end of the eyebrow, with care taken not to cause asymmetry. Following the preoperative marked alignments, a 5-0 Vicryl (Ethicon, Johnson & Johnson, USA) suture was initially passed through the orbicularis oculi muscle adjacent to the upper skin margin and then through the periosteum, located 7-8 mm superior and 5-7 mm lateral to the superior orbital rim (Figure 1). Two or three sutures were applied to the lateral third of the eyelid until sufficient augmentation of the subbrow soft tissues was achieved. Skin closure was subsequently performed with a 6-0 Prolene (Ethicon, Johnson & Johnson, USA) suture, which was removed between one week and ten days following surgery.

This modified brassiere suture technique is referred to as Pelin's Up and Away Suture (PUAWS). Three patients who underwent surgery using this technique had a postoperative follow-up of at least six months. The preoperative and postoperative appearances of these three patients are presented in Figure 2. A noticeable improvement in the temporal brow position in primary gaze was observed along with an increase in TPS and TPS/BFS ratio. The mean preoperative TPS was 2.35 mm (range: 0.71-5.15 mm) and mean postoperative TPS was 4.09 mm (range: 1.87-8.17 mm). The mean preoperative TPS/BFS ratio was 0.12 (range: 0.04-0.23) and the mean postoperative TPS/BFS ratio was 0.17 (range: 0.10-0.24). A summary of the patient data is shown in Table 1.

During internal browpexy, the reference point is set according to the brow position. In the PUAWS technique, we did not use a reference point. The orbicularis oculi muscle was simply sutured to the periosteum, similar to the brassiere technique, but instead of applying the sutures to the superior orbital rim, PUAWS sutures were applied 7 to 10 mm superotemporal to the orbital rim, enhancing the temporal support. We did not observe any postoperative asymmetry or significant complications, including nerve-related complications.

In 1997, Zarem et al.[3] described browpexy by lateral orbicularis muscle fixation as an adjunct to upper blepharoplasty intended to correct brow ptosis and enhance the tarsal sulcus. Later, modifications of the procedure focused on volume preservation. Goldberg described a "brassiere suture" technique in which the orbicularis oculi is sutured to the superior lateral orbital rim periosteum.[2] This technique has gained recognition for reinforcing the subbrow region and achieving a more youthful appearance.[4] In addition to lifting and supporting the brow fat pad, a higher TPS and TPS/BFS ratio were reported with this technique.[2] TPS and BFS are reliable measures for the aesthetic quantification of the upper face.[5,6] We also observed improvements in the TPS and TPS/BFS ratio with the PUAWS technique.

PUAWS is a superotemporal variation of the brassiere suture that aims to provide enhanced temporal support while preserving a natural upper eyelid contour and volume. By supporting the brow height both at the midline and temporally, this simple and effective suspension technique offers an alternative to the brassiere suture, which provides support but does not reliably elevate the brow. The present study is limited by its retrospective nature and limited sample size. Therefore, larger case series are required to reliably evaluate the reproducibility and durability of this technique's outcomes.

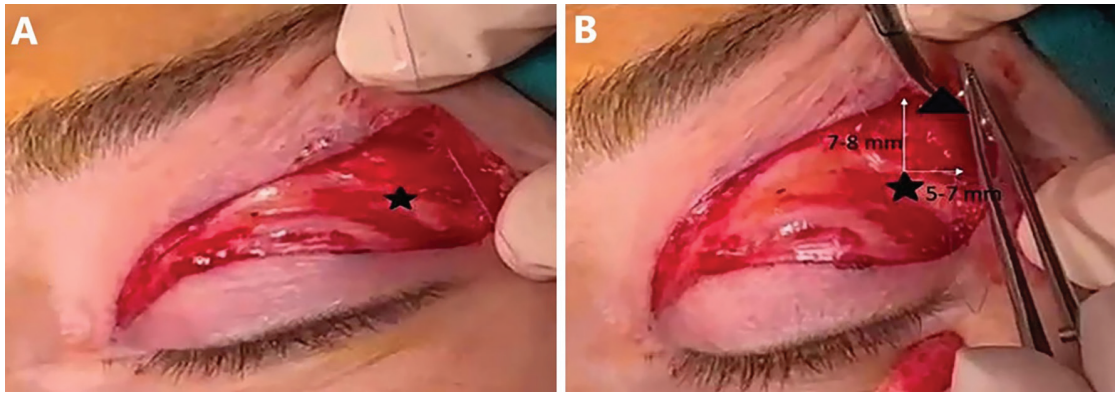


Figure 1. A) In the brassiere technique, the suture is passed through the periosteum at the superior lateral orbital rim (black star). B) In the PUAWS technique, the suture is passed up and away from the superior lateral orbital rim (black triangle)
PUAWS: Pelin's up and away suture

