frontiers | Research Topics

Reviews in ophthalmology 2023

Edited by
Georgios D. Panos and Rashmi Deshmukh

Published in
Frontiers in Medicine

ISSN 1664-8714
ISBN 978-2-8325-5263-6
DOI 10.3389/978-2-8325-5263-6

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Reviews in: Ophthalmology 2023

Topic editors
Georgios D. Panos — Aristotle University of Thessaloniki, Greece
Rashmi Deshmukh — L V Prasad Eye Institute, India

Citation
Panos, G. D., Deshmukh, R., eds. (2024). *Reviews in: Ophthalmology 2023*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-5263-6

Table of contents

frontiers | Frontiers in Medicine

TYPE Editorial
PUBLISHED 25 July 2024
DOI 10.3389/fmed.2024.1464594

OPEN ACCESS

EDITED AND REVIEWED BY
Jodhbir Mehta,
Singapore National Eye Center, Singapore

*CORRESPONDENCE
Georgios D. Panos
✉ gdpanos@gmail.com

RECEIVED 14 July 2024
ACCEPTED 16 July 2024
PUBLISHED 25 July 2024

CITATION
Panos GD and Deshmukh R (2024) Editorial: Reviews in: ophthalmology 2023.
Front. Med. 11:1464594.
doi: 10.3389/fmed.2024.1464594

Editorial: Reviews in: ophthalmology 2023

Georgios D. Panos[1,2]* and Rashmi Deshmukh[3]

[1]Department of Ophthalmology, AHEPA University Hospital, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece, [2]Division of Ophthalmology and Visual Sciences, School of Medicine, Faculty of Medicine and Health Sciences, University of Nottingham, Nottingham, United Kingdom, [3]Cornea and Refractive Surgery Service, LV Prasad Eye Institute, Kallam Anji Reddy Campus, Hyderabad, India

KEYWORDS

ophthalmology, reviews, retina, cornea, cataract, strabismus and pediatric ophthalmology

Editorial on the Research Topic
Reviews in: ophthalmology 2023

Introduction

Welcome to the Research Topic, "*Reviews in: ophthalmology 2023*." As we step into another year of exploration and discovery in the field of ophthalmology, this Research Topic is dedicated to encapsulating the pivotal advancements, enduring challenges, and future trajectories that define our current understanding of ocular health and disease. The year 2023 marks another milestone in the relentless pursuit of knowledge, driven by innovative research and technological breakthroughs that continue to transform the landscape of eye care.

In this Research Topic, we have meticulously curated a series of reviews that encompass a broad spectrum of ophthalmological research, from the latest in retinal therapy and glaucoma management to cutting-edge surgical techniques and pediatric ophthalmology developments. These reviews provide an insightful snapshot of contemporary knowledge, emphasizing the progress achieved and the obstacles that remain.

Each review in this Research Topic offers a unique and comprehensive perspective, underscoring the depth and diversity of current ophthalmic research. From assessing the efficacy of novel therapeutic approaches and surgical advancements to dissecting the genetic intricacies of ocular diseases, these articles represent the forefront of ophthalmic science and clinical practice.

As we present "*Reviews in: ophthalmology 2023*," our aim is to enhance the understanding of the current ophthalmological landscape, inspire continued research, and ultimately contribute to the advancement of patient care. We invite you to explore these thought-provoking reviews, expand your knowledge, and join us in the ongoing journey to understand the complexities of the human eye.

Summaries of articles

Ożóg et al. provide an in-depth review of the epiretinal membrane (ERM), a pathological tissue formed at the vitreoretinal interface, which can cause significant vision disturbances. Their article explores the etiology, epidemiology, pathophysiology,

and treatment of ERM, highlighting the various cell types and cytokines involved in its formation.

Guo et al. conducted a meta-analysis to evaluate subclinical changes in corneal dendritic cell density (CDCD) and corneal subbasal nerve density (CSND) in asymptomatic contact lens wearers. Their findings indicate an increase in CDCD among contact lens wearers, while no significant difference was observed in CSND, underscoring the utility of *in vivo* confocal microscopy (IVCM) for such assessments.

Qu et al. delve into the complexities of neovascular glaucoma, a condition often resulting from central retinal vein occlusion that can lead to blindness. Their review discusses the pathogenesis of the disease and evaluates the efficacy of pan-retinal photocoagulation and intravitreal anti-VEGF injections, recommending a combined approach for better long-term outcomes.

Wang et al. assess the efficacy and safety of intrastromal lenticule implantation for hyperopia correction through a comprehensive meta-analysis. They report significant improvements in uncorrected distance visual acuity and spherical equivalent refractive outcomes, while calling for further research on corneal biomechanics and long-term safety.

Yeh et al. review the etiologies and management of childhood blindness in West Africa, a critical global health issue affecting millions of children. Their study highlights treatable causes such as cataracts and vitamin A deficiency, emphasizing the need for ongoing research to standardize reporting and implement effective public health measures.

Lin et al. (a) examine the rotational stability of toric intraocular lenses (IOLs), which are designed to correct corneal astigmatism. They discuss various factors influencing postoperative rotation and advocate for a personalized approach to minimize rotation and enhance visual outcomes.

Gong et al. review the complications associated with Implantable Collamer Lens (ICL) surgery, particularly those affecting intraocular pressure (IOP). They provide detailed insights into common and rare complications, such as residual viscoelastic and Toxic Anterior Segment Syndrome (TASS), emphasizing prevention and early diagnosis.

Zhang et al. explore the impact of exercise and physical activity on various ocular diseases. Their review highlights the benefits of exercise on conditions like dry eye disease, cataracts, and glaucoma, and discusses mechanisms such as improved blood circulation and reduced oxidative stress, advocating for further research into exercise-based therapeutic strategies.

Gan et al. provide a systematic review of complications associated with XEN gel stent implantation, a minimally invasive procedure for glaucoma. They identify common and rare complications and stress the importance of vigilant postoperative monitoring and early intervention.

Lentz et al. review the effects of hyperbaric conditions, such as those experienced during SCUBA diving, on intraocular pressure (IOP). They find that increased atmospheric pressure generally reduces IOP, though the underlying mechanisms remain unclear. The authors highlight the potential of hyperbaric chambers for glaucoma treatment, while noting the need for further research.

Lin et al. (b) investigate anterior capsular contraction syndrome (ACCS), a complication that can occur after cataract surgery, affecting visual outcomes. Their review covers the pathogenesis, clinical course, and management of ACCS, calling for more research to develop optimal prevention and intervention strategies.

The reviews compiled in this Research Topic not only highlight the latest advancements and therapeutic strategies but also address the ongoing challenges and gaps in our understanding of ocular diseases. We hope that these reviews will inspire further research and innovation, ultimately leading to improved care for patients with ocular diseases. As we look toward the future, it is clear that the work of today's researchers and clinicians will pave the way for tomorrow's breakthroughs in eye care. We encourage you to dive into these insightful reviews, learn something new, and get involved in the exciting developments in ophthalmological research. By staying informed and engaged, we can all help improve vision health and the quality of life for those affected by eye diseases. Thank you for your dedication to ophthalmology, and we eagerly anticipate the progress and discoveries to come.

Author contributions

GP: Writing – original draft, Supervision, Methodology. RD: Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

frontiers | Frontiers in Medicine

TYPE Review
PUBLISHED 13 March 2023
DOI 10.3389/fmed.2023.1149803

OPEN ACCESS

EDITED BY
Michele Lanza,
The University of Campania Luigi Vanvitelli, Italy

REVIEWED BY
Stefano Barabino,
University of Milan, Italy
Weihua Yang,
Jinan University, China

*CORRESPONDENCE
Kai Hu
✉ Kai_hu@nju.edu.cn

†These authors have contributed equally to this work and share first authorship

SPECIALTY SECTION
This article was submitted to Ophthalmology, a section of the journal Frontiers in Medicine

RECEIVED 23 January 2023
ACCEPTED 27 February 2023
PUBLISHED 13 March 2023

CITATION
Guo R, Jiang J, Zhang Y, Liang Q, Chen T and Hu K (2023) Evaluation of corneal dendritic cell density and subbasal nerve density in contact lens wearers using IVCM: A systematic review and meta-analysis. *Front. Med.* 10:1149803. doi: 10.3389/fmed.2023.1149803

Evaluation of corneal dendritic cell density and subbasal nerve density in contact lens wearers using IVCM: A systematic review and meta-analysis

Rongjie Guo†, Jiaxuan Jiang†, Yanan Zhang†, Qi Liang, Taige Chen and Kai Hu*

Department of Ophthalmology, The Affiliated Drum Tower Hospital, Medical School of Nanjing University, Nanjing, China

Purpose: To evaluate the subclinical changes in corneal dendritic cell density (CDCD) and corneal subbasal nerve density (CSND) in asymptomatic contact lens (CL) wearers.

Methods: Databases including PubMed, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials were searched for trials and studies reporting the changes of corneal CDCD and CSND in contact lens wearers published until 25 June 2022. PRISMA guidelines as well as recommended meta-analysis practices were followed. Meta-analysis was conducted using RevMan V.5.3 software.

Results: After the screening, 10 studies with 587 eyes of 459 participants were included. Seven studies reported the data of CDCD. Compared with the control group, CDCD in the CL wearers was higher (18.19, 95% CI 18.8–27.57, $p = 0.0001$). Type of *in vivo* confocal microscopy (IVCM), wear duration, and frequency of lens change were sources of heterogeneity. The difference in CSND between CL wearers and the control group was insignificant, and subgroup analysis did not reveal a source of heterogeneity.

Conclusion: Overall, CDCD increased in CL wears, while CSND did not show significant differences. IVCM is a feasible tool to assess subclinical changes in CL wearers.

KEYWORDS

contact lens (CL), IVCM, dendritic cells, nerve, corneal

Introduction

Contact lenses (CL) are an essential part of vision care worldwide. It is commonly used to correct refraction and slow the progression of myopia. However, up to 75% of CL wearers reported eye discomfort, which can lead to CL intolerance (1, 2). A significant number of CL wearers are clinically diagnosed with dry eye disease (DED) (2). Asymptomatic contact lens wearers refer to CL wearers who have not been clinically diagnosed with CL-related diseases such as DED and who have no subjective discomfort. Subclinical changes in asymptomatic

contact lens wearers still require attention. Previous studies have demonstrated that wearing contact lenses leads to changes in the corneal nerves and increase in infiltrating immune cells (3, 4). The alteration in the corneal nerves is responsible for the symptom of eye discomfort (5), and the increased immune cells reflect rising levels of inflammation on the ocular surface (6). Changes in the corneal nerves and inflammation levels are core factors in the pathogenesis of DED and mediate the development of CL-related DED (7). Thus, the subclinical corneal changes of CL wearers and their relation to CL discomfort requires in-depth investigation.

As a non-invasive method, in vivo confocal microscopy (IVCM) has become increasingly important in diagnosing ocular and systemic diseases. Due to its ease of operation and 800× magnification of living cell structures, IVCM allows clinicians to observe the eye at the cellular level under *in vivo* conditions (8). In recent years, studies using IVCM have focused on assessing the cornea's neuronal changes and inflammatory states. Studies in multiple diseases have demonstrated the alteration in the corneal nerves and increased immune cells, such as keratitis (9) and corneal dystrophies (10).

Although several studies have investigated the effects of CL on the ocular surface using IVCM, divergent results were yielded. Multiple clinical trials have examined the effects of CL wearing on the corneal nerve density; however, the field has yet to reach a consensus. Therefore, we conducted a meta-analysis of clinical trials to evaluate the effects of CL on the cornea, including corneal subbasal nerve density (CSND) and corneal dendritic cell density (CDCD).

Methods

Search methods

The following databases were searched for studies published up to 25 June 2022: Pubmed, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials, using these search strategies (Contact Lens OR Lens, Contact OR Lenses, Contact) and (in vivo confocal microscopy OR confocal microscopy OR IVCM).

Eligibility criteria for considering studies

Articles were included if they reported corneal dendritic cell density (CDCD) and corneal sub-basal nerve density (CSND) detected by in vivo confocal microscopy (IVCM). Exclusion Criteria were as follows: (1) subjects included minors; (2) inappropriate article type: such as reviews, case reports, conference papers, editorials, short surveys, or letters; (3) published not in English; (4) studies only contained cells and animal experiments; (5) subjects with systemic or ocular diseases or surgery history.

Data collection

Search results from all electronic databases were exported to Endnote X9 reference management software for screening. The titles and abstracts of the articles were independently evaluated by two reviewers (RG and JJ). In cases of disagreements, full texts of articles were screened, and ambiguity was solved by discussion or consulting a third reviewer (KH). Data from included studies were extracted by a single reviewer (RG) in Microsoft Excel and checked by a second reviewer (JJ). Extracted information includes: the first author of the article, year of publication, country of the first author, journal of publication, number of patients, sample size (eyes), age of patients, gender of patients, type of IVCM systems, CL type, CL wearing duration, the mean and standard deviation of CDCD, and CSND.

Risk of bias assessment

The studies included in this research consisted of case-control studies and cross-sectional studies. The 11-item checklist recommended by the Agency for Healthcare Research and Quality was used to assess the risk of bias in cross-sectional studies. Each study was judged as follows: low quality = 0-3, moderate quality = 4-7, and high quality = 8-11. The risk of bias in case-control studies was assessed by the Newcastle-Ottawa Scale. Article quality was judged as low quality = 0–5 stars, medium quality = 6-7 stars, and high quality = 8–9 stars.

Data synthesis and analysis

We used Review Manager Software 5.3® for statistical analysis. The data were analyzed by using the mean difference. We calculated the weighted mean difference (WMD) and associated 95% confidence interval (CI) for CDCD and CSND. Pooled estimates of effects were calculated by using random effects models. Heterogeneity was quantified by the I^2 statistic; $I^2 > 50\%$ defined high heterogeneity between studies. Subgroup analyses were performed when $I^2 > 50\%$ to compare the heterogeneity as follows: country of study, type of IVCM, type of contact lens, CL wearing duration, and whether a daily change of CL.

Results

Search results

After a systematic literature search, 2,121 references were identified, and 10 randomized clinical trials that met the inclusion criteria were included (**Figure 1**). The included studies consist of 2 case-control studies (11, 12) and 8 cross-sectional studies (5, 13–19). A total of 459 patients with 587 eyes were included. Details about the included studies are shown in **Table 1**.

Quality assessment

One trial was considered to have an overall high risk of bias. Nine studies were of moderate quality, although some uncertain risk of bias remained. Subgroup analysis for the outcome comparing low versus moderate quality trials was performed. More details are shown in **Table 2**.

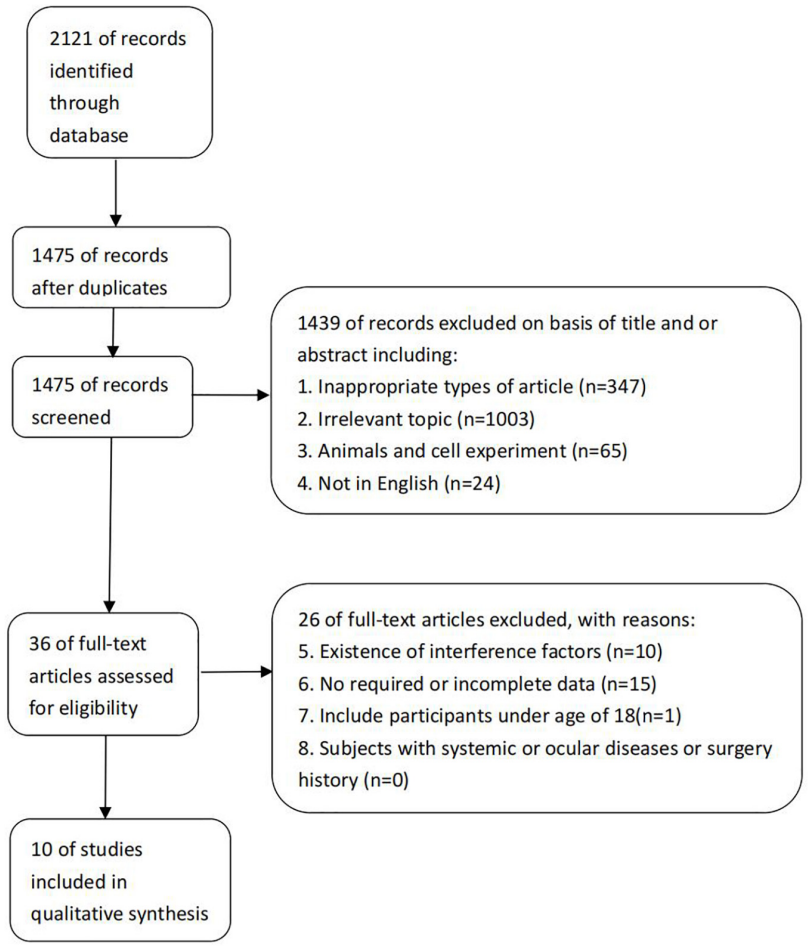

FIGURE 1
Flow diagram of the studies selection process.

Corneal dendritic cell density

Seven studies were included in this analysis. CDCD was significantly higher in CL wearers than in controls, with an overall RR of 18.19 (95% CI 18.8–27.57, $p = 0.0001$), which supports the inflammatory ocular environment of CL wearers. The included studies showed high heterogeneity ($I^2 = 72\%$). The detailed results can be found in Figure 2. The subgroup analysis of the country and the type of contact lens also showed high heterogeneity. In the subgroup analysis of the type of IVCM, the HRTIII/RCM subgroup showed lower heterogeneity ($I^2 = 53\%$, $p = 0.1$). In the comparison grouped by wearing duration, the subgroups with a wearing duration of $\leq$3 months and >3 months both showed very low heterogeneity ($I^2 = 25\%$, $p = 0.26$ vs. $I^2 = 0\%$, $p = 0.55$). CL wearing time of more than 3 months significantly upregulated CDCD (RR 32.68, 95% CI 21.22–44.13, $p < 0.0001$). Daily contact lens replacement was also a source of heterogeneity. Both the daily disposable CL ($I^2 = 41\%$, $p = 0.18$) and daily reusable CL ($I^2 = 48\%$, $p = 0.15$) subgroups showed low heterogeneity. The daily disposable CL group (RR 32.68, 95% CI 21.22–44.13, $p < 0.0001$) showed a higher CDCD than the daily reusable CL group (RR 32.68, 95% CI 21.22–44.13, $p < 0.0001$). Further details are provided in Table 3.

Corneal subbasal nerve density

Five studies were included, and no significant difference was observed when assessing the change in CSND ($p = 0.09$), with an overall RR of −2.86 (95% CI -6.18–0.46). Wearing contact lenses did not significantly change CSND in the wearers compared to the controls. Included studies show high heterogeneity ($I^2 = 83\%$), and subgroup analysis did not reveal a source of heterogeneity. The details are shown in Figure 3 and Table 2.

Discussion

As a highly prevalent treatment method, CL are receiving increasing attention. Although a significant number of CL wearers are diagnosed with DED, subclinical changes in the corneas of the wearers who are not clinically diagnosed remain of concern. When searching electronic databases, we found that several relevant studies had included subjects diagnosed with DED. This study focuses on the subclinical changes in healthy CL wearers. Thus, only studies investigating asymptomatic healthy CL wearers were selected. Ten articles were included in this study after screening. We analyzed CDCD, CSND, and assessed the effects of quality of

TABLE 1 Characteristics of the included studies.

References	Eyes	Age (year)	Group	Quality	CDCD	CSND
Alzahrani et al. (11)	10	30 ± 5	Contact lens	Medium	√	
	10		Control			
Dogan et al. (13)	22	25.7 ± 8.2	Asymptomatic contact lens group	Moderate	√	
	28		Control			
Golebiowski et al. (14)	40	31.5 ± 5	Contact lens	Moderate		√
	40		Control			
Hu et al. (15)	16	27.3 ± 5.5	Asymptomatic contact lens group	Moderate		√
	16		Control			
López-De La Rosa et al. (5)	20	25 ± 5.19	Asymptomatic contact lens group	Moderate	√	√
	20		Control			
Lum et al. (16)	18	28 ± 10	Soft contact lens orthokeratology lens	Low		√
	18		Control			
Nombela-Palomo et al. (17)	35	24.8 ± 3.9	Orthokeratology lens	Moderate	√	
	21		Seefree			
	15		Control			
Saliman et al. (19)	20	31.1 ± 7.5	A2	Moderate	√	
	20		AO			
	20		Control			
Sindt et al. (18)	24	37 ± 14	Traditional hydrogel wearers	Moderate	√	
	82		Silicone hydrogel wearers			
	20		Control			
Tse et al. (12)	27	21.5 ± 3.9	Scleral lens	Medium	√	√
	27		Control			

CDCD, corneal dendritic cell density; CSND, corneal subbasal nerve density; A2, reusable Acuvue 2; AO, reusable Acuvue Oasys.

TABLE 2 Subgroup meta-analysis of CSND.

Subgroup	Group by	No of studies	Eyes	Heterogeneity I^2 (%)	WMD of CDCD (mm/mm^2) (95% CI)	*P*-value for heterogeneity
Country of study	Western countries	4	196	87%	−3.15 (−7.68, 1.37)	0.007
	Asian countries	1	32	N	−2.11 (−4.66, 0.44)	N
Type of IVCM	HRTII/RCM	3	148	86%	−3.34 (−7.75, 1.07)	N
	HRTIII/RCM	2	80	82%	−2.28 (-9.13, 4.56)	0.1
Wearing duration	≤ 3 months	1	40	N	−6.24 (-11.66, -0.82)	0.26
	> 3 months	3	108	90%	−3.01 (−7.81, 1.78)	0.55

WMD, weighted mean differences; CDCD, corneal dendritic cell density; IVCM, *in vivo* confocal microscopy.

the literature, country of study, type of IVCM, type of CL, wearing duration, and daily change on the outcomes.

Dendritic cells (DCs) are considered the most important resident corneal antigen-presenting cells (20). It has been demonstrated that corneal DCs are involved in multiple ocular surface diseases (21). The proliferation and maturation of DCs represent an inflammatory state of the ocular surface (22). Due to its real-time and non-invasive features, HRT/RCM of IVCM allows real-time observation of the corneal DCs from the cellular level.

Consistent with previous clinical findings, our overall results show a significant increase in CDCD in CL wearers (p = 0.0001). Our analysis demonstrated that even in asymptomatic healthy CL wearers, the cornea exhibited subclinical inflammation status. The changes, which were presented in asymptomatic healthy wearers, indicated that the inflammatory state was caused by CL, not CL-associated ocular surface diseases such as DED. Furthermore, we hypothesized that CL-induced subclinical inflammation was involved in the pathogenesis of DED in CL wearers. In subgroup analysis, the HRTIII/RCM subgroup showed lower heterogeneity compared to HRT/RCM and HRTII/RCM subgroups, suggesting that the results of studies using HRTIII/RCM for CDCD assessment are more stable and comparable.

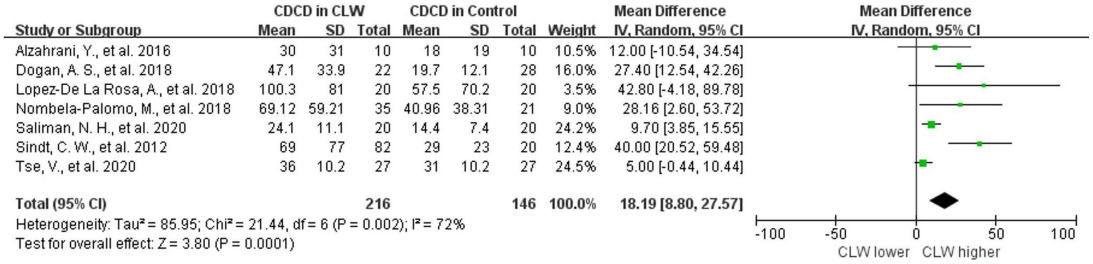

FIGURE 2
Forest plot of CDCD in CL wearer vs. control group. CI, confidence interval; IV, inverse variance; SD, standard deviation; CLW, contact lens wearers; CDCD, corneal dendritic cell density.

TABLE 3 Subgroup meta-analysis of CDCD.

Subgroup	Group by	No of studies	Eyes	Heterogeneity I^2 (%)	WMD of CDCD (mm/mm^2) (95% CI)	*P*-value for heterogeneity
Country of study	Western countries	6	50	69%	15.87 (6.29, 25.45)	0.007
	Asian countries	1	312	N	27.4 (12.54, 42.26)	N
Type of IVCM	HRT/RCM	2	156	91%	21.2 (−13.01, 55.40)	0.0007
	HRTII/RCM	2	56	N	28.16 (2.6, 53.72)	N
	HRTIII/RCM	3	150	53%	17.24 (5.14, 29.33)	0.1
Type of CL	Silicone hydrogel	3	192	83%	23.96 (5.55, 42.38)	0.002
	Hydrogel	1	20	N	12.00 (−10.54, 34.54)	N
	orthokeratology lens	1	56	N	28.16 (2.6, 53.72)	N
	Scleral lens	1	54	N	17.21 (7.8, 26.62)	N
Wearing duration	≤ 3 months	4	170	25%	7.81 (3.93, 11.68)	0.26
	> 3 months	3	192	0%	32.68 (21.22, 44.13)	0.55
Daily change	Daily disposable CL	3	172	41%	27.72 (17.25, 38.18)	0.18
	Daily reusable CL	3	150	48%	7.68 (3.74, 11.61)	0.15

WMD, weighted mean differences; CDCD, corneal dendritic cell density; IVCM, *in vivo* confocal microscopy; CL, contact lens.

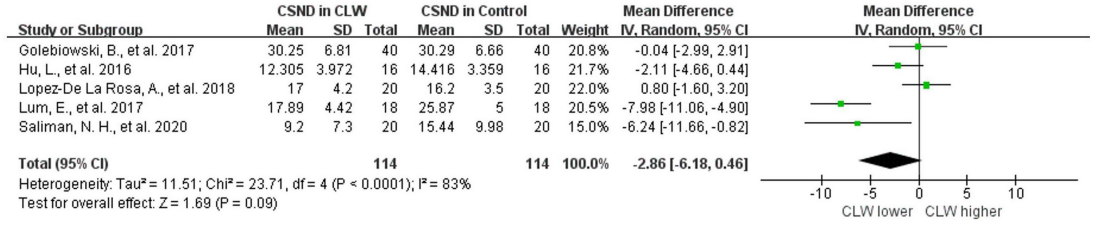

FIGURE 3
Forest plot of CSND in CL wearer vs. control group. CI, confidence interval; IV, inverse variance; SD, standard deviation; CLW, contact lens wearers; CSND, corneal sub-basal nerve density.

The changes in the cornea have been associated with CL wear duration. A recent study showed that the density of corneal DCs significantly increased 1 week after soft CL wear, peaked at 1 month, and decreased after 3 months of CL wear (23). In our study, the duration of CL wear in the included studies ranged from 8 h to 14 years. We set 3 months as the boundary to divide the duration of wear into more than or less than 3 months. Unlike previous studies, we found that CL wearing for more than 3 months resulted in upregulated corneal DCs density compared with CL wearing for less than 3 months, and there were significant differences between the two groups. This study included different materials and types of contact lenses, and a comparison of wear duration for a particular type of CL may be more relevant.

It was generally considered that daily reusable contact lenses had a more significant impact on the cornea and carried a greater risk of disease than daily disposable lenses (24). However, our analysis demonstrated the opposite results. The CDCD of the daily disposable CL group was higher than the daily reusable CL group. Nonetheless, only 6 articles were included in this subgroup analysis, and more research may be needed to confirm this conclusion.

It has been demonstrated by IVCM and animal experiments that the density of DCs in the central cornea is lower than in the peripheral cornea (20). Five of the seven studies included did not clarify whether the DCs were in the central or peripheral cornea. Based on the analysis of their reported amounts, we speculated that these results may be from the peripheral cornea, and contacted the authors for confirmation. In two other studies, both central and peripheral cornea data were reported. To maintain data consistency, we only selected peripheral corneal data from these two studies for analysis.

The effects of CL wear on corneal nerves have been controversial. A few studies using IVCM have shown that wearing CL does not affect corneal nerve density, morphology, and distribution (8). Patel et al. (25) reported no reduction in corneal nerve density after CL wear, but corneal sensitivity decreased in CL wearers compared with the controls. Some studies presented conflicting results. Lum et al. (3) demonstrated by IVCM that CL wear resulted in decreased central corneal nerve density. Hiraoka et al. (26) reported that overnight orthokeratology lens wearing down-regulated corneal nerve density. Herein, we included five studies for the analysis of corneal nerve density. Two of these five studies reported a reduction in corneal nerve density, and the other three showed no significant changes. Our results showed that CL wear did not significantly alter the corneal nerve density. Although the results had no statistical significance, the CL group still showed lower corneal nerve density.

Subgroup analysis of the corneal nerve density was also performed, but the results did not reveal the source of heterogeneity and the differences between subgroups. This may be due to the small number of studies included. In addition to corneal nerve density, some studies have also investigated nerve fiber tortuosity, nerve fiber interconnections, the density of nerve branches, and nerve reflectivity. However, fewer than three studies reported these data. Therefore, the data were not further analyzed.

Our results showed that wearing CL did not directly lead to changes in the corneal nerves. Some studies have reported that CL wear reduced corneal sensitivity (27, 28). The decrease in corneal sensitivity has been attributed to disrupted corneal metabolism, mechanical effects, and sensory adaptations (29) caused by CL. In addition, CL wear can lead to the development of dry eye disease, further contributing to corneal nerve changes associated with the disease.

Our study has the following limitations: First, the number of articles included in this study was limited. If more new articles that meet the inclusion criteria can be included, more convincing outcomes might be drawn. Second, despite the attempt to control potential sources of heterogeneity, there were differences in study design, patient populations, and IVCM measurements that could have influenced outcomes. Meta-analysis that contains more studies with less heterogeneity may avoid the effect of heterogeneity on the results.

In conclusion, CL wear was associated with an increase in CDCD. When evaluating CDCD with IVCM, the results were more stable with HRTIII/RCM. CDCD was also related to CL wear duration and whether the lenses were changed daily. Although wearing contact lenses slightly reduced CSND, it was not statically significant. IVCM appears to be a feasible tool to assess subclinical changes in CL wearers.

Author contributions

RG and KH conceived and designed the overall study. RG, JJ, YZ, and KH worked on data acquisition. RG and QL worked on data analysis and interpretation. RG and TC prepared the original manuscript. KH supervised and reviewed the manuscript. All authors read and approved the final version of the manuscript.

Funding

This study was supported by the National Natural Science Foundation of China (81870695), Natural Science Foundation of Jiangsu Province (SBK2020022490), Key Program of Nanjing Science and Technology Development Plan (ZKX20022), Nanjing Science and Technology Development Plan (YKK21095), and Clinical Trials from the Affiliated Drum Tower Hospital, Medical School of Nanjing University.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Vajdic C, Holden B, Sweeney D, Cornish R. The frequency of ocular symptoms during spectacle and daily soft and rigid contact lens wear. *Optom Vis Sci.* (1999) 76:705–11. doi: 10.1097/00006324-199910000-00022

2. Begley C, Caffery B, Nichols K, Chalmers R. Responses of contact lens wearers to a dry eye survey. *Optom Vis Sci.* (2000) 77:40–6.

3. Lum E, Golebiowski B, Swarbrick H. Mapping the corneal sub-basal nerve plexus in orthokeratology lens wear using *in vivo* laser scanning confocal microscopy. *Invest Ophthalmol Vis Sci.* (2012) 53:1803–9. doi: 10.1167/iovs.11-8706

4. Zhivov A, Stave J, Vollmar B, Guthoff R. *In vivo* confocal microscopic evaluation of Langerhans cell density and distribution in the normal human corneal epithelium.

Graefes Arch Clin Exp Ophthalmol. (2005) 243:1056–61. doi: 10.1007/s00417-004-1075-8

5. López-De La Rosa A, Arroyo-Del Arroyo C, Cañadas P, López-Miguel A, Calonge M, Enríquez-De-Salamanca A, et al. Are contact lens discomfort or soft contact lens material properties associated with alterations in the corneal sub-basal nerve plexus? *Curr Eye Res.* (2018) 43:487–92. doi: 10.1080/02713683.2017.1420804

6. Cavalcanti B, Cruzat A, Sahin A, Pavan-Langston D, Samayoa E, Hamrah P. *In vivo* confocal microscopy detects bilateral changes of corneal immune cells and nerves in unilateral herpes zoster ophthalmicus. *Ocul Surf.* (2018) 16:101–11. doi: 10.1016/j.jtos.2017.09.004

7. Calonge M, Enríquez-de-Salamanca A, Diebold Y, González-García M, Reinoso R, Herreras J, et al. Dry eye disease as an inflammatory disorder. *Ocul Immunol Inflamm.* (2010) 18:244–53. doi: 10.3109/09273941003721926

8. Cruzat A, Qazi Y, Hamrah P. *In Vivo* confocal microscopy of corneal nerves in health and disease. *Ocul Surf.* (2017) 15:15–47. doi: 10.1016/j.jtos.2016.09.004

9. Hamrah P, Cruzat A, Dastjerdi M, Zheng L, Shahatit B, Bayhan H, et al. Corneal sensation and subbasal nerve alterations in patients with herpes simplex keratitis: An *in vivo* confocal microscopy study. *Ophthalmology.* (2010) 117:1930–6. doi: 10.1016/j.ophtha.2010.07.010

10. Mocan M, Yilmaz P, Irkec M, Orhan M. *In vivo* confocal microscopy for the evaluation of corneal microstructure in keratoconus. *Curr Eye Res.* (2008) 33:933–9. doi: 10.1080/02713680802439219

11. Alzahrani Y, Pritchard N, Efron N. Changes in corneal Langerhans cell density during the first few hours of contact lens wear. *Cont Lens Anterior Eye.* (2016) 39:307–10. doi: 10.1016/j.clae.2016.02.008

12. Tse V, Zhou Y, Truong T, Lin K, Tan B, Lin M. Corneal health during three months of scleral lens wear. *Optom Vis Sci.* (2020) 97:676–82. doi: 10.1097/OPX.0000000000001566

13. Dogan A, Gurdal C, Arslan N. Corneal confocal microscopy and dry eye findings in contact lens discomfort patients. *Cont Lens Anterior Eye.* (2018) 41:101–4. doi: 10.1016/j.clae.2017.08.001

14. Golebiowski B, Chao C, Stapleton F, Jalbert I. Corneal nerve morphology, sensitivity, and tear neuropeptides in contact lens wear. *Optom Vis Sci.* (2017) 94:534–42. doi: 10.1097/OPX.0000000000001063

15. Hu L, Chen J, Zhang L, Sun X, Huang J, Xie W, et al. Effects of Long-term Soft Contact Lenses on Tear Menisci and Corneal Nerve Density. *Eye Contact Lens.* (2016) 42:196–201. doi: 10.1097/ICL.0000000000000177

16. Lum E, Golebiowski B, Swarbrick H. Reduced corneal sensitivity and sub-basal nerve density in long-term orthokeratology lens wear. *Eye Contact Lens.* (2017) 43:218–24. doi: 10.1097/ICL.0000000000000285

17. Nombela-Palomo M, Felipe-Marquez G, Hernandez-Verdejo J, Nieto-Bona A. Short-term effects of overnight orthokeratology on corneal sub-basal nerve plexus morphology and corneal sensitivity. *Eye Contact Lens.* (2018) 44:77–84. doi: 10.1097/ICL.0000000000000282

18. Sindt C, Grout T, Critser D, Kern J, Meadows D. Dendritic immune cell densities in the central cornea associated with soft contact lens types and lens care solution types: A pilot study. *Clin Ophthalmol.* (2012) 6:511–9. doi: 10.2147/OPTH.S28083

19. Saliman N, Morgan P, MacDonald A, Maldonado-Codina C. Subclinical inflammation of the ocular surface in soft contact lens wear. *Cornea.* (2020) 39:146–54. doi: 10.1097/ICO.0000000000002192

20. Hamrah P, Liu Y, Zhang Q, Dana M. The corneal stroma is endowed with a significant number of resident dendritic cells. *Invest Ophthalmol Vis Sci.* (2003) 44:581–9.

21. Hu K, Harris D, Yamaguchi T, von Andrian U, Hamrah P. A dual role for corneal dendritic cells in herpes simplex keratitis: Local suppression of corneal damage and promotion of systemic viral dissemination. *PLoS One.* (2015) 10:e0137123. doi: 10.1371/journal.pone.0137123

22. Hao R, Ding Y, Li X. Alterations in corneal epithelial dendritic cell in Sjogren's syndrome dry eye and clinical correlations. *Sci Rep.* (2022) 12:11167. doi: 10.1038/s41598-022-15537-4

23. Xu Y, Xu Z, Shu X, Liu Q, Wang Y, Xia J, et al. Dynamic changes of ocular surface in first-time contact lens wearers and the effective factors of contact lens discomfort. *Front Med.* (2022) 9:833962. doi: 10.3389/fmed.2022.833962

24. Carnt N, Minassian D, Dart J. Acanthamoeba keratitis risk factors for daily wear contact lens users: A case-control study. *Ophthalmology.* (2023) 130:48–55. doi: 10.1016/j.ophtha.2022.08.002

25. Patel S, McLaren J, Hodge D, Bourne W. Confocal microscopy *in vivo* in corneas of long-term contact lens wearers. *Invest Ophthalmol Vis Sci.* (2002) 43:995–1003.

26. Hiraoka T, Kaji Y, Okamoto F, Oshika T. Corneal sensation after overnight orthokeratology. *Cornea.* (2009) 28:891–5. doi: 10.1097/ICO.0b013e31819c4fb1

27. Polse K. Etiology of corneal sensitivity changes accompanying contact lens wear. *Invest Ophthalmol Vis Sci.* (1978) 17:1202–6.

28. Stapleton F, Tan M, Papas E, Ehrmann K, Golebiowski B, Vega J, et al. Corneal and conjunctival sensitivity to air stimuli. *Br J Ophthalmol.* (2004) 88:1547–51.

29. Stapleton F, Marfurt C, Golebiowski B, Rosenblatt M, Bereiter D, Begley C, et al. The TFOS international workshop on contact lens discomfort: Report of the subcommittee on neurobiology. *Invest Ophthalmol Vis Sci.* (2013) 54:TFOS71–97. doi: 10.1167/iovs.13-13226

frontiers | Frontiers in Medicine

TYPE Review
PUBLISHED 10 August 2023
DOI 10.3389/fmed.2023.1121270

OPEN ACCESS

EDITED BY
Georgios D. Panos,
Nottingham University Hospitals NHS Trust, United Kingdom

REVIEWED BY
Laura De Luca,
University of Messina, Italy
Livio Vitiello,
University of Salerno, Italy
Maddalena De Bernardo,
University of Salerno, Italy

*CORRESPONDENCE
Mateusz Kamil Ożóg
✉ mateusz.ozog@sum.edu.pl

RECEIVED 11 December 2022
ACCEPTED 24 July 2023
PUBLISHED 10 August 2023

CITATION
Ożóg MK, Nowak-Wąs M and Rokicki W (2023) Pathophysiology and clinical aspects of epiretinal membrane – review.
Front. Med. 10:1121270.
doi: 10.3389/fmed.2023.1121270

Pathophysiology and clinical aspects of epiretinal membrane – review

Mateusz Kamil Ożóg[1,2]*, Marta Nowak-Wąs[1,3] and Wojciech Rokicki[3,4]

[1]Department of Histology and Cell Pathology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland, [2]Department of Histology, Cytophysiology and Embryology, Faculty of Medicine, Academy of Silesia, Zabrze, Poland, [3]Department of Ophthalmology, Kornel Gibiński University Clinical Center, Medical University of Silesia, Katowice, Poland, [4]Department of Ophthalmology, Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland

The epiretinal membrane (ERM) is a pathological tissue formed at the vitreoretinal interface. The formation of this tissue is associated with numerous symptoms related to disturbances of vision. These types of lesions may arise idiopathically or be secondary to eye diseases, injuries and retinal surgeries. ERM tissue contains numerous cell types and numerous cytokines, which participate in its formation. The aim of this paper is to summarize information about the etiology, epidemiology, pathophysiology and treatment of ERM, with a brief description of the main cells that build the ERM – as well as the cytokines and molecules related to ERM pathogenesis – being provided in addition.

KEYWORDS

epiretinal membrane, macular pucker, myofibroblasts, pre-macular fibrosis, retina, cellophane maculopathy

1. Introduction

The epiretinal membrane (ERM), commonly known as macular pucker or cellophane maculopathy, is a pathological tissue formed at the junction of the vitreous body and the retina – the vitreoretinal interface. The formation of this tissue is associated with symptoms related to visual disturbances. The lesions of this type may arise idiopathically or be secondary to eye diseases, injuries and retinal surgery. In the case of idiopathic changes, a number of factors may favor the development of these lesions (1).

ERM tissue contains many cell types deriving from different parts of eyeball: retinal pigment epithelium (RPE) cells, fibrocytes, fibrous astrocytes, myofibroblast-like cells, glial cells, endothelial cells (ECs), and macrophages. The cellular composition of this tissue varies individually and depends on the cause of the lesions and the participation of numerous cytokines such as growth factors, tumor necrosis factor (TGF) or chemokines (2).

The aim of this paper is to summarize information on the etiology, epidemiology, pathophysiology, and treatment of ERM.

2. Pathophysiology of ERM

The vitreous body, consisting of a colorless, highly hydrated gel matrix, fills the space called the vitreous chamber located posteriorly to the ciliary body. The vitreous body adheres loosely to the retina, connecting most strongly around the ora serrata and the optic nerve (3). Its outer layer – vitreous cortex – is made of collagen, while the inside is filled with vitreous humor

containing mainly water (98–99%), fibrous protein called vitrosin, type II collagen fibers, glycosaminoglycans, hyaluronates, opticins and other proteins (4).

The vitreous body contains a small number of cells, mainly phagocytes, that remove cellular debris and hyalocytes the main function of which is to produce hyaluronans (5). Vitreous body is involved in maintaining proper intraocular pressure, protecting the lens against oxidative stress and is one of the optical centers (3, 6).

With age, an increase in liquefaction and fiber aggregation occurs, one which may lead to many ophtalmic diseases (7, 8). As a result of these processes, the volume of the vitreous body decreases, the said body collapses, and the collagen fibers reorganize. This leads to changes in the shape of the vitreous body and posterior vitreous detachment (PVD). If this process is not complete, and macula and vitreous body come into contact, a posterior vitreomacular adhesion (VMA) is formed at the point of this contact. This process may lead to the formation of vitreomacular traction (VMT), which involves foveal contour distortion and retinal layer disorders, with a possible elevation of the retina above the pigment epithelium (RPE), not interrupting, however, the retina's continuity. In this state most patients self-heal due to completion of PVD. When VMT is not self-healed and a hole in the macula occurs, the next step in the evolution of the pathology could be vitreoschisis, which occurs in the case of the half of PVD patients. During this process posterior vitreous cortex splits, leaving the outermost layer attached to the macula, while the remainder of the vitreous collapses forward. This can lead to the proliferation within the retinal vitreous residue, i.e., the formation of an epiretinal membrane (ERM) (9, 10) (Figure 1).

Formed ERM tissue can cause macular edema or distortion of the vitreoretinal interface, which may lead to visual disturbances, including blurred vision and a reduction of visual acuity (11) (Figure 2).

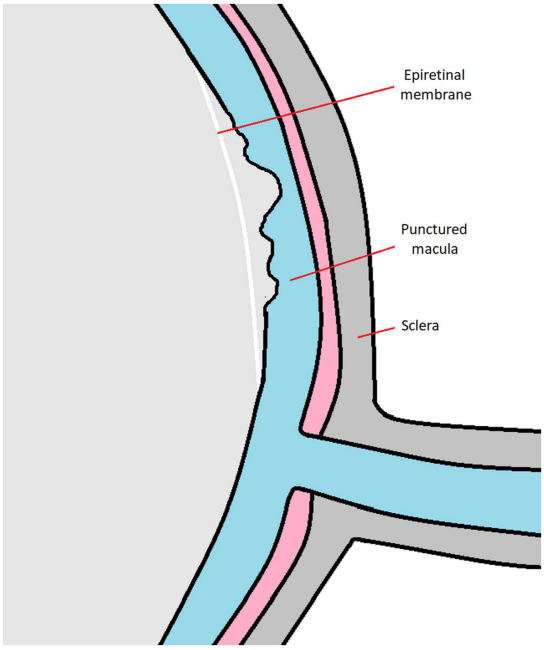

FIGURE 1
This illustration presents ERM tissue in relation to other eyeball parts.

2.1. ERM tissue formation

Pathological cell proliferation on the internal limiting membrane (ILM) surface is the basis for the formation of pathological tissue at the interface between the vitreous body and the retina. As a result of PVD, ILM dehiscence occurs, which leads to the migration of microglial cells to the surface. Microglial cells then interact with the neighboring hyalocytes and laminocytes of the vitreous cellular membrane (12). These cells then differentiate into fibroblast-like cells, which are directly responsible for the formation of the collagen scaffolding of the ERM (13, 14) (Figure 3).

ERMs can arise idiopathically or secondary to certain disease states, and as a result of a trauma or surgery within the eyeball.

In the case of the idiopathic ERM retinal glial cells, hyalocytes, fibroblasts, and myofibroblasts generated by cell migration and differentiation of microglial cells, hyalocytes, and laminocytes predominate (2, 14).

In secondary ERM, the presence of the retinal pigment epithelial cells, macrophages, T cells, and B cells is observed due to inflammation appearing in the etiology of this lesion (15, 16).

The leading theory presents the sequence of changes leading to the emergence of the ERM thus:

1) Microglial cells migrate to the surface of the retina as a consequence of PVD and the resulting formation of the cracks within the ILM.
2) The fragments of the vitreous membrane remaining on the surface of the ILM contain hyalocytes, which, due to contact with microglial cells, differentiate into myofibroblasts, while microglial cells may differentiate into fibroblasts.
3) PVD-induced ILM avulsion enhances the action of some ERM-promoting cytokines (17–19).

2.2. Idiopathic ERM

The idiopathic form of ERM affects approximately 95% of patients and is directly related to cellular proliferation resulting from PVD.

It is possible to distinguish 2 types of iERM. Type I is formed due to collagen of the vitreous body coming into contact with the internal limiting membrane (ILM) of the retina, which results in the production of a collagen membrane separating the two structures. Type II, on the other hand, results from cell proliferation that takes place directly on the ILM surface with or without a small layer of collagen in between (20).

2.3. Secondary ERM

The secondary form of ERM develops in the course of eye diseases or as a result of injuries of the eyeball or the surgeries performed on it.

As a result of these disorders, inflammation within the retina occurs, which leads to an inflammatory infiltration and, ultimately, a migration of cells from other layers of the retina to the ERM being in the process of formation (21) (Table 1).

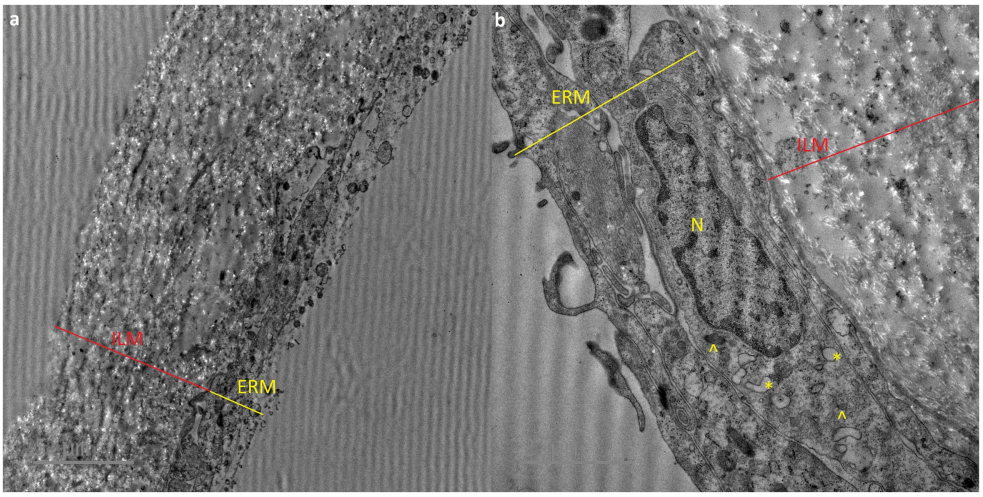

FIGURE 2
Transmission electron micrograph showing epiretinal membrane (ERM) and internal limiting membrane (ILM). a – original micrograph showing comparison of ERM and ILM structure (original magnification x4200), b – micrograph showing detailed structure of ERM and phagocytes: N – cell nuclei, asterix (*) – vacuoles, arrowhead (^) – dense granules (magnificated and focused micrograph a).

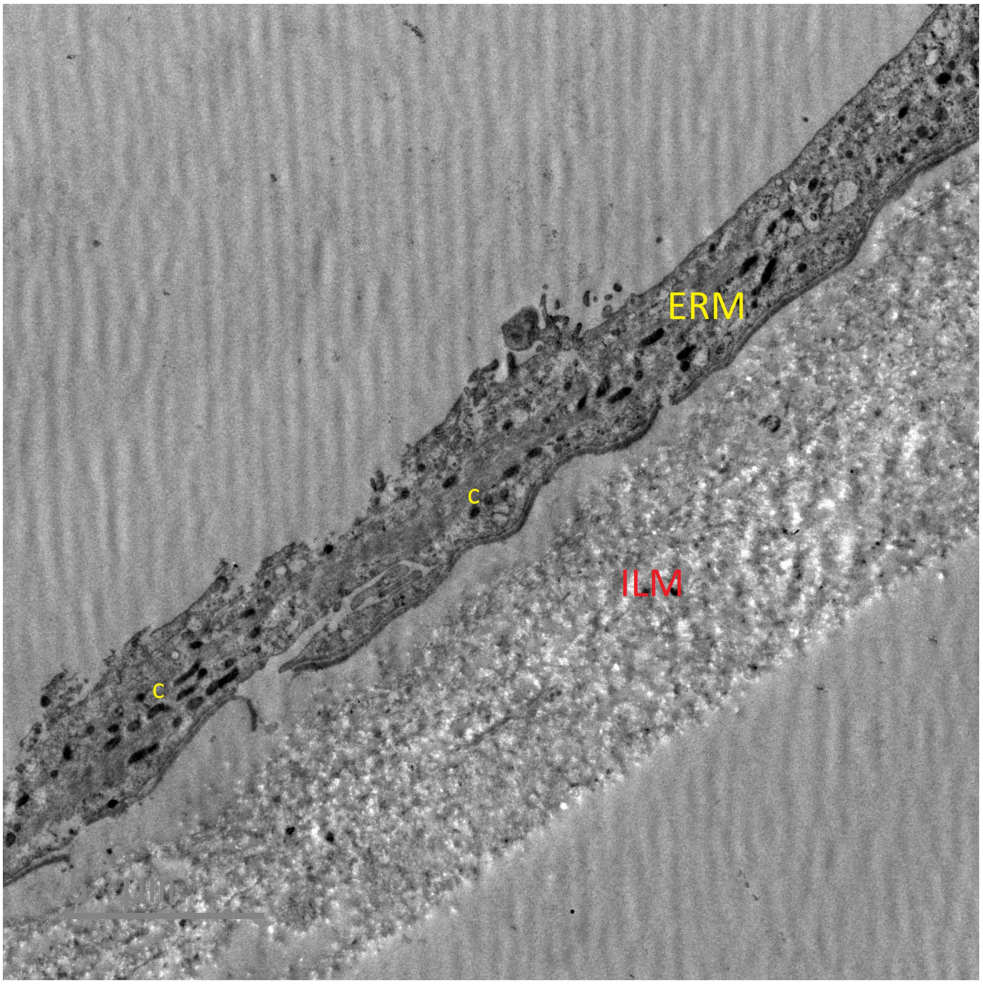

FIGURE 3
Transmission electron micrograph showing collagen fibers in epiretinal membrane. ERM – epiretinal membrane, ILM – internal limiting membrane, c – collagen fibers.

3. Histopatology of ERM

3.1. The cells that build ERM

ERM is usually made up of two layers placed on the ILM. The outer layer directly overlying the ILM consists of randomly oriented proteins, while the inner layer consists of one or more layers of cells from the retina (22). The cells observed are glial cells, hyalocytes, RPE cells, macrophages, fibroblasts, and myofibroblast-like cells. Apart from the latter type, the source of the cells within the ERM is uncertain. It is known, however, that myofibroblast-like cells are formed by differentiating from other cell types within ERM (22, 23) (Table 2).

TABLE 1 Diseases associated with secondary ERM.

Type of complication	Disease entities
Iatrogenic	Cataract surgery
	Vitrectomy surgery
	Retinopexy (laser or cryotherapy)
Retinal vascular diseases	Diabetic retinopathy
	Retinal vascular occlusive disease
	Coat's disease
	Retinal arteriolar macroaneurysm
	Radiation retinopathy
	Sickle-cell retinopathy
Intraocular tumors	Retinal haemangioblastoma
	Vasoproliferative tumor
	Choroidal melanoma
	Hamartoma of the retina and retinal pigment epithelium combined
	Retinal astrocytic hamartoma
Vitreomacular traction disorders	Macular hole
	Vitreomacular traction syndrome
Other retinal diseases	Retinal tears
	Retinitis pigmentosa
Other diseases of the eyeball	Uveitis
	Myopia
	Trauma
	Age-related macular degeneration
	Neurofibromatosis type 2

3.2. Cytokines and molecules related to ERM pathogenesis

A number of cytokines and molecules related to this process which directly or indirectly influence the development of this pathology have been identified. These cells are responsible for the production of proteins that constitute the ERM extracellular matrix (31) (Table 3).

4. Epidemiology

The main risk factors for ERM are age and PVD. PVD is observed in the case of 70% of patients in the initial stages of the disease. Although PVD can appear early in life or childhood, ERM usually appears after the age of 50, and the risk of its appearance increases exponentially with age.

Gender was not observed to exert any influence as to the risk of the appearance of ERM, although some studies indicate a slight predominance of women among the afflicted (60). Statistically, significant differences in risk of occurrence seem to emerge due to ethnicity – in studies concerning the American society, the highest number of ERM cases is identified in the population of Chinese origin, followed by the ethnic groups of, respectively, Latin American, Caucasian and African descent.

Geographic differences were also observed to play a part: ERM is more common in Europe and South America, and the

TABLE 2 Cells that built epiretinal membranes.

Type of cells	Description
Glial cells	Microglia are small cells of a monocytic / macrophagal origin, placed in retina and optic nerve. Those cells as parts of ERM tissue produce TGF-beta, which is mainly involved in the differentiation of myofibroblast-like cells (24).
	Within the ERM there is low abundance of astrocytes (which migrate from retina and optical nerve), the presence of which appears more prominent in other vitreomacular traction disorders such as vitreomacular traction syndrome (VMTS), lamellar macular holes (LMHs) and myopic traction maculopathies (24).
	The proliferation of Muller cells (a characteristic type of cells in retina) is believed to be one of the direct causes of ERM formation as source of proinflamatory cytokines (25, 26).
Hyalocytes	These are phagocytic cells, also of monocytic/macrophagal origin found on the surface of the vitreous base. Main function of this cells is production of elements of the extracellular matrix. These cells are responsible for the production of TGF-b which is a major contributor to the differentiation of myofibroblast-like cells (27, 28).
Retinal pigment epithelium (RPE) cells	These cells, originally forming single layer arranged at the outermost layer of the retina, migrate through retinal breaks and attach themselves to the inner retina. They are likely to transform to myofibroblast-like cells (22).
Macrophages	The presence of macrophages within lesion (which could be found by default in cornea, uveal tract and choroid) can be observed mainly in the secondary ERM associated with vitreous haemorrhage. They are the source of many cytokines involved in the pathophysiology of the lesion (29, 30).
Fibroblasts and myofibroblast-like-cells	These cells are responsible for the production of proteins forming the ERM intercellular matrix and produce many pro-inflammatory cytokines (22).

TABLE 3 Cytokines and molecules involved in epiretinal formation.

Cytokine or molecule	Description
Vascular endothelial growth factor (VEGF)	VEGF is a growth factor that stimulates mitosis and endothelial cell migration and chemotactic factor for leukocytes. One of the main factors stimulating the production of VEGF is tissue hypoxia – in the case of its appearance, any type of cell is able to commence the production of VEGF (23).
	One of the phenomena observed in the course of PDR is capillary oclusion in the retina, which, by causing hypoxia, increases the expression of VEGF by the cells that build the retina (32). Pathological retinal angiogenesis promotes the formation of subretinal hemorrhages, which in turn promotes the development of ERM (33).
	Increased VEGF expression has been observed not only in the retina of ERM patients, but also within the lesion itself. Additionally, the presence of VEGF receptors in ERM-forming cells was demonstrated. This suggests that VEGF acts as a growth factor for ERM-forming cells (34, 35).
Placenta growth factor (PlGF)	PlGF is a homologue of VEGF that shares receptors with it, but displays significantly lower mitogenic properties on endothelial cells. PlGF has been demonstrated to act synergistically with VEGF and its low expression significantly stimulates the action of VEGF (36).
Tumor necrosis factor-alpha (TNF-a)	TNF-α is a family of pro-inflammatory cytokines with pleiotropic effects. They participate in the pathogenesis of many diseases such as cancer and autoimmune diseases (37). In the case of the eyeball, TNF-a participates in the neovascularization of the retina after hypoxia (38).
Platelet-derived growth factor (PDGF)	PDGF is a cytokine that plays major role in wound healing. Its expression has been confirmed in the cases of many types of cells, such as endothelial cells, macrophages and fibroblasts (39). High expression of this factor has been demonstrated in the case of all retinal proliferative diseases (40). The expression of this factor in the eyeball is probably stimulated by retinal hypoxia. Apart from the proangiogenic effect of PDGF, this cytokine is also a mitogenic and chemotactic factor for RPE and glial cells (41).
Transforming growth factors-b (TGF-b)	TGF-b is a family of cytokines that exhibit pleiotropic effects on tissues. These cytokines are involved in the control of the proliferation and migration of endothelial cells (34, 42). Within the ERM, this cytokine is responsible for the differentiation of cells into fibroblast-like cells – responsible mainly for the production of ERM-building proteins (43).
Angiopoietins	It is a group of proangiogenic cytokines that are of greatest importance in embryonic angiogenesis. It is of great importance in the maturation and stabilization of blood vessels (44, 45).
Interleukin-6 (IL-6)	It is a pleiotropic cytokine that plays an important role in the activation of lymphocytes (46). Increased expression of this cytokine has been observed in the course of retinal injuries and in the case of diabetic patients (47, 48).
Vascular cell adhesion molecules	Intracellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), E-selectin, and P-selectin play an important role in the circulation of leukocytes in areas of inflammation. TNF-α (and other cytokines) increase their expression, which in turn increases the migration of leukocytes to the surrounding tissues (49, 50).
Tenascin-C	Tenascin-C is an extracellular glycoprotein that modulates cell growth and adhesion. Its participation is essential in the process of blood vessel sprouting (51, 52).
Basic fibroblast growth factor (bFGF)	bFGF is a growth factor and a signaling protein involved in cell growth, morphogenesis and tissue regeneration. It plays an important role in the survival of cells subjected to stress (53). Expression of bFGF and its receptors has been demonstrated within the retina, where they probably influence the course of retinal ischemia (54–56).
Hepatocyte growth factor (HGF)	HGF is a kinase that plays an important role in regulating cell growth and morphogenesis. It has been shown to be pro-angiogenic (57).
Glial cell line-derived neurotrophic factor (GDNF)	GDNF is a cytokine that promotes the survival of many types of nerve cells. It is usually secreted by astrocytes, oligodendrocytes, Schwann cells and motor neurons (58). It has a chemotactic effect on glial cells (59).

least common in Asia. This phenomenon is probably related to lifestyle and diet. Other factors contributing to the development of ERM are obesity, type II diabetes, hypertension and hypercholesterolaemia (60, 61).

5. Symptoms and diagnosis

The symptoms reported by patients depend on the stage (phase of development) and type of ERM. In some cases, the presence of ERM does not produce clinical symptoms and is diagnosed accidentally. Patients usually complain of: visual disturbances – metamorphopsia, micropsia or macropsia, photopsia, decreased visual acuity, diplopia, and a loss of central vision. The diagnosis of ERM is based on a clinical examination and Optical Coherence Tomography (OCT). In the case of fundoscopy, a cellophane reflex or wrinkling on the retinal surface resulting from the contracture of the membrane can be observed. It usually affects the foveal and parafoveal area. Cystoid macular oedema (CMO), lamellar or full-thickness macular holes (MHs) and/or small retinal hemorrhages can be seen in association with ERM. The diagnosis of idiopathic ERM is based on the exclusion of other ophthalmic diseases like retinal vascular diseases including diabetic retinopathy, retinal vein occlusion, uveitis and other inflammatory diseases, trauma, intraocular tumors, and retinal tear or detachment (62).

There are several ERM classification systems based on OCT findings. No classification, however, is currently suggested for general use in clinical practice (63) (Figure 4).

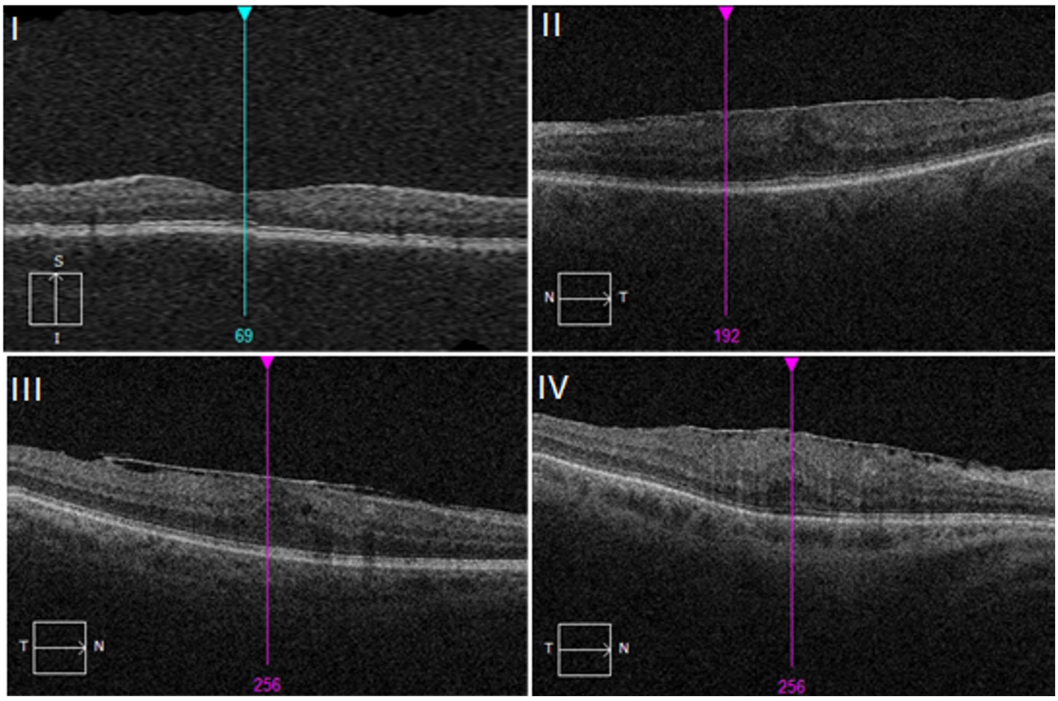

FIGURE 4
Stages of ERM showed on optical coherence tomography (OCT) images. I – ERMs are mild and thin. Foveal depression is present. II – ERMs with a widening of the outer nuclear layer and loss of the foveal depression. III – ERMs with continuous ectopic inner foveal layers crossing the entire foveal area. IV – ERMs are thick with continuous ectopic inner foveal layers and disrupted retinal layers. Based on clasification by Govetto et al. (64).

TABLE 4 Optical coherence tomography staging scheme proposed by Govetto et al. (64).

Stage	Description
I	Thin layer of ERM on the retinal surface; foveal depression is present; the layered structure of the retina is preserved
II	Presence of ERM accompanied by the loss of the foveal depression; widening of the retinal outer nuclear layer, the layered structure of the retina is preserved
III	ERMs with continuous (ectopic inner foveal layers) hyporeflective or hyperreflective band, extending from the inner nuclear layer (INL) and inner plexiform layer (IPL) crossing the entire foveal area; foveal depression is absent; the layered structure of the retina is preserved
IV	Thick ERM with continuous ectopic inner foveal layers; foveal depression is absent; distortion of the retinal layers

From the additional diagnostic tools, one worth mentioning is fluorescein angiography (FA), which is useful in the case of secondary ERM when it comes to identifying preoperatively the underlying cause of like intraocular tumors or retinal vascular diseases. Macular edema can also be confirmed with angiography (62). The OCT examination allows not only to deepen the diagnosis, but also to distinguish different stages of the ERM development (64) (Table 4 and Figure 5).

6. ERM treatment

The management options for ERM are limited and consist of observation or surgical intervention. Official guidelines for performing the surgical ERM removal have not been established. Before taking appropriate intervention measures, it is advisable to discuss with the patient all the possible benefits and complications related to the surgery in relation to the severity of the patient's symptoms and their lifestyle (65).

During the surgical intervention called pars plana vitrectomy (PPV), the epiretinal membrane is removed and the retinal tractions are released. ILM is considered to be the scaffold for myofibroblast proliferation, thus it is commonly removed alongside with ERM, in order to minimize the risk of ERM recurrence. Sometimes PPV is combined with a simultaneous cataract surgery involving intraocular lens implantation (phacovitrectomy). During the surgery, special dyes, like triamcinolone acetonide, trypan blue, indocyanine green (ICG), and brilliant blue, are used to distinguish ERM from the retinal layers (66).

It is possible to discern two types of PPV – complete vitrectomy, which involves the whole vitreous body being detached from the retina and removed, and limited vitrectomy, which involves removing only the central part of the vitreous body. Most of the times, the complete vitrectomy is performed, however, there is no difference when it comes to the results of it and the limited vitrectomy. Limited vitrectomy is usually faster and potentially produces fewer long-term side effects (67).

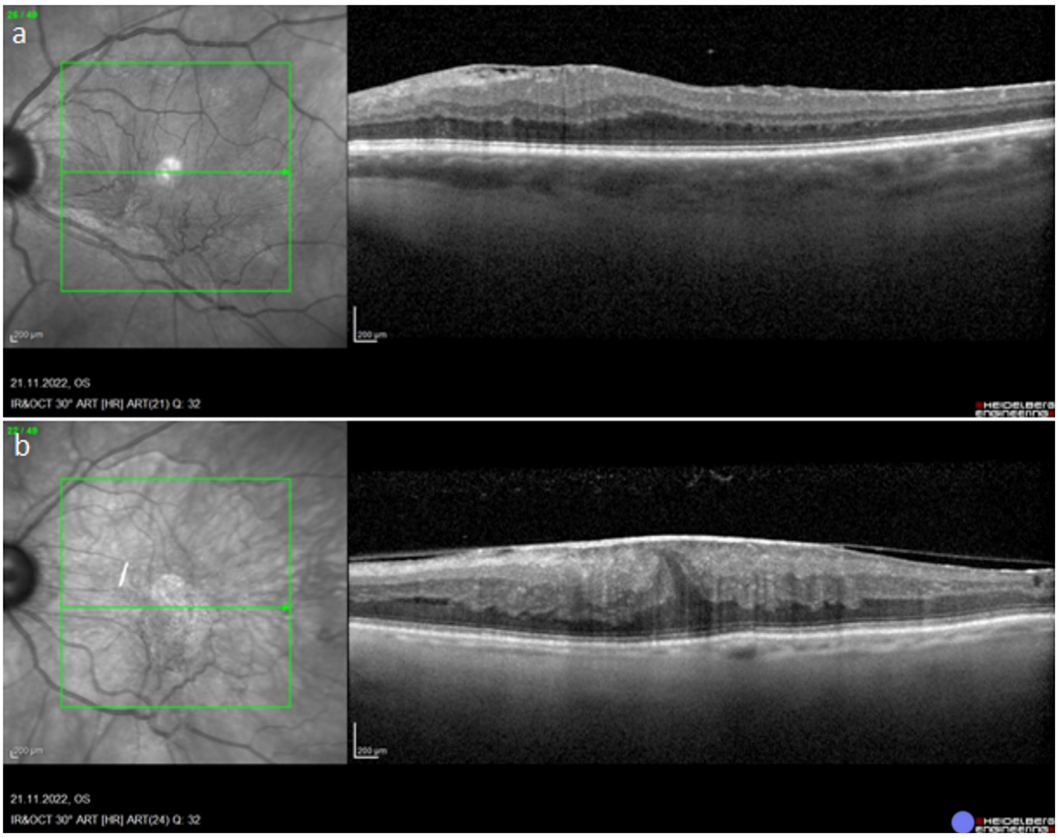

FIGURE 5
OCT images showing stage 3 and stage 4 of ERM. a – stage 3, b – stage 4.

The surgical treatment of ERM provides excellent postoperative visual outcomes and is a relatively safe procedure. Improvement in the vascularity of the choroid was also observed (68). Like any other surgical intervention, ERM surgery can cause complications, such as endophtalmitis, retinal detachment or ERM recurrence (69).

7. Conclusion

It is estimated that the main risk factor that significantly preceding the development of ERM, i.e., PDV, occurs in about 2% of the population. The main epidemiological factor associated with PDV is old age (60, 61, 70). An increased incidence of ERM is therefore to be expected due to the aging of the population. By understanding the successive processes leading to the formation of ERM, we better understand the causes of not only this pathology but also PDV. Currently, it is not possible to predict the development of this pathology based on biochemical tests, while the development of knowledge about the histological structure of ERM and the expression of cytokines and molecules related to ERM pathophysiology may in the future allow for the detection of a biochemical marker allowing for early detection of ERM development without the need for costly OCT, development guidelines for qualifying patients for surgical treatment and a potential conservative treatment regimen. Currently, there is also no prophylaxis for idiopathic ERM development, but by understanding the inflammatory factors involved in this process, it will be possible to develop some. In the case of secondary ERM, in addition to reducing the risk by appropriate treatment of the cause, it is possible, thanks to potential biochemical markers, to include some of these patients in regular observation due to high risk of ERM development.

Author contributions

MO and MN-W: conceptualization and writing—original draft preparation. WR: writing—review and editing, and supervision. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Kwok AK, Lai TY, Yuen KS. Epiretinal membrane surgery with or without internal limiting membrane peeling. *Clin Exp Ophthalmol* (2005) 33:379–85. doi: 10.1111/j.1442-9071.2005.01015.x

2. Oberstein SY, Byun J, Herrera D, Chapin EA, Fisher SK, Lewis GP. Cell proliferation in human epiretinal membranes: characterization of cell types and correlation with disease condition and duration. *Mol Vis* (2011) 17:1794–805.

3. Rękas M., Rejdak M. (2020). *Choroby ciała szklistego i powierzchni szklistkowo-siatkówkowej.Siatkówka i ciało szkliste.BCSC12.Seria Basic and clinical science course*. Edra Urban & Partner, Wrocław, Poland *2020*. pp. 371–374

4. Donati S, Caprani SM, Airaghi G, Vinciguerra R, Bartalena L, Testa F, et al. Vitreous substitutes: the present and the future. *Biomed Res Int* (2014) 2014:351804. doi: 10.1155/2014/351804

5. Boneva SK, Wolf J, Wieghofer P, Sebag J, Lange AKC. Hyalocyte functions and immunology. *Expert Rev Ophthalmol* (2022) 17:249–62. doi: 10.1080/17469899.2022.2100763

6. Ankamah E, Sebag J, Ng E, Nolan JM. Vitreous antioxidants, degeneration, and vitreo-retinopathy: exploring the links. *Antioxidants (Basel)* (2019, 2019) 9, 9:7. doi: 10.3390/antiox9010007

7. Los LI, van der Worp RJ, van Luyn MJA, Hooymans JMM. Age-related liquefaction of the human vitreous body: LM and TEM evaluation of the role of proteoglycans and collagen. *Invest Opthalmol Vis Sci* (2003) 44:2828–33. doi: 10.1167/iovs.02-0588

8. Tram NK, Swindle-Reilly KE. Rheological properties and age-related changes of the human vitreous humor. *Front Bioeng Biotechnol* (2018) 6:199. doi: 10.3389/fbioe.2018.00199

9. Ramovecchi P, Salati C, Zeppieri M. Spontaneous posterior vitreous detachment: a glance at the current literature. *World J Exp Med* (2021) 11:30–6. doi: 10.5493/wjem.v11.i3.30

10. Moon SY, Park SP, Kim Y-K. Evaluation of posterior vitreous detachment using ultrasonography and optical coherence tomography. *Acta Ophthalmol* (2020) 98:e29–35. doi: 10.1111/aos.14189

11. Frisina R, De Salvo G, Tozzi L, Gius I, Sahyoun JY, Parolini B, et al. Effects of physiological fluctuations on the estimation of vascular flow in eyes with idiopathic macular pucker. *Eye (Lond)* (2022) 37:1470–8. doi: 10.1038/s41433-022-02158-4

12. Tsotridou E, Loukovitis E, Zapsalis K, Pentara I, Asteriadis S, Tranos P, et al. A review of last decade developments on epiretinal membrane pathogenesis. *Med Hypothesis Discov Innov Ophthalmol* (2020) 9:91–110.

13. Bianchi L, Altera A, Barone V, Bonente D, Bacci T, De Benedetto E, et al. Untangling the extracellular matrix of idiopathic epiretinal membrane: a path winding among structure, interactomics and translational medicine. *Cells* (2022) 11:2531. doi: 10.3390/cells11162531

14. Myojin S, Yoshimura T, Yoshida S, Takeda A, Murakami Y, Kawano Y, et al. Gene expression analysis of the irrigation solution samples collected during vitrectomy for idiopathic epiretinal membrane. *PLoS One* (2016) 11:e0164355. doi: 10.1371/journal.pone.0164355

15. Sheybani A, Harocopos GJ, Rao PK. Immunohistochemical study of epiretinal membranes in patients with uveitis. *J Ophthalmic Inflamm Infect* (2012) 2:243–8. doi: 10.1007/s12348-012-0074-x

16. Ueki M, Morishita S, Kohmoto R, Fukumoto M, Suzuki H, Sato T, et al. Comparison of histopathological findings between idiopathic and secondary epiretinal membranes. *Int Ophthalmol* (2016) 36:713–8. doi: 10.1007/s10792-016-0194-7

17. Yamashita T, Uemura A, Sakamoto T. Intraoperative characteristics of the posterior vitreous cortex in patients with epiretinal membrane. *Graefes Arch Clin Exp Ophthalmol* (2008) 246:333–7. doi: 10.1007/s00417-007-0745-8

18. Hamoudi H. Epiretinal membrane surgery: an analysis of sequential or combined surgery on refraction, macular anatomy and corneal endothelium. *Acta Ophthalmol* (2018) 96:1–24. doi: 10.1111/aos.13690

19. Foos RY. Vitreoretinal juncture; epiretinal membranes and vitreous. *Invest Ophthalmol Vis Sci* (1977) 16:416–22.

20. Wiznia RA. Posterior vitreous detachment and idiopathic preretinal macular gliosis. *Am J Ophthalmol* (1986) 102:196–8. doi: 10.1016/0002-9394(86)90144-3

21. Lee GW, Lee SE, Han SH, Kim SJ, Kang SW. Characteristics of secondary epiretinal membrane due to peripheral break. *Sci Rep* (2020) 10:20881. doi: 10.1038/s41598-020-78093-9

22. da Silva RA, Roda VM, Matsuda M, Siqueira PV, Lustoza-Costa GJ, Wu DC. Cellular components of the idiopathic epiretinal membrane. *Graefes Arch Clin Exp Ophthalmol* (2022) 260:1435–44. doi: 10.1007/s00417-021-05492-7

23. Shibuya M. (2011). Vascular endothelial growth factor (VEGF) and its receptor (VEGFR) signaling in angiogenesis: a crucial target for anti-and pro-Angiogenic therapies. *Genes Cancer* 2:1097–1105. doi: 10.1177/1947601911423031

24. Vishwakarma S, Gupta RK, Jakati S, Tyagi M, Pappuru RR, Reddig K, et al. Molecular assessment of Epiretinal membrane: activated microglia, oxidative stress and inflammation. *Antioxidants (Basel)* (2020) 9:654. doi: 10.3390/antiox9080654

25. Bringmann A, Wiedemann P. Involvement of Müller glial cells in epiretinal membrane formation. *Graefes Arch Clin Exp Ophthalmol* (2009) 247:865–83. doi: 10.1007/s00417-009-1082-x

26. Colakoglu A, Balci AS. Potential role of Müller cells in the pathogenesis of macropsia associated with epiretinal membrane: a hypothesis revisited. *Int J Ophthalmol* (2017) 10:1759–67. doi: 10.18240/ijo.2017.11.19

27. Schumann RG, Gandorfer A, Ziada J, Scheler R, Schaumberger MM, Wolf A, et al. Hyalocytes in idiopathic epiretinal membranes: a correlative light and electron microscopic study. *Graefes Arch Clin Exp Ophthalmol* (2014) 252:1887–94. doi: 10.1007/s00417-014-2841-x

28. Kohno RI, Hata Y, Kawahara S, Kita T, Arita R, Mochizuki Y, et al. Possible contribution of hyalocytes to idiopathic epiretinal membrane formation and its contraction. *Br J Ophthalmol* (2009) 93:1020–6. doi: 10.1136/bjo.2008.155069

29. Tang S, Gao R, Wu DZ. Macrophages in human epiretinal and vitreal membranes in patients with proliferative intraocular disorders. *Yan Ke Xue Bao* (1996) 12:28–32.

30. Baek J, Park HY, Lee JH, Choi M, Lee JH, Ha M, et al. Elevated M2 macrophage markers in epiretinal membranes with ectopic inner foveal layers. *Invest Ophthalmol Vis Sci* (2020) 61:19. doi: 10.1167/iovs.61.2.19

31. Joshi M, Agrawal S, Christoforidis JB. Inflammatory mechanisms of idiopathic epiretinal membrane formation. *Mediat Inflamm* (2013) 2013:192582. doi: 10.1155/2013/192582

32. Bianchi E, Ripandelli G, Feher J, Plateroti AM, Plateroti R, Kovacs I, et al. Occlusion of retinal capillaries caused by glial cell proliferation in chronic ocular inflammation. *Folia Morphol (Warsz)* (2015) 74:33–41. doi: 10.5603/FM.2015.0006

33. Giachos I, Chalkiadaki E, Andreanos K, Symeonidis C, Charonis A, Georgalas I, et al. Epiretinal membrane-induced intraretinal neovascularization. *Am J Ophthalmol Case Rep* (2021) 23:101180. doi: 10.1016/j.ajoc.2021.101180

34. Stafiej J, Kaźmierczak K, Linkowska K, Żuchowski P, Grzybowski T, Malukiewicz G. Evaluation of TGF-Beta 2 and VEGF*α* gene expression levels in Epiretinal membranes and internal limiting membranes in the course of retinal detachments, proliferative diabetic retinopathy, macular holes, and idiopathic Epiretinal membranes. *J Ophthalmol* (2018) 2018:8293452. doi: 10.1155/2018/8293452

35. Rezzola S, Guerra J, Krishna Chandran AM, Loda A, Cancarini A, Sacristani P, et al. VEGF-independent activation of Müller cells by the vitreous from proliferative diabetic retinopathy patients. *Int J Mol Sci* (2021) 22:2179. doi: 10.3390/ijms22042179

36. Lennikov A, Mukwaya A, Fan L, Saddala MS, De Falco S, Huang H. Synergistic interactions of PlGF and VEGF contribute to blood-retinal barrier breakdown through canonical NFκB activation. *Exp Cell Res* (2020) 397:112347. doi: 10.1016/j.yexcr.2020.112347

37. Jang DI, Lee A-H, Shin H-Y, Song H-R, Park J-H, Kang T-B, et al. The role of tumor necrosis factor alpha (TNF-α) in autoimmune disease and current TNF-α inhibitors in therapeutics. *Int J Mol Sci* (2021) 22:2719. doi: 10.3390/ijms22052719

38. Mirshahi A, Hoehn R, Lorenz K, Kramann C, Baatz H. Anti-tumor necrosis factor alpha for retinal diseases: current knowledge and future concepts. *J Ophthalmic Vis Res* (2012) 7:39–44.

39. Andrae J, Gallini R, Betsholtz C. Role of platelet-derived growth factors in physiology and medicine. *Genes Dev* (2008) 22:1276–312. doi: 10.1101/gad.1653708

40. Edqvist PHD, Niklasson M, Vidal-Sanz M, Hallböök F, Forsberg-Nilsson K. Platelet-derived growth factor over-expression in retinal progenitors results in abnormal retinal vessel formation. *PLoS One* (2012) 7:e42488. doi: 10.1371/journal.pone.0042488

41. Vinores SA, Henderer JD, Mahlow J, Chiu C, Derevjanik NL, Larochelle W, et al. Isoforms of platelet-derived growth factor and its receptors in epiretinal membranes: immunolocalization to retinal pigmented epithelial cells. *Exp Eye Res* (1995) 60:607–19. doi: 10.1016/s0014-4835(05)80003-x

42. Hachana S, Larrivée B. TGF-β superfamily signaling in the eye: implications for ocular pathologies. *Cells* (2022) 11:2336. doi: 10.3390/cells11152336

43. Kanda A, Noda K, Hirose I, Ishida S. TGF-β-SNAIL axis induces Müller glial-mesenchymal transition in the pathogenesis of idiopathic epiretinal membrane. *Sci Rep* (2019) 9:673. doi: 10.1038/s41598-018-36917-9

44. Pafumi I, Favia A, Gambara G, Papacci F, Ziparo E, Palombi F, et al. Regulation of Angiogenic functions by angiopoietins through calcium-dependent signaling pathways. *Biomed Res Int* (2015) 2015:965271:1–14. doi: 10.1155/2015/965271

45. Joussen AM, Ricci F, Paris LP, Korn C, Quezada-Ruiz C, Zarbin M. Angiopoietin/Tie2 signalling and its role in retinal and choroidal vascular diseases: a review of preclinical data. *Eye* (2021) 35:1305–16. doi: 10.1038/s41433-020-01377-x

46. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. *Cold Spring Harb Perspect Biol* (2014) 6:a016295. doi: 10.1101/cshperspect.a016295

47. Ghasemi H. Roles of IL-6 in ocular inflammation: a review. *Ocul Immunol Inflamm* (2018) 26:37–50. doi: 10.1080/09273948.2016.1277247

48. Limb GA, Kapur S, Woon H, Franks WA, Jones SE, Chignell AH. Expression of mRNA for interleukin 6 by cells infiltrating epiretinal membranes in proliferative vitreoretinopathy. *Agents Actions* (1993) 38:C73–6. doi: 10.1007/BF01991142

49. Harjunpää H, Llort AM, Guenther C, Fagerholm SC. Cell adhesion molecules and their roles and regulation in the immune and tumor microenvironment. *Front Immunol* (2019) 10:1078. doi: 10.3389/fimmu.2019.01078

50. Tang S, Le-Ruppert KC, Gabel VP. Expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) on proliferating vascular endothelial cells in diabetic epiretinal membranes. *Br J Ophthalmol* (1994) 78:370–6. doi: 10.1136/bjo.78.5.370

51. Chiquet M. Tenascin-C: from discovery to structure-function relationships. *Front Immunol* (2020) 11:611789. doi: 10.3389/fimmu.2020.611789

52. Kobayashi Y, Yoshida S, Zhou Y, Nakama T, Ishikawa K, Arita R, et al. The role of tenascin-C in fibrovascular membrane formation in diabetic retinopathy. *Invest Ophthalmol Vis Sci* (2015) 56:224.

53. Yun YR, Won JE, Jeon E, Lee S, Kang W, Jo H, et al. Fibroblast growth factors: biology, function, and application for tissue regeneration. *J Tissue Eng* (2010) 2010:218142. doi: 10.4061/2010/218142

54. Cassidy L, Barry P, Shaw C, Duffy J, Kennedy S. Platelet derived growth factor and fibroblast growth factor basic levels in the vitreous of patients with vitreoretinal disorders. *Br J Ophthalmol* (1998) 82:181–5. doi: 10.1136/bjo.82.2.181

55. Frank RN, Amin RH, Eliott D, Puklin JE, Abrams GW. Basic fibroblast growth factor and vascular endothelial growth factor are present in epiretinal and choroidal neovascular membranes. *Am J Ophthalmol* (1996) 122:393–403. doi: 10.1016/s0002-9394(14)72066-5

56. Hueber A, Wiedemann P, Esser P, Heimann K. Basic fibroblast growth factor mRNA, bFGF peptide and FGF receptor in epiretinal membranes of intraocular proliferative disorders (PVR and PDR). *Int Ophthalmol* (1996) 20:345–50. doi: 10.1007/BF00176889

57. Ding X, Zhang R, Zhang S, Zhuang H, Xu G. Differential expression of connective tissue growth factor and hepatocyte growth factor in the vitreous of patients with high myopia versus vitreomacular interface disease. *BMC Ophthalmol* (2019) 19:25. doi: 10.1186/s12886-019-1041-1

58. Shpak AA, Guekht AB, Druzhkova TA, Troshina AA, Gulyaeva N. Glial cell line-derived neurotrophic factor in patients with age-related cataract. *Invest Ophthalmol Vis Sci* (2021) 62:718.

59. Nishikiori N, Tashimo A, Mitamura Y, Ohtsuka K. Glial cell line–derived neurotrophic factor in the vitreous of patients with proliferative diabetic retinopathy. *Invest Ophthalmol Vis Sci* (2005) 46:3103.