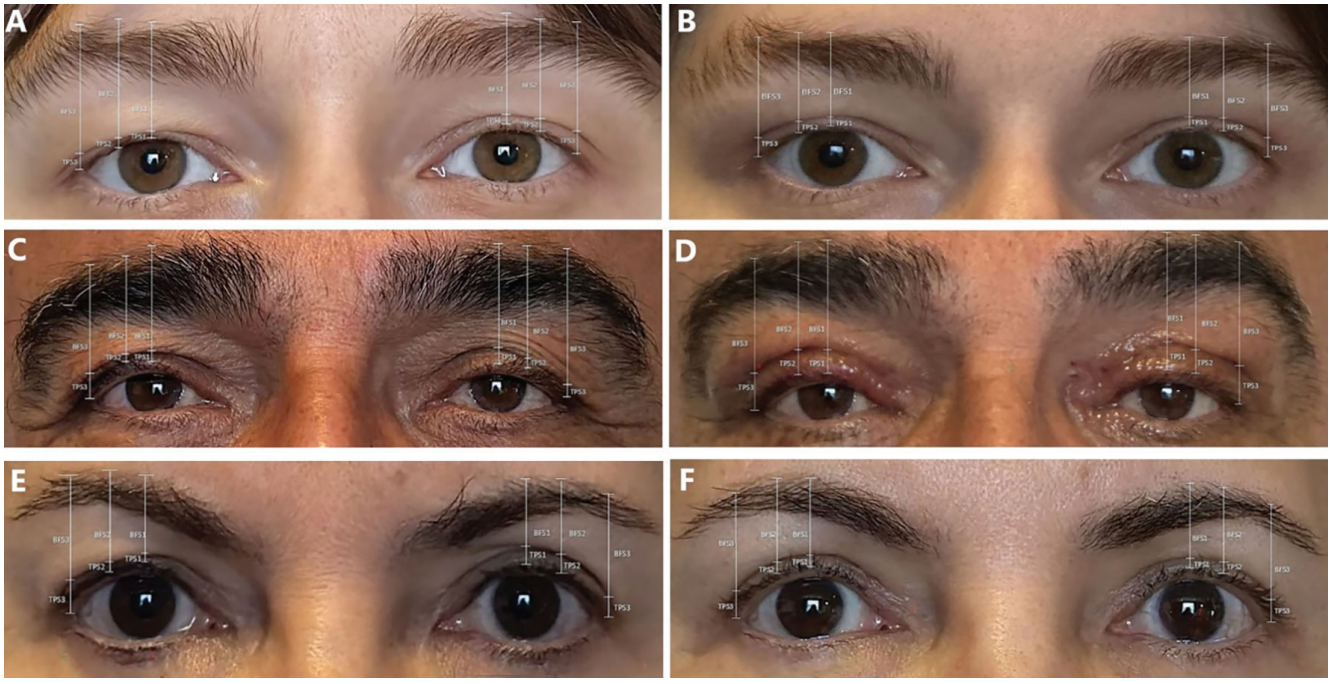


Figure 2. Preoperative and postoperative photographs of three patients. Patient 1 preoperatively (A) and postoperatively (B). Patient 2 preoperatively (C) and postoperatively (D). Patient 3 preoperatively (E) and postoperatively (F)

Table 1. TPS and BFS values before and after surgery

Location	Case no	Eye	Preoperative TPS (mm)	Preoperative BFS (mm)	Postoperative TPS (mm)	Postoperative BFS (mm)	Preoperative TPS/BFS	Postoperative TPS/BFS
Center of pupil	1	Right	0.98	15.06	1.87	18.09	0.07	0.10
		Left	1.33	14.17	1.96	17.29	0.09	0.11
	2	Right	1.34	13.85	2.28	17.68	0.10	0.13
		Left	2.65	13.83	3.13	17.41	0.19	0.18
	3	Right	2.18	23.77	4.67	27.76	0.09	0.17
		Left	3.46	25.05	6.02	28.75	0.14	0.21
Lateral limbus	1	Right	0.71	16.76	2.14	19.07	0.04	0.11
		Left	1.65	14.62	2.47	17.91	0.11	0.14
	2	Right	1.35	16.14	2.28	19.09	0.08	0.12
		Left	2.21	14.75	2.94	17.68	0.15	0.17
	3	Right	1.54	22.03	5.12	27.76	0.07	0.18
		Left	2.12	25.31	5.21	28.93	0.08	0.18
Lateral canthus	1	Right	2.05	18.81	3.92	23.08	0.11	0.17
		Left	3.03	17.02	4.01	21.84	0.18	0.18
	2	Right	5.15	22.00	5.24	25.42	0.23	0.21
		Left	3.40	19.80	4.97	23.80	0.17	0.21
	3	Right	4.88	27.75	7.27	31.53	0.18	0.23
		Left	2.31	30.64	8.17	33.78	0.08	0.24

TPS: Tarsal platform show, BFS: Brow fat span

Ethics

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

Declarations

Authorship Contributions

Surgical and Medical Practices: P.K., Concept: P.K., Design: P.K., Data Collection or Processing: P.K., S.K.Ö., Analysis or Interpretation: S.K.Ö., G.D.Ş., Literature Search: S.K.Ö., G.D.Ş., Writing: P.K., S.K.Ö., G.D.Ş.

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

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References

1. Stanek JJ, Fuller JC, Hilger PA. Brassiere suture technique in upper eyelid blepharoplasty. JAMA Facial Plast Surg. 2019;21:458-459.
2. Figueiredo MN, Tao J, Akaishi P, Limongi RM. Tarsal platform show after upper eyelid blepharoplasty with or without brassiere sutures. Arq Bras Oftalmol. 2017;80:345-349.
3. Zarem HA, Resnick JI, Carr RM, Wootton DG. Browpexy: lateral orbicularis muscle fixation as an adjunct to upper blepharoplasty. Plast Reconstr Surg. 1997;100:1258-1261.
4. Eftekhari K, Peng GL, Landsberger H, Douglas R, Massry GG. The brow fat pad suspension suture: safety profile and clinical observations. Ophthalmic Plast Reconstr Surg. 2018;34:7-12.
5. Goldberg RA, Lew H. Cosmetic outcome of posterior approach ptosis surgery (an American Ophthalmological Society thesis). Trans Am Ophthalmol Soc. 2011;109:157-167.
6. Papageorgiou KI, Ang M, Chang SH, Kohn J, Martinez S, Goldberg RA. Aesthetic considerations in upper eyelid retraction surgery. Ophthalmic Plast Reconstr Surg. 2012;28:419-423.

Letter to the Editor

A Novel Reversible Tube Ligation Technique for Managing Hypotony After Paul Glaucoma Implant Surgery in Uveitic Glaucoma

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Dear Editor,

Persistent hypotony and hypotony maculopathy are vision-threatening conditions that may develop after glaucoma surgery, especially in eyes with chronic uveitis in which ciliary body function can be highly variable.[1,2,3,4] In such eyes, the balance between aqueous production and outflow is fragile, and even small changes in inflammatory activity may lead to significant hypotony.[5] We report a case of severe hypotony maculopathy after glaucoma drainage device implantation in a monocular patient with uveitic glaucoma, successfully reversed through temporary tube occlusion and targeted anti-inflammatory treatment.