60. Xiao W, Chen X, Yan W, Zhu Z, He M. Prevalence and risk factors of epiretinal membranes: a systematic review and meta-analysis of population-based studies. *BMJ Open* (2017) 7:e014644. doi: 10.1136/bmjopen-2016-014644

61. Ng CH, Cheung N, Wang JJ, Islam AF, Kawasaki R, Meuer SM, et al. Prevalence and risk factors for epiretinal membranes in a multi-ethnic United States population. *Ophthalmology* (2010) 118:694–9. doi: 10.1016/j.ophtha.2010.08.009

62. Fung AT, Galvin J, Tran T. Epiretinal membrane: a review. *Clin Exp Ophthalmol* (2021) 49:289–308. doi: 10.1111/ceo.13914

63. Stevenson W, Prospero Ponce CM, Agarwal DR, Gelman R, Christoforidis JB. Epiretinal membrane: optical coherence tomography-based diagnosis and classification. *Clin Ophthalmol* (2016) 10:527–34. doi: 10.2147/OPTH.S97722

64. Govetto A, Lalane RA 3rd, Sarraf D, Figueroa MS, Hubschman JP. Insights into Epiretinal membranes: presence of ectopic inner foveal layers and a new optical coherence tomography staging scheme. *Am J Ophthalmol* (2017) 175:99–113. doi: 10.1016/j.ajo.2016.12.006

65. Folk JC, Adelman RA, Flaxel CJ, Hyman L, Pulido JS, Olsen TW. Idiopathic epiretinal membrane and vitreomacular traction preferred practice pattern(®) guidelines. *Ophthalmology* (2016) 123:P152–81. doi: 10.1016/j.ophtha.2015.10.048

66. Matoba R, Morizane Y. Surgical treatment of epiretinal membrane. *Acta Med Okayama* (2021) 75:403–13. doi: 10.18926/AMO/62378

67. Forlini M, Date P, D'Eliseo D, Rossini P, Bratu A, Volinia A, et al. Limited vitrectomy versus complete vitrectomy for epiretinal membranes: a comparative multicenter trial. *J Ophthalmol* (2020) 2020:1. doi: 10.1155/2020/6871207

68. Meduri A, Oliverio GW, Trombetta L, Giordano M, Inferrera L, Trombetta CJ. Optical coherence tomography predictors of favorable functional response in Naïve diabetic macular edema eyes treated with dexamethasone implants as a first-line agent. *J Ophthalmol* (2021) 2021:1. doi: 10.1155/2021/6639418

69. Dawson SR, Shunmugam M, Williamson TH. Visual acuity outcomes following surgery for idiopathic epiretinal membrane: an analysis of data from 2001 to 2011. *Eye (Lond)* (2014) 28:219–24. doi: 10.1038/eye.2013.253

70. Shen Z, Duan X, Wang F, Wang N, Peng Y, Liu DTL, et al. Prevalence and risk factors of posterior vitreous detachment in a Chinese adult population: the Handan eye study. *BMC Ophthalmol* (2013) 13:33. doi: 10.1186/1471-2415-13-33

frontiers | Frontiers in Medicine

TYPE Review
PUBLISHED 08 January 2024
DOI 10.3389/fmed.2023.1280776

OPEN ACCESS

EDITED BY
Georgios D. Panos,
Nottingham University Hospitals NHS Trust, United Kingdom

REVIEWED BY
Kunbei Lai,
Sun Yat-sen University, China
Kenji Matsushita,
Osaka University, Japan

*CORRESPONDENCE
Hong Wu
✉ wu_hong@jlu.edu.cn

RECEIVED 21 August 2023
ACCEPTED 12 December 2023
PUBLISHED 08 January 2024

CITATION
Qu S, Zou Y, Yang L and Wu H (2024) The progress of assessment methods and treatments of neovascular glaucoma secondary to central retinal vein occlusion. *Front. Med.* 10:1280776. doi: 10.3389/fmed.2023.1280776

The progress of assessment methods and treatments of neovascular glaucoma secondary to central retinal vein occlusion

Sheng Qu, Ying Zou, Li Yang and Hong Wu*

Department of Ophthalmology, The Second Hospital of Jilin University, Changchun, China

Neovascular glaucoma is a condition that results from central retinal vein occlusion and often leads to blindness. Accurate evaluation and appropriate treatment are crucial for patients. However, there is currently no uniform and clear standard to differentiate between ischemic and non-ischemic central retinal vein occlusion. Also, the assessment of neovascular glaucoma progression is uncertain. Meanwhile, although pan-retinal photocoagulation is a standard treatment to prevent the onset of neovascular glaucoma, its actual efficacy and the timing of intervention remain highly controversial. It is still challenging to balance the risks of side effects in the visual field against the uncertain effectiveness of the treatment. This paper delves into the pathogenesis of neovascular glaucoma to understand the development of therapeutic approaches. By taking into account various assessment criteria of central retinal vein occlusion and neovascular glaucoma over the years, combining functional tests and morphological tests provides the most accurate and rigorous solution. The age of patients, the extent, location, and duration of retinal ischemia are the primary factors that affect the severity and extent of ischemic central retinal vein occlusion and induce serious complications. From the perspective of prevention and treatment, the ischemic index is closely related to the development of neovascularization. The paper provides essential insights into the mechanism, efficacy, complications, and optimal timing of pan-retinal photocoagulation. Comparing the treatment effects of pan-retinal photocoagulation and intravitreal anti-VEGF injections, we suggest a combination of both treatments to explore effective treatment with fewer side effects in the long term. This article details the debate on the above issues and explores ideas for the clinical diagnosis and preventive treatment of neovascular glaucoma that results from ischemic central retinal vein occlusion.

KEYWORDS

neovascular glaucoma, central retinal vein occlusion, pan-retinal photocoagulation, anti-VEGF, neovascularization

1 Introduction

Neovascular glaucoma is the most severe consequence of central retinal vein occlusion (CRVO) that can lead to blindness (1). Therefore, early diagnosis and prompt treatment are essential for patients suffering from neovascular glaucoma (NVG). Further research on the pathogenesis of NVG can aid in the diagnosis and the treatment. Among the various factors contributing to the etiology and pathogenesis of NVG, vascular endothelial growth factor (VEGF) is a significant area of interest. It is responsible for elevated intraocular pressure (IOP), a major symptom of NVG (2).

It is vital to accurately assess patients with CRVO before treatment to reduce the risk of NVG. However, there is still controversy surrounding the criteria for differentiating between ischemic CRVO (iCRVO) and non-ischemic CRVO (3). A unified and effective evaluation standard is expected to be established in the future. During follow-up, it is important to pay attention to the risk factors for the transformation of ischemic to non-ischemic CRVO. Additionally, the severity of CRVO should be evaluated based on high-risk factors for NVG, such as visual acuity and non-perfused areas (4, 5).

The traditional treatment option to prevent ocular neovascularization, especially NVG, is prophylactic pan-retinal photocoagulation (6). However, more research is needed to explore the efficacy and timing of pan-retinal photocoagulation (PRP) (3). It is also important to note that PRP may cause visual field damage to patients with CRVO. The intravitreal anti-VEGF injection has been applied to inhibit neovascular development, but observations have shown that anti-VEGF only delays the development of NVG rather than preventing it (7, 8). Several clinical trials have investigated PRP in combination with anti-VEGF injections, with further research needed in this area (8, 9).

This paper aims to provide an overview of the pathogenesis and diagnosis of NVG. It also offers critical insights into the mechanism, timing, efficacy, and complications of PRP and discusses the treatment effects of PRP and intravitreal anti-VEGF injections. The essay provides ideas for developing clinical diagnosis and treatment of NVG secondary to iCRVO.

2 Etiology and pathogenesis of NVG

Tissue hypoxia and pathologic neovascularization of the anterior eye segment cause NVG, resulting in increased intraocular pressure and glaucomatous optic neuropathy (10, 11).

Over the last few decades, the role of VEGF has received extensive attention in RVO. VEGF is a secreted mitogen (12) that promotes angiogenesis and increases vessel permeability (13–16). A recent review (17) concluded that VEGF-VEGFR2 damages tight intercellular junctions by inhibiting occluding and destroys the blood-retinal barrier by activating MMP-9.

In 1995, research using an *in vitro* model showed that VEGF levels from the retina were closely related to the onset of angiogenesis (18). Subsequent studies have demonstrated that when the iris is exposed to VEGF for a sufficient amount of time, non-inflammatory iris neovascularization can occur, potentially leading to NVG in non-human primate eyes (19). Additionally, studies have shown that VEGF-specific antagonists can significantly suppress iris neovascularization in mice and non-human primates with retinal ischemia (20, 21). Pe'er et al. (22) used a VEGF-specific probe to investigate elevated VEGF production in thin whole-eye sections of patients with CRVO, revealing that VEGF is upregulated in response to retinal hypoxia in eyes with CRVO. Furthermore, a study has demonstrated that there is significantly more aqueous VEGF in ischemic CRVO than in non-ischemic CRVO (23), indicating the need for early anti-VEGF therapy in iCRVO patients.

The loss of a significant angiogenesis inhibitor such as pigment epithelium-derived factor (PEDF) can also lead to angiogenesis (24, 25).

As described, we can conclude that the common hypothesis is that a hypoxic environment in ischemia CRVO disrupts the balance between angiogenic stimulating factors (like VEGF) and angiogenic inhibitors (like PEDF) that are closely controlled to maintain homeostasis (25, 26). This disruption can explain the formation of new vessels and fibrous tissue in the root and stroma of the iris (27), leading to the formation of peripheral anterior synechia and secondary angle closure (28). The result is highly elevated intraocular pressure, which can cause glaucomatous optic neuropathy and ultimately lead to NVG (10, 27).

3 Risk factors of NVG secondary to RVO

3.1 RVO classification

3.1.1 CRVO and BRVO

Retinal vein occlusion (RVO) is classified by the location of the obstruction, primarily involving either the branch retinal vein obstruction (BRVO) or the central retinal vein obstruction (29, 30). Our paper focuses solely on discussing NVG that occurs as a result of CRVO. This is because, BRVO disease rarely results in NVG, unlike CRVO. A prospective observation of 264 eyes with major and macular BRVO over 3–20 years revealed that ocular NV occurred in 28.8% of the major BRVO cases, while none of the macular BRVO cases showed any evidence of ocular NV (31). Firstly, retinal ischemia-perfusion caused by BRVO is not sufficient to cause NV. The severity and extent of retinal ischemia are major factors in ocular NV development in patients with RVO (5, 31). RVO necessitates an ischemic perfused area of over 50% to derive NV (1). BRVO results from venous obstruction of any branch of the central retinal vein; major BRVO is defined as retinal vein obstruction in one quadrant, whereas macular BRVO is defined

Abbreviations: ANV, angle neovascularization; AS-OCTA, en-face anterior-segment optical coherence tomography angiography; CRVO, central retinal vein occlusion; CRT, central retinal thickness; CVOS, Central Vein Occlusion Study Group; ERG, electroretinography; FA, fluorescein angiography; iCRVO, ischemia CRVO; INV, iris neovascularization; IOP, intraocular pressure; IRS-1, receptor substrate-1; ISI, ischemic index; IVB, intravitreal bevacizumab injection; MMP-9, matrix metalloproteinase 9; NVG, neovascular glaucoma; OCTA, optical coherence tomography angiography; PEDF, pigment epithelium-derived factor; p-MLM, prominent middle limiting membrane sign; PRN, pro re nata; PRP, pan-retinal photocoagulation; RAPD, relative afferent pupillary defect; RPE, retinal pigmented epithelium; RVO, retinal vein occlusion; TGF, transforming growth factor; UWFFA, ultra-widefield fluorescein angiography; VA, visual acuity; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2.

as obstruction of small intra-macular veins (32). Thus, in patients with BRVO, NV occurs only in severe ischemic major BRVO with extensive capillary non-perfusion (33). Secondly, even if NV is present in branch retinal vein occlusion BRVO, the likelihood of NVG is extremely low. NV in BRVO mostly occurs in the retina and macula (31). But the mechanism of NVG is anterior chamber stenosis caused by NV of the anterior chamber or angle (11).

Further studies may be necessary to develop a consensus standard with both sufficient specificity and sensitivity to differentiate non-ischemic CRVO from ischemic CRVO.

3.1.2 Ischemic and non-Ischemic CRVO

Central retinal vein occlusion (CRVO) is differentiated into ischemic and non-ischemic CRVO by Hayreh (34). It is crucial to differentiate between the two types during the first clinical visit as it helps to improve the effectiveness of treatment and reduce unnecessary damage caused by treatment (3). A prospective clinical study (35) has shown that these two types of CRVO have different clinical features, results, complications, and prognoses, which require different treatments. Previous studies have indicated that the incidence of iris neovascularization (INV), angle neovascularization (ANV), and secondary NVG is significantly higher in the ischemic type than in the non-ischemic type, based on the natural history of the two types of CRVO (4, 31, 36). However, there is still a debate around the criteria for evaluating the methodology and these indicators for assessment.

3.1.2.1 Morphologic tests

As technology has evolved, morphological testing has undergone constant innovation.

In earlier years, fundus fluorescein angiography (FA) was often used as the sole criterion to differentiate between the two types of CRVO to visualize retinal capillary occlusion. In 1993, CVOS (37) identified that the presence of at least 10-disk areas of non-perfusion is a significant risk factor for the development of ischemic or non-ischemic CRVO. Further research conducted in 1997 revealed that visual acuity worse than 20/200, 30 or more-disk areas of obliteration, and moderate to severe venous tortuosity are also crucial factors in predicting the occurrence of CRVO (5). However, data suggests that eyes with less than 30-disk diameters of non-perfusion from fluorescein fundus angiography have a low risk of developing CRVO, provided there are no other risk factors (38). In contrast, eyes with 75 or more-disk diameters of retina capillary occlusion have the highest chance of developing CRVO (38). Therefore, Hayreh (39) argues that the previous standard relying solely on the 10-disk diameters of non-perfusion is not sufficient to accurately distinguish between ischemic and non-ischemic CRVO, which can lead to an imprecise diagnosis, prognosis, and management.

Optical coherence tomography angiography (OCTA) is a fast and trustworthy investigational modality for patients with RVO, which can appraise the deep retina capillary non-perfusion area and morphology of the foveal avascular zone (40–42). OCTA can qualitatively illustrate most of the clinically relevant findings in retinal venous occlusion (40–42).

Central retinal vein occlusion (CRVO) cases with a hyperreflective line located in the outer plexiform layer, called prominent middle limiting membrane sign (p-MLM), had worse final visual outcomes and were more likely to be diagnosed with ischemia CRVO (43).

Even so, within the various limitations of the early stages of CRVO, morphological examinations do not always provide comprehensive and reliable evidence (39).

3.1.2.2 Comprehensive assessment

Hayreh (44) conducted a five-year prospective investigation to establish a standard for distinguishing between ischemic and non-ischemic types. **Table 1** shows four functional tests and two morphologic tests required for this purpose (44). The functional tests included visual acuity (VA), visual fields, relative afferent pupillary defect (RAPD), and electroretinography (ERG). The morphologic tests included ophthalmoscopy and FA (44). According to Hayreh (44), by combining all these tests in the early acute stage of almost all cases, we can effectively differentiate ischemic from non-ischemic types.

Nonetheless, different researchers have different emphases on classification criteria. Hayreh's (44) research consistently reported that the combination of RAPD and ERG examination results can increase diagnostic sensitivity and identify 97% of cases. Joussen (45) emphasized the discovery of iris neovascularization or angle neovascularization to diagnose the disease and considered fluorescein angiography the most practical method to detect the degree of ischemia. The Central Vein Occlusion Study Group (CVOS) preferred to rely on the statistical significance of visual acuity rather than initial fluorescein angiography in diagnosis (5).

In conclusion, we still require a significant amount of clinical data to develop more accurate and current diagnostic criteria.

3.2 Risk factors for transition to iCRVO

It is worth noting that various studies have indicated that non-ischemic CRVO has the potential to progress into ischemic CRVO at some point (44, 35). Therefore, it would be valuable to conduct research identifying early warning signs of this transition from non-ischemic CRVO to ischemic CRVO.

Age development has been identified as an important factor in the transition of non-ischemic CRVO. Studies show that within 18 months from the first diagnosis of non-ischemic CRVO,

TABLE 1 Functional and morphologic tests for differentiation of CRVO (44).

Test		Parameters
Functional tests	RAPD	> 0.70 log unit
	ERG	b-wave amplitude < 60% of normal or reduced by ≥ 1 SD
	Visual acuity	6/120 or worse
	Visual fields	Central scotoma and peripheral defect or cannot see I2e target of Goldmann perimeter
Morphologic tests	Ophthalmoscopy	≥ Moderate hemorrhages in posterior retina
	Fluorescein fundus angiography	Retinal capillary obliteration

individuals aged 65 or older are more likely to convert to iCRVO than other control groups (30).

Meanwhile, the type of CRVO may change with disease progression. Studies have shown that 15% of eyes that were previously perfused turn ischemic within the first four follow-up months (5). A total of 34% of cases become ischemic after three years (5).

The development of ultra-widefield fluorescein angiography (UWFFA) has led to the establishment of the ischemic index (IsI) as a sensitive and specific tool for classifying CRVO types (46, 47). Several studies have demonstrated that a baseline IsI > 35% increases the likelihood of being diagnosed with ischemic CRVO after a systemic examination (46). Additionally, patients with IsI > 35% have a higher probability of converting to ischemic CRVO within one year of onset (46).

Recent research has indicated that the presence of primary open-angle glaucoma in CRVO also significantly indicates an increased risk of developing iCRVO and subsequent NVG, leading to a worse visual outcome (48).

3.3 Monitoring of NVG occurrence

After diagnosing iCRVO, it is important to determine the severity of the condition to assess the likelihood of developing NVG. The most significant indicators for this assessment are VA and non-perfusion (5). It is equally important to examine the anterior chamber for NV to prevent the development of NVG. Ultrasound, OCT, and FA can be used for prophylactic examination of NVG.

In 1994, Williamson and Baxter (49) analyzed the relevance between the development of INV and the blood velocities measured by non-invasive color Doppler imaging. This showed that color Doppler imaging could be a routine evaluation for patients examined less than 3 months from the first diagnosis of the occlusion (49).

A retrospective study highlighted that higher central retinal thickness (CRT) on OCT at follow-up is a risk factor for the development of NVG (8). Additionally, the en-face anterior-segment OCTA (AS-OCTA) has been published as a non-invasive method for detecting INV or iris vasculature distribution (50, 51). The data indicates that AS-OCTA quantitative examination corresponds to the results from slit-lamp microscopy and provides more detailed iris vasculature images than iris FA (52, 53).

The extent, location, and duration of retinal ischemia are crucial in determining the degree of perfusion (54). Several studies have reported that OCTA results significantly correlate with non-perfused areas on FA and provide more detailed information about anatomy and blood flow (42, 55, 56). Recently, some analysts have attempted to link the IsI to the degree of non-perfusion to predict the development of NV. A prospective study by Tsui et al. (57) indicated that the IsI calculated from ultra-widefield FA was linked to NV, and eyes with evidence of NV had an IsI over 45%. DeBoer et al. (58) analyzed data from 11 eyes and concluded that patients with low IsI values in the peripheral areas were less likely to develop NVG, with no significant increase in non-perfused areas. One study by Nicholson et al. (4) also reported that posterior pole non-perfused areas of more than 10 indicate a greater risk of neovascularization compared with peripheral non-perfused areas greater than 10. Wykoff et al. (59) pointed out that eyes with anterior NV showed a weaker correlation with the level of retinal non-perfusion than posterior segment NV. It would be helpful to have more information on the connection between IsI and neovascularization development to establish a greater degree of accuracy on whether IsI can be applied in the prediction of NVG.

Currently, there is still no reasonable standard that can be proven by clinical practice, which requires a lot of clinical trials to verify.

4 PRP in iCRVO

4.1 PRP effect in reducing INV/ANV

There is a limited number of historical studies on the effect of a single PRP in the development of INV/ANV. By analyzing several highly credible prospective studies conducted in the 1990s, we can see contrasting perspectives.

One survey by the CVOS group N found that patients did not see a significant benefit from PRP before the occurrence of INV/ANV (38). Instead, they found that laser treatment was effective in reducing anterior segment neovascularization when INV/ANV appeared during strict and timely follow-up (38).

A study conducted by Hayreh et al. (60), over a long period of time showed that PRP did not have any positive effect in preventing NVG as a result of iCRVO. On the contrary, it led to a certain degree of peripheral visual field degradation in many treated eyes (60). The study indicated that the incidence of INV was significantly lower in the laser group than in the non-laser group, but only when PRP was given within three months after the onset of iCRVO (60). However, their report showed no statistically significant difference in the incidence of NVG between the laser and non-laser groups (60). This result may be explained from three aspects. Firstly, according to the pathology of NVG, the obstruction of trabecular meshwork by fibrovascular tissue proliferating onto the anterior chamber angle plays an equally significant role (61), usually secondary to widespread posterior segment ischemia (62). Hence, both INV and ANV play a critical role in developing NVG in most cases (38). However, the studies by Hayreh et al. (60) denied the effect of early PRP on ANV, which may affect the positive impact of PRP on NVG. Secondly, the lower possibility of NVG in iCRVO may decrease the efficacy of PRP statistically. Finally, the study by Hayreh et al. (60) showed that PRP may have missed the best time for treatment after INV occurred due to the absence of close follow-up. When high IOP has formed, it is difficult for PRP to have an expected therapeutic effect on NVG (3, 60).

Some researchers also questioned the necessity of PRP in iCRVO, considering the development of anterior segment NV and the result of NVG. In 2012, Hayreh and Zimmerman (63) published a strict paper defining iCRVO by the criteria from their previous study. The data showed that within 6 months of the onset of ischemic CRVO, the incidence rate of iris NV was 49%, angular NV was 39%, and NVG was 29% (63). Despite different study designs and the vague standard of iCRVO, we can still conclude from most studies (31, 64–66) that no more than 49% of iCRVO cases will result in INV or/and ANV, and not all INV or/and ANV will lead to the emergence of NVG. The data suggests that about 55% of patients with ischemic CRVO may never develop an NVG outcome (1).

4.2 Side effects of PRP

Excessive PRP spot density may lead to a reduction or defect in the peripheral field of view.

In 1990, Hayreh et al. (60) presented an analysis and discussion on how PRP produces apparent constriction and a noticeable peripheral visual field loss. This result led to a debate on whether PRP does more harm than good to most eyes with iCRVO. Oosterhuis and Sedney (67) and Laatikainen et al. (68) also found severe visual field constriction in the treated eyes in their investigations into PRP treatment in CRVO.

Visual fields will also decline in the natural history of CRVO. A study by Hayreh et al. (69) found that 55% of patients with ischemic CRVO have a 55% probability of developing scotoma within 3 months of onset, with most being central blind spots. Besides, 17% of patients with ischemic CRVO present with peripheral visual field defects at first diagnosis (69). Another study by Hayreh (70) reported that in patients with CRVO and moderate to severe visual field defects at the beginning, the occurrence of NVG deteriorated the visual field of 76% of the eyes (70). In contrast, 38% of the eyes without NVG had visual field deterioration.

As Hayreh et al. (60) mentioned, if patients with iCRVO who will not develop into NVG receive unnecessary PRP treatment, the loss of the peripheral visual field caused by PRP treatment will worsen the vision of patients with central scotoma shown by CRVO. This proves that PRP has no value in treatment and is seriously detrimental.

It's important to note that although the occurrence of NVG is not very common and PRP has the potential to cause visual field and vision problems, NVG is a serious and irreversible condition that can lead to blindness. Therefore, it's not advisable to avoid PRP prophylaxis simply out of caution. These findings also have significant implications for understanding the necessity of follow-up to determine the extent and severity of iCRVO to decide when PRP is suitable for the case.

4.3 Best time for PRP

As mentioned earlier, the findings of CVOS research support the idea that prophylactic PRP may not entirely prevent INV/ANV (38). But PRP is still a recommended option when INV/ANV occurs to prevent NVG (38). Therefore, guidelines by the European Society of Retina Specialists suggest that "PRP should be recommended only after iris neovascularization becomes visible, requiring weekly or biweekly follow-up of patients with extensive capillary non-perfusion." (6) However, since it is often difficult to maintain close follow-up, guidelines suggest early prophylactic PRP (within 90 days of the onset of the CRVO) as a second choice to take precautions against INV in ischemic CRVO (6), as confirmed by the results of the study by Hayreh et al. (60).

Observing the eyes with iCRVO closely for the first 6 months is crucial to predict early NVG (63). After the first 6 months, observation can be less frequent (63). Studies conducted by Hayreh (29) in 1983 and by Zimmerman (63) in 2012 indicate that anterior segment NV is most likely to occur during the first 6 to 7 months, as shown in **Figure 1**. After this period, the chances of its occurrence are minimal (29, 63). Additionally, over 80% of cases of NVG develop within 6–8 months (29, 63).

According to Hayreh et al.'s (29) research, early prophylactic PRP within 90 days is as effective as PRP after INV appears, since the incidence of INV increases rapidly in the first 3 months. Researchers have found that NVG, also known as 100-day glaucoma, usually occurs within three months of iCRVO onset by analyzing the cumulative chance of NVG secondary to iCRVO (1, 29, 69).

4.4 Mechanism of PRP

Neovascular glaucoma is a severe and blinding disease that can result from ischemic CRVO, which occurs when the trabecular meshwork becomes blocked by proliferated fibrovascular tissue (71). INV and ANV are both indicators of non-perfusion and can increase the risk of developing NVG (60, 72). For many years, researchers have recommended PRP as a preventive measure against INV/ANV in patients with iCRVO (3, 6). Specifically, they have suggested PRP as a standard treatment after iCRVO to prevent the onset of NVG (3, 6). However, it is still debatable whether it is wise for patients with iCRVO to receive PRP to reduce the risk of NVG.

The treatment mechanism of photocoagulation has two main assumptions: (1) to establish a hyperoxic environment causing vasoconstriction (73, 74), and (2) to adjust the angiogenic stimulating factors and angiogenic inhibiting factors to suppress neovascularization.

Oxygen pressure in the retina is determined by the balance between oxygen diffusion by retinal arterioles and oxygen consumption by retinal tissue (75). Photocoagulation damages the pigment epithelium-photoreceptor complex (73), which consumes oxygen. Simultaneously, it destroys viable retinal tissue to increase oxygen diffusion from the choroid (76). Animals breathing air or 100% O_2 at atmospheric pressure show that the photocoagulated retinal areas have a higher partial pressure of oxygen than the normal retina (77–80). Therefore, photocoagulation creates a hyperoxic state that causes retinal vasoconstriction (73, 74).

Retinal photocoagulation affects VEGF and PEDF levels. With the in-depth discovery of VEGF, it has been found that the retinal pigmented epithelium (RPE), astrocytes, Müller cells, vascular endothelium, and ganglion cells create this growth factor (81). PRP can destroy many retinal cells to restrain NV and the NVG. Additionally, a study has demonstrated a temporal alteration and transcriptional activity caused by retinal laser photocoagulation in the area of VEGF production (82). However, Itaya et al. (83) showed the contrary result: the growth factor, mainly from the recruited monocytes, is upregulated at the early stage in the sensory retina and RPE-choroid after retinal scatter laser photocoagulation. Nevertheless, upregulation of angiogenic inhibitors, like PEDF and TGF-beta 2, has been found following PRP (84–86). Further experimental investigations are necessary to estimate whether PRP downgrades VEGF and upgrades PEDF levels.

When considering the use of PRP as a preventive treatment for NVG, there are two aspects to consider. Firstly, it is still controversial whether PRP is a suitable option for reducing the growth of anterior segment NV (1, 3). Secondly, we need to

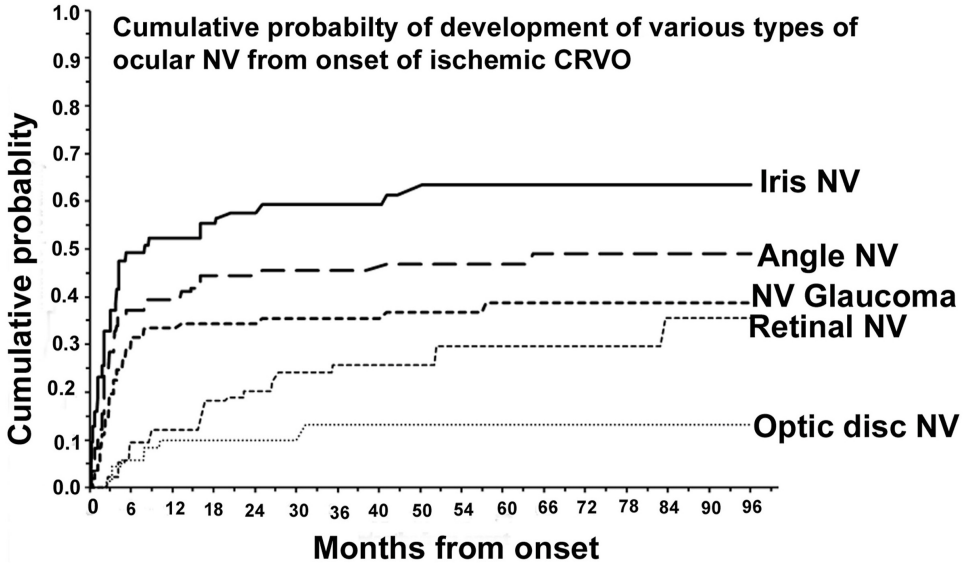

FIGURE 1
Cumulative probability of various types of ocular NV after diagnosing ischemic CRVO. Reprinted with permission from Hayreh (3). Copyright© 2021 Elsevier Ltd.

consider the impact of laser treatment on vision (3, 60, 87). By taking both of these points into account, we can evaluate the pros and cons of using PRP in iCRVO.

5 PRP and anti-VEGF

5.1 Anti-VEGF is not a substitute for PRP

To date, several studies have increasingly suggested anti-VEGF injections to abate INV and thus make it play a role in the prevention and treatment of NVG (88). Several researchers have reported the regression of iris neovascularization with intravitreal and intracameral bevacizumab (89–91). Likewise, some data have investigated that single anti-VEGF therapy plays a significant role in reducing the increase of IOP (92–94). These pieces of evidence suggest that the aggressive blockade of VEGF may be effectively applied to prevent NVG in iCRVO. However, it is still controversial whether anti-VEGF can completely replace traditional PRP therapy.

Blocking vascular endothelial growth factor does not stably prevent neovascular complications, but only delays their onset (7, 8). A small-scale study by Inatani et al. (94, 95) concluded that intravitreal aflibercept injection leads to meaningful IOP reductions in 5 weeks. But another study found that high levels of CRT remained at 1-month follow-up after initial IVB therapy, demonstrating the poor efficacy of single anti-VEGF therapy alone (8). A long-term comparison study also pointed out that the decrease of IOP has no difference between the eyes with and without anti-VEGF in the longer follow-up (96). Therefore, in a randomized controlled study of ranibizumab application in CRVO, Campochiaro et al. (97, 98) reported that monthly ranibizumab injections could reduce the proportion of eyes with retinal capillary obstruction and the progression of retinal non-perfusion. However, the proportion of eyes with retinal non-perfusion increased after six months when researchers changed monthly ranibizumab injections to pro re nata (PRN) injections (97). Sophie (99) described the same result: resumption of the PRN blockage of VEGF would reverse retina non-perfusion. NVG statistically occurs an average of 7 months after the last anti-VEGF injection (8, 100). Namely, intravitreal anti-VEGF functionally delays the occurrence time of the neovascularization compared to the natural history in patients with iCRVO (100, 101).

The short-term and incomplete inhibitory effect of anti-VEGF can be attributed to the short half-life (102, 103), the complexity of multiple pathways in ocular angiogenesis (26), and the limitation that anti-VEGF only works on the existing VEGF (104).

As can be seen, VEGF inhibition cannot stably control the development of inner retinal non-perfusion and IOP for a long time. Comparing anti-VEGF therapy with PRP to without PRP, researchers illustrated that PRP substantially plays a leading role in delaying and decreasing the need for IOP control instead of bevacizumab administration (96). All of the above suggests anti-VEGF as adjuvant therapy instead of an alternative treatment for PRP.

5.2 PRP combined with anti-VEGF

Clinical experts recommend anti-VEGF drug injections taken within 5–14 days before undergoing vitreous surgeries (105). To begin with, the characteristic of anti-VEGF to rapidly regressing NV prolongs the PRP treatment time window. PRP usually takes several weeks to make efforts (106). While anti-VEGF treatment can effectively bring the IOP under control within 1 month (107). For another, injecting anti-VEGF before PRP treatment reduces postoperative complications, including hyphema and NVG (93, 108–110). High levels of VEGF in the perioperative period predict

postoperative vitreous hemorrhage and neovascular glaucoma (111, 112). In order to prevent recurrence of NV-related vitreous hemorrhage (VN) after PRP, intravitreal injection of anti-VEGF every 3–4 months is recommended (113).

Nevertheless, it is unclear whether combination therapy can reduce PRP side effects and improve efficacy. Several studies have achieved effective long-term treatment by combining known endogenous angiogenesis inhibitors with conventional PRP therapy (9, 114, 115). Further, the treatment program's effectiveness and potential adverse effects were evaluated through tests such as assessment of VA, control of IOP, and evaluation of retinal function. Unexpectedly, PRP with anti-VEGF treatment does not improve or deteriorate the low VA outcomes significantly (9, 96, 116). Regarding the improvement of IOP control, researchers hold different views. Combination therapy has several benefits for treating IOP conditions. Firstly, it results in a quicker and more consistent reduction in IOP and a faster regression of NV (9). Additionally, studies conducted by Vasudev et al. (114) have shown that combination therapy helps maintain open-angle documented by fundoscopy over time. However, it is worth noting that combination therapy does not significantly improve IOP reduction in the long term (96, 116). Evaluating the retinal function by full-field ERG, the outcomes demonstrated that the photoreceptor function in patients with NVG was decreased by bevacizumab therapy (116), which leads to worse side effects of therapy. As described, while anti-VEGF creates conditions for PRP, further studies are needed to confirm the gainful effects of combination therapy in large samples of long-term research.

In recent years, intracameral injections of anti-VEGF have been proposed to achieve quicker and more precise therapeutic outcomes (117). VEGF primarily derives from the retina, with possible supplementary sources in the ciliary epithelium (118). In primate eyes, intravitreal anti-VEGF injections resulted in the highest drug concentrations in the iris and atrial angle on day 1, and in the ciliary body on day 4 (119). Administration of intracameral anti-VEGF injections seems to have more targeted therapeutic effects for INV and ANV. Further trials are needed to confirm the benefits of this surgical approach. Meanwhile, when injecting drugs into silicone oil-filled eyes, it is tough to ensure proper concentration in the vitreous cavity (117). Therefore, injecting drugs into the anterior chamber is a viable option for treating NVG in these patients (117).

6 NVG treatment

Glaucoma is classified into three stages according to the progression of the disease (109). Pre-glaucoma (Phase I) is characterized by the presence of INV with normal IOP levels. With elevated IOP, the NVG is divided into open-angle (Phase II) and closed-angle (Phase III) types.

The primary objective of NVG therapy is to inhibit NV and decrease IOP. If PRP and anti-VEGF treatments are ineffective at Phase I, conventional glaucoma medications and surgical procedures are suggested.

Medications for glaucoma are divided into two main categories: IOP-lowering and anti-inflammatory. Drugs that topically reduce aqueous production include β adrenoceptor blockers, α-2 adrenoceptor agonists, and carbonic anhydrase inhibitors (109). If the target IOP is still not reached with medication, there are surgical options to help with the obstruction of aqueous humor outflow. These options include trabeculectomy, glaucoma drainage devices, and minimally invasive internal drainage procedures (120). In cases where the first surgery fails, refractory glaucoma can be treated with surgical options that reduce the amount of aqueous humor produced by the ciliary, such as cyclophotocoagulation or cyclocryotherapy (120).

7 Conclusion

In the medical field, PRP remains a commonly used treatment for NVG prophylaxis. It is recommended that patients undergo PRP as soon as possible after being diagnosed with iCRVO, ideally within 90 days. However, the effectiveness and safety of PRP in treating and managing NVG secondary to iCRVO is still uncertain, and more randomized controlled clinical trials are needed to determine the optimal treatment time and reliable indications for PRP. Additionally, PRP can cause side effects and complications, such as losing the peripheral visual fields (60). Therefore, further research is needed to establish definitive evidence of the etiopathogenesis of NVG and the mechanism of PRP treatment. This will help promote the development of PRP or other advanced treatment options.

Intravitreal anti-VEGF injections are performed before vitrectomy to rapidly ablate neovascularization and to allow for PRP treatment while reducing the risk of surgical complications such as vitreous hemorrhage (105). In addition to the combination of PRP and known anti-VEGF treatments, further research could be done to assess the effectiveness of new substances that regulate angiogenesis, such as PEDF (24, 25), and inflammatory proteins, such as interleukin-6 (121, 122). Recently, a new emulsion-formulated antisense oligonucleotide has been developed to prevent NV by blocking insulin receptor substrate-1 (IRS-1) in the intraocular retina with topical eye drops (123). This treatment, which has attracted significant attention in preventing NVG, is currently in phase II/III trials and shows excellent potential (123). Gene therapy for endogenous angiogenic inhibitors also has attractive prospects, such as plasminogen kringle 5 (124, 125), recombinant adeno-associated virus (126), gene transfer of prolyl hydroxylase domain 2 (127), and more.

It is important to note that there are several limitations in clinical diagnosis and follow-up due to the subjective consciousness of patients and hospital equipment. Patients often do not seek preventive treatment, and even fewer complete follow-up procedures on time. To assess ischemic and non-ischemic CRVO, visual acuity and RAPD examinations are commonly conducted. However, inadequate inspection can lead to incorrect assessments and limited treatment options. Additionally, insufficient attention to angle NV can delay the preventive treatment of NVG. A study has shown that ANV can occur without pupillary margin involvement in CRVO, indicating the need for screening gonioscopy (65).

In conclusion, the effectiveness of PRP in preventing NVG as a complication of CRVO still requires further exploration. A substantial amount of evidence is needed, ranging from basic research to clinical practice. Diagnostic methods and prophylactic protocols for NVG also need to be further improved.

Author contributions

SQ: Writing – review & editing, Conceptualization, Investigation, Writing – original draft. YZ: Investigation, Writing – review & editing. LY: Writing – review & editing. HW: Conceptualization, Funding acquisition, Methodology, Project administration, Writing – review & editing.

Funding

The authors declare financial support was received for the research, authorship, and/or publication of this article. This study was supported by grant from the Department of Science and Technology of Jilin Province (grant numbers: 20190304028YY and 20200404103YY). They provided financial support for the work conducted to prepare this review manuscript but was not involved directly in preparation of the manuscript or in the decision to publish.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Hayreh S. Neovascular glaucoma. *Prog Retinal Eye Res.* (2007) 26:470–485. doi: 10.1016/j.preteyeres.2007.06.001

2. Nishinaka A, Tanaka M, Aoshima K, Kuriyama A, Sasaki T, Otsu W, et al. The pathological association between the anterior eye segment and the retina in a murine model of neovascular glaucoma. *FASEB J.* (2022) 36:e22323. doi: 10.1096/fj.202101917R

3. Hayreh S. Photocoagulation for retinal vein occlusion. *Prog Retinal Eye Res.* (2021) 85:100964. doi: 10.1016/j.preteyeres.2021.100964

4. Nicholson L, Vazquez-Alfageme C, Patrao N, Triantafyllopolou I, Bainbridge J, Hykin P, et al. Retinal nonperfusion in the posterior pole is associated with increased risk of neovascularization in central retinal vein occlusion. *Am J Ophthalmol.* (2017) 182:118–25. doi: 10.1016/j.ajo.2017.07.015

5. The Central Vein Occlusion Study Group. Natural history and clinical management of central retinal vein occlusion. . *Arch Ophthalmol.* (1997) 115:486–91. doi: 10.1001/archopht.1997.01100150488006

6. Schmidt-Erfurth U, Garcia-Arumi J, Gerendas B, Midena E, Sivaprasad S, Tadayoni R, et al. Guidelines for the management of retinal vein occlusion by the European Society of Retina Specialists (EURETINA). *Ophthalmologica.* (2019) 242:123–62. doi: 10.1159/000502041

7. Brown D, Wykoff C, Wong T, Mariani A, Croft D, Schuetzle K, et al. Ranibizumab in preproliferative (ischemic) central retinal vein occlusion: the rubeosis anti-VEGF (RAVE) trial. *Retina.* (2014) 34:1728–35. doi: 10.1097/IAE.0000000000000191

8. Lee Y, Kim Y. Central retinal thickness changes and risk of neovascular glaucoma after intravitreal bevacizumab injection in patients with central retinal vein occlusion. *Sci Rep.* (2022) 12:2051. doi: 10.1038/s41598-022-06121-x

9. Ehlers J, Spirn M, Lam A, Sivalingam A, Samuel M, Tasman W. Combination intravitreal bevacizumab/panretinal photocoagulation versus panretinal photocoagulation alone in the treatment of neovascular glaucoma. *Retina.* (2008) 28:696–702. doi: 10.1097/IAE.0b013e3181679c0b

10. Mannina A, Olivier M, Patrianakos T. Neovascular glaucoma. *Dis Mon.* (2021) 67:101137. doi: 10.1016/j.disamonth.2021.101137

11. Havens S, Gulati V. Neovascular glaucoma. *Dev Ophthalmol.* (2016) 55:196–204. doi: 10.1159/000431196

12. Shweiki D, Itin A, Soffer D, Keshet E. Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis. *Nature.* (1992) 359:843–5. doi: 10.1038/359843a0

13. Senger D, Galli S, Dvorak A, Perruzzi C, Harvey V, Dvorak H. Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. *Science.* (1983) 219:983–5. doi: 10.1126/science.6823562

14. Leung D, Cachianes G, Kuang W, Goeddel D, Ferrara N. Vascular endothelial growth factor is a secreted angiogenic mitogen. *Science.* (1989) 246:1306–9. doi: 10.1126/science.2479986

15. Keck P, Hauser S, Krivi G, Sanzo K, Warren T, Feder J, et al. Vascular permeability factor, an endothelial cell mitogen related to PDGF. *Science.* (1989) 246:1309–12. doi: 10.1126/science.2479987

16. Plate K, Breier G, Weich H, Risau W. Vascular endothelial growth factor is a potential tumour angiogenesis factor in human gliomas in vivo. *Nature.* (1992) 359:845–8. doi: 10.1038/359845a0

17. Tang Y, Cheng Y, Wang S, Wang Y, Liu P, Wu H. Review: the development of risk factors and cytokines in retinal vein occlusion. *Front Med.* (2022) 9:910600. doi: 10.3389/fmed.2022.910600

18. Shima D, Adamis A, Ferrara N, Yeo K, Yeo T, Allende R, et al. Hypoxic induction of endothelial cell growth factors in retinal cells: identification and characterization of vascular endothelial growth factor (VEGF) as the mitogen. *Mol Med.* (1995) 1:182–93.

19. Tolentino M, Miller J, Gragoudas E, Chatzistefanou K, Ferrara N, Adamis A. Vascular endothelial growth factor is sufficient to produce iris neovascularization and neovascular glaucoma in a nonhuman primate. *Arch Ophthalmol.* (1996) 114:964–70. doi: 10.1001/archopht.1996.01100140172010

20. Adamis A, Shima D, Tolentino M, Gragoudas E, Ferrara N, Folkman J, et al. Inhibition of vascular endothelial growth factor prevents retinal ischemia-associated iris neovascularization in a nonhuman primate. *Arch Ophthalmol.* (1996) 114:66–71. doi: 10.1001/archopht.1996.01100130062010

21. Bhisitkul R, Robinson G, Moulton R, Claffey K, Gragoudas E, Miller J. An antisense oligodeoxynucleotide against vascular endothelial growth factor in a nonhuman primate model of iris neovascularization. *Arch Ophthalmol.* (2005) 123:214–9. doi: 10.1001/archopht.123.2.214

22. Pe'er J, Folberg R, Itin A, Gnessin H, Hemo I, Keshet E. Vascular endothelial growth factor upregulation in human central retinal vein occlusion. *Ophthalmology.* (1998) 105:412–6. doi: 10.1016/S0161-6420(98)93020-2

23. Jung S, Kim K, Sohn S, Yang S. Association of aqueous humor cytokines with the development of retinal ischemia and recurrent macular edema in retinal vein occlusion. *Invest Ophthalmol Vis Sci.* (2014) 55:2290–6. doi: 10.1167/iovs.13-13587

24. Gao G, Ma J. Tipping the balance for angiogenic disorders. *Drug Discov Today.* (2002) 7:171–2. doi: 10.1016/s1359-6446(01)02160-2

25. Spranger J, Osterhoff M, Reimann M, Ristow M, Francis M, Cristofalo V, et al. Loss of the antiangiogenic pigment epithelium-derived factor in patients with angiogenic eye disease. *Diabetes.* (2001) 50:2641–5. doi: 10.2337/diabetes.50.12.2641

26. Zhang S, Ma J. Ocular neovascularization: implication of endogenous angiogenic inhibitors and potential therapy. *Prog Retinal Eye Res.* (2007) 26:1–37. doi: 10.1016/j.preteyeres.2006.09.002

27. Nadal J, Carreras E, Kudsieh B, Canut M. Neovascular glaucoma treatment with extraction of anterior chamber fibrovascular tissue. *JAMA Ophthalmol.* (2013) 131:1083–5. doi: 10.1001/jamaophthalmol.2013.426

28. John T, Sassani J, Eagle R. The myofibroblastic component of rubeosis iridis. *Ophthalmology.* (1983) 90:721–8. doi: 10.1016/s0161-6420(83)34520-6

29. Hayreh S, Rojas P, Podhajsky P, Montague P, Woolson R. Ocular neovascularization with retinal vascular occlusion-III. *Ophthalmology.* (1983) 90:488–506.

30. Hayreh S, Zimmerman M, Podhajsky P. Incidence of various types of retinal vein occlusion and their recurrence and demographic characteristics. *Am J Ophthalmol.* (1994) 117:429–41. doi: 10.1016/s0002-9394(14)70001-7

31. Hayreh S, Rojas P, Podhajsky P, Montague P, Woolson R. Ocular neovascularization with retinal vascular occlusion-III. Incidence of ocular neovascularization with retinal vein occlusion. *Ophthalmology.* (1983) 90:488–506. doi: 10.1016/s0161-6420(83)34542-5

32. Choi Y, Jee D, Kwon J. Characteristics of major and macular branch retinal vein occlusion. *Sci Rep.* (2022) 12:14103. doi: 10.1038/s41598-022-18414-2

33. Battaglia Parodi M, Bandello F. Branch retinal vein occlusion: classification and treatment. *Ophthalmologica.* (2009) 223:298–305. doi: 10.1159/000213640

34. Hayreh S. Occlusion of the central retinal vessels. *Br J Ophthalmol.* (1965) 49:626–45. doi: 10.1136/bjo.49.12.626

35. Hayreh S. Classification of central retinal vein occlusion. *Ophthalmology.* (1983) 90:458–74. doi: 10.1016/s0161-6420(83)34530-9

36. Hayreh S, Zimmerman M. Fundus changes in central retinal vein occlusion. *Retina.* (2015) 35:29–42. doi: 10.1097/IAE.0000000000000256

37. Central Vein Occlusion Study Coordinating Center. Baseline and early natural history report: the central vein occlusion study. *Arch Ophthalmol.* (1993) 111:1087. doi: 10.1001/archopht.1993.01090080083022

38. The Central Vein Occlusion Study Group. A randomized clinical trial of early panretinal photocoagulation for ischemic central vein occlusion. The Central Vein Occlusion Study Group N report. *Ophthalmology.* (1995) 102:1434–44. doi: 10.1016/S0161-6420(95)30848-2

39. Hayreh S. Prevalent misconceptions about acute retinal vascular occlusive disorders. *Prog Retinal Eye Res.* (2005) 24:493–519. doi: 10.1016/j.preteyeres.2004.12.001

40. Coscas F, Glacet-Bernard A, Miere A, Caillaux V, Uzzan J, Lupidi M, et al. Optical coherence tomography angiography in retinal vein occlusion: evaluation of superficial and deep capillary plexa. *Am J Ophthalmol.* (2016) 161:160–71.e1–2. doi: 10.1016/j.ajo.2015.10.008

41. Nobre Cardoso J, Keane P, Sim D, Bradley P, Agrawal R, Addison P, et al. Systematic evaluation of optical coherence tomography angiography in retinal vein occlusion. *Am J Ophthalmol.* (2016) 163:93–107.e6. doi: 10.1016/j.ajo.2015.11.025

42. Kashani A, Lee S, Moshfeghi A, Durbin M, Puliafito C. Optical coherence tomography angiography of retinal venous occlusion. *Retina.* (2015) 35:2323–31. doi: 10.1097/IAE.0000000000000811

43. Ko J, Kwon O, Byeon S. Optical coherence tomography predicts visual outcome in acute central retinal vein occlusion. *Retina.* (2014) 34:1132–41. doi: 10.1097/IAE.0000000000000054

44. Hayreh S, Klugman M, Beri M, Kimura A, Podhajsky P. Differentiation of ischemic from non-ischemic central retinal vein occlusion during the early acute phase. *Graefes Arch Clin Exp Ophthalmol.* (1990) 228:201–17. doi: 10.1007/BF00920022

45. Joussen A. *Retinal Vascular Disease*. Berlin: Springer (2007).

46. Thomas A, Thomas M, Finn A, Fekrat S. Use of the ischemic index on widefield fluorescein angiography to characterize a central retinal vein occlusion as ischemic or nonischemic. *Retina.* (2019) 39:1033–8. doi: 10.1097/IAE.0000000000002126

47. Glacet-Bernard A, Miere A, Houmane B, Tilleul J, Souied E. Nonperfusion assessment in retinal vein occlusion: comparison between ultra-widefield fluorescein angiography and widefield optical coherence tomography angiography. *Retina.* (2021) 41:1202–9. doi: 10.1097/IAE.0000000000002993

48. Wittström E, Ponjavic V, Lövestam-Adrian M, Larsson J, Andréasson S. Electrophysiological evaluation and visual outcome in patients with central retinal vein occlusion, primary open-angle glaucoma and neovascular glaucoma. *Acta Ophthalmol.* (2010) 88:86–90. doi: 10.1111/j.1755-3768.2008.01424.x

49. Williamson T, Baxter G. Central retinal vein occlusion, an investigation by color Doppler imaging. Blood velocity characteristics and prediction of iris neovascularization. *Ophthalmology.* (1994) 101:1362–72. doi: 10.1016/s0161-6420(94)31173-0

50. Shiozaki D, Sakimoto S, Shiraki A, Wakabayashi T, Fukushima Y, Oie Y, et al. Observation of treated iris neovascularization by swept-source-based en-face anterior-segment optical coherence tomography angiography. *Sci Rep.* (2019) 9:10262. doi: 10.1038/s41598-019-46514-z

51. Akagi T, Uji A, Huang A, Weinreb R, Yamada T, Miyata M, et al. Conjunctival and intrascleral vasculatures assessed using anterior segment optical coherence tomography angiography in normal eyes. *Am J Ophthalmol.* (2018) 196:1–9. doi: 10.1016/j.ajo.2018.08.009

52. Zett C, Stina D, Kato R, Novais E, Allemann N. Comparison of anterior segment optical coherence tomography angiography and fluorescein angiography for iris vasculature analysis. *Graefes Arch Clin Exp Ophthalmol.* (2018) 256:683–91. doi: 10.1007/s00417-018-3935-7

53. Ang M, Devarajan K, Tan A, Ke M, Tan B, Teo K, et al. Anterior segment optical coherence tomography angiography for iris vasculature in pigmented eyes. *Br J Ophthalmol.* (2021) 105:929–934. doi: 10.1136/bjophthalmol-2020-316930

54. Magargal L, Donoso L, Sanborn G. Retinal ischemia and risk of neovascularization following central retinal vein obstruction. *Ophthalmology.* (1982) 89:1241–5. doi: 10.1016/s0161-6420(82)34655-2

55. Balaratnasingam C, Inoue M, Ahn S, McCann J, Dhrami-Gavazi E, Yannuzzi L, et al. Visual acuity is correlated with the area of the foveal avascular zone in diabetic retinopathy and retinal vein occlusion. *Ophthalmology.* (2016) 123:2352–67. doi: 10.1016/j.ophtha.2016.07.008

56. Seknazi D, Coscas F, Sellam A, Rouimi F, Coscas G, Souied E, et al. Optical coherence tomography angiography in retinal vein occlusion: correlations between macular vascular density, visual acuity, and peripheral nonperfusion area on fluorescein angiography. *Retina.* (2018) 38:1562–70. doi: 10.1097/IAE.0000000000001737

57. Tsui I, Kaines A, Havunjian M, Hubschman S, Heilweil G, Prasad P, et al. Ischemic index and neovascularization in central retinal vein occlusion. *Retina.* (2011) 31:105–10. doi: 10.1097/IAE.0b013e3181e36c6d

58. DeBoer C, Wong B, Ameri H. Ischemic index and distribution of retinal capillary non-perfusion in neovascular glaucoma. *Front Biosci.* (2022) 27:24. doi: 10.31083/j.fbl2701024

59. Wykoff C, Brown D, Croft D, Major J, Wong T. Progressive retinal nonperfusion in ischemic central retinal vein occlusion. *Retina.* (2015) 35:43–7. doi: 10.1097/IAE.0000000000000277

60. Hayreh S, Klugman M, Podhajsky P, Servais G, Perkins E. Argon laser panretinal photocoagulation in ischemic central retinal vein occlusion. *Graefe's Arch Clin Exp Ophthalmol.* (1990) 228:281–96. doi: 10.1007/BF00920049

61. Gaskin B, Danesh-Meyer H. Neovascular glaucoma and sarcoidosis. *Eye.* (2005) 19:599–601. doi: 10.1038/sj.eye.6701542

62. Shazly T, Latina M. Neovascular glaucoma: etiology, diagnosis and prognosis. *Semin Ophthalmol.* (2009) 24:113–21. doi: 10.1080/08820530902800801

63. Hayreh S, Zimmerman M. Ocular neovascularization associated with central and hemicentral retinal vein occlusion. *Retina.* (2012) 32:1553–65. doi: 10.1097/IAE.0b013e318246912c

64. Chan C, Ip M, Vanveldhuisen P, Oden N, Scott I, Tolentino M, et al. SCORE Study report #11: incidences of neovascular events in eyes with retinal vein occlusion. *Ophthalmology.* (2011) 118:1364–72. doi: 10.1016/j.ophtha.2010.11.020

65. Browning D, Scott A, Peterson C, Warnock J, Zhang Z. The risk of missing angle neovascularization by omitting screening gonioscopy in acute central retinal vein occlusion. *Ophthalmology.* (1998) 105:776–84. doi: 10.1016/S0161-6420(98)95014-X

66. Recchia F, Carvalho-Recchia C, Hassan T. Clinical course of younger patients with central retinal vein occlusion. *Arch Ophthalmol.* (2004) 122:317–21. doi: 10.1001/archopht.122.3.317

67. Oosterhuis J, Sedney S. Photocoagulation in retinal vein thrombosis. *Ophthalmologica.* (1975) 171:365–79. doi: 10.1159/000307551

68. Laatikainen L, Kohner E, Khoury D, Blach R. Panretinal photocoagulation in central retinal vein occlusion: a randomised controlled clinical study. *Br J Ophthalmol.* (1977) 61:741–53. doi: 10.1136/bjo.61.12.741

69. Hayreh S, Podhajsky P, Zimmerman M. Natural history of visual outcome in central retinal vein occlusion. *Ophthalmology.* (2011) 118:119–33.e2. doi: 10.1016/j.ophtha.2010.04.019

70. Hayreh S. Ocular vascular occlusive disorders: natural history of visual outcome. *Prog Retinal Eye Res.* (2014) 41:1–25. doi: 10.1016/j.preteyeres.2014.04.001

71. Sivak-Callcott J, O'Day D, Gass J, Tsai J. Evidence-based recommendations for the diagnosis and treatment of neovascular glaucoma. *Ophthalmology.* (2001) 108:1767–76;quiz1777, 1800. doi: 10.1016/s0161-6420(01)00775-8

72. Hayreh S. Evidence-based recommendations for neovascular glaucoma. *Ophthalmology.* (2003) 110:2. doi: 10.1016/S0161-6420(02)01271-X

73. Pournaras C, Tsacopoulos M, Strommer K, Gilodi N, Leuenberger P. Scatter photocoagulation restores tissue hypoxia in experimental vasoproliferative microangiopathy in miniature pigs. *Ophthalmology.* (1990) 97:1329–33. doi: 10.1016/s0161-6420(90)32414-4

74. Riva C, Pournaras C, Tsacopoulos M. Regulation of local oxygen tension and blood flow in the inner retina during hyperoxia. *J Appl Physiol.* (1986) 61:592–8. doi: 10.1152/jappl.1986.61.2.592

75. Pournaras C, Riva C, Tsacopoulos M, Strommer K. Diffusion of O2 in the retina of anesthetized miniature pigs in normoxia and hyperoxia. *Exp Eye Res.* (1989) 49:347–60. doi: 10.1016/0014-4835(89)90045-6

76. Grunwald J, Riva C, Brucker A, Sinclair S, Petrig B. Effect of panretinal photocoagulation on retinal blood flow in proliferative diabetic retinopathy. *Ophthalmology.* (1986) 93:590–5. doi: 10.1016/s0161-6420(86)33691-1

77. Budzynski E, Smith J, Bryar P, Birol G, Linsenmeier R. Effects of photocoagulation on intraretinal PO2 in cat. *Invest Ophthalmol Vis Sci.* (2008) 49:380–9. doi: 10.1167/iovs.07-0065

78. Molnar I, Poitry S, Tsacopoulos M, Gilodi N, Leuenberger P. Effect of laser photocoagulation on oxygenation of the retina in miniature pigs. *Invest Ophthalmol Vis Sci.* (1985) 26:1410–4.

79. Diddie K, Ernest J. The effect of photocoagulation on the choroidal vasculature and retinal oxygen tension. *Am J Ophthalmol.* (1977) 84:62–6. doi: 10.1016/0002-9394(77)90325-7

80. Landers M, Stefansson E, Wolbarsht M. Panretinal photocoagulation and retinal oxygenation. *Retina.* (1982) 2:167–75. doi: 10.1097/00006982-198200230-00007

81. Penn J, Madan A, Caldwell R, Bartoli M, Caldwell R, Hartnett M. Vascular endothelial growth factor in eye disease. *Prog Retinal Eye Res.* (2008) 27:331–71. doi: 10.1016/j.preteyeres.2008.05.001

82. Xiao M, McLeod D, Cranley J, Williams G, Boulton M. Growth factor staining patterns in the pig retina following retinal laser photocoagulation. *Br J Ophthalmol.* (1999) 83:728–36. doi: 10.1136/bjo.83.6.728

83. Itaya M, Sakurai E, Nozaki M, Yamada K, Yamasaki S, Asai K, et al. Upregulation of VEGF in murine retina via monocyte recruitment after retinal scatter laser photocoagulation. *Invest Ophthalmol Vis Sci.* (2007) 48:5677–83. doi: 10.1167/iovs.07-0156

84. Ogata N, Tombran-Tink J, Jo N, Mrazek D, Matsumura M. Upregulation of pigment epithelium-derived factor after laser photocoagulation. *Am J Ophthalmol.* (2001) 132:427–9. doi: 10.1016/s0002-9394(01)01021-2

85. Ishida K, Yoshimura N, Yoshida M, Honda Y. Upregulation of transforming growth factor-beta after panretinal photocoagulation. *Invest Ophthalmol Vis Sci.* (1998) 39:801–7.

86. Hattenbach L, Beck K, Pfeilschifter J, Koch F, Ohrloff C, Schacke W. Pigment-epithelium-derived factor is upregulated in photocoagulated human retinal pigment epithelial cells. *Ophthalmic Res.* (2005) 37:341–6. doi: 10.1159/000088263

87. Hayreh S. Venous occlusive disease: management 25 years ago. *Retina.* (2006) 26:S51–62. doi: 10.1097/01.iae.0000236458.85522.96

88. Yip V, Yip L, Laude A. Subconjunctival bevacizumab for iris neovascularisation. *Lancet Diabetes Endocrinol.* (2014) 2:449–50. doi: 10.1016/S2213-8587(14)70070-1

89. Chilov M, Grigg J, Playfair T. Bevacizumab (Avastin) for the treatment of neovascular glaucoma. *Clin Exp Ophthalmol.* (2007) 35:494–6. doi: 10.1111/j.1442-9071.2007.01521.x

90. Avery R. Regression of retinal and iris neovascularization after intravitreal bevacizumab (Avastin) treatment. *Retina.* (2006) 26:352–4. doi: 10.1097/00006982-200603000-00016

91. Davidorf F, Mouser J, Derick R. Rapid improvement of rubeosis iridis from a single bevacizumab (Avastin) injection. *Retina.* (2006) 26:354–6. doi: 10.1097/00006982-200603000-00017

92. Foss A, Scott L, Rogers C, Reeves B, Ghanchi F, Gibson J, et al. Changes in intraocular pressure in study and fellow eyes in the IVAN trial. *Br J Ophthalmol.* (2016) 100:1662–7. doi: 10.1136/bjophthalmol-2015-307595

93. SooHoo J, Seibold L, Pantcheva M, Kahook M. Aflibercept for the treatment of neovascular glaucoma. *Clin Exp Ophthalmol.* (2015) 43:803–7. doi: 10.1111/ceo.12559

94. Inatani M, Higashide T, Matsushita K, Nagasato D, Takagi H, Ueki M, et al. Efficacy and safety of intravitreal aflibercept injection in Japanese patients with neovascular glaucoma: outcomes from the VENERA Study. *Adv Ther.* (2021) 38:1106–15. doi: 10.1007/s12325-020-01580-y

95. Inatani M, Higashide T, Matsushita K, Miki A, Ueki M, Iwamoto Y, et al. Intravitreal aflibercept in japanese patients with neovascular glaucoma: the VEGA Randomized Clinical Trial. *Adv Ther.* (2021) 38:1116–29. doi: 10.1007/s12325-020-01579-5

96. Olmos L, Sayed M, Moraczewski A, Gedde S, Rosenfeld P, Shi W, et al. Long-term outcomes of neovascular glaucoma treated with and without intravitreal bevacizumab. *Eye.* (2016) 30:463–72. doi: 10.1038/eye.2015.259

97. Campochiaro P, Bhisitkul R, Shapiro H, Rubio R. Vascular endothelial growth factor promotes progressive retinal nonperfusion in patients with retinal vein occlusion. *Ophthalmology.* (2013) 120:795–802. doi: 10.1016/j.ophtha.2012.09.032

98. Campochiaro P, Sophie R, Pearlman J, Brown D, Boyer D, Heier J, et al. Long-term outcomes in patients with retinal vein occlusion treated with ranibizumab: the RETAIN study. *Ophthalmology.* (2014) 121:209–19. doi: 10.1016/j.ophtha.2013.08.038

99. Sophie R, Hafiz G, Scott A, Zimmer-Galler I, Nguyen Q, Ying H, et al. Long-term outcomes in ranibizumab-treated patients with retinal vein occlusion; the role of progression of retinal nonperfusion. *Am J Ophthalmol.* (2013) 156:693–705. doi: 10.1016/j.ajo.2013.05.039

100. Rong A, Swaminathan S, Vanner E, Parrish R. Predictors of Neovascular glaucoma in central retinal vein occlusion. *Am J Ophthalmol.* (2019) 204:62–9. doi: 10.1016/j.ajo.2019.02.038

101. Casselholm de Salles M, Lindberg C, Epstein D. Neovascular glaucoma in patients with central retinal vein occlusion: a real-life study in the anti-VEGF era. *Acta Ophthalmol.* (2021) 99:e7–12. doi: 10.1111/aos.14500

102. Bakri S, Snyder M, Reid J, Pulido J, Singh R. Pharmacokinetics of intravitreal bevacizumab (Avastin). *Ophthalmology.* (2007) 114:855–9. doi: 10.1016/j.ophtha.2007.01.017

103. Beer P, Wong S, Hammad A, Falk N, O'Malley M, Khan S. Vitreous levels of unbound bevacizumab and unbound vascular endothelial growth factor in two patients. *Retina.* (2006) 26:871–6. doi: 10.1097/01.iae.0000233327.68433.02

104. Campochiaro P, Aiello L, Rosenfeld P. Anti-Vascular endothelial growth factor agents in the treatment of retinal disease: from bench to bedside. *Ophthalmology.* (2016) 123:S78–88. doi: 10.1016/j.ophtha.2016.04.056

105. Li S, Guo L, Zhou P, Tang J, Wang Z, Zhang L, et al. Comparison of efficacy and safety of intravitreal ranibizumab and conbercept before vitrectomy in Chinese proliferative diabetic retinopathy patients: a prospective randomized controlled trial. *Eye and Vis.* (2022) 9:44. doi: 10.1186/s40662-022-00316-z

106. Doft B, Blankenship G. Retinopathy risk factor regression after laser panretinal photocoagulation for proliferative diabetic retinopathy. *Ophthalmology.* (1984) 91:1453–7. doi: 10.1016/s0161-6420(84)34123-9

107. Rittiphairoj T, Roberti G, Michelessi M. Anti-vascular endothelial growth factor for neovascular glaucoma. *Cochrane Database Syst Rev.* (2023) 4:CD007920. doi: 10.1002/14651858.CD007920.pub4

108. Takihara Y, Inatani M, Kawaji T, Fukushima M, Iwao K, Iwao M, et al. Combined intravitreal bevacizumab and trabeculectomy with mitomycin C versus trabeculectomy with mitomycin C alone for neovascular glaucoma. *J Glaucoma.* (2011) 20:196–201. doi: 10.1097/IJG.0b013e3181d9ce12

109. Wakabayashi T, Oshima Y, Sakaguchi H, Ikuno Y, Miki A, Gomi F, et al. Intravitreal bevacizumab to treat iris neovascularization and neovascular glaucoma secondary to ischemic retinal diseases in 41 consecutive cases. *Ophthalmology.* (2008) 115:1571–80, 1580.e1–3. doi: 10.1016/j.ophtha.2008.02.026.

110. Moraczewski A, Lee R, Palmberg P, Rosenfeld P, Feuer W. Outcomes of treatment of neovascular glaucoma with intravitreal bevacizumab. *Br J Ophthalmol.* (2009) 93:589–93. doi: 10.1136/bjo.2008.151472

111. Wakabayashi Y, Usui Y, Okunuki Y, Ueda S, Kimura K, Muramatsu D, et al. Intraocular VEGF level as a risk factor for postoperative complications after vitrectomy for proliferative diabetic retinopathy. *Invest Ophthalmol Vis Sci.* (2012) 53:6403. doi: 10.1167/iovs.12-10367

112. Nisic F, Jovanovic N, Mavija M, Alimanovic-Halilovic E, Nisic A, Lepara O, et al. Vitreous concentrations of vascular endothelial growth factor as a potential biomarker for postoperative complications following pars plana vitrectomy. *Aoms.* (2019) 15:449–56. doi: 10.5114/aoms.2018.73208

113. Lim J, Lee S, Sung J, Kim J, Nam K. Effect of prophylactic anti-VEGF injections on the prevention of recurrent vitreous hemorrhage in PDR patients after PRP. *Sci Rep.* (2022) 12:14484. doi: 10.1038/s41598-022-17214-y

114. Vasudev D, Blair M, Galasso J, Kapur R, Vajaranant T. Intravitreal bevacizumab for neovascular glaucoma. *J Ocul Pharmacol Ther.* (2009) 25:453–8. doi: 10.1089/jop.2009.0036

115. Yazdani S, Hendi K, Pakravan M, Mahdavi M, Yaseri M. Intravitreal bevacizumab for neovascular glaucoma: a randomized controlled trial. *J Glaucoma.* (2009) 18:632–7. doi: 10.1097/IJG.0b013e3181997211

116. Wittström E, Holmberg H, Hvarfner C, Andréasson S. Clinical and electrophysiologic outcome in patients with neovascular glaucoma treated with and without bevacizumab. *Eur J Ophthalmol.* (2012) 22:563–74. doi: 10.5301/ejo.5000089

117. Bai L, Tariq F, He Y, Zhang S, Wang F. Intracameral anti-VEGF injection for advanced neovascular glaucoma after vitrectomy with silicone oil tamponade. *Int J Ophthalmol.* (2021) 14:456–60. doi: 10.18240/ijo.2021.03.20

118. Chalam K, Brar V, Murthy R. Human ciliary epithelium as a source of synthesis and secretion of vascular endothelial growth factor in neovascular glaucoma. *JAMA Ophthalmol.* (2014) 132:1350–4. doi: 10.1001/jamaophthalmol.2014.2356

119. Peters S, Heiduschka P, Julien S, Bartz-Schmidt K, Schraermeyer U. Immunohistochemical localisation of intravitreally injected bevacizumab in the anterior chamber angle, iris and ciliary body of the primate eye. *Br J Ophthalmol.* (2008) 92:541–4. doi: 10.1136/bjo.2007.133496

120. Murphy C, Ogston S, Cobb C, MacEwen C. Recent trends in glaucoma surgery in Scotland, England and Wales. *Br J Ophthalmol.* (2015) 99:308–12. doi: 10.1136/bjophthalmol-2013-304465

121. Chen K, Wu C, Roy S, Lee S, Liu J. Increased interleukin-6 in aqueous humor of neovascular glaucoma. *Investig Ophthalmol Vis Sci.* (1999) 40:2627–32.

122. Kovacs K, Marra K, Yu G, Wagley S, Ma J, Teague G, et al. Angiogenic and inflammatory vitreous biomarkers associated with increasing levels of retinal ischemia. *Invest Ophthalmol Vis Sci.* (2015) 56:6523–30. doi: 10.1167/iovs.15-16793

123. Lorenz K, Scheller Y, Bell K, Grus F, Ponto K, Bock F, et al. A prospective, randomised, placebo-controlled, double-masked, three-armed, multicentre phase II/III trial for the Study of a Topical Treatment of Ischaemic Central Retinal Vein Occlusion to Prevent Neovascular Glaucoma – the STRONG study: study protocol for a randomised controlled trial. *Trials.* (2017) 18:128. doi: 10.1186/s13063-017-1861-3

124. Zhang S, Sima J, Shao C, Fant J, Chen Y, Rohrer B, et al. Plasminogen kringle 5 reduces vascular leakage in the retina in rat models of oxygen-induced retinopathy and diabetes. *Diabetologia.* (2004) 47:124–31. doi: 10.1007/s00125-003-1276-4

125. Zhang D, Kaufman P, Gao G, Saunders R, Ma J. Intravitreal injection of plasminogen kringle 5, an endogenous angiogenic inhibitor, arrests retinal neovascularization in rats. *Diabetologia.* (2001) 44:757–65. doi: 10.1007/s001250051685

126. Lai Y, Shen W, Brankov M, Lai C, Constable I, Rakoczy P. Potential long-term inhibition of ocular neovascularisation by recombinant adeno-associated virus-mediated secretion gene therapy. *Gene Ther.* (2002) 9:804–13. doi: 10.1038/sj.gt.3301695

127. Takei A, Ekström M, Mammadzada P, Aronsson M, Yu M, Kvanta A, et al. Gene transfer of prolyl hydroxylase domain 2 inhibits hypoxia-inducible angiogenesis in a model of choroidal neovascularization. *Sci Rep.* (2017) 7:42546. doi: 10.1038/srep42546

frontiers | Frontiers in Medicine

TYPE Review
PUBLISHED 07 February 2024
DOI 10.3389/fmed.2024.1351272

OPEN ACCESS

EDITED BY
Horace Massa,
Hôpitaux Universitaires de Genève (HUG), Switzerland

REVIEWED BY
Francesco D'Oria,
Azienda Ospedaliero Universitaria Consorziale Policlinico di Bari, Italy
Carlos Lisa,
University of Oviedo, Spain

*CORRESPONDENCE
Zonghui Yan
✉ y1966@21cn.com
Jiantao Wang
✉ wangjiantao65@126.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 06 December 2023
ACCEPTED 25 January 2024
PUBLISHED 07 February 2024

CITATION
Gong D, Deng S, Dang K, Yan Z and Wang J (2024) Causes and management strategies for elevated intraocular pressure after implantable collamer lens implantation. *Front. Med.* 11:1351272. doi: 10.3389/fmed.2024.1351272

Causes and management strategies for elevated intraocular pressure after implantable collamer lens implantation

Di Gong[1†], Simin Deng[2†], Kuanrong Dang[1†], Zonghui Yan[1*] and Jiantao Wang[1*]

[1]Shenzhen Eye Hospital, Jinan University, Shenzhen Eye Institute, Shenzhen, Guangdong, China, [2]The 2nd Clinical Medical College (Shenzhen People's Hospital) of Jinan University, Shenzhen, China

With the widespread application of Implantable Collamer Lens (ICL) implantation surgery in the field of myopia correction, a comprehensive understanding of its potential complications, especially those related to intraocular pressure (IOP), becomes crucial. This article systematically reviews various complications that may lead to IOP elevation after ICL surgery. Firstly, common complications after ICL surgery, including residual viscoelastic, steroid response, and excessive vault of the ICL, are detailed, emphasizing their potential impact on intraocular pressure. Regarding residual viscoelastic, we delve into its direct relationship with postoperative elevated IOP and possible preventive measures. For steroid response, we stress the importance of timely adjustment of steroid therapy and monitoring intraocular pressure. Additionally, excessive vault of the ICL is considered a significant potential issue, and we elaborate on its mechanism and possible management methods. In further discussion, we focus on relatively rare complications such as Toxic Anterior Segment Syndrome (TASS), Urrets-Zavalia Syndrome (UZS), Pigment Dispersion Syndrome (PDS), and malignant glaucoma. For these relatively rare complications, this review thoroughly explores their potential mechanisms, emphasizes the importance of prevention, and provides guidance for early diagnosis and treatment. This is a comprehensible review that aims to offer eye care professionals a comprehensive understanding and effective management guidance for complications of elevated IOP after ICL surgery, ultimately providing optimal care for patients' visual health.

KEYWORDS

intraocular pressure, implantable collamer lens, complications, management strategies, ophthalmic surgery

1 Introduction

Implantable Collamer Lens (ICL), a type of intraocular lens used for correcting refractive errors, can be implanted between the iris and crystalline lens. It is widely employed for correcting various degrees of refractive errors, including myopia, hyperopia, and astigmatism. ICL as also used to treat irregular astigmatism in etcatic corneal disorders such as keratoconus (1). ICL implantation surgery with a crystalline lens offers excellent visual correction, relatively low risk, reversibility, and a broad range of applicability. It is suitable not only for patients who do not meet the conditions for corneal laser surgery but also provides additional correction options for those with a desire for spectacle independence (2).

Before the clinical application of the V4c lens, patients undergoing ICL surgery (such as V4a, V4b) required YAG laser peripheral iridotomy before implantation to facilitate postoperative aqueous humor circulation. The new generation ICL V4c, however, incorporates three very small holes in the lens design. The central hole of the ICL V4c not only allows smoother aqueous humor flow from the posterior to the anterior chamber, effectively preventing postoperative elevated intraocular pressure (3). Simultaneously, the presence of the central hole, by providing more natural aqueous humor circulation around the lens, may help reduce the occurrence of postoperative cataracts (4–6). Therefore, the widespread use of V4c effectively reduces the occurrence of complications after ICL implantation (7).

Despite being considered a safe and effective method for refractive correction, ICL surgery is associated with a variety of postoperative complications. Common complications include abnormal vault of the lens, malpositioning of the lens, loss and decompensation of corneal endothelial cells, elevated intraocular pressure (IOP), cataract formation, and night vision symptoms (8). Among these, elevated IOP accounts for approximately 10.8% of post-ICL complications, presenting with symptoms such as eye bulging, eye pain, and even systemic symptoms like headache and nausea. Common causes of post-ICL elevated IOP include steroid response, residual viscoelastic, pupil block, iris pigment deposition, and narrow anterior chamber angle (ACA) (9). Early detection of signs of elevated IOP and appropriate interventions can minimize the damage associated with IOP elevation. Therefore, understanding the causes and management strategies of elevated IOP after ICL surgery is of paramount importance. This paper is a comprehensible review of the common causes of elevated IOP after ICL implantation and their management strategies, with a view to providing guidance to surgeons performing ICL surgery.

2 Residual ophthalmic viscosurgical device

The initial surge in IOP following ICL implantation occurs on the first day postoperatively, primarily due to the mechanical obstruction of the trabecular meshwork caused by residual ophthalmic viscosurgical devices (OVD) (9). OVDs are commonly utilized in intraocular surgeries to maintain anterior chamber stability and protect corneal endothelial cells during the surgical process (10). Early postoperative elevated IOP due to residual viscosurgical substance in ICL surgery often presents with unbearable eye pain and corneal epithelial edema. The measured IOP peaks are commonly at 30 mmHg or higher, posing a potential risk of retinal artery occlusion and anterior ischemic optic neuropathy. To prevent postoperative IOP elevation related to viscosurgical residue, a crucial step is the thorough removal of OVD during surgery.

Currently, commonly used viscosurgical substances in ophthalmology include sodium hyaluronate (HA) and hydroxypropyl methylcellulose (HPMC). Studies suggest that HA, characterized by high cohesiveness and dispersion, is challenging to completely flush from the anterior chamber, making it more likely to cause postoperative elevated IOP. On the other hand, HPMC, mainly possessing viscosity, is relatively easier to remove from the anterior chamber (9). However, a study by Ganesh S et al. compared the effects of using 2% HPMC and 1% HA as viscosurgical agents during ICL surgery on postoperative IOP and surgical time. The results indicated that, compared to 2% HPMC, the HA group had a shorter total surgical time and a lower incidence of acute elevated IOP (11). Due to the current lack of comparative research between the two types of OVDs in ICL, further evidence from evidence-based medicine is needed to guide the choice of viscosurgical substances.

The application of OVD in traditional ICL implantation is known as the two-step OVD technique, involving two injections of OVD into the anterior chamber during the surgery. The first injection occurs after completing the corneal incision, where the OVD is injected to maintain anterior chamber stability. The second injection is performed after implanting the ICL lens, aiming to protect corneal endothelial cells from mechanical damage while adjusting the ICL to the posterior chamber. Subsequently, balanced salt solution (BSS) is used to flush the OVD after placing the ICL in the appropriate position (12). Due to limited operating space, OVD residue that has entered the posterior chamber may be challenging to completely wash out, leading to trabecular meshwork blockage and, in severe cases, causing pupil-blocking glaucoma. The streamlined steps for the operation of the min-OVD technique are shown in Figure 1. In recent years, experienced surgeons have introduced a one-step viscosurgical device technique, also known as the minimum ophthalmic viscosurgical device (min-OVD) technique, to address the issue of posterior chamber OVD residue. The min-OVD technique skips the first OVD injection, immediately implanting the ICL after completing the corneal incision. The viscosurgical substance is then injected between the ICL and corneal endothelium, followed by washing the OVD after adjusting the ICL to its proper position. This technique prevents OVD from entering the posterior chamber, significantly reduces the difficulty of thoroughly flushing the OVD, thereby decreasing the occurrence of postoperative elevated intraocular pressure (IOP) and improving surgical quality (13, 14).

Building on the min-OVD technique, some surgeons have proposed the non-ophthalmic viscosurgical device (non-OVD) technique. This approach completely avoids the use of OVD and BSS while maintaining anterior chamber stability during surgery (15–17). Zhang Z et al. compared the safety of min-OVD and non-OVD techniques for ICL implantation by evaluating visual outcomes, corneal endothelial cell density (ECD), and corneal densitometry at 1, 2, 3, and 24 h postoperatively. The results showed no statistically significant differences in visual outcomes between the two groups, while the non-OVD group had significantly shorter surgical times, and IOP at 1 and 2 h postoperatively was significantly lower than that in the min-OVD group (17). The non-OVD technique may be a safer method for ICL implantation as it completely eliminates ocular viscosurgical device-related complications. However, this method also forfeits the positive effects of viscosurgical substances, potentially leading to issues such as anterior chamber disappearance, operational challenges, and loss of corneal endothelial cells. Therefore, surgeons may choose the OVD application method based on their experience.

Management Strategy: If patients experience symptoms such as eye swelling, headache, or nausea and vomiting within 24 h after ICL surgery, the possibility of postoperative OVD residue should be considered. After sufficient communication with the patient, removing the eye dressing and conducting slit-lamp observation and IOP measurement is recommended. If the IOP in the operated eye is only mildly elevated, short-term application of ocular hypotensive eye drops may be considered. If the intraocular pressure in the operated eye exceeds 30 mmHg and continues to rise, considering another anterior chamber washout is advisable to thoroughly remove the remaining viscosurgical substance, thus preventing further visual function damage caused by acute elevated IOP.

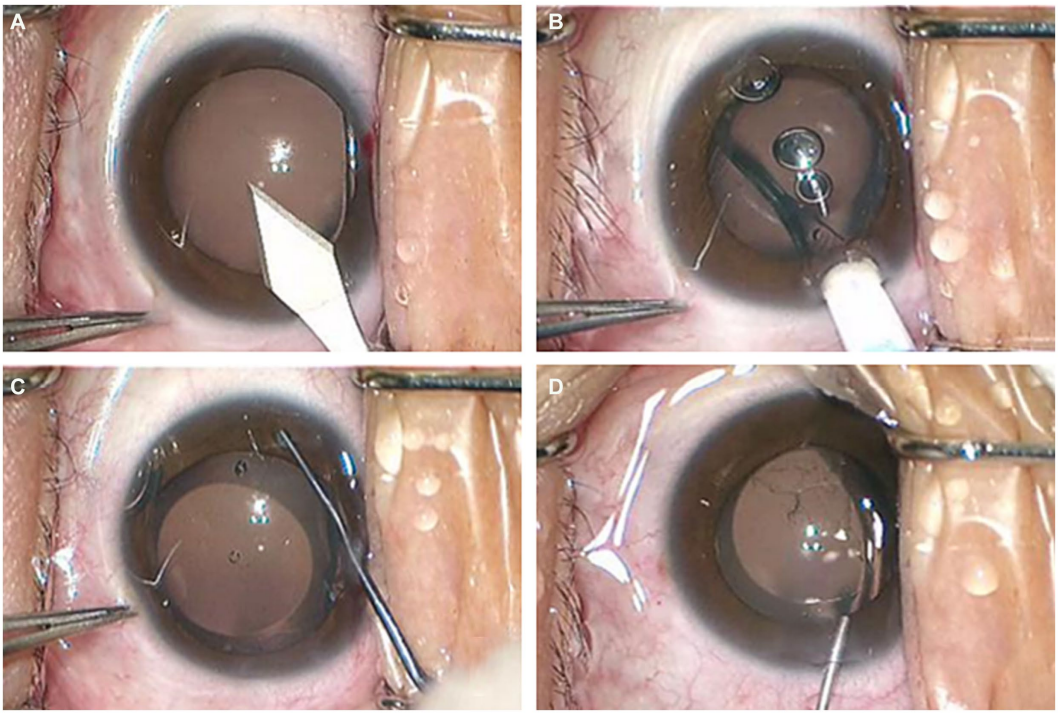

FIGURE 1
The streamlined steps for the operation of the min-OVD technique. **(A)** incision in the temporal transparent cornea; **(B)** implantation of ICL; **(C)** injection of the OVD into the anterior chamber and adjust the lens to proper position; **(D)** thoroughly flushing the OVD.

3 Steroid response

The second peak of elevated IOP after ICL surgery typically occurs between 1 to 4 weeks postoperatively. Steroid-induced ocular hypertension (SIOH) is the primary cause of IOP elevation after ICL surgery, accounting for approximately 64% of cases due to routine local application of corticosteroid eye drops. The concept of SIOH is generally defined as an IOP increase of >10 mmHg compared to the baseline after corticosteroid use, with clinical significance. In the general population, SIOH is estimated to occur in approximately 15–30% of cases (9, 18, 19). SIOH may lead to further damage to the optic nerve and visual function, resulting in steroid-induced glaucoma (SIG) (20).

The exact mechanisms of SIOH and SIG are not fully understood, but a reduction in trabecular meshwork outflow is considered a major contributor to elevated IOP (18). Cortisol, as the most crucial human glucocorticoid, plays a vital role in stress responses and the regulation of natural feedback mechanisms, suppressing inflammatory reactions. Therefore, glucocorticoids have broad pharmacological applications for treating various diseases. Through membrane diffusion and binding to intracellular receptors, glucocorticoids initiate a cascade of signaling events, ultimately affecting the expression of hundreds of genes. This implies a highly individualized response potential to glucocorticoid treatment, including adverse reactions in susceptible patients. The results of the first polymorphic whole-genome association study designed to identify genetic variations related to SIOH revealed two new genes, GPR158 and HCG22, associated with the disease, offering prospects for prediction and diagnosis (20). In addition to specific genetic mutations, various risk factors have been identified, primarily including a personal or family history of primary open-angle glaucoma (POAG), with the type, route of administration, dosage, and duration of treatment also playing crucial roles (19, 21). The Precision Medicine Initiative announced by President Obama in the 2015 State of the Union address outlined how it would extend to ophthalmic practice, presenting an opportunity for the effective application of precision medicine in SIOH/SIG (20).

Management Strategy: High-risk patients receiving corticosteroid therapy after ICL surgery should be closely monitored. If elevated eye pressure occurs between 1 to 4 weeks postoperatively, discontinuation or replacement with a lower-potency corticosteroid is recommended, accompanied by the topical application of glaucoma medications. In most SIOH patients, eye pressure typically returns to normal within 1 to 4 weeks after discontinuing steroids. However, approximately 1–5% of patients show no response to medication and require further glaucoma surgical intervention. The most commonly used procedure is trabeculectomy, but drainage device implantation or cyclodestructive surgery can also be considered (19).

4 Excessive ICL vault

ICL vault refers to the space between the ICL and the natural lens or iris of the eye. The height of the vault is an important factor in determining the postoperative results of ICL implantation surgery (22). If the vault is too low, it can lead to contact between the ICL and the natural lens or iris, causing potential complications such as cataract formation or pigment dispersion syndrome. On the other hand, if the vault is too high, it can lead to increased IOP and potential complications such as glaucoma (23, 24). Figure 2 shown the excessive

vault after ICL implantation, causing stenosis of the anterior chamber angle. Previous studies have investigated the effect of ICL vault height on postoperative results，they found that a vault height of 250–750 microns is generally considered ideal for optimal postoperative outcomes. A vault within this range minimizes the risk of complications such as cataract formation and pigment dispersion syndrome while also reducing the risk of increased IOP (2).

Although the exact mechanism of IOP caused by excessive ICL vault needs to be further explored, existing studies suggest that may be related to mechanical compression, inflammation and pigment dispersion (25, 26). First, the excessive ICL vault can cause mechanical compression of the surrounding structures, including the ciliary body and the iris. This compression can directly cause the ciliary body obstruct and the anterior chamber angle narrow or closure, potentially affecting the production and drainage of aqueous humor, leading to IOP. Furthermore, excessive vault can also lead to inflammation and pigment dispersion syndrome, where inflammatory and pigment granules from the iris are released into the anterior chamber. These cause the aqueous humor outflow blockage and resistance, leading to IOP. IOP due to excessive ICL vault after surgery can present with various clinical signs, including anterior chamber shallowing, corneal edema, iridocorneal touch, even if glaucomatous optic nerve changes (27). When such signs appear after operation, we should consider the possibility of IOP caused by excessive ICL vault.

Various factors can affect the position and stability of the ICL within the eye, ultimately impacting the vault, which including ICL size and power, anterior chamber depth (ACD), crystalline lens rise (CLR), angle Kappa, iris configuration, surgical technique, postoperative position, intraocular pressure and natural lens movement (28–30). The study showed that ICL diameter and ACD were the most influential factors, a relatively larger ICL diameter and a greater preoperative ACD directly result in higher postoperative vault. In addition, CLR, refers to the anterior movement of the natural crystalline lens within the eye, is also an important factor in ICL surgery (31). CRL can affect the position and movement of the natural lens and the ICL, excessive CLR can lead to potential complications such as contact between the ICL and the natural lens, which may result in elevated IOP. Therefore, accurate preoperative ocular measurements, such as ACD, white-to-white (WTW) distance, angle-to-angle (ATA) distance, angle Kappa, accommodative amplitude, sulcus-to-sulcus (STS) diameter and anterior segment optical coherence tomography (AS-OCT) are very important for preoperative crystal selection and appropriate postoperative ICL vault prediction (22, 32, 33).