A 21-year-old woman with anti-nuclear antibody-positive juvenile idiopathic arthritis-associated uveitis presented with uncontrolled intraocular pressure (IOP) in her only seeing eye, which had undergone pars plana vitrectomy 15 years earlier for vitreous opacity and tractional retinal detachment. The fellow eye had lost vision due to chronic uveitic complications and dense band keratopathy (Figure 1B). At presentation, the best-corrected visual acuity (BCVA) was 0.8 in the right eye, and IOP measured 36 mmHg despite maximal tolerated medical therapy. The cornea was clear and the intraocular lens was centered (Figure 1A). Fundus examination revealed a healthy optic disc and macula (Figure 1C), and peripapillary retinal nerve fiber layer and macular optical coherence tomography (OCT) were within normal limits (Figure 1D, E).

Given the patient's monocular status and refractory IOP elevation despite maximal medical therapy, a Paul Glaucoma Implant (Advanced Ophthalmic Innovations Pte Ltd, Singapore, Republic of Singapore) was placed with an intraluminal 6-0 polypropylene ripcord (Prolene suture; Ethicon, Raritan, NJ, USA). The tube was advanced entirely within a scleral tunnel beneath a scleral flap and subsequently introduced into the anterior chamber through a 26-gauge needle tract. On postoperative day 1, IOP was 13 mmHg with stable visual acuity. However, by postoperative day 10, the patient developed acute visual deterioration to 0.1 accompanied by hypotony (IOP 3 mmHg). The anterior chamber remained well formed and tube position was appropriate (Figure 2A), but fundus examination revealed chorioretinal folds consistent with hypotony maculopathy (Figure 2B), which was confirmed on macular OCT (Figure 2C). Anterior chamber reformation with a 3.0% sodium hyaluronate ophthalmic viscosurgical device (Hyotek 3%; Teknomek Medikal Malzemeleri Sanayi ve Ticaret Ltd. Şti., Ergene, Tekirdağ, Türkiye) resulted in transient IOP recovery; however, recurrent hypotony developed at the first month of follow-up, necessitating further flow-modulating intervention.

Hypotony maculopathy is a vision-threatening complication that may lead to permanent structural distortion and irreversible visual loss if not promptly addressed.[6] To modulate aqueous outflow in a controlled and reversible manner, an ab interno, stepwise tube ligation

Keywords: Uveitic glaucoma, hypotony maculopathy, Paul glaucoma implant, tube shunt, tube occlusion technique

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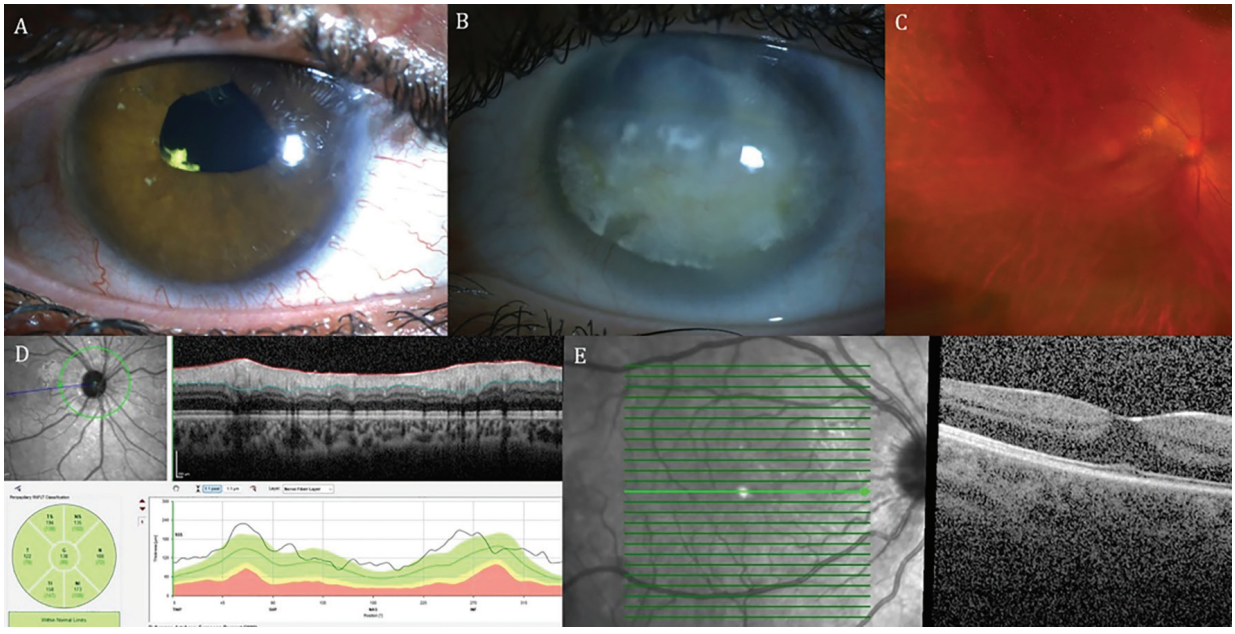


Figure 1. Preoperative clinical findings. A) Anterior segment photograph of the right eye, which was the patient's only seeing eye, showing a clear cornea and centered intraocular lens. B) Anterior segment photograph of the non-seeing fellow eye demonstrating dense band keratopathy and chronic uveitic sequelae. C) Preoperative color fundus photograph of the right eye showing a healthy-appearing optic disc and macula. D) Peripapillary retinal nerve fiber layer optical coherence tomography (OCT) of the right eye within normal limits. E) Macular OCT of the right eye showing preserved foveal contour and normal retinal layering before surgery