Management Strategies: Prior to surgery, precise measurements of various anterior segment parameters can be obtained through devices such as AS-OCT, Ultrasound Biomicroscopy (UBM), and Anterior Segment Comprehensive Analyzer (Pentacam). By considering multiple factors and using predictive equations, a reasonable selection of ICL size can be made, greatly reducing the risk of postoperative elevated IOP due to excessive vault. Where device availability permits, intraoperative use of OCT assisted ICL implantation helps to achieve the ideal vault (34). After ICL implantation, regular observation of vault changes using slit-lamp microscopy and AS-OCT can help prevent early elevated IOP and glaucoma, thus avoiding late-stage vision impairment (35). Figure 3 shows observation of lens vault using slit lamp after ICL implantation. Since the axial rotation of the ICL can lead to changes in vault height, the axial variations after ICL implantation should also be considered as indicators for long-term observation. If postoperative vault is excessively high and causes an increase in IOP, timely use of antiglaucoma medications to lower IOP is recommended to prevent further damage to the eyes. Furthermore, if the patient was implanted with a lens that is not a toric ICL, the vault can usually be reduced by rotating the lens in the vertical axis (36, 37). In cases of pupillary block glaucoma, laser iridotomy or iridectomy may be necessary, and if needed, the ICL should be promptly removed.

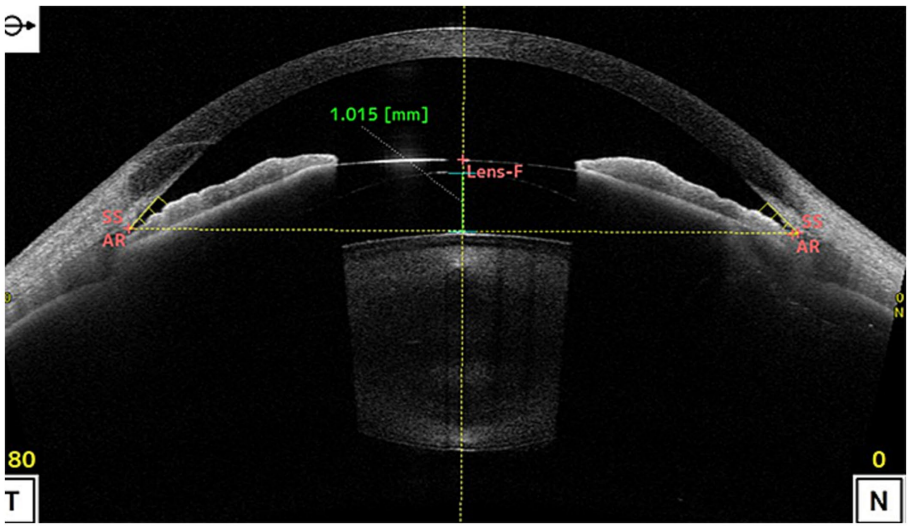

FIGURE 2
shows the vault was as high as 1.015 mm after ICL implantation, causing stenosis of the anterior chamber angle. (SS, scleral spur; AR, angle recess; Lens-F, lens anterior surface intersection. The horizontal yellow dotted line is the SS connection line, and the vertical yellow dotted line is the mid-penetration line of the SS connection line. The green dotted line is the indicator line of the crystal vault).

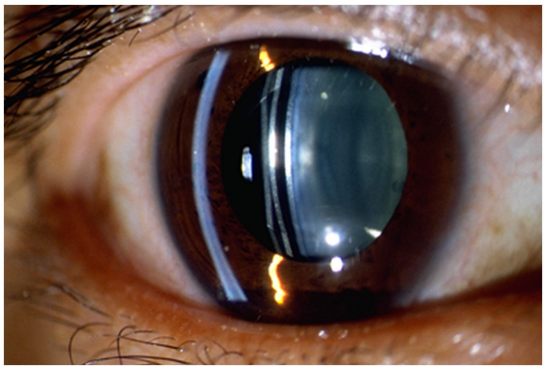

FIGURE 3
Shows observation of lens vault using slit lamp after ICL implantation.

5 Toxic anterior segment syndrome

Toxic Anterior Segment Syndrome (TASS) is a rare and potentially destructive aseptic inflammatory reaction occurring in intraocular surgery. It is associated with the entry of various non-infectious toxic substances into the anterior segment of the eye. Unlike infectious endophthalmitis, this inflammatory reaction is limited to the anterior segment, and Gram stain and bacterial cultures of aqueous and vitreous humor are negative. Known major causes include preservatives in ophthalmic solutions, denatured viscoelastic substances, bacterial endotoxins, and inflammation induced by artificial intraocular lenses (38). Although ICL implantation surgery is less time-consuming and involves fewer steps, the entry of non-infectious toxic substances is difficult to avoid, and there have been occasional reports of TASS occurring after ICL implantation (39–41). TASS typically manifests acutely within 12 to 48 h postoperatively, with some cases exhibiting delayed reactions. Key symptoms include elevated intraocular pressure, corneal edema, and other anterior segment inflammatory reactions. In severe cases, fibrinous exudation in the anterior chamber and even purulent accumulation may occur. The primary mechanism leading to increased intraocular pressure in TASS is the early inflammatory exudate blocking the trabecular meshwork, resulting in elevated intraocular pressure. Some reports also suggest that severe inflammatory reactions triggered by TASS can lead to iris adhesions, causing pupillary block and ultimately resulting in acute elevation of intraocular pressure. TASS may also cause permanent damage to the trabecular meshwork, leading to chronic elevation of intraocular pressure (41).

Management Strategy: The most critical differential diagnosis for TASS is infectious endophthalmitis. The management of TASS should primarily focus on prevention because once toxic substances enter the eye, clinicians have limited measures to address the ensuing inflammatory response. Early diagnosis and treatment of TASS are crucial for maintaining the integrity of eye function and structure, and timely intervention can result in 100% recovery without sequelae. The primary treatment for TASS involves the topical or systemic application of corticosteroids. Corticosteroid eye drops should be instilled every 1–2 h, especially on the first day of onset, to prevent the progression of inflammatory reactions. Routine anterior chamber irrigation should not be performed for severe anterior chamber reactions to avoid exacerbating anterior chamber damage. Daily examinations using slit-lamp microscopy and intraocular pressure measurements are essential. Once intraocular pressure is under control and the cornea becomes transparent, signs of damage to the angle should be examined. The prognosis of TASS depends on the type, quantity, and duration of exposure to toxic substances. If the inflammatory response is mild, recovery can occur within days to weeks. In cases of moderate severity, recovery may take weeks to months, with the possibility of residual corneal edema and mild intraocular pressure elevation. Severe cases may result in permanent corneal opacity and secondary glaucoma, requiring medical or even surgical treatment.

6 Urrets-Zavalia syndrome

Urrets-Zavalia Syndrome (UZS) is an unexplained pupillary dilation that occurs after intraocular surgery. UZS is very uncommon, especially in the implantation of the new generation ICL V4c. Patients typically present with symptoms such as glare, halos, and photophobia. On examination, elevated IOP, enlarged pupils, and unresponsiveness to miotic drugs are observed (42). In addition to these manifestations, UZS can lead to angle closure in the anterior chamber, further increasing IOP and causing significant damage to the patient's eye health (43). Although the syndrome is rare, there have been occasional reports of UZS occurring after ICL implantation (44–46). The exact pathogenesis of UZS after ICL implantation is unclear, but early postoperative elevation of IOP, increased intraocular pressure, and the presence of air or gas in the anterior chamber appear to be significant risk factors for UZS after ophthalmic surgery (42). Immediate control of postoperative elevated intraocular pressure, light responsiveness after dilation, and responsiveness to 2% pilocarpine eye drops have been reported as potential reversible predictive factors for UZS (45). Despite the relatively low reported incidence of UZS, the associated visual symptoms can significantly impact patients' daily lives, necessitating ophthalmologists to take necessary management measures.

Management Strategy: In cases of short-term pupillary dilation combined with elevated intraocular pressure after ICL surgery, UZS should be considered after common complications have been ruled out. Treatment options for UZS include mannitol, topical application of intraocular pressure-lowering medications, removal of air or gas from the anterior chamber, and, if necessary, iris resection to relieve anterior chamber angle closure and prevent the development of secondary glaucoma (42, 43).

7 Pigment dispersion syndrome

Although manufacturers have not reported glaucoma secondary to pigment dispersion as a severe adverse consequence following ICL implantation, occasional cases of PDS after ICL implantation have been documented (47, 48). Pigment Dispersion Syndrome (PDS) is a condition primarily affecting young, myopic adults. The primary mechanism involves the release and deposition of iris pigment in various structures of the anterior segment of the eye. While most patients experiencing pigment dispersion episodes are asymptomatic, extreme photophobia, eye pain, redness, and blurred vision may occur. Other characteristic signs include iris contact, iris concavity, 360° peripheral iris transillumination, increased pigment deposition

in the trabecular meshwork, and pigment deposition on the corneal endothelium (Krukenberg spindle). Due to pigment deposition causing trabecular meshwork blockage and reducing outflow facility, there is an increased risk of elevated IOP and pigment dispersion glaucoma (PDG) (49).

The implantation of the ICL can induce pigment deposition in the trabecular meshwork and elevated IOP in the short term, leading to the development of secondary glaucoma in the late postoperative period. This is primarily attributed to laser iridotomy or iris friction with the ICL. However, there are also reports suggesting that the implantation of ICL has no effect on pigment changes in the trabecular meshwork (50). Conversely, the results of a prospective observational study indicate a significant improvement in the morphology of iris concavity in highly myopic patients after EVO ICL implantation, reducing the risk of intraocular pigment dispersion caused by iris concavity (51).

Management Strategy: Given the risk of permanent visual field loss, both patients and healthcare professionals should be aware that PDG is a serious postoperative complication that threatens vision. Due to the dynamic changes in the posterior chamber over time, PDG may occur several years after the implantation of the ICL. Therefore, close monitoring of IOP is essential, and meticulous slit-lamp examinations should be conducted to assess signs of pigment dispersion, including increased pigment deposition observed in the angle during gonioscopy. UBM and AS-OCT can aid in evaluating changes in ICL positioning over time. Once PDG and secondary elevation of IOP occur, prompt management with IOP-lowering and anti-inflammatory treatments is warranted. If necessary, ICL removal should be considered to reduce friction between the lens and the iris. Multiple studies have confirmed the safety and effectiveness of filtration surgery in treating pigmentary glaucoma, but evidence supporting minimally invasive glaucoma surgery for pigmentary glaucoma is currently insufficient (47, 52).

8 Malignant glaucoma

Malignant glaucoma is a rare and alarming complication, with few reported cases following ICL implantation (53–55). If not promptly addressed, the condition of malignant glaucoma can persist, eventually leading to corneal decompensation, glaucomatous optic neuropathy, and blindness. The mechanism behind malignant glaucoma is not yet fully understood, and the most widely accepted theory is Shaffer's proposal that anterior rotation of the ciliary body causes aqueous to accumulate in the vitreous cavity (56). In a study by Senthil et al., researchers suggested that the occurrence of malignant glaucoma after ICL surgery may be due to stimulation and inflammatory reactions to the ciliary body following ICL placement, resulting in anterior rotation of the ciliary body, shallowing of the anterior chamber (AC), and misdirection of aqueous humor into the vitreous cavity (54). There are also reports suggesting that the cause of malignant glaucoma after ICL implantation could be an undersized ICL, leading to congestion of the ciliary body and damage to the zonules, resulting in relatively poor forward flow of aqueous humor, forcing a reverse flow into the vitreous cavity, ultimately forming a malignant cycle (53).

Management Strategy: The diagnosis of malignant glaucoma after ICL surgery is primarily based on clinical manifestations such as postoperative elevated IOP, corneal edema, and anterior chamber disappearance. It is crucial to exclude conditions such as pupil block, excessively high ICL vault, and suprachoroidal hemorrhage. Once malignant glaucoma is confirmed, prompt resolution of aqueous humor blockade is imperative. Drug therapy is the first-line treatment for malignant glaucoma, involving the local use of potent ciliary muscle paralytics, topical anti-inflammatory drugs, and aqueous humor suppressants, coupled with systemic administration of hyperosmotic agents. If conservative treatment proves ineffective, further interventions such as vitrectomy combined with iridotomy or iridectomy, with or without ICL removal, may be necessary (54, 55, 57).

9 Discussion

In summary, as a widely used surgical method for myopia correction, ICL implantation still presents various complications, with IOP elevation being a relatively common occurrence. This paper provides a comprehensive analysis of the causes of IOP elevation after ICL implantation and management strategies, as summarized in Table 1. The aim is to offer ICL surgeons an in-depth reference to enhance the safety of the procedure, reduce the risk of complications, and provide patients with better corrective options. Future research could further explore predictive factors for IOP elevation after ICL surgery, safer surgical techniques, and more effective treatment methods to continuously optimize the outcomes of this corrective approach.

Author contributions

DG: Writing – original draft, Writing – review & editing. SD: Conceptualization, Investigation, Writing – original draft. KD: Conceptualization, Writing – original draft. ZY: Project administration, Supervision, Writing – review & editing. JW: Funding acquisition, Project administration, Supervision, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was funded by the Shenzhen Fund for Guangdong Provincial High-level Clinical Key Specialties (No. SZGSP014), funded by the National Nature Science Foundation of China (No. 82070961), funded by the Shenzhen Key Medical Discipline Construction Fund (No. SZXK037), funded by the Shenzhen Science and Technology Program (No. JCYJ20220818103207015), funded by the SanMing Project of Medicine in Shenzhen (No. SZSM202311012).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

TABLE 1 Causes of elevated IOP after ICL implantation and management strategies.

Causes	Clinical manifestation	Management strategies
Residual ophthalmic viscosurgical device	Intolerable ocular pain and corneal epithelial oedema in the first 24 h. Peak intraocular pressure (IOP) is usually 30 mmHg or higher, and residual viscoelastic in the anterior chamber can be observed by slit lamp.	1. Surgeons can choose the OVD application method based on their own experience. 2. If the IOP is only mildly elevated, short-term application of ocular hypotensive eye drops may be considered. 3. If the IOP exceeds 30 mmHg and continues to rise, it is advisable to consider re-flushing the anterior chamber to thoroughly remove the remaining viscosurgical substance.
Steroid response	IOP elevation usually occurs 1 to 4 weeks after surgery.	1. Discontinuation or replacement with a lower-potency corticosteroid is recommended, accompanied by the topical application of glaucoma medications. 2. If the intraocular pressure continues to rise, further surgical treatment is required. The most common surgery is trabeculectomy, but implantation of a drainage device or ciliary disruption may also be considered.
Excessive ICL vault	Corneal oedema, anterior chamber shallowness, iridocorneal contact, and imaging findings suggesting an vault>750um can be observed after surgery.	1. Precise measurement of various anterior segment parameters before surgery, and reasonable selection of ICL model. 2. If conditions permit, OCT can be used during surgery. 3. Use slit lamp microscope and AS-OCT to observe the crystalline arch regularly after surgery. 4. Apply glaucoma medications to reduce IOP in a prompt period of time. 5. If the patient has a lens that is not a toric ICL, the vault can usually be lowered by rotating the lens in the vertical axis. 6. In cases of pupillary block glaucoma, laser iridotomy or iridectomy may be necessary, and if needed, the ICL should be promptly removed.
Toxic anterior segment syndrome (TASS)	Acute manifestation within 12–48 h after surgery, with the main symptoms including elevated IOP, corneal oedema and other anterior segment inflammatory reactions	1. Excluding infectious endophthalmitis 2. The main method is topical or systemic application of steroids. 3. The routine anterior chamber flushing should not be carried out, which may aggravate the damage of the anterior chamber.
Urrets-Zavalia syndrome (UZS)	Early postoperative symptoms such as glare, halos and photophobia, signs such as increased intraocular pressure, pupil dilation and unresponsiveness to pupillary medication can be observed.	1. Mannitol, topical use of drugs to reduce intraocular pressure. 2. Remove air or gas from the anterior chamber. 3. If necessary, iridectomy can be conducted to alleviate the closure of the anterior chamber angle.
Pigment dispersion syndrome (PDS)	Induced in the short-term postoperative period, may present with extreme photophobia, ocular pain, eye redness and blurred vision, with signs including iris contact, iris concavity, 360° peripheral iris transillumination, increased pigment deposition in the trabecular meshwork, and pigment deposition on the corneal endothelium (Krukenberg spindle).	1. Detailed slit lamp examination to assess for signs of pigment dispersio. 2. IOP lowering and anti-inflammatory therapy should be performed as soon as PDG and secondary IOP elevation are present. 3. Consider removal of the ICL if necessary to reduce friction between the lens and the iris. 4. Filtration surgery is safe and effective in the treatment of pigmentary glaucoma.
Malignant glaucoma	Elevated IOP, corneal edema and anterior chamber disappearance occurred in the early postoperative period.	1. exclude conditions such as pupil block, excessively high ICL vault, and suprachoroidal hemorrhag. 2. Pharmacological treatment is the first line of treatment for malignant glaucoma, including topical potent ciliary muscle paralysers, topical anti-inflammatory agents and aqueous humor inhibitors, as well as systemic hypertonic agents. 3. If conservative treatment is not effective, further surgical intervention is required, such as vitrectomy combined with iridotomy or iridectomy, with or without removal of the ICL.

Publisher's note

References

1. D'Oria F, Bagaglia SA, Alio del Barrio JL, Alessio G, Alio JL, Mazzotta C. Refractive surgical correction and treatment of keratoconus. *Surv Ophthalmol.* (2024) 69:122–39. doi: 10.1016/j.survophthal.2023.09.005

2. Montés-Micó R, Ruiz-Mesa R, Rodríguez-Prats JL, Tañá-Rivero P. Posterior-chamber phakic implantable collamer lenses with a central port: a review. *Acta Ophthalmol.* (2021) 99:e288–301. doi: 10.1111/aos.14599

3. Higueras-Esteban A, Ortiz-Gomariz A, Gutiérrez-Ortega R, Villa-Collar C, Abad-Montes JP, Fernandes P, et al. Intraocular pressure after implantation of the Visian implantable Collamer Lens with CentraFLOW without iridotomy. *Am J Ophthalmol.* (2013) 156:800–805.e1. doi: 10.1016/j.ajo.2013.05.018

4. Shiratani T, Shimizu K, Fujisawa K, Uga S, Nagano K, Murakami Y. Crystalline lens changes in porcine eyes with implanted phakic IOL (ICL) with a central hole. *Graefes Arch Clin Exp Ophthalmol.* (2008) 246:719–28. doi: 10.1007/s00417-007-0759-2

5. Fernández-Vigo JI, Macarro-Merino A, Fernández-Francos J, de-Pablo-Gómez-de-Liaño L, Martínez-de-la-Casa JM, García-Feijóo J, et al. Computational study of aqueous humor dynamics assessing the vault and the pupil diameter in two posterior-chamber Phakic lenses. *Invest Ophthalmol Vis Sci.* (2016) 57:4625–31. doi: 10.1167/iovs.16-19900

6. Chen X, Wang X, Xu Y, Cheng M, Han T, Wang X, et al. Long-term comparison of vault and complications of implantable Collamer Lens with and without a central hole for high myopia correction: 5 years. *Curr Eye Res.* (2022) 47:540–6. doi: 10.1080/02713683.2021.2012202

7. Wannapanich T, Kasetsuwan N, Reinprayoon U. Intraocular implantable Collamer Lens with a central hole implantation: safety, efficacy, and patient outcomes. *Clin Ophthalmol.* (2023) 17:969–80. doi: 10.2147/OPTH.S379856

8. Zhang H, Gong R, Zhang X, Deng Y. Analysis of perioperative problems related to intraocular implantable Collamer Lens (ICL) implantation. *Int Ophthalmol.* (2022) 42:3625–41. doi: 10.1007/s10792-022-02355-w

9. Almalki S, Abubaker A, Alsabaani NA, Edward DP. Causes of elevated intraocular pressure following implantation of phakic intraocular lenses for myopia. *Int Ophthalmol.* (2016) 36:259–65. doi: 10.1007/s10792-015-0112-4

10. Gerberich AJ, Ipema HJ. A primer on ocular viscosurgical devices. *Am J Health Syst Pharm*. (2021) 78:2020–32. doi: 10.1093/ajhp/zxab228

11. Ganesh S, Brar S. Comparison of surgical time and IOP spikes with two ophthalmic viscosurgical devices following Visian STAAR (ICL, V4c model) insertion in the immediate postoperative period. *Clin Ophthalmol*. (2016) 10:207–11. doi: 10.2147/OPTH.S89487

12. Chen X, Shen Y, Xu H, Wang X, Zhou X. One-year natural course of corneal densitometry in high myopic patients after implantation of an implantable collamer lens (model V4c). *BMC Ophthalmol*. (2020) 20:50. doi: 10.1186/s12886-020-1320-x

13. Miao HM, Zhao F, Niu LL, Zhao J, Wang XY, Zhao XT. One-step viscoelastic agent technique for ICL V4c implantation for myopia. *Int J Ophthalmol*. (2021) 14:1359–64. doi: 10.18240/ijo.2021.09.10

14. Chen D, Cui G, Wang X, Li Y, Luo Y. Safety of the minimum ophthalmic Viscosurgical device technique in Phakic implantable Collamer Lens implantation. *J Refract Surg*. (2020) 36:42–8. doi: 10.3928/1081597X-20191119-02

15. Pan AP, Wen LJ, Shao X, Zhou KJ, Wang QM, Qu J, et al. A novel ophthalmic viscosurgical device-free phakic intraocular lens implantation makes myopic surgery safer. *Eye Vis*. (2020) 7:18. doi: 10.1186/s40662-020-00185-4

16. Kim BK, Chung YT. Comparison of clinical outcomes of implantable collamer lens implantation with and without use of an ophthalmic viscosurgical device. *J Cataract Refract Surg*. (2021) 47:198–203. doi: 10.1097/j.jcrs.0000000000000417

17. Zhang Z, Niu L, Zhao J, Miao H, Chen Z, Shen Y, et al. Safety of EVO ICL implantation with an ophthalmic Viscosurgical device-free technique in the early 24 h after surgery. *Front Med*. (2021) 8:764653. doi: 10.3389/fmed.2021.764653

18. Razeghinejad MR, Katz LJ. Steroid-induced iatrogenic glaucoma. *Ophthalmic Res*. (2012) 47:66–80. doi: 10.1159/000328630

19. Roberti G, Oddone F, Agnifili L, Katsanos A, Michelessi M, Mastropasqua L, et al. Steroid-induced glaucoma: epidemiology, pathophysiology, and clinical management. *Surv Ophthalmol*. (2020) 65:458–72. doi: 10.1016/j.survophthal.2020.01.002

20. Fini ME, Schwartz SG, Gao X, Jeong S, Patel N, Itakura T, et al. Steroid-induced ocular hypertension/glaucoma: focus on pharmacogenomics and implications for precision medicine. *Prog Retin Eye Res*. (2017) 56:58–83. doi: 10.1016/j.preteyeres.2016.09.003

21. Abouzeid H, Sintzoff L. Corticosteroids and glaucoma. *Rev Med Suisse*. (2023) 19:643–7. doi: 10.53738/REVMED.2023.19.820.643

22. Alfonso JF, Fernández-Vega L, Lisa C, Fernandes P, Jorge J, Micó RM. Central vault after phakic intraocular lens implantation: correlation with anterior chamber depth, white-to-white distance, spherical equivalent, and patient age. *J Cataract Refract Surg*. (2012) 38:46–53. doi: 10.1016/j.jcrs.2011.07.035

23. Gimbel HV, LeClair BM, Jabo B, Marzouk H. Incidence of implantable Collamer lens-induced cataract. *Can J Ophthalmol*. (2018) 53:518–22. doi: 10.1016/j.jcjo.2017.11.018

24. Choi JH, Lim DH, Nam SW, Yang CM, Chung ES, Chung TY. Ten-year clinical outcomes after implantation of a posterior chamber phakic intraocular lens for myopia. *J Cataract Refract Surg*. (2019) 45:1555–61. doi: 10.1016/j.jcrs.2019.06.015

25. Fernandes P, González-Méijome JM, Madrid-Costa D, Ferrer-Blasco T, Jorge J, Montés-Micó R. Implantable collamer posterior chamber intraocular lenses: a review of potential complications. *J Refract Surg*. (2011) 27:765–76. doi: 10.3928/1081597X-20110617-01

26. Packer M. The implantable Collamer Lens with a central port: review of the literature. *Clin Ophthalmol*. (2018) 12:2427–38. doi: 10.2147/OPTH.S188785

27. Shen Y, Chen X, Xian Y, Wang X, Wang X, Zhou X. Safety of intraocular pressure measurement using air-puff tonometer after implantable collamer lens implantation. *J Cataract Refract Surg*. (2022) 48:900–5. doi: 10.1097/j.jcrs.0000000000000886

28. Trancón AS, Manito SC, Sierra OT, Baptista AM, Serra PM. Determining vault size in implantable collamer lenses: preoperative anatomy and lens parameters. *J Cataract Refract Surg*. (2020) 46:728–36. doi: 10.1097/j.jcrs.0000000000000146

29. Igarashi A, Shimizu K, Kato S, Kamiya K. Predictability of the vault after posterior chamber phakic intraocular lens implantation using anterior segment optical coherence tomography. *J Cataract Refract Surg*. (2019) 45:1099–104. doi: 10.1016/j.jcrs.2019.02.020

30. Chen X, Miao H, Naidu RK, Wang X, Zhou X. Comparison of early changes in and factors affecting vault following posterior chamber phakic implantable Collamer Lens implantation without and with a central hole (ICL V4 and ICL V4c). *BMC Ophthalmol*. (2016) 16:161. doi: 10.1186/s12886-016-0336-8

31. Fan L, Chang Z, Xu Y, Yin X, Wang Z. The non-uniform distribution of horizontal and vertical crystalline Lens rise using optical coherence tomography. *J Refract Surg*. (2023) 39:354–9. doi: 10.3928/1081597X-20230207-02

32. Hu X, Wang P, Zhu C, Yuan Y, Liu M, Ke B. Transient reduction in the retinal microvascular network following implantation surgery of implantable collamer lens: an OCT angiography study. *Mol Vis*. (2021) 27:466–79.

33. Tang C, Chen J, Liu Y, Sun T, Duan H, Liu Y, et al. Assessing the efficacy of four methods established by four parameters in ICL size selection and relevant influencing factors: a prospective cohort study. *Int Ophthalmol*. (2023) 43:4861–7. doi: 10.1007/s10792-023-02888-8

34. Zaldivar R, Zaldivar R, Adamek P, Cerviño A. Intraoperative adjustment of implantable collamer lens vault by lens rotation aided by intraoperative OCT. *J Cataract Refract Surg*. (2022) 48:999–1003. doi: 10.1097/j.jcrs.0000000000000915

35. Tang C, Sun T, Sun Z, Duan H, Liu Y, Zhao L, et al. Evaluation of biometric indicators of anterior segment parameters after ICL implantation by swept-source optical coherence tomography. *BMC Ophthalmol*. (2023) 23:193. doi: 10.1186/s12886-023-02942-0

36. Matarazzo F, Day AC, Fernandez-Vega Cueto L, Maurino V. Vertical implantable collamer lens (ICL) rotation for the management of high vault due to lens oversizing. *Int Ophthalmol*. (2018) 38:2689–92. doi: 10.1007/s10792-017-0757-2

37. Jiang Y, Luo Y, Li Y, Lu T. The long-term observation of the rotation of implantable collamer lens as the management of high postoperative vault. *Front Med*. (2023) 10:1104047. doi: 10.3389/fmed.2023.1104047

38. Cornut PL, Chiquet C. Toxic anterior segment syndrome. *J Fr Ophtalmol*. (2011) 34:58–62. doi: 10.1016/j.jfo.2010.08.006

39. Pintiliuc C, Ricaud X, Costantini E. Toxic anterior segment syndrome following EyePCL implantation in a hyperopic patient. *J Fr Ophtalmol*. (2022) 45:272–6. doi: 10.1016/j.jfo.2021.12.009

40. Singh A, Gupta N, Kumar V, Tandon R. Toxic anterior segment syndrome following phakic posterior chamber IOL: a rarity. *BMJ Case Rep*. (2018) 11. doi: 10.1136/bcr-2018-225806

41. Mimouni M, Alio Del Barrio JL, Alio JL. Occlusion of AquaPORT flow in a case of toxic anterior segment syndrome following implantable Collamer Lens surgery causing severe pupillary block. *J Refract Surg*. (2020) 36:856–9. doi: 10.3928/1081597X-20201015-01

42. Magalhães OA, Kronbauer CL, Müller EG, Sanvicente CT. Update and review of Urrets-Zavalia syndrome. *Arq Bras Oftalmol*. (2016) 79:202–4. doi: 10.5935/0004-2749.20160059

43. Narang P, Narang R. Innovation Urrets-Zavalia syndrome. *Indian J Ophthalmol*. (2022) 70:3166. doi: 10.4103/ijo.IJO_896_22

44. Al Habash A, Al Arfaj K, Al Abdulsalam O. Urrets-Zavalia syndrome after implantable Collamer lens placement. *Digit J Ophthalmol*. (2015) 21:1–11. doi: 10.5693/djo.02.2014.09.002

45. Niruthisard D, Kasetsuwan N. Unilateral Urrets-Zavalia syndrome after implantable Collamer Lens implantation: a case report and review of the literature. *J Med Case Rep*. (2021) 15:467. doi: 10.1186/s13256-021-03063-2

46. Fraenkel D, Hamon L, Weinstein I, Seitz B, Daas L. Urrets-Zavalia syndrome after implantation of a Phakic intraocular Lens. *Klin Monatsbl Augenheilkd*. (2023) 240:77–9. doi: 10.1055/a-1610-9239

47. Ye C, Patel CK, Momont AC, Liu Y. Advanced pigment dispersion glaucoma secondary to phakic intraocular collamer lens implant. *Am J Ophthalmol Case Rep*. (2018) 10:65–7. doi: 10.1016/j.ajoc.2018.01.046

48. Brandt JD, Mockovak ME, Chayet A. Pigmentary dispersion syndrome induced by a posterior chamber phakic refractive lens. *Am J Ophthalmol*. (2001) 131:260–3. doi: 10.1016/S0002-9394(00)00606-1

49. Bustamante-Arias A, Ruiz-Lozano RE, Carlos Alvarez-Guzman J, Gonzalez-Godinez S, Rodriguez-Garcia A. Pigment dispersion syndrome and its implications for glaucoma. *Surv Ophthalmol*. (2021) 66:743–60. doi: 10.1016/j.survophthal.2021.01.002

50. Chun YS, Park IK, Lee HI, Lee JH, Kim JC. Iris and trabecular meshwork pigment changes after posterior chamber phakic intraocular lens implantation. *J Cataract Refract Surg*. (2006) 32:1452–8. doi: 10.1016/j.jcrs.2006.04.023

51. Zhang Z, Niu L, Liu T, Shen Y, Shang J, Zhao J, et al. Primary observations of EVO ICL implantation for high myopia with concave iris. *Eye Vis*. (2023) 10:18. doi: 10.1186/s40662-023-00335-4

52. Okafor K, Vinod K, Gedde SJ. Update on pigment dispersion syndrome and pigmentary glaucoma. *Curr Opin Ophthalmol*. (2017) 28:154–60. doi: 10.1097/ICU.0000000000000352

53. Kodjikian L, Gain P, Donate D, Rouberol F, Burillon C. Malignant glaucoma induced by a phakic posterior chamber intraocular lens for myopia. *J Cataract Refract Surg*. (2002) 28:2217–21. doi: 10.1016/S0886-3350(02)01213-0

54. Senthil S, Choudhari NS, Vaddavalli PK, Murthy S, Reddy J, Garudadri CS. Etiology and Management of Raised Intraocular Pressure following posterior chamber Phakic intraocular Lens implantation in myopic eyes. *PLoS One*. (2016) 11:e0165469. doi: 10.1371/journal.pone.0165469

55. Chanbour WA, Cherfan CG, Jarade EF, Khoury JM. Unilateral malignant Glaucoma Postbilateral implantable Collamer Lens: effect of Miotics. *Middle East Afr J Ophthalmol*. (2019) 26:181–3. doi: 10.4103/meajo.MEAJO_197_18

56. Kaushik S. Commentary: malignant Glaucoma - have we finally found an answer? *Indian J Ophthalmol*. (2019) 67:1206–7. doi: 10.4103/ijo.IJO_134_19

57. Unterlauft JD, Schawkat M, Häner N, Lincke J, Zinkernagel MS. Therapy of malignant glaucoma. *Fortschr Ophthalmol*. (2022) 119:1155–9. doi: 10.1007/s00347-022-01718-z

frontiers | Frontiers in Medicine

TYPE Review
PUBLISHED 13 February 2024
DOI 10.3389/fmed.2024.1349496

OPEN ACCESS

EDITED BY
Georgios D. Panos,
Nottingham University Hospitals NHS Trust, United Kingdom

REVIEWED BY
Jin Li,
Wenzhou Medical University, China
Hun Lee,
University of Ulsan, Republic of Korea

*CORRESPONDENCE
Jin Yang
✉ jin_er76@hotmail.com

†These authors have contributed equally to this work

RECEIVED 04 December 2023
ACCEPTED 30 January 2024
PUBLISHED 13 February 2024

CITATION
Lin X, Ma D and Yang J (2024) Insights into the rotational stability of toric intraocular lens implantation: diagnostic approaches, influencing factors and intervention strategies.
Front. Med. 11:1349496.
doi: 10.3389/fmed.2024.1349496

Insights into the rotational stability of toric intraocular lens implantation: diagnostic approaches, influencing factors and intervention strategies

Xuanqiao Lin[1,2,3,4†], Dongmei Ma[1,2,3†] and Jin Yang[1,2,3*]

[1]Eye Institute and Department of Ophthalmology, Eye & ENT Hospital, Fudan University, Shanghai, China, [2]Key NHC Laboratory of Myopia, Fudan University, and Laboratory of Myopia, Chinese Academy of Medical Sciences, Shanghai, China, [3]Shanghai Key Laboratory of Visual Impairment and Restoration, Shanghai, China, [4]Eye Hospital and School of Ophthalmology and Optometry, Wenzhou Medical University, Wenzhou, China

Toric intraocular lenses (IOLs) have been developed to enhance visual acuity impaired by cataracts and correct corneal astigmatism. However, residual astigmatism caused by postoperative rotation of the toric IOL is an important factor affecting visual quality after implantation. To decrease the rotation of the toric IOL, significant advancements have been made in understanding the characteristics of toric IOL rotation, the factors influencing its postoperative rotation, as well as the development of various measurement techniques and interventions to address this issue. It has been established that factors such as the patient's preoperative refractive status, biological parameters, surgical techniques, postoperative care, and long-term management significantly impact the rotational stability of the toric IOL. Clinicians should adopt a personalized approach that considers these factors to minimize the risk of toric IOL rotation and ensure optimal outcomes for each patient. This article reviews the influence of various factors on toric IOL rotational stability. It discusses new challenges that may be encountered to reduce and intervene with rotation after toric IOL implantation in the foreseeable future.

KEYWORDS

astigmatism, cataract surgery, toric intraocular lenses, rotational stability, reposition

1 Introduction

According to various studies, it has been estimated that approximately 15 to 29% of patients with cataracts exhibit corneal or refractive-based astigmatism exceeding 1.5 diopters (D) (1, 2). Cataract surgery, which has evolved into a refractive procedure to reduce patients' dependence on spectacles, can effectively correct regular astigmatism through toric intraocular lens (IOL) implantation (3, 4). However, the rotation of toric IOLs is a significant factor that impacts the visual outcomes (5). Various studies have demonstrated that a misalignment of toric IOLs by approximately 1° can reduce astigmatic correction by approximately 3.3%. Moreover, a misalignment of 30° may fail to correct or even increase astigmatism on a new axis (6, 7). Enhancing the rotational stability of toric IOLs has become a critical focus of contemporary refractive cataract surgery. Recent advancements in technology, particularly in

IOL materials and design, have significantly improved the rotational stability of toric IOLs, leading to more precise visual outcomes (8–10).

This article provides a comprehensive review of the research conducted on the rotational stability of toric IOLs, along with the factors affecting their stability (Table 1).

2 Method to evaluate the rotation of toric IOL

2.1 Subjective measurement method

Rotation can be directly evaluated using a slit lamp equipped with degree marks on the beam, which is considered the gold standard for assessing the rotation of toric IOLs. By aligning the slit beam with the toric IOL axis markings in the dilated eye, the slit-lamp axis position was recorded and compared with the baseline axis position (initial measurement data) to determine the degree of rotation. This method is simple to perform and has minimal equipment requirements; however, it has certain limitations. As this is a subjective measurement method, the patient's head position and other subjective factors can influence the results. Previous studies have shown that this method may have an error range of approximately 1–2 (11).

2.2 Objective measurement method

With the advancement of technology, various objective measurements have become available in clinical practice to assess the rotation of toric IOLs. Wolffsohn proposed a new photography method called digital retroillumination, independent of eye rotation (12). Using iTrace wavefront aberrometry (Tracey Technologies Corp., Houston, TX, United States), the intraocular astigmatic axis of patients was recorded, and the actual axis of the IOLs inside the eye (perpendicular to the intraocular astigmatism axis) was calculated (13). In the study by Lucisano et al. (14), an anterior segment optical coherence tomography system was used to assess the topographic astigmatic axis and the postoperative position of the axis simultaneously. However, when objective devices, inadequate pupil dilation, fibrosis in later stages and senile rings in the elderly can potentially obstruct the accuracy of toric markings (15). Similarly, the issue of improper patient head positioning may arise Therefore, none of these methods have been able to replace the traditional slit-lamp observation. Deep learning, similar toconvolutional neural network (CNN), may potentially enhance the accuracy of analysis.

TABLE 1 Risk factors for rotation of toric IOLs in this review.

	Risk factors
Biological parameters	Long axial length
	Large dimensions of the capsular bag
	With-the-rule and oblique astigmatism
Characteristics of toric IOL	C-loop haptic design
	Polymethyl methacrylate materia
	Small toric IOL diameter
Surgery factors	Inaccuracy in marking
	Unsuitable CCC diameter
	Postoperative hypotonia
	Incomplete removal of the OVD
	Grade 4 ACO
	Nd: YAG laser posterior capsulotomy
	CTR was not implanted
Other risk factors	Excessive physical activity

IOL, intraocular lens; CCC, continuous curvilinear capsulorhexis; OVD, ophthalmic viscosurgical device; ACO, anterior capsular opacification; Nd:YAG, Neodymium:YAG; CTR, capsular tension ring.

3 Characteristics of toric IOL rotation

3.1 The timing of toric IOL rotation

To ensure the timely detection of early postoperative rotation of toric IOLs and maintain long-term visual stability, it is important to investigate the timing and trends of rotational changes in toric IOLs postoperatively. Rotations of the C-loop haptic IOL were observed as early as 1 h after surgery, with most occurring within the initial 10 days (8, 16, 17). Our team recently reached a similar conclusion in plate-haptic toric IOLs (18). The results revealed that most rotations in the toric IOL occurred within the first 3 days postoperatively, with the maximum degree occurring between 1 h and 1 day after surgery. All the patients included in the study underwent outpatient surgery. This necessitated commuting between the hospital and their homes for postoperative examination the following day, which may have contributed to the maximum rotation of the IOL observed between 1 h and 1 day postoperatively. As for the long-term stability, a previous study showed that the diameter of the capsular bag gradually decreased after cataract surgery. This suggests that IOL stability increased as the capsular bag contracted (19). Seth et al. observed that the rotation change between 1 and 3 months after surgery was significantly smaller than at other time points (20). The rotation of the toric IOL may decrease when the anterior and posterior capsules fuse. Capsule fusion typically begins at approximately 2 weeks, and minimal IOL rotation is observed after 1 month.

3.2 The direction of toric IOL rotation

Both clockwise and counterclockwise rotations are possible postoperatively and primarily depend on the IOL design (8, 21). In past studies, the C-loop haptic toric IOL has been described as tending to rotate clockwise (8, 22). However, according to recent research, there is no consensus, as counterclockwise (23) and no direction (24) tendencies have been reported. This can be attributed to a reduction in the circumference of the capsular bag, which may exert pressure on the haptics (25). Regarding the plate-haptic toric IOL, no specific rotation direction has been identified yet (26). Further research is needed to investigate the relationship between the direction of postoperative rotation and the design of toric IOLs.

4 Risk factors for rotation of toric IOL

4.1 Biological parameters and toric IOL rotation

4.1.1 Axial length (AL) and toric IOL rotation

Early studies suggested that the AL of the eye is one of the main factors contributing to the early postoperative rotation of IOLs following cataract surgery (8, 22, 27). Vass et al. (28) indicated that a longer AL may be associated with a wider capsule width, potentially leading to the implantation of mismatched IOLs. Large capsular bags may reduce friction between the capsular bag and the haptic, decreasing IOL stability (29). Furthermore, in cases where the AL is longer, the implanted IOL tends to be thinner and has a smaller volume, further diminishing the contact and friction between the IOL and capsular bag (27). However, He et al. (30) examined rotational stability in patients with an AL > 25 mm and did not find a significant correlation between AL and rotation. This study also found that in eyes with longer AL, there was no positive correlation between AL and capsule diameter. Moreover, previous research has shown that the plate-haptic toric IOL remains relatively stable and is not significantly affected by an increase in AL (25, 31, 32). For patients with a long AL, the implantation of a toric IOL can still be considered a correction for astigmatism. Nonetheless, factors such as fragile zonules and posterior subcapsular cataracts should be considered in patients with highly myopic eyes. In these eyes, the occurrence of capsular contraction syndrome (CCS) and IOL dislocation is relatively higher, relating to these factors, presenting a significant challenge to the stability of toric IOLs (33, 34).

4.1.2 Dimensions of the capsular bag and toric IOL rotation

Earlier investigations have indicated a strong correlation between rotation and the dimensions of the capsular bag (35). However, currently, there are no devices for the direct and accurate measurement of capsular bag size. Consequently, estimations based on parameters such as the white-to-white (WTW) distance (distance between the horizontal borders of the corneal limbus) and the anterior segment length (distance from the corneal endothelium to the posterior crystalline lens) are sometimes used to approximate the capsular bag dimensions (19, 36). It is recommended to subtract 1 mm from the WTW. If WTW exceeds 12.5 mm, it indicates a significant risk of rotation (37). WTW indirectly reflects the horizontal diameter of the lens capsule. Lens thickness (LT) represents the anterior–posterior diameter of the lens capsule (38). Our study found a strong association among LT, age, and toric IOL rotation. Specifically, our results suggest that toric IOLs may have a higher tendency to rotate in eyes aged ≥70 years and with a LT of ≥4.48 mm (18). With age increasing, there are often increases in LT (39). Li et al. (40) reported a similar finding. Consequently, the combined factors of WTW and LT play a synergistic role in determining the volume of the anterior segment and offer a three-dimensional perspective for estimating the bag size. Utilizing these two parameters in conjunction makes it plausible to anticipate a higher level of predictability in the preoperative assessment of rotational stability in toric IOLs (36). However, some studies have suggested no correlation between LT and toric IOL rotation (17, 30). Additional studies are necessary to confirm the relationship between the LT and rotation.

4.1.3 Direction of corneal astigmatism and toric IOL rotation

The direction of corneal astigmatism may determine the orientation of toric IOL implantation, which could be attributed to the different designs of toric IOLs and the diameter of the vertical capsular bag (41, 42). Several studies comparing loop-haptic toric IOLs found that patients with with-the-rule (WTR) and oblique astigmatism are more prone to significant rotational deviations than patients with against-the-rule astigmatism (43, 44). In addition, in a study conducted by Miyake et al. involving 378 eyes, they reported that out of six eyes with the AcrySof IQ toric IOL that experienced IOL rotation of >20°, all had WTR astigmatism (8). A vertically fixated IOL may exhibit a higher propensity for rotation. Regarding the plate-haptic toric IOL, no definitive conclusion indicates a relationship between the rotation of the toric IOL and the direction of corneal astigmatism. In order to achieve precise analysis and calculation of corneal astigmatism, it is essential to develop novel technologies capable of yielding improved data.

4.2 Characteristics of toric IOLs and toric IOL rotation

4.2.1 Shape design and rotation of toric IOL

Toric IOLs can be classified into one- or three-piece designs, with haptic structures available in C-loop or plate haptic configurations. The design of these IOLs is critical for ensuring rotational stability. According to a study by Gyöngyössy et al. (45), one-piece C-loop haptic toric IOLs exhibit excellent long-term rotational stability without postoperative complications.

Kramer et al. compared different brands of C-loop haptic toric IOLs, namely, AcrySof and Tecnis (46). The results revealed that the rotational stability of the AcrySof toric IOL was higher than that of the latter. In a study conducted by Sun et al. (26) the long-term rotational stability of two designs of toric IOLs (AcrySof toric IOL with a C-loop haptic and AT TORBI 709 M IOL with a plate haptic) was comprehensively investigated at the 3-month postoperative mark. The plate-haptic IOL exhibited superior stability compared to the toric IOL with a C-loop haptic (36). The plate-haptic toric IOL was anchored to the capsular bag through its four haptics, resulting in increased friction between the lens and capsular bag, thereby reducing the effects of capsular bag compression and rotation. Additionally, the presence of two positioning holes at the corners of the IOL allowed for the migration of lens epithelial cells, further enhancing the stability of the lens. With its one-piece 'C' shaped loop, the IOL might have had a reduced frictional interaction with the capsular bag due to the space between the lens column and the haptic, potentially leading to IOL rotation. Nevertheless, it has also been reported that the loop-haptic design exhibits excellent memory and flexibility, effectively addressing optical fluctuations resulting from capsular bag shrinkage and ensuring stable positioning within the capsular bag (47). The rotational stability of toric IOLs with different shape designs requires further investigation with larger sample sizes.

Therefore, new designs are being constantly developed. A new type of toric IOL, Mini Toric Ready (SIFI S.p.A.), has recently been introduced to the market (48). This innovative design features four fenestrated haptics that enhance the surface area of contact between the IOL and equator of the capsular bag. Fenestrations also facilitate

interactions between the anterior and posterior capsules of the eye. As a result, this novel IOL demonstrated superior long-term rotational stability compared to the conventional two-haptic toric IOL. In contrast to the previous generation of TECNIS monofocal IOL, the TECNIS Toric II IOL (Johnson & Johnson Vision) has undergone design modification with frosted haptics. This modification aims to increase the friction between the haptic and equator of the capsular bag, leading to a remarkable improvement in postoperative rotational stability compared to its predecessor (49, 50). We can expect the continuous emergence of new toric IOL designs in the future.

4.2.2 Material design and rotation of toric IOL

The first reported toric IOL made of polymethyl methacrylate (PMMA) exhibited substantial postoperative rotation (2). Various materials, including hydrophobic acrylates, hydrophilic acrylates, and silicone gels, can be used to produce toric IOLs. The materials used in IOLs play a significant role in determining their stability. For example, the adhesiveness of the lens surface is believed to promote stability (51). In particular, hydrophobic acrylic IOLs exhibit stronger adhesion owing to the charge effect and higher fibronectin content (26). Prior research has indicated that toric IOLs made with hydrophobic acrylates exhibit superior postoperative rotational stability compared to those made with hydrophilic acrylates (43, 52). The occurrence rate of postoperative complications, such as rotation, may vary depending on the adhesive force of the posterior capsule for different materials of IOLs.

4.2.3 Size and rotation of toric IOL

Toric IOLs with a smaller overall diameter, especially for eyes with larger capsular bags, can alleviate contact between the lens and capsular bags, thus increasing the risk of rotation. Chang et al. (29) found that a Toric IOL with a total diameter of 11.2 mm (Staar AA4203TL) had a lower incidence of rotation than a Toric IOL with a total diameter of 10.8 mm (Staar AA4203TF). Different IOL sizes may result in variations in surgical duration and technique, potentially leading to rotation.

4.3 Surgery factors and toric IOL rotation

4.3.1 Manual marking and computer navigation

Accurate alignment is a fundamental prerequisite for effective refractive correction using toric IOLs. Traditionally, manual marking has been the most frequently described technique for surgical eye marking prior to placing a toric IOL (53). Although the accuracy of manual marking methods is high, computer-guided methods, such as observing plane inconsistencies or tracking dye diffusion, have been developed to overcome the limitations of manual approaches (54). The digital methods are based on previous research, specifically iris fingerprint techniques (55), intraoperative wavefront aberrometry (56), or techniques that use real-time eye tracking based on iris and blood vessel characteristics. Recently, Elhofi et al. (57) found clinically and statistically significant differences between digital and manual marking procedures using Verion, a digital marker published by Alcon Laboratories, Inc. Their findings indicated that preoperative planning and intraocular digital guidance for toric IOL implantation offer advantages over manual marking, resulting in reduced postoperative rotation. Therefore, the Callisto Eye system (Carl Zeiss Meditec AG) is an application of a new virtual reality-based technology that theoretically has the potential to optimize the alignment of artificial IOL and achieve optimal refractive outcomes. It proved that the computer-assisted marker system provided better results than manual marking regarding the postoperative IOL alignment (54). Additionally, using a digital system results in faster intraoperative IOL alignment and shorter overall surgical time (53). In the future, with the involvement of artificial intelligence, we expect improved accuracy and effectiveness of digital marking systems.

4.3.2 Continuous curvilinear capsulorhexis (CCC) and toric IOL rotation

A well-centered CCC that covers approximately 0.5 mm of the IOL is crucial for ensuring the long-term stability of the IOL postoperatively. Insufficient coverage of the IOL owing to excessive tearing of the capsulorhexis causes postoperative rotation. In contrast, a smaller capsulorhexis can lead to anterior capsule contraction, affecting IOL stability. In a study by He et al. (30) there was a positive correlation between TECNIS toric IOL rotation and capsulorhexis size. Therefore, a moderately smaller CCC contributes to improved rotational stability. However, recent studies have attributed the factors affecting IOL rotational stability to the state of anterior capsule coverage over the IOL optical surface, suggesting that complete coverage leads to significantly greater stability than partial coverage. The size of the capsulorhexis did not have a significant impact on rotational stability. Hence, ensuring that the CCC completely covers the IOL optical surface can help achieve postoperative rotational stability without excessively reducing the capsulorhexis size to avoid excessive anterior capsule contraction (17). Considering the commonly used diameter of C-loop toric IOLs in the current market is approximately 6 mm, a capsulorhexis diameter of approximately 5.0–5.5 mm is generally recommended. A retrospective study suggested that the capsulorhexis size is crucial in preventing lens rotation. The study concluded that maintaining a capsulorhexis diameter ranging from 5.0 to 5.8 mm effectively enhanced the rotational stability of Toric IOLs (40). Currently, research on the impact of CCC diameter on the postoperative rotational stability of toric IOLs with plate haptics is limited. Future studies should explore this aspect in greater detail.

4.3.3 Other surgical factors and toric IOL rotation

Studies have shown that postoperative hypotonia and incomplete removal of the ophthalmic viscosurgical device (OVD) can lead to postoperative IOL rotation (58, 59). Postoperative changes in pressure can destabilize the anterior chamber, leading to decreased rotational stability. Tak introduced hydroimplantation, using balanced salt solution (BSS), to maintain anterior chamber shape during the implantation of IOL, instead of using OVD (60). In a study by Chen et al. (61), the hydroimplantation technique yielded outcomes comparable to the conventional technique using an OVD. However, the non-OVD technique offers several advantages, including increased efficiency, reduced surgical time and cost, and elimination of concerns regarding OVD-induced elevated intraocular pressure. Additionally, the hydroimplantation technique ensures complete IOL fixation on the posterior capsule, which is particularly important for AcySof toric IOLs (59). This technique is also beneficial for decreasing the misalignment of toric IOLs during surgery and ensuring postoperative

stability. Further research is needed to explore the impact of these operative factors on rotational stability.

4.4 Anterior capsular opacification (ACO) grade and toric IOL rotation

The grading of ACO is negatively correlated with the degree of rotation of Toric IOLs and is an independent factor affecting long-term rotational stability (27). One contributing factor is the increased adhesion between the IOL and the capsule caused by anterior capsular fibrosis. In addition, capsular shrinkage resulting from capsular fibrosis can reduce the space available for the IOL, thereby enhancing its stability. As a result, preserving some lens epithelial cells (LECs) from the anterior capsule during cortical aspiration may help minimize rotation and subsequently reduce residual astigmatism (RAS) (62). Therefore, among ACO grades 0 to 3, a higher ACO grade may help reduce Toric IOLs' rotation (63). However, grade 4 ACO, characterized by excessive capsular bag contraction, can induce anterior folding of the IOL, leading to optical decentration or tilting and severe visual impairment (64). Besides, ACO and sac shrinkage risks with hydrophobic acrylics are lower than those with hydrophilic acrylics and silica gels (65). Nevertheless, the effects of the materials presented here on rotation contradict those of previous reports, which indicated that the hydrophilic acrylic toric IOL exhibited similar rates of postoperative misalignment and surgical repositioning in comparison to the hydrophobic acrylic toric IOL (43). This suggests the necessity for additional research.

4.5 Neodymium:YAG (Nd:YAG) laser posterior capsulotomy and toric IOL rotation

Posterior capsule opacification (PCO), a postoperative complication, can directly contribute to the asymmetric contraction of the capsular bag, leading to rotational instability of Toric IOLs (66). However, effective research is lacking to establish a direct correlation between the PCO and lens rotation stability. The most commonly used clinical method to treat PCO, Nd: YAG laser posterior capsulotomy, carries the potential risk of inducing rotational instability in toric IOLs (67). Due to the ACO, preserving a certain number of LECs may help improve the rotational stability of toric IOLs. However, the migration of LECs may also further increase the incidence of PCO. Further research is needed to determine whether anterior capsule polishing, as a method for removing residual LECs following cataract surgery, can enhance the rotational stability of toric IOLs.

4.6 Other factors and toric IOL rotation

Excessive physical activity during the early postoperative period is assumed to increase the likelihood of toric IOL rotation, and in a multicenter study conducted by our team, a patient who underwent right-eye toric IOL implantation participated in a marathon race a few days after surgery (68). During the 1-week follow-up, the toric IOL in the patient's right eye rotated by more than 80°. The patient had undergone toric IOL implantation in the left eye a few weeks prior and remained stable postoperatively. Vigorous activity in the early postoperative period may contribute to toric IOL rotation. As significant rotation of toric IOLs typically occurs within the first 3 days after surgery, it is clinically advisable to advise patients to avoid strenuous activities, especially during the first 3 days postoperatively (68).

5 Interventions for toric IOL rotation

5.1 Intraoperative interventions for toric IOL rotation

Previous studies have provided evidence supporting using a capsular tension ring (CTR) to limit the rotation of plate-haptic or C-loop haptic toric IOL (11, 69, 70). After the implantation of the CTR, the capsular sac is effectively supported, enhancing its symmetry. The anterior capsules tightened, reducing the contraction of the anterior capsule. In contrast, the posterior capsule closely adheres to the optical portion of the IOL, reducing the asymmetrical contraction of the capsular bag and minimizing the tilt and eccentricity of the IOL, thereby increasing rotational stability. Additionally, by reducing the gap between the posterior capsule and the IOL, the migration and proliferation of lens epithelial cells are prevented, which further contributes to the improved rotational stability of the IOL (71). There is no definitive consensus regarding the ideal timing for CTR implantation. A recent meta-analysis has been conducted by our team (72), and it was demonstrated that the use of CTR significantly improves the rotational stability of toric IOLs by mitigating the influence of LT. Based on these findings, the co-implantation of CTR is strongly recommended for patients with LT of ≥4.5 mm, WTW of ≥11.6 mm, or high astigmatism.

The implantation methods of CTR also exhibited variations. Safran employed a single CTR in conjunction with Toric IOL implantation (73). Sagiv et al. (74) preferred the combined implantation of two CTRs. Ucar et al. (70) employed suture fixation between the CTR and Toric IOL following the combined CTR and Toric IOL implantation. Jiang et al. (75) conducted a 6-month follow-up study on patients to compare the outcomes of two different types of CTR during toric IOL implantation in cataract surgery. One type featured two eyelets; in contrast, the other type had four eyelets. The CTR with four eyelets provided an additional contact area with the toric IOL as it exerted pressure on the posterior capsule. The two additional eyelets helped secure the toric IOL onto the posterior capsule, increasing the contact area and reducing the rotation risk by enhancing friction. However, no consensus exists on whether CTRs should be implanted during surgery. Further research is required to compare the effects of different designs, materials, and surgical techniques on rotational stability.

5.2 Postoperative interventions for toric IOL rotation

5.2.1 Surgical approaches for repositioning the toric IOLs

The intraoperative methods for rotating toric IOLs vary depending on the duration since the initial surgery and the extent of attachment

between the IOL and the capsular bag (68). If repositioning surgery is performed approximately 3 weeks after cataract surgery, the previous corneal incision is reopened. Subsequently, the OVD is injected into the anterior capsule bag, and the toric IOL is rotated to the desired position. Alignment of the IOL axis is meticulously confirmed, and the incision is hydrated after complete removal of the OVD. If repositioning surgery is performed within 3 weeks postoperatively, two incisions are made on the lateral side of the cornea. One incision is used for anterior-chamber irrigation; the other is used for IOL repositioning. However, this method does not require OVD. Previous studies indicated that repositioning surgery is necessary when the rotation of the toric IOL exceeds 10° from the intended axis. If the rotation is <10° and the change in refractive power of the eye is below 0.50 D, it generally does not significantly impact vision (76).

5.2.2 Timing for the surgery to reposition the toric IOLs

Many other studies have used previously reported timeframes of 1–3 weeks (2, 77). During our team's retrospective evaluation of 2,745 eyes that underwent toric IOL implantation, a realignment procedure was necessary in 1.68% of cases (68). In this study, the optimal time for repositioning was approximately 15 days, which aligns with previous findings. However, calibrating the lens prematurely may result in lens rotation. Our team found that immediate postoperative repositioning was not the optimal timing choice (68). While delaying the calibration process can result in a more secure fixation of the IOLs within the capsule, it is important to note that rotation occurring after firm fixation has the potential to cause zonular rupture (2, 47, 68). Hence, ensuring proper stability entails selecting the optimal timing for the repositioning procedure and carefully assessing any potential complications in the patient. Research has shown that conducting back-calculation before determining the optimal axis and predicting post-rotational refraction based on the current position and cylinder power of the IOL can lead to improved refractive outcomes, particularly for IOLs with high cylinder power (78). As for recurrent postoperative toric IOL rotation cases, a new technique involving transscleral and trans capsular suture passage through haptics in two opposite directions has been reported (79).

5.3 Correction of RAS after toric IOL implantation

In rare cases where a significant RAS cannot be corrected solely by repositioning due to prolonged postoperative time or excessive RAS, various options can be considered, including corneal ablation procedures, arcuate keratotomy, or IOL replacement (58). Among ablative procedures, photorefractive keratectomy and laser-assisted *in situ* keratomileusis (LASIK) yield similar outcomes; however, LASIK is preferred because of its faster visual rehabilitation and satisfactory results (80–82). Excimer LASIK has been proven superior to IOL replacement and piggyback IOL, significantly reducing spherical and cylindrical refractive errors (83). Generally, a waiting period of approximately 3 months after cataract surgery is considered appropriate (84). However, this procedure may not be feasible under certain conditions. For example, it may not be recommended for patients with corneas at risk of developing post-laser ectasia (85). Additionally, the necessary technology may not be readily available in some public health systems and departments. Thus, it is more important to prevent the postoperative rotation of the toric IOL than to focus on correcting it.

6 Conclusion

Several factors affect the rotational stability of toric IOLs. Consequently, clinicians should analyze each patient's situation in a more personalized manner, considering the preoperative refractive status, anatomical structures, surgical techniques, postoperative care, and even long-term management of posterior capsule opacification to minimize postoperative toric IOL rotation to the greatest extent possible. Conventional manual marking has been replaced by image-guided systems and intraoperative aberrometry, which offer markless IOL alignment and contribute to a reduction in postoperative IOL rotation. Whether CTR implantation is necessary to reduce postoperative rotation of toric IOLs remains controversial. With advancements in design and materials, new IOLs are being introduced for commercial use that provide improved visual quality and demonstrate good rotational stability. More relevant studies are anticipated in future research.

Author contributions

XL: Conceptualization, Investigation, Writing – original draft, Writing – original draft. DM: Conceptualization, Writing – review & editing. JY: Conceptualization, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer JL declared a shared parent affiliation with the author XL to the handling editor at the time of review.

Publisher's note

References

1. Hoffer KJ. Biometry of 7,500 cataractous eyes. *Am J Ophthalmol*. (1980) 90:360–8. doi: 10.1016/s0002-9394(14)74917-7

2. Till JS, Yoder PR Jr, Wilcox TK, Spielman JL. Toric intraocular lens implantation: 100 consecutive cases. *J Cataract Refract Surg*. (2002) 28:295–301. doi: 10.1016/s0886-3350(01)01035-5

3. Hoffmann PC, Auel S, Hütz WW. Results of higher power toric intraocular lens implantation. *J Cataract Refract Surg*. (2011) 37:1411–8. doi: 10.1016/j.jcrs.2011.02.028

4. Qiu X, Shi Y, Han X, Hua Z, Lu Y, Yang J. Toric intraocular lens implantation in the correction of moderate-to-high corneal astigmatism in cataract patients: clinical efficacy and safety. *J Ophthalmol*. (2021) 2021:5960328. doi: 10.1155/2021/5960328

5. Lehmann RP, Houtman DM. Visual performance in cataract patients with low levels of postoperative astigmatism: full correction versus spherical equivalent correction. *Clin Ophthalmol*. (2012) 6:333–8. doi: 10.2147/opth.S28241

6. Titiyal JS, Kaur M, Jose CP, Falera R, Kinkar A, Bageshwar LM. Comparative evaluation of toric intraocular lens alignment and visual quality with image-guided surgery and conventional three-step manual marking. *Clin Ophthalmol*. (2018) 12:747–53. doi: 10.2147/opth.S164175

7. Schallhorn SC, Hettinger KA, Pelouskova M, Teenan D, Venter JA, Hannan SJ, et al. Effect of residual astigmatism on uncorrected visual acuity and patient satisfaction in pseudophakic patients. *J Cataract Refract Surg*. (2021) 47:991–8. doi: 10.1097/j.jcrs.0000000000000560

8. Miyake T, Kamiya K, Amano R, Iida Y, Tsunehiro S, Shimizu K. Long-term clinical outcomes of toric intraocular lens implantation in cataract cases with preexisting astigmatism. *J Cataract Refract Surg*. (2014) 40:1654–60. doi: 10.1016/j.jcrs.2014.01.044

9. Savini G, Mularoni A, Destro E, Barboni P, Schiano-Lomoriello D. Rotational stability of a new progressive toric hydrophobic intraocular lens with gradually decreasing cylinder power. *J Refract Surg*. (2023) 39:374–80. doi: 10.3928/1081597x-20230424-02

10. Thomas BC, Khoramnia R, Auffarth GU, Holzer MP. Clinical outcomes after implantation of a toric intraocular lens with a transitional conic toric surface. *Br J Ophthalmol*. (2018) 102:313–6. doi: 10.1136/bjophthalmol-2017-310386

11. Zhao Y, Li J, Yang K, Li X, Zhu S. Combined special capsular tension ring and toric iol implantation for management of astigmatism and high axial myopia with cataracts. *Semin Ophthalmol*. (2018) 33:389–94. doi: 10.1080/08820538.2016.1247181

12. Wolffsohn JS, Buckhurst PJ. Objective analysis of toric intraocular lens rotation and centration. *J Cataract Refract Surg*. (2010) 36:778–82. doi: 10.1016/j.jcrs.2009.12.027

13. Grohlich M, Miháltz K, Lasta M, Weingessel B, Vécsei-Marlovits V. Evaluation of postoperative astigmatism correction and postoperative rotational stability of two toric intraocular lenses. *Klin Monatsbl Augenheilkd*. (2017) 234:796–804. doi: 10.1055/s-0043-100656

14. Lucisano A, Ferrise M, Balestrieri M, Busin M, Scorcia V. Evaluation of postoperative toric intraocular lens alignment with anterior segment optical coherence tomography. *J Cataract Refract Surg*. (2017) 43:1007–9. doi: 10.1016/j.jcrs.2017.05.025

15. Bhogal-Bhamra GK, Sheppard AL, Kolli S, Wolffsohn JS. Rotational stability and centration of a new toric lens design platform using objective image analysis over 6 months. *J Refract Surg*. (2019) 35:48–53. doi: 10.3928/1081597x-20181204-01

16. Patel CK, Ormonde S, Rosen PH, Bron AJ. Postoperative intraocular lens rotation: a randomized comparison of plate and loop haptic implants. *Ophthalmology*. (1999) 106:2190–6. doi: 10.1016/s0161-6420(99)90504-3

17. Sasaki K, Eguchi S, Miyata A, Nishimura T, Miyata K, Hasegawa Y, et al. Anterior capsule coverage and rotational stability of an acrylic toric intraocular lens. *J Cataract Refract Surg*. (2021) 47:618–21. doi: 10.1097/j.jcrs.0000000000000489

18. Ma D, Shen J, Qiu T, Zhang L, Hua Z, Cai L, et al. Rotational stability of plate-haptic toric intraocular lenses in asian eyes: risk period for intraocular lens rotation and its influencing factors. *J Cataract Refract Surg*. (2023) 49:253–8. doi: 10.1097/j.jcrs.0000000000001107

19. Kim JH, Lee D, Cha YD, Oh SH, Mah KC, Lee MS. The analysis of predicted capsular bag diameter using modified model of capsule measuring ring in asians. *Clin Experiment Ophthalmol*. (2008) 36:238–44. doi: 10.1111/j.1442-9071.2008.01726.x

20. Seth SA, Bansal RK, Ichhpujani P, Seth NG. Comparative evaluation of two toric intraocular lenses for correcting astigmatism in patients undergoing phacoemulsification. *Indian J Ophthalmol*. (2018) 66:1423–8. doi: 10.4103/ijo.IJO_73_18

21. Pärssinen O, Räty J, Klemetti A, Lyyra AL, Timonen J. Compression forces of haptics of selected posterior chamber lenses. *J Cataract Refract Surg*. (1997) 23:1237–46. doi: 10.1016/s0886-3350(97)80322-7

22. Shah GD, Praveen MR, Vasavada AR, Vasavada VA, Rampal G, Shastry LR. Rotational stability of a toric intraocular lens: influence of axial length and alignment in the capsular bag. *J Cataract Refract Surg*. (2012) 38:54–9. doi: 10.1016/j.jcrs.2011.08.028

23. Oshika T, Fujita Y, Hirota A, Inamura M, Inoue Y, Miyata K, et al. Comparison of incidence of repositioning surgery to correct misalignment with three toric intraocular lenses. *Eur J Ophthalmol*. (2020) 30:680–4. doi: 10.1177/1120672119834469

24. Singh A, Kapoor G, Baranwal VK, Kalra N. Rotational stability of toric intraocular lenses. *Med J Armed Forces India*. (2022) 78:68–73. doi: 10.1016/j.mjafi.2020.03.014

25. Zhu X, Meng J, He W, Rong X, Lu Y. Comparison of the rotational stability between plate-haptic toric and c-loop haptic toric iols in myopic eyes. *J Cataract Refract Surg*. (2020) 46:1353–9. doi: 10.1097/j.jcrs.0000000000000259

26. Sun J, Bai H, Cui W, Wu X. Comparison of clinical outcome after implantation of two toric intraocular lenses with different haptic type: a prospective randomized controlled trial. *Graefes Arch Clin Exp Ophthalmol*. (2023). doi: 10.1007/s00417-023-06232-9

27. Zhu X, He W, Zhang K, Lu Y. Factors influencing 1-year rotational stability of acrysof toric intraocular lenses. *Br J Ophthalmol*. (2016) 100:263–8. doi: 10.1136/bjophthalmol-2015-306656

28. Vass C, Menapace R, Schmetterer K, Findl O, Rainer G, Steineck I. Prediction of pseudophakic capsular bag diameter based on biometric variables. *J Cataract Refract Surg*. (1999) 25:1376–81. doi: 10.1016/s0886-3350(99)00204-7

29. Chang DF. Early rotational stability of the longer staar toric intraocular lens: fifty consecutive cases. *J Cataract Refract Surg*. (2003) 29:935–40. doi: 10.1016/s0886-3350(02)01843-6

30. He S, Chen X, Wu X, Ma Y, Yu X, Xu W. Early-stage clinical outcomes and rotational stability of tecnis toric intraocular lens implantation in cataract cases with long axial length. *BMC Ophthalmol*. (2020) 20:204. doi: 10.1186/s12886-020-01465-2

31. Tataru CP, Dogaroiu AC, Tataru CI, Dogaroiu C. Enhancing rotational stability of toric intraocular lenses using a type 2l cionni capsular tension ring in patients with high myopia. *J Cataract Refract Surg*. (2019) 45:1219–21. doi: 10.1016/j.jcrs.2019.05.045

32. Buhl L, Langer J, Kassumeh S, Kreutzer TC, Mayer WJ, Priglinger SG. Rotational stability of plate haptic toric intraocular lenses after combined 25-gauge vitrectomy and cataract surgery. *Int J Ophthalmol*. (2023) 16:1231–6. doi: 10.18240/ijo.2023.08.07

33. Fan Q, Han X, Zhu X, Cai L, Qiu X, Lu Y, et al. Clinical characteristics of intraocular lens dislocation in chinese han populations. *J Ophthalmol*. (2020) 2020:8053941. doi: 10.1155/2020/8053941

34. Klysik A, Kaszuba-Bartkowiak K, Jurowski P. Axial length of the eyeball is important in secondary dislocation of the intraocular lens, capsular bag, and capsular tension ring complex. *J Ophthalmol*. (2016) 2016:6431438. doi: 10.1155/2016/6431438

35. Ruhswurm I, Scholz U, Zehetmayer M, Hanselmayer G, Vass C, Skorpik C. Astigmatism correction with a foldable toric intraocular lens in cataract patients. *J Cataract Refract Surg*. (2000) 26:1022–7. doi: 10.1016/s0886-3350(00)00317-5

36. Yao Y, Meng J, He W, Zhang K, Wei L, Cheng K, et al. Associations between anterior segment parameters and rotational stability of a plate-haptic toric intraocular lens. *J Cataract Refract Surg*. (2021) 47:1436–40. doi: 10.1097/j.jcrs.0000000000000653

37. Novis C. Astigmatism and toric intraocular lenses. *Curr Opin Ophthalmol*. (2000) 11:47–50. doi: 10.1097/00055735-200002000-00007

38. Meng J, Wei L, He W, Qi J, Lu Y, Zhu X. Lens thickness and associated ocular biometric factors among cataract patients in shanghai. *Eye Vis (Lond)*. (2021) 8:22. doi: 10.1186/s40662-021-00245-3

39. Jonas JB, Iribarren R, Nangia V, Sinha A, Pardhi P, Shukla R, et al. Lens position and age: the Central India eye and medical study. *Invest Ophthalmol Vis Sci*. (2015) 56:5309–14. doi: 10.1167/iovs.15-16796

40. Li S, Li X, He S, Zheng Q, Chen X, Wu X, et al. Early postoperative rotational stability and its related factors of a single-piece acrylic toric intraocular lens. *Eye (Lond)*. (2020) 34:474–9. doi: 10.1038/s41433-019-0521-0

41. Dong EY, Joo CK. Predictability for proper capsular tension ring size and intraocular lens size. *Korean J Ophthalmol*. (2001) 15:22–6. doi: 10.3341/kjo.2001.15.1.22

42. Lee H, Kim TI, Kim EK. Corneal astigmatism analysis for toric intraocular lens implantation: precise measurements for perfect correction. *Curr Opin Ophthalmol*. (2015) 26:34–8. doi: 10.1097/icu.0000000000000119

43. Haripriya A, Gk S, Mani I, Chang DF. Comparison of surgical repositioning rates and outcomes for hydrophilic vs hydrophobic single-piece acrylic toric iols. *J Cataract Refract Surg*. (2021) 47:178–83. doi: 10.1097/j.jcrs.0000000000000415

44. Lee BS, Chang DF. Comparison of the rotational stability of two toric intraocular lenses in 1273 consecutive eyes. *Ophthalmology*. (2018) 125:1325–31. doi: 10.1016/j.ophtha.2018.02.012

45. Gyöngyössy B, Jirak P, Schönherr U. Long-term rotational stability and visual outcomes of a single-piece hydrophilic acrylic toric iol: a 1.5-year follow-up. *Int J Ophthalmol*. (2017) 10:573–8. doi: 10.18240/ijo.2017.04.12

46. Kramer BA, Hardten DR, Berdahl JP. Rotation characteristics of three toric monofocal intraocular lenses. *Clin Ophthalmol*. (2020) 14:4379–84. doi: 10.2147/opth.S285818

47. Wu J, Yang C, Yin Y, Liu L, Wang H. Impact of material and lens design on repositioning surgery of toric intraocular lenses: a single-arm meta-analysis. *J Ophthalmol*. (2022) 2022:6699596. doi: 10.1155/2022/6699596

48. Savini G, Alessio G, Perone G, Rossi S, Schiano-Lomoriello D. Rotational stability and refractive outcomes of a single-piece aspheric toric intraocular lens with 4 fenestrated haptics. *J Cataract Refract Surg*. (2019) 45:1275–9. doi: 10.1016/j.jcrs.2019.05.015

49. Zeilinger J, Hienert J, Ruiss M, Pilwachs C, Findl O. Rotational stability of a new toric intraocular lens with an advanced optical profile. *J Cataract Refract Surg*. (2023) 49:584–8. doi: 10.1097/j.jcrs.0000000000001158

50. Takaku R, Nakano S, Iida M, Oshika T. Influence of frosted haptics on rotational stability of toric intraocular lenses. *Sci Rep*. (2021) 11:15099. doi: 10.1038/s41598-021-94293-3

51. Vandekerckhove K. Rotational stability of monofocal and trifocal intraocular toric lenses with identical design and material but different surface treatment. *J Refract Surg*. (2018) 34:84–91. doi: 10.3928/1081597x-20171211-01

52. Maedel S, Hirnschall N, Chen YA, Findl O. Rotational performance and corneal astigmatism correction during cataract surgery: aspheric toric intraocular lens versus aspheric nontoric intraocular lens with opposite clear corneal incision. *J Cataract Refract Surg*. (2014) 40:1355–62. doi: 10.1016/j.jcrs.2013.11.039

53. Mayer WJ, Kreutzer T, Dirisamer M, Kern C, Kortuem K, Vounotrypidis E, et al. Comparison of visual outcomes, alignment accuracy, and surgical time between 2 methods of corneal marking for toric intraocular lens implantation. *J Cataract Refract Surg*. (2017) 43:1281–6. doi: 10.1016/j.jcrs.2017.07.030

54. Raucau M, El Chehab H, Agard E, Lagenaite C, Dot C. Toric lens implantation in cataract surgery: automated versus manual horizontal axis marking, analysis of 50 cases. *J Fr Ophtalmol*. (2018) 41:e1–9. doi: 10.1016/j.jfo.2017.11.002

55. Osher RH. Iris fingerprinting: new method for improving accuracy in toric lens orientation. *J Cataract Refract Surg*. (2010) 36:351–2. doi: 10.1016/j.jcrs.2009.09.021

56. Packer M. Effect of intraoperative aberrometry on the rate of postoperative enhancement: retrospective study. *J Cataract Refract Surg*. (2010) 36:747–55. doi: 10.1016/j.jcrs.2009.11.029

57. Elhofi AH, Helaly HA. Comparison between digital and manual marking for toric intraocular lenses: a randomized trial. *Medicine (Baltimore)*. (2015) 94:e1618. doi: 10.1097/md.0000000000001618

58. Núñez MX, Henriquez MA, Escaf LJ, Ventura BV, Srur M, Newball L, et al. Consensus on the management of astigmatism in cataract surgery. *Clin Ophthalmol*. (2019) 13:311–24. doi: 10.2147/opth.S178277

59. Kodavoor SK, Divya J, Dandapani R, Ramamurthy C, Ramamurthy S, Sachdev G. Randomized trial comparing visual outcomes of toric intraocular lens implantation using manual and digital marker. *Indian J Ophthalmol*. (2020) 68:3020–4. doi: 10.4103/ijo.IJO_465_20

60. Tak H. Hydroimplantation: foldable intraocular lens implantation without an ophthalmic viscosurgical device. *J Cataract Refract Surg*. (2010) 36:377–9. doi: 10.1016/j.jcrs.2009.10.042

61. Chen Y, Cao Q, Xue C, Huang Z. Comparison of two techniques for toric intraocular lens implantation: Hydroimplantation versus ophthalmic viscosurgical devices. *BMC Ophthalmol*. (2018) 18:109. doi: 10.1186/s12886-018-0758-6

62. Yan Q, Perdue N, Sage EH. Differential responses of human lens epithelial cells to intraocular lenses in vitro: hydrophobic acrylic versus pmma or silicone discs. *Graefes Arch Clin Exp Ophthalmol*. (2005) 243:1253–62. doi: 10.1007/s00417-005-1181-2

63. Saldanha MJ, Benjamin L, Patel CK. Postoperative rotation of a 3-piece loop-haptic acrylic intraocular lens. *J Cataract Refract Surg*. (2009) 35:1751–5. doi: 10.1016/j.jcrs.2009.05.024

64. Yokogawa H, Sanchez PJ, Mayko ZM, Straiko MD, Terry MA. Astigmatism correction with toric intraocular lenses in descemet membrane endothelial keratoplasty triple procedures. *Cornea*. (2017) 36:269–74. doi: 10.1097/ico.0000000000001124

65. Pérez-Vives C. Biomaterial influence on intraocular lens performance: an overview. *J Ophthalmol*. (2018) 2018:2687385. doi: 10.1155/2018/2687385

66. Vukich JA, Ang RE, Straker BJK, Janakiraman DP, Smith PJ, Batlle JF, et al. Evaluation of intraocular lens rotational stability in a multicenter clinical trial. *Clin Ophthalmol*. (2021) 15:3001–16. doi: 10.2147/opth.S309214

67. Jampaulo M, Olson MD, Miller KM. Long-term staar toric intraocular lens rotational stability. *Am J Ophthalmol*. (2008) 146:550–553.e2. doi: 10.1016/j.ajo.2008.05.040

68. Ma D, Yu W, Cai L, Shen J, Guo T, Chen X, et al. Optimal timing of repositioning surgery for a plate-haptic toric intraocular lens: a multicenter retrospective study. *J Refract Surg*. (2023) 39:120–6. doi: 10.3928/1081597x-20221221-02

69. Rastogi A, Khanam S, Goel Y, Thacker P, Kumar P. Comparative evaluation of rotational stability and visual outcome of toric intraocular lenses with and without a capsular tension ring. *Indian J Ophthalmol*. (2018) 66:411–5. doi: 10.4103/ijo.IJO_875_17

70. Ucar F, Ozcimen M. Can toric iol rotation be minimized? Toric iol-capsular tension ring suturing technique and its clinical outcomes. *Semin Ophthalmol*. (2022) 37:158–63. doi: 10.1080/08820538.2021.1933545

71. Miyoshi T, Fujie S, Yoshida H, Iwamoto H, Tsukamoto H, Oshika T. Effects of capsular tension ring on surgical outcomes of premium intraocular lens in patients with suspected zonular weakness. *PLoS One*. (2020) 15:e0228999. doi: 10.1371/journal.pone.0228999

72. Ma D, Han X, Hua Z, Shen J, Zhang L, Qiu T, et al. Propensity-matched comparison of postoperative stability and visual outcomes of toric intraocular lens with or without a capsular tension ring and updated meta-analysis. *Graefes Arch Clin Exp Ophthalmol*. (2023) 261:989–98. doi: 10.1007/s00417-022-05851-y

73. Safran SG. Use of a capsular tension ring to prevent early postoperative rotation of a toric intraocular lens in high axial myopia. *JCRS Online Case Rep*. (2015) 3:41–3. doi: 10.1016/j.jcro.2015.02.001

74. Sagiv O, Sachs D. Rotation stability of a toric intraocular lens with a second capsular tension ring. *J Cataract Refract Surg*. (2015) 41:1098–9. doi: 10.1016/j.jcrs.2015.04.004

75. Jiang HM, Liang K, Tao LM. Comparative evaluation of rotational stability of toric iols with four-eyelet vs two-eyelet capsular tension rings in eyes with high myopia. *Int J Ophthalmol*. (2021) 14:378–82. doi: 10.18240/ijo.2021.03.07

76. Felipe A, Artigas JM, Díez-Ajenjo A, García-Domene C, Alcocer P. Residual astigmatism produced by toric intraocular lens rotation. *J Cataract Refract Surg*. (2011) 37:1895–901. doi: 10.1016/j.jcrs.2011.04.036

77. Oshika T, Inamura M, Inoue Y, Ohashi T, Sugita T, Fujita Y, et al. Incidence and outcomes of repositioning surgery to correct misalignment of toric intraocular lenses. *Ophthalmology*. (2018) 125:31–5. doi: 10.1016/j.ophtha.2017.07.004

78. Müller-Kassner A, Sartory T, Müller M, Varna-Tigka K, Mayer WJ, Kreutzer T, et al. Refractive and visual outcome of misaligned toric intraocular lens after operative realignment. *Am J Ophthalmol*. (2021) 224:150–7. doi: 10.1016/j.ajo.2020.11.024

79. Arjmand P, Chan TY, Ahmed II. Transscleral suture fixation following recurrent toric intraocular lens rotation. *J Cataract Refract Surg*. (2015) 41:912–7. doi: 10.1016/j.jcrs.2015.04.008

80. Alfonso JF, Fernández-Vega L, Montés-Micó R, Valcárcel B. Femtosecond laser for residual refractive error correction after refractive lens exchange with multifocal intraocular lens implantation. *Am J Ophthalmol*. (2008) 146:244–250.e1. doi: 10.1016/j.ajo.2008.03.022

81. Kim P, Briganti EM, Sutton GL, Lawless MA, Rogers CM, Hodge C. Laser in situ keratomileusis for refractive error after cataract surgery. *J Cataract Refract Surg*. (2005) 31:979–86. doi: 10.1016/j.jcrs.2004.08.054

82. Fan YY, Sun CC, Chen HC, Ma DH. Photorefractive keratectomy for correcting residual refractive error following cataract surgery with premium intraocular lens implantation. *Taiwan J Ophthalmol*. (2018) 8:149–58. doi: 10.4103/tjo.tjo_51_18

83. Fernández-Buenaga R, Alió JL, Pérez Ardoy AL, Quesada AL, Pinilla-Cortés L, Barraquer RI. Resolving refractive error after cataract surgery: Iol exchange, piggyback lens, or lasik. *J Refract Surg*. (2013) 29:676–83. doi: 10.3928/1081597x-20130826-01

84. Moshirfar M, McCaughey MV, Santiago-Caban L. Corrective techniques and future directions for treatment of residual refractive error following cataract surgery. *Expert Rev Ophthalmol*. (2014) 9:529–37. doi: 10.1586/17469899.2014.966817

85. Wan Q, Wang D, Ye H, Tang J, Han Y. A review and meta-analysis of corneal cross-linking for post-laser vision correction ectasia. *J Curr Ophthalmol*. (2017) 29:145–53. doi: 10.1016/j.joco.2017.02.008

frontiers | Frontiers in Medicine

TYPE Systematic Review
PUBLISHED 16 February 2024
DOI 10.3389/fmed.2024.1320235

OPEN ACCESS

EDITED BY
Georgios D. Panos,
Nottingham University Hospitals NHS Trust, United Kingdom

REVIEWED BY
Pablo De Gracia,
University of Detroit Mercy, United States
Ratnakar Tripathi,
University of Missouri, United States

*CORRESPONDENCE
Xuejun Fang
✉ fangxuejun@aierchina.com

RECEIVED 12 October 2023
ACCEPTED 06 February 2024
PUBLISHED 16 February 2024

CITATION
Wang Y, Zheng J, Guo Z and Fang X (2024) Efficacy and safety of small-incision corneal intrastromal lenticule implantation for hyperopia correction: a systematic review and meta-analysis.
Front. Med. 11:1320235.
doi: 10.3389/fmed.2024.1320235

Efficacy and safety of small-incision corneal intrastromal lenticule implantation for hyperopia correction: a systematic review and meta-analysis

Yue Wang[1], Jingjing Zheng[1], Zuofeng Guo[1] and Xuejun Fang[1,2]*

[1]Ophthalmology, Liaoning Aier Eye Hospital, Shenyang, China, [2]AIER School of Ophthalmology, Central South University, Changsha, China

Purpose: To assess the efficacy and safety of intrastromal lenticule implantation for the treatment of hyperopia.

Methods: A systematic search of PubMed, Web of Science, Embase, Cochrane Library, China National Knowledge Internet, and Wan Fang Database identified studies on small-incision intrastromal lenticule implantation for hyperopia correction until January 2023. The Joanna Briggs Institute (JBI) critical appraisal tool was used to assess the quality of the retrospective research, and the Methodological Index for Non-randomized Studies (MINORS) was used to assess the quality of the prospective research. This study included postoperative visual outcomes, corneal morphology, and biomechanical outcomes.

Results: A total of 456 articles were identified, of which 10 were included in the meta-analysis. Ten single-arm studies involving 190 eyes were included. A meta-analysis demonstrated that corneal intrastromal lenticule implantation treatment significantly improved hyperopia. Uncorrected distance visual acuity (UDVA) significantly improved compared to the preoperative value (p=0.027), corrected distance visual acuity showed no difference compared to the preoperative value (p=0.27), and 87% eyes have no loss of one or more lines in the Snellen lines of CDVA (p<0.00001). There was a significant difference between the spherical equivalent refractive (SE) and preoperative examination (p<0.00001), 52% of eyes had ±0.5 diopters (D) postoperative SE (p<0.00001), and 74% eyes had ±1.0 D postoperative SE (p<0.00001). The central corneal thickness (CCT) increased by 72.68μm compared to that preoperatively (p<0.00001), and corneal curvature increased by 4.18D (p<0.00001). The Q-value decreased by 0.82 (p<0.00001), and higher-order aberration (HOA) decreased by 0.66 (p<0.00001).

Conclusion: Small-incision intrastromal lenticule implantation may be an effective solution for correcting hyperopia. The effect of improved vision is significant, but further exploration is needed for changes in corneal biomechanics and long-term safety.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/, identifier: CRD42023432343.

KEYWORDS

lenticule implantation, hyperopia, small incision lenticule extraction, refractive, meta-analysis

1 Introduction

Hyperopia not only leads to blurred vision, but also poses a risk factor for diseases such as strabismus and bilateral amblyopia (1). For patients who want to correct hyperopia through refractive surgery, transepithelial photorefractive keratectomy (T-PRK), femtosecond laser-assisted *in-situ* keratomileusis (FS-LASIK) and small incision lenticule extraction (SMILE) can be used for the correction of hyperopia. These surgical methods can effectively correct hyperopia and ametropia; however, they all increase the risk of corneal swelling, refractive regression, and corneal epithelial implantation after surgery (2–4).

SMILE produces a corneal intrastromal lenticule with a diameter of 6–7 mm and a thickness of typically 30–130 μm while correcting myopia. Currently, there are reports of the application of corneal intrastromal lenticule in the treatment of diseases such as keratoconus (KC), corneal ulcers, corneal dilation caused by corneal refractive surgery, and corneal infection perforation (5–8). In addition, corneal intrastromal lenticule implantation has also been applied to the surgical treatment of hyperopia, and the postoperative effects are significant (9, 10). The long-term safety of corneal intrastromal lenticule implantation for hyperopia has not been confirmed, and owing to difficulties in preserving corneal intrastromal lenticule, it has not yet been widely approved for clinical use.

More recently, the number of SMILE surgeries has rapidly increased worldwide, and research on the preservation and reuse of corneal intrastromal lenticules is also becoming more mature. Corneal intrastromal lenticules can be preserved using various methods, including ultra-low temperature freezing, glycerol preservation, and commercial cryopreservation solutions (11, 12). This study conducted a systematic review of clinical studies on the treatment of hyperopia with corneal intrastromal lenticule implantation, and a meta-analysis of postoperative indicators such as UDVA, CDVA, CCT, corneal curvature, HOAs, and changes in corneal biomechanics. The aim was to explore the effectiveness and safety of corneal intrastromal lenticule implantation in the treatment of hyperopia, and to provide new treatment ideas for corneal refractive surgery for clinical hyperopia refractive errors.

2 Methods

We performed a systematic review and meta-analysis in accordance with the Reporting Items for Systematic Reviews and Meta-Analyses Statement (13). This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO; ID: CRD42023398935). The study adhered to the tenets of the Declaration of Helsinki.

2.1 Search strategy

Two researchers (YW and JZ) independently performed database searches of PubMed, EMBASE, Web of Science, the Cochrane Library, China National Knowledge Internet, and the Wanfang Database to identify relevant studies on small-incision corneal intrastromal lenticule implantation for hyperopia correction up to 2023.01.01. The search terms included "small-incision intrastromal lenticule," "lenticule implantation," and "hyperopia." The search strategy was determined after multiple pre-searches, combined with subject headings and free words.

2.2 Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) the research subjects are hyperopia patients who have undergone small-incision corneal intrastromal lenticule implantation surgery. (2) For single-arm studies, the treatment modality in the included studies was corneal intrastromal lenticule implantation. For case-control studies, the experimental group comprised eyes treated with corneal intrastromal lenticule implantation, and there were no limitations on the control group intervention measures. (3) Studies that reported at least one major outcome (UDVA, CDVA, SE, and CCT) or secondary outcome (corneal biomechanical indicators and HOAs). (4) The patients included in the study had no other eye diseases. (5) Complete at least three months of follow-up.

The exclusion criteria were as follows: (1) the included patients are not those who have undergone small incision matrix lens transplantation surgery. (2) Lack of standard deviation in the research results. (3) No outcome was related to the purpose of the study. (4) Data with significant errors in research results. (5) Studies with fewer than five eyes were included. (6)Research involving duplicate patients.

The study was independently reviewed by two researchers (YW, JZ) to determine whether the included studies met the inclusion or exclusion criteria. When there was any disagreement, a third researcher (ZG) participated.

2.3 Data extraction

For all included studies, the basic characteristics of the article and the main clinical data were extracted. The basic characteristics of the article included: the lead author, year of publication, language of publication, sample size of patients and eyes, age, surgical method, and postoperative outcomes.

The primary outcome measures were visual outcome, refractive outcome, and corneal morphology change. The visual outcome included the mean logMAR value of uncorrected distance visual acuity (UDVA), mean logMAR value of corrected distance visual acuity (CDVA), and the eyes changes in the Snellen chart of CDVA. The refractive outcome included the mean postoperative spherical equivalent (SE), the percentage of eyes within ±0.5 diopters (D) of the target refraction and the percentage of eyes within ±1.0 D. The corneal morphology change outcome included the mean increment of corneal curvature and changes in central corneal thickness (CCT).

Secondary outcomes included postoperative high-order aberrations (HOAs), changes in *Q* values, and corneal biomechanical indicators. Among them, corneal biomechanical indicators include Corneal compensated intraocular pressure (IOPcc), Goldmann correlated intraocular pressure (IOPg), corneal hysteresis (CH), and corneal resistance factor (CRF).

Data were extracted independently by two authors (YW and JZ), and any differences were resolved through discussion until consensus was reached or a third author (ZG) is consulted.

2.4 Assessment of risk of bias

The Joanna Briggs Institute (JBI) critical appraisal tool was used to evaluate the methodological quality of retrospective studies (14, 15), and the Methodological Index for Non-randomized Studies (MINORS) was used to evaluate the methodological quality of prospective studies (16, 17). Studies were not included in our analysis if they scored lower than 6 out of 8 (75%) in retrospective studies, the scores of prospective studies must be greater than 10, and two reviewers (YW and JZ) independently evaluated the quality of the include studies. If there was a disagreement, another reviewer (ZG) participated in the discussion to obtain the results. Funnel plot and Egger's test were used to evaluate the risk of publication bias, with $p < 0.05$ indicating a statistically significant bias.

2.5 Statistical analysis

Statistical analysis was conducted using Stata V.16.0 software (StataCorp, College Station), and forest maps were created using RevMan software (version 5.4.1; Cochrane Collaboration). In this meta-analysis, continuous variables were extracted as mean and standard deviation (mean ± SD), and estimated using the weighted mean difference (WMD), and 95% confidential intervals (CI). Random-effects models were used when study heterogeneity was high ($I^2 > 50\%$), and fixed-effects models were used when heterogeneity was low ($I^2 \leq 50\%$) (18, 19).

3 Results

3.1 Study selection

We identified 465 related articles through a preliminary search, of which 171 duplicate articles were excluded using EndNote X9 software (Clarivate Analytics, US), and 294 articles underwent title and abstract reviews. After selecting titles and abstracts, 272 studies were excluded for the following reasons: irrelevant topics ($n = 75$), inconsistent research contents ($n = 64$), reviews ($n = 53$), case reports ($n = 18$), *in vitro* experimental studies ($n = 17$), animal studies ($n = 39$), literature corrections ($n = 2$), letters ($n = 2$), and conference literature ($n = 1$). A total of 22 articles were reviewed, of which 12 were excluded for the following reasons: no major outcome ($n = 3$), missing data ($n = 3$), and duplicate data ($n = 6$). The remaining 10 reports met the qualification criteria and were included in the meta-analysis (9, 10, 20–27). The literature screening process is illustrated in Figure 1.

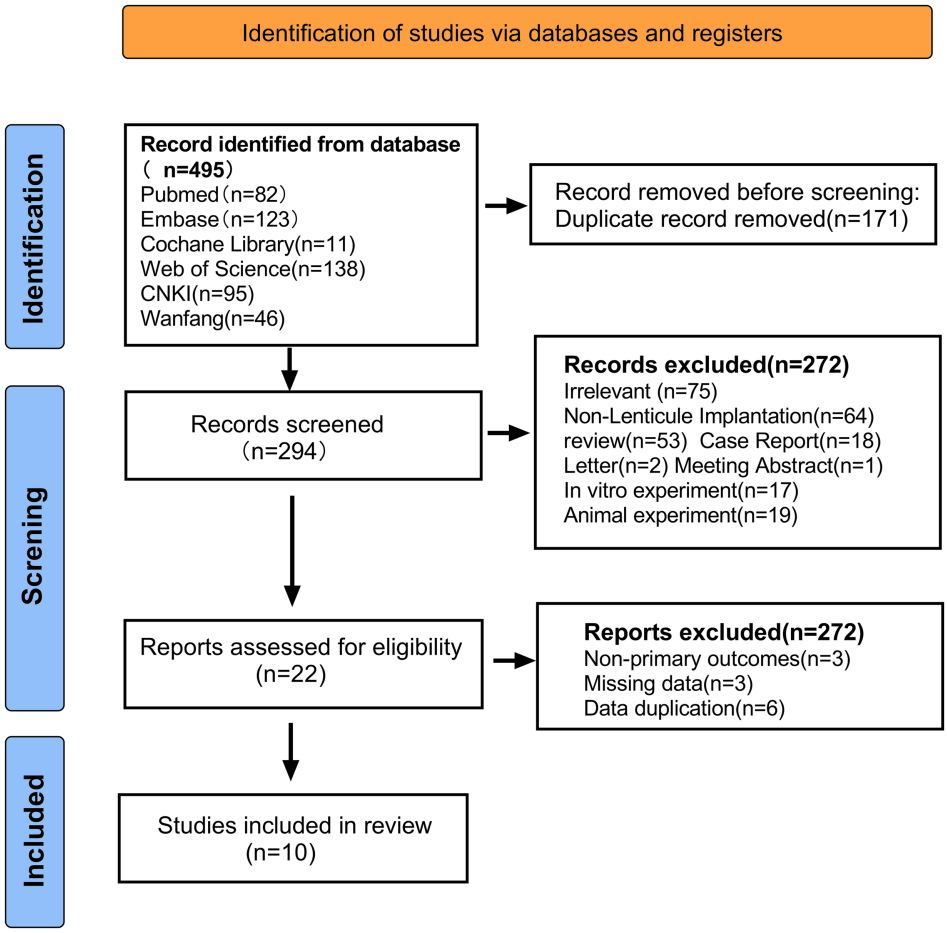

FIGURE 1
Preferred reporting items for systematic reviews and meta-analyses flow diagram of study selection.

3.2 Study characteristics

A total of 130 (190 eyes) cases were included in the study, with an average age of 24.98 (95% CI: [22.51, 27.44]). The characteristics of the included studies are summarized in Table 1.

3.3 Quality assessment

Six of ten prospective single-arm uncontrolled studies (9, 21–23, 25, 26) were evaluated using the MINORs, with a score of 11–13 (Table 2A). The remaining four retrospective uncontrolled studies (10, 20, 24, 27) were evaluated using the JBI case series key assessment checklist and met 9 or more of the 10 criteria (Table 2B). The quality of the included studies met these criteria.

3.4 Outcomes

3.4.1 Visual outcomes

A total of six studies (9, 20, 22, 24–26) reported the of logMAR values of postoperative UDVA. At the last follow-up, postoperative UDVA increased by 0.40 logMAR compared to preoperative UDVA (WMD = −0.40, 95% CI: [−0.61, −0.19], $I^2 = 88\%$, $p = 0.0002$, Figure 2A). A total six studies (9, 21–23, 25, 26) reported the logMAR values of postoperative CDVA. At the last follow-up, postoperative CDVA increased by 0.02 logMAR compared to preoperative CDVA (WMD = −0.02, 95% CI: [−0.05, −0.01], $I^2 = 0\%$; $p = 0.27$, Figure 2B). All studies reported changes in the Snellen of CDVA. 87% of eyes had no loss of one or more lines in the Snellen lines of the CDVA after surgery (95% CI: [0.73, 1.01], $I^2 = 0\%$, $p < 0.0001$, Figure 2C). Sensitivity analysis showed that, regardless of which article was excluded, the changes in UDVA and CDVA were stable, with no changes in heterogeneity or results.

3.4.2 Refraction outcome

All 10 studies reported the results of postoperative SE, which decreased by 5.73D compared to preoperative SE, (WMD = −5.73, 95% CI: [−6.04, −5.42], $I^2 = 82\%$, $p < 0.00001$, Figure 3A). A total of 5 studies (21–24, 26) reported the results of the proportion of postoperative and expected refractive error within the range of ±0.5D, and the proportion of postoperative and expected refractive error within the range of ±0.5D was 51% (95% CI: [0.27, 0.74], $I^2 = 0\%$, $p < 0.0001$, Figure 3B). A total of four studies (20, 22, 24, 26) indicated that 74% of the eyes had an error range of ±1.0D compared to the expected SE. (95% CI: [0.54, 0.94], $I^2 = 0\%$, $p < 0.0001$, Figure 3C).

TABLE 1 The basic clinical characteristics of included studies.

Study	Language	Design	Eyes	Surgical	Lenticule Implantation	Age	Outcomes
		single-arm study			Autologous/ Allogeneic	Mean ± SD	
Jing Zhang (10)	English	Retrospective	24	SMILE	Allogeneic	26.40 ± 5.82	UDVA, CDVA, SE, HOAs, CCT, IOPg, IOPcc, CH, CRF, Km, Q value
Jie Hou (20)	English	Retrospective	31	SMILE	Allogeneic	20.00 ± 1.48	UDVA, SE, CD, CCT, Km
Meng Li (23)	English	Prospective	10	LASIK	Autologous	24.70 ± 5.82	CDVA, SE
Jiawei Wu (21)	English	Prospective	10	LASIK/PTK	Allogeneic	22.80 ± 3.29	CDVA, SE, Q value, HOAs
Ling Sun (24)	English	Prospective	5	LASIK	Autologous	24.60 ± 5.30	UDVA, CDVA, SE, Km, CCT
Shengtao Liu (26)	English	Prospective	5	SMILE	Allogeneic	21.00 ± 2.60	UDVA, CDVA, SE, Q value, CCT, Km
Shengtao Liu (25)	English	Prospective	14	SMILE	Allogeneic	29.00 ± 9.17	UDVA, CDVA, SE, CCT, Km
Sheetal Brar (22)	English	Retrospective	42	SMILE	Allogeneic	27.04 ± 5.33	UDVA, CDVA, SE, CCT, Km, Q value, HOAs
Mengfei Hu (27)	Chinese	Retrospective	12	SMILE	Autologous	29.25 ± 5.02	SE, CCT, Km
Yuehua Zhou (9)	Chinese	Prospective	37	SMILE	Allogeneic	28.00 ± 9.00	SE, Km, IOPg, IOPcc, CH, CRF,CCT

SMILE, small incision lenticule extraction; LASIK, laser *in situ* keratomileusis; UDVA, uncorrected distance visual acuity; SE, spherical equivalent; CCT, central corneal thickness; Km, *K* value; CD, corneal densitometry; IOPg, Goldmann correlated intraocular pressure; IOPcc, corneal compensated intraocular pressure; CH, corneal hysteresis; CFR, corneal resistance factor.

TABLE 2 Quality assessment of included studies.

(A) MINORS index for included non-randomized studies									
Study	I	II	III	IV	V	VI	VII	VIII	Total
Meng Li (23)	2	2	2	2	1	2	2	0	13
Jiawei Wu (21)	2	2	2	2	1	2	2	0	13
Ling Sun (24)	2	2	2	2	1	2	2	0	13
Shengtao Liu (26)	2	2	2	2	0	2	2	0	12
Shengtao Liu (25)	2	2	2	2	0	2	2	0	12
Yuehua Zhou (9)	2	2	2	2	1	2	2	0	13

(B) JBI critical appraisal checklist for case series for included retrospective studies											
Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Overall appraisal
Jing Zhang (10)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Include
Jie Hou (20)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Include
Sheetal Brar (22)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Include
Mengfei Hu (27)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Include

Sensitivity analysis shows that regardless of which article is excluded, the changes in the above results are stable, with no heterogeneity or changes in the results.

3.4.3 CCT and corneal curvature

A total of eight studies (9, 10, 20, 22, 24–27) reported the results of CCT, with an average increase of 72.68 μm in postoperative CCT compared to preoperative CCT (WMD = 72.68, 95% CI: [55.00, 90.36], $I^2 = 82\%$; $p < 0.00001$, Figure 4A). Seven studies (9, 10, 20, 22, 24, 25, 27) reported the results of corneal curvature, with an average increase of 4.18D in postoperative corneal curvature compared to preoperative (WMD = 4.18, 95% CI: [3.65, 4.71], $I^2 = 8\%$; $p < 0.00001$,Figure 4B). Sensitivity analysis showed that regardless of which article was excluded, the changes in CCT and corneal curvature were stable, with no changes in heterogeneity or results.

3.4.4 HOAs and *Q*-value

Three studies (21, 22, 26) reported the results of *Q*-values, with a difference of −0.82 between postoperative and preoperative *Q*-values, indicating a relative tendency towards swelling (WMD = −0.82; 95% CI: [−1.10, −0.53], $I^2 = 90\%$, $p < 0.00001$, Figure 5A). Two studies (21, 22) reported the results of HOAs, with a difference of −0.55 between postoperative and preoperative HOAs (WMD = −0.55, 95% CI: −[0.66, −0.45], $I^2 = 0\%$, $p < 0.00001$, Figure 5B). Sensitivity analysis showed that regardless of which article was excluded, the changes in *Q*-values and HOAs were stable, with no changes in heterogeneity or results.

3.4.5 Corneal biomechanics

Two studies (9, 10) reported the results of corneal biomechanical indicators, including IOPg, IOPcc, CH, and CRF. IOPg decreased by 2.25 mmHg compared to that before surgery (WMD = −2.25; 95% CI: [−3.50, −1.01]; $I^2 = 0\%$; $p = 0.0004$, Figure 6A). There was no significant difference in IOPcc compared to preoperative values (WMD = −0.88, 95% CI: [−1.92, 0.15], $I^2 = 0\%$; $p = 0.10$, Figure 6B). CH increased by 1.02 compared to the preoperative value (WMD = 1.02, 95% CI: [0.29, 1.96], $I^2 = 40\%$, $p = 0.006$, Figure 6C). There was no significant difference in postoperative CFR compared to preoperative values (WMD = 0.02, 95% CI: [−1.03, 1.06], $I^2 = 57\%$, $p = 0.97$, Figure 6D). Sensitivity analysis shows that regardless of which article is excluded, heterogeneity and results will change.

3.4.6 Sensitivity analysis and publication bias

Publication bias was evaluated intuitively using a funnel plot of postoperative changes in UDVA (Figure 7A), CDVA (Figure 7B), SE (Figure 7C), and CCT (Figure 7D). We also conducted Egger regression to quantitatively evaluate publication bias, and found that *p* (UDVA) = 0.54, *p* (CDVA) = 0.81, *p* (SE) = 0.49, and *p* (CCT) = 0.31, indicating that the funnel plot was symmetric, and there was no publication bias in this study.

4 Discussion

This study included 10 studies with a total of 130 patients (190 eyes). The meta-analysis results showed that the postoperative UDVA of corneal intrastromal lenticule implantation for hyperopia was significantly increased. The proportion of postoperative CDVA that reached or surpassed the preoperative CDVA was 87%. The proportion of postoperative SE error within ±0.5D was 52%, and the proportion of postoperative SE error within ±0.1.0D was 74%. The above results suggest that the application of corneal intrastromal lenticule implantation to correct hyperopia can effectively improve the refractive state of patients and achieve correction of refractive errors. Although LASIK surgery can also achieve the effect of correct hyperopia, significant refractive regression was observed in long-term follow-up studies (28, 29). Studies by Zhang (10), Li (23), and Sheetal (22) were followed up for 1 year, 2 years, and 3 years (1–7 years) after surgery, all showing good refractive stability.

The difference in postoperative *Q*-value compared to the preoperative *Q*-value was −0.82, which is directly related to the implantation of corneal intrastromal lenticule, leading to a relative

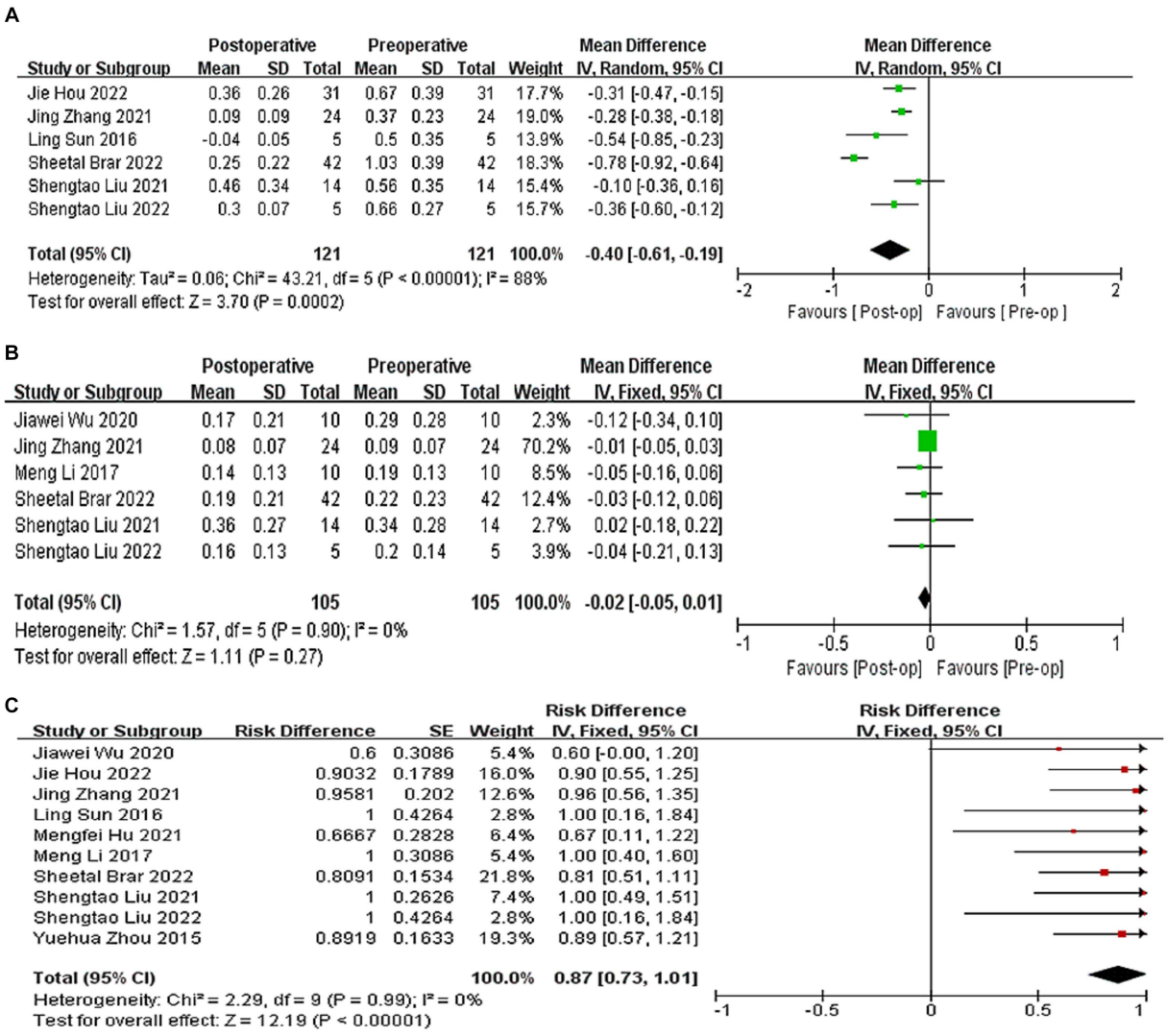

FIGURE 2
(A) Forest plot showing the weighted mean difference of postoperative UDVA (logMAR) and preoperative UDVA (logMAR). **(B)** Forest plot showing the weighted mean difference of postoperative CDVA (logMAR) and preoperative CDVA (logMAR). **(C)** Forest plot showing the risk difference of postoperative CDVA (Snellen).

tendency of the cornea to bulge. After surgery, HOAs decreased by 0.55 compared to before surgery. In theory, the smaller the eccentricity of the optical region center, the lower the introduction of higher-order aberrations (30). SMILE surgery is superior to LASIK in this regard (31, 32). Different types of corneal refractive surgery can cause changes in the *Q*-value (33). Currently, *Q*-value guided LASIK surgery can be performed, and a large amount of clinical data has achieved good results (34, 35). However, this issue needs to be addressed further in the treatment of hyperopia with corneal intrastromal lenticule implantation.

The average increase in postoperative CCT compared to preoperative was 72.68 μm. After surgery, the corneal curvature increased by an average of 4.18D compared to before surgery. Corneal intrastromal lenticule implantation increases corneal thickness and effectively preserves corneal stromal thickness, avoiding the risk of corneal dilation (36). Postoperative corneal topography shows that the central part of the cornea has become significantly convex, with increased curvature, which changes the refractive power of the central part of the cornea and corrects hyperopia. At the same time, this new surgical method for correcting hyperopia avoids the possibility of passive formation of excessively high central curvature of the cornea and does not lead to surgically induced KC. In addition, changing corneal morphology through implantation is a reversible surgical approach when there are other diseases that require feasible lenticule removal surgery. In our meta-analysis, the results of the two included studies were inconsistent, and convincing and consistent evidence regarding corneal biomechanical indicators has not yet been found, which deserves further validation through case-control studies.

The corneal stroma accounts for 90% of the corneal thickness, which is crucial for ensuring the corneal transparency and refractive function necessary for normal vision. Currently, scientific research on corneal stroma mainly includes acellular or decellularized and decellularized human or animal corneas and non-corneal tissues, acellular bioengineered stromal scaffolds, tissue adhesives, 3D

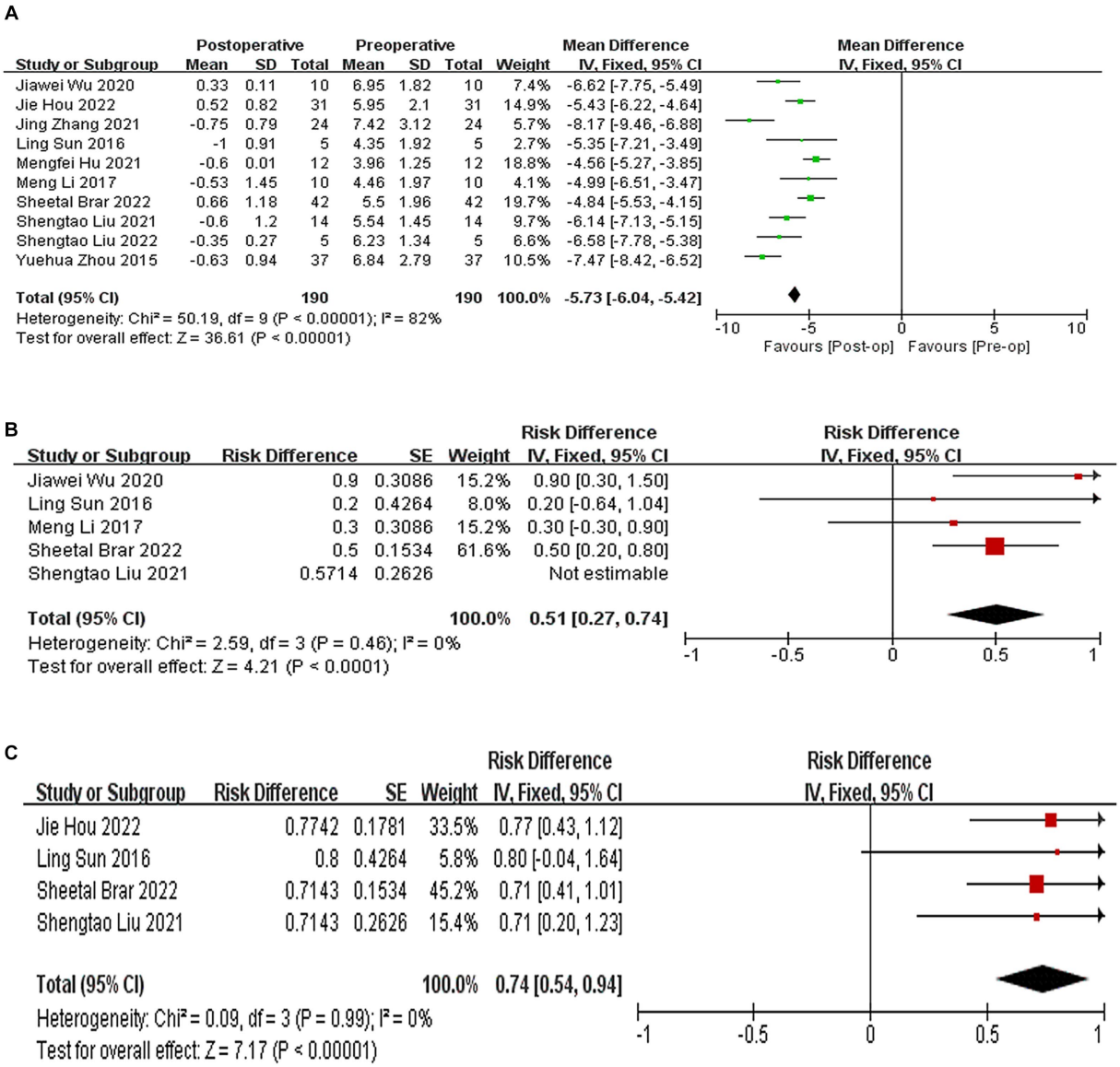

FIGURE 3
(A) Forest plot showing the weighted mean difference of postoperative SE and preoperative SE. **(B)** Forest plot showing the risk difference of postoperative and expected refractive error within the range of ±0.5D. **(C)** Forest plot showing the risk difference of postoperative and expected refractive error within the range of ±1.D.

bioprinting, and stromal stem cell therapy (37, 38). As of 2022, the global surgical volume of SMILE has exceeded 6 million cases, generating a large number of corneal stromal lenses annually. Currently, attempts have been made to apply corneal intrastromal lenticule for the treatment of diseases such as hyperopia correction, ulcerative keratitis, KC, and corneal dilation after LASIK; however, they have not yet achieved widespread clinical application. When using corneal intrastromal lenticule implantation to treat hyperopia, the corneal stroma tissue implanted in the capsule has an ordered arrangement of collagen fibers, with a lens diameter of 6.5 mm, without blood vessels or lymphatic tissue. The corneal stroma capsule is in a sterile environment, and the donor corneal stroma is not in contact with aqueous humor or tears. Therefore, the probability of corneal graft rejection and corneal infection is very low. However, in Brar's study (22), four eyes experienced immune rejection, all of which were cryopreserved. The use of fresh corneal intrastromal lenticules can also improve graft survival and reduce the rejection rate (39). At present, research has achieved non-traditional cryopreservation of corneal stromal lenses, improving their activity and meeting the needs of corneal intrastromal lenticule implantation (40–42).

4.1 Study limitations

Through literature review and meta-analysis, we found that there are few studies on the treatment of hyperopia with corneal intrastromal lenticule implantation, and the research design has certain limitations. The number of included research cases was small, and due to the limited number of cases, it was not possible to perform subgroup analysis of corneal intrastromal lenticule implantation surgery and

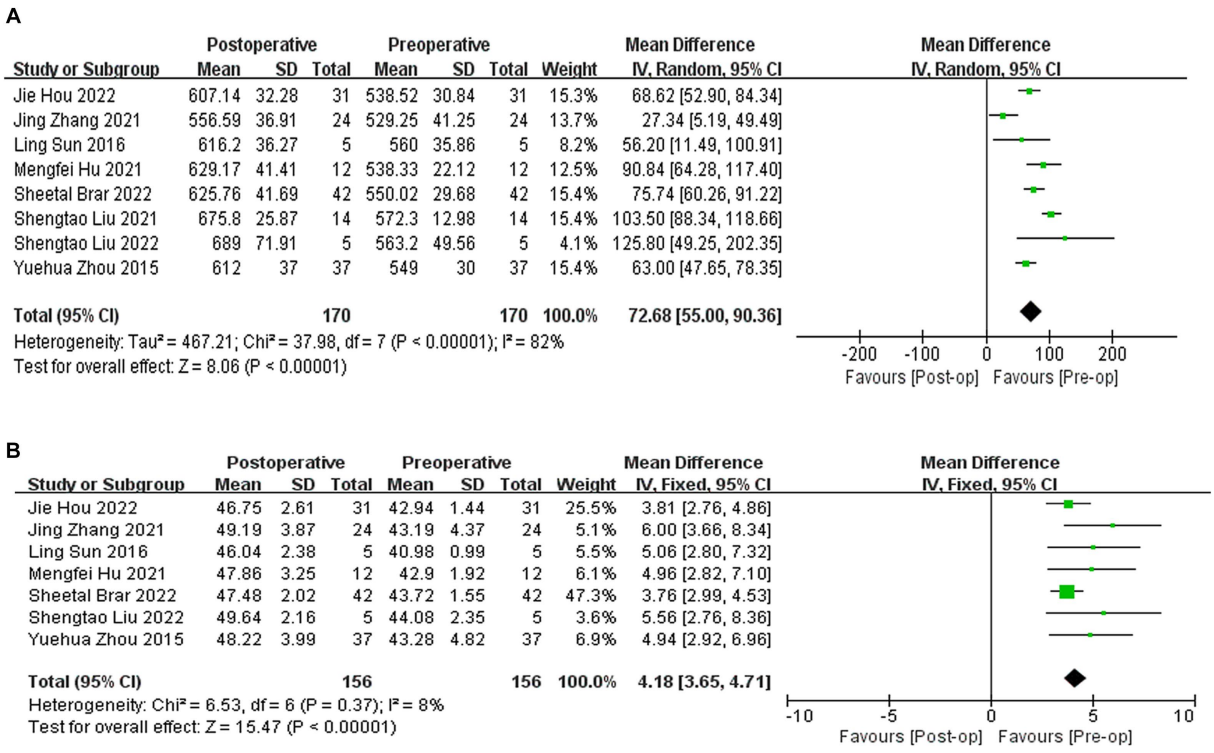

FIGURE 4
(A) Forest plot showing the weighted mean difference of postoperative CCT and preoperative CCT. **(B)** Forest plot showing the weighted mean difference of postoperative corneal curvature and preoperative corneal curvature.

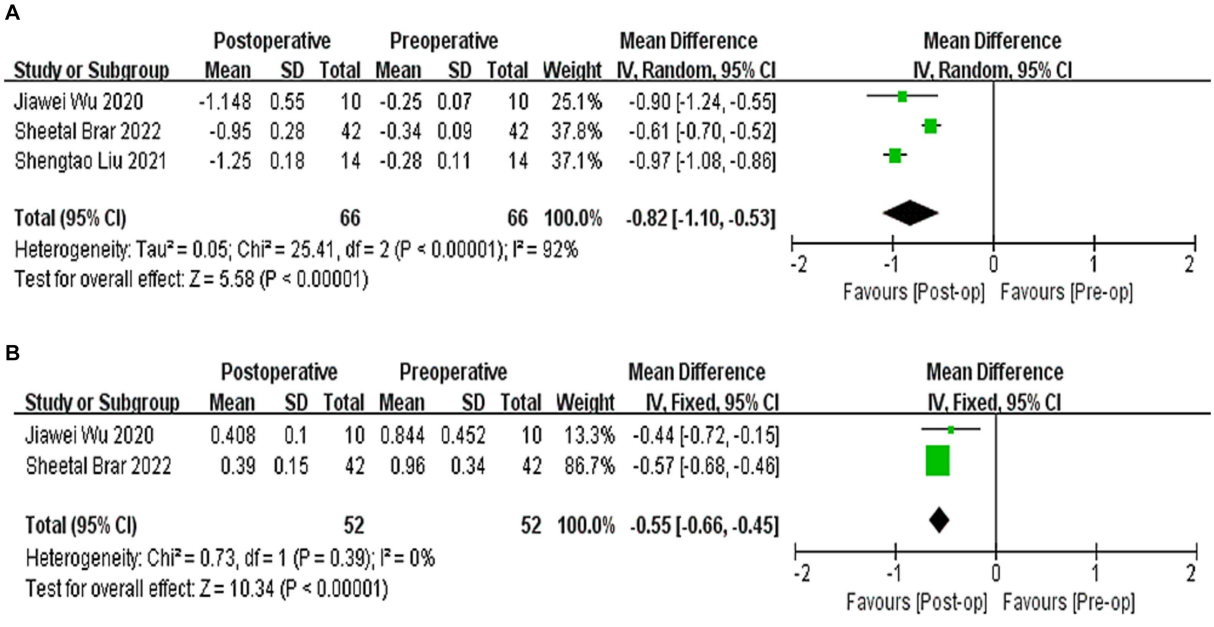

FIGURE 5
(A) Forest plot showing the weighted mean difference of postoperative *Q*-values and preoperative *Q*-values. **(B)** Forest plot showing the weighted mean difference of postoperative HOAs and preoperative HOAs.

autologous and allogeneic transplantation. In our actual clinical work, while paying attention to postoperative visual acuity recovery, we should also pay attention to the long-term safety and changes in corneal morphology after surgery. There is relatively little research on corneal biomechanics and corneal curvature, and the research results have a certain degree of difference. In-depth research can be conducted

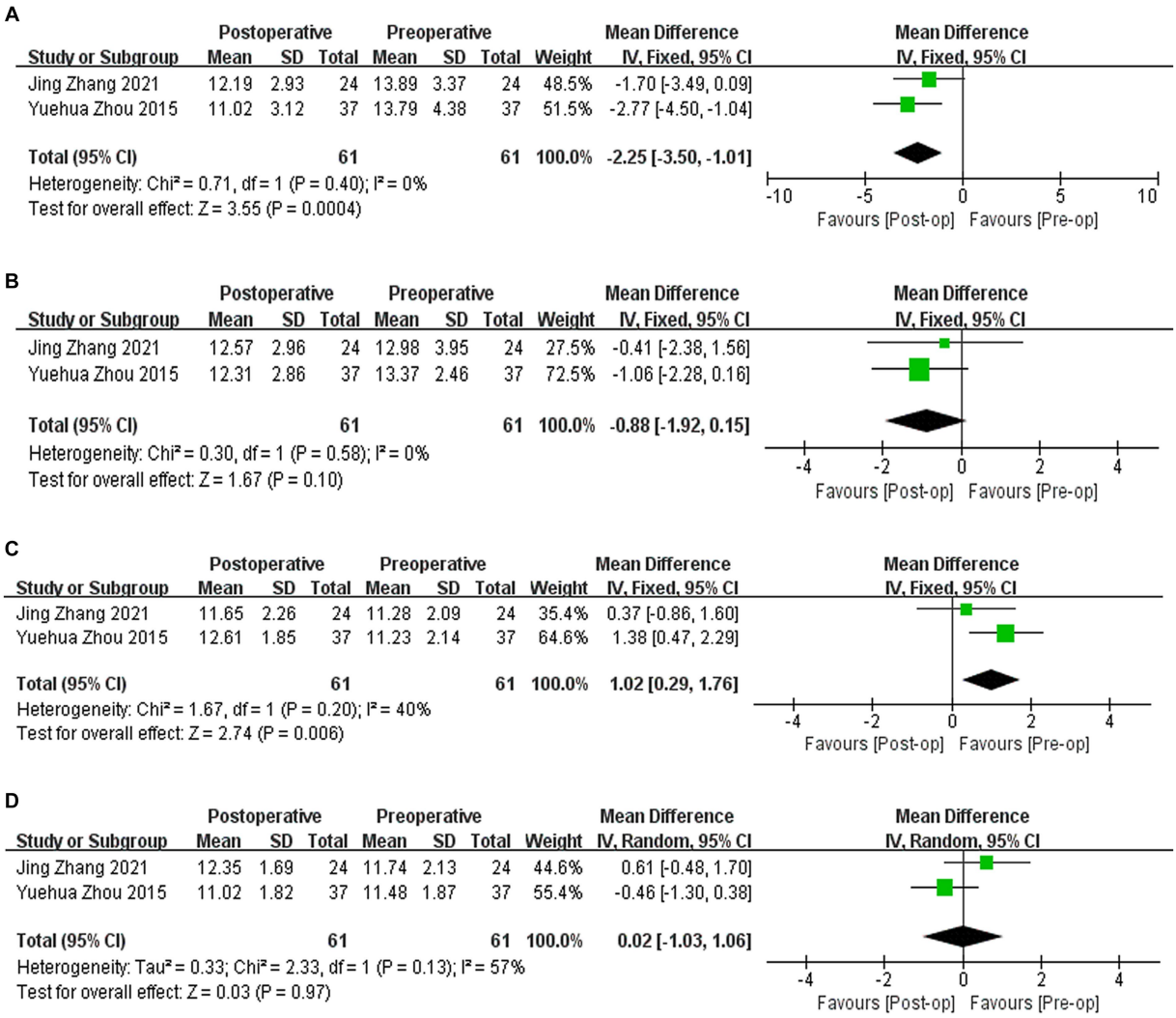

FIGURE 6
(A) Forest plot showing the weighted mean difference of postoperative IOPg and preoperative IOPg. **(B)** Forest plot showing the weighted mean difference of postoperative IOPcc and preoperative IOPcc. **(C)** Forest plot showing the weighted mean difference of postoperative CH and preoperative CH. **(D)** Forest plot showing the weighted mean difference of postoperative CRF and preoperative CRF.

in future clinical studies to address this issue, providing more sufficient evidence for the safety and effectiveness of corneal intrastromal lenticule implantation in the treatment of hyperopia.

5 Conclusion

Corneal intrastromal lenticule implantation surgery can effectively improve the refractive state of patients with hyperopia, improve their vision, and reduce the risk of postoperative corneal dilation and keratoconus caused by corneal refractive surgery, achieving the reversibility of corneal refractive surgery.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

YW: Formal analysis, Resources, Writing – original draft. JZ: Formal analysis, Writing – review & editing. ZG: Project administration, Writing – review & editing. XF: Funding acquisition, Visualization, Writing – original draft.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. Shenyang Science and Technology Bureau: 22-321-33-87 Hunan Provincial Science and Technology Department: 2020SK50111.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

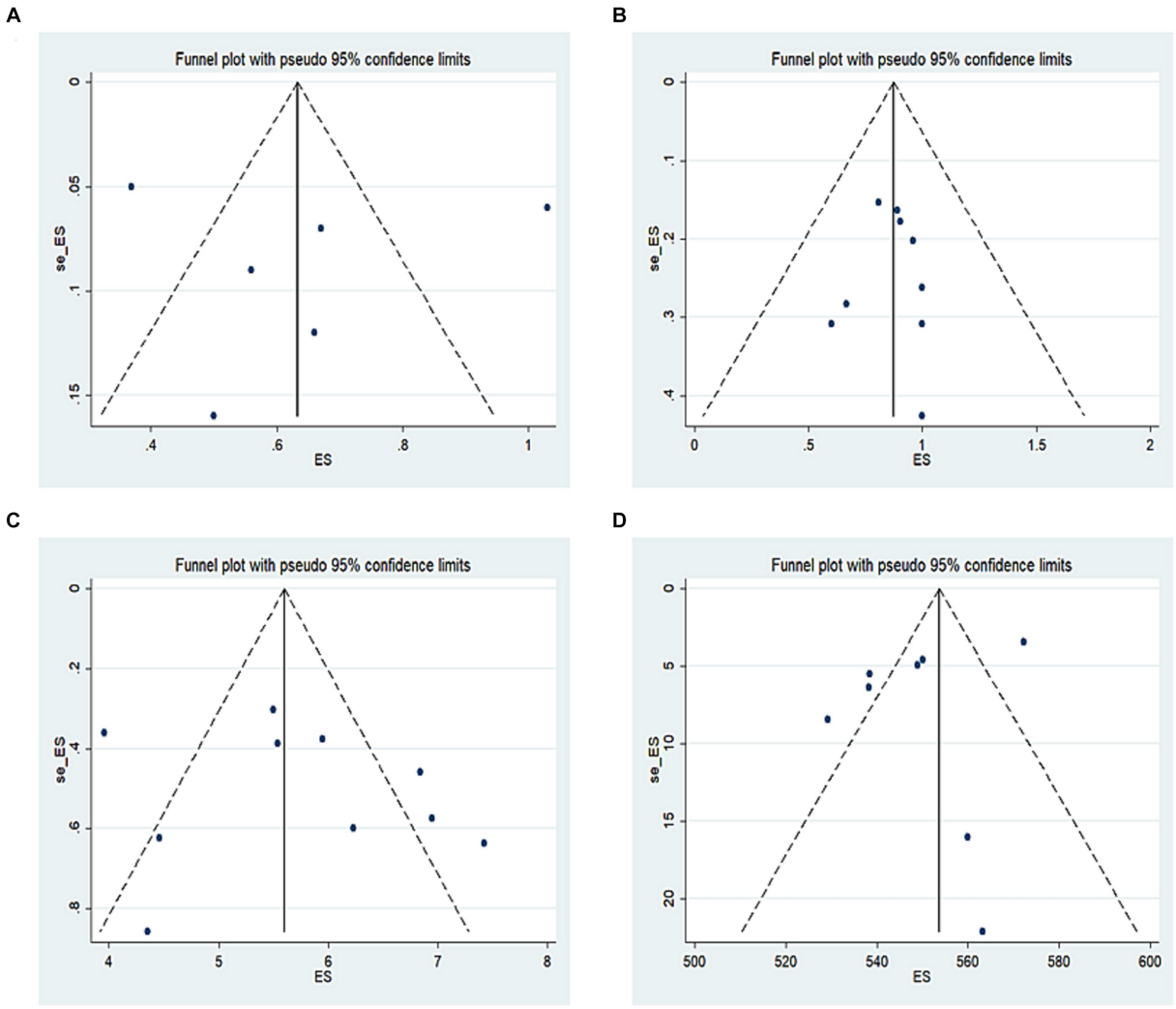

FIGURE 7
(A) Funnel plot of postoperative changes in UDVA, **(B)** funnel plot of postoperative changes in CDVA, **(C)** funnel plot of postoperative changes in SE, **(D)** funnel plot of postoperative changes in CCT.

Publisher's note

References

1. Kulp MT, Ciner E, Ying GS, Candy TR, Moore BD, Orel-Bixler D. Vision screening, vision disorders, and impacts of hyperopia in young children: outcomes of the vision in preschoolers (VIP) and vision in preschoolers – hyperopia in preschoolers (VIP-HIP) studies. *Asia-Pacific J Ophthalmol.* (2022) 11:52–8. doi: 10.1097/APO.0000000000000483

2. Biscevic A, Pidro A, Pjano MA, Grisevic S, Ziga N, Bohac M. Lasik as a solution for high hypermetropia. *Med Arch.* (2019) 73:191–4. doi: 10.5455/medarh.2019.73.191-194

3. Lee BS. Accuracy and stability of hyperopic treatments. *Curr Opin Ophthalmol.* (2014) 25:281–5. doi: 10.1097/ICU.0000000000000066

4. El-Helw MA, Emarah AM. Predictability and stability of refraction with increasing optical zone diameter in hyperopic LASIK. *Clin Ophthal.* (2010) 4:455–8. doi: 10.2147/OPTH.S11007

5. Pedrotti E, Cozzini T, Fasolo A, Bonacci E, Bonetto J, Merz T, et al. Small-incision lenticule addition in ex vivo model of ectatic human corneas. *Int Ophthalmol.* (2019) 39:2575–81. doi: 10.1007/s10792-019-01106-8

6. Fasolo A, Galzignato A, Pedrotti E, Chierego C, Cozzini T, Bonacci E, et al. Femtosecond laser-assisted implantation of corneal stroma lenticule for keratoconus. *Int Ophthalmol.* (2021) 41:1949–57. doi: 10.1007/s10792-021-01739-8

7. Jiang Y, Li Y, Liu XW, Xu J. A novel tectonic keratoplasty with femtosecond laser intrastromal lenticule for corneal ulcer and perforation. *Chin Med J.* (2016) 129:1817–21. doi: 10.4103/0366-6999.186639

8. Pant OP, Hao JL, Zhou DD, Lu CW. Tectonic keratoplasty using femtosecond laser lenticule in pediatric patients with corneal perforation secondary to blepharokeratoconjunctivitis: a case report and literature review. *J Int Med Res.* (2019) 47:2312–20. doi: 10.1177/0300060519841163

9. Zhou Y, Zhang J, Zheng Y, Liu Q, Wei W, Wang N. The early clinical efficacy of allogeneic corneal lens inlays in correction of hyperopia. *Zhonghua Yan Ke Za Zhi [Chin J Ophthalmol]*. (2015) 51:683–8.

10. Zhang J, Zhou Y. Small incision lenticule extraction (SMILE) combined with allogeneic intrastromal lenticule inlay for hyperopia with astigmatism. *PLoS One*. (2021) 16:7667. doi: 10.1371/journal.pone.0257667

11. Santra M, Liu YC, Jhanji V, Yam GH. Human SMILE-derived stromal Lenticule scaffold for regenerative therapy: review and perspectives. *Int J Mol Sci*. (2022) 23:967. doi: 10.3390/ijms23147967

12. Yin H, Qiu P, Wu F, Zhang W, Teng W, Qin Z, et al. Construction of a corneal stromal equivalent with SMILE-derived lenticules and fibrin glue. *Sci Rep*. (2016) 6:33848. doi: 10.1038/srep33848

13. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. (2009) 6:e1000097. doi: 10.1371/journal.pmed.1000097

14. Santos WMD, Secoli SR, Püschel VAA. The Joanna Briggs institute approach for systematic reviews. *Rev Lat Am Enfermagem*. (2018) 26:e3074. doi: 10.1590/1518-8345.2885.3074

15. Magesh S, John D, Li WT, Li Y, Mattingly-app A, Jain S, et al. Disparities in COVID-19 outcomes by race, ethnicity, and socioeconomic status: a systematic-review and meta-analysis. *JAMA Netw Open*. (2021) 4:e2134147. doi: 10.1001/jamanetworkopen.2021.34147

16. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg*. (2003) 73:712–6. doi: 10.1046/j.1445-2197.2003.02748.x

17. Hou K, Yu Z, Jia Y, Fang H, Shao S, Huang L, et al. Efficacy and safety of ibrutinib in diffuse large B-cell lymphoma: a single-arm meta-analysis. *Crit Rev Oncol Hematol*. (2020) 152:103010. doi: 10.1016/j.critrevonc.2020.103010

18. West CP, Dyrbye LN, Erwin PJ, Shanafelt TD. Interventions to prevent and reduce physician burnout: a systematic review and meta-analysis. *Lancet*. (2016) 388:2272–81. doi: 10.1016/S0140-6736(16)31279-X

19. Chia MA, Taylor JR, Stuart KV, Khawaja AP, Foster PJ, Keane PA, et al. Prevalence of diabetic retinopathy in indigenous and non-indigenous Australians: a systematic review and meta-analysis. *Ophthalmology*. (2023) 130:56–67. doi: 10.1016/j.ophtha.2022.07.024

20. Hou J, Wang Y, Zhang J, Lei Y, Ma Z, Zhang Y, et al. Corneal densitometry after allogeneic small-incision intrastromal lenticule implantation for hyperopia correction. *BMC Ophthalmol*. (2022) 22:286. doi: 10.1186/s12886-022-02454-3

21. Wu J, Xiong L, Wang Z, Reinstein DZ, Vida RS, Archer TJ. Correction of moderate to high hyperopia with implantation of an allogeneic refractive lenticule. *J Refract Surg*. (2020) 36:772–9. doi: 10.3928/1081597X-20200826-01

22. Brar S, Ganesh S, Sriganesh SS, Bhavsar H. Femtosecond intrastromal Lenticule implantation (FILI) for management of moderate to high hyperopia: 5-year outcomes. *J Refract Surg*. (2022) 38:348–54. doi: 10.3928/1081597X-20220503-01

23. Li M, Li M, Sun L, Ni K, Zhou X. Predictive formula for refraction of autologous lenticule implantation for hyperopia correction. *J Refract Surg*. (2017) 33:827–33. doi: 10.3928/1081597X-20171016-01

24. Sun L, Yao P, Li M, Shen Y, Zhao J, Zhou X. The safety and predictability of implanting autologous lenticule obtained by SMILE for hyperopia. *J Refract Surg*. (2015) 31:374–9. doi: 10.3928/1081597X-20150521-03

25. Liu S, Zhang X, Zhou X. Toric Lenticule implantation for correction of hyperopia and astigmatism following small incision Lenticule intrastromal Keratoplasty with the triple marking method. *J Refract Surg*. (2022) 38:82–8. doi: 10.3928/1081597X-20211117-01

26. Liu S, Wei R, Choi J, Li M, Zhou X. Visual outcomes after implantation of allogenic Lenticule in a 100-mu m pocket for moderate to high hyperopia: 2-year results. *J Refract Surg*. (2021) 37:734–40. doi: 10.3928/1081597X-20210730-02

27. Hu M, Li S, Xing X. The attempt for correcting the hyperopia and anisometropia with the femtosecond laser corneal stromal lenticule extraction and autologous transplantation. *Zhonghua Yan Wai Shang Za Zhi*. (2021) 43:e9. doi: 10.3760/cma.j.cn116022-20210608-00179

28. Llovet F, Galal A, Benitez-del-Castillo JM, Ortega J, Martin C, Baviera J. One-year results of excimer laser in situ keratomileusis for hyperopia. *J Cataract Refract Surg*. (2009) 35:1156–65. doi: 10.1016/j.jcrs.2009.03.014

29. Dave R, O'Brart DPS, Wagh VK, Lim WS, Patel P, Lee J, et al. Sixteen-year follow-up of hyperopic laser in situ keratomileusis. *J Cataract Refract Surg*. (2016) 42:717–24. doi: 10.1016/j.jcrs.2016.03.028

30. Nassiri N, Sheibani K, Azimi A, Khosravi FM, Heravian J, Yekta A, et al. Refractive outcomes, contrast sensitivity, HOAs, and patient satisfaction in moderate myopia: Wavefront-optimized versus tissue-saving PRK. *J Refract Surg*. (2015) 31:683–90. doi: 10.3928/1081597X-20150831-01

31. Miraftab M, Hashemi H, Aghamirsalim M, Fayyaz S, Asgari S. Matched comparison of corneal higher order aberrations induced by SMILE to femtosecond assisted LASIK and to PRK in correcting moderate and high myopia: 3.00mm vs. 6.00mm. *BMC Ophthalmol*. (2021) 21:e3. doi: 10.1186/s12886-021-01987-3

32. Zhou X, Qin B, Han T, Shang J, Chen Z, Zhao J, et al. Long-term observation of higher-order aberrations and microdistortions in Bowman's layer after small incision Lenticule extraction for the correcting myopia with spherical equivalent higher than −9.0 diopters. *Front Med*. (2022) 9:814810. doi: 10.3389/fmed.2022.814810

33. Mostafa MM, Abdelmotaal H, Abdelazeem K, Goda I, Abdel-Radi M. *Q*-value customized versus wavefront-optimized ablation in femtosecond laser-assisted LASIK for myopia and myopic astigmatism: a prospective contralateral comparative study. *Eye Vision*. (2022) 9:43. doi: 10.1186/s40662-022-00312-3

34. Iqbal M, Elmassry A, Mounir A, Ibrahim O, Soliman A. A novel *Q*-value-based nomogram for single intracorneal ring segment implantation versus standard manufacturer's nomogram combined with accelerated cross-linking for treatment of keratoconus: a randomized controlled trial. *Acta Ophthalmol*. (2021) 99:e501–11. doi: 10.1111/aos.14611

35. Zhang J, Zheng L, Zhao X, Sun Y, Feng W, Yuan M. Corneal aberrations after small-incision lenticule extraction versus *Q* value-guided laser-assisted in situ keratomileusis. *Medicine*. (2019) 98:e14210. doi: 10.1097/MD.0000000000014210

36. Bohac M, Koncarevic M, Pasalic A, Biscevic A, Merlak M, Gabric N, et al. Incidence and clinical characteristics of post LASIK ectasia: a review of over 30,000 LASIK cases. *Semin Ophthalmol*. (2018) 33:869–77. doi: 10.1080/08820538.2018.1539183

37. Lagali N. Corneal stromal regeneration: current status and future therapeutic potential. *Curr Eye Res*. (2020) 45:278–90. doi: 10.1080/02713683.2019.1663874

38. Mohan RR, Kempuraj D, D'Souza S, Ghosh A. Corneal stromal repair and regeneration. *Prog Retin Eye Res*. (2022) 91:101090. doi: 10.1016/j.preteyeres.2022.101090

39. Liu R, Zhao J, Xu Y, Li M, Niu L, Liu H, et al. Femtosecond laser-assisted corneal small incision allogenic intrastromal lenticule implantation in monkeys: a pilot study. *Invest Ophthalmol Vis Sci*. (2015) 56:3715–20. doi: 10.1167/iovs.14-15296

40. Mohamed-Noriega K, Toh KP, Poh R, Balehosur D, Riau A, Htoon HM. Cornea lenticule viability and structural integrity after refractive lenticule extraction (ReLEx) and cryopreservation. *Mol Vis*. (2011) 17:3437–49.

41. Liu YC, Williams GP, George BL, Soh YQ, Seah XY, Peh GSL, et al. Corneal lenticule storage before reimplantation. *Mol Vis*. (2017) 23:753–64.

42. Xia F, Zhao J, Fu D, Qin B, Chen Z, Zhao Y, et al. Comparison of the effects of temperature and dehydration mode on glycerin-based approaches to SMILE-derived Lenticule preservation. *Cornea*. (2022) 41:470–7. doi: 10.1097/ICO.0000000000002846

frontiers | Frontiers in Medicine

TYPE Review
PUBLISHED 19 February 2024
DOI 10.3389/fmed.2024.1366576

OPEN ACCESS

EDITED BY
Georgios D. Panos,
Nottingham University Hospitals NHS Trust, United Kingdom

REVIEWED BY
Katarzyna Krysik,
Wojewódzki Szpital Specjalistyczny nr 5 Sosnowiec, Poland
Xu Chen,
Shanghai Aier Eye Hospital, China

*CORRESPONDENCE
Jin Yang
✉ jin_er76@hotmail.com

†These authors have contributed equally to this work

RECEIVED 06 January 2024
ACCEPTED 05 February 2024
PUBLISHED 19 February 2024

CITATION
Lin X, Ma D and Yang J (2024) Exploring anterion capsular contraction syndrome in cataract surgery: insights into pathogenesis, clinical course, influencing factors, and intervention approaches.
Front. Med. 11:1366576.
doi: 10.3389/fmed.2024.1366576

Exploring anterion capsular contraction syndrome in cataract surgery: insights into pathogenesis, clinical course, influencing factors, and intervention approaches

Xuanqiao Lin[1,2,3,4†], Dongmei Ma[1,2,3†] and Jin Yang[1,2,3*]

[1]Eye Institute and Department of Ophthalmology, Eye & ENT Hospital, Fudan University, Shanghai, China, [2]Key NHC Laboratory of Myopia, Fudan University, Laboratory of Myopia, Chinese Academy of Medical Sciences, Shanghai, China, [3]Shanghai Key Laboratory of Visual Impairment and Restoration, Shanghai, China, [4]Eye Hospital and School of Ophthalmology and Optometry, Wenzhou Medical University, Wenzhou, China

Anterior capsular contraction syndrome (ACCS) is a challenging complication that can occur following phacoemulsification cataract surgery. Characterized by capsular bag wrinkling, intraocular lens (IOL) decentration and tilt, ACCS can have negative effects on visual outcomes and patient satisfaction. This review aims to investigate the pathogenesis, clinical course, influencing factors, and intervention approaches for ACCS after cataract surgery. By understanding the underlying mechanisms and identifying factors that contribute to ACCS, surgeons can enhance their ability to predict and manage this complication. Various intervention strategies are discussed, highlighting their importance in reducing complications and improving surgical outcomes. However, further research is needed to determine optimal prevention and management strategies through long-term follow-up and comparative analyses. Advancements in this field will ultimately lead to improved visual outcomes and optimized cataract surgery for patients.

KEYWORDS

capsular contraction syndrome, cataract surgery, intraocular lenses, capsular tension ring, laser anterior capsulotomy

1 Introduction

In modern cataract surgery techniques, phacoemulsification has become the preferred method for lens extraction (1, 2). However, as these techniques have been widely applied, it has been increasingly recognized that there are some less common postoperative complications (3). Anterior capsular contraction syndrome (ACCS), characterized by capsular wrinkling, fibrosis leading to reduced equatorial diameter of the capsular bag, intraocular lens (IOL) decentration and tilt, was initially named by Davison (4). The ACCS will have a negative impact on the patient's vision and visual quality. In severe cases, it may also lead to IOL dislocation (5–7). As a result, research on the factors influencing ACCS and intervention measures has become the foundation for ensuring postoperative visual quality stability in patients, especially for high myopia, retinitis pigmentosa (RP), and other high-risk patients.

Therefore, this article provides a comprehensive review of the research progress, influencing factors, and intervention measures for ACCS following cataract surgery (Table 1).

2 Pathogenesis of ACCS

The pathogenesis of ACCS is not fully understood but can be primarily categorized into two aspects: cellular and mechanical.

The cellular pathogenesis involves various factors such as trauma during cataract surgery, inflammatory response following IOL implantation, disruption of the blood-aqueous barrier and blood-retinal barrier, and stimulation from IOLs. These factors can stimulate residual lens epithelial cells (LECs) present at the capsulorhexis opening, leading to the production of excessive ECM, mainly collagen fibers (8). The proliferation and transdifferentiation of LECs ultimately result in ACCS, posterior capsule opacity (PCO), and other complications. In this process, the involvement of various cytokines has been confirmed, including interleukin (IL), transforming growth factor-beta (TGF-β), and alpha-smooth muscle actin (α-SMA) (9, 10). For instance, the inability of TGF-β2 in the aqueous humor to inhibit LECs activity and induce apoptosis due to the obstruction of aqueous humor circulation caused by IOL implantation leads to LECs proliferation (11, 12).

As for mechanical studies, it has been indicated that the decrease or enlargement of the capsulorhexis area is associated with the resultant centrifugal force from the contraction of normal lens fibers and the resultant centripetal force from the contraction of lens fibers at the edge of the capsulorhexis area (13, 14). Therefore, ACCS occurs in patients with weaken zonules because of the imbalance between the centrifugal force generated by the contraction of zonules and the centripetal force generated by the contraction of lens fibers at the edge of the capsulorhexis area. This supports the application of capsular tension ring (CTR) for intervening ACCS (14, 15). Wang et al. (16) suggested that the mechanism by which Neodymium:YAG (Nd:YAG) anterior capsulotomy prevents further deterioration of ACCS may be related to the relaxation of stress on the anterior capsule following continuous curvilinear capsulorhexis (CCC). The biomechanical mechanisms of ACCS need to be given sufficient attention in future researches.

3 Incidence and course of ACCS

Early studies have shown that the incidence of ACCS ranges from 1.4% to 14.0%, with most cases occurring within 3 to 30 weeks after surgery. After 3 months, the contraction of the capsular bag slows down and tends to stabilize (4, 17). However, with recent in-depth studies, we have found that the course of ACCS can develop in the weeks to years following surgery and in high-risk patients such as those with pseudoexfoliation (PEX), high myopia, and RP, the incidence of ACCS may increase to 10% to 30% or more (18, 19). Furthermore, a comprehensive population study with a 30 years follow-up indicates that late in-the-bag IOL dislocation can occur after cataract surgery, ranging from 6 months to 25 years or even longer, and it is associated with zonular dehiscence and capsular bag contraction (20, 21).

However, not all cases of ACCS will necessarily result in IOL dislocation. The progression of ACCS can be divided into multiple stages (4, 7). In the early stage (approximately less than 1 month) of ACCS, the patient exhibits fibrosis of the capsulorhexis edge, along with mild thickening and opacification of the anterior capsule. Wrinkling of the capsular bag is observed, resulting in a slight reduction in the area of

TABLE 1 Influencing factors for ACCS in this review.

	Risk factors	Prevention factors
CCC factor	Oversized or undersized capsulorhexis area diameter	Suitable capsulorhexis area diameter
IOL factors	Hydrophilic material	Hydrophobic material
	Single-piece design	"Peak-like" shape edge design
	C-Loop haptic	Plate haptic
	Hinge-based accommodative IOL	More haptics IOL
Diseases factors	High myopia	No Relevant Diseases
	RP	
	Uveitis	
	PEX syndrome	
	Diabetes	
	Dystrophia myotonica	
Intervention factors	No Intervention Conducted	Anterior capsule polishing
		Implantation of CTR
		IOL modification
		Anti-inflammatory medications
		Prophylactic laser anterior capsulotomy
Other factors	Advanced age	

ACCS, anterior capsular contraction syndrome; CCC, continuous curvilinear capsulorhexis; IOL, intraocular lens; RP, retinitis pigmentosa; PEX, pseudoexfoliation; CTR, capsular tension ring.

CCC. Visual acuity and contrast sensitivity remain unaffected, and the patient does not experience significant glare symptoms. With the continuous progression of capsular bag contraction, the area of CCC significantly decreases. The degree of contraction varies in different quadrants, with the opening tending to shrink more rapidly in the corresponding quadrants. This leads to a slight displacement of IOL. At this point, due to the change in the position of IOL, there is a change in refractive status. Research has shown that when the decentration of the IOL exceeds 1.0 mm or the tilt angle is greater than 5 degrees, it will have an impact on vision (22, 23). Additionally, the contraction of the capsule causes wrinkling of the posterior capsule, resulting in the Maddox rod effect, which can induce glare. As time passes, the area of the anterior capsular opening continues to decrease due to the contraction of the capsular bag, leading to compression on the haptics, causing them to bend and resulting in more significant eccentricity and displacement (24). Finally, when the zonules are unable to withstand the contraction of the capsular bag, it can result in zonular dehiscence and dislocation of the IOLs. Based on the patient's corrected distance visual acuity, fibrotic tissue appearance, and residual anterior chamber opening, previous researchers have clinically graded the ACCS (Table 2) (23). With the continuous advancement in research on ACCS, early intervention for high-risk patients has led to a reduction in the number of severe ACCS cases. Future studies should focus on determining the precise timing of capsular contraction, in order to better determine the appropriate follow-up schedule.

4 Influencing factors for ACCS

4.1 Impact of CCC on ACCS

The direction of changes in the capsulorhexis area diameter is directly related to the size due to the forces generated during fibrosis contraction (14). An appropriately sized CCC maintains the opening area of the anterior capsule during postoperative capsular fibrosis, ensuring a stable position of the IOL within the capsular bag and preventing PCO (25, 26). Through the comparison of openings with different capsulorhexis diameters, Joo et al. (24) propose that a CCC larger than 5.5 mm exhibits an increasing trend in the subsequent changes of the opening area of the anterior capsule, while a CCC smaller than 5.0 mm results in a gradual reduction in the opening area of the anterior capsule. When the CCC is too small or off-center, postoperative wrinkling and contraction of the capsular bag can lead to a decrease in the opening area of the anterior capsule and even the occurrence of IOL decentration (24). However, the capsulorhexis area larger than 6.5 mm can damage the attachment point of the zonules, reducing the safety of the surgical procedure and causing zonular laxity. Therefore, when implanting an IOL with an optic diameter of 6.0 mm, the capsulorhexis area diameter should be in the range of 5.5 to 6.0 mm. Our team also recommends performing such diameter for highly myopic patients (27). In order to reduce the incidence of ACCS in patients at high risk of capsular contraction, it is essential to conduct further research to determine the optimal capsulorhexis size.

4.2 Impact of IOL characteristics on ACCS

4.2.1 Optic of IOL

It has been observed that IOL optic materials have a significant impact on this condition among the controllable factors (28). The materials of optic can also be classified based on their chemical properties, such as silicone gel, hydrogel polymethyl-methacrylate (PMMA) and acrylate acid. Several previous studies have consistently reported that the extent of ACCS is greater after implantation of silicone or hydrogel IOLs compared to PMMA or acrylic IOLs (28, 29). However, currently, acrylic IOLs are the most commonly used in clinical practice, with PMMA IOLs being almost obsolete. Furthermore, in terms of the acrylic IOLs' reaction to water, IOLs can also be categorized into hydrophilic and hydrophobic materials. Chen et al. (30) conducted a large-scale meta-analysis which showed that greater ACCS occurred in hydrophilic IOL groups compared to hydrophobic IOL groups at postoperative 1 month, 3 months, 6 months, and 1 year, which is consistent with most studies (31). The findings may be explained by the adhesion of optic materials to the capsule. During the early stages following implantation, the superior biocompatibility of hydrophobic IOLs enables them to securely adhere to the capsule, limiting space for LECs proliferation and ECM synthesis. Consequently, this reduces fibrosis and contraction of the anterior capsule (32). In order to improve the biocompatibility of optic, scientists have started to modify IOLs and have achieved promising results (33). In the future, it will be necessary to further compare the impact of different materials on ACCS and develop new types of IOL materials.

TABLE 2 Classification of anterior capsular contraction syndrome.

Grade[a]	Residual AC opening (mm)	Fibrotic tissue appearance	IOL status	Refractive changes	Visual symptoms
I	<4.0	Dense white fibrosis ring at capsulotomy edge	Haptic deformation	None to minimal	None to mild night glare, light sensitivity
II	<3.0	Fibrosis ring visible in pupil margin	IOL tilt <10° or IOL decentration <1.0 mm Zonule stress	SE change >0.5 D/internal astigmatism	Decrease in CDVA <2 lines
III	<2.0	Fibrosis ring in central visual zone (2.0 mm), possibly asymmetric	IOL tilt >10° or IOL decentration >1.0 mm IOL optic deformation	Internal astigmatism, HOAs	Decrease in CDVA >2 lines image distortion
IV	<1.0	IOL surface covered by dense white phimosis material	Loosening of capsular bag or ciliary body detachment	Refraction not measurable	Decrease in CDVA >3 lines

AC, anterior capsule; CDVA, corrected distance visual acuity; HOAs, higher order aberrations; IOL, intraocular lens; SE, spherical equivalent.[a]From this table, 3 of 5 columns must be fulfilled to be graded I to IV.

The optical edge of the IOL includes sharp-edged and round-edged. In recent years, extensive research on PCO has confirmed that square-edged designed IOLs can inhibit the growth of LECs from the peripheral capsular bag towards the visual axis, thereby preventing posterior capsule opacification (34). However, the impact of such IOLs on ACCS remains unclear. Recent research has revealed that an anterior edge design with a "peak-like" shape is more effective than a flat design in preventing the spread of LECs towards the edge of the anterior capsule opening. It helps to maintain the morphology of the anterior capsule opening during the early stages after surgery (35). Additionally, a few studies have indicated that certain factors, such as single-piece design or IOLs with thin optics, may increase the risk of capsule contraction (32, 36). However, research on the optic design is still far from sufficient, and further in-depth studies are needed to understand its impact on ACCS.

4.2.2 Haptic of IOL

The haptic component of a IOL plays a crucial role in the interaction with the capsular bag. Regarding the materials commonly used for IOL haptics, including PMMA, polyvinylidene fluoride (PVDF), and acrylate, current studies have indicated that the material of IOL haptics does not have a significant impact on capsule contraction (6, 37). Some studies have compared an IOL with a PMMA haptic and a hydrophobic acrylic optic (Hoya YA60BBR; Hoya, Tokyo, Japan) to other commonly used IOLs. Although no statistically significant differences were found, it was observed that the ACCS of this type of IOL was less than others at 3 months postoperatively. Additional researches are required to explore the IOLs that effectively minimize ACCS.

In contrast to the optic, the haptic of the IOL has a greater mechanical influence on the capsulorrhexis area through direct interaction with the capsular bag (38). As the lens capsule is surrounded by the zonule system, an imbalance of forces can occur due to unmatched number, position, and shape of the haptics (35). For instance, plate haptic IOLs are known to exhibit more pronounced ACCS due to less capsule dilation caused by the centrifugal haptics (38). Moreover, the number and arrangement of haptics may interact with the capsule in a more complex manner. Studies have indicated that IOLs with four haptics can provide more precise fixation within the capsule, resulting in a larger contact area and more stable capsulorhexis margins (39). Choi et al. (38) suggested that to prevent ACCS, it is essential that the haptics uniformly support the zonule. For hinge-based accommodative IOLs, the presence of a hinge makes it more susceptible to the effects of ACCS, which can impact surgical outcomes (40). However, there is currently a lack of research on whether the presence of a hinge can trigger ACCS. Exploring effective haptic designs that minimize ACCS remains a critical area for additional research and study.

4.3 Impact of ocular and systemic diseases on ACCS

4.3.1 High myopia

High myopia, defined by a refractive error exceeding −6.0 diopters (D) or an axial length (AL) greater than 26 mm, is more common in Asian populations (27). According to our research based on a large sample of over 4000 cataract patients, the incidence of ACCS in highly myopic cataract patients was reported to be 2.1%, which is significantly higher compared to the incidence rate of 0.15% to 0.86% observed in the general population with age-related cataracts (41). Tehrani et al. (42) proposed that the degree of capsular contraction is positively correlated with AL, based on their measurements of eye axis and postoperative capsular bag diameters in 58 patients within 6 months after surgery. This implies that as the AL increases, the degree of capsular contraction also increases. As the axial length of the eye increases, there can be elongation and weakening of the zonular processes. This can be attributed to the imbalance between the size of the lens and the size of the eyeball (15). Additionally, the heightened levels of growth factors and proinflammatory status in highly myopic eyes are believed to play a role in the proliferation of LECs, leading to the development of ACCS (43). Our team identified elevated levels of TGF-β2 in the aqueous humor and upregulated expression of TGF-βRII (the type II receptor for TGF-β2) in LECs in highly myopic cataract patients, particularly in those with dark nuclei. This finding suggests that the severity of ACCS may be related to the severity of cataracts (27). Both inflammation and zonular weakness have a combined impact on the development of ACCS in highly myopic patients. In more severe cases, as Jeon and Kim reported, the incidence of IOL dislocation in highly myopic patients was significantly greater compared to the general patient population (44). Therefore, in Chinese patients, high myopia is the most common risk factor for in-the-bag IOL dislocation (45). Hence, in clinical practice, for highly myopic patients, it is advisable to select IOLs with milder capsular contraction and implement appropriate intervention measures to prevent the occurrence of severe ACCS and even IOL dislocation (Figure 1).

4.3.2 Retinitis pigmentosa

The association between ACCS and RP was initially reported by Hayashi et al. (46). On the one hand, in patients with RP, zonular weakness has been documented and is associated with the imbalance between the outward zonular force and inward force caused by capsular fibrosis at the capsulorrhexis margin (47). The degeneration of zonule might be caused by a lipid peroxidative mechanism (48, 49). Researches have also demonstrated that degeneration of photoreceptors can lead to an upregulation of pro-inflammatory

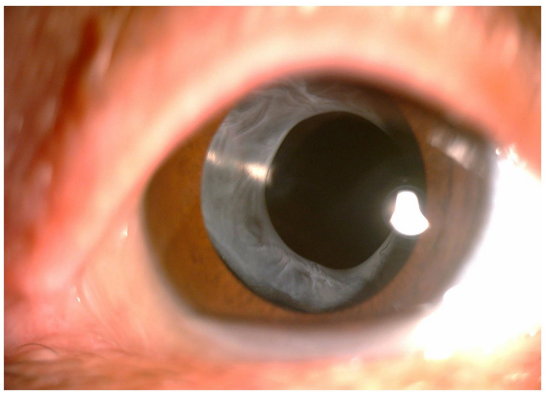

FIGURE 1
Anterior segment photograph of anterior capsular contraction syndrome in a high myopia patient.

cytokines and chemokines, resulting in the development of a chronic inflammatory state in patients with RP (50). RP was also reported to be one of the predisposing factors of late spontaneous IOL-capsular bag complex dislocation (49, 51). On the other hand, recently, numerous studies have confirmed the role of inflammatory response and cytokines, such as platelet-derived growth factor AA (PDGF-AA), matrix metalloproteinase-2 (MMP-2), MMP3, MMP-7 and MMP-8, in the development of ACCS following cataract surgery in RP patients (52, 53). That may reveal the pathogenesis of ACCS in RP patients. Additionally, the liquefaction of the vitreous may lead to postoperative insufficient support of the capsular bag, which could potentially become one of the reasons for IOL dislocation (53). Further works are required to determine the conclusive evidence of the pathogenesis to identify targeted and effective therapeutics, and specific prevention to limit the occurrence of surgical complication (Figure 2).

4.3.3 Uveitis

Uveitis is a prevalent ocular condition characterized by inflammatory processes that cause structural and functional damage to both the anterior and posterior segments of the eye (54). In the past, cataract surgery was not recommended for patients with intraocular inflammation due to the higher risk of complications after the procedure (55). In uveitis cases, it is possible for inflammation to extend to the pars plicata, leading to zonular instability. The inflammation of the ciliary body can exacerbate the destabilization of the zonules at their insertion sites. This is related to the adherence of white blood cells or fibrin on the surface of the ciliary body (56). Moreover, patients with uveitis not only experience inflammation associated with the condition itself but also in relation to the cataract surgery procedure. The presence of inflammatory factors stimulates LECs to secrete an increased amount of growth factors, which promotes fibrotic growth of the capsular bag. This ultimately increases the risk of early occurrence of ACCS (54). In the study conducted by Chen et al. (57), it was found that the active inflammation tends to subside by 3 months, while the restoration of blood-aqueous barrier function may require a longer period of time. In order to minimize the occurrence of postoperative ACCS, it is of utmost importance to adequately control inflammation prior to surgery, ensure meticulous surgical technique, and enhance anti-inflammatory measures during the postoperative period (58, 59). Nevertheless, uveitis is a broad classification, and further research is needed to understand the impact of different types of uveitis on ACCS (Figures 3, 4).

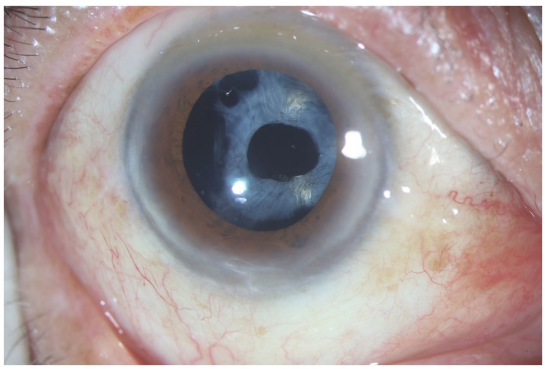

FIGURE 2
Anterior segment photograph of anterior capsular contraction syndrome in a retinitis pigmentosa patient.

4.3.4 PEX syndrome

PEX is a disorder of the ECM that is associated with aging and can result in various ocular complications (60). The prevalence of PEX shows significant variation based on geographic location and ethnicity. Studies examining specific populations have revealed a higher occurrence (ranging from 25% to 30%) in certain ethnic groups, including northern Scandinavians, Saudi Arabians, and Navajo Indians (61, 62). Previous studies have indicated that the accumulation of PEX material causes mechanical weakening of the zonule and disrupts their attachment to the ciliary epithelial basement membrane, both at their origins and insertions. Moreover, PEX eyes demonstrate heightened elastinolysis, resulting in enzymatic degradation of the zonules and increased fragility (63). Ruotsalainen and Tarkkanen (64) conducted a study and concluded that the elevated rate of complications observed in eyes with PEX could be attributed to the presence of relatively fragile zonules commonly found in PEX cases. Furthermore, it has been reported that PEX can compromise the integrity of the blood-aqueous barrier (65, 66), leading to the increased release of inflammatory cytokines and ECM material into the anterior chamber. This can further contribute to the occurrence of ACCS. Additionally, PEX is the most common underlying condition for spontaneous in-the-bag IOL dislocation (19). It is currently believed that implanting a CTR or postoperative use of nonsteroidal anti-inflammatory drugs (NSAIDs) can be effective in reducing postoperative ACCS in patients with PEX (62, 67, 68). Currently, many substances have been found to be possibly associated with PEX and ACCS. Identifying and potentially distinguishing factors involved in the complex pathophysiological steps corresponding to LEC stress response remains a priority, which may help prevent the occurrence of these two complications.

4.3.5 Diabetes

Takamura et al. (69) found that diabetes mellitus serves as a systemic risk factor for capsule contraction, especially in the presence of diabetic retinopathy (DR), when comparing the ACO area with nonproliferative DR, those without DR, and those without DM. Further, the intensity of aqueous flare in diabetic patients 1 week after surgery was significantly correlated with the severity of ACCS postoperatively. On the other hand, researchers have demonstrated through immunohistochemical analysis that LECs in diabetic eyes exhibit higher levels of IL-1 and TGF-β activities compared to normal eyes. Diabetic eyes show a stronger proliferation of LECs compared to normal eyes (9). The glycemic control could potentially impact the severity of postoperative ACCS. However, despite a case report (70), there is currently a lack of research investigating the relationship between patients' blood glucose or glycated hemoglobin levels and the severity of ACCS.

As for intervention for ACCS in diabetic patients, preventing anterior inflammation may play a critical role in inhibiting the development of postoperative ACCS. NSAIDs have been demonstrated to inhibit the synthesis of prostaglandins, suppressing anterior inflammation (69). Recently, Baldysiak-Figiel et al. (71) have discovered that octreotide exhibits the capacity to decrease proliferative responses of LECs and effectively inhibits cell

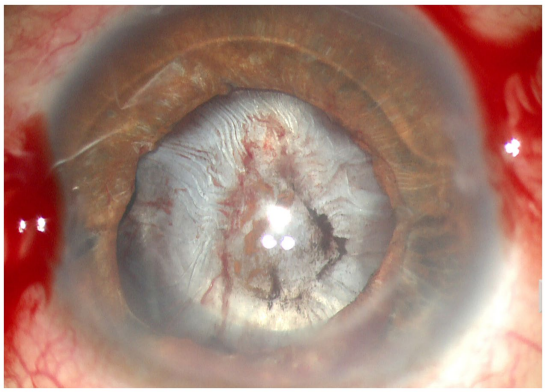

FIGURE 3
Anterior segment photograph of anterior capsular contraction syndrome in a chronic iridocyclitis patient.

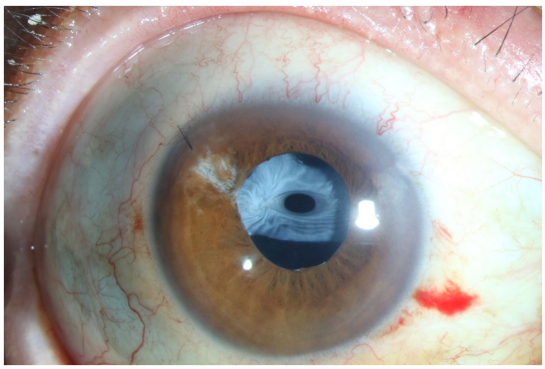

FIGURE 4
Anterior segment photograph of anterior capsular contraction syndrome in a traumatic sympathetic ophthalmia patient.

proliferation induced by growth factors. This suggests that octreotide shows potential as a medication for preventing growth factor-related proliferative complications, including PCO and ACCS, in diabetic patients undergoing cataract surgery.

4.3.6 Dystrophia myotonica

Dystrophia myotonica, an autosomal dominant disease, is caused by a mutation in the dystrophia myotonica protein kinase gene. It has been found to have a higher prevalence in European regions compared to non-European regions, and it was observed to be rare in East Asia and sub-Saharan Africa (72). Some researchers proposed that in dystrophia myotonica, the atrophy of the ciliary body may lead to an imbalance of forces, specifically an unopposed centripetal force at the margin of the capsulorhexis (73). It is possible that LECs in individuals with dystrophia myotonica have a higher tendency to undergo an exaggerated fibroblastic, proliferative response after cataract surgery, leading to increased contractility following metaplasia to myofibroblasts. Genetic examinations of LECs in dystrophia myotonica patients have revealed the presence of the dystrophia myotonica-protein kinase (DMPK) gene mutation in these cells (74). However, there is only a few research in this area and more studies are needed to gain further insights.

4.3.7 Other disease factors

In clinical practice, in addition to the aforementioned conditions, other diseases have been reported to be associated with ACCS, such as chronic angle-closure glaucoma (75, 76), Marfan syndrome (77) and those following full-thickness penetrating keratoplasty (78). These may also be associated with weakened zonules or inflammatory responses. However, currently, there is a lack of research revealing the correlation between these diseases and ACCS. It is anticipated that more studies in these fields will be conducted in the future to shed light on these associations.

4.4 Other influencing factors

Many studies have indicated that advanced age (≥80 years old) is a risk factor for ACCS after cataract surgery, possibly due to the increased fragility of zonules in elderly individuals (4, 20). This suggests that the older the patient, the more important it is to implement appropriate interventions. Recent study has indicated that in congenital cataract patients who undergo surgery at a younger age, there is a significantly increased level of proinflammatory cytokines in the aqueous humor postoperatively. However, there is no statistically significant correlation between these cytokine levels and postoperative capsular contraction (10). Further research could explore the relationship between age and the incidence of ACCS, but it is essential to consider the differences in the etiology of cataract patients across different age groups.

5 Interventions for ACCS

5.1 Intraoperative intervention methods

5.1.1 Anterior capsule polishing

Reducing the number of LECs can be considered as one of the intervention methods for postoperative ACCS. Currently, several approaches are being employed in clinical practice to clear LECs, including the use of antimetabolic drug mitomycin (79), drug-loaded delivery systems (80), and physical treatments (81) such as heating or cryotherapy. However, each of these approaches has its limitations.

In contrast, anterior capsule polishing is considered most widely used method (82–84). The ultrasound irrigation and aspiration tip has been identified as the most effective instrument for mechanical polishing (85). Numerous studies have demonstrated that the aspiration of LECs from the anterior lens capsule is a beneficial approach in preserving the size of a capsulorhexis, subsequently serving as a preventive measure against ACCS (83, 86, 87). The study by Zhao et al. (88) compared a group of cataract patients in which anterior capsule polishing was performed in one eye and not in the other. They successfully demonstrated that this approach reduces the severity of anterior capsule contraction and enhances the stability of IOLs in highly myopic patients. However, the efficacy of anterior capsule polishing during phacoemulsification surgery continues to be a topic of debate and controversy (89). Also, as the cataract becomes more mature, the zonule become increasingly delicate (90), eventually leading to the IOL dislocation, a condition in which the aspiration of anterior epithelial cells can become remarkably challenging or even unfeasible. Thus, for patients at high risk of ACCS, a thorough

examination of the zonular condition is essential before considering anterior capsule polishing. Combining anterior capsule polishing with CTR implantation may be a safer approach.

5.1.2 Implantation of CTR

The implantation of CTRs provides centrifugal force to redistribute forces between existing zonules, preventing force concentration and protecting fragile areas. This effectively prevents significant capsular bag shrinkage in eyes with or without zonular weakness. This preservation plays a crucial role in preventing substantial decentration and tilt of the IOL, as well as the occurrence of severe ACCS. This helps to maintain the effective position and stability of the IOL, improve higher-order aberrations, and enhance visual quality (91). Therefore, we recommend the intraoperative implantation of CTR for cataract patients who have risk factors, as a preventive measure against postoperative ACCS (30, 92). For instance, a retrospective study conducted on patients undergoing cataract surgery with RP revealed that the incidence of ACCS was lower in those who received CTR implantation compared to those without CTR (93). In a 3 months follow-up study of 20 highly myopic patients with axial length exceeding 28 mm, Yang et al. (94) found that those who received CTR implantation had lager ACO area and less pronounced IOL tilt compared to those without CTR implantation. However, even with the implantation of a CTR, complete prevention of IOL dislocation may not be guaranteed (95). Interestingly, although there is limited similar research, Vanags et al. (96) compared the effect of a basic (11 or 12 mm) or Cionni (12 mm) CTR on ACCS. They observed differences in the effects at 1 month after the surgery, with the larger diameter CTR demonstrating better intervention outcomes. Looking ahead, further research into CTRs is expected to shed light on their optimal use and effectiveness in preventing ACCS and IOL dislocation. Moreover, in recent years, several modified CTR designs have emerged, awaiting further investigation and study.