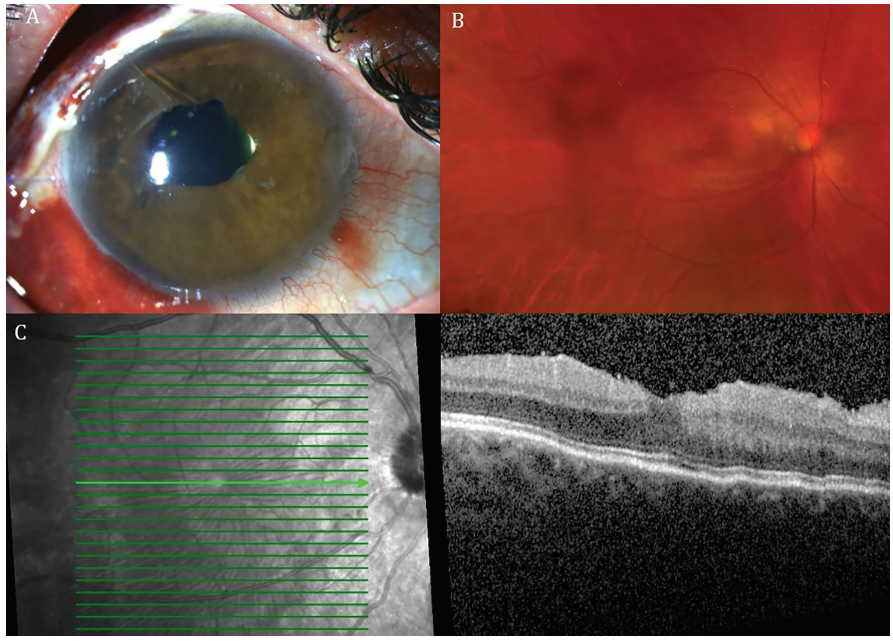


Figure 2. Acute hypotony maculopathy following Paul Glaucoma Implant surgery. A) Postoperative anterior segment photograph showing a well-formed anterior chamber and appropriate anterior chamber tube position. B) Color fundus photograph obtained during the hypotony episode showing chorioretinal folds involving the posterior pole. C) Macular optical coherence tomography demonstrating undulating retinal and choroidal folds consistent with hypotony maculopathy

technique was performed (Figure 3A-F). The intraluminal 6-0 Prolene ripcord suture introduced from the distal end of the tube during the initial surgery was left in place. For the ligation procedure, a second 6-0 Prolene ripcord suture was advanced intraluminally from the proximal end of the tube to provide partial flow restriction without complete occlusion (Figure 3A, B). Subsequently, a 10-0 nylon suture was advanced ab interno from the anterior surface of the tube, guided across the anterior chamber, and externalized through a contralateral paracentesis (Figure 3C). The externalized suture was then reintroduced into the anterior chamber and redirected posterior to the tube, creating a loop encircling the tube body (Figure 3D). This loop was tied externally using a 3-1-1 knot configuration and seated onto the tube body to achieve external ligation without conjunctival dissection (Figure 3E). Finally, the intrachamber ends of the 10-0 nylon suture were trimmed with microsurgical forceps, ensuring that the cut ends remained posterior to the tube to minimize the risk of postoperative corneal endothelial trauma (Figure 3F). This configuration enabled graded and reversible modulation of aqueous outflow while preserving the structural integrity of the drainage device. However, IOP remained 5-6 mmHg, accompanied by corneal edema and anterior chamber inflammation one week after the tube ligation (Figure 4A), suggesting that hypotony was driven not only by overfiltration but also by ciliary body hyposecretion related to uveitic flare.

Four-quadrant anterior sub-Tenon triamcinolone injections (Kenacort-A 40 mg/mL; Bristol-Myers Squibb, New York, NY, USA) were administered to rapidly suppress inflammation and restore ciliary body function, a well-established therapeutic strategy in inflammatory hypotony.[7,8] Within one week, corneal edema and intraocular inflammation resolved (Figure 4B), and IOP gradually increased to physiologic levels. Two months later, IOP stabilized at 16 mmHg. Fundus examination showed resolution of macular folds (Figure 4C), and macular OCT confirmed restoration of normal foveal contour and retinal layering (Figure 4D). Final BCVA returned to 0.8. The patient remained under systemic and topical anti-inflammatory/immunomodulatory treatment consisting of topical prednisolone acetate 1% three times