5.1.3 IOL modification

The biocompatibility of IOL is a crucial aspect in minimizing postoperative inflammation. In the past, IOL modification, especially the utilization of heparin-surface-modified (HSM) IOLs, has been widely employed for several years to enhance their biocompatibility. The application of heparin surface modification technology was initially introduced to PMMA lenses in the early 1990s, and it has demonstrated notable benefits in reducing inflammation (97). It can effectively mitigate the breakdown of the blood-aqueous barrier and diminish the foreign body response and imparts a negative charge to the surface of IOLs, thereby reducing the associated complications (98). In studies conducted by Krall et al., the inflammation levels of HSM hydrophobic acrylic IOLs were compared to un-coated acrylic IOLs. The findings revealed that in the early postoperative stage, the HSM IOL group exhibited lower inflammation levels compared to the un-coated IOL group. However, Maedel et al. (99) found that the heparin surface modification had no impact on postoperative ACCS when implanting hydrophobic acrylic IOLs. Furthermore, Tan et al. (100) conducted a new synthesis of a hydrophilic copolymer, and the resulting modified IOL demonstrated a significant reduction in postoperative inflammation and ACO. We can anticipate the development of more modified materials that can be used to prevent ACCS.

5.2 Postoperative intervention methods

5.2.1 Anti-inflammatory medications

Inflammatory response is a significant factor that influences capsular contraction. Therefore, it is crucial to administer anti-inflammatory treatment before and after the surgery to high-risk patients with significant inflammatory reactions (101). Researchers have found that both NSAIDs and corticosteroids are effective in preventing ACCS in rabbit eyes (102). On the other hand, both corticosteroids and NSAIDs are associated with noticeable side effects when used long-term, which necessitates caution, particularly in patients such as PEX, RP, and uveitis (103). However, there is currently limited research on the use of anti-inflammatory drugs for preventing ACCS. Further studies are needed to explore this area in depth.

5.2.2 Laser anterior capsulotomy

To prevent the occurrence of ACCS, Davison first proposed performing Nd:YAG laser anterior capsulotomy 2–3 weeks after cataract surgery (4). For patients with mild cases of ACCS, it is a simple non-surgical treatment option. Nd:YAG laser primarily works through the ionization effect, generating plasma within the target tissue. It utilizes the shockwave produced by the resulting explosion to disrupt and disintegrate the tissue. This makes it an ideal non-surgical choice for treating ACCS (104). Hayashi et al. (105) analyzed the anterior capsulotomy area before and after Nd:YAG laser capsulotomy in 32 eyes, and found that contrast sensitivity at most visual angles significantly improved following the procedure. The way of laser incision needs to be adjusted based on the degree of wrinkling in the anterior capsule. In the early stages of capsular contraction, before any visual impairment occurs, incisions can be made near the area of contraction. When the size of the anterior opening is smaller than the size of the pupil and accompanied by fibrotic proliferation of the anterior capsule, a radial Nd:YAG laser capsulotomy should be performed in all four quadrants. Interestingly, Hayashi et al. (106) compared the effects of different numbers of incisions and found that three relaxing incisions made in the anterior capsule decrease anterior capsule contraction, whereas two incisions do not. Further, it is reported that more than four incisions without extending beyond the IOL optic edge are needed to prevent free-floating remnants from dropping into the anterior chamber, impacting the sight during reading (107). Regarding the capsulotomy method, radial incision is currently the most widely used. Elmohamady et al. (108) found that circular Nd:YAG anterior capsulotomy is considered more effective and safe than radial capsulotomy in a 1 year follow-up study. However, it is important to note that capsular contraction or Nd:YAG laser anterior capsulotomy carries the risk of zonular breakage or weakening. Furthermore, anterior capsulotomy alone cannot halt the progression of intrinsic zonular weakness (109, 110). Complications such as hyphema, inflammation, and elevated intraocular pressure can occur as secondary effects of Nd:YAG laser anterior capsulotomy (111). With the advancement of technology, the utilization of femtosecond laser technology in cataract surgery has allowed for a less invasive and safer approach, minimizing injury to the zonules. This technique has been widely adopted to effectively and safely enlarge the capsulorhexis (112). Further research is needed to investigate whether a femtosecond laser can offer advantages over existing treatment methods in intervening ACCS (Figure 5).

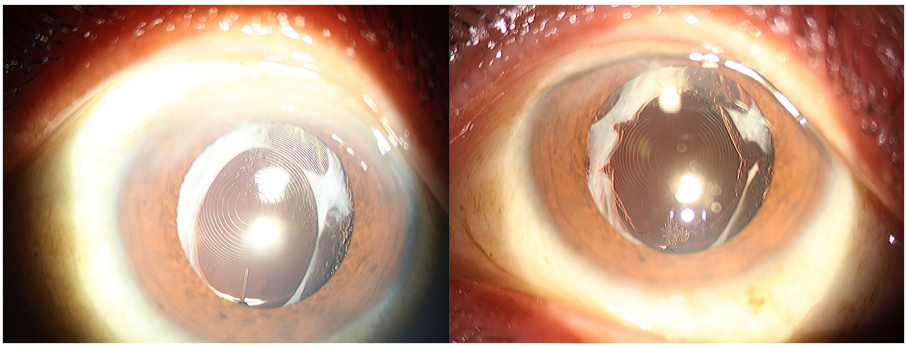

FIGURE 5
Anterior segment photographs in a patient with capsular contraction syndrome before (left) and after (right) Neodymium:YAG laser anterior capsulotomy.

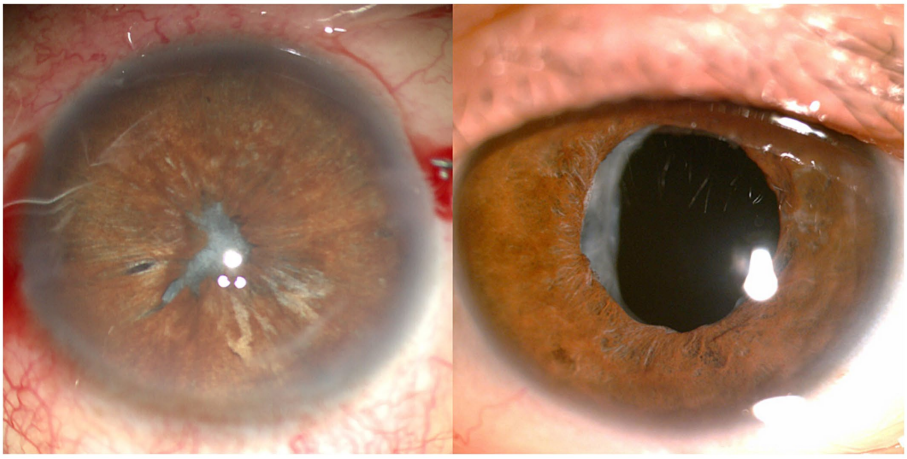

FIGURE 6
Anterior segment photographs in a patient with capsular contraction syndrome before (left) and after (right) capsular bag relaxation surgery.

5.2.3 Surgical methods for intervention in ACCS

For patients with severe ACCS, the presence of densely hyperplastic fibers that cannot be disrupted by laser treatment poses a challenge. Moreover, the large fragments of fibrous membrane that result from the disruption of hyperplastic fibers may not be absorbed spontaneously. In these cases capsular bag relaxation surgery (CBRS) emerges as a suitable alternative (113). The CBRS procedure in this study involved two techniques: actinoid relaxing incision and secondary CCC, the latter is mainly used for cases where the anterior capsular opening is approaching closure. The traditional method mainly use capsulorhexis forceps, whereas Yeh et al. (114) proposed using a vitrector handpiece to achieve a more circular opening, albeit at the cost of increased time consumption. However, it is worth noting that this method may have drawbacks when dealing with poor zonular function, as it can potentially cause zonule damage and result in IOL deviation (40). Additionally, for patients with severe conditions such as IOL dislocation, anterior capsule release may be not effective. In such cases, procedures such as IOL suspension or ciliary sulcus suture fixation may be necessary to restore good visual acuity for the patient (115). Importantly, it should be clear that thorough preoperative assessment and proactive postoperative prevention are essential. These are far more important than surgical treatment (Figure 6).

6 Conclusion

In conclusion, ACCS remains a challenging complication in cataract surgery, affecting both the visual outcomes and patient satisfaction. Important factors influencing capsular contraction include surgical techniques, choice of IOL, intraocular inflammation and various diseases. Interventions include avoiding excessive manipulation of intraocular tissues, utilizing IOLs with good biocompatibility, managing intraocular inflammation appropriately, and regular follow-up with prompt management of early capsular contraction. These interventions are vital in reducing surgical complications and improving surgical outcomes. Future studies should focus on long-term follow-up and comparative analyses to determine the most successful interventions for preventing and managing ACCS. Ultimately, with continued research and advancements,

we can strive towards minimizing the occurrence of this syndrome and optimizing visual results for cataract surgery patients.

Author contributions

XL: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. DM: Investigation, Writing – review & editing. JY: Conceptualization, Supervision, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Sela TC, Hadayer A. Continuous curvilinear capsulorhexis—a practical review. *Semin Ophthalmol*. (2022) 37:583–92. doi: 10.1080/08820538.2022.2054663

2. Hu WF, Chen SH. Advances in capsulorhexis. *Curr Opin Ophthalmol*. (2019) 30:19–24. doi: 10.1097/icu.0000000000000539

3. Wilson ME Jr, Trivedi RH, Bartholomew LR, Pershing S. Comparison of anterior vitrectorhexis and continuous curvilinear capsulorhexis in pediatric cataract and intraocular lens implantation surgery: a 10-year analysis. *J AAPOS*. (2007) 11:443–6. doi: 10.1016/j.jaapos.2007.03.012

4. Davison JA. Capsule contraction syndrome. *J Cataract Refract Surg*. (1993) 19:582–9. doi: 10.1016/s0886-3350(13)80004-1

5. Marenco M, Mangiantini P, Scuderi L, Lambiase A, Sacchetti M. A modified femtosecond laser technique for anterior capsule contraction syndrome. *J Ophthalmol*. (2020) 2020:9423267. doi: 10.1155/2020/9423267

6. Michael K, O'Colmain U, Vallance JH, Cormack TG. Capsule contraction syndrome with haptic deformation and flexion. *J Cataract Refract Surg*. (2010) 36:686–9. doi: 10.1016/j.jcrs.2009.09.042

7. Chen L, Zhong Y, Yao K, Fu Q. Effect of intraocular lens material and haptic design on anterior capsule contraction after cataract surgery: a systematic review and meta-analysis. *Graefes Arch Clin Exp Ophthalmol*. (2023). doi: 10.1007/s00417-023-06230-x [Epub ahead of preprint].

8. Tsinopoulos I, Symeonidis C, Frangou E, Dimitrakos SA. Capsule contraction syndrome in eight cases of hydrophobic one-piece intraocular lens implantation. *Clin Exp Optom*. (2008) 91:469–72. doi: 10.1111/j.1444-0938.2007.00243.x

9. Hayashi Y, Kato S, Maeda T, Kaiya T, Kitano S. Immunohistologic study of interleukin-1, transforming growth factor-beta, and alpha-smooth muscle actin in lens epithelial cells in diabetic eyes. *J Cataract Refract Surg*. (2005) 31:2187–92. doi: 10.1016/j.jcrs.2005.03.063

10. Zhao Y, Deng X, Chang P, Hu M, Li Z, Zhang F, et al. Expression profiles of inflammatory cytokines in the aqueous humor of children after congenital cataract extraction. *Transl Vis Sci Technol*. (2020) 9:3. doi: 10.1167/tvst.9.8.3

11. Yu XH, Liu SY, Li CF. TGF-β2-induced NEAT1 regulates lens epithelial cell proliferation, migration and EMT by the miR-26a-5p/FANCE axis. *Int J Ophthalmol*. (2021) 14:1674–82. doi: 10.18240/ijo.2021.11.05

12. Wang J, Zhang J, Xiong Y, Li J, Li X, Zhao J, et al. TGF-β regulation of microRNA miR-497-5p and ocular lens epithelial cell mesenchymal transition. *Sci China Life Sci*. (2020) 63:1928–37. doi: 10.1007/s11427-019-1603-y

13. Kim ES, Kim M, Lee SJ, Han SB, Yang HK, Hyon JY. Postoperative occlusion of visual axis with fibrous membrane in the presence of anterior capsular phimosis in a patient with pseudoexfoliation syndrome: a case report. *BMC Ophthalmol*. (2016) 16:213. doi: 10.1186/s12886-016-0394-y

14. Kurz S, Krummenauer F, Hacker P, Pfeiffer N, Dick HB. Capsular bag shrinkage after implantation of a capsular bending or capsular tension ring. *J Cataract Refract Surg*. (2005) 31:1915–20. doi: 10.1016/j.jcrs.2005.06.046

15. Klysik A, Kaszuba-Bartkowiak K, Jurowski P. Axial length of the eyeball is important in secondary dislocation of the intraocular lens, capsular bag, and capsular tension ring complex. *J Ophthalmol*. (2016) 2016:6431438. doi: 10.1155/2016/6431438

16. Wang YL, Wang ZZ, Zhao L, Xiong SH, Li Q, Wang NL, et al. Finite element analysis of neodymium: yttrium-aluminum-garnet incisions for the prevention of anterior capsule contraction syndrome. *Chin Med J*. (2013) 126:692–6. doi: 10.3760/cma.j.issn.0366-6999.20123244

17. Dahlhauser KF, Wroblewski KJ, Mader TH. Anterior capsule contraction with foldable silicone intraocular lenses. *J Cataract Refract Surg*. (1998) 24:1216–9. doi: 10.1016/s0886-3350(98)80014-x

18. Hong Y, Li H, Sun Y, Ji Y. A review of complicated cataract in retinitis pigmentosa: pathogenesis and cataract surgery. *J Ophthalmol*. (2020) 2020:6699103. doi: 10.1155/2020/6699103

19. Bisevac J, Anisimova NS, Nagymihály R, Kristianslund O, Katta K, Noer A, et al. Long-term myofibroblast persistence in the capsular bag contributes to the late spontaneous in-the-bag intraocular lens dislocation. *Sci Rep*. (2020) 10:20532. doi: 10.1038/s41598-020-77207-7

20. Pueringer SL, Hodge DO, Erie JC. Risk of late intraocular lens dislocation after cataract surgery, 1980–2009: a population-based study. *Am J Ophthalmol*. (2011) 152:618–23. doi: 10.1016/j.ajo.2011.03.009

21. Dabrowska-Kloda K, Kloda T, Boudiaf S, Jakobsson G, Stenevi U. Incidence and risk factors of late in-the-bag intraocular lens dislocation: evaluation of 140 eyes between 1992 and 2012. *J Cataract Refract Surg*. (2015) 41:1376–82. doi: 10.1016/j.jcrs.2014.10.040

22. Nabh R, Ram J, Pandav SS, Gupta A. Visual performance and contrast sensitivity after phacoemulsification with implantation of aspheric foldable intraocular lenses. *J Cataract Refract Surg*. (2009) 35:347–53. doi: 10.1016/j.jcrs.2008.10.043

23. Gerten G, Schultz M, Oberheide U. Treating capsule contraction syndrome with a femtosecond laser. *J Cataract Refract Surg*. (2016) 42:1255–61. doi: 10.1016/j.jcrs.2016.07.020

24. Joo CK, Shin JA, Kim JH. Capsular opening contraction after continuous curvilinear capsulorhexis and intraocular lens implantation. *J Cataract Refract Surg*. (1996) 22:585–90. doi: 10.1016/s0886-3350(96)80014-9

25. Birinci H, Kuruoğlu S, Oge I, Oge F, Acar E. Effect of intraocular lens and anterior capsule opening type on posterior capsule opacification. *J Cataract Refract Surg*. (1999) 25:1140–6. doi: 10.1016/s0886-3350(99)00119-4

26. Langwińska-Wośko E, Broniek-Kowalik K, Szulborski K. The impact of capsulorhexis diameter, localization and shape on posterior capsule opacification. *Med Sci Monit*. (2011) 17:CR577–82. doi: 10.12659/msm.881984

27. Zhu XJ, Chen MJ, Zhang KK, Yang J, Lu Y. Elevated tgf-β2 level in aqueous humor of cataract patients with high myopia: potential risk factor for capsule contraction syndrome. *J Cataract Refract Surg*. (2016) 42:232–8. doi: 10.1016/j.jcrs.2015.09.027

28. Hayashi K, Hayashi H. Intraocular lens factors that may affect anterior capsule contraction. *Ophthalmology*. (2005) 112:286–92. doi: 10.1016/j.ophtha.2004.11.013

29. Hartman M, Rauser M, Brucks M, Chalam KV. Evaluation of anterior capsular contraction syndrome after cataract surgery with commonly used intraocular lenses. *Clin Ophthalmol*. (2018) 12:1399–403. doi: 10.2147/opth.S172251

30. Chen CX, Wang JD, Zhang JS, Xiong Y, Li J, Chen SY, et al. Effect of lens capsular tension ring on preventing capsular contraction syndrome in the surgery of retinitis pigmentosa combined with cataract: retrospective case series. *Int J Clin Pract*. (2021) 75:e14272. doi: 10.1111/ijcp.14272

31. Wang Y, Wang W, Zhu Y, Xu J, Luo C, Yao K. Comparison study of anterior capsule contraction of hydrophilic and hydrophobic intraocular lenses under the same size capsulotomy. *Transl Vis Sci Technol*. (2022) 11:24. doi: 10.1167/tvst.11.1.24

32. Pérez-Vives C. Biomaterial influence on intraocular lens performance: an overview. *J Ophthalmol*. (2018) 2018:2687385. doi: 10.1155/2018/2687385

33. Krall EM, Arlt EM, Jell G, Strohmaier C, Bachernegg A, Emesz M, et al. Intraindividual aqueous flare comparison after implantation of hydrophobic intraocular lenses with or without a heparin-coated surface. *J Cataract Refract Surg*. (2014) 40:1363–70. doi: 10.1016/j.jcrs.2013.11.043

34. Sacu S, Menapace R, Findl O. Effect of optic material and haptic design on anterior capsule opacification and capsulorrhexis contraction. *Am J Ophthalmol*. (2006) 141:488–493.e2. doi: 10.1016/j.ajo.2005.10.041

35. Liu Q, Zhang S, Wang X, Liu J, Zhou G, Yuan X. Effects of intraocular lens anterior edge design on anterior capsule morphology changes following femtosecond laser-assisted capsulotomy. *BMC Ophthalmol*. (2022) 22:515. doi: 10.1186/s12886-022-02751-x

36. Savini G, Barboni P, Ducoli P, Borrelli E, Hoffer KJ. Influence of intraocular lens haptic design on refractive error. *J Cataract Refract Surg*. (2014) 40:1473–8. doi: 10.1016/j.jcrs.2013.12.018

37. Kim SY, Yang JW, Lee YC, Kim SY. Effect of haptic material and number of intraocular lens on anterior capsule contraction after cataract surgery. *Korean J Ophthalmol*. (2013) 27:7–11. doi: 10.3341/kjo.2013.27.1.7

38. Choi M, Lazo MZ, Kang M, Lee J, Joo CK. Effect of number and position of intraocular lens haptics on anterior capsule contraction: a randomized, prospective trial. *BMC Ophthalmol*. (2018) 18:78. doi: 10.1186/s12886-018-0742-1

39. Mingels A, Koch J, Lommatzsch A, Pauleikhoff D, Heiligenhaus A. Comparison of two acrylic intraocular lenses with different haptic designs in patients with combined phacoemulsification and pars plana vitrectomy. *Eye*. (2007) 21:1379–83. doi: 10.1038/sj.eye.6702446

40. Page TP, Whitman J. A stepwise approach for the management of capsular contraction syndrome in hinge-based accommodative intraocular lenses. *Clin Ophthalmol*. (2016) 10:1039–46. doi: 10.2147/opth.S101325

41. Zhang K, Zhu X, Chen M, Sun X, Yang J, Zhou P, et al. Elevated transforming growth factor-β2 in the aqueous humor: a possible explanation for high rate of capsular contraction syndrome in high myopia. *J Ophthalmol*. (2016) 2016:5438676. doi: 10.1155/2016/5438676

42. Tehrani M, Dick HB, Krummenauer F, Pfirrmann G, Boyle T, Stoffelns BM. Capsule measuring ring to predict capsular bag diameter and follow its course after foldable intraocular lens implantation. *J Cataract Refract Surg*. (2003) 29:2127–34. doi: 10.1016/s0886-3350(03)00352-3

43. Zhu X, Zhang K, He W, Yang J, Sun X, Jiang C, et al. Proinflammatory status in the aqueous humor of high myopic cataract eyes. *Exp Eye Res*. (2016) 142:13–8. doi: 10.1016/j.exer.2015.03.017

44. Jeon S, Kim HS. Clinical characteristics and outcomes of cataract surgery in highly myopic Koreans. *Korean J Ophthalmol*. (2011) 25:84–9. doi: 10.3341/kjo.2011.25.2.84

45. Fan Q, Han X, Luo J, Cai L, Qiu X, Lu Y, et al. Risk factors of intraocular lens dislocation following routine cataract surgery: a case-control study. *Clin Exp Optom*. (2021) 104:510–7. doi: 10.1080/08164622.2021.1878829

46. Hayashi K, Hayashi H, Matsuo K, Nakao F, Hayashi F. Anterior capsule contraction and intraocular lens dislocation after implant surgery in eyes with retinitis pigmentosa. *Ophthalmology*. (1998) 105:1239–43. doi: 10.1016/s0161-6420(98)97028-2

47. Park TK, Chung SK, Baek NH. Changes in the area of the anterior capsule opening after intraocular lens implantation. *J Cataract Refract Surg*. (2002) 28:1613–7. doi: 10.1016/s0886-3350(02)01378-0

48. Dikopf MS, Chow CC, Mieler WF, Tu EY. Cataract extraction outcomes and the prevalence of zonular insufficiency in retinitis pigmentosa. *Am J Ophthalmol*. (2013) 156:82. doi: 10.1016/j.ajo.2013.02.002

49. Lee HJ, Min SH, Kim TY. Bilateral spontaneous dislocation of intraocular lenses within the capsular bag in a retinitis pigmentosa patient. *Korean J Ophthalmol*. (2004) 18:52–7. doi: 10.3341/kjo.2004.18.1.52

50. Guo C, Otani A, Oishi A, Kojima H, Makiyama Y, Nakagawa S, et al. Knockout of ccr2 alleviates photoreceptor cell death in a model of retinitis pigmentosa. *Exp Eye Res*. (2012) 104:39–47. doi: 10.1016/j.exer.2012.08.013

51. Jin-Poi T, Shatriah I, Khairy-Shamel ST, Zunaina E. Rapid anterior capsular contraction after phacoemulsification surgery in a patient with retinitis pigmentosa. *Clin Ophthalmol*. (2013) 7:839–42. doi: 10.2147/opth.S42122

52. Lu B, Yin H, Tang Q, Wang W, Luo C, Chen X, et al. Multiple cytokine analyses of aqueous humor from the patients with retinitis pigmentosa. *Cytokine*. (2020) 127:154943. doi: 10.1016/j.cyto.2019.154943

53. Nguyen XT, Moekotte L, Plomp AS, Bergen AA, van Genderen MM, Boon CJF. Retinitis pigmentosa: current clinical management and emerging therapies. *Int J Mol Sci*. (2023) 24:24. doi: 10.3390/ijms24087481

54. Bajraktari G, Jukić T, Kalauz M, Oroz M, Radolović Bertetić A, Vukojević N. Early and late complications after cataract surgery in patients with uveitis. *Medicina*. (2023) 59:59. doi: 10.3390/medicina59101877

55. Elgohary MA, McCluskey PJ, Towler HM, Okhravi N, Singh RP, Obikpo R, et al. Outcome of phacoemulsification in patients with uveitis. *Br J Ophthalmol*. (2007) 91:916–21. doi: 10.1136/bjo.2007.114801

56. Ganesh SK, Sen P, Sharma HR. Late dislocation of in-the-bag intraocular lenses in uveitic eyes: an analysis of management and complications. *Indian J Ophthalmol*. (2017) 65:148–54. doi: 10.4103/ijo.IJO_938_16

57. Chen W, Lin HT, Wu CR, Xie CF, Huang XK, Chen WR. Clinical research of anterior chamber inflammation after phacoemulsification surgery in patients with complicated cataract secondary to uveitis. *Zhonghua Yan Ke Za Zhi*. (2013) 49:212–6. doi: 10.3760/cma.j.issn.0412-4081.2013.03.006

58. Rauz S, Stavrou P, Murray PI. Evaluation of foldable intraocular lenses in patients with uveitis. *Ophthalmology*. (2000) 107:909–19. doi: 10.1016/s0161-6420(00)00056-7

59. Chan NS, Ti SE, Chee SP. Decision-making and management of uveitic cataract. *Indian J Ophthalmol*. (2017) 65:1329–39. doi: 10.4103/ijo.IJO_740_17

60. Schlötzer-Schrehardt U, Naumann GO. Ocular and systemic pseudoexfoliation syndrome. *Am J Ophthalmol*. (2006) 141:921–937.e2. doi: 10.1016/j.ajo.2006.01.047

61. Benitez-del-Castillo Sanchez J, Morion-Grande M, Marco-Garcia MC, Parron-Carreño T. Epidemiology of pseudoexfoliation syndrome: demystifying legends and looking to the future. *Arch Soc Esp Oftalmol*. (2015) 90:455–7. doi: 10.1016/j.oftal.2015.07.002

62. Shingleton BJ, Crandall AS, Ahmed II. Pseudoexfoliation and the cataract surgeon: preoperative, intraoperative, and postoperative issues related to intraocular pressure, cataract, and intraocular lenses. *J Cataract Refract Surg*. (2009) 35:1101–20. doi: 10.1016/j.jcrs.2009.03.011

63. Schlötzer-Schrehardt U, Naumann GO. A histopathologic study of zonular instability in pseudoexfoliation syndrome. *Am J Ophthalmol*. (1994) 118:730–43. doi: 10.1016/s0002-9394(14)72552-8

64. Ruotsalainen J, Tarkkanen A. Capsule thickness of cataractous lenses with and without exfoliation syndrome. *Acta Ophthalmol*. (1987) 65:444–9. doi: 10.1111/j.1755-3768.1987.tb07021.x

65. Shingleton BJ, Marvin AC, Heier JS, O'Donoghue MW, Laul A, Wolff B, et al. Pseudoexfoliation: high risk factors for zonule weakness and concurrent vitrectomy during phacoemulsification. *J Cataract Refract Surg*. (2010) 36:1261–9. doi: 10.1016/j.jcrs.2010.02.014

66. Abela-Formanek C, Amon M, Schauersberger J, Schild G, Kruger A. Postoperative inflammatory response to phacoemulsification and implantation of 2 types of foldable intraocular lenses in pseudoexfoliation syndrome. *Klin Monatsbl Augenheilkd*. (2000) 217:10–4. doi: 10.1055/s-2000-10377

67. Mayer-Xanthaki CF, Hirnschall N, Pregartner G, Gabriel M, Falb T, Sommer M, et al. Capsular tension ring as protective measure against in-the-bag dislocations after cataract surgery. *J Cataract Refract Surg*. (2023) 49:154–8. doi: 10.1097/j.jcrs.0000000000001060

68. Malekahmadi M, Kazemi S, Sharifipour F, Ostadian F, Mahdian Rad A, Mirdehghan MS. Effect of capsular tension ring implantation on predicted refractive error after cataract surgery in patients with pseudoexfoliation syndrome. *Int J Ophthalmol*. (2020) 13:587–90. doi: 10.18240/ijo.2020.04.09

69. Takamura Y, Tomomatsu T, Arimura S, Tomomatsu Y, Matsumura T, Takihara Y, et al. Anterior capsule contraction and flare intensity in the early stages after cataract surgery in eyes with diabetic retinopathy. *J Cataract Refract Surg*. (2013) 39:716–21. doi: 10.1016/j.jcrs.2012.12.029

70. Kim EC, Hwang HS, Kim MS. Anterior capsular phimosis occluding the capsulorhexis opening after cataract surgery in a diabetic patient with high hemoglobin a1c. *Semin Ophthalmol*. (2013) 28:68–71. doi: 10.3109/08820538.2012.754480

71. Baldysiak-Figiel A, Jong-Hesse YD, Lang GK, Lang GE. Octreotide inhibits growth factor-induced and basal proliferation of lens epithelial cells in vitro. *J Cataract Refract Surg*. (2005) 31:1059–64. doi: 10.1016/j.jcrs.2004.08.056

72. Thornton CA. Myotonic dystrophy. *Neurol Clin*. (2014) 32:705–19. doi: 10.1016/j.ncl.2014.04.011

73. Rosa N, Lanza M, Borrelli M, De Bernardo M, Palladino A, Di Gregorio MG, et al. Low intraocular pressure resulting from ciliary body detachment in patients with myotonic dystrophy. *Ophthalmology*. (2011) 118:260–4. doi: 10.1016/j.ophtha.2010.06.020

74. Abe T, Sato M, Kuboki J, Kano T, Tamai M. Lens epithelial changes and mutated gene expression in patients with myotonic dystrophy. *Br J Ophthalmol*. (1999) 83:452–7. doi: 10.1136/bjo.83.4.452

75. Chang PY, Chang SW. Rapid anterior capsular phimosis after cataract surgery in a patient with chronic angle closure glaucoma. *Taiwan J Ophthalmol*. (2015) 5:192–4. doi: 10.1016/j.tjo.2014.10.003

76. George R, Jayarajan M, Chandran P. Rapid anterior capsular phimosis in a patient without risk factors for anterior capsule contraction syndrome. *JAMA Ophthalmol*. (2023) 141:e230409. doi: 10.1001/jamaophthalmol.2023.0409

77. Canabrava S, Pinheiro L, Chaves V, Barrientos R. Late internalized double-flanged polypropylene with canabrava technique in patient with Marfan syndrome. *Eur J Ophthalmol*. (2023) 33:NP23–6. doi: 10.1177/11206721221092216

78. Joshi RS, Wadekar P. Complete occlusion of anterior capsular opening in patient operated for cataract with penetrating keratoplasty. *Cureus*. (2022) 14:e25178. doi: 10.7759/cureus.25178

79. Fernandez V, Fragoso MA, Billotte C, Lamar P, Orozco MA, Dubovy S, et al. Efficacy of various drugs in the prevention of posterior capsule opacification: experimental study of rabbit eyes. *J Cataract Refract Surg*. (2004) 30:2598–605. doi: 10.1016/j.jcrs.2004.05.013

80. Eibl-Lindner KH, Wertheimer C, Kampik A. Intraocular lens as a drug delivery device: state of the art and future perspective. *Klin Monatsbl Augenheilkd*. (2016) 233:172–8. doi: 10.1055/s-0041-109512

81. Bretton RH, Kash RL, Schanzlin DJ. Use of bipolar diathermy to prevent posterior capsule opacification. *J Cataract Refract Surg*. (2002) 28:866–73. doi: 10.1016/s0886-3350(01)01256-1

82. Baile R, Sahasrabuddhe M, Nadkarni S, Karira V, Kelkar J. Effect of anterior capsular polishing on the rate of posterior capsule opacification: a retrospective analytical study. *Saudi J Ophthalmol*. (2012) 26:101–4. doi: 10.1016/j.sjopt.2010.11.006

83. Liu B, Zhang L, Fang S. Efficacy and safety of anterior capsule polishing in cataract patients: a meta-analysis. *Am J Transl Res*. (2023) 15:3662–73.

84. Tadros A, Bhatt UK, Abdul Karim MN, Zaheer A, Thomas PW. Removal of lens epithelial cells and the effect on capsulorhexis size. *J Cataract Refract Surg*. (2005) 31:1569–74. doi: 10.1016/j.jcrs.2005.01.027

85. Mathey CF, Kohnen TB, Ensikat HJ, Koch HR. Polishing methods for the lens capsule: histology and scanning electron microscopy. *J Cataract Refract Surg*. (1994) 20:64–9. doi: 10.1016/s0886-3350(13)80046-6

86. Gabriel de Figueiredo C, Bordin de Figueiredo G, de Figueiredo J. Aspiration of anterior lens epithelium cells to prevent capsule contraction syndrome in pseudoexfoliation syndrome. *J Cataract Refract Surg*. (2019) 45:523–4. doi: 10.1016/j.jcrs.2018.12.014

87. Bang SP, Yoo YS, Jun JH, Joo CK. Effects of residual anterior lens epithelial cell removal on axial position of intraocular lens after cataract surgery. *J Ophthalmol*. (2018) 2018:9704892. doi: 10.1155/2018/9704892

88. Wang D, Yu X, Li Z, Ding X, Lian H, Mao J, et al. The effect of anterior capsule polishing on capsular contraction and lens stability in cataract patients with high myopia. *J Ophthalmol*. (2018) 2018:8676451. doi: 10.1155/2018/8676451

89. Liu X, Cheng B, Zheng D, Liu Y, Liu Y. Role of anterior capsule polishing in residual lens epithelial cell proliferation. *J Cataract Refract Surg*. (2010) 36:208–14. doi: 10.1016/j.jcrs.2009.08.020

90. Bartholomew RS ed. Phakodonesis. A sign of incipient lens displacement. *Br J Ophthalmol*. (1970) 54:663–6. doi: 10.1136/bjo.54.10.663

91. Zhao Y, Li J, Yang K, Li X, Zhu S. Combined special capsular tension ring and toric IOL implantation for management of astigmatism and high axial myopia with cataracts. *Semin Ophthalmol*. (2018) 33:389–94. doi: 10.1080/08820538.2016.1247181

92. Shingleton BJ, Neo YN, Cvintal V, Shaikh AM, Liberman P, O'Donoghue MW. Outcome of phacoemulsification and intraocular lens implantion in eyes with pseudoexfoliation and weak zonules. *Acta Ophthalmol*. (2017) 95:182–7. doi: 10.1111/aos.13110

93. Bayyoud T, Bartz-Schmidt KU, Yoeruek E. Long-term clinical results after cataract surgery with and without capsular tension ring in patients with retinitis pigmentosa: a retrospective study. *BMJ Open*. (2013) 3:3. doi: 10.1136/bmjopen-2013-002616

94. Yang S, Jiang H, Nie K, Feng L, Fan W. Effect of capsular tension ring implantation on capsular stability after phacoemulsification in patients with weak zonules: a randomized controlled trial. CTR implantation in cataract patients with weak zonules. *BMC Ophthalmol*. (2021) 21:19. doi: 10.1186/s12886-020-01772-8

95. Takimoto M, Hayashi K, Hayashi H. Effect of a capsular tension ring on prevention of intraocular lens decentration and tilt and on anterior capsule contraction after cataract surgery. *Jpn J Ophthalmol*. (2008) 52:363–7. doi: 10.1007/s10384-008-0570-6

96. Vanags J, Erts R, Laganovska G. Anterior capsule opening contraction and late intraocular lens dislocation after cataract surgery in patients with weak or partially absent zonular support. *Medicina*. (2021) 57:35. doi: 10.3390/medicina57010035

97. Ravalico G, Tognetto D, Baccara F. Heparin-surface-modified intraocular lens implantation in eyes with pseudoexfoliation syndrome. *J Cataract Refract Surg*. (1994) 20:543–9. doi: 10.1016/s0886-3350(13)80235-0

98. Del Vecchio PJ, Bizios R, Holleran LA, Judge TK, Pinto GL. Inhibition of human scleral fibroblast proliferation with heparin. *Invest Ophthalmol Vis Sci*. (1988) 29:1272–6.

99. Maedel S, Hirnschall N, Chen YA, Findl O. Effect of heparin coating of a foldable intraocular lens on inflammation and capsular bag performance after cataract surgery. *J Cataract Refract Surg*. (2013) 39:1810–7. doi: 10.1016/j.jcrs.2013.05.040

100. Tan X, Zhan J, Zhu Y, Cao J, Wang L, Liu S, et al. Improvement of uveal and capsular biocompatibility of hydrophobic acrylic intraocular lens by surface grafting with 2-methacryloyloxyethyl phosphorylcholine-methacrylic acid copolymer. *Sci Rep*. (2017) 7:40462. doi: 10.1038/srep40462

101. Hayashi H, Hayashi K, Nakao F, Hayashi F. Area reduction in the anterior capsule opening in eyes of diabetes mellitus patients. *J Cataract Refract Surg*. (1998) 24:1105–10. doi: 10.1016/s0886-3350(98)80105-3

102. Mukai K, Matsushima H, Gotoh N, Aose M, Satoshi W, Wataru T, et al. Efficacy of ophthalmic nonsteroidal antiinflammatory drugs in suppressing anterior capsule contraction and secondary posterior capsule opacification. *J Cataract Refract Surg*. (2009) 35:1614–8. doi: 10.1016/j.jcrs.2009.03.054

103. Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs (NSAIDS) and organ damage: a current perspective. *Biochem Pharmacol*. (2020) 180:114147. doi: 10.1016/j.bcp.2020.114147

104. Moussa G, Ch'ng SW, Kalogeropoulos D, Abdel-Karim Z, Panthagani J, Andreatta W. Comparing the outcomes of YAG laser anterior capsulotomies performed by an advanced nurse practitioner to ophthalmologists in the management of anterior capsular contraction syndrome. *J Am Assoc Nurse Pract*. (2022) 34:1133–8. doi: 10.1097/jxx.0000000000000775

105. Hayashi K, Hayashi H. Effect of anterior capsule contraction on visual function after cataract surgery. *J Cataract Refract Surg*. (2007) 33:1936–40. doi: 10.1016/j.jcrs.2007.06.068

106. Hayashi K, Yoshida M, Nakao F, Hayashi H. Prevention of anterior capsule contraction by anterior capsule relaxing incisions with neodymium:yttrium-aluminum-garnet laser. *Am J Ophthalmol*. (2008) 146:23–30.e1. doi: 10.1016/j.ajo.2008.02.015

107. Wilde C, Ross A, Awad M, Chen HC, Dua HS. Management of anterior capsular contraction syndrome: pitfall of circular capsulotomy technique with the neodymium YAG laser. *Eye*. (2018) 32:1546–8. doi: 10.1038/s41433-018-0125-0

108. Elmohamady MN, Elhabbak A, Gad EA. Circular YAG laser anterior capsulotomy for anterior capsule contraction syndrome. *Int Ophthalmol*. (2019) 39:2497–503. doi: 10.1007/s10792-019-01094-9

109. Tuft SJ, Talks SJ. Delayed dislocation of foldable plate-haptic silicone lenses after Nd:YAG laser anterior capsulotomy. *Am J Ophthalmol*. (1998) 126:586–8. doi: 10.1016/s0002-9394(98)00124-x

110. Gimbel HV, Condon GP, Kohnen T, Olson RJ, Halkiadakis I. Late in-the-bag intraocular lens dislocation: incidence, prevention, and management. *J Cataract Refract Surg*. (2005) 31:2193–204. doi: 10.1016/j.jcrs.2005.06.053

111. Chawla JS, Shaikh MH. Neodymium: YAG laser parabolic anterior capsulotomy in extreme capsule contraction syndrome. *J Cataract Refract Surg*. (1999) 25:1415–7. doi: 10.1016/s0886-3350(99)00154-6

112. Kecik M, Schweitzer C. Femtosecond laser-assisted cataract surgery: update and perspectives. *Front Med*. (2023) 10:1131314. doi: 10.3389/fmed.2023.1131314

113. Panagopoulos A, Chalioulias K, Kirkby GR. A new approach in the surgical management of anterior capsular phimosis syndrome. *Ophthalmic Res*. (2009) 42:221–3. doi: 10.1159/000232947

114. Yeh PC, Goins KM, Lai WW. Managing anterior capsule contraction by mechanical widening with vitrector-cut capsulotomy. *J Cataract Refract Surg*. (2002) 28:217–20. doi: 10.1016/s0886-3350(01)01031-8

115. Chan CK, Agarwal A, Agarwal S, Agarwal A. Management of dislocated intraocular implants. *Ophthalmol Clin N Am*. (2001) 14:681–93. doi: 10.1016/s0896-1549(05)70267-4

frontiers | Frontiers in Medicine

TYPE Mini Review
PUBLISHED 19 February 2024
DOI 10.3389/fmed.2024.1349093

OPEN ACCESS

EDITED BY
Georgios D. Panos,
Nottingham University Hospitals NHS Trust, United Kingdom

REVIEWED BY
Rim Kahloun,
The Associated Ophthalmologists of Monastir, Tunisia
Vivek Gupta,
All India Institute of Medical Sciences, India

*CORRESPONDENCE
Steven Yeh
✉ syeh@unmc.edu
Jean-Claude Mwanza
✉ jean-claude_mwanza@med.unc.edu

†These authors have contributed equally to this work and share first authorship

RECEIVED 04 December 2023
ACCEPTED 01 February 2024
PUBLISHED 19 February 2024

CITATION
Yeh C, Huang C, Huang Y, Hartley CD, Fashina T, Ashby N, Miller C, Shantha JG, Justin GA, Chan RVP, Mattia JG, Vandy MJ, Harrison-Williams L, Mustapha J, Mwanza JC and Yeh S (2024) Childhood vision impairment and blindness in West Africa: public health measures and implications for systemic health. *Front. Med.* 11:1349093. doi: 10.3389/fmed.2024.1349093

Childhood vision impairment and blindness in West Africa: public health measures and implications for systemic health

Caleb Yeh[1†], Crystal Huang[1†], Ye Huang[2], Caleb D. Hartley[1], Tolulope Fashina[1], Nathaniel Ashby[3], Chase Miller[3], Jessica G. Shantha[4], Grant A. Justin[5], R. V. Paul Chan[2], John G. Mattia[6], Matthew J. Vandy[6], Lloyd Harrison-Williams[6], Jalikatu Mustapha[6], Jean-Claude Mwanza[7]* and Steven Yeh[1,8]*

[1]Truhlsen Eye Institute, University of Nebraska Medical Center, Omaha, NE, United States, [2]Department of Ophthalmology and Visual Sciences, University of Illinois Chicago, Chicago, IL, United States, [3]Creighton University School of Medicine, Omaha, NE, United States, [4]F.I. Proctor Foundation, Department of Ophthalmology, University of California, San Francisco, San Francisco, CA, United States, [5]Walter Reed Army National Military Medical Center, Bethesda, MD, United States, [6]National Eye Health Programme, Sierra Leone Ministry of Health and Sanitation, Freetown, Sierra Leone, [7]Department of Ophthalmology, University of North Carolina, Chapel Hill, NC, United States, [8]Global Center for Health Security, University of Nebraska Medical Center, Omaha, NE, United States

Childhood blindness is an issue of global health impact, affecting approximately 2 million children worldwide. Vision 2020 and the United Nations Sustainable Development Goals previously identified childhood blindness as a key issue in the twentieth century, and while public health measures are underway, the precise etiologies and management require ongoing investigation and care, particularly within resource-limited settings such as sub-Saharan Africa. We systematically reviewed the literature on childhood blindness in West Africa to identify the anatomic classification and etiologies, particularly those causes of childhood blindness with systemic health implications. Treatable causes included cataract, refractive error, and corneal disease. Systemic etiologies identified included measles, rubella, vitamin A deficiency, and Ebola virus disease. While prior public health measures including vitamin A supplementation and vaccination programs have been deployed in most countries with reported data, multiple studies reported preventable or reversible etiologies of blindness and vision impairment. Ongoing research is necessary to standardize reporting for anatomies and/or etiologies of childhood blindness to determine the necessity of further development and implementation of public health measures that would ameliorate childhood blindness and vision impairment.

KEYWORDS

childhood blindness, severe vision impairment, measles, vitamin A deficiency, West Africa, refractive error, Ebola, childhood vision impairment

1 Introduction

Childhood vision health, which includes both the prevention and treatment of ophthalmic disease, remains a key global health initiative related to the United Nations Sustainable Development Goals and in the International Agency for the Prevention of Blindness (IAPB) Vision 2020 plan (1). The recent "2030 in Sight" strategy document published by the IAPB has

reinforced childhood vision initiatives including the goal of eye health programs in every school by 2030 (2).

The magnitude of childhood blindness is profound, with an estimated 2 million blind children worldwide (3). Blind children also have a higher mortality rate compared to sighted children, given systemic risk factors including measles and vitamin A deficiency that can be associated with mortality and childhood blindness (4). Moreover, the number of blind children living in developing countries within sub-Saharan Africa is disproportionately high. This disparity is due to a combination of factors including supply chain challenges, limited health infrastructure, access to trained subspecialists, and cultural and social factors that may change healthcare-seeking behavior (5). Immunization and nutritional supplementation, which are critical to childhood vision health, for conditions such as measles and vitamin A deficiency (VAD), respectively, may vary between and within countries, although efforts have been made to improve these areas of health prevention. The UNICEF Multiple Indicator Cluster Survey (MICS) has provided valuable insight into country-level data that highlights improvements in vitamin A supplementation and measles vaccination over time (6).

The relationship between childhood blindness and systemic disease may involve infectious disease processes, nutritional deficiencies, and inherited conditions where vision impairment and systemic illness may intersect. Prior research has identified measles and corneal blindness along with VAD as key risk factors (7), although public measures in some countries, including measles immunization and vitamin A supplementation programs, have been deployed to combat these ailments (8). Nonetheless, epidemiologic studies of childhood blindness may reveal additional infectious disease conditions, including rubella, toxoplasmosis, and recent reports of Ebola virus disease (EVD) in association with childhood vision loss.

Within West Africa and other developing countries, childhood blindness surveys have been employed to provide useful information about the epidemiology of blindness (9). We sought to systematically review ophthalmologic studies to determine anatomic locations of blindness, precise etiologies of blindness identified, and whether key relationships between childhood vision impairment and systemic illness could be identified. This synthesis of the literature examines studies of schools for the blind and key informant interviews of communities in multiple countries in West Africa to ascertain the risk factors, anatomic and etiologic causes of childhood vision impairment, as well as systemic disease associations.

2 Methods

We performed a PubMed literature search without date restrictions to identify the causes of childhood visual impairment and blindness (VI/BL) in West Africa (Figure 1). We identified a total of 75 papers following the United Nations definition of West Africa and included the following countries: Benin, Burkina Faso, Cabo Verde, Chad, Gambia, Ghana, Guinea, Guinea-Bissau, Ivory Coast, Liberia, Mali, Mauritania, Niger, Nigeria, Saint Helena, Ascension, and Tristan da Cunha, Senegal, Sierra Leone. One study combined outcomes from Togo, Ghana, Benin, and Chile as well as Southeast Asia (10).

Search terms included multiple countries in West Africa, including the previously mentioned United Nations country list. Search terms related to childhood vision impairment included "blindness," "vision impairment," and "vision loss." The majority of articles reviewed followed the WHO definition of vision impairment and blindness for classification of subjects assessed. WHO criteria for "moderate visual impairment" included better eyes worse than 6/18 and equal to or better than 6/60, while "severe visual impairment" included better eyes worse than 6/60 and equal to or better than 3/60. Blindness was defined as worse than 3/60 in the better seeing eye. The articles assessed in our study utilized the WHO/Prevention of Blindness Examination record for children (11). Articles selected for full review met the following criteria: documented visual acuities and reported causes of VI/BL, greater than or equal to 20 subjects assessed, and data were derived from a country in West Africa. Manuscripts could also include research where multiple countries were assessed, provided that at least one West African country was reviewed. Demographic restrictions including maximum mean age of 18 years-old or younger, and studies could include females, males, or unreported. Our literature search focused on peer-reviewed manuscripts in English and studies including quantitative data while excluding systematic reviews and meta-analyses.

Papers selected for a full review were assessed for the following parameters where available: reporting country, practice setting, data extraction method, number of patients assessed, rural or urban setting, associated systemic diseases, study population (e.g., blind school or community-based study), classification of vision loss, year(s) when the study was published, key recommendations, and etiology of disease associated with vision loss. In addition to etiologic causes of blindness, we also extracted the anatomical locations of blindness from the studies. If the study contained both anatomic and etiologic disease associations, both were included in the summary (Table 1) and key observations were summarized in this review.

Besides these parameters related to childhood blindness, we also recorded the methodology for each study, and obtained anatomic and etiologic data by distributing surveys to patients using one of two methodologies: (1) School for the blind surveillance methodology; or (2) Key informant (KI) method. The schools for the blind surveillance method involves the selection of these school(s) from the region the study assessed, followed by measurements of the students' visual acuities and eye examinations. The methodologies often utilized a magnifying loupe and penlight to observe the anterior segment and either the indirect or direct ophthalmoscopes to observe the posterior segment of the eye. The KI method involved the selection and training of KIs to identify children in their communities who are suspected of having visual impairment. The children then received an eye exam, in which their visual acuity, etiology, and anatomical cause of VI/BL were documented.

3 Results/findings

Our review of childhood blindness in West Africa resulted in 75 studies of which 13 were selected and abstracted for full review by the two primary authors (CY and CH). The majority of the studies were performed in Nigeria ($n = 8$) with additional studies in Ghana ($n = 3$), Sierra Leone ($n = 1$), and one study that contained data from Togo, Ghana, and Benin (11). The results of our study are shown in Table 1 and are categorized by country.

Patient cohorts were examined from schools for the blind surveillance ($n = 10$) and through KI methods ($n = 3$). Of the 13 studies

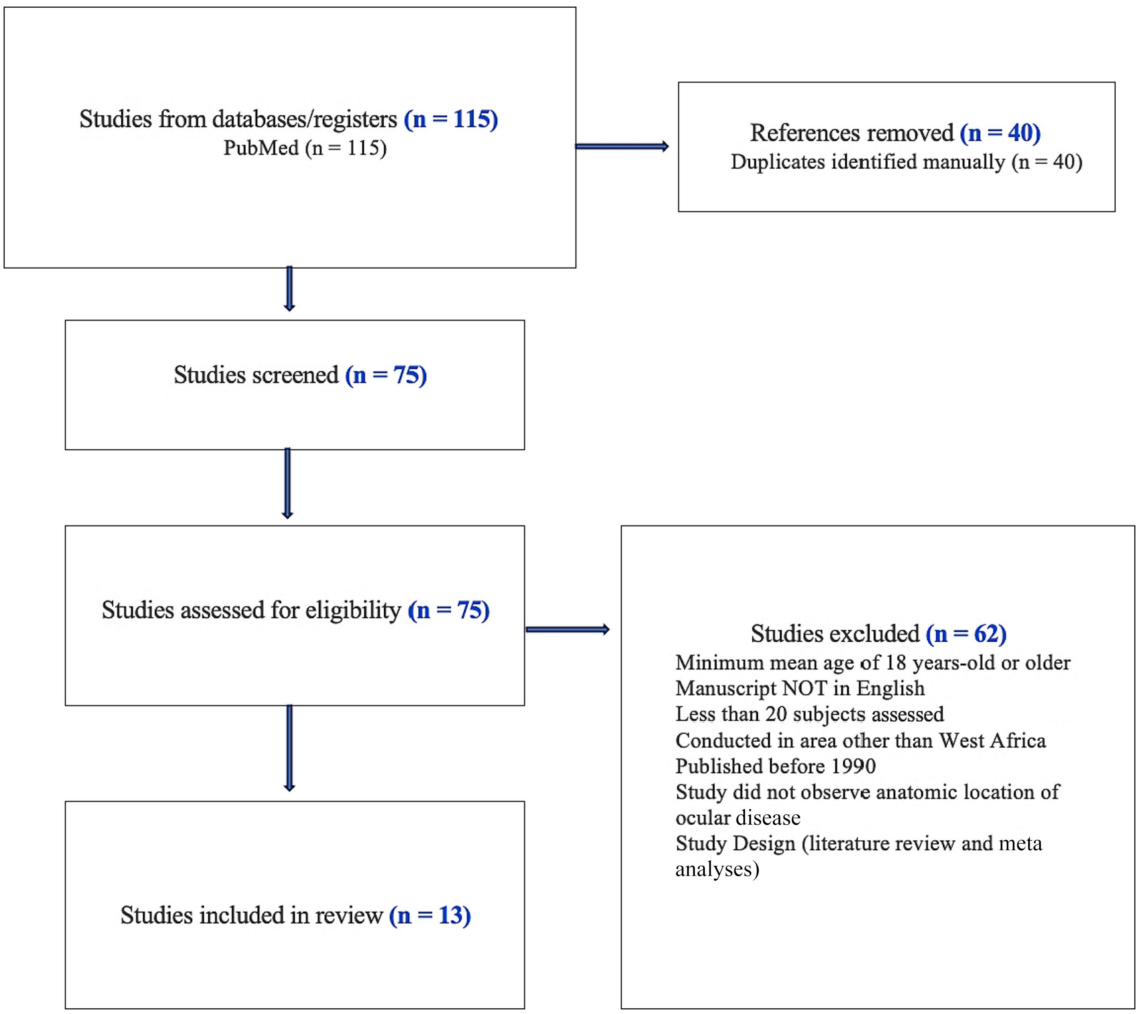

FIGURE 1
PRISMA diagram.

reviewed, 4 studies (30.8%) classified causes of childhood blindness by anatomic location only and 9 (69.2%) classified studies according to both anatomic location and etiology. We identified 10 of 13 studies (76.9%) where any systemic disease association (i.e., 1 or more attributable systemic conditions) was described in association with childhood blindness.

3.1 Etiologic categories of systemic disease associated with childhood vision impairment infectious diseases

A spectrum of pathogens was identified as causes or in association with blindness including viral, parasitic, and bacterial causes. Viral diseases included measles, rubella, and Ebola. Parasitic diseases included toxoplasmosis. Onchocerciasis was not recorded in the manuscripts reviewed. Ophthalmia neonatorum due to chlamydia was also observed.

Measles was the most commonly occurring infectious disease identified in the studies reviewed, appearing as an etiologic cause of severe VI/BL in 9 of 13 (69.2%) studies. Of these studies, the percentage of measles defined as an etiologic cause of severe VI/BL ranged from 10 to 26%. Measles was the most identified etiologic cause of severe VI/BL in 4 (44.4%) studies; however, oftentimes, it was grouped with other causes, including 2 studies in which the collective group including measles was the most common etiologic cause of blindness.

Rubella was the second most common systemic disease defined as an etiologic cause, identified in 6 of 13 studies (46.2%) with percentages ranging from 2 to 7%.

In one study where pediatric Ebola survivors and close-contacts were examined, uveitis was observed in 10.8% of Ebola survivors compared to 1.7% of close-contacts (21). In patients in whom uveitis was identified, vision impairment was observed in a high proportion of individuals. Ocular complications were also found to be significantly associated with a reduction in vision-related quality of life in both Ebola survivors and close-contact control patients.

Non-viral infectious diseases associated with childhood blindness were found in a lower percentage of patients. Specifically, toxoplasmosis varied between 1 and 6.5% while ophthalmia neonatorum was attributed to childhood blindness in 0.4–2% of patients in the studies reviewed.

TABLE 1 Anatomic and etiologic causes of childhood blindness by West African country.

References	Setting/Data extraction method	No. patients assessed	Anatomic diagnosis	Etiologic diagnosis	Associated systemic diagnoses
Nigeria					
Ezegwui et al. (12)	Three schools for the blind in southeastern Nigeria (Oji River, Enugu State; Isulo, Anambra State; and Afara, Umuahia Abia State)	142	Cataract (23.6%) Corneal scarring (21.4%) Phthisis bulbi (12.1%) Glaucoma/Buphthalmos (9.3%) Microphthalmos or Disorganized globe (9.3%) Retina (7.9%) Optic nerve atrophy (7.1%) Uncorrected aphakia (5%) Retinitis pigmentosa (5%)	Measles (25%) Rubella (7.9%) Trauma. (7.2%) HTEM (7.2%)	Measles (25%) Rubella (7.9%)
Mosuro et al. (13)	All the schools for the blind in Oyo State, Nigeria (located in Ogbomosho, Oyo, Ibadan, and Eruwa)	86	Cornea (29.1%) Lens (26.7%) Retina/Optic nerve (18.6%) Optic atrophy (14%) Glaucoma (13%) Globe (10.5%) Cortical blindness (2.3%) Ocular inflammation (3.5%)	Measles (29.1%) Congenital cataract (26.7%) Glaucoma (12.8%) Congenital rubella syndrome (4.7%)	Measles keratopathy/VAD in (29.1%) Rubella (4.7%)
Omolase et al. (14)	Owo School for the Blind	62	Cataract (21%) Glaucoma (12.9%) Phthisis bulbi (9.7%) Microphthalmia (3.2%) Leucoma (9.7%) Retinitis pigmentosa (11.3%) Optic atrophy (12.9%) Squint (3.2%) Aphakia (3.2%) Anophthalmus (1.6%) Maculopathy (1.6%) Pseudophakia (1.6%)	Hereditary (21%) Intrauterine (37.1%) Childhood (16.1%) Unknown (22.6%) Trauma (3.2%)	Toxoplasmosis (6.5%)
Muhammad et al. (15)	Gwadabawa local government area (LGA)/ KI Method	58	Corneal opacity (55%) PB (20%) Cataract (15%) Anterior uveitis (10%)	Childhood factor (75%) Hereditary (10%) Couching (5%)	Childhood factors (VAD, infectious keratitis, and trauma) (75%)
Duke et al. (16)	Child Eye health tertiary facility (CEHTF) at the University of Calabar Teaching Hospital using KI Method	1,020	Lens (35%) Cataract (28%) Whole globe (19%) Cornea (16%) Retina (8%) Optic nerve (8%) Refractive error (8%) Cortical blindness (4%) Nystagmus (1%)		NR
Aghaji et al. (17)	3 schools in Southeast Nigeria (data extraction method not specified)	127	Cataract (28.2%) Whole globe (27.6%) Cornea (20.5%) Glaucoma/Bupthalmos (1%) Optic NERVE (7.9%) Retina (3.9%)	Measles/VAD (18.6%) Rubella (5.8%) HTEM (4.8%) Trauma (3.2%)	Measles/VAD (18.6%) Rubella (5.8%)

(Continued)

TABLE 1 (Continued)

References	Setting/Data extraction method	No. patients assessed	Anatomic diagnosis	Etiologic diagnosis	Associated systemic diagnoses
Olowoyeye et al. (8)	Nigeria Society for the Blind Vocational Training Center, PSB, and Nigeria Farm Craft Center for the Blind	116	Phthisis bulbi (17.2%) Optic nerve atrophy (17.2%) Corneal scarring (12%) Retina dystrophy (7.8%) Cataract (6.9%) Microphthalmos (5.2%) Buphthalmos (5.2%) Retinal detachment (4.3%) Glaucoma (1.7%) Aphakia (3.4%) ROP (0.9%)	Measles (12.9%) CNS infections (8.6%) Rubella (4.3%) Trauma (1.7%) Malaria (1.7%)	Measles (12.9%)
Aghaji et al. (18)	South-Eastern Nigeria (ages 0–15 years)/KI Method	68	Cataract (40%) Optic atrophy (13.3%) Corneal scar (13.3%) Refractive error (13.3%) Microphthalmia (6.7%). Optic nerve hypoplasia (6.7%) Phthisis bulbi (6.7%)	Hereditary factors (26.7%) Prenatal factors (6.7%)	NR
Ghana					
Ntim-Amponsah et al. (19)	School for the Blind at Akropong, Ghana	199	Cornea (42.21%) Congenital and acquired globe abnormalities (37.19%) Lens (23.12%) Glaucoma (15.58%) Retina (9.05%) Optic nerve (8.54%) Tumor (2.01%) Anophthalmos (0.50%)	Measles (26.6%) Traditional Medicine (25.1%) Trauma (3.0%) Malnutrition (2.5%)	Measles (26.6%) Malnutrition (2.5%)
Huh et al. (7)	Wa Methodist School for the Blind in Northern Ghana, survey	190	Optic nerve atrophy (12%) Corneal scar (11%) Glaucoma (9%) Microphthalmos (9%) Cataract (9%) Cortical blindness (7%) Phthisis bulbi (4%) Uveitis (4%) Retinitis pigmentosa (2%) Refractive error (2%)	Other unknown etiology (22%) Abnormality since birth (17%) Hereditary Disease (15%) Measles (10%)	Measles (10%) and Rubella (2%)
Ilechie et al. (20)	The Akropong (the oldest school for the blind in Ghana) and Cape Coast Schools for the blind in southern Ghana, and the Wa School for the Blind in northern Ghana survey	252	Cataract (24.2%) Corneal scarring (19.8%) Glaucoma (9.9%) Corneal dystrophy (5.6%) Microphthalmos (5.2%) Other retinal lesions (5.2%) Cortical blindness (4%) Aphakia (1.6%)	VAD (6.7%) Measles (6.4%) Toxoplasmosis (3.6%) Rubella (2.8%) Trauma (3.6%) HTEM (3.2%) Retinitis pigmentosa (1.2%) Albinism (0.4%) Ophthalmia neonatorum (0.4%) Retinoblastoma (0.4%)	Measles/VAD (13.1%) Rubella (2.8%)

(Continued)

TABLE 1 (Continued)

References	Setting/Data extraction method	No. patients assessed	Anatomic diagnosis	Etiologic diagnosis	Associated systemic diagnoses
Sierra Leone					
Shantha et al. (21)	Lowell and Ruth Gess Kissy Eye Hospital in Freetown, Sierra Leone	81	Vernal keratoconjunctivitis (21%) Corneal scar (12%) Glaucoma (6%) Uveitis (7%) Synechiae (3%) Cataracts (2%) Corneal edema (2%)		Ebola survivors (70%) Close contact (57%)
Ghana, Togo, Benin					
Gilbert et al. (10)	Blind Schools (does not specify)	284	CS/PB (35.9%) Retina (20.4%) Lens (15.5%) Glaucoma (13%) Whole globe (8.5%) Optic nerve (5.6%) Uvea (1.1%)	VAD/measles/TEM (29%) Rubella (7%) Ophthalmia neonatorum (2%)	VAD/Measles/TEM (29%) Rubella (7%)

HTEM, harmful traditional eye medicine; TEM, traditional eye medicine; ROP, retinopathy of prematurity; CS, corneal scar; PB, phthisis bulbi; VAD, vitamin A deficiency; ROP, retinopathy of prematurity. NR: not reported.

3.2 Nutritional deficiencies

Prior studies have documented the association of VAD with xerophthalmia, corneal ulceration, and blindness. Concomitant measles infection with associated keratitis compounds VAD leading to corneal scarring (CS). In addition, malnourishment and immune dysfunction from VAD predisposes children to measles.

In the setting of severe ulceration and perforation from VAD, phthisis bulbi (PB) may also ensue. Given the inter-relatedness of these conditions, several studies combined VAD and measles as a collective cause of vision loss (13, 17, 19, 20). The proportion of children with blindness due to this combination of VAD and measles ranged between 13.1 and 29% in these studies.

3.3 Harmful traditional eye medicine/ trauma

Harmful traditional eye medicine (HTEM) is a common cause of severe VI/BL resulting from a combination of factors that may include a lack of access to medical treatment and healthcare services or dissatisfaction with health care providers. These treatments can involve the direct instillation of herbal preparations into the eye (19). HTEM was found to be the etiological cause of blindness in four studies, ranging from 4.8% to as high as 25.1% of patients assessed.

Trauma was found to be an etiological cause of blindness in six studies, varying between 2.3 and 7%. Whether other systemic traumatic injuries were observed concomitantly was not specifically recorded.

3.4 Hereditary and genetic causes

Hereditary factors classified as an etiologic cause of severe VI/BL were found to be the etiologic cause in three studies ranging from 15 to 26.7%.

3.5 Anatomic locations of disease leading to childhood vision impairment

Besides assessing the systemic associations of childhood blindness, multiple studies classified childhood blindness according to anatomic location including corneal scarring/phthisis bulbi (CS/PB), cataract, or glaucoma. The most common anatomic locations defined are summarized.

3.6 Cornea

Corneal disease was the most commonly defined anatomic location of blindness observed in our review of the literature. In four studies, corneal disease was the most common anatomic cause or location of blindness, reported in 29.1–42% of patients (10, 13, 15, 19). The most common cause documented was CS, and often associated with PB, leading to these two terms appearing as the cause of blindness in several studies. The combined category of CS and PB was responsible for 35.9% of visual impairment in a study by Gilbert et al. (10). Corneal opacity, which potentially could be associated with CS, was observed in 55% of the patients with visual impairment in a report by Muhammad et al. (15). In this report, CS alone was the most common cause of blindness. Seventy-five percent of etiologies in this

report were associated with a childhood factor including VAD and measles, comprising patients with CS and PB.

3.7 Lens

Of the 13 studies reviewed, the most common lenticular conditions leading to blindness—"cataract" and "aphakia"—were present in 11 and 5 studies, respectively. Cataract was observed to be an anatomic cause of blindness in 11 studies, leading to blindness from an estimated 7–40% of the VI/BL and notably was the leading cause of blindness in 5 studies (12, 14, 17, 18, 20). Patients were referred for surgery in several reports, but the outcomes were not reported in these manuscripts.

Aphakia was associated with 1.6–5% of VI/BL. Aphakia was deemed to be associated with rubella or intrauterine causes of blindness in the studies where aphakia was documented.

3.8 Retina

Blindness due to retinal disease was variable across 5 studies in which these anatomic locations were documented and ranged from 3.9 to 20.4%. These diseases included retinoblastoma, retinitis pigmentosa (RP), retinopathy of prematurity (ROP), and retinal detachment. RP, a hereditary disease, was the most commonly appearing retinal cause of blindness while retinoblastoma and ROP were documented in <1% of cases in two independent studies (8, 20). Of the 4 studies discussing RP, the percentage of blindness caused by RP ranged from 1.2 to 11.3%. Given the findings that may overlap between retinal disorders and optic nerve disease, one study combined both anatomic locations and reported that 18.6% of patient blindness was located at the retina and optic nerve (13).

3.9 Optic nerve and glaucoma

The most common optic nerve finding associated with blindness was optic atrophy, which was reported in 6 studies with a frequency of blindness association ranging between 7.1 and 17.2%. Glaucoma was reported in 11 studies and led to VI/BL in 2 to 40% of patients with vision impairment. Congenital glaucoma, which was sometimes grouped with buphthalmos, was identified in over 12% of patients in one study (17).

3.10 Whole globe and other categories of childhood blindness

The terminology "Whole Globe" was included as an anatomic location or cause of blindness in all the studies reviewed. This category was perhaps the most diverse group, encompassing conditions such as glaucoma and buphthalmos, as well as conditions such as PB. PB was described in association with corneal scarring in multiple studies, representing an unfortunate, final common pathway from multiple etiologies (e.g., untreated uveitis, corneal perforation from measles/VAD and use of HTEM).

Microphthalmia/Microphthalmos also fell into this category as a cause of visual impairment in 5 studies. This disease could also be attributed to congenital rubella and while infrequent, the range of blindness associated with microphthalmos varied in a significant minority of patients ranging from 3.2 to 9%.

Other notable categories of childhood blindness that were observed infrequently included refractive error (2–13%) and uveitis (4–10%) including patients with a history of EVD or clinical manifestations indicative of toxoplasmosis. Cortical blindness was identified ranged from 2.3 to 7% in 4 studies where this was reported.

3.11 Child vision health and quality-of-life

The relationship of child vision health and impairment with quality-of-life reduction has been reported previously. However, whether pediatric vision health predicts poorer quality-of-life in resource-limited countries is less well-characterized. In the literature search conducted, we also assessed whether specific relationships were observed between child VI/BL and quality-of-life metrics.

Shantha et al. assessed vision impairment in a cross-sectional study of EVD survivors or close-contact control patients at the Lowell and Ruth Gess Eye Hospital in Sierra Leone (21). Eighty-one pediatric patients were evaluated for visual acuity, eye disease, and quality-of-life changes. Quality of Life was assessed using the Pediatric Quality of Life Inventory Version 4·0 (PedsQL) and Effect of Youngsters Eyesight on Quality-of-Life (Eye-Q), with a comparison between Ebola survivors and close contact control patients. A high proportion of EVD survivors showed eye disease with 47% of eyes demonstrating ocular disease, while 32% of eyes in the close-contact control population also showed ocular findings. Interestingly, when ocular findings were observed, individuals in both the EVD and control cohort showed a reduction in vision-related quality of life and function. These indicate that while pediatric EVD survivors were observed to have a higher prevalence of uveitis and ocular inflammation, the eye disease burden within the entire cohort including control patients was high and contributed to reduced quality of life.

4 Impact of public health interventions on child vision health and blindness

While the studies in West Africa are illustrative of the burden of disease ranging from anterior segment to posterior segment disease, as well as whole globe changes, public health interventions and their impact have continued to be deployed with variability across countries and even regions within countries. Within Nigeria, Olowoyeye et al. described a significant decrease in VI/BL from 2000 to 2017, which could be associated with public health measures including an increase in measles immunization, vitamin A supplementation, and the establishment of tertiary eye facilities through implementation initiatives aligned with the WHO's VISION 2020 initiative (8).

In Ghana, health sector reform in 1997 coincided with an increase in measles immunization coverage and a notable decrease in the proportion of CS/PB-caused VI/BL (7). Within Ilechie et al. reported

a higher proportion of students located in South Ghana became blind between the age cohort of 1–15 compared to North Ghana (20). This observation could potentially be associated with an increase in the coverage of measles immunization and vitamin A supplementation programs within Northern Ghana. Moreover, the use of HTEM remains a leading issue, as Ntim-Amponsah et al. reported corneal blindness due to HTEM as around 13% people who had eye disease in a Ghanaian community resorted to traditional herbal medicine (19). Evidenced-based, public health measures targeting both different countries and regions within countries are clearly needed.

5 Discussion

A comprehensive synthesis of the literature from West Africa showed that the major anatomic causes of blindness included CS and lens/cataract-related, while a significant minority of patients showed evidence of VI/BL from optic neuropathy, glaucoma, and retinal disease. Within the literature reviewed, viral diseases including measles, rubella, and Ebola virus were observed to lead to vision impairment, but nutritional deficiencies, in particular, VAD contributed to disease morbidity (Table 2). Other genetic/hereditary conditions and neoplastic disease including retinoblastoma were observed. However, many of the most prevalent diseases and etiologies for childhood blindness are preventable including cataract, refractive error, and corneal conditions not associated with PB. In addition, with growing interventions and the importance of childhood screening, blindness secondary to congenital glaucoma and retinal disease can also be prevented with early identification and prompt treatment.

Another major focus of this synthesis of the literature from West Africa was related to the relationships of systemic illness with childhood blindness, given prior documented relationships between vision loss and childhood morbidity and mortality. Vitamin A supplementation has led to widespread reduction in VAD symptoms and associated morbidity and mortality; however, within the literature reviewed, we still found 13.1–29.1% of patients who had ocular findings associated with VAD. Therefore, while the increase in vitamin A supplementation has hinted toward improvements in ocular diseases instigated by VAD, the progress has varied between countries and even within countries. Within Nigeria, improved eye health has been realized. Yet, within Ghana, improvements were seen through a decrease in CS/PB cases in northern Ghana from 1987 to 2014 compared to an increase in cases from 1989 to 2003 within southern Ghana (20). Rubella was the only other systemic disease that was prevalent enough to warrant a specific recommendation, which suggested additional research be conducted to assess the necessity of vaccination in Nigeria (8).

TABLE 2 Leading causes of childhood blindness in West Africa.

Category	Key causes
Infectious diseases	Measles Rubella Malaria Ebola Other central nervous system infections Ophthalmia neonatorum
Nutritional deficiencies	Vitamin A deficiency (VAD)
Prenatal factors	Congenital rubella syndrome Toxoplasmosis
Hereditary factors	Glaucoma Retinitis pigmentosa
Others	Trauma Harmful traditional eye medicine Couching Cortical blindness

Identification of ophthalmic findings due to malaria, chlamydia and gonorrhea in ophthalmia neonatorum, and Ebola are reminders of the range of infectious diseases that may lead to eye disease, potentially requiring anti-infective or anti-inflammatory therapies.

Our review of the literature revealed some limitations inherent to reporting with the two major methods of reporting being the KI method or the child schools for the blind surveillance method. Potential advantages of utilizing the KI method include avoidance of sampling bias through surveillance of government areas/local communities as opposed to just blind schools. However, because the process is labor intensive, undercoverage bias is possible due to the small number of VI/BL children whom key informants can identify. Additionally, a relatively high proportion of identified individuals do not show up to their eye examinations, further decreasing the number of patients assessed.

Limitations of schools for the blind surveillance method include the high male-to-female ratio, which may potentially reflect selection bias as many female VI/BL students are withheld from attending schools for the blind. In some scenarios, SVI children might attend regular schools or be denied entry into schools for the blind due to other handicaps. Schools for the blind studies are also potentially under-representative of rural areas as all the studies of blind schools reviewed were set in urban areas. National approaches to population-based data in West African countries could minimize the population biases associated with assessment of children from blind schools and could provide more accurate epidemiological data. Significant heterogeneity was also observed in reporting as overlap between anatomic and precise etiologic causes of blindness. For example, congenital cataract could be reported as both an anatomic and etiologic cause of blindness, but the underlying etiology (i.e., infectious, genetic, or other) could not be determined from the manuscript. Despite these limitations, a full understanding of childhood blindness through literature from West Africa and other countries within sub-Saharan Africa represent an opportunity to align terminology, identify relationships between child vision health and systemic illness that would inform public health measures for vision health intervention.

Public health recommendations including VAD and measles immunization were found to have made positive impacts on reporting countries such as Nigeria and Northern Ghana, which are consistent with the United Nations Sustainable Development Goals and WHO's Vision 2020 plan. The importance of childhood vision screening through school programs is further emphasized in the IAPB 2030 in Sight strategic document. Other key recommendations that have been emphasized include additional research and studies to obtain a better grasp on both regional etiological patterns and the necessity of certain vaccines, eye health education of local communities to raise awareness on the benefits of early screenings of infants to identify diseases like

cataract and glaucoma. A better understanding of traditional eye medicines and remedies, as well as awareness of primary and tertiary eye care services could potentially reduce cases of preventable blindness. Interestingly, as there were cases of treatable vision loss identified in children enrolled in schools for the blind, strengthening vision health and vision rehabilitation services for schools for the blind could also be emphasized across public and private sectors.

6 Conclusion

With the wide range of causes of childhood blindness reported, the spectrum of disease in different countries within West Africa and landscape of childhood vision impairment likely requires further investigation to inform public health measures. Placing a greater emphasis on the research of etiologic causes of childhood blindness would help initiate preventative measures unique to each region while observing the development and evolution of these causes. Additional research focusing on a national assessment of the relationship between childhood blindness and infectious diseases could also improve the distribution of immunizations such as the MMR vaccine. The implementation of standardized vision screening protocols with national databases could align defined causes of childhood blindness with resources via local Ministries of Health and external partnerships.

Author contributions

CY: Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing, Data curation, Formal analysis. CH: Data curation, Formal analysis, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing, Conceptualization. YH: Conceptualization, Investigation, Methodology, Resources, Writing – review & editing, Project administration, Supervision. CDH: Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing, Data curation, Formal analysis. TF: Data curation, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing, Funding acquisition. NA: Investigation, Methodology, Project administration, Writing – review & editing, Conceptualization, Visualization. CM: Investigation, Methodology, Project administration, Visualization, Writing – review & editing. JS: Investigation, Methodology, Project administration, Writing – review & editing, Funding acquisition, Resources, Supervision. GJ: Investigation, Methodology, Project administration, Supervision, Writing – review & editing, Conceptualization. RC: Investigation, Methodology, Project administration, Supervision, Writing – review & editing, Resources, Validation, Visualization. JMa: Investigation, Project administration, Supervision, Writing – review & editing. MV: Investigation, Project administration, Supervision, Writing – review & editing. LH-W: Investigation, Project administration, Supervision, Writing – review & editing, Conceptualization, Resources, Validation. JMu: Conceptualization, Investigation, Project administration, Resources, Supervision, Writing – review & editing, Methodology. J-CM: Conceptualization, Investigation, Methodology, Project administration, Resources, Writing – review & editing, Funding acquisition. SY: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing – review & editing, Supervision, Writing – original draft.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This project was supported by the National Eye Institute of the National Institutes of Health under award numbers NIH R01 EY029594 (SY), NIH K23 EY030158 (JS), and Research to Prevent Blindness, New York, NY (RC). The content was solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Health or the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply the endorsement by the U.S. Government. Grant support was also provided by the Macula Society Retina Research Foundation, ARVO Mallinckrodt Young Investigator Grant, and the Stanley M. Truhlsen Family Foundation, Inc.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. World Health Organization. *Preventing blindness in children: report of WHO/IAPB scientific meeting*. Geneva: WHO (2000).

2. Gilbert C, Foster A. Blindness in children: control priorities and research opportunities. *Br J Ophthalmol*. (2001) 85:1025–7. doi: 10.1136/bjo.85.9.1025

3. Bourne R, Steinmetz JD, Flaxman S, Briant PS, Taylor HR, Resnikoff S, et al. Trends in prevalence of blindness and distance and near vision impairment over 30 years: an analysis for the global burden of disease study. *Lancet Glob Health*. (2021) 9:e130–43. doi: 10.1016/S2214-109X(20)30425-3

4. The International Agency for the Prevention of Blindness. *2030 in sight strategy document*. (2021). Available at: https://www.iapb.org/learn/resources/2030-in-sight-strategy-document/.

5. Bechange S, Jolley E, Tobi P, Mailu E, Sentongo J, Chulu T, et al. Understanding patient health-seeking behavior to optimize the uptake of cataract surgery in rural Kenya, Zambia, and Uganda: findings from a multisite qualitative study. *Int Health*. (2022) 14:i57–63. doi: 10.1093/inthealth/ihab061

6. *2021 multiple Indicator cluster survey/National Immunization Coverage Survey Report*. UNICEF for every child. Available at: www.unicef.org (Accessed January 28, 2024).

7. Huh GJ, Simon J, Prakalapakorn GS. Causes of childhood blindness in Ghana: results from a blind school survey in upper West region, Ghana, and review of the literature. *Int Ophthalmol*. (2018) 38:1415–23. doi: 10.1007/s10792-017-0600-9

8. Olowoyeye AO, Musa KO, Aribaba OT, Onakoya AO, Akinsola FB. Pattern of childhood visual impairment and blindness among students in schools for the visually impaired in Lagos state: an update. *Niger Postgrad Med J*. (2018) 25:105–11. doi: 10.4103/npmj.npmj_27_18

9. Steinkuller PG, Du L, Gilbert C, Foster A, Collins ML, Coats DK. Childhood blindness. *J Am Assoc Pediatr Ophthalmol Strabismus*. (1999) 3:26–32. doi: 10.1016/s1091-8531(99)70091-1

10. Gilbert CE, Canovas R, Hagan M, Rao S, Foster A. Causes of childhood blindness: results from West Africa, South India and Chile. *Eye*. (1993) 7:184–8. doi: 10.1038/eye.1993.39

11. World Health Organization. *International statistical classification of diseases and related health problems, 11th revision (ICD-11): chapter 7 - vision function*. Geneva: World Health Organization (2019). Available at: https://iris.who.int/bitstream/handle/10665/328717/9789241516570-eng.pdf?sequence=18 (Accessed December 30, 2023).

12. Ezegwui IR, Umeh RE, Ezepue UF. Causes of childhood blindness: results from schools for the blind in south eastern Nigeria. *Br J Ophthalmol*. (2003) 87:20–3. doi: 10.1136/bjo.87.1.20

13. Mosuro AL, Ajaiyeoba AI, Bekibele CO, Eniola MS, Adedokun BA. Survey of low vision among students attending schools for the blind in Nigeria: a descriptive and interventional study. *Middle East Afr J Ophthalmol*. (2012) 19:382–91. doi: 10.4103/0974-9233.102744

14. Omolase CO, Aina AS, Omolase BO, Omolade EO. Causes of blindness and visual impairment at the school for the blind Owo, Nigeria. *Ann Ibadan Postgrad Med*. (2008) 6:49–52. doi: 10.4314/aipm.v6i1.64042

15. Muhammad N, Nuhu MM, Aliyu JM, Rabiu MM. Tracing children with blindness and visual impairment using the key informant survey in a district of North-Western Nigeria. *Middle East Afr J Ophthalmol*. (2010) 17:330–4. doi: 10.4103/0974-9233.71601

16. Duke R, Otong E, Iso M, Okorie U, Ekwe A, Courtright P, et al. Using key informants to estimate prevalence of severe visual impairment and blindness in children in Cross River state, Nigeria. *J AAPOS*. (2013) 17:381–4. doi: 10.1016/j.jaapos.2013.05.004

17. Aghaji A, Okoye O, Bowman R. Causes and emerging trends of childhood blindness: findings from schools for the blind in Southeast Nigeria. *Br J Ophthalmol*. (2015) 99:727–31. doi: 10.1136/bjophthalmol-2014-305490

18. Aghaji AE, Ezegwui IR, Shiweobi JO, Mamah CC, Okoloagu MN, Onwasigwe EN. Using key informant method to determine the prevalence and causes of childhood blindness in south-eastern Nigeria. *Ophthalmic Epidemiol*. (2017) 24:401–5. doi: 10.1080/09286586.2017.1320412

19. Ntim-Amponsah CT, Amoaku WMK. Causes of childhood visual impairment and unmet low-vision care in blind school students in Ghana. *Int Ophthalmol*. (2008) 28:317–23. doi: 10.1007/s10792-007-9134-x

20. Ilechie A, Wanye S, Abraham CH, Sarpong JB, Abu E, Abokyi S, et al. Inter-regional trends in causes of childhood blindness and low vision in Ghana. *Clin Exp Optom*. (2020) 103:684–92. doi: 10.1111/cxo.13041

21. Shantha JG, Canady D, Hartley C, Cassedy A, Miller C, Angeles-Han ST, et al. Ophthalmic sequelae and psychosocial impact in pediatric Ebola survivors. *eClinicalMedicine*. (2022) 49:101483–3. doi: 10.1016/j.eclinm.2022.101483

frontiers | Frontiers in Medicine

TYPE Review
PUBLISHED 22 March 2024
DOI 10.3389/fmed.2024.1353624

OPEN ACCESS

EDITED BY
Georgios D. Panos,
Nottingham University Hospitals NHS Trust, United Kingdom

REVIEWED BY
Pan Long,
Western Theater General Hospital, China
Je Hyun Seo,
VHS Medical Center, Republic of Korea
Jeffrey Boatright,
Emory University, United States
Yuanbo Liang,
Affiliated Eye Hospital of Wenzhou Medical University, China

*CORRESPONDENCE
Chaohua Deng
✉ dengchaohua1988@hotmail.com
Junming Wang
✉ eyedrwjm@163.com

†These authors have contributed equally to this work

RECEIVED 11 December 2023
ACCEPTED 12 March 2024
PUBLISHED 22 March 2024

CITATION
Zhang Q, Jiang Y, Deng C and Wang J (2024) Effects and potential mechanisms of exercise and physical activity on eye health and ocular diseases.
Front. Med. 11:1353624.
doi: 10.3389/fmed.2024.1353624

Effects and potential mechanisms of exercise and physical activity on eye health and ocular diseases

Qiuxiang Zhang†, Yuxian Jiang†, Chaohua Deng* and Junming Wang*

Department of Ophthalmology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

In the field of eye health, the profound impact of exercise and physical activity on various ocular diseases has become a focal point of attention. This review summarizes and elucidates the positive effects of exercise and physical activities on common ocular diseases, including dry eye disease (DED), cataracts, myopia, glaucoma, diabetic retinopathy (DR), and age-related macular degeneration (AMD). It also catalogues and offers exercise recommendations based on the varying impacts that different types and intensities of physical activities may have on specific eye conditions. Beyond correlations, this review also compiles potential mechanisms through which exercise and physical activity beneficially affect eye health. From mitigating ocular oxidative stress and inflammatory responses, reducing intraocular pressure, enhancing mitochondrial function, to promoting ocular blood circulation and the release of protective factors, the complex biological effects triggered by exercise and physical activities reveal their substantial potential in preventing and even assisting in the treatment of ocular diseases. This review aims not only to foster awareness and appreciation for how exercise and physical activity can improve eye health but also to serve as a catalyst for further exploration into the specific mechanisms and key targets through which exercise impacts ocular health. Such inquiries are crucial for advancing innovative strategies for the treatment of eye diseases, thereby holding significant implications for the development of new therapeutic approaches.

KEYWORDS

exercise, physical activity, ocular diseases, oxidative stress, inflammation

1 Introduction

Eye health is vital for maintaining physical and mental well-being, which has extensive implications on individual quality of life, economic prosperity of nations, and sustainable development of societies (1). However, global eye health statistics show an alarming picture, with more than 2.2 billion people worldwide suffering from visual impairment, of whom more than 1 billion face moderates to severe visual impairment or even complete blindness (2). Unfortunately, numerous instances of visual impairment within this demographic can be prevented or intervened early, such as cataracts, refractive errors and glaucoma (2). Nevertheless, countless individuals and families endure the repercussions of visual impairment or complete loss of vision due to obstacles in obtaining affordable and high-quality eye care and treatment (2). Recognizing that eye health is a global public priority and repositioning it as a development and health issue,

the Global Commission on Eye Health has gained increased attention (1).

In recent years, exercise and physical activity have gained growing attention as cost-effective, feasible and accessible lifestyle interventions for the treatment of various human ailments, notably cardiovascular and other chronic diseases (3). Several studies have indicated that long-term regular exercise and physical activity serve as crucial and modifiable interventions for enhancing the management of diverse medical conditions, including, but not limited to, hypertension, diabetes, obesity, cancer, osteoporosis, osteoarthritis, and depression (4). A cohort study of 110,482 healthy middle-aged adults over an 8 years period revealed that low physical fitness was linked to a higher incidence of mortality from various causes (5). It has been reported that physical inactivity has the highest prevalence among risk factors that can be intervened upon by humans (3). Despite the extensively documented benefits of physical activity in many systemic disorders, exercise is underutilized as an intervention in practice. Astonishingly, only about 26% of men and 19% of women are estimated to meet international physical activity guidelines (6, 7).

The positive impacts of exercise on eye health are increasingly recognized and widely validated by a growing body of research (8–11). This review synthesizes existing studies to describe the potential benefits of exercise and physical activities on common ocular diseases. Based on current epidemiological evidence and exercise guidelines, this review provides exercise recommendations for early to mid-stage patients of specific ocular diseases or high-risk individuals who are physically fit for exercise. It is hoped that this will elevate the awareness and importance of exercise in eye health among various sectors of society. Additionally, this review summarizes and elucidates possible mechanisms through which exercise and physical activity impact common ocular diseases, including direct mechanisms such as lowering intraocular pressure and blood glucose, as well as indirect mechanisms like inhibiting oxidative stress and inflammatory responses, and promoting the release of protective factors. The discussion on mechanisms aims to encourage researchers to delve deeper into unveiling the specific mechanisms and key targets through which exercise positively affects eye health, thereby providing theoretical support for the development of new treatment strategies for ocular diseases.

2 Exercise and physical activity

For sedentary people, the lack of specific knowledge about exercise is one of the main obstacles to the implementation of effective "exercise therapy," including the differentiation and selection of the type and intensity of exercise (Figure 1).

2.1 Simple classification

The terms "exercise" and "physical activity" are frequently used interchangeably in literature. Nonetheless, a thorough analysis of these two concepts reveals that they are not precisely the same (12). Exercise refers to organized, planned physical activity that can be categorized into three groups: aerobic exercise, resistance training, and flexibility training. Aerobic exercise uses oxygen as the primary energy supply and includes activities such as running, cycling, swimming, brisk walking, and jumping rope. Resistance training, also known as strength training, involves countering external resistance to increase muscle strength and mass. This can include weight lifting, gymnastics,

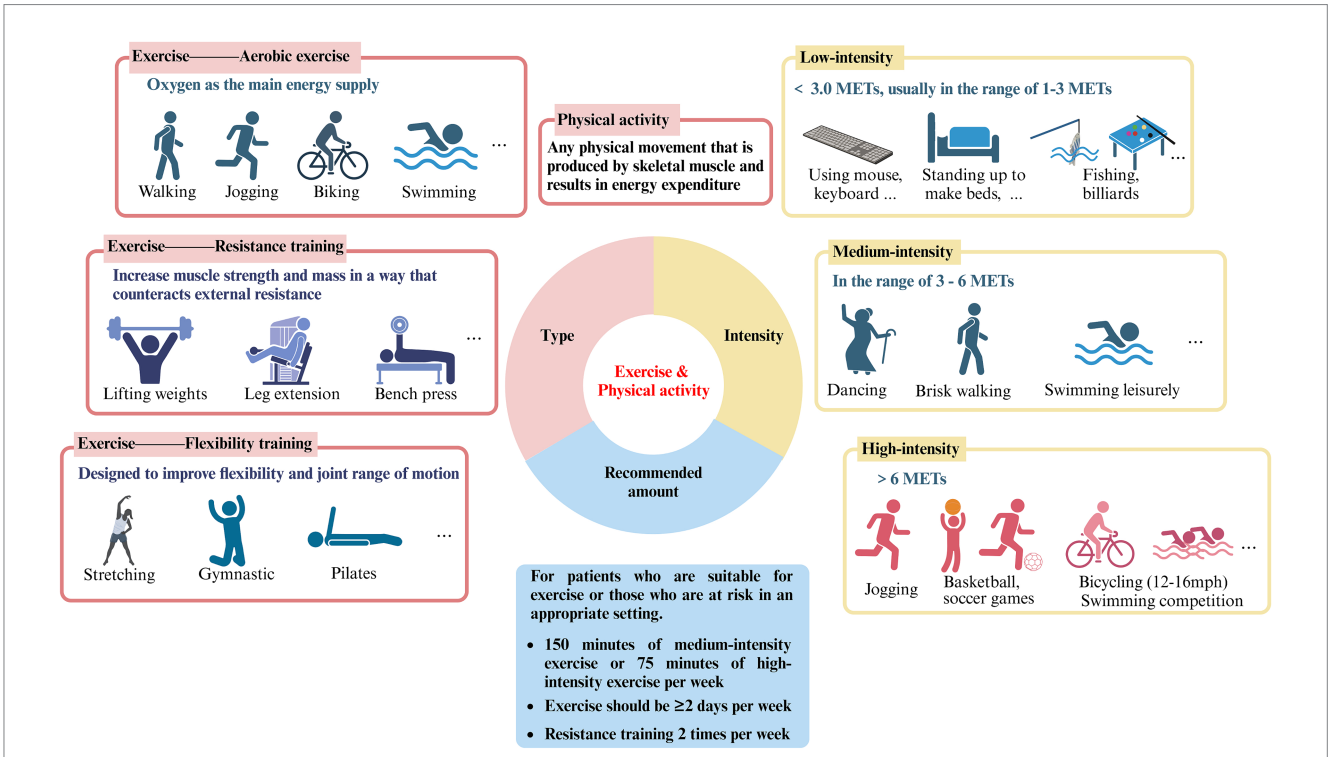

FIGURE 1
Type, intensity and recommended amount of exercise and physical activity (created with Biorender.com).

pull-ups, and the use of devices such as machines or rubber bands. Flexibility training is designed to increase flexibility and joint range of motion and includes activities such as yoga, Pilates, stretching, and gymnastics (13). Physical activity involves a variety of movements generated by skeletal muscles, leading to energy expenditure and encompassing an extensive array of occupational, recreational, and daily activities (12). However, overly detailed requirements and divisions have the potential to confuse and overwhelm individuals in regards to the implementation of "exercise therapy," leading to a decrease in enthusiasm towards adhering to it. Based on the above explanations, it appears that various exercise modalities have been subsumed into the broader category of physical activity, potentially accounting for why the two terms are often used synonymously in existing literature. Therefore, this review does not make a specific distinction between the two.

2.2 Intensity

Variations in exercise intensity have been strongly associated with effects on ocular disease. The metabolic equivalent of task (MET) is a unit of measurement of the body's energy expenditure at different levels of activity, with 1 MET representing the energy expenditure of a person at quiet sitting and rest, which is approximately 3.5 mcal/kg/min (14). It allows for the comparison of various forms of exercise and physical activity relative to energy expenditure during periods of rest, thus classifying the intensity of exercise, which is widely recognized and applied (15).

Low-intensity exercise has an energy expenditure of less than 3.0 METs, usually in the range of 1–3 METs, and specifically includes walking slowly (2.0), sitting and using hand tools such as mice and keyboards (1.5), standing for light physical activities such as making beds and washing dishes (1.5–2.5), playing pool (2.5), fishing (2.5), throwing darts (2.5), playing a musical instrument (2.0–2.5), etc.

Moderate-intensity exercise has METs between 3–6, comparable to a brisk walk which significantly accelerates the heart rate. Similar physical activities include washing windows, cars (3.0), sweeping floors (3.0–3.5), carrying & stacking wood (5.5), playing badminton recreationally (4.5), bicycling slowly on flat ground (6.0), dancing (3.0–4.5), playing table tennis (4.0), swimming leisurely (6.0), playing volleyball noncompetitively playing volleyball noncompetitively (3.0–4.0), etc.

High-intensity exercise, with jogging being a typical example, is defined as exercise greater than 6.0 METs, which can cause shortness of breath and a large increase in heart rate. Also included are carrying heavy loads such as bricks (7.5), heavy farming such as bailing hay (8.0), basketball game (8.0), bicycling on flat terrain with moderate (12–14 mph) or fast (14–16 mph) effort (8.0–10.0), cross country skiing (7.0–9.0), playing soccer (7.0–10.0), swimming with moderate to hard effort (8–11), playing competitive volleyball at the gym or beach (8.0), etc.

2.3 Modulation of ocular physiology by exercise and physical activity

The biological effects of exercise and physical activity extend across multiple facets and locations, positively impacting eye health by maintaining the health of normal physiological mechanisms of the eye and offering protection against diseases. Research indicates that exercise can increase tear production, contributing to the stability of the tear film and improvements in DED (16). In terms of corneal health, exercise regulates intraocular pressure, aiding in the maintenance of corneal health and mitigating acute corneal thinning and endothelial cell damage caused by acute high intraocular pressure (17). For the lens, there is a negative correlation between the intensity of physical activity and the degree of lens opacity (18); moderate exercise can reduce levels of inflammation and oxidative stress, slowing down the aging process of the lens (19). Exercise and physical activity also aid in weight control, reduces blood pressure and blood sugar levels, thus diminishing the impact of metabolic factors on the structure and function of the lens (20). The retina, with its intricate structure and complex functions, has a high blood flow and is susceptible to internal and external pathogenic factors. Exercise contributes to improving retinal microvascular blood supply and oxygen return, maintaining the health and functionality of retinal cells (21). Furthermore, exercise enhances the body's antioxidative capacity and anti-inflammatory responses, protecting retinal cells from oxidative stress and inflammation, thereby reducing the risk of ocular diseases such as AMD and DR (22, 23). By boosting the expression of various neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), exercise potentially offers retinal neuroprotection (24). Additionally, exercise can lower the risk of diabetes, hypertension, and other chronic diseases, preventing associated retinal pathologies such as DR.

2.4 Recommendations

According to the Global Recommendations on Physical Activity for Health and the United States Health and Human Services Physical Activity Guidelines for Adults, it is advised that adults engage in at least 150 min of moderate-intensity exercise or 75 min of vigorous-intensity exercise per week, with the possibility of combining both types based on individual circumstances (7, 25, 26). Exercise sessions should be spread across at least 2 days per week, and additionally, engaging in resistance training twice weekly is also recommended. Pertaining to eye health, the epidemiological evidence cited in this review primarily focuses on the positive impacts of moderate to vigorous-intensity exercise on specific ocular diseases, with the included study subjects being well-suited for physical activity. Consequently, we recommend that early to mid-stage patients of the ocular diseases listed in this review (who are in good physical condition) or high-risk individuals, persistently engage in long-term moderate to vigorous-intensity physical activities, such as running, walking, swimming, and cycling, in a suitable environment to potentially slow the progression of diseases or ameliorate symptoms. It should be noted that our recommendations come with certain prerequisites, as this review does not purport to suggest that exercise can serve as a direct treatment modality for specific ocular conditions. When afflicted with any eye disease, seeking medical assistance always takes precedence. Our aim is for patients to thoroughly assess their own conditions against the backdrop of medical treatment and consider maintaining physical activity and exercise as a supplementary means to assist treatment and improve their condition.

3 Effects of exercise and physical activity on ocular diseases

3.1 DED

3.1.1 Effect of exercise and physical activity on DED

DED is a chronic disease affecting the ocular surface, caused by various factors and thought to be a functional unit disorder of the lacrimal gland, resulting in insufficient quantity and quality of tears to lubricate the eyes (27, 28). DED can cause persistent symptoms of irritation or burning in the eyes and vision impairment that negatively impacts daily life. Epidemiological studies have found that up to 75% of adults over the age of 40 may have DED, and it tends to worsen over time once it develops (29, 30).

In recent years, ample evidence has linked DED with lifestyle, highlighting the impact of exercise, diet, and sleep on its development (31). Two extensive cross-sectional studies based on questionnaires discovered that an increased level of exercise contributes to a reduced prevalence of DED. Individuals experiencing DED had reduced physical activity levels and increased sedentary behavior compared to those without DED (32, 33). Additionally, research indicates that physical activity can positively impact alleviating symptoms of DED. A cross-sectional study conducted among 944 web-based workers in China revealed that individuals who engaged in exercise at a minimum of three times per week experienced significantly reduced discomfort associated with their eyes, including decreased visual clarity (34). Another randomized controlled trial focusing on sedentary young adults in the office setting observed a significant decrease in discomfort symptoms, including eye pain, soreness, and eyestrain, after 3 months of exercise following an exercise guideline (35). These findings imply that exercise and physical activity may contribute to delaying the onset and slowing the progression of DED.

3.1.2 Potential mechanisms

Numerous studies have demonstrated that loss of tear film homeostasis is the central mechanism of DED (31). In addition, tear hyperosmolarity, ocular surface inflammation, oxidative stress, ocular surface injury, and neurosensory abnormalities have all been identified as significant etiological factors in DED (36). Based on pathophysiological differences, DED can be classified into two categories: aqueous-deficient dry eye (ADDE) and evaporative dry eye (EDE) (29). Tear hyperosmolarity caused by decreased tear production (ADDE) or excessive evaporation (EDE) is one of the fundamental mechanisms of DED. Elevated osmolarity triggers apoptosis in epithelial cells and goblet cells, consequently reducing the lubrication ability of the ocular surface. This results in rapid tear film breakup and an additional rise in hyperosmolarity, thereby creating a self-perpetuating cycle. With increasing osmolarity, ocular surface damage increases and oxidative stress intensifies, eventually resulting in tear film homeostasis disruption (37). Studies have shown a temporary surge in tear volume and extended tear film rupture following aerobic exercise, indicating enhanced tear film stability (16). A prospective cross-sectional study involving 43 healthy participants found significant reductions in tear fluid levels of inflammation-related cytokine, including interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-4, IL-5, and dozens of others, after a 20 min exercise session in comparison to the baseline levels (38). More excitingly, exercise reduced the tear fluid concentration of the marker of oxidative stress, 8-hydroxy-2′-deoxyguanosine (8-OHdG), suggesting that exercise may play a role in alleviating DED by reducing the oxidative stress present in tears (39) (see Table 1).

3.2 Myopia

3.2.1 Effect of exercise and physical activity on myopia

Myopia, or nearsightedness, is the prevalent refractive error that results in images being focused in front of the retina due to overstretching of the eye's axis, thus making distant objects appear blurry (51). This condition is most prevalent during childhood and early adulthood (51). Myopia is a widespread ophthalmic disease globally, with an incidence of up to 80%–90% among young populations in certain regions of East and Southeast Asia (52). Its prevalence poses an escalating health issue worldwide. Any degree of myopia increases the likelihood of pathologic changes in ocular tissues, with a corresponding positive co-relation to the severity of myopia (53). High and pathological myopia substantially raise the likelihood of encountering vision-related complications such as glaucoma, retinal detachment, and macular degeneration (54). Therefore, preventing the onset of myopia and delaying its progression have been identified as crucial targets for public health interventions related to myopia (52).

Numerous studies have shown that physical activity positively affects the prevention of myopia and delays its progression (55–58). Those who engage in physical activity for over 3 h a week stand to reduce their chances of developing myopia by approximately 40% (40). One cohort study discovered a critical relevance between higher levels of physical activity and a reduction in the incidence of myopia, and that sedentary behavior increases the risk of myopia (59). Another longitudinal cohort study, based on a questionnaire, found that myopic students spend less time engaging in physical activity per day compared to nonmyopic students (60). Additionally, multiple studies have identified a substantial inverse relationship between time spent outdoors and the onset of myopia, with outdoor time being one of the primary protective factors against myopia (61, 62). A recent meta-analysis presented a notable nonlinear negative correlation between the time spent outside and the prevalence of myopia (63).

3.2.2 Potential mechanisms

The specific mechanisms by which exercise and physical activity prevent and protect against myopia have not yet been clearly established. Some studies have proposed potential mechanisms. Physical activity and exercise can cause the choroidal layer to dilate by enhancing blood flow, potentially hindering eye axis lengthening (64). Studies on animals suggest that eye growth is suppressed when blood flow and choroidal thickness increase (65, 66). Exercise and physical activity may also impact myopia in non-visual ways by influencing vascular function, blood pressure, peripheral and central growth factors, insulin resistance, oxidative stress and inflammation (60). Prior studies have shown that exercise-induced growth hormone and these systemic mechanisms are involved in regulating ocular growth (60). Additionally, studies have shown that engaging in outdoor exercise is more effective in preventing and controlling myopia compared to indoor exercise (62). This is due to the stronger light

environment outdoors, which is considered to be a crucial factor in myopia protection (62). Research on animals has demonstrated that myopic susceptibility and dopamine-related genes and proteins can be affected by light intensity and peripheral defocus (67). Among these, dopamine has been found to hinder ocular axis growth, and its protective effects can be counteracted by the presence of its antagonist, spiperone (68). Environmentally influenced peripheral defocus might also contribute to the emergence or progression of myopia (69, 70). When engaging in outdoor sports, objects are typically positioned farther away from the eyes, and refractive conditions are uniform, thus reducing peripheral defocus and decelerating eye axis growth to prevent myopia (53) (see Table 1).

3.3 Cataract

3.3.1 Effect of exercise and physical activity on cataract

The lens is a transparent structure located at the front section of the eye that resembles a convex lens and possesses elastic properties. As one of the refractive media of the eye, the lens has the capacity to alter its shape due to its elasticity, enabling it to refract and focus light rays from varying distances onto the retina, consequently producing a sharp image (71). Cataract refers to the loss of clarity in the lens caused by clouding resulting from various factors (72). Globally, cataracts are a major contributor to visual impairment and blindness. Research indicates that this condition also increases the likelihood of depression and decreases life expectancy (73).

Long-term regular exercise and physical activity have demonstrated a favorable effect on the development and progression of cataract. Two prospective studies indicate that both moderate-intensity (walking) and high-intensity (running) exercise significantly reduce the risk of cataracts in men (9, 11) and women (9). Meanwhile, a case–control study identified an inverse relationship between lens cloudiness and the intensity of physical activity (18). Additionally, various detailed studies were conducted on different types, intensities, and durations of physical activity and exercise. The findings revealed a significant negative correlation between total physical activity and cataract incidence (49). Individuals who participated in rigorous physical labor experienced a 16% reduced risk of developing cataracts compared to those who led a sedentary lifestyle. Similarly, individuals who engaged in walking or biking for over 60 min daily recorded a 12% lowered prevalence of cataracts in comparison to those who rarely partook in such activities (49). Low-intensity physical activities, such as housework, did not seem to be associated with cataract risk (49). The evidence from these studies indicates that engaging in moderate to high intensity exercise and physical activity over a prolonged period can have a more clear-cut and recognized effect on reducing the risk of cataract.

3.3.2 Potential mechanisms

3.3.2.1 Enhancement of antioxidant defense in the lens

It is currently believed that reactive oxygen species (ROS) damage directly contributes to crystal clouding (72). Aging is an important driver of this process. In youth, antioxidants from the aqueous humor are sufficient to scavenge oxygen free radicals to prevent oxidative damage to the lens and, together with nutrients, maintain high metabolic activity of the lens, which is essential for normal clarity and refractive index (71). The levels of antioxidant enzymes, including dismutase (SOD) and glutathione peroxidase (GPX), in both the serum and lens notably decline with age (74). Furthermore, the level of reduced glutathione (GSH), which is the most critical antioxidant factor in the lens, decreases almost linearly and to an even greater extent (75, 76).

Research has indicated that consistent aerobic exercise aids in improving cellular capacity to fight against excessive build-up of ROS (77). Regular moderate-to high-intensity exercise increases the activity of endogenous antioxidant enzymes (SOD, GPX, and CAT), which improves the antioxidant capacity of the lens and slows down the aging process (78). However, this antioxidant effect does not appear to apply to all forms of exercise. For a single session of vigorous aerobic exercise, ROS and reactive nitrogen species are overproduced as a result of rapidly increased metabolism, which may instead induce oxidative stress and related injury (49). Therefore, finding the right form of exercise (regular and periodic exercise of moderate or higher intensity) is also crucial for improving lens turbidity.

3.3.2.2 Suppression of inflammation

Inflammation is an additional crucial risk factor for cataract. Inflammation is intimately related to oxidative stress, and both tend to occur concurrently in multiple pathological conditions, such as cataract (79). An 11 years cohort study found that elevated plasma C-reactive protein (CRP) levels were significantly associated with the risk of developing cataract (80). Aging is a major factor in age-related cataract, and chronic inflammation is one of the hallmarks of aging (81). With aging, circulating levels of pro-inflammatory factors such as IL-6, TNF-α, and CRP generally increase (82). Regular exercise has been found to reduce circulating levels of IL-6 and CRP, which has been associated with exercise-induced upregulation of the anti-inflammatory factors lipocalin and IL-10 (83, 84). In addition, after 10–12 weeks of appropriate exercise in sedentary elderly subjects, circulating levels of TLR4 and other pro-inflammatory biomarkers were found to be reduced to levels similar to those in young adults (19). These findings suggest that chronic inflammation during aging may be ameliorated or even reversed by appropriate exercise, thereby decreasing the likelihood of cataract development or delaying the progression of crystalline opacity.

Analogous to oxidative stress, the modulation of inflammation by exercise and physical activity is strongly connected to the type and intensity of exercise and the physical state of the exerciser. Different studies on resistance and aerobic exercise have found that both have inhibitory effects on chronic inflammation, but aerobic exercise seems to be better suited to modulate the immune system and markers of inflammation in older adults than resistance exercise (85, 86). In contrast, prolonged resistance exercise did not produce positive anti-inflammatory effects in frail older adults.

3.3.2.3 Amelioration of some systemic diseases

Various systemic diseases play a role in the onset and advancement of cataract. Men with hyperlipidemia (≥250 mg/dL) were discovered to have a heightened risk of developing cataract (87). Diabetic patients have a 5-fold increased risk of cataract compared to normal subjects (20). Case-control studies have identified a heightened risk of cataract in populations with hypertension, particularly in the case of posterior

TABLE 1 Effects of exercise and physical activity on common eye diseases: insights into myopia, cataract and DED with potential mechanisms explored.

Disease	Citation	Pre-clinical vs. clinical	Study design	Study population	Interventions	Study duration/ follow-up period	Key findings	Potential mechanism
Myopia	Hansen et al. (40)	Clinical	Prospective cohort	1,443 participants	Physical activity (≥3 h/week)	16 years	Participating in three or more hours of physical activity per week significantly reduced the likelihood of developing myopia	(1) Increased release of dopamine facilitated by stronger light (outdoor exercise) (2) Reduction in time spent in near-work activities (3) Involvement of induced growth hormone in growth regulation of the eye
	Holton et al. (41)	Clinical	Cross-sectional	6,200 participants	Outdoor activity (≥1 h/day)	5 years	An hour of outdoor activity a day reduced the odds of being myopic by 13%	
	He et al. (42)	Clinical	Prospective cohort	1,903 schoolchildren	An additional 40 min class of outdoor activities	3 years	Cumulative incidence of myopia in intervention group is 9.1% lower than control group	
	French et al. (43)	Clinical	Cohort study	863 schoolchildren	Outdoor activity	6 years	The trend toward higher rates of myopia was more pronounced among children who spent less time outdoors	
	Lee et al. (44)	Clinical	Cross-sectional	5,048 male military conscripts	Outdoor activity	3 years	Less outdoor activity significantly associated with myopia prevalence	
	Ip et al. (45)	Clinical	Cross-sectional	2,339 schoolchildren	Outdoor activity	/	Outdoor exercise negatively correlates with myopia rates	
DED	Kawashima et al. (32)	Clinical	Cross-sectional	425 office workers	High, moderate or low PA	/	More Exercise, lower dry eye quality of life scores	(1) Improvement in tear film stability (by increasing tear volume and prolonging tear film breakup) (2) Reduction of tear inflammation and oxidative stress levels
	Kawashima et al. (35)	Clinical	Randomized controlled trial	36 office workers	Aerobic and resistance exercises	2 months	Higher level of physical activity was associated with a lower prevalence of DED	
	Cheng et al. (34)	Clinical	Cross-sectional	915 office workers	Physical activity	/	Higher level of physical activity was associated with fewer symptoms of DED	
	Nugyen et al. (46)	Clinical	Cross-sectional	48,418 subjects	Sedentary behavior	6 years	Higher sedentary time increased the risk of DED	
	Vera et al. (47)	Clinical	Quasi-experimental	19 helicopter pilots	Treadmill exercise	10 min	Exercise reduced tear osmolarity	
	Peart et al. (48)	Clinical	Quasi-experimental	12 subjects	Cycloergometer exercise	15 min	Exercise reduced ocular surface disease index	
	Sun et al. (39)	Clinical	Experimental	52 healthy and DED patients	Jogging	30 min	Exercise was associated with increased tear break-up time	
	Hanyuda et al. (33)	Clinical	Cross-sectional	102,582 participants	Physical activity	6 years	Lack of exercise linked to higher risk of DED among middle-aged and elderly in Japan	

(Continued)

10.3389/fmed.2024.1353624

TABLE 1 (Continued)

Disease	Citation	Pre-clinical vs. clinical	Study design	Study population	Interventions	Study duration/ follow-up period	Key findings	Potential mechanism
Cataract	Williams (9)	Clinical	Prospective cohort	29,025 male and 11,967 female	Running	7 years	Vigorous physical activity delayed the onset of cataract	(1) Inhibition of oxidative stress and enhancement of antioxidant capacity (2) Suppression of inflammation and enhancement of anti-inflammatory capacity (3) Regulation of blood glucose, blood pressure and blood lipids
	Williams (11)	Clinical	Prospective cohort	32,610 runners and 14,917 walkers	Different levels of exercise	6.2 years	Moderate (walking) and vigorous (running) exercise were both significantly associated with lower cataract risk	
	Paunksnis et al. (18)	Clinical	Comparative	110 patients and 50 controls	Physical activity (>5,900 min/week)	/	The intensity of lens opacity and cataract are significantly related to physical activity	
	Zheng et al. (49)	Clinical	Prospective cohort	52,660 participants	Different levels of physical activity	12.1 years	High physical activity may be associated with decreased risk of age-related cataract	
	López-Sánchez et al. (50)	Clinical	Cross-sectional	17,777 participants	Physical activity	1 year	Physical activity was significantly associated with cataract	

subcapsular cataract. Moreover, a linear relationship exists between blood pressure and the risk of cataract (88, 89).

The advantageous impacts of exercise and physical activity on regulating blood glucose, blood pressure, and blood lipid levels are well acknowledged. The American Diabetes Association (ADA) recommends adults with diabetes to participate in at least 150 min of moderate-intensity physical activity per week (90). A systematic review and meta-analysis suggests that a combination of moderate-to high-intensity aerobic exercise and resistance training followed by regular exercise (≥4 weeks) reduces blood pressure by approximately 2–5 mmHg in normotensive adults and 5–7 mmHg in hypertensive adults (91). Exercise and physical activity are now thought to improve hyperlipidemia by modulating plasma lipoprotein levels, and a randomized controlled clinical trial found a significant increase in plasma high density lipoprotein (HDL) (4.4 mg/dL) in the exercise group after 1 year of regular exercise (running at least 8 km per week) (92).

Similarly, the extent to which exercise improves systemic disease is strongly linked to the duration and intensity of exercise. In hyperlipidemia, for example, a significant correlation was found between weekly exercise distance and low-density lipoprotein cholesterol ($r = -0.31$), plasma HDL cholesterol ($r = 0.48$) and HDL2 ($r = 0.41$). In addition, regular exercise for at least up to 9 months was required to observe significant changes in lipid profiles (93, 94) (see Table 1).

3.4 Glaucoma

3.4.1 Effect of exercise and physical activity on glaucoma

Glaucoma is the primary cause of irreversible vision loss globally (95). As a classification of neurodegenerative diseases, is characterized by the gradual degeneration of retinal ganglion cells (RGCs) and axons (96). Degeneration of the optic nerve results in cupping, which is the distinctive appearance of the optic disc and accompanying loss of vision (97). Intraocular pressure (IOP) is the most significant, and the only controllable risk factor for glaucoma, so reducing IOP through medication or surgery is currently the mainstay of glaucoma treatment (98). However, some clinical studies have found that glaucoma patients continue to progress even when IOP is lowered (99).

In recent years, numerous studies have disclosed that modifiable environmental factors, such as exercise, smoking, alcohol consumption, and nutrition, possess a significant impact on the development of glaucoma (100). Long-term, regular exercise and physical activity have been demonstrated to reduce the incidence of glaucoma or slow its progression (8, 101, 102). A prospective study including 9,519 adults for up to 5 years discovered a significantly lower occurrence of glaucoma in those who abided by physical activity guidelines compared to those who did not engage in exercise (2.24% versus 1.14%) (8). A further retrospective analysis examined 24 patients with primary open-angle glaucoma (POAG) or pseudoexfoliation glaucoma and found that those who engaged in exercise habits (≥30 min per week) experienced less glaucomatous visual field deterioration compared to these non-exercising counterparts (10).

A considerable amount of research suggests that exercise and physical activity have the potential to prevent and mitigate various

forms of damage to RGCs and optic nerves (103). A cross-sectional study with over 40,000 participants discovered that increased levels of physical activity led to an augmentation of the thickness in the plexiform layer within the retina (104). Experimental studies offer more unambiguous evidence. An experiment investigating age-related optic nerve injury revealed that regular aerobic exercise (swimming for 60 min per day, 5 days per week for 6 weeks) led to similar responses to acute ischemia-reperfusion-induced optic nerve injury in older mice (12 months) as compared to non-exercised young mice (3 months) (105). Additionally, exercise reduced injury-induced retinal neuroinflammation in aged mice. Another study on injury caused by optic nerve severance demonstrated that retinal ganglion cell survival significantly increased following a 4 weeks period of aerobic exercise, specifically running at 9 m/min for 30 min per day (106).

The effect of exercise and physical activity on glaucoma is intricately linked to the type and intensity of exercise undertaking. In a substantial 7.7 years cohort study comprising over 29,854 male runners belonging to running clubs located throughout the United States, an evident dose-dependent correlation was discovered between exercise patterns and glaucoma hazards, with swifter running speeds and longer running distances demonstrating a decreased risk of glaucoma (107). Another retrospective study involving 10,243 South Korean men aged 40 or older uncovered an inverse relationship between the development of glaucoma and engagement in medium-to-high intensity physical activity (108). Furthermore, a longitudinal study observing 141 patients with glaucoma discovered that the rate of visual field loss decreased with increased moderate to high activity levels (according to accelerometer measurements) (109). However, another study revealed that low and high-intensity exercise might elevate the risk of glaucoma in comparison to the moderate-intensity exercise recommended by the American College of Sports Medicine (ACSM) guidelines (110). The study also uncovered that undertaking high-intensity exercise daily was linked to a greater occurrence of glaucoma than exercising three times weekly. It is noteworthy that not all types of exercise and physical activity are advantageous for individuals with glaucoma. The study has demonstrated that engaging in vigorous isometric workouts such as wall push, suspension training, resistance band training, among others, as well as performing exercises in inverted body positions, and playing high-resistance wind instruments such as trumpet, trombone, French horn, and others have been shown to elevate IOP, thereby elevating the risk of developing glaucoma (111, 112).

It should be noted that there are multiple types of glaucoma, and exercise and physical activity may be considered a risk factor for certain types, such as pigmentary glaucoma. Pigmentation of corneal endothelial cells occurs in patients with pigment dispersion syndrome. When pigment particles enter the trabecular meshwork endothelial cells, they can gradually lead to pigment overload and death of the trabecular meshwork cells. This, in turn, causes trabecular collapse, obstruction of atrial aqueous outflow pathways, and increased intraocular pressure. Ultimately, this can lead to pigmentary glaucoma (113). Studies have shown that after aerobic exercise, patients with pigmented dispersion syndrome and pigmentary glaucoma experience a dispersion of pigments in the anterior chamber that is significantly increased (114, 115). A patient with pigment dispersion syndrome presented with typical symptoms of elevated IOP, blurred vision, and halos after strenuous exercise (116). However, after expanding the sample size, it was found that exercise did not significantly increase clinical IOP in patients with pigmentary glaucoma (117). Iris depressions have been suggested as a possible mechanism for pigment release (118). Patients with pigmentary glaucoma experience a significant increase in iris depressions following exercise (119). Research has demonstrated that exercise can increase the IOP pulse and affect atrial fluid dynamics, resulting in enhanced cyclic atrial fluid flow through the pupil. This, combined with reverse pupillary obstruction, can cause intermittent excessive iris depression, leading to an increase in pigment dispersion (119). Although current research does not suggest that all patients with pigmentary dispersion syndrome or pigmentary glaucoma should avoid all forms of exercise, highly stimulating exercise should be avoided as much as possible. It is necessary for these patients to carefully consider their condition and seek evaluation by a healthcare professional prior to exercising at a low or moderate intensity (114).

3.4.2 Potential mechanisms

3.4.2.1 Regulation of IOP

Excessive IOP can compress, deform, and alter the sieve plate on the inner eye wall, leading to mechanical axonal damage and transit disorders that impede the brainstem's provision of trophic factors to RGCs (120). When IOP exceeds ocular perfusion pressure (OPP), blood supply to the optic nerve is restricted (121). The various factors listed above ultimately lead to the demise of RGCs and initiate the onset of glaucoma. Lowering IOP is a crucial factor in preventing and delaying the progression of glaucoma through exercise and physical activity (122). According to a randomized controlled study, a notable decrease in IOP was observed among healthy adults who engaged in 20 min of aerobic exercise with a return to baseline levels in approximately 1 h (123). Furthermore, post-exercise IOP levels decreased by 2.7 mmHg in a study of resistance training (124). Another prospective, interventional study found that aerobic exercise reduced the baseline level of IOP in subjects with glaucoma by 4.6 ± 0.4 mmHg after 3 months, and this reduction was maintained for 3 weeks (125). Therefore, examining the specific mechanisms by which exercise improves glaucoma requires an examination of how exercise regulates IOP. Maintaining normal intraocular pressure depends on a balanced interplay between the production of aqueous humor by the ciliary body and its drainage through the trabecular meshwork and uveoscleral outflow pathway (96). The present study suggests that acute exercise may alter IOP by, among other things, decreasing blood pH, increasing plasma osmolality, increasing blood lactate, decreasing norepinephrine concentration, increasing the nitric oxide/endothelin ratio (resulting in increased NO production and decreased endothelin content), stimulating β2 receptors, and altering ocular blood flow after exercise (122). Different types of exercise have been found to have varying effects on IOP regulation. Isometric exercise has primarily been associated with hyperventilation and hypocapnia, resulting in a decrease in IOP, while isotonic exercise has been primarily linked to an increase in colloid osmolality (126–128). However, research on the mechanisms by which long-term exercise and physical activity impact baseline levels of IOP is lacking, which suggests an avenue for future research.

TABLE 2 Effects of exercise and physical activity on common eye diseases: insights into glaucoma with potential mechanisms explored.

Disease	Citation	Pre-clinical vs. clinical	Study design	Study population	Interventions	Study duration/ follow-up period	Key findings	Potential mechanism
Glaucoma	Yan et al. (123)	Clinical	Paired comparative	29 healthy participants	Jogging	20 min	A decrease in IOP after aerobic exercise in healthy subjects	(1) Decrease in intraocular pressure (decreases blood pH, increases plasma osmolality and blood lactate, decreases norepinephrine concentration…) (2) Inhibition of oxidative stress and inflammation (3) Improvement of mitochondrial dysfunction (4) Increased protective myokine expression (BDNF, Irisin…)
	Yeak et al. (129)	Clinical	Prospective, interventional cohort	45 healthy participants	Aerobic exercise and strength training	6 weeks	Regular exercise significantly reduces intraocular pressure in healthy people	
	Meier et al. (8)	Clinical	Prospective cohort	9,519 participants	Physical activity	5.7 years	Higher level of physical activity was associated with a lower risk of incident glaucoma	
	Yokota et al. (10)	Clinical	Retrospective cohort	24 POAG patients	Exercise (≥30 min/week)	3 years	Glaucoma progresses slower in patients with self-reported exercise habits	
	Madjedi et al. (104)	Clinical	Cross-sectional	3,627 participants	Physical activity	5 years	Higher overall PA level was associated with thicker mGCIPL	
	Williams et al. (107)	Clinical	Prospective epidemiologic cohort	29,854 male runners	Running	7.7 years	Vigorous physical activity may reduce glaucoma risk	
	Seo et al. (108)	Clinical	Cross-sectional	10,243 men	Different intensity of exercise	5 years	Exercise intensity negatively correlates with odds of developing glaucoma	
	Lee et al. (109)	Clinical	Longitudinal, observational study	141 participants	Different intensity of exercise	1 week	Moderate-to-vigorous physical activity was associated with slower visual field loss in glaucoma patients	
	Lawson et al. (24)	Pre-clinical	Randomised controlled	48 mice	Treadmill exercise (5 days/week, 60 min, 10 m/min)	2 weeks	Exercise increased retinal BDNF protein levels by 20% compared with inactive mice	
	Kim et al. (130)	Pre-clinical	Randomised controlled	24 mice	Treadmill exercise (3 days/week, 30–60 min, 5–12 m/min)	12 weeks	Regular exercise can reduce retinal oxidative stress	
	He et al. (106)	Pre-clinical	Randomised controlled	24 mice	Treadmill exercise (5 days/week, 30 min, 9 m/min)	4 weeks	Treadmill training effectively rescues RGCs that develop neurodegeneration after optic nerve transection	
	Chrysostomou et al. (105)	Pre-clinical	Randomised controlled	30 mice	Swimming (5 days/week, 60 min)	6 weeks	Exercise protects the aged optic nerve against functional loss	

10.3389/fmed.2024.1353624

3.4.2.2 Inhibition of oxidative stress and inflammation in the trabecular meshwork and retina

Oxidative stress, cellular senescence, and mitochondrial dysfunction increase in the aging retina and are significant risk factors for glaucoma (131). Oxidative stress and lipid peroxidation are principle initial contributors to the onset of para-inflammation in the retina (132). ROS activate retina-resident macrophages and neuroimmune cells, such as microglia and astrocytes, which release proinflammatory mediators and trigger neuroinflammation, ultimately accelerating the death of RGCs (132). Moreover, the trabecular meshwork serves as the "gateway" of aqueous humor outflow in the eye and is a highly vulnerable tissue to oxidative stress. This stress disrupts the normal drainage of aqueous fluids and ultimately leads to increased intraocular pressure and damage to the optic nerve (131). Research has shown that individuals with glaucoma exhibit elevated levels of oxidative stress markers, including 8-OH-dG and malondialdehyde, within their aqueous humor, trabecular meshwork, and serum (133, 134).

Prolonged aerobic exercise has been demonstrated to reduce oxidative stress and enhance antioxidant capacity in elderly individuals (135). An experimental study demonstrated a reduction in levels of oxidative stress within the retinas of mice after 12 weeks of regular bench running exercise (5–12 m/min, 30–60 min/day, 3 days/week) (130). This provides more direct evidence of the benefits of aerobic exercise. Previous studies have revealed that aerobic exercise reduces inflammatory factors in the bloodstream, spinal cord, cortex, and hippocampus, such as IL-1, IL-6, and TNF-α (136). At present, there is no direct evidence indicating that exercise ameliorates retinal inflammation, it has been found that exercise-induced myokine Irisin can inhibit oxygen-induced pathological angiogenesis, inflammation, and apoptosis in the retina *in vivo* (137).

3.4.2.3 Improvement of mitochondrial function

Mitochondria contribute to oxidative stress in living organisms. Mitochondrial dysfunction is a critical aspect of aging, characterized by changes in biogenesis, protein inhibition, mitochondrial autophagy, and kinetics (138, 139). The retina is among the most metabolically active tissues within the body and contains a substantial quantity of mitochondria. These mitochondria are primarily located in the myelin-free axons of RGCs and the inner segments of photoreceptors, fulfilling a crucial role in normal energy transportation (140). Mitochondrial dysfunction, potentially caused by various mechanisms such as dysregulation of signaling, dysfunction of pathways, genetic variations, and oxidative stress, is significantly associated with a majority of blinding eye conditions, including glaucoma (141, 142). The mitochondria in the RGCs are the first to be affected by glaucoma (143). Furthermore, the expression of OPA 1, a gene that is present in RGCs soma and axons and linked to both spontaneous and hereditary mitochondrial optic neuropathy, exhibits noteworthy down-regulation in patients identified with POAG, providing evidence of a genetic association connecting mitochondrial function and POAG (144). Mitochondrial abnormalities in morphology, reduced mass, decreased oxidative capacity, and abnormal autophagy, among other factors, can all contribute to glaucoma development (142).

Numerous studies indicate that aerobic exercise boosts the mitochondrial biosynthetic pathway and cellular respiratory capacity, leading to improved mitochondrial mass, structure, and function. Exercise improves an organism's resilience against inhibitors of mitochondrial complex I, which is the initial enzyme-protein complex in the mitochondrial OXPHOS pathway. The downregulation of this complex may result in mitochondrial dysfunction. Physical activity also boosts the expression of mRNAs associated with mitochondrial complex I (145). Experimental studies have demonstrated that aerobic exercise can preserve mitochondrial metabolism by preventing age-related mitochondrial damage in skeletal muscle, achieved through inhibiting mitochondrial schizopyranin expression in a PGC-1α-dependent manner (146). Other studies have indicated that aerobic exercise enhances mitochondrial biogenesis and function by activating Nrf2 (139). Elevated mRNA levels of lysosome-associated membrane protein 2 (LAMP-2), Atg and LC3II in lateral femoral muscles was found in overweight older women after 6 months of weight loss and moderate-intensity exercise. Additionally, this study discovered that lifelong physical activity preserves LC3II and Atg at youthful levels (147). This indicates that physical activity enhances mitochondrial autophagy and consequently attenuates mitochondrial dysfunction. However, further validation is necessary to determine whether these particular mechanisms apply to the optic nerve injury model of glaucoma.

3.4.2.4 Facilitating the release of protective factors

3.4.2.4.1 BDNF

BDNF, a protein from the neurotrophic factor family, is produced by retinal neurons like RGCs, anaplastic synaptic cells, retinal neuroglia (Müller cells), astrocytes, and photoreceptors (148). It has been shown that BDNF protects RGCs' survival in pathological conditions such as glaucoma and optic nerve injury (149). BDNF can enhance the retina's resistance to injury by regulating the formation and maintenance of retinal neural circuits. Studies have shown that exercise can effectively prevent complement-mediated synapse loss (150). This helps to resist neurodegenerative changes in the structure, function, and molecules of the inner retina caused by glaucoma (151, 152). Currently, BDNF is widely recognized as a pivotal factor that mediates the impact of exercise on varying forms of retinal damage (153). Aerobic exercise, including long-term endurance training and short-term acute exercise, enhances circulating levels of BDNF in both healthy and chronically ill individuals. However, resistance training did not have such an effect (154). Experimental studies have found that damaged retinas of untrained mice had significantly decreased levels of BDNF, whereas retinal BDNF levels were significantly increased in trained mice (24). The primary mechanism of BDNF action relates to its binding to the TrkB receptor, which triggers the initiation of numerous signaling cascades. Activated TrkB enhances Erk1/2, which are responsible for retinal ganglion cell (RGC) survival, while concurrently inhibiting glycogen synthase kinase 3β (GSK3β) activity through enhancing PI3K/Akt signaling, thereby promoting neuronal axon growth and cell survival (152, 155). Inhibiting TrkB effectively impairs the ameliorative effects of exercise on retinal damage in disease models, including glaucoma and DR (150). In a mouse model of glaucoma, administration of BDNF resulted in increased survival of the RGC and improved retinal function (156).

Furthermore, insulin-like growth factor-1 (IGF-1) and neurotrophic growth factor (NGF) have also been validated for their neuroprotective effects in cases of retinal injury (103). Nonetheless, it is still unclear if they contribute to the protective effects of exercise, necessitating further comprehensive investigation.

3.4.2.4.2 Dopamine

Dopaminergic neurons are considered a crucial component of the motor system, with physical exercise and activity known to stimulate dopamine release (157, 158). Extensive animal studies have demonstrated that regular aerobic activities such as running and swimming lead to significant increases in serum and brain dopamine levels in mice or rats (158, 159). The dopaminergic system's role in regulating the balance of aqueous humor dynamics, a key pathophysiological process in glaucoma, has been widely studied since the 1980s. Dopamine's activity is mediated primarily through five G protein-coupled receptors belonging to two subfamilies: the D1-like receptors (D1R and D5R) and the D2-like receptors (D2R, D3R, and D4R) (160). Activation of D2R and D3R helps lower intraocular pressure (161–164). Many classic D2R agonists, including bromocriptine, cabergoline, lisuride, and lergotrile, have been used to reduce intraocular pressure in humans and animals (160). In 2000, a study on the selective D3R agonist 7-OH-DPAT revealed its potential role in reducing rabbit intraocular pressure, marking the first indication of D3R's involvement in lowering eye pressure (163). Subsequent research on various D3R agonists and D3R$^{-/-}$ mice further confirmed this view (165, 166). The presence of D3R in the sympathetic nerve fibers of the ciliary body suggests that D3R activation could block the inflow of aqueous humor, thereby reducing intraocular pressure (162). A recent study by Reyes-Resina et al. (167) found that D3R expression in the ciliary body slices of glaucoma patients was significantly lower than that in controls, although the sample size of two was too small for statistical analysis, the findings undeniably further elucidate the connection between the dopaminergic system and glaucoma. While D2R and D3R have been detected in the human retina, there is a lack of research on abnormalities in the dopaminergic system within the retina of glaucoma patients. However, a study on a quail model of glaucoma found a reduction in dopaminergic cells and dopamine rhythms in the retina following glaucoma (168). In summary, physical exercise and activity may positively impact glaucoma by promoting dopamine release and its interaction with D2R and D3R. Nonetheless, this hypothesis requires further substantiation through more in-depth and direct evidence (see Table 2).

3.5 DR

3.5.1 Effect of exercise and physical activity on DR

DR is the leading retinal vascular ailment that results in visual impairments like floaters, distorted vision, blurry vision, and in more severe cases, retinal detachment that can cause total or partial vision loss (169). DR can also affect the macula and lead to diabetic macular edema (DME). DME is featured by vascular leakage and results in swelling of the macula, which is the primary reason for blindness among diabetic patients (170).

Clinical studies have confirmed that regular exercise or physical activity and maintaining a healthy diet can significantly reduce the risk of developing diabetes and related ocular complications (171). A retrospective study of 3,031 adults demonstrated that individuals who consistently engaged in higher levels of physical activity over an extended period had a lower incidence of DR (172). Conversely, a sedentary lifestyle was found to significantly increase the likelihood of diabetic patients developing DR (173). Another pre-and post-clinical trial conducted on patients with DR indicated significant reductions in fasting blood glucose and central macular thickness in participants who underwent long-term moderate-intensity aerobic exercise regularly (45 min, three times per week for 12 weeks) (174). Basic research has provided further evidence that 8 weeks of treadmill exercise (8 m/min, 30 min per day, 6 days per week) yielded a significant reduction in retinal vascular endothelial growth factor (VEGF) expression and retinal cell apoptosis in diabetic mice models (175).

The intensity of exercise and physical activity is associated with their ameliorative effect on DR. Previous research suggests that the benefits of moderate-intensity aerobic exercise and physical activity for DR are greater than those of low-and high-intensity exercise (176). High-intensity interval training (HIIT) has been found to enhance choriocapillaris perfusion in healthy individuals. Nevertheless, clinical trial studies have not observed any ameliorative effects of HIIT on the microvasculature in patients with type 1 diabetes (T1D) (177, 178). At present, research on the influence of exercise and physical activity on DR primarily concentrates on the advantages of aerobic exercise. Additional studies are necessary to explore and showcase the impacts of other forms of exercise and physical activity on DR.

3.5.2 Potential mechanisms

3.5.2.1 Regulation of blood glucose

Briefly, DR is a microangiopathy with a complex pathophysiology and unclear pathogenesis (179). Various studies have established a correlation between hyperglycemia and retinal microvascular damage, indicating the former as a major and direct cause (180). Hyperglycemia leads to several pathophysiological alterations, such as oxidative stress, accumulation of sorbitol and advanced glycosylation end-products (AGEs), activation of protein kinase C (PKC), chronic neuroinflammation, and others (181). These pathways result in dysfunction of the vascular endothelium of the retina, marked by the loss of pericytes and endothelial cells, thinning of the basement membrane, increased retinal permeability, and the absence of neuroprotective molecules (182, 183). Retinal vascular endothelial dysfunction worsens retinal hypoxia, neuronal dysfunction, and leads to the development of various angiogenic factors such as VEGF, growth hormone-insulin-like growth factor (GH-IGF), and erythropoietin. Ultimately, this results in retinal neoangiogenesis, which is a typical feature of DR and a hallmark of its progressive development (182, 184).

The effectiveness of exercise and physical activity in improving blood glucose levels has been well-established through numerous studies. Different types of physical activity, like aerobic exercise, resistance training, and high-intensity interval exercise (HIIE), have been found to boost blood glucose levels in patients with type 2 diabetes by augmenting insulin sensitivity, promoting mitochondrial function, and adjusting metabolic parameters such as blood pressure and blood lipids (185–191). It has been found that combined exercise produces a more significant effect on blood glucose intervention than any single type of exercise alone (192, 193). A meta-analysis on resistance training demonstrated that high-intensity resistance training is more effective than low or moderate-intensity for reducing insulin levels and overall glycemic management (189). Furthermore, numerous studies indicate that engaging in exercise after a meal is

more effective in regulating glycemic levels by reducing sudden spikes in blood glucose. The advantages are particularly evident for exercise sessions lasting 45 min or longer (188, 194).

3.5.2.2 Retinal neuroprotection

A rising number of studies have shown that pure microvascular injury cannot fully elucidate the pathogenesis of DR. Neuroretinal damage is found to be equally indispensable in DR's development, even before microvascular injury (195). Diabetes mellitus influences the functioning and structure of all retinal cell types, and an increased expression of apoptotic markers of RGCs (caspase-3, Fas, and Bax) was noticed in diabetic patients' retinas (196). Animal studies show that hyperglycemia speeds up retinal neuron apoptosis in mice, while also promoting glial cell activation and impaired metabolism (195). Additionally, a rat model of diabetes-induced early retinal neuropathy showed reduced BDNF levels, which further increased aberrant autophagy (197). BDNF upregulation has been suggested as a possible therapeutic avenue for DR, as it protects retinal cells by restoring proper autophagic responses in the retina (198).

As previously described, exercise and physical activity enhance the expression of multiple neurotrophic factors, including mainly BDNF, exhibiting greater levels, particularly in the retina and serum (24). BDNF has the potential to mitigate DR by promoting neuroretinal repair and survival caused by ischemia through the activation of TrkB and corresponding downstream pathways (199, 200).

3.5.2.3 Inhibition of hyperglycemia-induced oxidative stress and inflammation in retinal vessels

Oxidative stress is a significant contributor to the development of DR due to hyperglycemia leading to ROS overproduction (201). Oxidative stress causes damage to the cytoarchitecture and mitochondria, leading to apoptosis and depletion of pericytes (one of the major cell types of the retinal microvasculature, which controls endothelial cell proliferation and protects endothelial cells from lipid peroxide-induced damage), ultimately triggering or exacerbating the onset and progression of DR (202–204). Additionally, oxidative stress activates the inflammatory cascade. It has been found that hyperglycemia can lead to abnormal signaling pathways, among them phosphoinositide 3-kinase/Akt/protein kinase B and inducible NOS (iNOS). One specific manifestation is the inhibition of eNO synthase (eNOS) activation and the promotion of up-regulation of inflammatory mediators such as iNOS, IL-6, and TNF-α (205). The paracrine inflammatory response is activated, causing abnormal interactions between leukocytes and endothelial cells, ultimately resulting in retinal microvascular damage (132).

Exercise has been found to provide protection to retinal cells from damage caused by diabetes by inhibiting inflammatory and oxidative stress that are fundamental to the disease (22). For DR, Cheng et al. (175) reported that engaging in long-term regular platform running exercise could suppress vascular inflammation and oxidative stress in diabetic mice by upregulating miR-181b through activation of AMPK, further improving endothelial dysfunction in DR. Another study, based on a survey of 157 patients with retinopathy, found a negative correlation between moderate to high intensity physical activity and systemic inflammation (206).

3.5.2.4 Others

Chronic hyperglycemia-induced retinal microvascular pathological changes and structural abnormalities can result in hemodynamic abnormalities that could facilitate DR progression (183, 207). Studies have shown that exercise may improve retinal hemodynamics by promoting the expression of related adipokines, such as lipocalin, in the plasma and retina. Fundamental research has discovered that lipocalin impedes tube formation in human retinal microvascular endothelial cells. This suggests that lipocalin could be a potential treatment target for angiogenesis in DR (208). In a clinical study involving patients diagnosed with type 2 diabetes, researchers found that an increase in plasma lipocalin levels was positively associated with retinal vessel diameter, retinal blood velocity and flow, while being negatively associated with the total peripheral resistance of retinal arteries (209).

Furthermore, exercise and physical activity may improve DR by influencing 25-hydroxyvitamin D (25 OH-D) levels. A wealth of evidence supports the notion that enhanced physical activity leads to better 25 OH-D status in individuals of all ages, which is linked to microvascular events (210–212). It has been shown that the impact of physical activity on fasting blood sugar levels may be influenced by the genotype of the vitamin D receptor (213) (see Table 3).

3.6 AMD

3.6.1 Effect of exercise and physical activity on AMD

The macula is situated in the posterior central portion of the retina, representing the most visually acute part of the retina. AMD is a degenerative condition of the macula caused by the malfunction of retinal pigment epithelium (RPE) and the death of photoreceptor cells (219). AMD is the primary cause of irreversible vision impairment in individuals aged 60 and above. Advanced AMD can drastically diminish visual acuity, impacting overall quality of life (220). Clinically, AMD has two subtypes: non-neovascular and neovascular (219). Between 80 to 85% of patients are diagnosed with non-neovascular AMD, characterized by the loss of photoreceptors and RPE cells, and exposure of the underlying choroidal vessels, generally leading to a better visual prognosis. Conversely, neovascular AMD, marked by the formation of new blood vessels beneath the RPE, within the retina, or under the retina, accounts for less patient numbers but is responsible for nearly 80% of severe vision loss associated with AMD (221, 222).

Age is considered the primary factor in AMD, while smoking is the top modifiable risk factor associated with AMD (219). However, several studies have also confirmed the correlation between exercise and AMD. A study spanning 15 years and including 3,874 adults indicated a marked reduction in the incidence of neovascular AMD among those who maintained an active lifestyle (exercising at least thrice weekly) over an extended period, compared to those who remained inactive. After adjusting

TABLE 3 Effects of exercise and physical activity on common eye diseases: insights into DR and AMD with potential mechanisms explored.

Disease	Citation	Pre-clinical vs. clinical	Study design	Study population	Interventions	Study duration/ follow-up period	Key findings	Potential mechanism
DR	Wang et al. (214)	Clinical	Retrospective cohort	3,031 adults	Different levels of physical activity	/	More physical activity and less sedentary lifestyles associated with lower prevalence of DR	(1) Regulation of blood glucose, blood pressure and blood lipids (2) Inhibition of oxidative stress and inflammation (3) Improvement in hemodynamics (4) Regulation of BDNF, 25 (OH)D
	Loprinzi et al. (173)	Clinical	Cross-sectional	282 diabetic patients	Sedentary behavior	1 year	Sedentary lifestyle significantly increased the likelihood of diabetic patients developing DR	
	Soleimani et al. (174)	Clinical	Before-after clinical trial	40 DR subjects	Moderate-intensity aerobic exercise (3 times/week, 45 min)	12 weeks	Lower FBS (mg/dL) and CMT (microns) in moderate-intensity aerobic exercise group	
	Cheng et al. (175)	Pre-clinical	Randomised controlled	30 mice	Running exercise	8 weeks	Chronic exercise alleviates endothelial dysfunction, vascular inflammation, and oxidative stress	
AMD	Knudtson et al (215)	Clinical	Prospective cohort	3,874 participants	Physical activity	15 years	Physical activity reduced the risk of exudative AMD by 70% in 15 years	(1) Inhibition of oxidative stress and inflammation (2) Production of adipokines promotes
	Ulańczyk et al. (216)	Clinical	Cross-sectional	330 AMD cases and 121 controls	Physical activity	/	Physical exercise might delay AMD progression and help retain better visual function	
	McGuinness et al. (23)	Clinical	Prospective cohort	41,514 participants	Vigorous exercise (frequent ≥3 times/week and less frequent 1–2 times/week)	6 months	Vigorous exercise is protective against moderate AMD in women	
	Zhang et al. (217)	Pre-clinical	Randomised controlled	20 mice	Exercise	5 weeks	Exercise partially preserves retinal function	
	Cui et al. (218)	Pre-clinical	Randomised controlled	22 mice	Treadmill running (6 times/week, 60 min, 15 m/min)	4 weeks	Treadmill training protects laser-induced CNV and enhances anti-angiogenic efficacy	

10.3389/fmed.2024.1353624

for variables, the study discovered that incorporating more daily walks into one's routine can reduce the risk of developing AMD (215). A sedentary lifestyle can exacerbate AMD progression, whereas patients who engage in regular exercise and physical activity tend to have better vision (216). Additionally, a systematic review and meta-analysis determined that physical activity is linked to a decreased incidence of both early and late-stage AMD (223). Animal studies indicate that aerobic exercise may safeguard photoreceptor cells and RPE from harm and hinder reduction in retinal and photoreceptor layer thickness in a mouse model of retinal degeneration (217).

3.6.2 Potential mechanisms

Various risk factors for AMD, such as age, smoking, diet, sun exposure, and alcohol consumption, can induce or exacerbate a common pathophysiologic process known as oxidative stress at the molecular level (224). The macula ensures high metabolic activity to safeguard the large amount of energy required for light sensing and visual signal processing by the cone cells. This finding suggests that the macula is exposed to high levels of ROS, making it more susceptible to damage from oxidative stress (224). In atrophic AMD, accumulated ROS directly damage the cell membranes, DNA, and proteins of RPE cells and photoreceptor cells, leading to structural and functional impairments. Oxidative damage also results in the accumulation of cellular metabolic byproducts like lipofuscin within the RPE cells, further exacerbating cellular dysfunction and death by disrupting autophagy and affecting normal metabolism (222, 225). VEGF-mediated abnormal vascular generation is a key factor inducing CNV in late-stage neovascular AMD. The NF-κB pathway, activated under oxidative stress, translocates to the nucleus, directly enhancing VEGF gene transcription and stimulating neovascularization (226, 227). Signaling pathways such as MAPK and PI3K/Akt are also involved in the regulation of VEGF by oxidative stress (228, 229). ROS clearance is a popular research topic in AMD treatment. Studies demonstrate that engaging in regular exercise and physical activity can boost the activity of antioxidant enzymes, halt neovascularization (230), and increase resistance to oxidative stress (23).

Inflammation plays a significant role in the pathophysiology of AMD. Research has shown that the AMD pathology is accompanied by the infiltration of various inflammatory cells, primarily microglia and macrophages. Inflammatory responses, mediated by the release of cytokines such as TNF-α and Interleukins, activate signaling pathways including NF-κB and MAPK. This process not only damages RPE and photoreceptor cells but also enhances the transcription and translation of the VEGF gene, inducing retinal neovascularization (231). Laser-induced choroidal neovascularization in CNV mice was restrained by experimental depletion of macrophages (232). Studies indicate that exercise and physical activity play a significant role in inhibiting the inflammatory response through down-regulating the expression of inflammatory factors and adhesion molecules, promoting the release of the anti-inflammatory adipokine lipocalin, decreasing macrophage activation and aggregation, and inhibiting microglial cell expression (218, 233) (see Table 3).

4 Conclusion and perspectives

This review synthesizes the current knowledge on the impact and potential mechanisms of exercise and physical activity on common ocular diseases such as DED, cataracts, myopia, glaucoma, DR, and AMD, as depicted in Figures 2–6. It provides a relatively comprehensive elucidation of the relationship between physical activities and eye health. According to existing research, it can be inferred that for individuals suffering from DED, myopia, cataracts, glaucoma, DR, and AMD, or those at high risk, when physical activity is appropriately tailored to their conditions, long-term, regular exercise of moderate to vigorous intensity can help delay the onset and progression of these diseases or alleviate their symptoms. This offers a promising avenue for the prevention and treatment strategies of a variety of ocular diseases. Aligning with the Global recommendations on physical activity for health and United States Health and Human Services physical activity guidelines for adults (25, 26), combined with the findings of this review, we propose that for early to mid-stage patients or at-risk groups of these ocular diseases, long-term adherence to moderate-intensity physical activities (≥150 min per week) like running, walking, and cycling in suitable environments (considering temperature, humidity, light intensity, etc.) could be instrumental in preventing or delaying the progression of these common eye conditions.

The impact of exercise and physical activity on other eye disorders has also been thoroughly researched. For instance, studies on retinitis pigmentosa (RP) have discovered that patients maintaining higher levels of physical activity exhibit superior overall visual function, color vision, and peripheral vision compared to their less active counterparts, despite the limited sample size and reliance on subjective questionnaire surveys. These findings necessitate further validation in future research (234, 235). Additionally, the benefits of exercise and physical activity on retinal microvasculature, including reductions in blood pressure and glucose levels, decreased plasma viscosity, and enhanced antioxidative capacity of red blood cells (236–239), suggest potential improvements in the development and progression of retinal vein occlusion (RVO), a condition significantly influenced by high blood sugar, hypertension, arteriolar narrowing, or occlusions (240). Moreover, the positive effects of exercise and physical activity on autoimmune diseases, such as rheumatoid arthritis, may extend to uveitis, a common extra-articular manifestation of rheumatoid arthritis (4, 241, 242). In the regulatory mechanisms, a novel myokine, irisin, induced by exercise and secreted by skeletal muscles, has been shown to be downregulated in the aqueous humor of patients with RVO and AMD, as well as in the retinas of mice with oxygen-induced retinopathy, suggesting it may be a marker of retinal damage (137, 243). Current research indicates that irisin can exert anti-inflammatory, antioxidative, and anti-apoptotic neuroprotective effects through several signaling pathways, including Akt and ERK1/2 (244), integrin αVβ5/AMPK (245), and ROS-NLRP3 (246), among others. Further investigation into the impact of this molecule on ocular diseases may enrich the understanding of exercise's protective mechanisms and potentially offer a new therapeutic strategy for neuroprotection of the visual system.

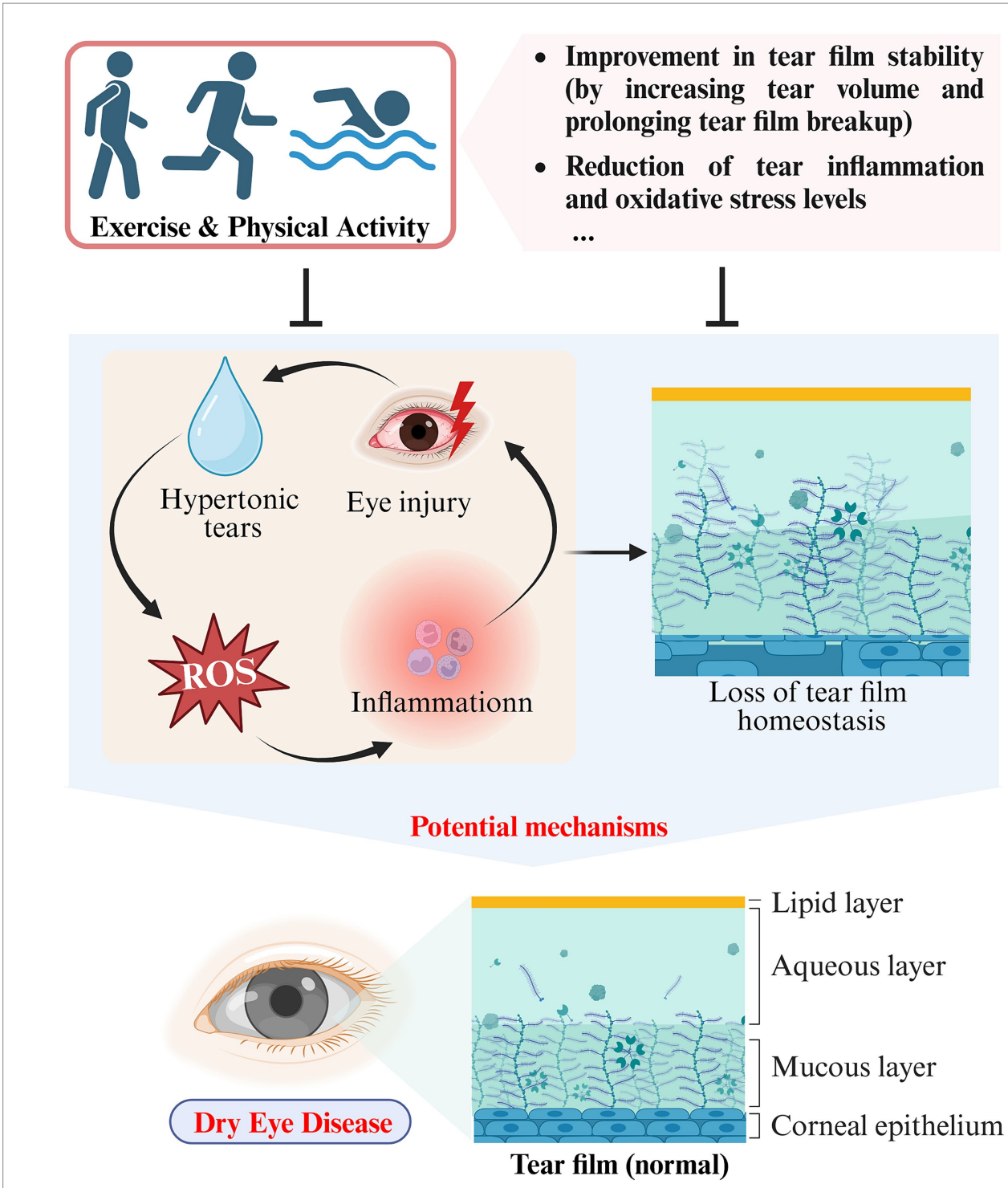

FIGURE 2
Schematic representation of the impact and potential mechanisms of exercise and physical activity on DED (created with Biorender.com).

It's noteworthy that in epidemiological studies included in this review, the form and intensity of exercise were adapted to the subjects. Under this premise, the positive impact of exercise or physical activity on dry eye syndrome, cataracts, glaucoma, diabetic retinopathy, and other ocular diseases has been validated. However, it is undeniable that in certain specific situations, exercise and physical activity should be reduced or even temporarily prohibited. These include: (1) late stages or acute episodes of vision-impacting ocular diseases, such as cataracts, glaucoma, diabetic retinopathy, where the patient's vision and/or visual field is severely compromised, making the positive impact of exercise and physical activity almost negligible and potentially exacerbating the condition or increasing the risk of accidental injury (111, 247, 248); (2) the recovery period following ocular surgery (e.g.,

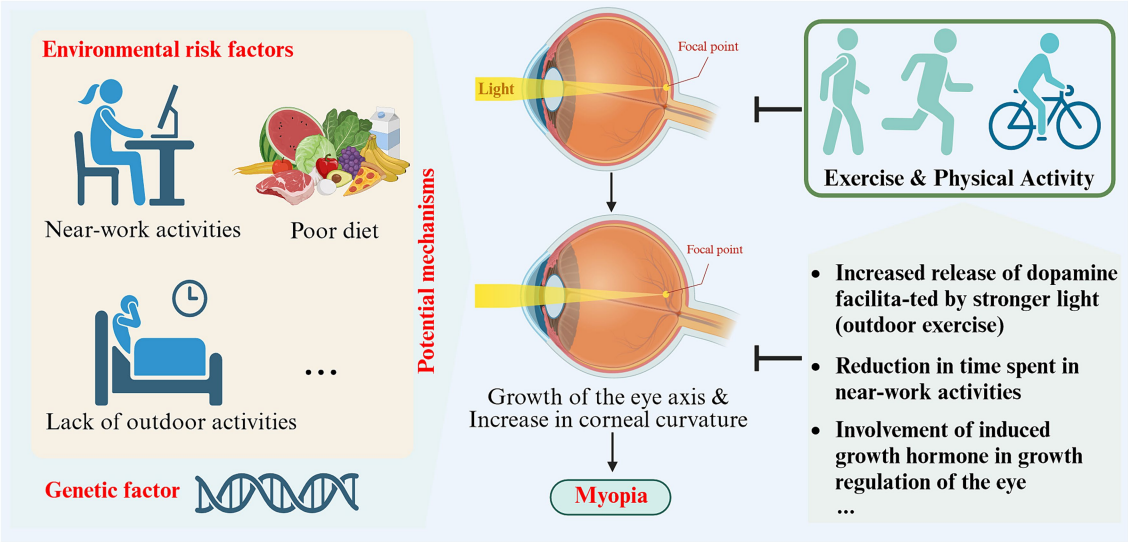

FIGURE 3
Schematic representation of the impact and potential mechanisms of exercise and physical activity on myopia (created with Biorender.com).

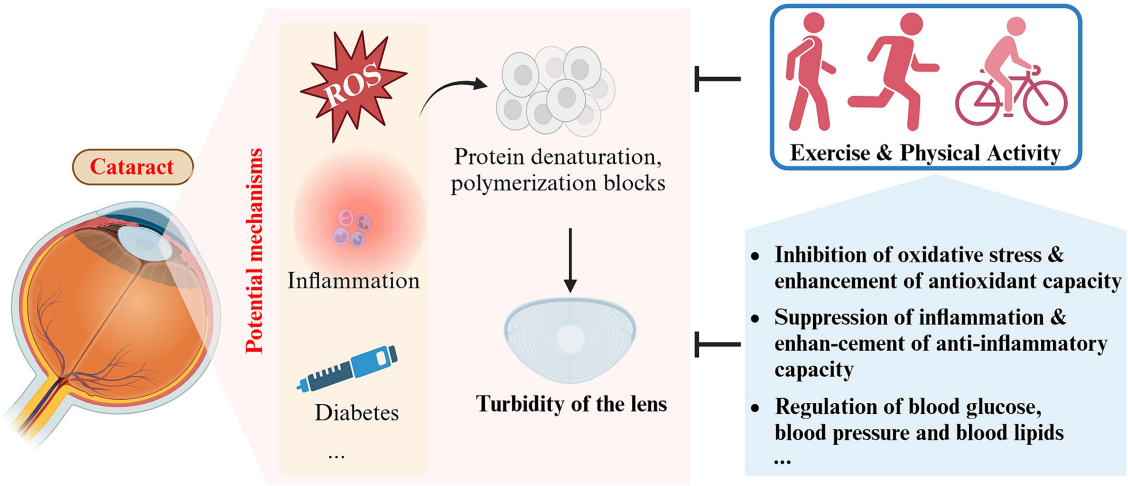

FIGURE 4
Schematic representation of the impact and potential mechanisms of exercise and physical activity on cataract (created with Biorender.com).

cataract surgery, vitrectomy, laser treatment), where vigorous exercise should be avoided to ensure proper healing of the wound (249, 250); (3) environments that are dry, windy, or dusty may exacerbate symptoms of dry eye syndrome, and intense sunlight or dim lighting may worsen eye pressure issues in glaucoma patients (251–253); (4) patients with high myopia are at increased risk of retinal detachment and should avoid high-impact and vibration-inducing activities, such as running and lifting heavy objects (254); (5) when specific complications are present, such as diabetic retinopathy patients with concurrent macular edema, short-term high-intensity exercise should be avoided (255).

This review aims to summarize the positive effects of exercise and physical activity on common ocular diseases, but this does not imply that exercise and physical activity can directly serve as a treatment modality. Seeking medical assistance and clinical treatment is necessary and primary for any ocular disease. We hope this review serves as a catalyst to stimulate interest among researchers and medical professionals in further exploring the relationship between exercise and eye health. We look forward to future studies revealing the specific mechanisms and key targets through which exercise benefits ocular health, thereby facilitating the development of innovative strategies for treating eye diseases.

This review also has limitations. Different studies may involve participants of varying ages, genders, races, etc., and employ different forms of exercise and physical activity, leading to

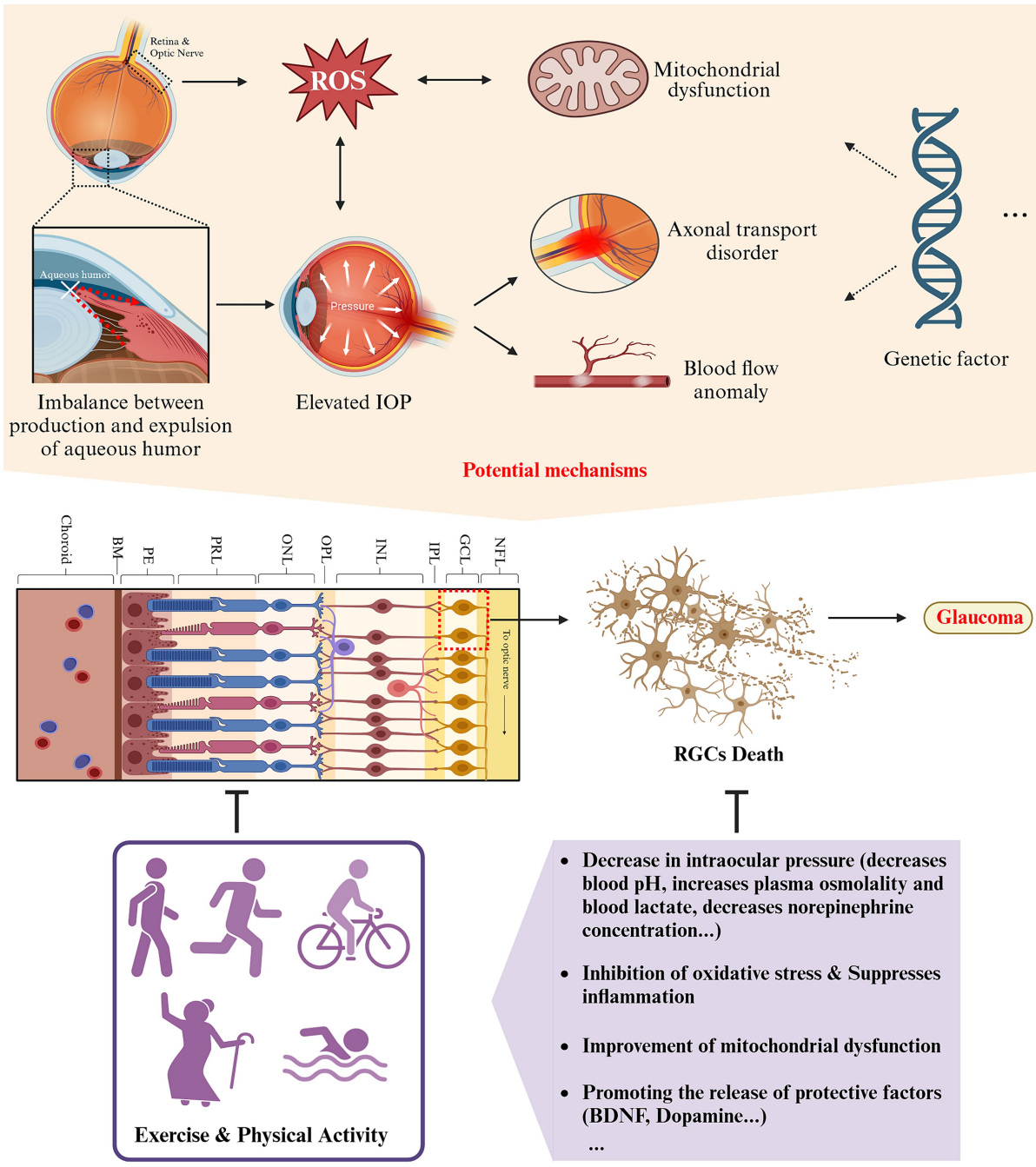

FIGURE 5
Schematic representation of the impact and potential mechanisms of exercise and physical activity on glaucoma (created with Biorender.com).

variability in type, intensity, frequency, and duration. The classification of exercise intensity in this review utilizes metabolic equivalents (METs), a widely accepted standard. However, it is not the sole method available; other measures such as maximum oxygen uptake (VO_2 Max), heart rate, and heart rate reserve also have their advantages. Relying on a single measurement standard could potentially affect our interpretation and summary of the outcomes. Additionally, long-term follow-up studies included in the review may be subject to response bias, such as self-reported exercise and physical activity data potentially being influenced by respondents' subjective biases. There are also certain limitations and gaps in research on different types of eye diseases. For example, some studies may not have accounted for confounding factors, such as genetic predispositions, environmental factors, and behavioral factors (e.g., near work and screen time usage), making it difficult to ascertain the impact of exercise on dry eye syndrome and myopia. In the case of diseases like AMD, existing research lacks unified recommendations for specific types of exercise, intensity, frequency, and duration, making it challenging to provide optimal exercise guidelines.

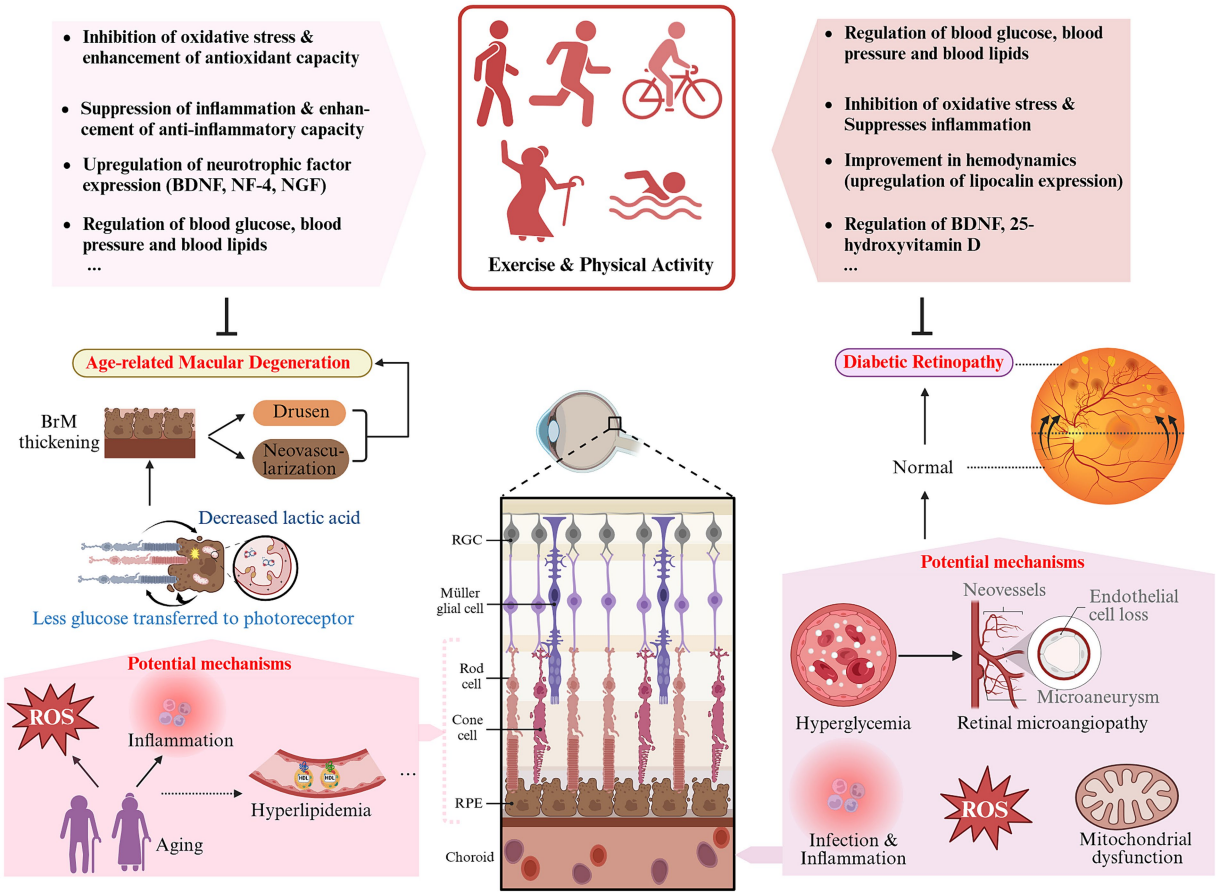

FIGURE 6
Schematic representation of the impact and potential mechanisms of exercise and physical activity on DR and AMD (created with Biorender.com).

Author contributions

QZ: Writing – original draft, Writing – review & editing. YJ: Writing – original draft, Writing – review & editing. CD: Writing – original draft, Writing – review & editing. JW: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This research was funded by the grants from National Natural Science Foundation of China grant numbers (82101125, 81974133, and 82271089).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Burton MJ, Ramke J, Marques AP, Bourne RRA, Congdon N, Jones I, et al. The Lancet Global Health Commission on global eye health: vision beyond 2020. *Lancet Glob Health*. (2021) 9:e489–551. doi: 10.1016/s2214-109x(20)30488-5

2. Assi L, Chamseddine F, Ibrahim P, Sabbagh H, Rosman L, Congdon N, et al. A global assessment of eye health and quality of life: a systematic review of systematic reviews. *JAMA Ophthalmol*. (2021) 139:526–41. doi: 10.1001/jamaophthalmol.2021.0146

3. Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, et al. The physical activity guidelines for Americans. *JAMA*. (2018) 320:2020–8. doi: 10.1001/jama.2018.14854

4. Pedersen BK, Saltin B. Exercise as medicine—evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scand J Med Sci Sports*. (2015) 25:1–72. doi: 10.1111/sms.12581

5. Blair SN, Kohl HW 3rd, Paffenbarger RS Jr, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality. A prospective study of healthy men and women. *JAMA*. (1989) 262:2395–401. doi: 10.1001/jama.262.17.2395

6. Blair SN. Physical inactivity: the biggest public health problem of the 21st century. *Br J Sports Med*. (2009) 43:1–2.

7. Barker K, Eickmeyer S. Therapeutic exercise. *Med Clin North Am*. (2020) 104:189–98. doi: 10.1016/j.mcna.2019.10.003

8. Meier NF, Lee DC, Sui X, Blair SN. Physical activity, cardiorespiratory fitness, and incident glaucoma. *Med Sci Sports Exerc*. (2018) 50:2253–8. doi: 10.1249/mss.0000000000001692

9. Williams PT. Prospective epidemiological cohort study of reduced risk for incident cataract with vigorous physical activity and cardiorespiratory fitness during a 7-year follow-up. *Invest Ophthalmol Vis Sci*. (2009) 50:95–100. doi: 10.1167/iovs.08-1797

10. Yokota S, Takihara Y, Kimura K, Takamura Y, Inatani M. The relationship between self-reported habitual exercise and visual field defect progression: a retrospective cohort study. *BMC Ophthalmol*. (2016) 16:147. doi: 10.1186/s12886-016-0326-x

11. Williams PT. Walking and running are associated with similar reductions in cataract risk. *Med Sci Sports Exerc*. (2013) 45:1089–96. doi: 10.1249/MSS.0b013e31828121d0

12. Mann S, Beedie C, Jimenez A. Differential effects of aerobic exercise, resistance training and combined exercise modalities on cholesterol and the lipid profile: review, synthesis and recommendations. *Sports Med*. (2014) 44:211–21. doi: 10.1007/s40279-013-0110-5

13. Zhao JL, Jiang WT, Wang X, Cai ZD, Liu ZH, Liu GR. Exercise, brain plasticity, and depression. *CNS Neurosci Ther*. (2020) 26:885–95. doi: 10.1111/cns.13385

14. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR Jr, Tudor-Locke C, et al. 2011 compendium of physical activities: a second update of codes and MET values. *Med Sci Sports Exerc*. (2011) 43:1575–81. doi: 10.1249/MSS.0b013e31821ece12

15. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc*. (2007) 39:1423–34. doi: 10.1249/mss.0b013e3180616b27

16. Abokyi S, Mensah SN, Otchere H, Akoto YO, Ntodie M. Differential effect of maximal incremental treadmill exercise on tear secretion and tear film stability in athletes and non-athletes. *Exp Eye Res*. (2022) 214:108865. doi: 10.1016/j.exer.2021.108865

17. Ko YC, Liu CJ, Lau LI, Wu CW, Chou JC, Hsu WM. Factors related to corneal endothelial damage after phacoemulsification in eyes with occludable angles. *J Cataract Refract Surg*. (2008) 34:46–51. doi: 10.1016/j.jcrs.2007.07.057

18. Paunksnis A, Kusleika S, Kusleikaite M. The relationship of the intensity of lens opacity with physical activity. *Medicina*. (2006) 42:738–43.

19. Stewart LK, Flynn MG, Campbell WW, Craig BA, Robinson JP, McFarlin BK, et al. Influence of exercise training and age on $CD14^+$ cell-surface expression of toll-like receptor 2 and 4. *Brain Behav Immun*. (2005) 19:389–97. doi: 10.1016/j.bbi.2005.04.003

20. Ang MJ, Afshari NA. Cataract and systemic disease: a review. *Clin Experiment Ophthalmol*. (2021) 49:118–27. doi: 10.1111/ceo.13892

21. Anuradha S, Healy GN, Dunstan DW, Klein R, Klein BE, Cotch MF, et al. Physical activity, television viewing time, and retinal microvascular caliber: the multi-ethnic study of atherosclerosis. *Am J Epidemiol*. (2011) 173:518–25. doi: 10.1093/aje/kwq412

22. Dharmastuti DP, Agni AN, Widyaputri F, Pawiroranu S, Sofro ZM, Wardhana FS, et al. Associations of physical activity and sedentary behaviour with vision-threatening diabetic retinopathy in Indonesian population with type 2 diabetes mellitus: Jogjakarta eye diabetic study in the community (JOGED.COM). *Ophthalmic Epidemiol*. (2018) 25:113–9. doi: 10.1080/09286586.2017.1367410

23. McGuinness MB, Karahalios A, Simpson JA, Guymer RH, Robman LD, Hodge AM, et al. Past physical activity and age-related macular degeneration: the Melbourne collaborative cohort study. *Br J Ophthalmol*. (2016) 100:1353–8. doi: 10.1136/bjophthalmol-2015-307663

24. Lawson EC, Han MK, Sellers JT, Chrenek MA, Hanif A, Gogniat MA, et al. Aerobic exercise protects retinal function and structure from light-induced retinal degeneration. *J Neurosci*. (2014) 34:2406–12. doi: 10.1523/jneurosci.2062-13.2014

25. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*. (2007) 116:1081–93. doi: 10.1161/circulationaha.107.185649

26. WHO Guidelines Approved by the Guidelines Review Committee. *Global recommendations on physical activity for health*. Geneva: World Health Organization (2010).