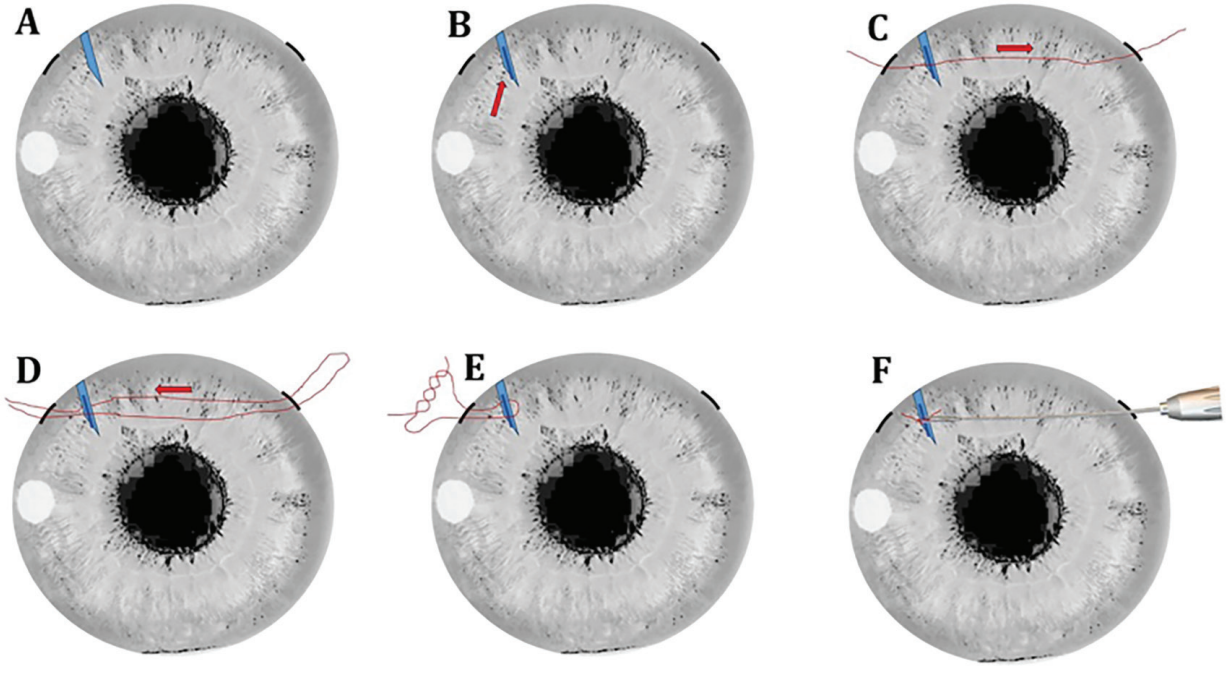


Figure 3. Stepwise ab interno tube ligation technique for controlled aqueous outflow modulation. A, B) A 6-0 Prolene suture is introduced intraluminally into the drainage tube to act as a ripcord and provide partial internal flow restriction. C) A 10-0 nylon suture is advanced ab interno from the anterior surface of the tube, guided across the anterior chamber, and externalized through the opposite paracentesis. D) The externalized suture is reintroduced into the anterior chamber and redirected posterior to the tube to form a loop around the tube body. E) The loop is tied externally using a 3-1-1 knot configuration and seated onto the tube, thereby producing external tube ligation without conjunctival dissection. F) The intraocular ends of the 10-0 nylon suture are trimmed posterior to the tube to reduce the risk of postoperative corneal endothelial trauma

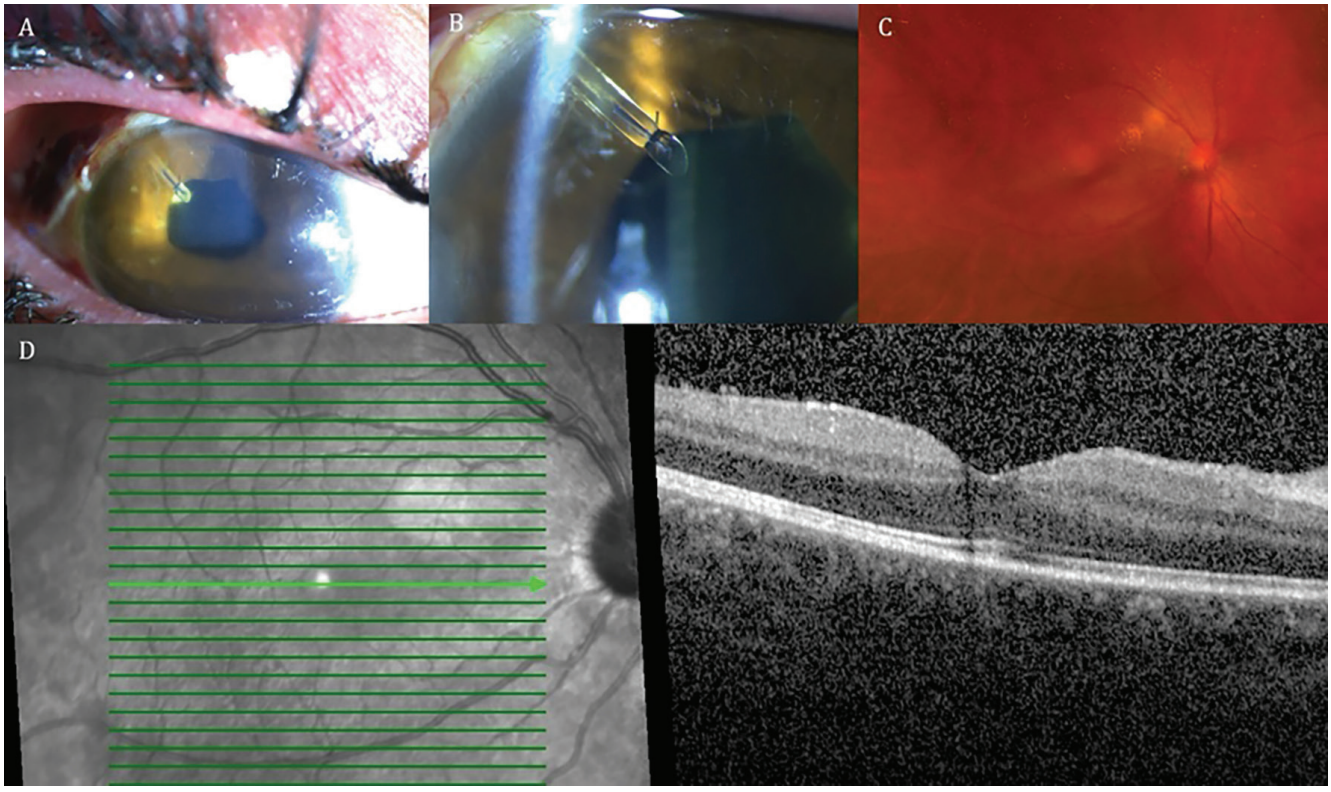


Figure 4. Post-intervention recovery following reversible tube ligation and anterior sub-Tenon triamcinolone. A) One week after tube ligation, the anterior segment showed corneal edema and anterior chamber inflammation while intraocular pressure remained low. B) After four-quadrant anterior sub-Tenon triamcinolone acetonide treatment, corneal edema and intraocular inflammation resolved. C) Follow-up color fundus photograph showing resolution of the macular folds. D) Follow-up macular optical coherence tomography confirming restoration of the normal foveal contour and retinal layering

daily (Pred Forte; AbbVie Inc., North Chicago, IL, USA), mycophenolate mofetil 500 mg twice daily (CellCept; F. Hoffmann-La Roche Ltd., Basel, Switzerland), oral methylprednisolone 32 mg once daily (Prednol; Mustafa Nevzat İlaç Sanayii A.Ş., Istanbul, Türkiye), azathioprine 50 mg twice daily (Imuran; GlaxoSmithKline, Brentford, UK), and adalimumab 40 mg once weekly (Humira; AbbVie Inc., North Chicago, IL, USA).

This case demonstrates that postoperative hypotony following glaucoma drainage device implantation in uveitic eyes should not be attributed solely to excessive aqueous outflow. Inflammatory ciliary body suppression must be considered, as its management differs fundamentally. In this patient, we implemented an ab interno, stepwise, and reversible flow-modulation strategy combining intraluminal 6-0 Prolene ripcord placement with loop-based 10-0 nylon tube ligation. This configuration not only allowed controlled elevation of IOP while inflammation was concurrently treated with sub-Tenon corticosteroid injections, but also preserved future flexibility of aqueous outflow. Should IOP rise during follow-up, graded restoration of tube patency can be achieved by first removing the intraluminal Prolene ripcord, creating an approximate 70-µm lumen, and, if further flow is required, by cutting the tube distal to the nylon ligation to establish a wider opening of approximately 127 µm. This stepwise outflow restoration preserves implant integrity, avoids surgical revision, and provides a temporal window for recovery of ciliary body function. In the present case, the initial intraluminal 6-0 Prolene ripcord was not removed during follow-up, as IOP stabilized after inflammation control and tube ligation. Nevertheless, an additional technical consideration is that removal of a 6-0 Prolene ripcord cut flush with the tube tip may be technically challenging if intraluminal adhesion develops over time. Should removal prove difficult, stepwise flow restoration may alternatively be achieved through distal tube trimming or selective release of external ligation sutures, thereby preserving implant integrity without conjunctival dissection.

From a pathophysiological standpoint, the second episode of hypotony occurring at one month was unlikely to be solely attributable to excessive aqueous outflow.

The transient IOP improvement after the initial viscoelastic injection may have coincided with temporary fluctuations in uveitic activity rather than representing definitive correction of overfiltration. Moreover, the persistence of hypotony despite mechanical flow restriction suggests that inflammatory ciliary body hyposecretion played a substantial role. The rapid anatomical and pressure recovery following sub-Tenon corticosteroid administration further supports this interpretation and underscores the importance of aggressive inflammation control in similar cases.

Although small-bore tube design and intraluminal ripcord stenting are intended to mitigate early postoperative hypotony, such measures provide partial rather than complete occlusion. Residual low-grade outflow may persist around the stent, particularly before capsule maturation increases resistance. In uveitic eyes, postoperative inflammatory fluctuations may further suppress ciliary body function, thereby shifting the balance toward hypotony despite flow-restricting strategies. Taken together, the prolonged and recurrent hypotony observed in this case most likely reflected a multifactorial process in which modest residual outflow and inflammation-related hyposecretion acted synergistically.

A further potential mechanism to consider in cases of persistent hypotony after drainage device implantation is peritubular leakage. In this patient, the tube was advanced entirely within a scleral tunnel and covered by a scleral flap without secondary scleral surface entry, reducing the likelihood of clinically significant leakage. The anterior chamber remained well formed and no Seidel-positive leakage was detected. Nevertheless, subtle microleakage cannot be completely excluded in prolonged hypotony scenarios.

In conclusion, early recognition of inflammatory hypotony, combined with targeted anti-inflammatory therapy and a flexible, reversible approach to aqueous outflow modulation, may enable both anatomical and functional recovery, even in monocular patients in whom visual preservation is critical. While this report represents a single case and should therefore be considered a proof-of-concept experience, it highlights a potentially adaptable strategy for managing complex hypotony scenarios. Further evaluation in larger case series is warranted to assess reproducibility, safety, and long-term outcomes.

Ethics

Informed Consent: Written informed consent was obtained from the patient for the publication of their clinical information and images.

Declarations

Authorship Contributions

Surgical and Medical Practices: A.Y.Ü., İ.G.G., H.B.Ö., Concept: A.Y.Ü., İ.G.G., Design: A.Y.Ü., İ.G.G., Data Collection or Processing: A.Y.Ü., İ.G.G., B.U., B.A., Analysis or Interpretation: A.Y.Ü., İ.G.G., Literature Search: A.Y.Ü., Writing: A.Y.Ü.

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

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References

1. Škrlová E, Svozílková P, Heissigerová J, Fichtl M. Pathogenesis and current methods of treatment of secondary uveitic glaucoma. A review. Cesk Slov Oftalmol. 2023;79:111-115.
2. Kalogeropoulos D, Sung VC. Pathogenesis of uveitic glaucoma. J Curr Glaucoma Pract. 2018;12:125-138.
3. Chaku M, Bajwa A, Lee JK, Netland PA. Treatment of uveitis and outcomes of glaucoma drainage implant surgery: a meta-analysis. Ocul Immunol Inflamm. 2020;28:833-838.
4. Satana B, Yalvac IS, Sungur G, Eksioglu U, Basarir B, Altan C, Duman S. Ahmed glaucoma valve implantation for uveitic glaucoma secondary to Behçet disease. J Glaucoma. 2015;24:607-612.
5. de Smet MD, Gunning F, Feenstra R. The surgical management of chronic hypotony due to uveitis. Eye (Lond). 2005;19:60-64.
6. Thomas M, Vajaranant TS, Aref AA. Hypotony maculopathy: clinical presentation and therapeutic methods. Ophthalmol Ther. 2015;4:79-88.
7. Ferreira BG, Marinho DR, Diligenti FT. Effects of sub-Tenon's triamcinolone injections in patients with uveitis. Arq Bras Oftalmol. 2018;81:323-329.
8. Nilforushan N, Abolfathzadeh N, Najafzadeh F, Samimifar D. Subtenon triamcinolone injection to treat serous choroidal detachment after glaucoma surgery: a case series. Eur J Ophthalmol. 2023;33:319-323.

Extension of a Severed Paul Glaucoma Implant Tube Using the Crawford Lacrimal Tube: A Novel Surgical Technique

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Dear Editor,

Glaucoma drainage devices (GDDs) are essential tools in the management of refractory glaucoma, particularly in patients with complex or secondary disease where traditional techniques are likely to fail. Among these devices, the Paul Glaucoma Implant (PGI; Advanced Ophthalmic Innovations, Singapore) has emerged as a promising alternative, especially in eyes at high risk of hypotony or surgical failure. Its low-profile, non-valved design has demonstrated efficacy and safety in multiple studies, offering favorable intraocular pressure (IOP) control with a low rate of complications.[1,2]

As with any GDD, intraoperative or postoperative complications may occur with the PGI. Although tube transection is rare, it is a particularly challenging complication that can compromise the function of an otherwise well-positioned implant. Tube transection may be identified during routine postoperative follow-up visits or during revision surgery, although it can also be inadvertently overlooked during exploration. When tube discontinuity occurs, options for salvage are limited. Complete device replacement is possible but increases surgical time, complexity, and cost. Therefore, several techniques have been described to re-establish tube continuity.

Methods for addressing tube discontinuity include the use of 22-gauge angiocatheter segments,[3] silastic sleeves,[4] and dedicated tube extenders,[5] although many commercial extenders have been discontinued and may no longer be readily available. An alternative is the "tube-in-tube" technique, which involves inserting one tube inside another to create a continuous lumen. This method has been applied by reusing sterilized surplus tube segments from previous GDD surgeries[6] or extending an Ahmed valve using a segment of Paul tube.[7]

Despite these options, there remains a need for low-cost, readily available, and biocompatible materials that ensure a secure, watertight connection between tube segments. Previous reports have described the use of Crawford lacrimal tubing to extend the tube of a GDD as a cost-effective alternative during revision surgery.[8]

The Crawford Lacrimal Intubation System (France Chirurgie Instrumentation S.A.S., Paris, France) is a commonly available instrument in ophthalmic surgery. The tubing component of the system is made of sterile medical-grade silicone—the same material as the Paul tube—and therefore provides smoothness, rigidity, and biocompatibility suitable for bridging severed tube ends.

Keywords: Paul glaucoma implant, Crawford tube, glaucoma drainage device, tube extension

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To the best of our knowledge, this is the first report describing the use of a Crawford lacrimal tube segment specifically to extend a severed tube of a PGI. The technique is simple, reproducible, and cost-effective and may serve as a practical alternative when conventional solutions are unavailable.

This method was successfully applied in a 76-year-old male patient who had undergone implantation of a PGI in the right eye two months earlier due to uncontrolled IOP despite maximal medical therapy. The patient presented for routine follow-up with signs of ocular inflammation, and slit-lamp examination revealed tube extrusion with transection of the drainage tube (Figure 1). Because the implant plate remained functional, the decision was made to extend the tube with a section of Crawford tube.

Under peribulbar anesthesia, a conjunctival peritomy was performed over the superotemporal quadrant. Blunt and sharp dissection exposed both the proximal (plate-attached) and distal (posterior chamber-directed) tube segments. The lumens were irrigated to ensure patency.

A 5- to 7-mm segment of Crawford tube was prepared. The tube's silicone composition and its lumen—practically identical to that of the Ahmed valve tube (Figure 2)—make it compatible with GDD tubing. However, its internal diameter (304 µm) is smaller than the external diameter of the Paul tube (467 µm), requiring gentle mechanical dilation to accommodate the tube.

A tube-in-tube configuration was created by dilating one end of the Crawford segment with forceps and introducing the proximal Paul tube into it, ensuring at least 3-4 mm of overlap to prevent dislocation. No sutures were used, relying on friction for stability.

The extended tube was reinserted into the posterior chamber by enlarging the existing communication tract with a 23-gauge needle. A fascia lata patch graft was placed for protection, and the conjunctiva was closed with 8-0 polyglactin sutures (Figure 3).

Postoperatively, the patient received topical antibiotics and corticosteroids. Follow-up assessments monitored IOP, tube stability, and inflammation.

The procedure was completed without complications. The reconstructed tube demonstrated a watertight, stable connection without kinking. The tube remained well-positioned in the posterior chamber, with good graft coverage. On postoperative day one, the anterior segment was quiet, with an IOP of 15 mmHg and no need for hypotensive medications. Subsequent follow-ups showed stable IOP and correct tube positioning.

These findings suggest that using Crawford tubing to extend a severed PGI tube is a safe and effective method that provides favorable short-term outcomes.

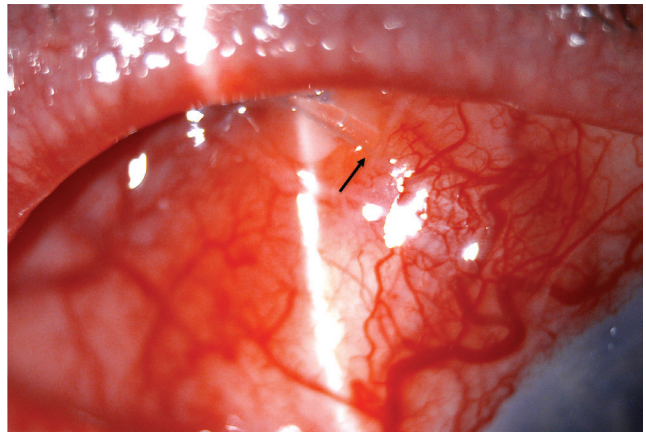


Figure 1. Slit-lamp photograph showing a severed tube of the Paul glaucoma implant (black arrow). The disconnection between the proximal and distal segments is visible in the superotemporal quadrant

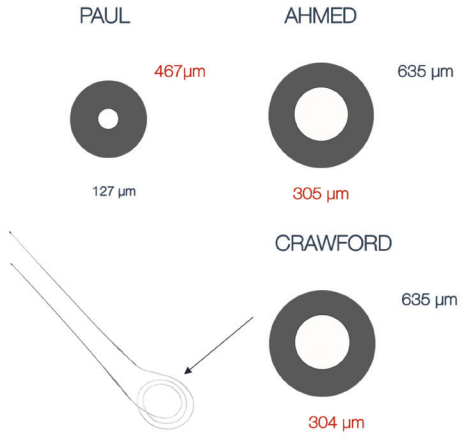


Figure 2. Comparative schematic representation of the external and internal diameters of the Paul and Ahmed glaucoma drainage device tubes and of Crawford lacrimal tube (black arrow indicates the silicone tubing component of the Crawford Lacrimal Intubation System). Note the similar lumen size between the Crawford and Ahmed tubes and the need to dilate the Crawford lumen to accommodate the external diameter of the Paul tube

Smith and Doyle[3] proposed angiocatheter-based extension as a cost-effective option that avoids explantation and replacement of the entire implant. However, the Crawford tube is more commonly used in ophthalmology and is generally more accessible. The same applies to the silastic sleeves described by Kooner.[4] The progressive discontinuation of dedicated extenders further limits alternatives, making readily available materials advantageous.

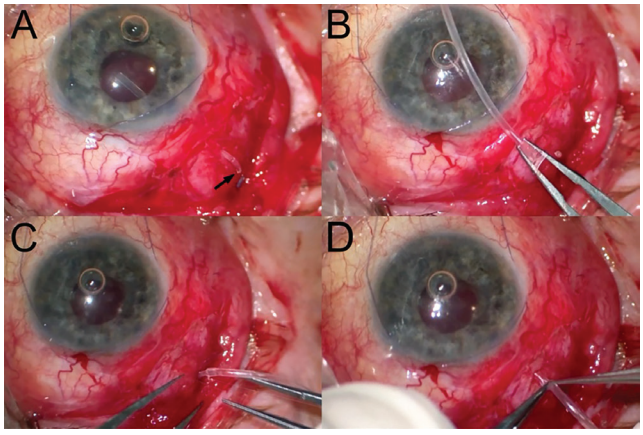


Figure 3. Intraoperative images illustrating the tube extension technique using a Crawford lacrimal tube segment. A) In situ view of the severed Paul glaucoma implant tube following extrusion (black arrow). B) Mechanical dilation of a short Crawford lacrimal tube segment using forceps to accommodate the Paul tube. C) Tube-in-tube configuration, with the proximal Paul tube inserted into the Crawford tube segment, ensuring adequate overlap for stability. D) Reintroduction of the extended tube into the posterior chamber through the existing sclerotomy

Regarding tube-in-tube techniques, using a segment of PGI tube to extend an Ahmed valve has been described.[7] However, this solution cannot be applied when the remaining PGI tube is insufficient, and it increases cost by sacrificing part of a functioning implant. The technique proposed by Pandav et al.[6] relied on leftover GDD tube segments from previous surgeries, but GDD tubing materials are not designed for resterilization. Additionally, their technique placed the extension in the anterior chamber, whereas our approach utilizes the benefits of posterior chamber placement.

Posterior chamber positioning is associated with better endothelial outcomes compared to anterior chamber placement. Godinho et al.[9] observed significant endothelial cell loss over time in eyes with anterior chamber tubes, whereas ciliary sulcus or posterior chamber placement showed no significant endothelial cell density changes. Zhang et al.[10] reported a significantly greater monthly endothelial loss in anterior chamber placement compared with ciliary sulcus positioning.

The Crawford tube provides a practical, biocompatible, and widely available solution for reconstructing severed tubes in PGIs. The technique is safe, reproducible, and cost-effective, offering a viable alternative to full device replacement while preserving implant function and maintaining stable short-term anatomical and IOP outcomes.

Ethics

Informed Consent: Informed consent was obtained from the patient, including consent for the use of relevant clinical information and images for scientific and educational purposes.

Declarations

Authorship Contributions

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

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

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References

1. Khodeiry MM, Hassan AK, Elhusseiny AM, Lee RK, Sayed MS. Outcomes of the Paul glaucoma implant in refractory secondary glaucoma. Clin Ophthalmol. 2025;19:167-174.
2. Tan MCJ, Ong CW, Aquino MC, Lun KW, Sng CCA, Lim DKA, Loon SC, Koh VTC, Chew PTK. Three-year outcomes of the Paul glaucoma implant for treatment of glaucoma. J Glaucoma. 2024;33:478-485.
3. Smith MF, Doyle JW. Results of another modality for extending glaucoma drainage tubes. J Glaucoma. 1999;8:310-314.
4. Kooner KS. Repair of Molteno implant during surgery. Am J Ophthalmol. 1994;117:673.
5. Sarkisian SR, Netland PA. Tube extender for revision of glaucoma drainage implants. J Glaucoma. 2007;16:637-639.
6. Pandav SS, Gautam N, Thattaruthody F. Tube-in-tube: a solution for retracted tube. J Curr Glaucoma Pract. 2021;15:44-46.
7. Berman T, Au L. A new "tube-in-tube" method to extend glaucoma drainage devices using Paul glaucoma implant. J Curr Glaucoma Pract. 2024;18:130-133.
8. Fechter HP, Sarkisian SR, Budenz DL, Piovanetti O, Feldman RM, Horsley MB, Kahook MY. How do I extend a tube? Five approaches to the surgical revision of a glaucoma drainage device. Glaucoma Today. 2009:37-40.
9. Godinho G, Barbosa-Breda J, Oliveira-Ferreira C, Madeira C, Melo A, Falcão-Reis F, Estrela-Silva S. Anterior chamber versus ciliary sulcus Ahmed glaucoma valve tube placement: longitudinal evaluation of corneal endothelial cell profiles. J Glaucoma. 2021;30:170-174.
10. Zhang Q, Liu Y, Thanapaisal S, Oatts J, Luo Y, Ying GS, Wang J, McLeod SD, Gedde SJ, Han Y. The effect of tube location on corneal endothelial cells in patients with Ahmed glaucoma valve. Ophthalmology. 2021;128:218-226.