27. Rouen PA, White ML. Dry eye disease: prevalence, assessment, and management. *Home Healthc Now*. (2018) 36:74–83. doi: 10.1097/nhh.0000000000000652

28. Thulasi P, Djalilian AR. Update in current diagnostics and therapeutics of dry eye disease. *Ophthalmology*. (2017) 124:S27–s33. doi: 10.1016/j.ophtha.2017.07.022

29. Stapleton F, Alves M, Bunya VY, Jalbert I, Lekhanont K, Malet F, et al. TFOS DEWS II epidemiology report. *Ocul Surf*. (2017) 15:334–65. doi: 10.1016/j.jtos.2017.05.003

30. Ayaki M, Negishi K. Decrease of tear break-up time at Japanese eye clinics during five consecutive years. *Sci Rep*. (2022) 12:6848. doi: 10.1038/s41598-022-11035-9

31. Kojima T, Dogru M, Kawashima M, Nakamura S, Tsubota K. Advances in the diagnosis and treatment of dry eye. *Prog Retin Eye Res*. (2020) 78:100842. doi: 10.1016/j.preteyeres.2020.100842

32. Kawashima M, Uchino M, Yokoi N, Uchino Y, Dogru M, Komuro A, et al. The association between dry eye disease and physical activity as well as sedentary behavior: results from the Osaka study. *J Ophthalmol*. (2014) 2014:943786. doi: 10.1155/2014/943786

33. Hanyuda A, Sawada N, Uchino M, Kawashima M, Yuki K, Tsubota K, et al. Physical inactivity, prolonged sedentary behaviors, and use of visual display terminals as potential risk factors for dry eye disease: JPHC-NEXT study. *Ocul Surf*. (2020) 18:56–63. doi: 10.1016/j.jtos.2019.09.007

34. Cheng X, Song M, Kong J, Fang X, Ji Y, Zhang M, et al. Influence of prolonged visual display terminal use and exercise on physical and mental conditions of internet staff in Hangzhou, China. *Int J Environ Res Public Health*. (2019) 16:1829. doi: 10.3390/ijerph16101829

35. Kawashima M, Sano K, Takechi S, Tsubota K. Impact of lifestyle intervention on dry eye disease in office workers: a randomized controlled trial. *J Occup Health*. (2018) 60:281–8. doi: 10.1539/joh.2017-0191-OA

36. Zemanová M. Dry eye disease. A review. *Cesk Slov Oftalmol*. (2021) 77:107–19. doi: 10.31348/2020/29

37. Nakamura S, Shibuya M, Nakashima H, Hisamura R, Masuda N, Imagawa T, et al. Involvement of oxidative stress on corneal epithelial alterations in a blink-suppressed dry eye. *Invest Ophthalmol Vis Sci*. (2007) 48:1552–8. doi: 10.1167/iovs.06-1027

38. Li H, Li F, Zhou R, Gao K, Liang L, Zhang X. Aerobic exercise increases tear secretion and decreases inflammatory cytokines in healthy subjects. *Asia Pac J Ophthalmol*. (2020) 9:404–11. doi: 10.1097/apo.0000000000000281

39. Sun C, Chen X, Huang Y, Zou H, Fan W, Yang M, et al. Effects of aerobic exercise on tear secretion and tear film stability in dry eye patients. *BMC Ophthalmol*. (2022) 22:9. doi: 10.1186/s12886-021-02230-9

40. Hansen MH, Laigaard PP, Olsen EM, Skovgaard AM, Larsen M, Kessel L, et al. Low physical activity and higher use of screen devices are associated with myopia at the age of 16–17 years in the CCC2000 eye study. *Acta Ophthalmol*. (2020) 98:315–21. doi: 10.1111/aos.14242

41. Holton V, Hinterlong JE, Tsai CY, Tsai JC, Wu JS, Liou YM. A nationwide study of myopia in Taiwanese school children: family, activity, and school-related factors. *J Sch Nurs*. (2021) 37:117–27. doi: 10.1177/1059840519850619

42. He M, Xiang F, Zeng Y, Mai J, Chen Q, Zhang J, et al. Effect of time spent outdoors at school on the development of myopia among children in China: a randomized clinical trial. *JAMA*. (2015) 314:1142–8. doi: 10.1001/jama.2015.10803

43. French AN, Morgan IG, Mitchell P, Rose KA. Risk factors for incident myopia in Australian schoolchildren: the Sydney adolescent vascular and eye study. *Ophthalmology*. (2013) 120:2100–8. doi: 10.1016/j.ophtha.2013.02.035

44. Lee YY, Lo CT, Sheu SJ, Yin LT. Risk factors for and progression of myopia in young Taiwanese men. *Ophthalmic Epidemiol*. (2015) 22:66–73. doi: 10.3109/09286586.2014.988874.

45. Ip JM, Saw SM, Rose KA, Morgan IG, Kifley A, Wang JJ, et al. Role of near work in myopia: findings in a sample of Australian school children. *Invest Ophthalmol Vis Sci*. (2008) 49:2903–10. doi: 10.1167/iovs.07-0804

46. Nguyen L, Magno MS, Utheim TP, Hammond CJ, Vehof J. The relationship between sedentary behavior and dry eye disease. *Ocul Surf*. (2023) 28:11–7. doi: 10.1016/j.jtos.2023.01.002

47. Vera J, Jiménez R, Madinabeitia I, Masiulis N, Cárdenas D. A maximal incremental effort alters tear osmolarity depending on the fitness level in military helicopter pilots. *Ocul Surf*. (2017) 15:795–801. doi: 10.1016/j.jtos.2017.08.001

48. Peart DJ, Walshe IH, Sweeney EL, James E, Henderson T, O'Doherty AF, et al. The effect of acute exercise on environmentally induced symptoms of dry eye. *Physiol Rep*. (2020) 8:e14262. doi: 10.14814/phy2.14262

49. Zheng Selin J, Orsini N, Ejdervik Lindblad B, Wolk A. Long-term physical activity and risk of age-related cataract: a population-based prospective study of male and female cohorts. *Ophthalmology*. (2015) 122:274–80. doi: 10.1016/j.ophtha.2014.08.023

50. López-Sánchez GF, Pardhan S, Trott M, Sánchez-Castillo S, Jackson SE, Tully M, et al. The association between physical activity and cataracts among 17,777 people aged 15–69 years residing in Spain. *Ophthalmic Epidemiol*. (2020) 27:272–7. doi: 10.1080/09286586.2020.1730911

51. Dutheil F, Oueslati T, Delamarre L, Castanon J, Maurin C, Chiambaretta F, et al. Myopia and near work: a systematic review and meta-analysis. *Int J Environ Res Public Health*. (2023) 20:875. doi: 10.3390/ijerph20010875

52. Baird PN, Saw SM, Lanca C, Guggenheim JA, Smith Iii EL, Zhou X, et al. Myopia. *Nat Rev Dis Primers*. (2020) 6:99. doi: 10.1038/s41572-020-00231-4

53. Flitcroft DI. The complex interactions of retinal, optical and environmental factors in myopia aetiology. *Prog Retin Eye Res*. (2012) 31:622–60. doi: 10.1016/j.preteyeres.2012.06.004

54. Bullimore MA, Brennan NA. Myopia control: why each diopter matters. *Optom Vis Sci*. (2019) 96:463–5. doi: 10.1097/opx.0000000000001367

55. O'Donoghue L, Kapetanankis VV, McClelland JF, Logan NS, Owen CG, Saunders KJ, et al. Risk factors for childhood myopia: findings from the NICER study. *Invest Ophthalmol Vis Sci*. (2015) 56:1524–30. doi: 10.1167/iovs.14-15549

56. Read SA, Collins MJ, Vincent SJ. Light exposure and physical activity in myopic and emmetropic children. *Optom Vis Sci*. (2014) 91:330–41. doi: 10.1097/opx.0000000000000160

57. Khader YS, Batayha WQ, Abdul-Aziz SM, Al-Shiekh-Khalil MI. Prevalence and risk indicators of myopia among schoolchildren in Amman, Jordan. *East Mediterr Health J*. (2006) 12:434–9.

58. Mutti DO, Mitchell GL, Moeschberger ML, Jones LA, Zadnik K. Parental myopia, near work, school achievement, and children's refractive error. *Invest Ophthalmol Vis Sci*. (2002) 43:3633–40.

59. Guggenheim JA, Northstone K, McMahon G, Ness AR, Deere K, Mattocks C, et al. Time outdoors and physical activity as predictors of incident myopia in childhood: a prospective cohort study. *Invest Ophthalmol Vis Sci*. (2012) 53:2856–65. doi: 10.1167/iovs.11-9091

60. Jacobsen N, Jensen H, Goldschmidt E. Does the level of physical activity in university students influence development and progression of myopia?—a 2-year prospective cohort study. *Invest Ophthalmol Vis Sci*. (2008) 49:1322–7. doi: 10.1167/iovs.07-1144

61. Guo Y, Liu L, Lv Y, Tang P, Feng Y, Wu M, et al. Outdoor jogging and myopia progression in school children from rural Beijing: the Beijing children eye study. *Transl Vis Sci Technol*. (2019) 8:2. doi: 10.1167/tvst.8.3.2

62. Zhu Z, Chen Y, Tan Z, Xiong R, McGuinness MB, Müller A. Interventions recommended for myopia prevention and control among children and adolescents in China: a systematic review. *Br J Ophthalmol*. (2023) 107:160–6. doi: 10.1136/bjophthalmol-2021-319306

63. Xiong S, Sankaridurg P, Naduvilath T, Zang J, Zou H, Zhu J, et al. Time spent in outdoor activities in relation to myopia prevention and control: a meta-analysis and systematic review. *Acta Ophthalmol*. (2017) 95:551–66. doi: 10.1111/aos.13403

64. Karthikeyan SK, Ashwini DL, Priyanka M, Nayak A, Biswas S. Physical activity, time spent outdoors, and near work in relation to myopia prevalence, incidence, and progression: An overview of systematic reviews and meta-analyses. *Indian J Ophthalmol*. (2022) 70:728–39. doi: 10.4103/ijo.IJO_1564_21

65. Fitzgerald ME, Wildsoet CF, Reiner A. Temporal relationship of choroidal blood flow and thickness changes during recovery from form deprivation myopia in chicks. *Exp Eye Res*. (2002) 74:561–70. doi: 10.1006/exer.2002.1142.

66. Nickla DL. Transient increases in choroidal thickness are consistently associated with brief daily visual stimuli that inhibit ocular growth in chicks. *Exp Eye Res*. (2007) 84:951–9. doi: 10.1016/j.exer.2007.01.017.

67. Landis EG, Park HN, Chrenek M, He L, Sidhu C, Chakraborty R, et al. Ambient light regulates retinal dopamine signaling and myopia susceptibility. *Invest Ophthalmol Vis Sci*. (2021) 62:28. doi: 10.1167/iovs.62.1.28

68. Ashby RS, Schaeffel F. The effect of bright light on lens compensation in chicks. *Invest Ophthalmol Vis Sci*. (2010) 51:5247–53. doi: 10.1167/iovs.09-4689.

69. Bowrey HE, Zeng G, Tse DY, Leotta AJ, Wu Y, To CH, et al. The effect of spectacle lenses containing peripheral defocus on refractive error and horizontal eye shape in the Guinea pig. *Invest Ophthalmol Vis Sci*. (2017) 58:2705–14. doi: 10.1167/iovs.16-20240.

70. Mutti DO, Sinnott LT, Mitchell GL, Jones-Jordan LA, Moeschberger ML, Cotter SA, et al. Relative peripheral refractive error and the risk of onset and progression of myopia in children. *Invest Ophthalmol Vis Sci*. (2011) 52:199–205. doi: 10.1167/iovs.09-4826

71. Cicinelli MV, Buchan JC, Nicholson M, Varadaraj V, Khanna RC. Cataracts. *Lancet*. (2023) 401:377–89. doi: 10.1016/s0140-6736(22)01839-6

72. Liu YC, Wilkins M, Kim T, Malyugin B, Mehta JS. Cataracts. *Lancet*. (2017) 390:600–12. doi: 10.1016/s0140-6736(17)30544-5.

73. Lamoureux EL, Fenwick E, Pesudovs K, Tan D. The impact of cataract surgery on quality of life. *Curr Opin Ophthalmol*. (2011) 22:19–27. doi: 10.1097/ICU.0b013e3283414284

74. Kaur J, Kukreja S, Kaur A, Malhotra N, Kaur R. The oxidative stress in cataract patients. *J Clin Diagn Res*. (2012) 6:1629–32. doi: 10.7860/jcdr/2012/4856.2626

75. Michael R, Bron AJ. The ageing lens and cataract: a model of normal and pathological ageing. *Philos Trans R Soc B*. (2011) 366:1278–92. doi: 10.1098/rstb.2010.0300.

76. Chang D, Zhang X, Rong S, Sha Q, Liu P, Han T, et al. Serum antioxidative enzymes levels and oxidative stress products in age-related cataract patients. *Oxid Med Cell Longev*. (2013) 2013:587826:587826. doi: 10.1155/2013/587826

77. Radak Z, Zhao Z, Koltai E, Ohno H, Atalay M. Oxygen consumption and usage during physical exercise: the balance between oxidative stress and ROS-dependent adaptive signaling. *Antioxid Redox Signal*. (2013) 18:1208–46. doi: 10.1089/ars.2011.4498

78. He F, Li J, Liu Z, Chuang CC, Yang W, Zuo L. Redox mechanism of reactive oxygen species in exercise. *Front Physiol*. (2016) 7:486. doi: 10.3389/fphys.2016.00486

79. Ahmad A, Ahsan H. Biomarkers of inflammation and oxidative stress in ophthalmic disorders. *J Immunoassay Immunochem*. (2020) 41:257–71. doi: 10.1080/15321819.2020.1726774

80. Schaumberg DA, Ridker PM, Glynn RJ, Christen WG, Dana MR, Hennekens CH. High levels of plasma C-reactive protein and future risk of age-related cataract. *Ann Epidemiol*. (1999) 9:166–71. doi: 10.1016/s1047-2797(98)00049-0

81. El Assar M, Angulo J, Rodríguez-Mañas L. Oxidative stress and vascular inflammation in aging. *Free Radic Biol Med*. (2013) 65:380–401. doi: 10.1016/j.freeradbiomed.2013.07.003

82. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol A*. (2014) 69:S4–9. doi: 10.1093/gerona/glu057.

83. Sallam N, Laher I. Exercise modulates oxidative stress and inflammation in aging and cardiovascular diseases. *Oxid Med Cell Longev*. (2016) 2016:7239639–2. doi: 10.1155/2016/7239639

84. Monteiro-Junior RS, de Tarso Maciel-Pinheiro P, da Matta Mello Portugal E, da Silva Figueiredo LF, Terra R, Carneiro LSF, et al. Effect of exercise on inflammatory profile of older persons: systematic review and meta-analyses: systematic review and meta-analyses. *J Phys Act Health*. (2018) 15:64–71. doi: 10.1123/jpah.2016-0735

85. Brooks N, Layne JE, Gordon PL, Roubenoff R, Nelson ME, Castaneda-Sceppa C. Strength training improves muscle quality and insulin sensitivity in Hispanic older adults with type 2 diabetes. *Int J Med Sci*. (2006) 4:19–27. doi: 10.7150/ijms.4.19.

86. Abd El-Kader SM, Al-Shreef FM. Inflammatory cytokines and immune system modulation by aerobic versus resisted exercise training for elderly. *Afr Health Sci*. (2018) 18:120–31. doi: 10.4314/ahs.v18i1.16

87. Hiller R, Sperduto RD, Reed GF, D'Agostino RB, Wilson PW. Serum lipids and age-related lens opacities: a longitudinal investigation: the Framingham studies. *Ophthalmology*. (2003) 110:578–83. doi: 10.1016/s0161-6420(02)01762-1

88. Klein BE, Klein R, Jensen SC, Linton KL. Hypertension and lens opacities from the beaver dam eye study. *Am J Ophthalmol*. (1995) 119:640–6. doi: 10.1016/s0002-9394(14)70223-5.

89. Yu X, Lyu D, Dong X, He J, Yao K. Hypertension and risk of cataract: a meta-analysis. *PLoS One*. (2014) 9:e114012. doi: 10.1371/journal.pone.0114012.

90. Esefeld K, Kress S, Behrens M, Zimmer P, Stumvoll M, Thurm U, et al. Diabetes, sports and exercise. *Exp Clin Endocrinol Diabetes*. (2023) 131:51–60. doi: 10.1055/a-1946-3768

91. Cornelissen VA, Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. *J Am Heart Assoc*. (2013) 2:e004473. doi: 10.1161/jaha.112.004473

92. Wood PD, Haskell WL, Blair SN, Williams PT, Krauss RM, Lindgren FT, et al. Increased exercise level and plasma lipoprotein concentrations: a one-year, randomized, controlled study in sedentary, middle-aged men. *Metab Clin Exp*. (1983) 32:31–9. doi: 10.1016/0026-0495(83)90152-x

93. Figueroa A, Going SB, Milliken LA, Blew RM, Sharp S, Teixeira PJ, et al. Effects of exercise training and hormone replacement therapy on lean and fat mass in postmenopausal women. *J Gerontol A*. (2003) 58:266–70. doi: 10.1093/gerona/58.3.m266

94. He N, Ye H. Exercise and hyperlipidemia. *Adv Exp Med Biol*. (2020) 1228:79–90. doi: 10.1007/978-981-15-1792-1_5.

95. 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) 121:2081–90. doi: 10.1016/j.ophtha.2014.05.013.

96. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. *JAMA*. (2014) 311:1901–11. doi: 10.1001/jama.2014.3192.

97. Jayaram H, Kolko M, Friedman DS, Gazzard G. Glaucoma: now and beyond. *Lancet*. (2023) 402:1788–801. doi: 10.1016/s0140-6736(23)01289-8

98. Kang JM, Tanna AP. Glaucoma. *Med Clin North Am*. (2021) 105:493–510. doi: 10.1016/j.mcna.2021.01.004

99. Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M. Reduction of intraocular pressure and glaucoma progression: results from the early manifest glaucoma trial. *Arch Ophthalmol*. (2002) 120:1268–79. doi: 10.1001/archopht.120.10.1268

100. Perez CI, Singh K, Lin S. Relationship of lifestyle, exercise, and nutrition with glaucoma. *Curr Opin Ophthalmol*. (2019) 30:82–8. doi: 10.1097/icu.0000000000000553.

101. Yuan Y, Lin TPH, Gao K, Zhou R, Radke NV, Lam DSC, et al. Aerobic exercise reduces intraocular pressure and expands Schlemm's canal dimensions in healthy and primary open-angle glaucoma eyes. *Indian J Ophthalmol*. (2021) 69:1127–34. doi: 10.4103/ijo.IJO_2858_20

102. Ong SR, Crowston JG, Loprinzi PD, Ramulu PY. Physical activity, visual impairment, and eye disease. *Eye*. (2018) 32:1296–303. doi: 10.1038/s41433-018-0081-8

103. Tribble JR, Hui F, Jöe M, Bell K, Chrysostomou V, Crowston JG, et al. Targeting diet and exercise for neuroprotection and neurorecovery in glaucoma. *Cells*. (2021) 10:295. doi: 10.3390/cells10020295

104. Madjedi KM, Stuart KV, Chua SYL, Ramulu PY, Warwick A, Luben RN, et al. The association of physical activity with glaucoma and related traits in the UK Biobank. *Ophthalmology*. (2023) 130:1024–36. doi: 10.1016/j.ophtha.2023.06.009

105. Chrysostomou V, Kezic JM, Trounce IA, Crowston JG. Forced exercise protects the aged optic nerve against intraocular pressure injury. *Neurobiol Aging*. (2014) 35:1722–5. doi: 10.1016/j.neurobiolaging.2014.01.019

106. He YY, Wang L, Zhang T, Weng SJ, Lu J, Zhong YM. Aerobic exercise delays retinal ganglion cell death after optic nerve injury. *Exp Eye Res*. (2020) 200:108240. doi: 10.1016/j.exer.2020.108240.

107. Williams PT. Relationship of incident glaucoma versus physical activity and fitness in male runners. *Med Sci Sports Exerc*. (2009) 41:1566–72. doi: 10.1249/MSS.0b013e31819e420f.

108. Seo JH, Lee Y. Association of exercise intensity with the prevalence of glaucoma and intraocular pressure in men: a study based on the Korea National Health and Nutrition Examination Survey. *J Clin Med*. (2022) 11:4725. doi: 10.3390/jcm11164725

109. Lee MJ, Wang J, Friedman DS, Boland MV, De Moraes CG, Ramulu PY. Greater physical activity is associated with slower visual field loss in glaucoma. *Ophthalmology*. (2019) 126:958–64. doi: 10.1016/j.ophtha.2018.10.012

110. Lin SC, Wang SY, Pasquale LR, Singh K, Lin SC. The relation between exercise and glaucoma in a South Korean population-based sample. *PLoS One*. (2017) 12:e0171441. doi: 10.1371/journal.pone.0171441

111. McMonnies CW. Intraocular pressure and glaucoma: is physical exercise beneficial or a risk? *J Opt*. (2016) 9:139–47. doi: 10.1016/j.optom.2015.12.001.

112. Schuman JS, Massicotte EC, Connolly S, Hertzmark E, Mukherji B, Kunen MZ. Increased intraocular pressure and visual field defects in high resistance wind instrument players. *Ophthalmology*. (2000) 107:127–33. doi: 10.1016/s0161-6420(99)00015-9

113. Okafor K, Vinod K, Gedde SJ. Update on pigment dispersion syndrome and pigmentary glaucoma. *Curr Opin Ophthalmol*. (2017) 28:154–60. doi: 10.1097/icu.0000000000000352.

114. Haynes WL, Johnson AT, Alward WL. Effects of jogging exercise on patients with the pigmentary dispersion syndrome and pigmentary glaucoma. *Ophthalmology*. (1992) 99:1096–103. doi: 10.1016/s0161-6420(92)31845-7

115. Haynes WL, Johnson AT, Alward WL. Inhibition of exercise-induced pigment dispersion in a patient with the pigmentary dispersion syndrome. *Am J Ophthalmol*. (1990) 109:601–2. doi: 10.1016/s0002-9394(14)70696-8

116. Schenker HI, Luntz MH, Kels B, Podos SM. Exercise-induced increase of intraocular pressure in the pigmentary dispersion syndrome. *Am J Ophthalmol*. (1980) 89:598–600. doi: 10.1016/0002-9394(80)90073-2

117. Smith DL, Kao SF, Rabbani R, Musch DC. The effects of exercise on intraocular pressure in pigmentary glaucoma patients. *Ophthalmic Surg*. (1989) 20:561–7.

118. Campbell DG. Pigmentary dispersion and glaucoma. A new theory. *Arch Ophthalmol*. (1979) 97:1667–72. doi: 10.1001/archopht.1979.01020020235011

119. Jensen PK, Nissen O, Kessing SV. Exercise and reversed pupillary block in pigmentary glaucoma. *Am J Ophthalmol*. (1995) 120:110–2. doi: 10.1016/s0002-9394(14)73767-5

120. Qu J, Wang D, Grosskreutz CL. Mechanisms of retinal ganglion cell injury and defense in glaucoma. *Exp Eye Res*. (2010) 91:48–53. doi: 10.1016/j.exer.2010.04.002.

121. Kiyota N, Shiga Y, Ichinohasama K, Yasuda M, Aizawa N, Omodaka K, et al. The impact of intraocular pressure elevation on optic nerve head and choroidal blood flow. *Invest Ophthalmol Vis Sci*. (2018) 59:3488–96. doi: 10.1167/iovs.18-23872

122. Risner D, Ehrlich R, Kheradiya NS, Siesky B, McCranor L, Harris A. Effects of exercise on intraocular pressure and ocular blood flow: a review. *J Glaucoma*. (2009) 18:429–36. doi: 10.1097/IJG.0b013e31818fa5f3.

123. Yan X, Li M, Song Y, Guo J, Zhao Y, Chen W, et al. Influence of exercise on intraocular pressure, Schlemm's canal, and the trabecular meshwork. *Invest Ophthalmol Vis Sci*. (2016) 57:4733–9. doi: 10.1167/iovs.16-19475

124. Harris A, Malinovsky VE, Cantor LB, Henderson PA, Martin BJ. Isocapnia blocks exercise-induced reductions in ocular tension. *Invest Ophthalmol Vis Sci*. (1992) 33:2229–32.

125. Passo MS, Goldberg L, Elliot DL, Van Buskirk EM. Exercise training reduces intraocular pressure among subjects suspected of having glaucoma. *Arch Ophthalmol*. (1991) 109:1096–8. doi: 10.1001/archopht.1991.01080080056027

126. Kiuchi Y, Mishima HK, Hotehama Y, Furumoto A, Hirota A, Onari K. Exercise intensity determines the magnitude of IOP decrease after running. *Jpn J Ophthalmol*. (1994) 38:191–5.

127. Qureshi IA, Xi XR, Wu XD, Zhang J, Shiarkar E. The effect of physical fitness on intraocular pressure in Chinese medical students. *Zhonghua Yi Xue Za Zhi*. (1996) 58:317–22.

128. Harris A, Malinovsky V, Martin B. Correlates of acute exercise-induced ocular hypotension. *Invest Ophthalmol Vis Sci*. (1994) 35:3852–7.

129. Yeak Dieu Siang J, Mohamed M, Mohd Ramli NB, Zahari MB. Effects of regular exercise on intraocular pressure. *Eur J Ophthalmol*. (2022) 32:2265–73. doi: 10.1177/11206721211051236

130. Kim CS, Park S, Chun Y, Song W, Kim HJ, Kim J. Treadmill exercise attenuates retinal oxidative stress in naturally-aged mice: an immunohistochemical study. *Int J Mol Sci*. (2015) 16:21008–20. doi: 10.3390/ijms160921008

131. Baudouin C, Kolko M, Melik-Parsadaniantz S, Messmer EM. Inflammation in Glaucoma: from the back to the front of the eye, and beyond. *Prog Retin Eye Res*. (2021) 83:100916. doi: 10.1016/j.preteyeres.2020.100916

132. Xu H, Chen M, Forrester JV. Para-inflammation in the aging retina. *Prog Retin Eye Res*. (2009) 28:348–68. doi: 10.1016/j.preteyeres.2009.06.001

133. Wang J, Li M, Geng Z, Khattak S, Ji X, Wu D, et al. Role of oxidative stress in retinal disease and the early intervention strategies: a review. *Oxid Med Cell Longev*. (2022) 2022:7836828. doi: 10.1155/2022/7836828

134. Ferreira SM, Lerner SF, Brunzini R, Evelson PA, Llesuy SF. Oxidative stress markers in aqueous humor of glaucoma patients. *Am J Ophthalmol*. (2004) 137:62–9. doi: 10.1016/s0002-9394(03)00788-8

135. Bouzid MA, Filaire E, McCall A, Fabre C. Radical oxygen species, exercise and aging: an update. *Sports Med*. (2015) 45:1245–61. doi: 10.1007/s40279-015-0348-1

136. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nat Rev Immunol*. (2011) 11:607–15. doi: 10.1038/nri3041.

137. Zhang J, Liu Z, Wu H, Chen X, Hu Q, Li X, et al. Irisin attenuates pathological neovascularization in oxygen-induced retinopathy mice. *Invest Ophthalmol Vis Sci*. (2022) 63:21. doi: 10.1167/iovs.63.6.21.

138. Picca A, Calvani R, Bossola M, Allocca E, Menghi A, Pesce V, et al. Update on mitochondria and muscle aging: all wrong roads lead to sarcopenia. *Biol Chem*. (2018) 399:421–36. doi: 10.1515/hsz-2017-0331.

139. Angulo J, El Assar M, Álvarez-Bustos A, Rodríguez-Mañas L. Physical activity and exercise: strategies to manage frailty. *Redox Biol*. (2020) 35:101513. doi: 10.1016/j.redox.2020.101513

140. Osborne NN, Núñez-Álvarez C, Joglar B, Del Olmo-Aguado S. Glaucoma: focus on mitochondria in relation to pathogenesis and neuroprotection. *Eur J Pharmacol*. (2016) 787:127–33. doi: 10.1016/j.ejphar.2016.04.032

141. Schrier SA, Falk MJ. Mitochondrial disorders and the eye. *Curr Opin Ophthalmol*. (2011) 22:325–31. doi: 10.1097/ICU.0b013e328349419d.

142. Kuang G, Halimitabrizi M, Edziah AA, Salowe R, O'Brien JM. The potential for mitochondrial therapeutics in the treatment of primary open-angle glaucoma: a review. *Front Physiol*. (2023) 14:1184060. doi: 10.3389/fphys.2023.1184060

143. Williams PA, Harder JM, Foxworth NE, Cochran KE, Philip VM, Porciatti V, et al. Vitamin B_3 modulates mitochondrial vulnerability and prevents glaucoma in aged mice. *Science*. (2017) 355:756–60. doi: 10.1126/science.aal0092

144. Yang XJ, Ge J, Zhuo YH. Role of mitochondria in the pathogenesis and treatment of glaucoma. *Chin Med J*. (2013) 126:4358–65. doi: 10.3760/cma.j.issn.0366-6999.20131956

145. Norat P, Soldozy S, Sokolowski JD, Gorick CM, Kumar JS, Chae Y, et al. Mitochondrial dysfunction in neurological disorders: exploring mitochondrial transplantation. *npj Regen Med*. (2020) 5:22. doi: 10.1038/s41536-020-00107-x.

146. Leick L, Lyngby SS, Wojtaszewski JF, Pilegaard H. PGC-1α is required for training-induced prevention of age-associated decline in mitochondrial enzymes in mouse skeletal muscle. *Exp Gerontol*. (2010) 45:336–42. doi: 10.1016/j.exger.2010.01.011

147. Wohlgemuth SE, Lees HA, Marzetti E, Manini TM, Aranda JM, Daniels MJ, et al. An exploratory analysis of the effects of a weight loss plus exercise program on cellular quality control mechanisms in older overweight women. *Rejuvenation Res*. (2011) 14:315–24. doi: 10.1089/rej.2010.1132

148. Fudalej E, Justyniarska M, Kasarełło K, Dziedziak J, Szaflik JP, Cudnoch-Jędrzejewska A. Neuroprotective factors of the retina and their role in promoting survival of retinal ganglion cells: a review. *Ophthalmic Res*. (2021) 64:345–55. doi: 10.1159/000514441

149. Mansour-Robaey S, Clarke DB, Wang YC, Bray GM, Aguayo AJ. Effects of ocular injury and administration of brain-derived neurotrophic factor on survival and regrowth of axotomized retinal ganglion cells. *Proc Natl Acad Sci USA*. (1994) 91:1632–6. doi: 10.1073/pnas.91.5.1632

150. Chrysostomou V, Galic S, van Wijngaarden P, Trounce IA, Steinberg GR, Crowston JG. Exercise reverses age-related vulnerability of the retina to injury by preventing complement-mediated synapse elimination via a BDNF-dependent pathway. *Aging Cell*. (2016) 15:1082–91. doi: 10.1111/acel.12512

151. Gupta V, You Y, Li J, Gupta V, Golzan M, Klistorner A, et al. BDNF impairment is associated with age-related changes in the inner retina and exacerbates experimental glaucoma. *Biochim Biophys Acta*. (2014) 1842:1567–78. doi: 10.1016/j.bbadis.2014.05.026

152. Chitranshi N, Dheer Y, Abbasi M, You Y, Graham SL, Gupta V. Glaucoma pathogenesis and neurotrophins: focus on the molecular and genetic basis for therapeutic prospects. *Curr Neuropharmacol*. (2018) 16:1018–35. doi: 10.2174/1570159x16666180419121247

153. Chu-Tan JA, Kirkby M, Natoli R. Running to save sight: the effects of exercise on retinal health and function. *Clin Experiment Ophthalmol*. (2022) 50:74–90. doi: 10.1111/ceo.14023

154. Pardue MT, Chrenek MA, Schmidt RH, Nickerson JM, Boatright JH. Potential role of exercise in retinal health. *Prog Mol Biol Transl Sci*. (2015) 134:491–502. doi: 10.1016/bs.pmbts.2015.06.011.

155. Hu YS, Long N, Pigino G, Brady ST, Lazarov O. Molecular mechanisms of environmental enrichment: impairments in Akt/GSK3β, neurotrophin-3 and CREB signaling. *PLoS One*. (2013) 8:e64460. doi: 10.1371/journal.pone.0064460

156. Domenici L, Origlia N, Falsini B, Cerri E, Barloscio D, Fabiani C, et al. Rescue of retinal function by BDNF in a mouse model of glaucoma. *PLoS One*. (2014) 9:e115579. doi: 10.1371/journal.pone.0115579

157. Chen C, Nakagawa S. Physical activity for cognitive health promotion: an overview of the underlying neurobiological mechanisms. *Ageing Res Rev*. (2023) 86:101868. doi: 10.1016/j.arr.2023.101868

158. Meeusen R, De Meirleir K. Exercise and brain neurotransmission. *Sports Med*. (1995) 20:160–88. doi: 10.2165/00007256-199520030-00004.

159. Shimojo G, Joseph B, Shah R, Consolim-Colombo FM, De Angelis K, Ulloa L. Exercise activates vagal induction of dopamine and attenuates systemic inflammation. *Brain Behav Immun*. (2019) 75:181–91. doi: 10.1016/j.bbi.2018.10.005

160. Bucolo C, Leggio GM, Drago F, Salomone S. Dopamine outside the brain: the eye, cardiovascular system and endocrine pancreas. *Pharmacol Ther*. (2019) 203:107392. doi: 10.1016/j.pharmthera.2019.07.003.

161. Prünte C, Flammer J. The novel dopamine D-1 antagonist and D-2 agonist, SDZ GLC-756, lowers intraocular pressure in healthy human volunteers and in patients with glaucoma. *Ophthalmology*. (1995) 102:1291–7. doi: 10.1016/s0161-6420(95)30872-x.

162. Leggio GM, Bucolo C, Platania CB, Salomone S, Drago F. Current drug treatments targeting dopamine D3 receptor. *Pharmacol Ther*. (2016) 165:164–77. doi: 10.1016/j.pharmthera.2016.06.007

163. Chu E, Chu TC, Potter DE. Mechanisms and sites of ocular action of 7-hydroxy-2-dipropylaminotetralin: a dopamine$_3$ receptor agonist. *J Pharmacol Exp Ther*. (2000) 293:710–6.

164. Bucolo C, Leggio GM, Maltese A, Castorina A, D'Agata V, Drago F. Dopamine-$_3$ receptor modulates intraocular pressure: implications for glaucoma. *Biochem Pharmacol*. (2012) 83:680–6. doi: 10.1016/j.bcp.2011.11.031

165. Pescosolido N, Parisi F, Russo P, Buomprisco G, Nebbioso M. Role of dopaminergic receptors in glaucomatous disease modulation. *Biomed Res Int*. (2013) 2013:193048:193048. doi: 10.1155/2013/193048

166. Chu E, Socci R, Chu TC. PD128,907 induces ocular hypotension in rabbits: involvement of D2/D3 dopamine receptors and brain natriuretic peptide. *J Ocul Pharmacol Ther*. (2004) 20:15–23. doi: 10.1089/108076804772745428.

167. Reyes-Resina I, Awad Alkozi H, Del Ser-Badia A, Sánchez-Naves J, Lillo J, Jiménez J, et al. Expression of melatonin and dopamine D_3 receptor heteromers in eye ciliary body epithelial cells and negative correlation with ocular hypertension. *Cells*. (2020) 9:152. doi: 10.3390/cells9010152

168. Dkhissi O, Chanut E, Versaux-Botteri C, Minvielle F, Trouvin JH, Nguyen-Legros J. Changes in retinal dopaminergic cells and dopamine rhythmic metabolism during the development of a glaucoma-like disorder in quails. *Invest Ophthalmol Vis Sci*. (1996) 37:2335–44.

169. Liu Y, Wu N. Progress of nanotechnology in diabetic retinopathy treatment. *Int J Nanomedicine*. (2021) 16:1391–403. doi: 10.2147/ijn.S294807.

170. Zhang J, Zhang J, Zhang C, Zhang J, Gu L, Luo D, et al. Diabetic macular edema: current understanding, molecular mechanisms and therapeutic implications. *Cells*. (2022) 11:3362. doi: 10.3390/cells11213362

171. Testa R, Bonfigli AR, Prattichizzo F, La Sala L, De Nigris V, Ceriello A. The "metabolic memory" theory and the early treatment of hyperglycemia in prevention of diabetic complications. *Nutrients*. (2017) 9:437. doi: 10.3390/nu9050437

172. Wang YX, Wei WB, Xu L, Jonas JB. Physical activity and eye diseases. The Beijing eye study. *Acta Ophthalmol*. (2019) 97:325–31. doi: 10.1111/aos.13962

173. Loprinzi PD. Association of accelerometer-assessed sedentary behavior with diabetic retinopathy in the United States. *JAMA Ophthalmol*. (2016) 134:1197–8. doi: 10.1001/jamaophthalmol.2016.2400

174. Soleimani A, Soltani P, Karimi H, Mirzaei M, Esfahanian F, Yavari M, et al. The effect of moderate-intensity aerobic exercise on non-proliferative diabetic retinopathy in type II diabetes mellitus patients: a clinical trial. *Microvasc Res*. (2023) 149:104556. doi: 10.1016/j.mvr.2023.104556

175. Cheng CK, Shang W, Liu J, Cheang WS, Wang Y, Xiang L, et al. Activation of AMPK/miR-181b Axis alleviates endothelial dysfunction and vascular inflammation in diabetic mice. *Antioxidants*. (2022) 11:1137. doi: 10.3390/antiox11061137

176. Ren C, Liu W, Li J, Cao Y, Xu J, Lu P. Physical activity and risk of diabetic retinopathy: a systematic review and meta-analysis. *Acta Diabetol*. (2019) 56:823–37. doi: 10.1007/s00592-019-01319-4.

177. Zinn S, Nelis P, Minnebeck K, Hinder J, Eter N, Brand SM, et al. Effect of high-intensity interval training in patients with type 1 diabetes on physical fitness and retinal microvascular perfusion determined by optical coherence tomography angiography. *Microvasc Res*. (2020) 132:104057. doi: 10.1016/j.mvr.2020.104057

178. Alten F, Eter N, Schmitz B. Differential effects of high-intensity interval training (HIIT) on choriocapillaris perfusion in healthy adults and patients with type 1 diabetes mellitus (T1DM). *Microvasc Res*. (2021) 135:104128. doi: 10.1016/j.mvr.2020.104128

179. Barot M, Gokulgandhi MR, Patel S, Mitra AK. Microvascular complications and diabetic retinopathy: recent advances and future implications. *Future Med Chem*. (2013) 5:301–14. doi: 10.4155/fmc.12.206

180. Lutty GA. Effects of diabetes on the eye. *Invest Ophthalmol Vis Sci*. (2013) 54:ORSF81–7. doi: 10.1167/iovs.13-12979

181. Forbes JM, Cooper ME. Mechanisms of diabetic complications. *Physiol Rev*. (2013) 93:137–88. doi: 10.1152/physrev.00045.2011

182. Tomita Y, Lee D, Tsubota K, Negishi K, Kurihara T. Updates on the current treatments for diabetic retinopathy and possibility of future oral therapy. *J Clin Med*. (2021) 10:4666. doi: 10.3390/jcm10204666

183. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. *Lancet*. (2010) 376:124–36. doi: 10.1016/s0140-6736(09)62124-3.

184. Watanabe D, Suzuma K, Matsui S, Kurimoto M, Kiryu J, Kita M, et al. Erythropoietin as a retinal angiogenic factor in proliferative diabetic retinopathy. *N Engl J Med*. (2005) 353:782–92. doi: 10.1056/NEJMoa041773

185. Phielix E, Meex R, Moonen-Kornips E, Hesselink MK, Schrauwen P. Exercise training increases mitochondrial content and *ex vivo* mitochondrial function similarly in patients with type 2 diabetes and in control individuals. *Diabetologia*. (2010) 53:1714–21. doi: 10.1007/s00125-010-1764-2.

186. Kadoglou NP, Iliadis F, Angelopoulou N, Perrea D, Ampatzidis G, Liapis CD, et al. The anti-inflammatory effects of exercise training in patients with type 2 diabetes mellitus. *Eur J Cardiovasc Prev Rehabil*. (2007) 14:837–43. doi: 10.1097/HJR.0b013e3282efaf50.

187. Boulé NG, Kenny GP, Haddad E, Wells GA, Sigal RJ. Meta-analysis of the effect of structured exercise training on cardiorespiratory fitness in type 2 diabetes mellitus. *Diabetologia*. (2003) 46:1071–81. doi: 10.1007/s00125-003-1160-2.

188. Kanaley JA, Colberg SR, Corcoran MH, Malin SK, Rodriguez NR, Crespo CJ, et al. Exercise/physical activity in individuals with type 2 diabetes: a consensus statement from the American College of Sports Medicine. *Med Sci Sports Exerc*. (2022) 54:353–68. doi: 10.1249/mss.0000000000002800

189. Liu Y, Ye W, Chen Q, Zhang Y, Kuo CH, Korivi M. Resistance exercise intensity is correlated with attenuation of HbA1c and insulin in patients with type 2 diabetes: a systematic review and meta-analysis. *Int J Environ Res Public Health*. (2019) 16:140. doi: 10.3390/ijerph16010140

190. Karstoft K, Winding K, Knudsen SH, Nielsen JS, Thomsen C, Pedersen BK, et al. The effects of free-living interval-walking training on glycemic control, body composition, and physical fitness in type 2 diabetic patients: a randomized, controlled trial. *Diabetes Care*. (2013) 36:228–36. doi: 10.2337/dc12-0658

191. Nieuwoudt S, Fealy CE, Foucher JA, Scelsi AR, Malin SK, Pagadala M, et al. Functional high-intensity training improves pancreatic β-cell function in adults with type 2 diabetes. *Am J Physiol Endocrinol Metab*. (2017) 313:E314–e320. doi: 10.1152/ajpendo.00407.2016.

192. Sigal RJ, Kenny GP, Boulé NG, Wells GA, Prud'homme D, Fortier M, et al. Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes: a randomized trial. *Ann Intern Med*. (2007) 147:357–69. doi: 10.7326/0003-4819-147-6-200709180-00005

193. Schwingshackl L, Missbach B, Dias S, König J, Hoffmann G. Impact of different training modalities on glycaemic control and blood lipids in patients with type 2 diabetes: a systematic review and network meta-analysis. *Diabetologia*. (2014) 57:1789–97. doi: 10.1007/s00125-014-3303-z

194. Giannopoulou I, Fernhall B, Carhart R, Weinstock RS, Baynard T, Figueroa A, et al. Effects of diet and/or exercise on the adipocytokine and inflammatory cytokine levels of postmenopausal women with type 2 diabetes. *Metab Clin Exp*. (2005) 54:866–75. doi: 10.1016/j.metabol.2005.01.033

195. Antonetti DA, Barber AJ, Bronson SK, Freeman WM, Gardner TW, Jefferson LS, et al. Diabetic retinopathy: seeing beyond glucose-induced microvascular disease. *Diabetes*. (2006) 55:2401–11. doi: 10.2337/db05-1635

196. Abu-El-Asrar AM, Dralands L, Missotten L, Al-Jadaan IA, Geboes K. Expression of apoptosis markers in the retinas of human subjects with diabetes. *Invest Ophthalmol Vis Sci*. (2004) 45:2760–6. doi: 10.1167/iovs.03-1392

197. Adornetto A, Gesualdo C, Laganà ML, Trotta MC, Rossi S, Russo R. Autophagy: a novel pharmacological target in diabetic retinopathy. *Front Pharmacol*. (2021) 12:695267. doi: 10.3389/fphar.2021.695267

198. Trotta MC, Gesualdo C, Herman H, Gharbia S, Balta C, Lepre CC, et al. Systemic beta-hydroxybutyrate affects BDNF and autophagy into the retina of diabetic mice. *Int J Mol Sci*. (2022) 23:10184. doi: 10.3390/ijms231710184

199. Liu Y, Tao L, Fu X, Zhao Y, Xu X. BDNF protects retinal neurons from hyperglycemia through the TrkB/ERK/MAPK pathway. *Mol Med Rep*. (2013) 7:1773–8. doi: 10.3892/mmr.2013.1433

200. Kaviarasan K, Jithu M, Arif Mulla M, Sharma T, Sivasankar S, Das UN, et al. Low blood and vitreal BDNF, LXA4 and altered Th1/Th2 cytokine balance are potential risk factors for diabetic retinopathy. *Metab Clin Exp*. (2015) 64:958–66. doi: 10.1016/j.metabol.2015.04.005

201. He M, Long P, Chen T, Li K, Wei D, Zhang Y, et al. ALDH2/SIRT1 contributes to type 1 and type 2 diabetes-induced retinopathy through depressing oxidative stress. *Oxid Med Cell Longev*. (2021) 2021:1641717. doi: 10.1155/2021/1641717

202. Li C, Miao X, Li F, Wang S, Liu Q, Wang Y, et al. Oxidative stress-related mechanisms and antioxidant therapy in diabetic retinopathy. *Oxid Med Cell Longev*. (2017) 2017:9702820. doi: 10.1155/2017/9702820

203. Kang Q, Yang C. Oxidative stress and diabetic retinopathy: molecular mechanisms, pathogenetic role and therapeutic implications. *Redox Biol*. (2020) 37:101799. doi: 10.1016/j.redox.2020.101799

204. Elahy M, Baindur-Hudson S, Cruzat VF, Newsholme P, Dass CR. Mechanisms of PEDF-mediated protection against reactive oxygen species damage in diabetic retinopathy and neuropathy. *J Endocrinol*. (2014) 222:R129–39. doi: 10.1530/joe-14-0065

205. Kowluru RA. Cross talks between oxidative stress, inflammation and epigenetics in diabetic retinopathy. *Cells*. (2023) 12:300. doi: 10.3390/cells12020300

206. Frith E, Loprinzi PD. Physical activity, muscle-strengthening activities, and systemic inflammation among retinopathy patients. *Diabetes Spectr*. (2019) 32:16–20. doi: 10.2337/ds18-0002.

207. Chistiakov DA. Diabetic retinopathy: pathogenic mechanisms and current treatments. *Diabetes Metab Syndr*. (2011) 5:165–72. doi: 10.1016/j.dsx.2012.02.025

208. Palanisamy K, Nareshkumar RN, Sivagurunathan S, Raman R, Sulochana KN, Chidambaram S. Anti-angiogenic effect of adiponectin in human primary microvascular and macrovascular endothelial cells. *Microvasc Res*. (2019) 122:136–45. doi: 10.1016/j.mvr.2018.08.002.

209. Omae T, Nagaoka T, Yoshida A. Relationship between retinal blood flow and serum adiponectin concentrations in patients with type 2 diabetes mellitus. *Invest Ophthalmol Vis Sci*. (2015) 56:4143–9. doi: 10.1167/iovs.15-16447

210. Makanae Y, Ogasawara R, Sato K, Takamura Y, Matsutani K, Kido K, et al. Acute bout of resistance exercise increases vitamin D receptor protein expression in rat skeletal muscle. *Exp Physiol*. (2015) 100:1168–76. doi: 10.1113/ep085207

211. Klenk J, Rapp K, Denkinger M, Nagel G, Nikolaus T, Peter R, et al. Objectively measured physical activity and vitamin D status in older people from Germany. *J Epidemiol Community Health*. (2015) 69:388–92. doi: 10.1136/jech-2014-204632

212. Al-Othman A, Al-Musharaf S, Al-Daghri NM, Krishnaswamy S, Yusuf DS, Alkharfy KM, et al. Effect of physical activity and sun exposure on vitamin D status of Saudi children and adolescents. *BMC Pediatr*. (2012) 12:92. doi: 10.1186/1471-2431-12-92

213. Zakaria WNA, Mohd Yunus N, Yaacob NM, Omar J, Wan Mohamed WMI, Sirajudeen KNS, et al. Association between vitamin D receptor polymorphisms (BsmI and FokI) and glycemic control among patients with type 2 diabetes. *Int J Environ Res Public Health*. (2021) 18:1595. doi: 10.3390/ijerph18041595

214. Wang W, Lo ACY. Diabetic retinopathy: pathophysiology and treatments. *Int J Mol Sci*. (2018) 19:1816. doi: 10.3390/ijms19061816

215. Knudtson MD, Klein R, Klein BE. Physical activity and the 15-year cumulative incidence of age-related macular degeneration: the Beaver Dam Eye Study. *Br J Ophthalmol*. (2006) 90:1461–3. doi: 10.1136/bjo.2006.103796

216. Ulańczyk Z, Grabowicz A, Cecerska-Heryć E, Śleboda-Taront D, Krytkowska E, Mozolewska-Piotrowska K, et al. Dietary and lifestyle factors modulate the activity of the endogenous antioxidant system in patients with age-related macular degeneration: correlations with disease severity. *Antioxidants*. (2020) 9:954. doi: 10.3390/antiox9100954

217. Zhang X, Girardot PE, Sellers JT, Li Y, Wang J, Chrenek MA, et al. Wheel running exercise protects against retinal degeneration in the I307N rhodopsin mouse model of inducible autosomal dominant retinitis pigmentosa. *Mol Vis*. (2019) 25:462–76.

218. Cui B, Guo X, Zhou W, Zhang X, He K, Bai T, et al. Exercise alleviates neovascular age-related macular degeneration by inhibiting AIM2 inflammasome in myeloid cells. *Metab Clin Exp*. (2023) 144:155584. doi: 10.1016/j.metabol.2023.155584

219. Mitchell P, Liew G, Gopinath B, Wong TY. Age-related macular degeneration. *Lancet*. (2018) 392:1147–59. doi: 10.1016/s0140-6736(18)31550-2

220. Fenwick EK, Cheung GCM, Gan AT, Tan G, Lee SY, Wong D, et al. Change in vision-related quality of life and influencing factors in Asians receiving treatment for neovascular age-related macular degeneration. *Br J Ophthalmol*. (2018) 102:377–82. doi: 10.1136/bjophthalmol-2017-310532

221. Thomas CJ, Mirza RG, Gill MK. Age-related macular degeneration. *Med Clin North Am*. (2021) 105:473–91. doi: 10.1016/j.mcna.2021.01.003.

222. Guymer RH, Campbell TG. Age-related macular degeneration. *Lancet*. (2023) 401:1459–72. doi: 10.1016/s0140-6736(22)02609-5.

223. Liu L, Majithia S, Tham YC. Physical activity and age-related macular degeneration: a systematic literature review and meta-analysis. *Am J Ophthalmol*. (2018) 185:123. doi: 10.1016/j.ajo.2017.10.013

224. Deng Y, Qiao L, Du M, Qu C, Wan L, Li J, et al. Age-related macular degeneration: epidemiology, genetics, pathophysiology, diagnosis, and targeted therapy. *Genes Dis*. (2022) 9:62–79. doi: 10.1016/j.gendis.2021.02.009

225. Moreno-García A, Kun A, Calero O, Medina M, Calero M. An overview of the role of lipofuscin in age-related neurodegeneration. *Front Neurosci*. (2018) 12:464. doi: 10.3389/fnins.2018.00464

226. Tang J, Kern TS. Inflammation in diabetic retinopathy. *Prog Retin Eye Res*. (2011) 30:343–58. doi: 10.1016/j.preteyeres.2011.05.002

227. Li G, Luna C, Liton PB, Navarro I, Epstein DL, Gonzalez P. Sustained stress response after oxidative stress in trabecular meshwork cells. *Mol Vis*. (2007) 13:2282–8.

228. Al-Shabrawey M, Hussein K, Wang F, Wan M, Elmasry K, Elsherbiny N, et al. Bone morphogenetic protein-2 induces non-canonical inflammatory and oxidative pathways in human retinal endothelial cells. *Front Immunol*. (2020) 11:568795. doi: 10.3389/fimmu.2020.568795

229. Paeng SH, Jung WK, Park WS, Lee DS, Kim GY, Choi YH, et al. Caffeic acid phenethyl ester reduces the secretion of vascular endothelial growth factor through the inhibition of the ROS, PI3K and HIF-1α signaling pathways in human retinal pigment epithelial cells under hypoxic conditions. *Int J Mol Med*. (2015) 35:1419–26. doi: 10.3892/ijmm.2015.2116.

230. Dong A, Xie B, Shen J, Yoshida T, Yokoi K, Hackett SF, et al. Oxidative stress promotes ocular neovascularization. *J Cell Physiol*. (2009) 219:544–52. doi: 10.1002/jcp.21698

231. McLeod DS, Bhutto I, Edwards MM, Silver RE, Seddon JM, Lutty GA. Distribution and quantification of choroidal macrophages in human eyes with age-related macular degeneration. *Invest Ophthalmol Vis Sci*. (2016) 57:5843–55. doi: 10.1167/iovs.16-20049

232. Espinosa-Heidmann DG, Suner IJ, Hernandez EP, Monroy D, Csaky KG, Cousins SW. Macrophage depletion diminishes lesion size and severity in experimental choroidal neovascularization. *Invest Ophthalmol Vis Sci*. (2003) 44:3586–92. doi: 10.1167/iovs.03-0038.

233. Siegert S, Cabuy E, Scherf BG, Kohler H, Panda S, Le YZ, et al. Transcriptional code and disease map for adult retinal cell types. *Nat Neurosci*. (2012) 15:487–95. doi: 10.1038/nn.3032

234. An AR, Shin DW, Kim S, Lee CH, Park JH, Park JH, et al. Health behaviors of people with retinitis pigmentosa in the Republic of Korea. *Ophthalmic Epidemiol*. (2014) 21:279–86. doi: 10.3109/09286586.2014.926939.

235. Levinson JD, Joseph E, Ward LA, Nocera JR, Pardue MT, Bruce BB, et al. Physical activity and quality of life in retinitis pigmentosa. *J Ophthalmol*. (2017) 2017:6950642. doi: 10.1155/2017/6950642

236. Huai P, Xun H, Reilly KH, Wang Y, Ma W, Xi B. Physical activity and risk of hypertension: a meta-analysis of prospective cohort studies. *Hypertension*. (2013) 62:1021–6. doi: 10.1161/hypertensionaha.113.01965

237. Streese L, Guerini C, Bühlmayer L, Lona G, Hauser C, Bade S, et al. Physical activity and exercise improve retinal microvascular health as a biomarker of cardiovascular risk: a systematic review. *Atherosclerosis*. (2020) 315:33–42. doi: 10.1016/j.atherosclerosis.2020.09.017

238. Becatti M, Marcucci R, Gori AM, Mannini L, Grifoni E, Alessandrello Liotta A, et al. Erythrocyte oxidative stress is associated with cell deformability in patients with retinal vein occlusion. *J Thromb Haemost*. (2016) 14:2287–97. doi: 10.1111/jth.13482

239. Tikellis G, Anuradha S, Klein R, Wong TY. Association between physical activity and retinal microvascular signs: the atherosclerosis risk in communities (ARIC) study. *Microcirculation*. (2010) 17:381–93. doi: 10.1111/j.1549-8719.2010.00033.x

240. Scott IU, Campochiaro PA, Newman NJ, Biousse V. Retinal vascular occlusions. *Lancet*. (2020) 396:1927–40. doi: 10.1016/s0140-6736(20)31559-2

241. Baillet A, Zeboulon N, Gossec L, Combescure C, Bodin LA, Juvin R, et al. Efficacy of cardiorespiratory aerobic exercise in rheumatoid arthritis: meta-analysis of randomized controlled trials. *Arthritis Care Res*. (2010) 62:984–92. doi: 10.1002/acr.20146

242. Lyngberg K, Danneskiold-Samsøe B, Halskov O. The effect of physical training on patients with rheumatoid arthritis: changes in disease activity, muscle strength and aerobic capacity. A clinically controlled minimized cross-over study. *Clin Exp Rheumatol*. (1988) 6:253–60.

243. Li X, Cao X, Zhao M, Bao Y. The changes of Irisin and inflammatory cytokines in the age-related macular degeneration and retinal vein occlusion. *Front Endocrinol*. (2022) 13:861757. doi: 10.3389/fendo.2022.861757.

244. Li DJ, Li YH, Yuan HB, Qu LF, Wang P. The novel exercise-induced hormone irisin protects against neuronal injury via activation of the Akt and ERK1/2 signaling pathways and contributes to the neuroprotection of physical exercise in cerebral ischemia. *Metab Clin Exp*. (2017) 68:31–42. doi: 10.1016/j.metabol.2016.12.003

245. Wang Y, Tian M, Tan J, Pei X, Lu C, Xin Y, et al. Irisin ameliorates neuroinflammation and neuronal apoptosis through integrin αVβ5/AMPK signaling pathway after intracerebral hemorrhage in mice. *J Neuroinflammation*. (2022) 19:82. doi: 10.1186/s12974-022-02438-6

246. Peng J, Deng X, Huang W, Yu JH, Wang JX, Wang JP, et al. Irisin protects against neuronal injury induced by oxygen-glucose deprivation in part depends on the inhibition of ROS-NLRP3 inflammatory signaling pathway. *Mol Immunol*. (2017) 91:185–94. doi: 10.1016/j.molimm.2017.09.014.

247. Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, et al. Interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev*. (2012) 2021:CD007146. doi: 10.1002/14651858.CD007146.pub3

248. To Q, Huynh VA, Do D, Do V, Congdon N, Meuleners L, et al. Falls and physical activity among cataract patients in Vietnam. *Ophthalmic Epidemiol*. (2022) 29:70–7. doi: 10.1080/09286586.2021.1893341

249. Shoss BL, Tsai LM. Postoperative care in cataract surgery. *Curr Opin Ophthalmol*. (2013) 24:66–73. doi: 10.1097/ICU.0b013e32835b0716.

250. Simó R, Hernández C. What else can we do to prevent diabetic retinopathy? *Diabetologia*. (2023) 66:1614–21. doi: 10.1007/s00125-023-05940-5

251. Caprioli J, Coleman AL. Blood pressure, perfusion pressure, and glaucoma. *Am J Ophthalmol*. (2010) 149:704–12. doi: 10.1016/j.ajo.2010.01.018

252. Wu Z, Ayton LN, Guymer RH, Luu CD. Low-luminance visual acuity and microperimetry in age-related macular degeneration. *Ophthalmology*. (2014) 121:1612–9. doi: 10.1016/j.ophtha.2014.02.005

253. Peng CC, Cerretani C, Braun RJ, Radke CJ. Evaporation-driven instability of the precorneal tear film. *Adv Colloid Interf Sci*. (2014) 206:250–64. doi: 10.1016/j.cis.2013.06.001

254. Morgan I, Rose K. How genetic is school myopia? *Prog Retin Eye Res*. (2005) 24:1–38. doi: 10.1016/j.preteyeres.2004.06.004

255. Browning DJ, Stewart MW, Lee C. Diabetic macular edema: evidence-based management. *Indian J Ophthalmol*. (2018) 66:1736–50. doi: 10.4103/ijo.IJO_1240_18.

frontiers | Frontiers in Medicine

TYPE Systematic Review
PUBLISHED 03 April 2024
DOI 10.3389/fmed.2024.1365259

OPEN ACCESS

EDITED BY
Rashmi Deshmukh,
L V Prasad Eye Institute, India

REVIEWED BY
Alessandro Marroni,
DAN Europe Foundation, Malta
Alessio Martucci,
University of Rome Tor Vergata, Italy

*CORRESPONDENCE
Bryan Chin Hou Ang
✉ drbryanang@gmail.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 04 January 2024
ACCEPTED 21 March 2024
PUBLISHED 03 April 2024

CITATION
Lentz PC, Lim SY, Betzler BK, Miller DD, Dorairaj SK and Ang BCH (2024) A deep dive into hyperbaric environments and intraocular pressure—a systematic review. *Front. Med.* 11:1365259. doi: 10.3389/fmed.2024.1365259

A deep dive into hyperbaric environments and intraocular pressure—a systematic review

Paul Connor Lentz[1†], Sheng Yang Lim[2†], Bjorn Kaijun Betzler[2], Darby D. Miller[3], Syril K. Dorairaj[3] and Bryan Chin Hou Ang[2,3,4*]

[1]Mayo Clinic Alix School of Medicine, Jacksonville, FL, United States, [2]Department of Ophthalmology, Tan Tock Seng Hospital, National Healthcare Group Eye Institute, Singapore, Singapore, [3]Department of Ophthalmology, Mayo Clinic, Jacksonville, FL, United States, [4]Department of Ophthalmology, Woodlands Health Campus, National Healthcare Group Eye Institute, Singapore, Singapore

Purpose: SCUBA diving exposes participants to a unique hyperbaric environment, but few studies have examined the effects of such an environment on intraocular pressure (IOP) and glaucoma. This systematic review aims to consolidate recent literature findings regarding the impact of increased atmospheric pressure on IOP and glaucoma.

Methods: Three online databases were searched to identify publications encompassing the subjects of diving or increased atmospheric pressure in conjunction with IOP or glaucoma. Three reviewers independently screened the publications and identified eligible articles. Relevant data was extracted from each article. The heterogeneity of the data precluded the conduct of a meta-analysis.

Results: Nine studies met the inclusion criteria. Six experimental studies employed hyperbaric chambers to measure IOP under simulated diving conditions. Among these, IOP exhibited a reduction with increased atmospheric pressures in four studies, while the findings of two studies were inconclusive. One study measured IOP pre- and post-dive and another measured IOP with and without a diving mask. Post-dive, a decrease in IOP was observed, and a statistically significant reduction was noted when subjects wore a diving mask. A retrospective study examining the incidence of acute angle closure glaucoma attack found no association with weather or atmospheric pressure.

Conclusion: The majority of studies found IOP to decrease with increased atmospheric pressure and after diving. The mechanisms underlying this reduction remain incompletely understood, with potential contributors including changes in ocular blood flow, sympathetic responses, and increased oxygenation. Hyperbaric chambers may have potential in future glaucoma treatments, but more studies are required to draw reliable conclusions regarding the safety of diving for glaucoma patients.

KEYWORDS

intraocular pressure, glaucoma, diving, atmospheric pressure, hyperbaric

Introduction

In recent years, SCUBA diving has seen significant growth in global popularity as both a professional and recreational activity (1, 2). While relatively safe with appropriate prerequisite training and certification, diving is still associated with potential risks. Divers are exposed to a hyperbaric environment, defined as an environment with increased atmospheric pressure, which may have diverse effects on the body, potentially exacerbating various medical conditions (3). Consequently, SCUBA diving presents several contraindications, including cardiac, pulmonary, otolaryngic, and neurologic diseases (4).

The effects of SCUBA diving on the eye have also been reported. These include conditions such as ocular barotrauma, caused by a pressure differential between the interior and exterior of the diving mask (mask squeeze) (5–7), ophthalmic manifestations of decompression sickness (8, 9) such as retinal vein occlusion and choroidal ischemia, as well as other ophthalmic manifestations, including nystagmus, diplopia, optic neuropathy, and visual field defects (10).

While the effects of diving on human physiology (11) have been well reported, its ocular manifestations, particularly on intraocular pressure (IOP), have been less studied. The relationship between diving and IOP can be important in patients with glaucoma, as IOP remains a major modifiable risk factor for the disease and has been shown to significantly influence disease progression. Glaucoma also remains the leading cause of irreversible blindness globally, with its prevalence estimated to be as high as 3.5% of adults, between the ages of 40 to 80 years old (12).

The hyperbaric environment (13) experienced during diving may affect IOP by various mechanisms, including peripheral vasoconstriction, as well as increased blood pressure and ocular perfusion pressure (14, 15). Besides high atmospheric pressures, several other factors experienced during diving, such as cold temperatures (16) and increased oxygen concentration (17–20), may also affect IOP.

Hence, this systematic review aims to summarize the current literature to provide a comprehensive overview of the effects of diving and hyperbaric environment on IOP.

Methods

This systematic review was conducted in accordance with the guidelines stated in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (21). An electronic search of the PubMed, Medline, and CENTRAL databases was performed from the date of database inception until July 1, 2023, as illustrated in Figure 1.

We limited our literature search to studies that explored the relationship between diving or increased atmospheric pressure, with IOP or glaucoma. A combination of subject headings and text headings were used to define search terms as needed. Our search included the terms "(Intraocular Pressure OR Glaucoma) AND (Diving OR Underwater OR Atmospheric Pressure OR Hyperbaric) NOT Oxygen." The decision was made to exclude the term "oxygen" from the search criteria to mitigate potential confounding factors, such as the inclusion of studies related to hyperbaric oxygen therapy. A secondary search was conducted by reviewing the references of all retrieved articles and relevant review articles to identify any additional potentially pertinent studies.

Three authors (PCL, LSY, BBK) independently assessed studies to determine eligibility for inclusion. In the event of discrepancies, differences were resolved by a senior author (SD, BCHA). Non-English articles and those that did not involve human participants were excluded from this review. Full text articles were assessed for eligibility. Papers unrelated to atmospheric pressure or diving, with a primary focus of high altitude or hypobaric environments, and those published over 25 years ago, were excluded from analysis. Ineligible article types included case reports, reviews, and letters to the editor. One report was excluded as it focused on sport diving.

A risk of bias assessment was performed by two authors (PCL, SYM) on applicable studies with the Risk of Bias in Non-Randomized Studies—of Intervention (ROBINS-I) tool (see Table 1) (22). Discrepancies in assessment were resolved through discussion until a consensus was reached.

Results

Study characteristics

Table 2 provides a summary of the key characteristics of the included studies. Two hundred and ninety studies were identified of which nine were eventually included. Six of the nine included studies focused on measuring IOP within hyperbaric chambers to simulate the increased atmospheric pressures experienced while diving. One retrospective study investigated potential correlations between changes in atmospheric pressure and weather patterns with acute closed-angle glaucoma attacks. One prospective study examined changes in eye parameters before and after SCUBA diving. The final study measured the IOP of subjects wearing a SCUBA diving mask, compared to baseline.

IOP before and after SCUBA diving

Deleu et al. was the only study reporting IOP readings measured pre- and post-diving in a healthy Caucasian population. Their results demonstrated a decrease in mean IOP from 16.4 ± 2.0 mmHg to 14.3 ± 2.3 mmHg (88.1%; $p < 0.0001$), measured 30 min after a 5-min dive to 25 meters, with the Nidek Tonoref III (NIDEK Co., Ltd., Tokyo, Japan) (23). This effect was found to be persistent, with IOP at the 60-min post-dive timepoint continuing to remain low compared to baseline, at 15.0 ± 2.7 mmHg (91.4%; $p < 0.0001$).

Hyperbaric chamber studies

Various articles studied the results of a high-pressure environment on IOP in a controlled setting within the hyperbaric chamber. Mazo et al. reported findings in a healthy population of students and instructors at the National Navy Diving and Rescue School in a multiplace hyperbaric chamber (24). IOP measurements were taken using a Tonopen XL (Reichert, Depew, New York, United States) at 10 min intervals. Measurements were recorded during simulated descent every 20 feet until reaching 2.8 absolute atmospheric pressure

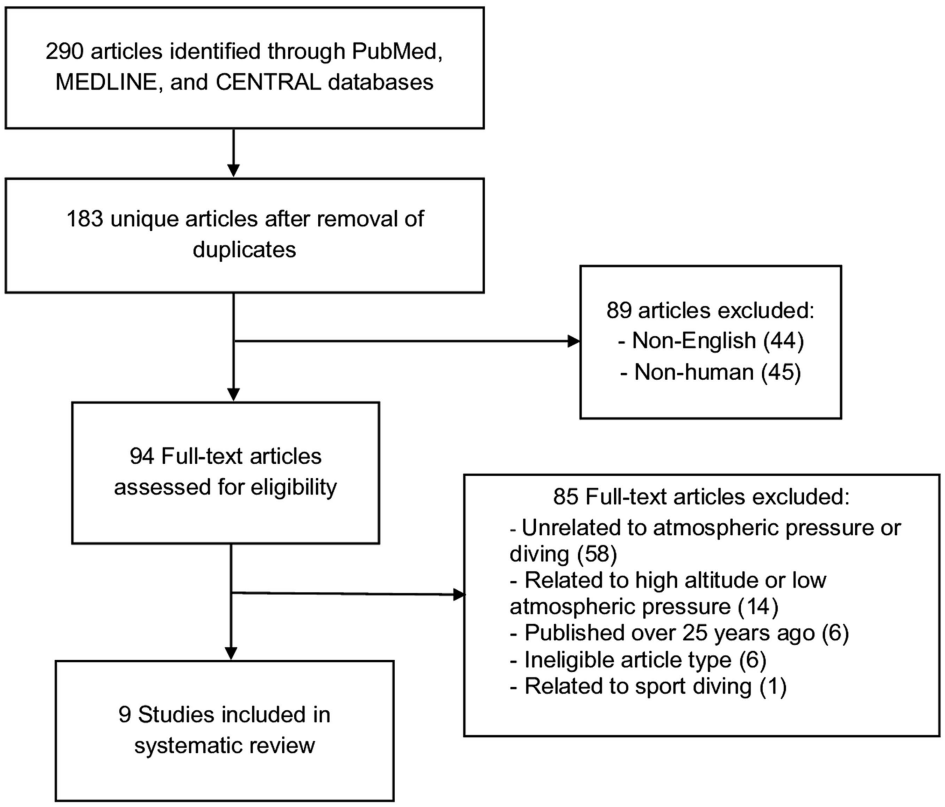

FIGURE 1
PRISMA flowchart.

(ATA) or 60 feet, and during simulated ascension at 50 and 30 feet. The mean adjusted IOP, adjusted for central corneal pachymetry, was found to decrease from 14.3 ± 2.2 mmHg to 13.1 ± 2.6 mmHg ($p = 0.012$) as the participants pressurized from sea level to 60 feet (2.8 ATA). During the depressurization phase to 30 feet, the mean adjusted IOP continued to decrease to 11.9 ± 2.7 mmHg ($p < 0.001$) and rose to 13.1 ± 2.9 mmHg ($p = 0.012$) by the end of the session, demonstrating a residual effect on IOP even after returning to lower atmospheric pressures.

Van De Veire et al. reported similar results in 27 healthy volunteers in a hyperbaric chamber, with the use of a Perkins applanation tonometer (Clement-Clarke International, Harlow, Essex, United Kingdom) (25). Mean IOP was found to decrease significantly from 11.8 mmHg to 10.7 mmHg in the right eye ($p = 0.024$) and 11.7 mmHg to 10.3 mmHg in the left eye ($p = 0.0006$) when pressure was increased from 1 to 2 bars (equal to conditions experienced during underwater diving at 10 m). The IOP remained low during the period of the atmospheric pressure increase over 40 min and was independent of temperature change. Additionally, IOP was found to remain decreased from baseline after completion of the hyperbaric cycle (60 min), with the IOP in the right eye reducing from 11.8 mmHg to 11.0 mmHg and left eye from 11.7 mmHg to 11.2 mmHg, although these changes did not reach statistical significance.

In addition to studying the absolute change in IOP in a high-pressure environment, two studies also compared measurements between IOP measuring devices. Vercellin et al. performed a comparison study between the Perkins applanation tonometry and Icare rebound tonometry (Icare, Tiolat Oy, Helsinki, Finland) on 12 eyes from 12 healthy volunteers (26). Measurements were taken with each type of tonometer on a different eye on all patients in a hyperbaric chamber at 1, 2, 3, and 4 bar during the compression phase and at 3 and 2 bar during the decompression phase. An acclimatization period of 5 min was given before each measurement. IOP measured with applanation tonometry had a mean baseline value of 13.8 ± 2.6 mmHg, decreasing to 10.2 ± 1.9 mmHg at 4 ATM ($p < 0.0001$). Rebound tonometry measured a mean baseline IOP of 15.3 ± 2.5 mmHg that decreased to 12.3 ± 1.7 mmHg at 4 ATM ($p < 0.0001$). IOP increased toward baseline with both tonometers during decompression. The difference between IOP measurements with each tonometer remained constant at each measurement.

Albis-Donado et al. also compared the difference in IOP measurements between two IOP measurement devices—the Goldmann applanation tonometry (GAT) and dynamic contour tonometry (DCT), within a hyperbaric chamber (27). Measurements were taken with both tonometers in 44 eyes from 22 healthy volunteers at 1, 1.1, 1.2, and 1.25 Queretaro Atmospheric Pressure (QATM). An acclimatization period of 5 min was given after each pressure change, prior to IOP measurement. The mean IOP measured with the GAT at 1 QATM was 12.2 ± 2.84 mmHg and measured 11.1 ± 2.8, 11.1 ± 2.5, 12.4 ± 3.1 mmHg at 1.1, 1.2, and 1.25 QATM, respectively. With the DCT, IOP was 16.4 ± 2.8 mmHg at 1 QATM and decreased to 15.6 ± 3.0, 15.4 ± 2.9, and 14.9 ± 2.7 mmHg at 1.1, 1.2, and1.25 QATM, respectively.

TABLE 1 Evaluation of evidence quality—ROBINS-I tool (22).

	Confounding[a]	Selection of participants	Classification of interventions	Deviations from intended interventions	Missing data	Measurements of outcomes	Selection of reported results	Overall ROB judgment
Deleu 2022	Low	Moderate	Low	Low	Low	Moderate	Low	Moderate
Mazo 2023	Low	Moderate	Low	Low	Low	Moderate	Low	Moderate
Van de Veire 2008	Low	Moderate	Low	Low	Moderate	Low	Low	Moderate
Vercellin 2021	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Albis-Donado 2020	Low	Moderate	Low	Low	Low	Moderate	Low	Moderate
Huang 2002	Low	Low	Low	Low	Low	Moderate	Low	Moderate
Peters 1999	Low	Low	Low	Low	Low	Moderate	Low	Moderate
Goenadi 2016	Low	Moderate	Low	Low	Low	Moderate	Low	Moderate
Bojić 2001[b]	Low	NA	NA	NA	NA	NA	NA	NA

[a]Confounding domain not applicable to before-after studies. [b]Robins-I Tool not applicable to retrospective observational studies. ROB, Risk of Bias.

Two studies examined the relationship between high-pressure environments and IOP in post-operative patients. Huang et al. conducted a prospective study to quantify the change in visual acuity and IOP with increased atmospheric pressure in eyes that underwent refractive surgery, compared to healthy control eyes with no prior refractive surgery (28). The study cohort included 6 eyes that had undergone radial keratotomy (RK), 5 eyes that had undergone myopic laser *in situ* keratomileusis (LASIK), and 9 control eyes. IOP was measured with Tonopen XL before, during, and after exposure to 4 ATM for 15 min in a hyperbaric chamber. No significant differences in IOP between the post-surgical and control groups were observed, leading authors to suggest that recreational diving could be safe post-RK or LASIK, although the study power was limited given the small number of participants. Similar findings were demonstrated by Peters et al., who compared visual acuity and IOP between 4 eyes which underwent previous RK against 4 control eyes matched for age and sex. Measurements were taken immediately before and after hyperbaric chamber exposure to a pressure of 3 ATM for 1 h (29). No significant change in mean IOP was found in either group.

Atmospheric pressure and angle closure glaucoma

Low light environments have been reported to increase the risk of acute angle closure glaucoma through causing physiological mydriasis (30). To explore this relationship, Bojićc et al. performed a retrospective study into the relationship between weather and meteorological factors and the incidence of acute angle closure glaucoma on 73 cases in Croatia (31). However, no significant correlation between atmospheric pressure and incidence rate of acute closed angle glaucoma was observed.

Impact of diving mask on IOP

To provide a watertight seal while diving, diving masks need to fit tightly against the periorbital region, with the potential risk of raising the IOP. Goenadi et al. explored this possible relationship by studying the effect of dive mask wearing on IOP, in a cohort of 40 eyes from 20 healthy volunteers (32). The AVIA Tono-Pen (Reichert Inc., NY, United States) was used to measure IOP at baseline with and without the diving mask (with the lenses removed) worn. Contrary to expectations, the mean IOP at baseline was 17.23 ± 2.18 mmHg, which decreased by 0.43 mmHg ($p < 0.05$) to 16.80 ± 2.57 mm Hg with the diving mask on.

Discussion

The studies included in this review largely demonstrated a decrease in IOP with increased atmospheric pressure, whether in a hyperbaric chamber or in an actual diving environment. Only two studies, Huang et al. (28) and Peters et al. (29) showed inconclusive results. This discrepancy may be attributed to the smaller sample sizes in these studies compared to others. Nonetheless, none of the studies in this review demonstrated an increase in IOP while diving.

The relationship between IOP and hyperbaric environments may be a result of several physiological mechanisms relating to changes in the partial pressure of oxygen and ocular blood flow, as well as other factors including exercise, temperature, and equipment. High atmospheric pressures result in peripheral vascular constriction, which in turn results in high ocular perfusion pressures, which may decrease IOP (13, 14). Changes in the partial pressure of oxygen may also cause vasoconstriction, which decreases IOP by decreasing choroidal blood volume (18), as demonstrated in animal models and human experiments (17–20). In hyperbaric chambers, at high atmospheric pressures the partial pressure of oxygen is also increased, hence resulting in a decrease in IOP.

In addition to environmental pressure and oxygenation, temperature may also influence IOP during diving. A recent study by Hartmann et al. showed a significant relationship between lower temperatures and increased IOP (33). This was attributed at least partly to higher systolic blood pressures, which increase with lower temperatures. Among the studies included in this review, only Van de Veire et al. (25) investigated the impact of temperature change on IOP. The study found a small decrease in IOP when temperatures were reduced from 28°C back to baseline (24°C), with the atmospheric pressure kept constant. However, this result did not reach statistical significance. Bojić et al. (31) revealed a significant correlation with winter months and the incidence of acute angle closure glaucoma, even though no correlation was found for hours of sunshine, air temperature and atmospheric pressure. This relationship was further supported by Zhu et al. who reported a rise in incidence of acute angle closure glaucoma in colder temperatures (34). This may be a result of mechanical or anatomical changes in the peripheral iris and angle structures (35), thus as divers are exposed to cold temperatures during their course of activity, predisposed individuals may possibly be also at a greater risk for acute angle closure glaucoma.

Exercise may also be a confounding variable that influences IOP during SCUBA diving, an activity that requires both endurance and strength, hence demanding significant energy expenditure (36). The relationship between exercise and IOP reduction has been well established (37–39), with this effect observed to be transient and directly correlating with the intensity of exercise (40). In the study by Deleu et al. (23), subjects underwent a dive for 25 min and authors postulated that the IOP reduction in their study may have been due to the sympathetic response triggered by exercise. An exercise-induced sympathetic response is accompanied by β2-adrenergic receptor activation, which is thought to contribute to increased aqueous humor outflow through an increase in trabecular meshwork thickness, along with expansion of both the area and perimeter of Schlemm's canal (41). Sympathetic activation also causes vasoconstriction of choroidal vasculature, which decreases choroidal blood flow and IOP. Other theories involve the physiological impact of exercise on blood parameters, including a decrease in blood pH, elevation of plasma osmolarity, and an increase in blood lactate levels, although the mechanisms behind these parameters and their influence on IOP remain poorly understood (40).

It should be noted that the use of different IOP measuring techniques and devices may affect IOP readings in environments with different atmospheric pressures. Albis-Donado et al. (27) reported increasing differences in IOP measurements between Goldmann applanation tonometry (GAT) and dynamic contour tonometry (DCT) with lower atmospheric pressures, with the difference in readings increasing by approximately 1 mmHg per 673 m of increased altitude above sea level. Authors concluded that the GAT may not adjust to changes in atmospheric pressure as well as DCT and hence the GAT may be less reliable at higher atmospheric pressures. The authors elaborated that DCT is able to calibrate itself by performing zeroing based on atmospheric pressure, whereas the results of applanation tonometry will be affected by changes in the absolute pressure and resistance to applanation when atmospheric pressure fluctuates (42). In contrast, Vercellin et al. (26) reported agreement between rebound and applanation tonometry IOP measurements with compression up to 4 bar, suggesting that rebound tonometry may be viable for assessing IOP within certain atmospheric pressure ranges.

Corneal thickness is another factor that has been studied in hyperbaric environments. Central corneal thickness (CCT) measurements have been known to confound tonometry readings, particularly when taken with the GAT (43, 44). Of the studies included in this review, only Mazo et al. (24) corrected IOP for CCT. Some studies (25, 28), demonstrated no significant changes in CCT during or after hyperbaric exposure, as well as with increased atmospheric pressure. Goenadi et al. (32) also did not find a correlation between CCT and IOP changes upon wearing of a diving mask. However, other studies have demonstrated CCT changes after exposure to hyperbaric environments, including Peters et al. (29), who reported slight corneal thinning following hyperbaric exposure, and Deleu et al. (23), who reported a statistically significant increase in mean CCT 30-min post-dive, which resolved 30-min later.

The use of diving masks may be expected to result in an increase in IOP due to mechanical compression of the orbits and the subsequent increase in episcleral venous pressure. However, Goenadi et al. (32) reported a small but statistically significant decrease in IOP when subjects donned a diving mask. While swimming goggles are known to elevate IOP (45), authors suggested that the larger frame of the diving mask likely allowed for a more extensive area of the mask to sit on the bony orbit, hence mitigating the pressure exerted on the periocular soft tissue and transmitted to the globe. Another study by Islam et al. did not demonstrate any significant change in IOP when subjects donned a diving dry suit (46).

This systematic review has revealed certain gaps in literature. First, none of the studies included in this review examined subjects exposed for more than 1 h at increased atmospheric pressure, nor measured the impact following repeated dives—which have been found to have subclinical ophthalmological effects (47). Second, structural and functional tests in the form of visual field testing or retinal nerve fiber layer thickness examination were not explored in any of the studies. These additional parameters may be useful in providing a better understanding of the effects of these environments on IOP, retinal nerve fiber layer health, and glaucoma. Third, likely due to feasibility and logistical considerations, most studies utilized hyperbaric chambers in their experiments. These conditions may not fully replicate the actual underwater environments experienced by divers. Fourth, the subjects included in all experiments in this review had healthy eyes which limits its applicability to glaucomatous eyes, which may exhibit a pathological response to environmental changes (48).

Limitations of this review include variations in atmospheric pressures, time intervals for measurements, and tonometry methods among the included studies. This high degree of heterogeneity among the studies may limit generalizability of the conclusions from this review. While studies have explored the relationship between

TABLE 2 Characteristics of included studies.

Author (year)	Title	Number of eyes (n)	Number of patients (n)	Age (years) mean (range)	Type of population	Methods	IOP measurement technique	IOP change (mmHg) mean (% reduction)	Pachymetry measured?	CCT at baseline (μm) mean (SD)	Final CCT (μm) mean (SD)
Deleu (2022)	Effect of SCUBA diving on ophthalmic parameters	15	15	Median age was 48.93 (28–72)	Healthy	IOP measured before diving, 30 and 60 min after a standard deep dive of 25 m depth for 25 min in a dedicated diving pool.	Air tonometry (Nidek Tonoref III)	−2.1 (−12.8%) at 30 min post-dive ($p < 0.0001$). −1.4 (−8.7%) at 60 min post-dive ($p < 0.0001$).	Yes	559.3 (27.8)	30 min post-dive: 566.5 (33.5; $p = 0.012$) 60 min post-dive: 562.9 (28.6; nonsignificant)
Mazo (2023)	Intraocular pressure changes under an atmospheric pressure spectrum in a multiplace hyperbaric chamber	48	24	30.6 (23–40)	Healthy	IOP measured in hyperbaric chamber at 0, 20, 40, 60, 50, 30, and 0 feet, respectively. 10 min spent between each measurement.	Tonopen XL	−1.2 (−8.4%) at 2.8 ATA (60 feet) ($p = 0.012$). Then −2.4 (−16.8%) after rising to 1.91 ATA (30 feet) ($p < 0.001$). Then −1.2 (−8.4%) when ending at 1 ATA (0 feet) ($p = 0.012$).	Yes	543.7 (30.4)	N/A
Van de Veire (2008)	Influences of atmospheric pressure and temperature on intraocular pressure	54	27	23.8 (18–44)	Healthy	IOP measured in hyperbaric chamber at 1 and 2 bar at 24 and 28 degrees celsius. It took 10 min to switch bar, 10–20 min for temperature change, and 5 min were given after each change for acclimatization.	Perkins applanation tonometry	Right eye: −1.1 (−9.3%) at 2 bar ($p = 0.024$). Left eye: −1.4 (−12.0%) at 2 bar (0.0006).	Yes	Not mentioned	N/A

(Continued)

10.3389/fmed.2024.1365259

TABLE 2 (Continued)

Author (year)	Title	Number of eyes (n)	Number of patients (n)	Age (years) mean (range)	Type of population	Methods	IOP measurement technique	IOP change (mmHg) mean (% reduction)	Pachymetry measured?	CCT at baseline (μm) mean (SD)	Final CCT (μm) mean (SD)
Vercellin (2021)	Agreement of rebound and applanation tonometry intraocular pressure measurements during atmospheric pressure change	12	12	43.6	Healthy	IOP measured in hyperbaric chamber with rebound and applanation tonometry at 1, 2, 3, and 4 bar during compression and 3 and 2 bar during decompression. 5 min rest period at each pressure.	Icare rebound tonometer Perkins applanation tonometer	Applanation: −3.6 (−26.1%) at 4 bar ($p < 0.0001$). Rebound: −3 (−19.6%) at 4 bar ($p < 0.0001$).	Yes	587.4 (12.5)	N/A
Albis-Donado (2020)	Effects of acute atmospheric pressure changes on dynamic contour tonometry and Goldmann applanation tonometry in normal individuals: a pilot study	44	22	33.4 (25–62)	Healthy	IOP measured with GAT and DCT in hyperbaric chamber at 1, 1.1, 1.2, and 1.25 QATM. Measurements taken after 5 min at each pressure.	Goldmann applanation tonometry Dynamic contour tonometry	GAT: +0.16 (+1.3%) at 1.25 QATM. DCT: −1.5 (−8.9%) at 1.25 QATM.	No	Not mentioned	N/A
Huang (2002)	Refractive change in response to acute hyperbaric stress in refractive surgery patients	20	10	52 (46–57) in RK group, 47 (45–48) in LASIK group, and 38 (21–48) in the control group.	6 eyes with previous RK. 5 eyes with previous LASIK. 9 healthy control eyes.	IOP measured before, during, and after spending 15 min at 4 ATM in a hyperbaric chamber.	Tonopen XL	No significant change in IOP for any group.	Yes	RK group: 564 (43) LASIK group: 501 (38) Control group: 528 (17)	RK group: 566 (44) LASIK group: 503 (39) Control group: 527 (16) (nonsignificant)

(Continued)

10.3389/fmed.2024.1365259

TABLE 2 (Continued)

Author (year)	Title	Number of eyes (n)	Number of patients (n)	Age (years) mean (range)	Type of population	Methods	IOP measurement technique	IOP change (mmHg) mean (% reduction)	Pachymetry measured?	CCT at baseline (μm) mean (SD)	Final CCT (μm) mean (SD)
Peters (1999)	Effect of increased atmospheric pressure on radial keratotomy	8	4	42.5 in control group and 51.5 in RK group	4 eyes with previous RK. 4 healthy control eyes.	IOP measured at baseline and in a hyperbaric chamber after 1 h at 3 ATM.	Unspecified	No change in mean IOP for either group.	Yes	Not mentioned	N/A
Goenadi (2016)	The effect of a diving mask on intraocular pressure in a healthy population	40	20	29.7	Healthy	IOP measured at baseline and with a diving mask (lens removed).	AVIA Tonopen	−0.4 (−2.5%) with mask on ($p < 0.05$).	Yes	544.4 (43.5)	N/A
Bojić (2001)	Acute angle-closed glaucoma and meteorological factors in split, croatia	73	73	57 women with mean age of 67.8 and 16 men with mean age 64.9.	Eyes with acute closed angle glaucoma.	Atmospheric pressure, sunshine hours, and air temperature data were correlated with incidence of acute closed angle glaucoma attacks.	N/A	N/A	N/A	N/A	N/A

IOP, intraocular pressure; CCT, central corneal thickness; SD, standard deviation; ATA, atmosphere absolute; QATM, Queretaro atmospheric pressure; ATM, atmospheric pressure.

10.3389/fmed.2024.1365259

hyperbaric environments and IOP, the precise mechanisms underlying these observations and findings remain poorly understood. More longitudinal studies performed under actual diving environmental conditions may be considered to more accurately assess the effect of diving on IOP and glaucoma.

Nonetheless, to the best knowledge of the authors, this systematic review is the first of its kind to consolidate current literature on the relationship between diving, hyperbaric environments and IOP. As diving becomes increasingly popular and the prevalence of glaucoma continues to rise, information in this niche area of ophthalmology and underwater medicine will become more valuable in the clinical care of divers with, or at risk of glaucoma.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

PL: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. SL: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. BB: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. DM: Writing – review & editing. SD: Writing – review & editing. BA: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This publication was made possible by a generous contribution from Joyce Baker to the Mayo Clinic Ophthalmology Department. Funding played no role in the design or conduct of the research in this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

References

1. Buzzacott P, Schiller D, Crain J, Denoble PJ. Epidemiology of morbidity and mortality in US and Canadian recreational scuba diving. *Public Health*. (2018) 155:62–8. doi: 10.1016/j.puhe.2017.11.011

2. Lippmann J. A review of snorkelling and scuba diving fatalities in Queensland, Australia, 2000 to 2019. *Diving Hyperb Med*. (2022) 52:108–18. doi: 10.28920/dhm52.2.108-118

3. Kovacs CR. Scuba diving and the stress response: considerations and recommendations for professional and recreational divers. *Int Marit Health*. (2023) 74:186–91. doi: 10.5603/imh.91707

4. Salahuddin M, James LA, Bass ES. SCUBA medicine: a first-responder's guide to diving injuries. *Curr Sports Med Rep*. (2011) 10:134–9. doi: 10.1249/JSR.0b013e31821b08ff

5. Barreiros P, Haddad V, Barreiros JP. Description of an eye barotrauma in scuba diving with clinical discussion. *J Coast Life Med*. (2017) 5:126–8. doi: 10.12980/jclm.5.2017J6-264

6. Butler FK, Gurney N. Orbital hemorrhage following face-mask barotrauma. *Undersea Hyperb Med*. (2001) 28:31–4.

7. Rudge FW. Ocular barotrauma caused by mask squeeze during a scuba dive. *South Med J*. (1994) 87:749–50. doi: 10.1097/00007611-199407000-00015

8. Iordanidou V, Gendron G, Khammari C, Rodallec T, Baudouin C. Choroidal ischemia secondary to a diving injury. *Retin Cases Brief Rep*. (2010) 4:262–5. doi: 10.1097/ICB.0b013e3181a3b9d6

9. Merle H, Drault JN, Gerard M, Alliot E, Mehdaoui H, Elisabeth L. Retinal vein occlusion and deep-sea diving. *J Fr Ophtalmol*. (1997) 20:456–60.

10. Butler FK. Diving and hyperbaric ophthalmology. *Surv Ophthalmol*. (1995) 39:347–66. doi: 10.1016/S0039-6257(05)80091-8

11. Lippmann J, Mc DTD, Stevenson C, Williams J, Mitchell SJ. Diving with pre-existing medical conditions. *Diving Hyperb Med*. (2017) 47:180–90. doi: 10.28920/dhm47.3.180-190

12. 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) 121:2081–90. doi: 10.1016/j.ophtha.2014.05.013

13. Luo X, Shen YM, Jiang MN, Lou XF, Shen Y. Ocular blood flow autoregulation mechanisms and methods. *J Ophthalmol*. (2015) 2015:864871:1–7. doi: 10.1155/2015/864871

14. Kim KE, Oh S, Baek SU, Ahn SJ, Park KH, Jeoung JW. Ocular perfusion pressure and the risk of open-angle Glaucoma: systematic review and Meta-analysis. *Sci Rep*. (2020) 10:10056. doi: 10.1038/s41598-020-66914-w

15. Westerweel PE, Rienks R, Sakr A, Taher A. Diving with hypertension and antihypertensive drugs. *Diving Hyperb Med*. (2020) 50:49–53. doi: 10.28920/dhm50.1.49-53

16. Fabiani C, Li Voti R, Rusciano D, Mutolo MG, Pescosolido N. Relationship between corneal temperature and intraocular pressure in healthy individuals: a clinical thermographic analysis. *J Ophthalmol*. (2016) 2016:1–7. doi: 10.1155/2016/3076031

17. Ersanli D, Akin T, Yildiz S, Akin A, Bilge AH, Uzun G. The effect of hyperbaric oxygen on intraocular pressure. *Undersea Hyperb Med*. (2006) 33:1–4.

18. Gallin-Cohen PF, Podos SM, Yablonski ME. Oxygen lowers intraocular pressure. *Invest Ophthalmol Vis Sci*. (1980) 19:43–8.

19. Hosking SL, Harris A, Chung HS, Jonescu-Cuypers CP, Kagemann L, Roff Hilton EJ, et al. Ocular haemodynamic responses to induced hypercapnia and hyperoxia in glaucoma. *Br J Ophthalmol*. (2004) 88:406–11. doi: 10.1136/bjo.2002.008995

20. Muir ER, Chandra SB, Narayanan D, Zhang V, Zhang I, Jiang Z, et al. Effects of chronic mild hyperoxia on retinal and choroidal blood flow and retinal function in the

DBA/2J mouse model of glaucoma. *PLoS One*. (2022) 17:e0266192. doi: 10.1371/journal.pone.0266192

21. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. (2009) 62:1006–12. doi: 10.1016/j.jclinepi.2009.06.005

22. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. (2016) 355:i4919. doi: 10.1136/bmj.i4919

23. Deleu L, Catherine J, Postelmans L, Balestra C. Effect of SCUBA diving on ophthalmic parameters. *Medicina*. (2022) 58:408. doi: 10.3390/medicina58030408

24. Mazo SEM, Peña FY, Ramírez JVO. Intraocular pressure changes under an atmospheric pressure spectrum in a multiplace hyperbaric chamber. *Arq Bras Oftalmol*. (2023) 87:e2022-0085. doi: 10.5935/0004-2749.2022-0085

25. Van de Veire S, Germonpre P, Renier C, Stalmans I, Zeyen T. Influences of atmospheric pressure and temperature on intraocular pressure. *Invest Ophthalmol Vis Sci*. (2008) 49:5392–6. doi: 10.1167/iovs.07-1578

26. Vercellin AV, Harris A, Siesky B, Zukerman R, Tanga L, Carnevale C, et al. Agreement of rebound and applanation tonometry intraocular pressure measurements during atmospheric pressure change. *PLoS One*. (2021) 16:e0259143. doi: 10.1371/journal.pone.0259143

27. Albis-Donado O, Rodríguez-Camacho B, Bhartiya S, Ramírez-Neria P, López-Star E, González-Daher P, et al. Effects of acute atmospheric pressure changes on dynamic contour tonometry and Goldmann Applanation tonometry in Normal individuals: a pilot study. *J Glaucoma*. (2020) 29:756–60. doi: 10.1097/IJG.0000000000001592

28. Huang ET, Twa MD, Schanzlin DJ, Van Hoesen KB, Hill M, Langdorf MI. Refractive change in response to acute hyperbaric stress in refractive surgery patients. *J Cataract Refract Surg*. (2002) 28:1575–80. doi: 10.1016/S0886-3350(02)01362-7

29. Peters NT, Borer RC Jr, Strauss MB. Effect of increased atmospheric pressure on radial keratotomy. *J Cataract Refract Surg*. (1999) 25:1620–3. doi: 10.1016/S0886-3350(99)00235-7

30. Hillman JS, Turner JD. Association between acute glaucoma and the weather and sunspot activity. *Br J Ophthalmol*. (1977) 61:512–6. doi: 10.1136/bjo.61.8.512

31. Bojić L, Vojniković B, Karelović D, Jukić-Lesina T. Acute angle-closed glaucoma and meteorological factors in Split, Croatia. *Coll Antropol*. (2001) 25:105–9.

32. Goenadi CJ, Law DZ, Lee JW, Ong EL, Chee WK, Cheng J. The effect of a diving mask on intraocular pressure in a healthy population. *Case Rep Ophthalmol*. (2016) 7:328–32. doi: 10.1159/000446423

33. Hartmann A, Grabitz SD, Hoffmann EM, Wild PS, Schmidtmann I, Lackner KJ, et al. Intraocular pressure and its relation to climate parameters—results from the Gutenberg health study. *Invest Ophthalmol Vis Sci*. (2023) 64:15. doi: 10.1167/iovs.64.7.15

34. Zhu Y, Li L, Han B, Sun X, Chen R, Lei Y, et al. Low ambient temperature and temperature drop as novel risk factors of acute glaucoma: a case-crossover study. *Environ Sci Pollut Res Int*. (2023) 30:56513–21. doi: 10.1007/s11356-023-26235-7

35. Casson RJ. Anterior chamber depth and primary angle-closure glaucoma: an evolutionary perspective. *Clin Experiment Ophthalmol*. (2008) 36:70–7. doi: 10.1111/j.1442-9071.2008.01672.x

36. Buzzacott P, Pollock NW, Rosenberg M. Exercise intensity inferred from air consumption during recreational scuba diving. *Diving Hyperb Med*. (2014) 44:74–8.

37. Alfaqeeh F, Djemai H, Hammad R, Hammad S, Noirez P, Dabayebeh IM. Effect of aerobic exercise at different intensities on intraocular pressure in young males. *J Glaucoma*. (2022) 31:868–73. doi: 10.1097/IJG.0000000000002110

38. Hong J, Zhang H, Kuo DS, Wang H, Huo Y, Yang D, et al. The short-term effects of exercise on intraocular pressure, choroidal thickness and axial length. *PLoS One*. (2014) 9:e104294. doi: 10.1371/journal.pone.0104294

39. Kawae T, Nomura T, Iwaki D, Nakashima Y, Fudeyasu K, Kataoka H, et al. Intraocular pressure fluctuation during aerobic exercise at different exercise intensities. *Healthcare (Basel)*. (2022) 10:1196. doi: 10.3390/healthcare10071196

40. Risner D, Ehrlich R, Kheradiya NS, Siesky B, McCranor L, Harris A. Effects of exercise on intraocular pressure and ocular blood flow: a review. *J Glaucoma*. (2009) 18:429–36. doi: 10.1097/IJG.0b013e31818fa5f3

41. Yan X, Li M, Song Y, Guo J, Zhao Y, Chen W, et al. Influence of exercise on intraocular pressure, Schlemm's canal, and the trabecular meshwork. *Invest Ophthalmol Vis Sci*. (2016) 57:4733–9. doi: 10.1167/iovs.16-19475

42. Boehm AG, Weber A, Pillunat LE, Koch R, Spoerl E. Dynamic contour tonometry in comparison to Intracameral IOP measurements. *Invest Ophthalmol Vis Sci*. (2008) 49:2472–7. doi: 10.1167/iovs.07-1366

43. Brandt JD. Corneal thickness in glaucoma screening, diagnosis, and management. *Curr Opin Ophthalmol*. (2004) 15:85–9. doi: 10.1097/00055735-200404000-00004

44. Ku JYF, Danesh-Meyer HV, Craig JP, Gamble GD, McGhee CNJ. Comparison of intraocular pressure measured by Pascal dynamic contour tonometry and Goldmann applanation tonometry. *Eye*. (2006) 20:191–8. doi: 10.1038/sj.eye.6701849

45. Morgan WH, Cunneen TS, Balaratnasingam C, Yu DY. Wearing swimming goggles can elevate intraocular pressure. *Br J Ophthalmol*. (2008) 92:1218–21. doi: 10.1136/bjo.2007.136754

46. Islam Y, Spears M, Brennan M, Pitkin A, Covington D. Effect of drysuit seals on intraocular pressure in non-immersed scuba divers. *Undersea Hyperb Med*. (2023) 50:307–12. doi: 10.22462/01.01.2023.26

47. Macarez R, Dordain Y, Hugon M, Kovalski JL, Guigon B, Bazin S, et al. Retentissement à long terme de la plongée sous-marine sur le champ visuel, la vision des couleurs et la sensibilité au contraste du plongeur professionnel. *J Fr Ophtalmol*. (2005) 28:825–31. doi: 10.1016/S0181-5512(05)81000-9

48. Doucette LP, Rasnitsyn A, Seifi M, Walter MA. The interactions of genes, age, and environment in glaucoma pathogenesis. *Surv Ophthalmol*. (2015) 60:310–26. doi: 10.1016/j.survophthal.2015.01.004

frontiers | Frontiers in Medicine

TYPE Review
PUBLISHED 06 May 2024
DOI 10.3389/fmed.2024.1360051

OPEN ACCESS

EDITED BY
Georgios D. Panos,
Nottingham University Hospitals NHS Trust, United Kingdom

REVIEWED BY
Matteo Sacchi,
IRCCS MultiMedica, Italy
Je Hyun Seo,
VHS Medical Center, Republic of Korea
Maddalena De Bernardo,
University of Salerno, Italy

*CORRESPONDENCE
Li Tang
✉ tangli-1a@wchscu.cn

†These authors have contributed equally to this work and share first authorship

RECEIVED 22 December 2023
ACCEPTED 22 April 2024
PUBLISHED 06 May 2024

CITATION
Gan L, Wang L, Chen J and Tang L (2024) Complications of XEN gel stent implantation for the treatment of glaucoma: a systematic review.
Front. Med. 11:1360051.
doi: 10.3389/fmed.2024.1360051

Complications of XEN gel stent implantation for the treatment of glaucoma: a systematic review

Lu Gan[1,2†], Lixiang Wang[1†], Jun Chen[1] and Li Tang[1*]

[1]Department of Ophthalmology, West China Hospital, Sichuan University, Chengdu, China, [2]Department of Ophthalmology, West China School of Public Health and West China Fourth Hospital, Sichuan University, Chengdu, China

Aim: This study was aimed to summarize the complications and their management associated with XEN gel stent implantation.

Methods: A systematic review of literature was conducted using Medline (via PubMed), EMBASE, the Cochrane Library databases, and China National Knowledge Infrastructure, from their inception to February 1, 2024.

Results: A total of 48 studies published between 2017 and 2024 were identified and included in the systematic review, including 16 original studies (retrospective or prospective clinical studies), 28 case reports, and 4 case series, which followed patients for up to 5 years. Early postoperative complications of XEN gel stent implantation include hypotony maculopathy (1.9–4.6%), occlusion (3.9–8.8%), suprachoroidal hemorrhage (SCH), choroidal detachment (0–15%), conjunctival erosion, and exposure of the XEN gel stent (1.1–2.3%), wound and bleb leaks (2.1%) and malignant glaucoma (MG) (2.2%). Mid-postoperative complications of XEN gel stent implantation included migration of XEN (1.5%), ptosis (1.2%), endophthalmitis (0.4–3%), macular edema (1.5–4.3%), hypertrophic bleb (8.8%) and subconjunctival XEN gel stent fragmentation (reported in 2 cases). Late postoperative complications reported in cases included spontaneous dislocation and intraocular degradation.

Conclusion: XEN gel stent implantation is a minimally invasive glaucoma surgery (MIGS) procedure for glaucoma, known for its potential to minimize tissue damage and reduce surgical duration. However, it is crucial to note that despite these advantages, there remains a risk of severe complications, including endophthalmitis, SCH, and MG. Therefore, postoperative follow-up and early recognition of severe complications are essential for surgical management.

KEYWORDS

XEN gel stent, glaucoma, complications, surgery, XEN 45 gel stent, review

Introduction

Glaucoma is the leading cause of irreversible blindness, and an estimated 111.8 million people aged 40–80 years old will be affected by glaucoma globally in 2040 (1, 2). The only confirmed modifiable glaucoma risk factor is elevated intraocular pressure (IOP). Multiple methods to reduce IOP have been explored and verified, including medications, laser, and surgery, with new therapies continuously revolutionizing glaucoma treatment (3). Trabeculectomy is a classical surgical method for glaucoma and has been the standard

procedure in many medical centers for decades, with sound evidence supporting its long-term efficacy and safety (4, 5). However, severe complications, including malignant glaucoma (MG), bleb-related infection, and expulsive choroidal hemorrhage (6), can occur.

The recent development of new devices that are significantly less invasive, collectively termed minimally invasive glaucoma surgery (MIGS), offers a new perspective on reducing IOP with lower risk, shorter operating times, and faster recovery (7). It is performed using a less invasive "*ab interno*" approach, which reduces damage to surrounding tissues and preserves the conjunctiva (8, 9). Currently, the XEN gel stent (Allergan PLC, Irvine, CA, United States) has been the only MIGS device that allows subconjunctival filtration and has been used to treat open-angle glaucoma (10). However, it has also been reported in some case series to be effective in treating angle closure glaucoma (11), uveitic glaucoma (12),neovascular glaucoma (13), iridocorneal endothelial (ICE) syndrome (14), and steroid-induced glaucoma (15). The XEN gel stent comes in three different diameters (45, 63, and 140 μm) to provide varying levels of IOP control.

The XEN45 is a tubular implant with a total length of 6 mm and an inner diameter of 45 μm, made of cross-linked porcine gelatin, a type of hydrophilic collagen. The implant is rigid when dry and becomes soft within 1–2 min when hydrated, adapting to the tissue shape, thus preventing migration and potential erosion. Studies have shown that the gel stent is approximately 100 times more flexible than the silicone tubing used in traditional tube–shunt surgery (16). The implant is housed in a disposable preloaded handheld inserter designed specifically for *ab interno* surgical implantation (7) (Figure 1A). It was designed based on principles of laminar fluid dynamics (Hagen–Poiseuille equation) to prevent early postoperative hypotony, as demonstrated by recent experimental studies (19). The rate of aqueous humor turnover is estimated to be 1.0–1.5% of the anterior chamber (AC) volume per minute, which is 2.4 ± 0.6 μL/min (mean ± standard deviation [SD], daytime measurements in adults aged 20–83 years), and the XEN45 provides a flow of 1.2 μL/min (at a 5 mmHg pressure gradient), offering approximately 6–8 mmHg flow resistance, which reduces the risk of hypotony (16).

The *ab interno* procedure involves inserting the Xen Gel Stent through a clear corneal incision, positioning it within the trabecular meshwork and extending it into the subconjunctival space. By creating a new drainage pathway that bypasses the trabecular meshwork, the Xen implant facilitates aqueous humor outflow from the anterior chamber to the subconjunctival space, where it is absorbed by the surrounding tissue (20). XEN gel stent implantation directly drains aqueous humor from the AC to the subconjunctival space, bypassing the resistance of the dysfunctional trabecular meshwork (16). XEN gel stent implantation has been reported to provide up to 56% reduction in IOP and a decrease in the average number of medications used by 2.7 at 12 months (21). Furthermore, it has a lower complication rate compared to conventional trabeculectomy (22). The advantages of XEN gel stent implantation include minimally invasive access through *ab interno*/*ab externo* approaches, preservation of the sclera and conjunctiva, better preservation of corneal endothelium, elimination of the need for iridectomy and sutures, and shorter surgery time (23). Additionally, XEN gel stent implantation can be performed alone or concurrently with cataract surgery (24). General recommendations for preoperative assessment, surgical technique, and postoperative follow-up of XEN gel stent implantation have been published (25). However, despite numerous clinical studies and case reports providing relevant information, a comprehensive summary of complications associated with this surgical method, especially rare ones, has not been compiled. In this systematic review, we aim to comprehensively summarize all complications of XEN 45 gel stent implantation, including their incidence, risk factors, available treatments, and preventive measures.

Abbreviations: Nd:YAG, neodymium-doped yttrium aluminum garnet; MIGS, minimal invasive glaucoma surgery; ICE, iridocorneal endothelial syndrome; IOP, intraocular pressure; HM, hypotony maculopathy; SCH, suprachoroidal hemorrhage; CD, choroidal detachment; MG, malignant glaucoma; ME, macular edema; AC, anterior chamber; SD, standard deviation.

Methods

Following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) (26), a comprehensive search of Medline (via Pubmed), EMBASE, the Cochrane Library databases, and China National Knowledge Infrastructure were performed from their conception to February 1st, 2024. The search was independently performed by two investigators, Lu Gan and Lixiang Wang, using a combination of keywords in English or their corresponding Chinese terms, including "XEN," "glaucoma," "micro-stent," "gel implant," and "MIGS." In addition to the computer-assisted search, the references in the articles retrieved from this bibliographic search were also manually searched and studied. The detailed steps and results of the search strategy are presented in Figure 2.

Studies published in English or Chinese were included in the review. The following criteria were used to select studies for the systematic review: (1) The study should be a prospective or retrospective cohort study, case report, case series, or letter to the editor. Reviews, editorial materials, and meeting abstracts were not included. (2) The surgery of interest should be XEN45 gel stent implantation, regardless of whether it was performed in combination with other surgeries (e.g., cataract surgery). (3) The post-operational complications should be reported. Exclusion criteria were as follows: (1) Animal studies. (2) Incomplete report of surgical complications or lack of essential data for analysis. (3) XEN63. (4) XEN140.

The data extracted from the included studies included author names, publication year, publication types, number of patients, age, sex, surgical method, surgical complications, and follow-up results. The data extraction process was independently conducted by two reviewers, Lu Gan and Lixiang Wang.

Systematic review

A total of 48 studies published between 2017 and 2024 were identified and included in the systematic review, including 16 original studies (retrospective or prospective clinical studies), 28 case reports, and 4 case series. Patients were followed for up to 5 years after XEN

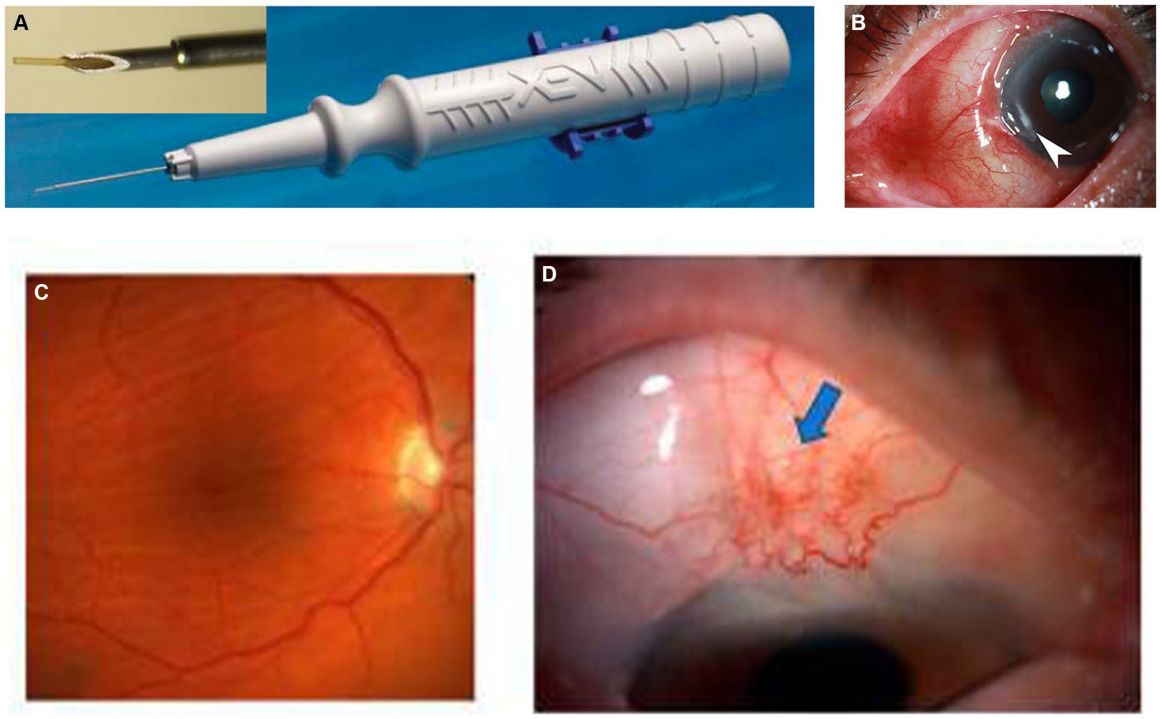

FIGURE 1
(A) Grover et al. (17). **(B)** Hypertrophic bleb. **(C,D)** Kosior-Jarecka et al. (18).

gel stent implantation. Below, we provided a summary of perioperative complications, their mechanisms, and management. A brief summary of surgical complications is listed in Table 1.

Early postoperative period (0–30 days)

Occlusion of XEN

Occlusion of the XEN stent lumen is a relatively common complication that can occur at various times after surgery, with a reported incidence between 3.9 and 8.8% (27, 28). The occluding objects can be blood clots, fibrous scar tissue, or the iris (29, 85) due to the stent's small internal lumen (29, 30, 86, 87). In Asian eyes with a relatively shallow AC and crowded anterior segment, there is an increased likelihood of anatomical obstruction of the XEN implant by the iris. Specialists have proposed several potential causes for this occlusion event, including the posterior positioning of the XEN gel stent opening, which results in a higher risk of iris occlusion; the short length of insertion into the AC; overactive filtration leading to local turbulence in the early postoperative period; and the patient habit of rubbing the surgical eye, resulting in shifting of the floppy iris. The approach to relieving occlusion depends on the etiology and nature of the occluding objects. For iris-related occlusion, argon laser peripheral iridoplasty or low energy neodymium-doped yttrium aluminum garnet (Nd:YAG) laser lysis of the blocking iris is commonly used to alleviate local occlusion (30). When the XEN gel stent implant is blocked with fibrin or blood clots, the occluding objects can be removed through intracameral injection of tissue plasminogen activator, ablation with Nd:YAG laser, or surgical clamping using internal limiting membrane forceps or vitreous scissors. Alternatively, surgery with a 10–0 nylon suture may be performed to recanalize the XEN gel stent (29, 31–34).

Hypotony maculopathy

HM is a relatively rare complication associated with XEN gel stent implantation that can occur within less than 1 week or more than 1 month, with a reported incidence of 1.9–4.6% (27, 62) (Figures 1C,D). Macular hypotony is characterized by a decrease in visual acuity caused by macular folds, retinal edema, papilledema, and vascular tortuosity. It is believed that low IOP levels cause thickening of the perifoveal choroid and sclera, resulting in their central displacement, which is visible as macular folds. Over time, these changes lead to photoreceptor damage and become irreversible, which may limit the recovery of visual function even after restoring normal IOP (35, 88). Several risk factors for hypotony after glaucoma surgery have been identified, including myopia, young age, the use of antimetabolites, pre-existing inflammation, aphakia, and old age accompanied by a thin conjunctiva and thinner central corneal thickness (36–38). Patients with high myopia are at a higher risk of developing ocular hypotony due to their thin scleral wall, which may result in potential leakage of aqueous humor from the scleral incision adjacent to the site of XEN gel stent insertion (39). Treatment options for hypotony after glaucoma surgery, mainly caused by over-filtrating blebs, include conservative management with topical autologous serum (40), transconjunctival compressive sutures (18), bleb injection of autologous blood (41) or viscoelastic material (42), as well as AC injection of viscoelastic material (43) or gas (44). Conservative management usually has minor and short-lasting effects. Surgical management involves transconjunctival flap suturing (45, 46), excision of thin blebs and conjunctival advancement (35), patch grafting using

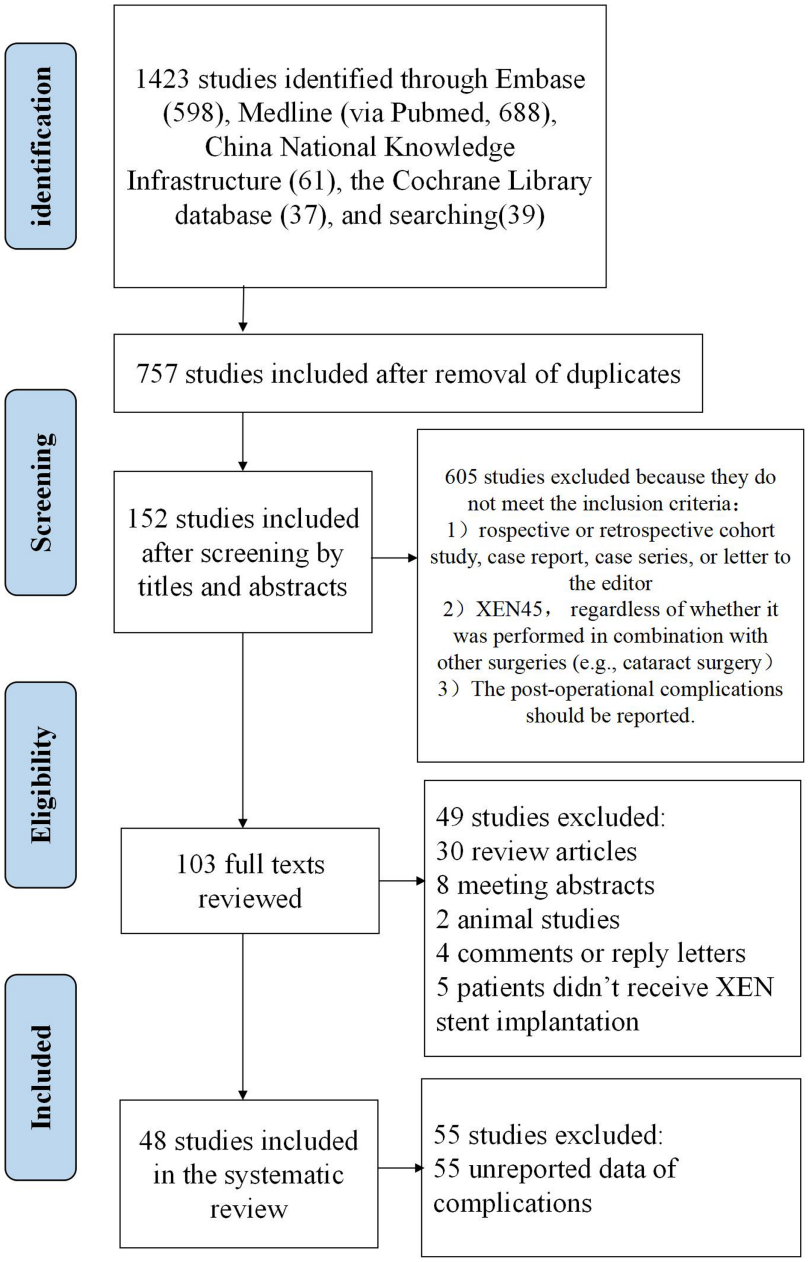

FIGURE 2
The flow diaphragm of study selection for the systematic review.

donor sclera (47, 89), donor cornea (90), as well as autologous conjunctiva (91, 92).

Suprachoroidal hemorrhage

SCH is characterized by the accumulation of blood in the potential space between the choroid and the sclera, originating from the long/short posterior ciliary artery. It is a potentially sight-threatening but rare complication of XEN gel stent implantation, which can occur both intraoperatively or postoperatively. A number of potential risk factors have been linked to the development of intra-/post-operative SCH, including high preoperative IOP, severe postoperative hypotony, aphakia, pseudophakia, anticoagulation, white race, prior intraocular surgery, low postoperative IOP, systemic hypertension, ischemic heart disease, as well as pulmonary disease (93, 94). The exact pathophysiology of SCH is not fully understood, but the increased preoperative IOP, sudden decreased IOP, and postoperative hypotony are accepted risk factors associated with this complication in XEN implantation (48). Several SCH patients have been reported to be related with XEN gel stent implantation, and some cases were complicated with retinal detachment requiring surgical interventions (49–52). Wang et al. reported an 86-year-old patient on rivaroxaban due to atrial fibrillation who developed "kissing" SCH 3 days after the surgery resulting from ocular hypotony, which resolved with prompt surgical drainage (49). A sudden decease in IOP within or post-surgery is identified as the most significant risk factor. Once SCH occurs, various methods should be used to control the bleeding and

TABLE 1 Summary of surgical complications of XEN gel stent implantation.

Complications	Incidence	Onset time	Management	References
Early postoperative period (0–30 days)				
Occlusion	3.9–8.8%	Different times after surgery	Nd: YAG laser ablation, intracameral plasminogen activator, surgical removal	(27–34)
Hypotony maculopathy	1.9–4.6%	<1 week or > 1 month	Conservative management (transconjunctival compressive sutures, bleb injection of autologous blood or viscoelastic material, and intracameral injection of viscoelastic material or gas) Surgical management (transconjunctival flap suturing, excision of thin blebs and conjunctival advancement, patch grafting)	(18, 35–47)
Suprachoroidal hemorrhage	N.A.	Both intraoperatively and postoperatively	surgical intervention (either by choroidal tap or par plana vitrectomy)	(48–52)
Choroidal detachment	0–15%	1 week	Spontaneously resolve or use topical or oral steroids and cycloplegics.	(17, 27, 53–56)
Conjunctival erosion and exposure of XEN gel stent	1.1–2.3%	Early after the implantation surgery or months later	Conservative methods (pressure patching, wearing contact lenses, crosslinking, and application of vitamin A ointments) Surgical management conjunctival grafting, *ab interno* repositioning of XEN gel stent through the anterior chamber, and direct suturing of the conjunctival defect	(57–61)
Wound and bleb leaks	2.1%	2 weeks or more than 3 months	Conservative treatment (therapeutic contact lens, autologous blood injection, injection of fibrin glue, application of cryotherapy, and laser treatment) Surgical procedures (amniotic membrane transplantation, conjunctival autograft, and conjunctival sliding)	(61–65)
Malignant glaucoma	2.2%	4 days	Laser capsulotomy, hyaloidotomy, or iridotomy, or by surgical methods such as vitrectomy or posterior capsulotomy	(66–69)
Ptosis	1.2%	Early after surgery	Spontaneously resolve, but surgical management is needed for persistent ptosis	(62)
Mid-postoperative period (1–6 months)				
XEN gel stent migration	1.5%	4 months	Replace with a new XEN stent	(17, 70)
Endophthalmitis	0.4–3%	More than 3 months	Removal of exposed stent, topical, systemic, and bleb revision	(12, 27, 55, 71–73)
Macular edema	1.5–4.3%	≥1 month	Spontaneously resolve	(62, 74, 75)
Hypertrophic bleb	8.8%	Months to years after surgery	Conservative therapies (injection of autologous platelet concentrates, blockage with viscoelastic of the *ab-interno* stent, and sealing with a tissue adhesive) Surgical management (scleral fixation sutures, bleb revision surgery).	(76–80)
Subconjunctival XEN gel stent fragmentation	2 cases	2–3 months	Observation or replace with a new XEN stent	(81, 82)
Late postoperative period (from 6 months)				
Late spontaneous dislocation	One case	6 months	Replace with a new XEN stent	(83)
Intraocular degradation	One case	3 years	Replace with a new XEN stent	(84)

preserve eyesight alongside the eyeball. Greater emphasis should be placed on preventive measures, and prompt action should be taken to close the wound. If the bleeding cannot be controlled, the sclera can be incised at a distance of 8–10 mm behind the limbus, which may allow for salvage of the SCH (95, 96). However, whether visual outcomes of early surgical intervention (via choroidal tap/par plana vitrectomy) turn out better in contrast to those of conservative management is still under debate. Particularly for cases with limited SCH, a wait-and-see strategy for the spontaneous absorption of bleeding is a reasonable choice, but close follow-up is essential (51).

For patients with known risk factors, including old age, anticoagulant use, and high IOP before surgery, SCH should be anticipated and promptly managed.

Choroidal detachment

CD is characterized by an abnormal accumulation of either blood or serum in the suprachoroidal space, which is located between the choroid and the sclera. Under physiological conditions, this space represents a potential volume owing to the close adjacency of the choroid and sclera. Under pathological conditions, fluid accumulation in this space may occur based on the changes in ocular fluid dynamics, specifically the equilibrium between hydrostatic and oncotic pressure. The incidence of CD following XEN gel stent implantation surgery varies from 0 to 15% in different studies and is considered a relatively common complication in some medical centers (17, 27, 53–56). The average time between XEN implantation and the onset of CD is approximately 1 week (56). Low post-operative IOP is a well-established risk factor for CD after glaucoma filtering surgeries. Patients who are taking multiple IOP-lowering medications before surgery are at an increased risk of developing CD after XEN gel stent implantation (97–99). The use of mitomycin C (MMC) may directly harm the ciliary epithelium, leading to decreased secretion. Additionally, the incidence of CD increases with age and is more frequent in the elderly, since their thin scleral wall makes the vortex veins susceptible to compression and leakage under increased venous pressure (56, 97, 99). The prognosis for CD is generally favorable, with most cases experiencing complete resolution within 5–30 days after onset. Patients may experience spontaneous resolution or use topical or oral steroids and cycloplegics as treatment options.

Conjunctival erosion and exposure of XEN gel stent

The erosion of the conjunctiva and extrusion of the XEN gel stent may occur shortly after the implantation surgery or months later. This mechanical complication has been reported in several studies (57, 100–102). Potential mechanisms for the initial conjunctival erosions include: (1) the administration of the anti-metabolite MMC; (2) the *ab interno* approach; (3) the subconjunctival position; (4) prolonged use of topical anti-glaucoma medications; as well as (5) mechanical stress, for instance, from elderly patients rubbing their eyes with their hands. The use of anti-metabolites can enhance the success rate of filtering surgery by mitigating the wound-healing process, yet it may increase the risk of bleb-related complications, like a thin-walled cystic bleb or surgically induced necrotizing scleritis (57, 58, 103). Since the XEN gel stent is implanted using the *ab interno* approach without the need for conjunctival dissection or sutures, there is a risk of malposition of the distal end of the implant. Continuous friction may then lead to conjunctival erosion and exposure of the stent (59). On the other hand, the application of topical anti-proliferative agents like MMC, to prevent conjunctival scarring and improve the success rate of glaucoma filtering surgery, is associated with the formation of thin-walled, cystic filtration blebs and may increase the risk of XEN gel exposure (104). Conservative methods, including pressure patching, wearing contact lenses, crosslinking, and application of vitamin A ointments remain the feasible way to manage bleb leakage (60, 61). When conservative methods fail, surgical management techniques such as the use of free conjunctival autograft, amniotic membrane graft, *ab interno* repositioning of the XEN gel stent through the AC, along with the direct suturing of the conjunctival defect have been shown to effectively repair the leaking conjunctiva and restore functional bleb (57–59). However, recurrent bleb leakage and exposure of the implant can still occur, making management challenging. Olate-Pérez et al. reported a case of managing a patient with conjunctival perforation that occurred 18 months after XEN gel stent implantation. The stent broke as the surgeon attempted to track the short distal end of the stent from the conjunctival side and was unable to be removed (57, 105). Therefore, caution should be taken during the implantation procedure, and the use of a fixation suture may be helpful, although further study is needed.

Bleb leakage

Bleb leakage is an uncommon but potentially sight-threatening complication of XEN gel stent implantation, with a reported incidence of 2.1% (62). Persistent conjunctival bleb leakage may cause over-infiltration and ocular hypotony, increasing the risk of infection, stent displacement, and endophthalmitis. During the surgery, the application of adjunctive antifibrotic agents such as mitomycin-C is responsible for creating a thin-walled perilimbal bleb that is prone to erosion and leakage. Additional risk factors consist of bleb manipulation, laser suturolysis, needling, or injection of autologous serum (63). In addition, some surgeons have found that dislocation and inappropriate positioning of the external part of the XEN gel stent, which directly rubs against the overlying conjunctiva, causes conjunctival erosion and subsequent leakage (106). The management of a leaking bleb includes conservative measures such as therapeutic contact lens as well as non-surgical treatments (autologous blood injection, fibrin glue injection, cryotherapy application, or laser treatment of the leaking bleb). Surgical procedures, including amniotic membrane transplantation, conjunctival autograft, as well as conjunctival sliding, can also be adopted (64). Conjunctival autograft can repair the leaking bleb, but sometimes replacement of the dislocated stent is required. In a case reported by Salinas et al., a 72-year-old female patient with bilateral pseudoexfoliation glaucoma and cataract received XEN gel stent implantation and phacoemulsification for both eyes at a one-week interval. Bleb leakage and exposure of the XEN gel stent occurred early after surgery at 2 weeks, which was managed by implantation of a new XEN gel stent and ab-externo bleb revision with removal of the old XEN gel stent (107). Surgeons need to carefully check the correct position of the stent during surgery to reduce the risk of direct conjunctival erosion. Some research suggests that a single session of crosslinking for a thin-filtered bleb with leakage following an episode of blebitis has demonstrated efficacy in resolving the bleb leakage (61, 63–65). The objective of employing crosslinking in a thin-walled leaking bleb is to promote the formation of covalent bonds in the collagen fibers of the conjunctival wall of the bleb, thereby enhancing its rigidity and resistance to rupture, reducing permeability, and thus preventing leakage (64). However, in instances where large holes are unlikely to seal, surgical management must be considered the preferred treatment option.

MG

MG is an uncommon but severe complication associated with all glaucoma surgeries. It presents with flattening of the central and peripheral AC and increased IOP with secondary angle closure. MG

can develop early after surgery or years later and can occur in phakic, aphakic, or pseudophakic eyes (108). Schlenker et al. reported the incidence of MG to be 2.2% in 187 patients undergoing XEN gel stent implantation with the application of MMC, similar to other types of glaucoma surgeries for angle closure glaucoma (66, 67). It can be difficult to identify MG early in its course before an increase in IOP develops. Ultrasound biomicroscopy of the eyes during a MG episode reveals anterior rotation of the ciliary processes that press against the lens equator and limit the normal flow through the AC (109). The mechanisms associated with MG are not fully understood. The misdirection of the aqueous humor backward into the vitreous cavity and the forward displacement of the lens-iris diaphragm are recognized etiologies for the development of MG (69). Managing MG is challenging. The goal of medical treatment is to decrease aqueous humor production and vitreous shrinkage while concurrently reducing resistance in the channel of aqueous humor flow into the AC. The current acceptable conservative treatment regimen includes applying atropine, phenylephrine, blockers, and acetazolamide locally, as well as administering a 50% glycerol solution orally and mannitol intravenously. Local corticosteroids help reduce the associated inflammatory process. If improvement is achieved, the dosage of hyperosmotic agents can be decreased, followed by carbonic anhydrase inhibitors. However, mydriatic cycloplegic medications should be continued (109). Nevertheless, it has been reported that symptoms of MG tend to reappear when drugs are discontinued or modified. Therefore, medical treatment is considered temporary and is used in conjunction with laser iridotomy, posterior capsulotomy, and hyaloidotomy. However, currently, only one case report has discussed the management of MG associated with XEN gel stent implantation, which is similar to other surgeries (68). The key aim is to disrupt the anterior displacement of the iris-lens diaphragm, either by laser capsulotomy, hyaloidotomy, or iridotomy, or by surgical methods such as vitrectomy or posterior capsulotomy (69). However, the prognosis of MG and its risk factors associated with XEN gel stent implantation are largely unknown.

Ptosis

Ptosis is a relatively rare complication associated with XEN gel stent implantation, with a reported incidence of 1.2% (62). Some proposed mechanisms for the cause of ptosis after surgery include lid edema from locally administered anesthetic, initial myotoxic effects, and compression of the upper eyelid against the orbital bones from the eyelid speculum, which reduces blood flow to the levator muscle and contributes to the edema (110, 111). Causes of temporary ptosis are believed to include eyelid edema, indirect infiltration of the LPS by retrobulbar or peribulbar anesthesia, and ocular surface disturbance (112). Permanent postoperative ptosis is widely thought to be due to dehiscence of the LPS aponeurosis. The majority of ptosis cases develop early after surgery and may spontaneously resolve, but surgical management is necessary for persistent ptosis. Possible reasons for the higher incidence of ptosis associated with XEN gel stent implantation include levator aponeurosis injury with speculum use for wide opening of the palpebral fissure and the difficulty in washing out the toxicity of MMC and xylocaine compared to trabeculectomy. A "wait-and-see" strategy for transient ptosis resolution is reasonable, but further research is needed to explore possible ways to reduce the risk of ptosis.

Mid-postoperative period (1–6 months)

Migration of XEN implant

The XEN gel stent implant is a highly flexible tube that easily conforms to the tissue shape and adopts an "S shape" when inserted into the AC through the scleral canal (16). However, if the XEN implant is not placed correctly, it can be affected by external forces such as blinking forces from the orbicularis muscle, friction, and micro-trauma, which may cause migration. Grover et al. reported an incidence of MG of 1.5% in 74 patients (17). As reported by Ali et al., when the XEN stent implant is placed deeper into the AC and the remaining length of the tube implanted under the subconjunctival space is less than 2 mm, the XEN implant becomes less flexible and its distal tips are angled obliquely, making it prone to dislocation under external forces (113). Therefore, it is recommended to carefully place the XEN implant with approximately 1 mm of visible insertion into the AC, approximately 3 mm of the exiting part out of the sclera, and 2 mm of the tube situated within the subconjunctival space (25). Prior to surgery, ensure appropriate treatment for patients with allergic eye disease to minimize eye rubbing and prevent stent migration as well as subsequent complications. While we cannot conclusively confirm eye rubbing as the primary trigger of this complication, it is probable that it played a role in the stent migration. Dervenis et al. presented a comparable case and proposed a modification in XEN stent design to prevent dislocation, for instance, a gradual increment in the lumen width (70).

Endophthalmitis

Endophthalmitis is a rare but potentially sight-threatening complication. Currently, only four studies have reported cases of endophthalmitis associated with XEN gel stent implantation. These cases occurred more than 3 months after surgery and were related to bleb complications (103, 114–116). The incidence of this condition is reported to be between 0.4 and 3% (27, 55, 71–73). Risk factors for bleb-related endophthalmitis include the use of anti-metabolites, a thin avascular bleb, bleb leakage, stent exposure, use of topical steroids, as well as young patient age (114). The common causative pathogens of bleb-related endophthalmitis are Streptococcus species, Moraxella, coagulase-negative Staphylococcus, and *Propionibacterium acnes* (117). Lim hypothesized that coinciding gastrointestinal infection and poor handwashing with stent exposure may lead to the transmission of intestinal pathogens to the conjunctiva and the onset of bleb infection (115). Erosion of the conjunctiva and exposure to the stent are the most common direct causes of endophthalmitis associated with XEN gel stent implantation, and prompt surgical management is essential (103, 115). The exposed stent is generally removed, and intensive infection control measures such as vitrectomy, intravitreal injection of antibiotics, bleb revision, subconjunctival antibiotics, and systemic antibiotics are applied (103). The IOP is managed medically and through other filtering surgeries after complete control of the infection. Simple bleb-related infections without stent exposure can be successfully managed conservatively with systemic and topical antibiotics and dexamethasone, without the need to remove the XEN gel stent. A good prognosis is possible for patients who receive prompt and intensive management, as evidenced by two reported cases that recovered within two lines of vision loss compared to their previous visual acuity (114). To reduce the risk of stent exposure and bleb-related complications, it is advised to use an

appropriate surgical technique including posterior application of anti-metabolites, minimizing migration of anti-metabolites toward the limbus, superior placement of the stent away from the lid margin and interpalpebral aperture, and early management of bleb erosion (114).

Macular edema

ME is a transient and generally benign condition associated with the combined therapy of XEN gel stent implantation and phacoemulsification. It has been reported to have an incidence of 1.5–4.3% (62, 74, 75). In a study that followed 261 eyes receiving XEN gel stent implantation with or without phacoemulsification for an average of 8.5 months, four cases of ME occurred. All of these cases occurred in eyes receiving the combination therapy and resolved spontaneously without further treatment (75). Oddone et al. reported seven cases of ME during a 12-month follow-up of 239 cases (62). The cause is believed to be post-phacoemulsification Irvine-Gass syndrome, but further studies are needed to confirm its cause and prognosis. The cases were self-limiting and did not have an impact on visual acuity or visual field.

Hypertrophic bleb

XEN gel stent implantation surgery creates an artificial drainage pathway for the aqueous humor into the subconjunctival space, where it is mainly absorbed by the conjunctival lymphatics. Similar to other filtering surgeries, it results in a local diffuse bleb that covers approximately one-fourth of the circumference. Hypertrophic bleb is a rare and late complication of XEN gel stent implantation surgery, which occurs months to years after the procedure (Figure 1B). It presents as an extensively enlarged bleb that covers large areas and may cause mechanical ectropion. Interestingly, most hypertrophic blebs form and extend toward the nasal conjunctiva. Tracers injected into the subconjunctival space have revealed that the nasal quadrant of the conjunctiva has three times more outflow pathways than the temporal quadrant, which corresponds to the dominant nasal distribution of the conjunctival lymphatic system (118–120). A retrospective cohort study followed 57 eyes with XEN gel stent implantation for 24 months and reported the development of nasal hypertrophic bleb in five eyes (8.8%). These blebs may recur after needle tapping (76). Managing hypertrophic bleb after XEN gel stent implantation is challenging, and the effects of different management methods have only been reported in a few case studies. Conservative therapies include injecting autologous platelet concentrates, blocking the ab-interno stent with viscoelastic material, and sealing the bleb with tissue adhesive. However, there is a potential risk of extensive bleb adhesion and increased IOP (77, 78). Some surgeons use scleral fixation sutures to restrict the infiltration of aqueous humor into the subconjunctival space and guide its outflow toward the posterior part of the eye (79, 80). A functional bled and drainage pathway is preserved but its efficacy and safety still need further evaluation. Yavuzer and Meşen employed the "drainage channel with sutures" approach to address a hypertrophic bleb complication that arose following the third month of XEN gel implantation (80). Pavičić-Astaloš et al. described a post-operative complication involving dysaesthesia attributed to a large hypertrophic inferonasal bleb that manifested 5 months following XEN implantation. The management involved bleb revision surgery in conjunction with scleral fixation sutures. No post-operative complications were reported, and intraocular pressure (IOP) was effectively controlled during the 20-month follow-up assessment (79).

Subconjunctival XEN gel stent fragmentation

The XEN gel stent is a hydrophilic implant made of gelatin, which quickly swells and becomes soft after implantation through hydration (17). Its gelatinous nature makes it highly compatible with the surrounding microenvironment and flexible enough to conform to the curvature within the subconjunctival space. However, there have been reports of breakage and fragmentation of the subconjunctival part when the surgeon attempted to relocate the stent using forceps (105). Novak-Laus et al. also reported a case of "spontaneous" fragmentation of the subconjunctival part of the XEN gel stent discovered during a regular follow-up visit 3 months after surgery in a patient who denied rubbing their eye or experiencing any incidental trauma that could explain the breakage (81). Despite the fragmentation of the stent, it was not replaced because the distal end remained in the Schlemm's canal and the patient maintained normal IOP (81). Bustros et al. reported a case where a fragment of the XEN gel implant was inadvertently damaged during the needling procedure, 2 months postoperatively. One month later, the patient's IOP remained controlled, and the bleb functioned well (82). It is pivotal for the surgeons to be cautious during the needling procedure. Particularly in cases where SCH impairs visibility, it is essential to postpone the procedure until optimal visibility can be ensured.

Although breakage of the XEN gel stent is a rare complication, with only two reported cases at present, further testing is required to assess the mechanical strength of the stent. It is important to avoid any forceful grasping of the stent during surgery.

Late postoperative period (from 6 months)

Late spontaneous dislocation of stent

As discussed above, most cases of XEN gel stent dislocation occur relatively soon after surgery due to inappropriate positioning of the stent and erosion of the conjunctiva covering. Late spontaneous dislocation of the XEN gel stent is generally rare and has only been reported in case studies, and its cause remains largely unknown. Boese et al. described a case of a 73-year-old male patient with advanced primary open angle glaucoma who underwent an uncomplicated combined phacoemulsification procedure with *ab interno* gelatin stent implantation. The stent remained in place during the 6-month follow-up period but spontaneously dislocated during a regular follow-up visit without any triggering events or subjective symptoms. The patient denied the history of any trauma or eye rubbing at any point. The cause of spontaneous stent dislocation remained poorly understood, and the authors suspected that insufficient scleral support may lead to the dislocation of the gelatin implant. Another possibility was that repeated deployment during the surgery might have resulted in a looser fit (83). Since further investigation and evidence are lacking, more research is required to calculate the incidence of this rare complication and explore ways to reduce the risk of spontaneous dislocation. Surgeons should maintain close follow-up to promptly detect stent dislocation.

Intraocular degradation

The XEN gel stent is made of porcine gelatin crosslinked with glutaraldehyde, which is hydrophilic in nature and quite stable

when implanted. The purpose of the crosslinking process is to ensure that the XEN gel stent serves as a permanent device for controlling IOP (16, 121). Preclinical studies have demonstrated that the structure of the XEN gel stent remains intact after 12 months of implantation in dog eyes and over 6 months in nonhuman primate eyes (16). However, a case with the degradation of the XEN gel stent was reported by Widder et al. in a 63-year-old patient, 3 years after implantation. No unique characteristics were identified in this patient, and the degradation primarily affected the intracameral and intrascleral parts of the stent. The degradation caused irregularities in the surface and lumen of the stent, resulting in loss of function. Surgical intervention was required to remove the degraded stent (84). Currently, there has been a lack of long-term observation regarding the implantation of XEN gel stents, and no other reports of intraocular degradation have been documented. However, it is possible that the incidence of intraocular degradation is underestimated, as non-functional stents are typically managed conservatively through needling, and only a few removed stents are carefully examined. Furthermore, it remains unclear whether the degraded materials in the eye are toxic or contribute to further blockage of the aqueous humor drainage system, necessitating further investigation.

Summary and conclusion

Currently, the implantation of XEN gel stents has been demonstrated as an effective method for controlling IOP in patients with early, moderate, advanced, or refractory glaucoma. Long-term observational studies with follow-up periods of up to 5 years support its safety and efficacy (122). Early postoperative complications of XEN gel stent implantation include HM (1.9–4.6%), occlusion (3.9–8.8%), SCH, CD (0–15%), conjunctival erosion, and exposure of the XEN gel stent (1.1–2.3%). Additionally, there may be incidents of wound and bleb leaks (2.1%) and MG (2.2% incidence). Mid-postoperative complications of XEN gel stent implantation include migration of the XEN stent (1.5% incidence), ptosis (1.2% incidence), endophthalmitis (0.4–3%), ME (1.5–4.3%), hypertrophic bleb (8.8% in 5 out of 57 eyes), and subconjunctival fragmentation (as reported in 2 cases) of the XEN gel stent. Late postoperative complications, which have only been reported in isolated cases, include late spontaneous dislocation and intraocular degradation. Our systematic review was the first comprehensive summary of complications associated with XEN gel stent implantation. It demonstrated rare complications, their incidence, mechanisms, and management methods. Most of these complications are mild and transient, and conservative therapy is usually sufficient. However, when conservative methods fail, surgical management has been shown to be effective. Among these complications, SCH, endophthalmitis, and MG are potentially sight-threatening but rare occurrences in XEN gel stent implantation. Surgeons must pay special attention to these complications. SCH, although rare, can be potentially sight-threatening. Conservative management and early surgical intervention, either through choroidal tap or pars plana vitrectomy, have also been reported (62). Endophthalmitis is a rare but potentially sight-threatening complication. In such cases, the exposed stent is typically removed, and intensive infection control measures such as vitrectomy, intravitreal injection of antibiotics, and systemic antibiotic use are applied (53). As for the management of MG, only one case report discussed the approach. It involves disrupting the anterior displacement of the iris-lens diaphragm, either through laser capsulotomy, hyaloidotomy, iridotomy, or surgical methods like vitrectomy or posterior capsulotomy (69).

The XEN 45 gel stent provides a surgical treatment option for glaucoma that is minimally invasive, resulting in shorter surgical time and less intraoperative discomfort for the patient compared to trabeculectomy. It can be performed as a standalone procedure or combined with phacoemulsification. Although it belongs to the category of MIGS and offers advantages such as reduced tissue damage and quicker surgical time, there is still a risk of severe complications, including endophthalmitis, SCH, and MG. Therefore, close monitoring and early identification of severe complications are crucial for surgeons.

Author contributions

LG: Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. LW: Data curation, Formal analysis, Writing – review & editing. JC: Conceptualization, Investigation, Writing – review & editing. LT: Funding acquisition, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Cadre Healthcare Research Program of Sichuan Province (Sichuan Cadre Research 2023–119), and the Science and Technology Planning Project of Sichuan Province (Key Research and Development Project) (no. 2020YFS0257).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1360051/full#supplementary-material

References

1. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. *JAMA*. (2014) 311:1901–11. doi: 10.1001/jama.2014.3192

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) 121:2081–90. doi: 10.1016/j.ophtha.2014.05.013

3. Coleman AL, Miglior S. Risk factors for Glaucoma onset and progression. *Surv Ophthalmol*. (2008) 53:S3–S10. doi: 10.1016/j.survophthal.2008.08.006

4. Lichter PR, Musch DC, Gillespie BW, Guire KE, Janz NK, Wren PA, et al. Interim clinical outcomes in the collaborative initial glaucoma treatment study comparing initial treatment randomized to medications or surgery. *Ophthalmology*. (2001) 108:1943–53. doi: 10.1016/S0161-6420(01)00873-9

5. Coleman AL. Advances in glaucoma treatment and management: surgery. *Invest Ophthalmol Vis Sci*. (2012) 53:2491–4. doi: 10.1167/iovs.12-9483l

6. Koike KJ, Chang PT. Trabeculectomy: a brief history and review of current trends. *Int Ophthalmol Clin*. (2018) 58:117–33. doi: 10.1097/IIO.0000000000000231

7. De Gregorio A, Pedrotti E, Stevan G, Bertoncello A, Morselli S. XEN glaucoma treatment system in the management of refractory glaucomas: a short review on trial data and potential role in clinical practice. *Clin Ophthalmol*. (2018) 12:773–82. doi: 10.2147/OPTH.S146919

8. Hohberger B, Welge-Lüßen UC, Lämmer R. MIGS: therapeutic success of combined Xen gel stent implantation with cataract surgery. *Graefes Arch Clin Exp Ophthalmol*. (2018) 256:621–5. doi: 10.1007/s00417-017-3895-3

9. De Gregorio A, Pedrotti E, Russo L, Morselli S. Minimally invasive combined glaucoma and cataract surgery: clinical results of the smallest *ab interno* gel stent. *Int Ophthalmol*. (2018) 38:1129–34. doi: 10.1007/s10792-017-0571-x

10. Mansouri K, Guidotti J, Rao HL, Ouabas A, D'Alessandro E, Roy S, et al. Prospective evaluation of standalone XEN gel implant and combined phacoemulsification-XEN gel implant surgery: 1-year results. *J Glaucoma*. (2018) 27:140–7. doi: 10.1097/IJG.0000000000000858

11. Asanad S, Kalarn S, Kaleem MA. Postoperative complications of ab-interno XEN implantation in primary angle closure glaucoma. *Am J Clin Exp Immunol*. (2021) 10:44–7.

12. Sng CCA, Wang J, Hau S, Htoon HM, Barton K. XEN-45 collagen implant for the treatment of uveitic glaucoma. *Clin Exp Ophthalmol*. (2018) 46:339–45. doi: 10.1111/ceo.13087

13. Tailor R, Lalias T. A case of refractory neovascular glaucoma treated with a XEN 45 implant. *J Glaucoma*. (2018) 27:929–30. doi: 10.1097/IJG.0000000000001033

14. Lin MM, Morgan WH, Kolomeyer NN, Moster SJ, Zheng CX, Giubilato A, et al. XEN gel stent to treat ICE syndrome: 4 cases. *J Glaucoma*. (2019) 28:1090–4. doi: 10.1097/IJG.0000000000001341

15. Sousa DC, Leal I, Abegão PL. Steroid-induced protracted severe ocular hypertension in a 14-year-old girl. *BMJ Case Rep*. (2018) 2018:bcr-2018-225244. doi: 10.1136/bcr-2018-225244

16. Lewis RA. *Ab interno* approach to the subconjunctival space using a collagen glaucoma stent. *J Cataract Refract Surg*. (2014) 40:1301–6. doi: 10.1016/j.jcrs.2014.01.032

17. Grover DS, Flynn WJ, Bashford KP, Lewis RA, Duh YJ, Nangia RS, et al. Performance and safety of a new *ab interno* gelatin stent in refractory Glaucoma at 12 months. *Am J Ophthalmol*. (2017) 183:25–36. doi: 10.1016/j.ajo.2017.07.023

18. Kosior-Jarecka E, Wróbel-Dudzińska D, Święch A, Żarnowski T. Bleb compressive sutures in the management of hypotony maculopathy after glaucoma surgery. *J Clin Med*. (2021) 10:2223. doi: 10.3390/jcm10112223

19. Sheybani A, Reitsamer H, Ahmed IIK. Fluid dynamics of a novel Micro-fistula implant for the surgical treatment of Glaucoma. *Invest Opthalmol Vis Sci*. (2015) 56:4789. doi: 10.1167/iovs.15-16625

20. Fea AM, Durr GM, Marolo P, Malinverni L, Economou MA, Ahmed I. XEN(®) gel stent: a comprehensive review on its use as a treatment option for refractory Glaucoma. *Clin Ophthalmol*. (2020) 14:1805–32. doi: 10.2147/OPTH.S178348

21. Buffault J, Baudouin C, Labbé A. XEN® gel stent for management of chronic open angle glaucoma: a review of the literature. *J Franc D'ophtalmol*. (2019) 42:e37–46. doi: 10.1016/j.jfo.2018.12.002

22. Schlenker MB, Gulamhusein H, Conrad-Hengerer I, Somers A, Lenzhofer M, Stalmans I, et al. Efficacy, safety, and risk factors for failure of standalone *ab interno* gelatin microstent implantation versus standalone trabeculectomy. *Ophthalmology*. (2017) 124:1579–88. doi: 10.1016/j.ophtha.2017.05.004

23. Olgun A, Duzgun E, Yildiz AM, Atmaca F, Yildiz AA, Sendul SY. XEN gel stent versus trabeculectomy: short-term effects on corneal endothelial cells. *Eur J Ophthalmol*. (2021) 31:346–53. doi: 10.1177/1120672120924339

24. Zakaria S, Ahmed C, Mehran NA, Sinha S, Razeghinejad R, Myers JS, et al. Long-term outcomes of subconjunctival gel stent with and without concomitant cataract surgery. *Investig Ophthalmol Vis Sci*. (2020) 61:947

25. Vera V, Sheybani A, Lindfield D, Stalmans I, Ahmed IIK. Recommendations for the management of elevated intraocular pressure due to bleb fibrosis after XEN gel stent implantation. *Clin Ophthalmol*. (2019) 13:685–94. doi: 10.2147/OPTH.S195457

26. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. (2009) 151:264–9. doi: 10.7326/0003-4819-151-4-200908180-00135

27. Karimi A, Lindfield D, Turnbull A, Dimitriou C, Bhatia B, Radwan M, et al. A multi-centre interventional case series of 259 ab-interno Xen gel implants for glaucoma, with and without combined cataract surgery. *Eye*. (2018) 33:469–77. doi: 10.1038/s41433-018-0243-8

28. Busch T, Skiljic D, Rudolph T, Bergström A, Zetterberg M. Four-year outcome of XEN 45 gel stent implantation in a Swedish population. *Clin Ophthalmol*. (2023) 17:1897–910. doi: 10.2147/OPTH.S412400

29. Ferreira NP, Pinto LA, Marques-Neves C. XEN gel stent internal ostium occlusion: ab-Interno revision. *J Glaucoma*. (2017) 26:e150–2. doi: 10.1097/IJG.0000000000000625

30. Tadrosse AF, Khouri AS. Laser iridoplasty to treat Iris-occluded XEN gel stent. *J Glaucoma*. (2020) 29:e91–2. doi: 10.1097/IJG.0000000000001589

31. Rho S, Lim SH. Combined argon laser peripheral iridoplasty and Nd: YAG laser shock wave therapy for recurrent XEN gel stent obstruction due to iris incarceration: a case report. *Medicine*. (2021) 100:E26652. doi: 10.1097/MD.0000000000026652

32. Scantling-Birch Y, Merzougui W, Lindfield D. Early postoperative lumen blockage of ab-interno gel stent (XEN) cleared with Nd:YAG laser. *Indian J Ophthalmol*. (2020) 68:524. doi: 10.4103/ijo.IJO_1051_19

33. Zalta AH, Sweeney CP, Zalta AK, Kaufman AH. Intracameral tissue plasminogen activator use in a large series of eyes with valved glaucoma drainage implants. *Arch Ophthalmol*. (2002) 120:1487–93. doi: 10.1001/archopht.120.11.1487

34. Zhang Y, Xiang H, Zhang Y, Tang L. Recanalization of Xen45 gel stent implant occlusion using 10-0 nylon suture in refractory glaucoma: a case report. *BMC Ophthalmol*. (2023) 23:418. doi: 10.1186/s12886-023-03109-7

35. Bitrian E, Song BJ, Caprioli J. Bleb revision for resolution of hypotony maculopathy following primary trabeculectomy. *Am J Ophthalmol*. (2014) 158:597–604.e1. doi: 10.1016/j.ajo.2014.05.021

36. Saeedi OJ, Jefferys JL, Solus JF, Jampel HD, Quigley HA. Risk factors for adverse consequences of low intraocular pressure after trabeculectomy. *J Glaucoma*. (2014) 23:e60–8. doi: 10.1097/IJG.0000000000000008

37. Stamper R. Bilateral chronic hypotony following trabeculectomy with mitomycin-C. *J Glaucoma*. (2001) 10:325–8. doi: 10.1097/00061198-200108000-00013

38. Silva RA, Doshi A, Law SK, Singh K. Postfiltration hypotony maculopathy in young Chinese myopic women with glaucomatous appearing optic neuropathy. *J Glaucoma*. (2010) 19:105–10. doi: 10.1097/IJG.0b013e3181a98a39

39. Sacchi M, Fea AM, Monsellato G, Tagliabue E, Villani E, Ranno S, et al. Safety and efficacy of *ab interno* XEN 45 gel stent in patients with Glaucoma and high myopia. *J Clin Med*. (2023) 12:2477. doi: 10.3390/jcm12072477

40. Matsuo H, Tomidokoro A, Tomita G, Araie M. Topical application of autologous serum for the treatment of late-onset aqueous oozing or point-leak through filtering bleb. *Eye*. (2005) 19:23–8. doi: 10.1038/sj.eye.6701422

41. Smith MF, Magauran RG, Betchkal J, Doyle JW. Treatment of postfiltration bleb leaks with autologous blood. *Ophthalmology*. (1995) 102:868–71. doi: 10.1016/S0161-6420(95)30941-4

42. Higashide T, Tagawa S, Sugiyama K. Intraoperative Healon5 injection into blebs for small conjunctival breaks created during trabeculectomy. *J Cataract Refract Surg*. (2005) 31:1279–82. doi: 10.1016/j.jcrs.2004.11.047

43. Hosoda S, Yuki K, Ono T, Tsubota K. Ophthalmic viscoelastic device injection for the treatment of flat anterior chamber after trabeculectomy: a case series study. *Clin Ophthalmol*. (2013) 7:1781–5. doi: 10.2147/OPTH.S51165

44. Kurtz S, Leibovitch I. Combined perfluoropropane gas and viscoelastic material injection for anterior chamber reformation following trabeculectomy. *Br J Ophthalmol*. (2002) 86:1225–7. doi: 10.1136/bjo.86.11.1225

45. Eha J, Hoffmann EM, Wahl J, Pfeiffer N. Flap suture--a simple technique for the revision of hypotony maculopathy following trabeculectomy with mitomycin C. *Graef Arch Clin Exp Ophthalmol*. (2008) 246:869–74. doi: 10.1007/s00417-007-0694-2

46. Shirato S, Maruyama K, Haneda M. Resuturing the scleral flap through conjunctiva for treatment of excess filtration. *Am J Ophthalmol*. (2004) 137:173–4. doi: 10.1016/j.ajo.2003.06.001

47. Haynes WL, Alward WL. Rapid visual recovery and long-term intraocular pressure control after donor scleral patch grafting for trabeculectomy-induced hypotony maculopathy. *J Glaucoma*. (1995) 4:200–1.

48. Vaziri K, Schwartz SG, Kishor KS, Fortun JA, Moshfeghi DM, Moshfeghi AA, et al. Incidence of postoperative suprachoroidal hemorrhage after glaucoma filtration surgeries in the United States. *Clin Ophthalmol*. (2015) 9:579–84. doi: 10.2147/OPTH.S78359

49. Wang K, Wang JC, Sarrafpour S. Suprachoroidal hemorrhage after XEN gel implant requiring surgical drainage. *J Curr Glauc Pract*. (2022) 16:132–5. doi: 10.5005/jp-journals-10078-1378

50. Liu JC, Green W, Sheybani A, Lind JT. Intraoperative suprachoroidal hemorrhage during Xen gel stent implantation. *Am J Ophthalmol Case Rep*. (2020) 17:100600. doi: 10.1016/j.ajoc.2020.100600

51. Prokosch-Willing V, Vossmerbaeumer U, Hoffmann E, Pfeiffer N. Suprachoroidal bleeding after XEN gel implantation. *J Glaucoma*. (2017) 26:e261–3. doi: 10.1097/IJG.0000000000000795

52. Rooney DM, Shadid HR, Siegel LI, Watnick RL, Lesser GR, Obertynski T, et al. Postoperative complications of *ab interno* gelatin microstent. *J Glaucoma*. (2019) 28:E77–81. doi: 10.1097/IJG.0000000000001194

53. Smith M, Charles R, Abdel-Hay A, Shah B, Byles D, Lim LA, et al. 1-year outcomes of the Xen45 glaucoma implant. *Eye*. (2019) 33:761–6. doi: 10.1038/s41433-018-0310-1

54. Gillmann K, Bravetti GE, Rao HL, Mermoud A, Mansouri K. Combined and stand-alone XEN 45 gel stent implantation: 3-year outcomes and success predictors. *Acta Ophthalmol*. (2021) 99:e531–9. doi: 10.1111/aos.14605

55. Reitsamer H, Sng C, Vera V, Lenzhofer M, Barton K, Stalmans I. Two-year results of a multicenter study of the *ab interno* gelatin implant in medically uncontrolled primary open-angle glaucoma. *Graef Arch Clin Exp Ophthalmol*. (2019) 257:983–96. doi: 10.1007/s00417-019-04251-z

56. Cutolo CA, Negri L, Olivari S, Cappelli F, Traverso CE, Iester M. Choroidal detachment after XEN gel stent implantation. *J Ophthalmol*. (2021) 2021:1–5. doi: 10.1155/2021/6674505

57. Arnould L, Theillac V, Moran S, Gatinel D, Grise-Dulac A. Recurrent exposure of XEN gel stent implant and conjunctival Erosion. *J Glaucoma*. (2019) 28:e37–40. doi: 10.1097/IJG.0000000000001146

58. Kingston EJ, Zagora SL, Symes RJ, Raman P, McCluskey PJ, Lusthaus JA. Infective necrotizing Scleritis after XEN gel stent with Mitomycin-C. *J Glaucoma*. (2022) 31:129–32. doi: 10.1097/IJG.0000000000001959

59. Santamaria-Alvarez JF, Lillo-Sopena J, Sanz-Moreno S, Caminal-Mitjana JM. Management of conjunctival perforation and XEN gel stent exposure by stent repositioning through the anterior chamber. *J Glaucoma*. (2019) 28:e24–6. doi: 10.1097/IJG.0000000000001109

60. Wu Z, Huang C, Huang Y, Zhang W, Ma D. Soft bandage contact lenses in management of early bleb leak following trabeculectomy. *Eye Sci*. (2015) 30:13–7. doi: 10.1016/s0161-6420(01)00763-1

61. Aktas Z, Aribas YK, Bilgihan K, Tefon AB. Collagen crosslinking-assisted treatment of a bleb leak: enhancement of vascularization around the bleb. *J Curr Glauc Pract*. (2021) 15:36–9. doi: 10.5005/jp-journals-10078-1290

62. Oddone F, Roberti G, Giammaria S, Posarelli C, Ghirelli G, Mastropasqua L, et al. Effectiveness and safety of XEN45 implant over 12 months of follow-up: data from the XEN-Glaucoma treatment registry. *Eye*. (2024) 38:103–11. doi: 10.1038/s41433-023-02642-5

63. Bochmann F, Azuara-Blanco A. Interventions for late trabeculectomy bleb leak. *Cochrane Database Syst Rev*. (2012) CD006769. doi: 10.1002/14651858.CD006769.pub2

64. Lázaro-Rodríguez V, Casado-López D, Tolosa FR. Conjunctival collagen crosslinking for the management of bleb leak. *Indian J Ophthalmol*. (2023) 71:276–9. doi: 10.4103/ijo.IJO_1444_22

65. Chan HMH, Choy BNK, Lai JSM. Effects of riboflavin and ultraviolet illumination on the biomechanical properties of conjunctiva. *Ophthalmic Res*. (2018) 60:87–93. doi: 10.1159/000478051

66. Schlenker MB, Ong JA, Wu P, Jinapriya D, Zack B, Dorey MW, et al. Surgeon experience as a risk factor for short-term failure for *ab interno* gelatin microstent: a Canadian multicenter propensity-matched study. *Ophthalmol Glaucoma*. (2022) 5:67–76. doi: 10.1016/j.ogla.2021.05.009

67. Luntz MH, Rosenblatt M. Malignant glaucoma. *Surv Ophthalmol*. (1987) 32:73–93. doi: 10.1016/0039-6257(87)90101-9

68. Montolío Marzo S, Lanzagorta Aresti A, Davó Cabrera JM, Alfonso Muñóz EA, Piá Ludeña JV, Palacios PE. Malignant glaucoma after XEN45 implant. *Arch Soc Esp Oftalmol*. (2019) 94:134–7. doi: 10.1016/j.oftal.2018.10.023

69. Fekih O, Zgolli HM, Mabrouk S, Abdejelil A, Zeghal I, Nacef L. Malignant glaucoma management: literature review. *Tunis Med*. (2019) 97:945–9. doi: 10.1038/s41433-018-0243-8

70. Dervenis N, Mikropoulou AM, Dervenis P, Lewis A. Dislocation of a previously successful XEN glaucoma implant into the anterior chamber: a case report. *BMC Ophthalmol*. (2017) 17:148. doi: 10.1186/s12886-017-0540-1

71. Heidinger A, Schwab C, Lindner E, Riedl R, Mossböck G. A retrospective study of 199 Xen45 stent implantations from 2014 to 2016. *J Glaucoma*. (2019) 28:75–9. doi: 10.1097/IJG.0000000000001122

72. Linton E, Au L. Technique of Xen implant revision surgery and the surgical outcomes: a retrospective interventional case series. *Ophthalmol Therapy*. (2020) 9:149–57. doi: 10.1007/s40123-020-00234-0

73. Ibáñez-Muñoz A, Soto-Biforcos VS, Rodríguez-Vicente L, Ortega-Renedo I, Chacón-González M, Rúa-Galisteo O, et al. XEN implant in primary and secondary open-angle glaucoma: a 12-month retrospective study. *Eur J Ophthalmol*. (2020) 30:1034–41. doi: 10.1177/1120672119845226

74. Szigiato AA, Touma S, Jabbour S, Lord F, Agoumi Y, Singh H. Efficacy of ab-interno gelatin microstent implantation in primary and refractory glaucoma. *Can J Ophthalmol*. (2023) 58:328–37. doi: 10.1016/j.jcjo.2022.02.012

75. Widder RA, Dietlein TS, Dinslage S, Kühnrich P, Rennings C, Rössler G. The XEN45 gel stent as a minimally invasive procedure in glaucoma surgery: success rates, risk profile, and rates of re-surgery after 261 surgeries. *Graef Arch Clin Exp Ophthalmol*. (2018) 256:765–71. doi: 10.1007/s00417-018-3899-7

76. Wanichwecharungruang B, Ratprasatporn N. 24-month outcomes of XEN45 gel implant versus trabeculectomy in primary glaucoma. *PLoS One*. (2021) 16:e0256362. doi: 10.1371/journal.pone.0256362

77. Jonas JB, Dugrillon A, Klüter H, Kamppeter B. Subconjunctival injection of autologous platelet concentrate in the treatment of overfiltrating bleb. *J Glaucoma*. (2003) 12:57–8. doi: 10.1097/00061198-200302000-00012

78. Fernández-García A, Romero C, Garzón N. "Dry Lake" technique for the treatment of hypertrophic bleb following XEN(®) gel stent placement. *Arch Soc Esp Oftalmol*. (2015) 90:536–8. doi: 10.1016/j.oftal.2015.03.003

79. Pavicic-Astalos J, Ankamah E, Nolan JM, Ng E, Garcia-Feijoo J. The use of fixation suture to treat Inferonasal hypertrophic bleb after Xen gel stent implant: a case report. *Case Rep Ophthalmol*. (2022) 13:253–8. doi: 10.1159/000523906

80. Yavuzer K, Mesen A. The treatment of a hypertrophic bleb after XEN gel implantation with the "Drainage Channel with sutures" method: a case report. *BMC Ophthalmol*. (2019) 19:245. doi: 10.1186/s12886-019-1249-0

81. Novak-Laus K, Knezevic L, Maric G, Zoric Geber M, Vatavuk Z. Subconjunctival fragmentation of a previously efficient Xen gel stent implantation and successful bleb formation: a case report. *Acta Clin Croat*. (2019) 58:767–70. doi: 10.20471/acc.2019.58.04.25

82. Bustros Y, Chaudhary A, Salinas L, Mansouri K. Cutting the subconjunctival fragment of the XEN gel implant during needling procedure. *Eur J Ophthalmol*. (2020) 30:NP11–5. doi: 10.1177/1120672118805876

83. Boese EA, Shah M. Late spontaneous dislocation of an *ab interno* gelatin microstent. *J Glaucoma*. (2018) 27:e84–6. doi: 10.1097/IJG.0000000000000897

84. Widder RA, Kuhnrich P, Hild M, Rennings C, Szumniak A, Rossler GF. Intraocular degradation of XEN45 gel stent 3 years after its implantation. *J Glaucoma*. (2019) 28:e171–3. doi: 10.1097/IJG.0000000000001364

85. Gillmann K, Mansouri K, Bravetti GE, Mermoud A. Chronic intraocular inflammation as a risk factor for XEN gel stent occlusion: a case of microscopic examination of a fibrin-obstructed XEN stent. *J Glaucoma*. (2018) 27:739–41. doi: 10.1097/IJG.0000000000001002

86. Eagle RC, Razeghinejad R. Xen gel stent occlusion with iris pigment epithelium. *Clin Experiment Ophthalmol*. (2020) 48:258–9. doi: 10.1111/ceo.13658

87. Gillmann K, Bravetti GE, Mansouri K. Delayed obstruction of XEN gel stent by cell debris in primary open-angle Glaucoma: a new insight into the pathophysiology of filtration device failure. *J Curr Glaucoma Pract*. (2019) 13:113–5. doi: 10.5005/jp-journals-10078-1258

88. Oyakhire JO, Moroi SE. Clinical and anatomical reversal of long-term hypotony maculopathy. *Am J Ophthalmol*. (2004) 137:953–5. doi: 10.1016/j.ajo.2003.11.019

89. Harizman N, Ben-Cnaan R, Goldenfeld M, Levkovitch-Verbin H, Melamed S. Donor scleral patch for treating hypotony due to leaking and/or overfiltering blebs. *J Glaucoma*. (2005) 14:492–6. doi: 10.1097/01.ijg.0000185618.98915.d2

90. Bochmann F, Kaufmann C, Kipfer A, Thiel MA. Corneal patch graft for the repair of late-onset hypotony or filtering bleb leak after trabeculectomy: a new surgical technique. *J Glaucoma*. (2014) 23:e76–80. doi: 10.1097/IJG.0000000000000014

91. Panday M, Shantha B, George R, Boda S, Vijaya L. Outcomes of bleb excision with free autologous conjunctival patch grafting for bleb leak and hypotony after glaucoma filtering surgery. *J Glaucoma*. (2011) 20:392–7. doi: 10.1097/IJG.0b013e3181e87efc

92. Dietlein TS, Lappas A, Rosentreter A. Secondary subconjunctival implantation of a biodegradable collagen-glycosaminoglycan matrix to treat ocular hypotony following trabeculectomy with mitomycin C. *Br J Ophthalmol*. (2013) 97:985–8. doi: 10.1136/bjophthalmol-2013-303357

93. Tuli SS, WuDunn D, Ciulla TA, Cantor LB. Delayed suprachoroidal hemorrhage after glaucoma filtration procedures. *Ophthalmology*. (2001) 108:1808–11. doi: 10.1016/S0161-6420(01)00763-1

94. Jeganathan VS, Ghosh S, Ruddle JB, Gupta V, Coote MA, Crowston JG. Risk factors for delayed suprachoroidal haemorrhage following glaucoma surgery. *Br J Ophthalmol*. (2008) 92:1393–6. doi: 10.1136/bjo.2008.141689

95. Nadarajah S, Kon C, Rassam S. Early controlled drainage of massive suprachoroidal hemorrhage with the aid of an expanding gas bubble and risk factors. *Retina*. (2012) 32:543–8. doi: 10.1097/IAE.0b013e31822058e9

96. Healey PR, Herndon L, Smiddy W. Management of suprachoroidal hemorrhage. *J Glaucoma*. (2007) 16:577–9. doi: 10.1097/IJG.0b013e318156a5a9

97. Haga A, Inatani M, Shobayashi K, Kojima S, Inoue T, Tanihara H. Risk factors for choroidal detachment after trabeculectomy with mitomycin C. *Clin Ophthalmol*. (2013) 7:1417–21. doi: 10.2147/OPTH.S46375

98. Iwasaki K, Kakimoto H, Arimura S, Takamura Y, Inatani M. Prospective cohort study of risk factors for choroidal detachment after trabeculectomy. *Int Ophthalmol*. (2020) 40:1077–83. doi: 10.1007/s10792-019-01267-6

99. Jampel HD, Musch DC, Gillespie BW, Lichter PR, Wright MM, Guire KE. Perioperative complications of trabeculectomy in the collaborative initial glaucoma

treatment study (CIGTS). *Am J Ophthalmol*. (2005) 140:16–22. doi: 10.1016/j.ajo.2005.02.013

100. Pérez-Torregrosa VT, Olate-Pérez Á, Cerdà-Ibáñez M, Gargallo-Benedicto A, Osorio-Alayo V, Barreiro-Rego A, et al. Combined phacoemulsification and XEN45 surgery from a temporal approach and 2 incisions. *Arch Soc Esp Oftalmol*. (2016) 91:415–21. doi: 10.1016/j.oftal.2016.02.006

101. Galal A, Bilgic A, Eltanamly R, Osman A. XEN Glaucoma implant with Mitomycin C 1-year follow-up: result and complications. *J Ophthalmol*. (2017) 2017:1–5. doi: 10.1155/2017/5457246

102. Hengerer FH, Kohnen T, Mueller M, Conrad-Hengerer I. *Ab interno* gel implant for the treatment of Glaucoma patients with or without prior Glaucoma surgery: 1-year results. *J Glaucoma*. (2017) 26:1130–6. doi: 10.1097/IJG.0000000000000803

103. Lapira M, Cronbach N, Shaikh A. Extrusion and breakage of XEN gel stent resulting in Endophthalmitis. *J Glaucoma*. (2018) 27:934–5. doi: 10.1097/IJG.0000000000001058

104. Wells AP, Cordeiro MF, Bunce C, Khaw PT. Cystic bleb formation and related complications in limbus- versus fornix-based conjunctival flaps in pediatric and young adult trabeculectomy with mitomycin C. *Ophthalmology*. (2003) 110:2192–7. doi: 10.1016/S0161-6420(03)00800-5

105. Olate-Pérez Á, Pérez-Torregrosa VT, Gargallo-Benedicto A, Escudero-Igualada R, Cerdà-Ibáñez M, Barreiro-Rego A, et al. Management of conjunctival perforation and late Seidel after XEN(®) surgery. *Arch Soc Esp Oftalmol*. (2018) 93:93–6. doi: 10.1016/j.oftal.2017.10.002

106. Montolio-Marzo S, Lanzagorta-Aresti A, Pia-Ludena JV, Davo-Cabrera JM. Conjunctival bleb tearing by XEN gel stent after conjunctival compression sutures. *Eur J Ophthalmol*. (2022) 32:NP76–8. doi: 10.1177/1120672120970862

107. Salinas L, Chaudhary A, Guidotti J, Mermoud A, Mansouri K. Revision of a leaking bleb with XEN gel stent replacement. *J Glaucoma*. (2018) 27:e11–3. doi: 10.1097/IJG.0000000000000811

108. Ruben S, Tsai J, Hitchings RA. Malignant glaucoma and its management. *Br J Ophthalmol*. (1997) 81:163–7. doi: 10.1136/bjo.81.2.163

109. Foreman-Larkin J, Netland PA, Salim S. Clinical Management of Malignant Glaucoma. *J Ophthalmol*. (2015) 2015:283707:1–6. doi: 10.1155/2015/283707

110. Rainin EA, Carlson BM. Postoperative diplopia and ptosis. A clinical hypothesis based on the myotoxicity of local anesthetics. *Arch Ophthalmol*. (1985) 103:1337–9. doi: 10.1001/archopht.1985.01050090089038

111. Crosby NJ, Shepherd D, Murray A. Mechanical testing of lid speculae and relationship to postoperative ptosis. *Eye*. (2013) 27:1098–101. doi: 10.1038/eye.2013.133

112. Bernardino CR, Rubin PA. Ptosis after cataract surgery. *Semin Ophthalmol*. (2002) 17:144–8. doi: 10.1076/soph.17.3.144.14782

113. Ali ZC, Khoo DI, Stringa F, Shankar V. Migration of xen45 implant: findings, mechanism, and management. *J Curr Glauc Pract*. (2019) 13:79–81. doi: 10.5005/jp-journals-10078-1253

114. Kerr NM, Wang J, Sandhu A, Harasymowycz PJ, Barton K. *Ab interno* gel implant-associated bleb-related infection. *Am J Ophthalmol*. (2018) 189:96–101. doi: 10.1016/j.ajo.2018.02.014

115. Lim R, Lim KS. XEN implant-related endophthalmitis. *Ophthalmology*. (2018) 125:209. doi: 10.1016/j.ophtha.2017.10.019

116. Karri B, Gupta C, Mathews D. Endophthalmitis following XEN stent exposure. *J Glaucoma*. (2018) 27:931–3. doi: 10.1097/IJG.0000000000001012

117. Higginbotham EJ, Stevens RK, Musch DC, Karp KO, Lichter PR, Bergstrom TJ, et al. Bleb-related endophthalmitis after trabeculectomy with mitomycin C. *Ophthalmology*. (1996) 103:650–6. doi: 10.1016/S0161-6420(96)30639-8

118. Akiyama G, Saraswathy S, Bogarin T, Pan X, Barron E, Wong TT, et al. Functional, structural, and molecular identification of lymphatic outflow from subconjunctival blebs. *Exp Eye Res*. (2020) 196:108049. doi: 10.1016/j.exer.2020.108049

119. Schulte-Merker S, Sabine A, Petrova TV. Lymphatic vascular morphogenesis in development, physiology, and disease. *J Cell Biol*. (2011) 193:607–18. doi: 10.1083/jcb.201012094

120. Gong P, Yu DY, Wang Q, Yu PK, Karnowski K, Heisler M, et al. Label-free volumetric imaging of conjunctival collecting lymphatics ex vivo by optical coherence tomography lymphangiography. *J Biophotonics*. (2018) 11:e201800070. doi: 10.1002/jbio.201800070

121. Yang G, Xiao Z, Long H, Ma K, Zhang J, Ren X, et al. Assessment of the characteristics and biocompatibility of gelatin sponge scaffolds prepared by various crosslinking methods. *Sci Rep*. (2018) 8:1616. doi: 10.1038/s41598-018-20006-y

122. Chaudhary A, Salinas L, Guidotti J, Mermoud A, Mansouri K. XEN gel implant: a new surgical approach in glaucoma. *Expert Rev Med Devices*. (2018) 15:47–59. doi: 10.1080/17434440.2018.1419060

Frontiers in Medicine

Translating medical research and innovation into improved patient care

A multidisciplinary journal which advances our medical knowledge. It supports the translation of scientific advances into new therapies and diagnostic tools that will improve patient care.

Discover the latest Research Topics

See more →

Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact