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The authors report and discuss the case of a 61-year-old Caucasian female who presented to a community emergency room with left periocular fullness and pain behind the left eye characterized as the "worst headache of my life." Her past medical history was remarkable for hypertension and a history of smoking. She denied any history of trauma or surgery.

Cover: Cystoid macular edema related to cataract surgery and topical prostaglandin analogs: Mechanism, diagnosis, and management. (page 496).

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Editorial

Survey of ophthalmology in the time of COVID-19

Check for updates

First, I want to pay tribute to the two Chinese ophthalmologists, Drs. Li Wenliang and Mei Zhongming, who were among the first medical professionals to lose their lives in the current coronavirus 2019 (COVID-19) pandemic. Late last year, Dr. Wenliang tried to warn colleagues about the appearance of a severe acute respiratory syndrome (SARS)-like coronavirus illness in his hospital and was then officially admonished and threatened with prosecution by local authorities. He is thought to have acquired the virus when treating an infected patient with acute angle-closure glaucoma.

Soon after the recognition of the COVID-19 pandemic, multiple manuscripts concerning this virus began to be submitted to the *Survey of Ophthalmology*. These have been declined because this journal is intended, at least in its Major Reviews section, to provide its readers with critical literature-based reviews that are expert perspectives on subjects of clinical relevance to ophthalmologists. Such reviews require that enough time has passed that at least a partial understanding of the subject has been reached. Most Major Reviews have some variation of "further study is required" (and often suggestions on how this should be accomplished) in their conclusions. For COVID-19, this would be a gross understatement.

The COVID-19 pandemic, while certainly clinically relevant, has resulted in information arriving at such speed that a review up to date at its writing would be out of date by its publication even a few months later. Literally hundreds of articles on COVID-19 are being published in medical journals each month, and to provide any meaningful perspective on such a dynamic subject would be a daunting task even for a weekly or online journal.

One of the common reasons that an outline or manuscript is sent back to its authors is that the research on the proposed subject is evolving, and even tentative conclusions are hard to reach. Often I encourage them to resubmit in a year or two when more data are available. This is the case with ocular manifestations of the COVID-19 pandemic. In the meantime, there are many other remarkable advances in ophthalmology that the *Survey of Ophthalmology* will continue to bring to the attention of our readers.

John W. Gittinger Jr., MD
Editor-in-Chief
Department of Ophthalmology
Massachusetts Eye and Ear Infirmary
Harvard Medical School
Boston, MA, USA
jgittinger@stellarmed.com

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Major review

Cystoid macular edema related to cataract surgery and topical prostaglandin analogs: Mechanism, diagnosis, and management

Gábor Holló, MD, PhD, DSc[a,*], *Tin Aung, FRCOpth, PhD*[b,c], *Louis B. Cantor, MD*[d], *Makoto Aihara, MD, PhD*[e]

[a] *Glaucoma Unit, Department of Ophthalmology, Semmelweis University, Budapest, Hungary*
[b] *Glaucoma Department, Singapore Eye Research Institute, Singapore National Eye Centre, Singapore*
[c] *Department of Opthalmology, National University of Singapore, Singapore*
[d] *Department of Opthalmology, Indiana University School of Medicine, Indianapolis, IN, USA*
[e] *Department of Opthalmology, University of Tokyo, Tokyo, Japan*

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ABSTRACT

Cystoid macular edema (CME) is a form of macular retina thickening that is characterized by the appearance of cystic fluid-filled intraretinal spaces. It has classically been diagnosed upon investigation after a decrease in visual acuity; however, improvements in imaging technology make it possible to noninvasively detect CME even before a clinically significant decrease in central vision. Risk factors for the development of CME include diabetic retinopathy, retinal vein occlusion, uveitis, and cataract surgery. It has been proposed that eyes with elevated intraocular pressure after cataract surgery, including those treated with prostaglandin analog eye drops, may be at higher risk for the development of CME. We summarize the current knowledge of the molecular mechanisms underlying CME, the potential role of ocular surgery and topical glaucoma medication in increasing the risk of CME, the newly developed imaging methods for diagnosing CME, and the clinical management of CME.

* Corresponding author: Gábor Holló, MD, PhD, DSc, Department of Ophthalmology, Semmelweis University, Mária u. 39, Budapest 1085, Hungary.
E-mail address: hollo.gabor@med.semmelweis-univ.hu (G. Holló).

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1. Introduction to cystoid macular edema

Cystoid macular edema (CME) is characterized by retinal thickening at the macula, associated with cystic changes in the outer plexiform and inner nuclear layers.[102] These cystic changes occur from the accumulation of fluid arising from inner and outer blood-retinal breakdown of the perifoveal capillaries, which is mediated by a number of inflammatory molecules.[40] CME may be classified as acute or chronic, whereby CME is present for less or more than 6 months, respectively. Clinical CME is typically established after diagnostic evaluation following the patient's visual complaint and is associated with impaired visual acuity, usually less than 20/40. Conversely, angiographic CME is largely asymptomatic and is typically diagnosed using imaging-based diagnostic techniques.[28]

A summary of the risk factors for CME is provided in Table 1. In general, CME is considered to be related to ocular inflammation. It is typically associated with uveitis, diabetic retinopathy, and retinal vein occlusion and is a common complication of cataract surgery.[57,88] Given the process of replacing the natural lens with an artificial intraocular lens during cataract surgery, CME that occurs after cataract surgery is referred to as pseudophakic CME. Pseudophakic CME, also known as Irvine-Gass syndrome, is one of the most common causes of decreased visual acuity after cataract surgery.[28,52,53] The incidence of clinical CME after cataract surgery is reported as 0.1–7.0% in studies where patients, including those with risk factors for CME, were assessed up to 4 months postoperatively.[22,28,58,79] The observed incidence of pseudophakic CME is much greater when eyes are assessed with fluorescein angiography (FA) or optical coherence tomography (OCT) compared with that reported after the development of patients' visual complaints.[33] This suggests that there are many clinically unrecognized cases of CME. Although clinically significant macular edema develops in only up to 6% of patients without diabetes after cataract surgery, this may occur in up to 56% of patients with mild to moderate diabetic retinopathy who did not have macular edema preoperatively.[120] In addition, pseudophakic CME is more likely to occur in eyes of patients with diabetes and preoperative diabetic retinopathy than in diabetic eyes without retinopathy.[85] Similarly, a history of retinal vein occlusion significantly increases the risk of developing CME after cataract surgery (odds ratio [95% confidence interval] = 47.12 [9.40–236.11]; $P < 0.001$).[39] Although glaucoma itself is not considered a risk factor for the development of CME after cataract surgery, untreated elevated intraocular pressure (IOP) with glaucomatous optic nerve or retinal nerve fiber layer damage and associated glaucomatous visual field defect has been shown to increase the risk of postoperative pseudophakic CME.[58] To date, studies have shown mixed results regarding the risk of pseudophakic CME after preoperative prostaglandin (PG) analog (PGA) use. Henderson and coworkers showed that, when patients with diabetes were excluded from the analysis as this was a confounding factor, preoperative use of PGAs significantly increased the risk of CME ($P = 0.04$); however, it was not stated if and when treatment was discontinued before surgery.[39] In a retrospective study of 12 patients receiving latanoprost, 8 patients deliberately discontinued treatment 1 week preoperatively, and 4 patients continued treatment. CME did not develop in those who discontinued treatment, whereas CME developed in those who continued the treatment ($P = 0.003$).[128] Other studies have suggested that preoperative use of PGAs does not increase the risk of CME.[22,57] PGAs are the current most commonly used standard-of-care medication option for patients with glaucoma. Given the potential association between the preoperative use of PGAs and the development of CME, this may indicate a risk for patients with glaucoma requiring cataract surgery.

The emergence of improved imaging technologies has indicated that the risk of angiographic CME after cataract surgery may be higher than previously reported[34]; therefore, this review will cover how current diagnostic practice has led to a revised understanding of CME, the risk of CME after cataract surgery in patients with glaucoma on IOP-lowering treatment, and the implications for managing PGA-related pseudophakic CME.

2. Diagnosis of CME

The traditional methods for evaluating macular thickening include slit-lamp biomicroscopy, indirect ophthalmoscopy, and fundus photography.[106,108] Although these methods identify exudates, hemorrhages, and microaneurysms, their usefulness is limited in identifying specific anatomic details at the vitreoretinal interface, and they are dependent on the extent of edema and the observer's level of experience and skill.[106] Therefore, postoperative CME is conventionally diagnosed by decreased visual acuity or by visualization of the accumulation of fluid in well-defined intraretinal spaces using FA or OCT.[34,108] Assessment by FA shows fluorescein leakage from the vasculature in a characteristic perifoveal petaloid pattern with or without fluid leakage from the optic disk, as well as fluorescein leakage from the macular capillaries and its pooling in the cystoid cavities.[20,34] The extent of fluid leakage observed does not always correlate with visual acuity, likely owing to the localization of the fluid accumulation.[28] Although FA was the most commonly used technique for diagnosing CME until recent years, the observation of fluorescein leakage only provides qualitative information on vascular exudation.[106] CME may also be detected by fundus autofluorescence (FAF), a noninvasive qualitative imaging technique that measures the fluorescence emitted by fluorophores of the retina at specific wavelengths. Blue FAF allows visualization of lipofuscin, which absorbs blue light at 470 nm and emits yellow/green light at 600–610 nm.[9] In CME, FAF may be used to visualize displacement of macular pigment and consequently the cysts associated with CME. FAF patterns observed in patients with CME have been shown to correspond well with the petaloid pattern observed with FA images; however, caution may be advised with this method, as FAF hypoautofluorescence without the petaloid pattern is observed in patients with intraretinal fluid.[82] This method is also limited by low signal strength, autofluorescence artifacts from the anterior segment, and the potential toxic effects of

Table 1 – Summary of the risk factors for CME

Conditions that may increase the risk of CME

- Uveitis[56]
- Diabetic retinopathy[22,88]
- Retinal vein occlusion[22,88]
- Neovascular age-related macular degeneration[96]
- Retinitis pigmentosa[35]
- Vitreous traction[47]
- Preoperative treatment with paclitaxel or docetaxel[130]
- Use of omidenepag isopropyl on Japanese pseudophakic eyes[26,C]
- Cataract surgery (3–12 weeks postoperatively)[22,88]
- The risk of CME with cataract surgery is increased with the following factors:
  - Surgery complicated with posterior capsule rupture and vitreous humor loss[88]
  - Diabetes mellitus or preoperative diabetic retinopathy[85,120]
  - Untreated elevated intraocular pressure[58]
  - History of retinal vein occlusion[39]
  - History of epiretinal membrane[39]
  - Preoperative use of prostaglandin analogs[39,*]
  - Postoperative use of prostaglandin analogs and β-blockers[119,*]

CME, cystoid macular edema.
* The duration of treatment was not provided in this study.

blue light excitation of the retina, including changes to circadian rhythm and dark adaption.[9] Visualization of CME using FA and FAF is shown in Fig. 1.

In recent years, OCT has become the standard diagnostic technique for identifying CME.[34,106] It has advantages over FA because it is a noninvasive and quantitative method that provides images of the retinal fluid-filled cystoid cavities as small, round, or oval hyporeflective spaces with highly reflective septa that bridge the retinal layers and separate the cavities.[24,106] The resulting image can be used to automatically quantify retinal thickness.[20,106,108] OCT evaluation shows macular thickening and cystic spaces in the inner nuclear layer and the outer plexiform layer in patients with CME, which is in line with histopathological studies. These cystoid spaces may initially be observed as development of microcystoid spaces in the inner nuclear layer using spectral-domain OCT[20,34,101]; however, microcystoid spaces may also be observed in patients with advanced glaucoma and in patients with other forms of optic atrophy.[36] This may lead to difficulties in differentiating microcysts associated with CME and those associated with forms of progressive retinal degeneration including optic nerve atrophy in patients with glaucoma.[36,123] Some studies have used methods such as OCT to differentiate pathologic causes of CME such as pseudophakic, uveitic, or diabetic CME; however, this application of OCT has not yet been validated, and in most cases, the patients' medical history provides sufficient information to determine the pathology.[46,77] Though the value of swept-source OCT in diagnosing CME has not yet been fully determined, this technique was used in one investigation to assess macular pathology after routine cataract surgery.[132] The advantages of swept-source over spectral-domain OCT imaging comprise faster scanning speed, resulting in denser scan patterns and larger scan areas, and the use of a longer wavelength and reduced sensitivity roll-off, which improves signal detection and increases likelihood of detecting weak signals from the deeper layers.[68] Therefore, it is likely that this method may be more widely used in future diagnosis of CME.

OCT angiography is an emerging noninvasive diagnostic technique that is increasingly used in clinical practice.[90] OCT angiography may be considered superior to FA owing to its ability to quantitatively measure retinal blood flow across separate layers, including the superficial capillary plexus and the deep capillary plexus, and can determine areas of decreased or absent retinal perfusion in the deep vascular plexus, localized to the cystoid spaces.[90,104] A comparison of a healthy eye and an eye with CME as presented by OCT and OCT angiography is shown in Fig. 2.

3. Pathology and pathophysiology of CME

Although the classic picture of CME is characterized by cysts in the outer plexiform layer, cysts initially form in the inner nuclear layer and, upon disease progression, they appear in the outer plexiform layer and the subretinal space.[102] This is coupled with capillary loss, which is observed in both the superficial capillary plexus and the deep capillary plexus during pseudophakic CME, but normalizes upon CME resolution.[20,104] This suggests that capillary nonperfusion in pseudophakic CME is temporary and that pseudophakic CME may have a different pathology compared with CME associated with retinal vascular occlusions.[20] CME also occurs in patients with a history of intraocular inflammation, such as uveitic syndromes; conditions that lead to predisposition to increased vascular permeability, such as diabetic retinopathy; or those with a history of intraocular surgery. Most studies agree that inflammation may play a key role in the development of CME, especially as inflammation may disrupt the blood-retinal and blood-aqueous barriers.[21,33] A number of proinflammatory mediators contribute to inflammation and vascular permeability after cataract surgery. These include endogenous prostaglandins (PGs); complement components; platelet-activating factors; cytokines; nitric oxide; and growth factors, such as vascular endothelial growth factor (VEGF) and insulin-like growth factor-1.[40,70] It has been suggested that, after cataract surgery, inflammatory mediators that accumulate in the aqueous humor damage the blood-aqueous barrier and diffuse through the vitreous to the retina where they cause blood-retinal barrier disruption.[70] Taken together, this suggests that underlying inflammation, complicated cataract surgery, or use of proinflammatory medications such as PGAs may increase the risk of development of CME.

4. CME in patients with glaucoma

The risk of CME in patients who receive postoperative PGAs after IOP-lowering glaucoma surgery has not yet been characterized. There are limited reports on CME after incisional glaucoma surgeries like trabeculectomy. One small study reported CME after trabeculectomy combined with intraoperative mitomycin C in 1 of the 26 operated eyes (3.8%), all of which had post-keratoplasty glaucoma.[44] It has been reported, however, that trabeculectomy may lead to increased

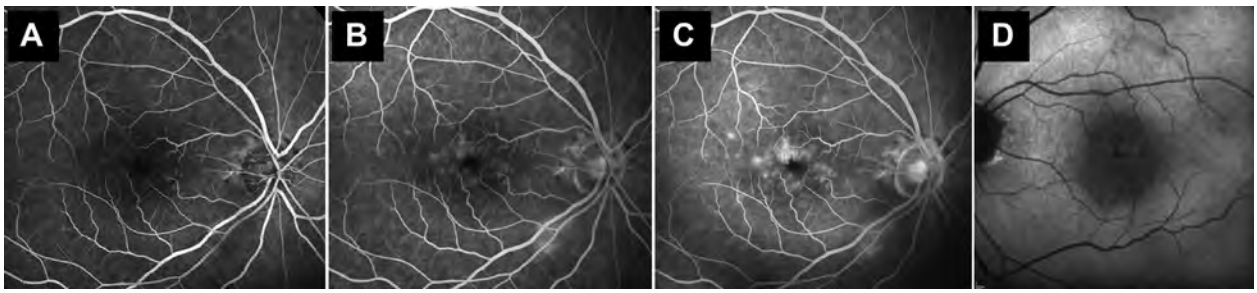

Fig. 1 – Imaging of CME using fluorescein angiography and fundus autofluorescence. Fluorescein angiography images of an eye with CME in *A*: the early arteriovenous phase; *B*: the late arteriovenous phase; and *C*: the late angiography phase. The leakage of fluorescein into the CME spaces increases during the consecutive angiography phases. *D*: Shows the appearance of CME using fundus autofluorescence. CME, cystoid macular edema.

macular thickness. In one prospective study, clinically significant macular thickening, defined as ≥17 μm, was observed in 2 of 34 patients (5.8%) within 1 month after trabeculectomy.[94] In this report, CME development was not significantly influenced by preoperative treatment with PGAs or the use of mitomycin C during surgery.[94] Similarly, it has been shown that trabeculectomy in 45 eyes of 44 patients led to a statistically significant increase in macular thickness from 164 ± 20 μm before surgery to 173 ± 19 μm 1 month postoperatively ($P < 0.0001$).[50] In this study, macular thickness returned to the preoperative value (165 ± 16 μm) at 3 months, and no patients had hypotony for more than 5 days after surgery.

EX-PRESS® shunt implantation and glaucoma drainage device surgery are also incisional IOP-lowering procedures. There have been few cases of CME reported in patients who underwent Baerveldt shunt implantation. In a retrospective case series investigating the implantation of the Baerveldt device in 24 eyes of 24 patients with uveitic glaucoma, CME occurred in 3 eyes (12.5%).[18] In both studies, there was an increased risk of CME in patients because of underlying uveitis. There were no reports of CME after Baerveldt shunt implantation in patients without uveitis. In a retrospective chart review of 16 patients with complicated secondary glaucoma, one case of CME development was reported 4 months after a Molteno device implantation; this patient had not received glaucoma medication after surgery but had previously undergone extracapsular cataract extraction and anterior chamber intraocular lens implantation, penetrating keratoplasty, and vitrectomy. These factors all likely contributed to the development of CME.[62] There are no published reports of CME development after Ahmed glaucoma valve or EX-PRESS shunt implantation.

There have been some instances of CME development after less invasive glaucoma procedures. Although few detailed studies have reported CME after selective laser trabeculoplasty, numerous case reports have been published. All but one reported case occurred in eyes that had previously undergone phacoemulsification with intraocular lens implantation, and the onset of the CME ranged from 12 hours to 4 weeks after laser treatment.[78,84,117,125] In the case in which CME was recognized 12 hours after selective laser trabeculoplasty, the patient used travoprost before the procedure, but it had not been administered postoperatively before the development of CME. This patient also had foveal opalescence due to subretinal fluid. The finding of CME after selective laser trabeculoplasty was considered uncommon, and the additional observation of subretinal fluid suggested that this was not a typical case of CME.[84] In terms of other laser procedures, CME occurred in 1 of 20 eyes (5%) treated with transscleral diode laser cyclophotocoagulation for the reduction of IOP after a failed Baerveldt glaucoma implantation.[80] In a small retrospective chart review of 10 eyes of 9 patients, combination of cyclophotocoagulation and glaucoma drainage device implantation led to CME in both eyes of 1 patient.[100] Although all other patients in this study had received cyclophotocoagulation and glaucoma drainage device implantation on separate occasions, this patient was the only individual to have received both treatments simultaneously. This may have been a contributing factor to the development of CME.

There are few reports of CME in relation to minimally invasive glaucoma surgical procedures. In a retrospective study of 21 eyes in 20 patients with pseudoexfoliative glaucoma who underwent XEN45 implantation with subconjunctival mitomycin C and had a minimum postoperative follow-up period of 12 months, one case of CME was recorded; however, this patient had undergone combined XEN implantation and phacoemulsification.[43] There were no additional reports published on CME development for other minimally invasive glaucoma surgery devices and procedures except for one case reported in a patient with pseudoexfoliative glaucoma after Kahook dual blade goniotomy.[7] The patient previously underwent an uncomplicated cataract surgery with intraocular lens implantation, had peripapillary hemorrhage, received multiple IOP-lowering treatments (including bimatoprost–timolol and brinzolamide–brimonidine fixed combinations, and oral carbonic anhydrase inhibitor medication), and two previous selective laser trabeculoplasty treatments. CME was reported 1 month after the Kahook dual blade goniotomy in this patient, but this could be attributable to the complicated ocular history.[7] In a retrospective, single-center, cohort study in which patients who underwent uneventful cataract surgery alone (n = 234) were compared with patients for whom cataract surgery was performed in combination with ab-interno glaucoma surgery (trabecular aspiration or ab-interno trabeculotomy; n = 126), no significant difference in the incidence of CME between the two groups

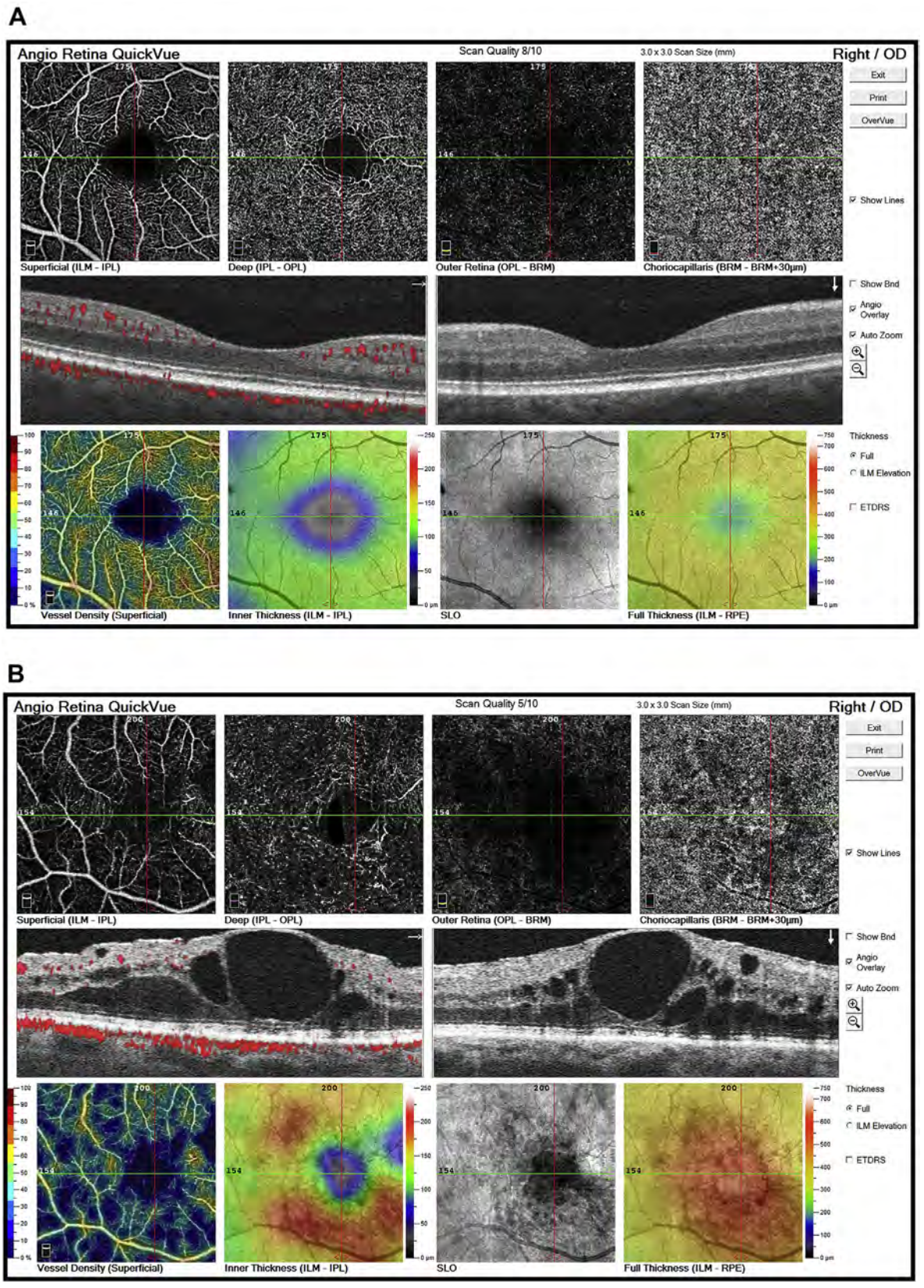

Fig. 2 – Comparison of macular OCT angiography findings between eyes with and without CME. *A*: OCT angiography image of a healthy macula. The retinal vessels and the capillaries are clearly defined in the superficial and deep layers and in the outer retina except for the foveal avascular zone. The macular retina layers (*middle row*) are normal, and the perfusion is indicated with *red* pseudocolor. The color-coded perfusion map (*bottom row*) shows normal superficial retinal perfusion.

was found 48 weeks after cataract surgery (cataract surgery only, 16 of 234 eyes [6.8%]; cataract and ab-interno surgery, 7 of 126 eyes [5.5%]; P = 0.676). This result suggests that trabecular aspiration and ab-interno trabeculectomy did not increase the risk of CME compared with cataract surgery alone.[91]

There is evidence in the literature to suggest that there may be an association between cataract surgery and the development of CME in patients with glaucoma, and in those who receive topical PGA therapy.[40,119] The incidence of pseudophakic CME varies depending on the diagnostic method and the cataract surgery technique. A comparison of CME after different cataract extraction techniques showed that the incidence of clinically significant CME was higher after extracapsular cataract extraction compared with intracapsular cataract extraction and phacoemulsification. The incidence of angiographic CME was higher after intracapsular cataract extraction and phacoemulsification than after extracapsular cataract extraction when detected using FA.[33] However, no difference in the risk of CME was reported between femtosecond laser–assisted cataract surgery and conventional cataract surgery.[59] The frequency of CME after uncomplicated cataract surgery, as measured by spectral-domain OCT, is significantly greater in patients with primary open-angle glaucoma (44%, 31/70 eyes) than in patients without glaucoma (21%, 14/68 eyes) (P = 0.003).[58] In this prospective study, the risk of CME in patients with glaucoma was highest in patients with primary open-angle glaucoma using PGAs compared with those who did not use PGAs (odds ratio = 5.51; P = 0.001).[58] This suggests that PGAs can play a role in the development of pseudophakic CME.[70]

5. The role of PGs in the development of pseudophakic CME

Endogenous PGs are lipid mediators that are produced from the cleavage of membrane phospholipids by phospholipase A2 to arachidonic acid. Arachidonic acid is subsequently metabolized by the cyclooxygenase (COX) enzymes (COX1 and COX2) to eventually produce thromboxanes and PGs (PGD_2, PGE_2, PGI_2, and $PGF_{2\alpha}$).[87] A summary of the ocular localization of PG receptors is provided in Table 2. Analogs of $PGF_{2\alpha}$ are commonly used to lower IOP in patients with open-angle glaucoma by increasing uveoscleral outflow of aqueous humor. This is thought to be due to extracellular matrix remodeling and relaxation of the ciliary muscle.[121]

A role for PGs in inducing blood-aqueous barrier disruption has been described, and the proposed mechanisms by which PGAs and postsurgical endogenous PGs increase the risk of CME after cataract surgery are shown in Fig. 3. The ciliary processes actively uptake PGs from ocular fluids.[13,14,55] This process was inhibited in a model of uveitis and led to accumulation of PGs in the anterior chamber, suggesting that active transport of PGs was interrupted.[14] Similarly, PGE_2, which influences vascular permeability, was increased in both the aqueous humor and vitreous body of rabbits that underwent intracapsular cataract extraction and received topical epinephrine, compared with those that received epinephrine and indomethacin, or did not undergo cataract extraction but received topical epinephrine.[74] This was attributed to impairment of ocular transport of PGE_2 by the ciliary processes after cataract surgery. Epinephrine-induced PG production leads to COX-dependent blood-aqueous barrier disruption, which can be inhibited by the COX inhibitor indomethacin, suggesting a role for PGs in increasing vascular permeability.[74] Elevation of PGE_2 and $PGF_{2\alpha}$ production levels in the aqueous humor immediately after cataract surgery has also been shown in humans.[70,93] In addition, a pooled analysis of phase 2 and 3 studies (N = 267) investigating omidenepag isopropyl, a nonprostaglandin prostanoid EP2 receptor agonist approved in Japan for the treatment of glaucoma and ocular hypertension, found CME in 5.2% of the treated patients. All patients with treatment-related CME had previously had cataract surgery with intraocular lens implantation.[26,C] For this reason, according to the Japanese package insert, omidenepag isopropyl is contraindicated in patients who have undergone cataract surgery with intraocular lens implantation or who are aphakic.[C] The lack of treatment-related CME in phakic eyes suggests that treatment-related risk of CME development may be specific to pseudophakic patients.

It is thought that the lens capsule acts as a diffusion barrier between the anterior and posterior segments and maintains topographical integrity of the anterior segment of the eye.[71,74] Intraocular lens implantation in cataract surgery may induce changes in the lens epithelial cells and other tissues of the anterior segment subjected to surgical stress and lead to endogenous production of COX2, PGE_2, and cytokines.[45,70] Miyake and coworkers proposed that the secretion of proinflammatory molecules and changes in lens-related barrier function after cataract surgery may contribute to the development of aqueous humor flare.[73] Aqueous humor flare, which appears as light scattering caused by protein in the aqueous humor at slit-lamp examination, reflects the disruption of the blood-aqueous barrier several weeks after cataract surgery.[73] It has been suggested that accumulated PGs in the aqueous chamber influence the production of inflammatory mediators. The inflammatory mediators can reach the posterior part of the eye via transvitreal diffusion and disrupt the blood-retinal barrier, which causes fluid

B: OCT angiography image of an eye with CME. Macular perfusion is reduced in the superficial and deep layers and in the outer retina and choriocapillaries compared with the healthy macula (*A*). On the color-coded perfusion map (*bottom left image*), the reduced capillary perfusion is indicated by the dominance of *blue* color. These perfusion findings reflect the CME cavities (*middle row*). Images for both patients were obtained using an AngioVue OCT imaging system with the 3 mm diameter macular scan size. BRM, Bruch membrane; CME, cystoid macular edema; ETDRS, Early Treatment Diabetic Retinopathy Study; ILM, internal limiting membrane; IPM, inner plexiform layer; OCT, optical coherence tomography; OD, right eye; OPL, outer plexiform layer; RPE, retinal pigment epithelium; SLO, scanning laser ophthalmoscopy.

Table 2 – A summary of ocular prostaglandin receptors

Prostaglandin	Prostaglandin receptor	Ocular localization
PGD_2	DP	Ciliary epithelium/process, longitudinal and circular ciliary muscles, retinal choroid, and iris in human eye sections[97]
PGE_2	EP1	Highest expression in epithelia of the cornea, conjunctiva, lens, and ciliary body; also found in trabecular endothelial cells and meshwork, vascular endothelial cells of the iris, retinal ganglion cells and photoreceptor cells, cells lining Schlemm's canal, collector channels, and scleral aqueous veins[92]
	EP2	Corneal epithelium, conjunctival epithelium at the limbus, and vascular endothelium of choriocapillaries. More abundant in the outer wall of Schlemm's canal and scleral cells, collector channels, and scleral aqueous veins than in the trabecular meshwork. Also found in the ciliary epithelium and ganglion cells and retinal nerve fiber layer[92]
	EP3	Corneal endothelium, keratocytes, endothelial cells of the trabecular meshwork, ciliary epithelium, conjunctival and iridal stromal cells, and retinal Müller cells. Moderate levels in endothelial cells lining Schlemm's canal and collector channels[92]
	EP4	Corneal endothelium, keratocytes, endothelial cells of the trabecular meshwork, ciliary epithelium, and conjunctival and iridal stromal cells. Also found in endothelial cells lining Schlemm's canal, the collector channels, aqueous veins, iridal vessels, and the retinal nerve fiber layer[92]
$PGF_{2\alpha}$	FP	Corneal epithelium, ciliary epithelium, circular portion of the ciliary muscle, and the iridal stromal and smooth muscle cells. Moderate levels in the outer portions of the trabecular meshwork and endothelial cells of Schlemm's canal, collector channels, and aqueous veins. Also found in vascular endothelial cells and ciliary muscle vasculature, but not in capillaries in the ciliary processes[92]
PGI_2	IP	Unknown, but gene expression studies suggest that there is more gene expression present in Schlemm's canal cells than in the trabecular meshwork[112]

accumulation in the retina.[70] It is unlikely, however, that PGAs directly influence normal blood-aqueous barrier function. Rather, they may prolong the production of endogenous proinflammatory mediators after incisional eye surgery, such as those produced by the lens epithelial cells after cataract surgery.[73] This has been supported by data showing that latanoprost, travoprost, and bimatoprost had no statistically significant effect on the blood-aqueous barrier of phakic eyes with primary open-angle glaucoma or ocular hypertension, which may indicate a specific risk of CME development in pseudophakic patients.[3]

According to general clinical experience, the temporary increase in endogenous aqueous humor PG levels after uncomplicated cataract surgery does not affect the blood-retina barrier in a clinically significant manner; however, mild CME can frequently be detected with OCT after uncomplicated cataract surgery in patients without visual symptoms.[67,98] By contrast, increased endogenous PG release after complicated cataract surgery or the cumulative effect of uncomplicated phacoemulsification and the use of topical PGAs in the early postoperative weeks may increase inflammation. This may lead to increased blood-aqueous and blood-retinal barrier permeability and clinically significant CME. In a randomized, double-masked trial, once-daily topical latanoprost (N = 37 eyes) significantly increased the incidence of fluorescein leakage into a cystic space, measured by FA, compared with topical placebo administration (N = 37 eyes) when both treatments were combined with topical corticosteroid (fluorometholone) drops (81% compared with 35%, respectively; $P < 0.01$).[70] By contrast, the incidence of fluorescein leakage in the same study was significantly lower when latanoprost was combined with diclofenac, a COX inhibitor, instead of fluorometholone (8.5% compared with 81%, respectively; $P < 0.05$). These results suggest that COX-mediated PG metabolism may have a role in increasing the risk of CME. It should be noted that because FA examination was done on all patients regardless of visual symptoms, CME may have been diagnosed in eyes without visual disturbance.[70] For this reason, caution should be exercised when treating high-risk eyes with PGAs. However, even in this population, the risk of visually significant CME is low; it developed in 5% of pseudophakic patients with additional risk factors after receiving latanoprost in a study of 40 patients.[111] It has been suggested that a risk-benefit analysis for each eye should be individually determined.[40] Other studies showing increased occurrence of CME in pseudophakic patients receiving PGAs are described in the next section of this review. Although CME leads to a noticeable decrease in visual acuity, withdrawal of the PGA and treatment of the CME leads to recovery of visual functions in most cases.[17,110,115,128]

6. Clinical experience with CME in topical PGA users

In one recent investigation, PGAs have recently been recommended for the prophylactic treatment of IOP elevation after uncomplicated cataract surgery.[42] As previously mentioned in this review, the use of PGAs typically does not cause CME in phakic patients with a normally functioning blood-ocular barrier but may increase the incidence of CME after cataract surgery.[3,30,129] In a retrospective study comprising data from 1659 cataract surgeries, preoperative use of PGAs was associated with a significant risk of the development of CME when patients with diabetes mellitus were excluded (odds ratio = 12.45).[39] Similarly, a nested case-control study (N = 508 cases) found that postoperative use of bimatoprost or travoprost/travoprost-z in the year before diagnosis of pseudophakic CME was significantly associated with increased incidence of pseudophakic CME.[119] In the same investigation, there was

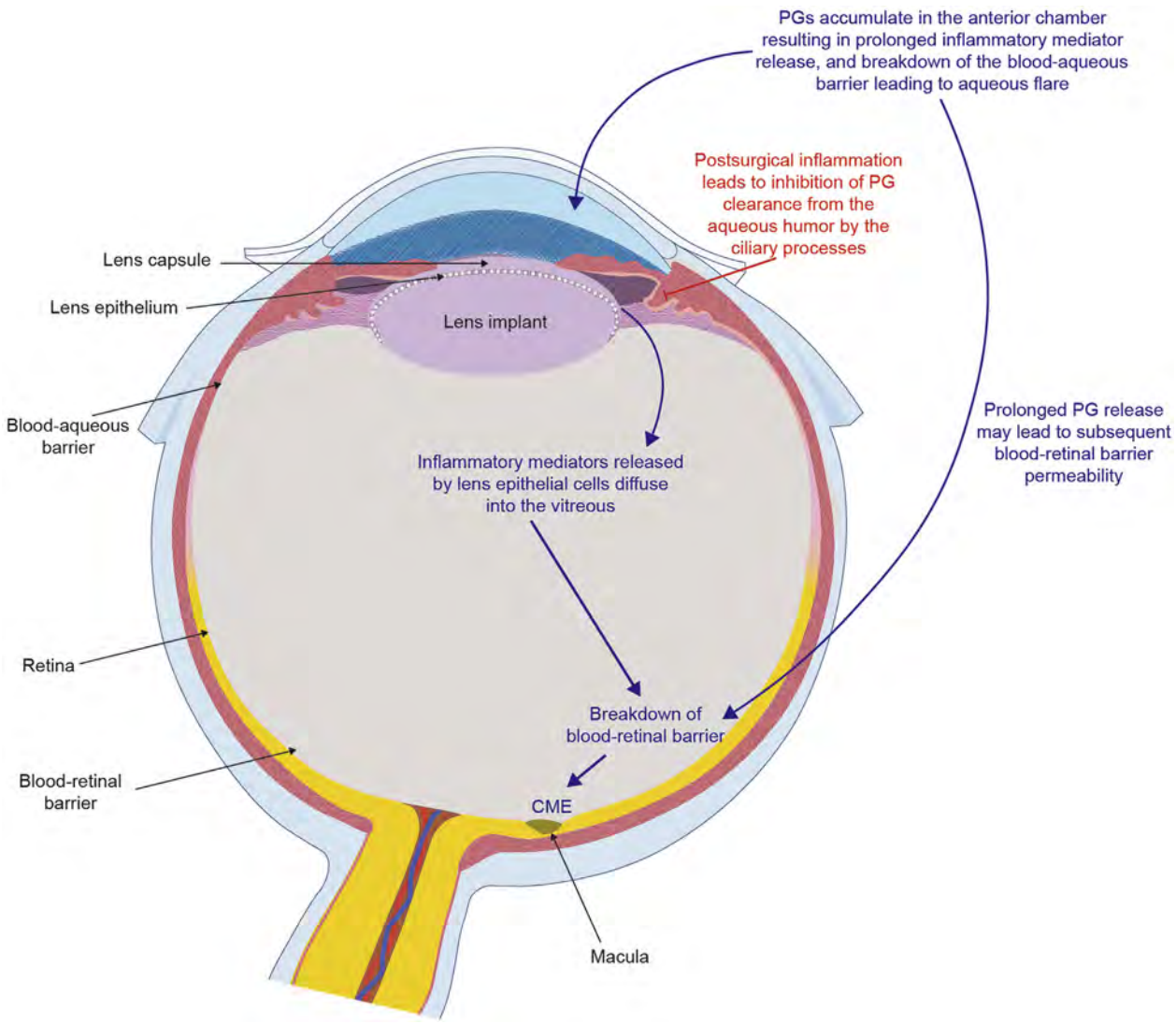

Fig. 3 – Proposed mechanism by which PGs increase the risk of CME after cataract surgery. After cataract surgery, lens epithelial cells and other anterior segment tissues are affected by surgical stress release inflammatory mediators. Postsurgical inflammation leads to inhibition of PG clearance from the aqueous humor by the ciliary processes, resulting in the accumulation of endogenous PG production in the anterior chamber. Accumulation of inflammatory mediators may result in blood-aqueous barrier breakdown. Transvitreal diffusion of inflammatory mediators to the retina may result in blood-retinal barrier breakdown and subsequent development of CME. CME, cystoid macular edema; PG, prostaglandin; PGA, prostaglandin analog.

no association found between pseudophakic CME and postsurgical use of latanoprost; however, the association was significant between overall PGA use (including latanoprost) and CME development (relative risk compared with no PGA use = 1.86). The difference between latanoprost and the other PGAs was not explained. In a prospective, randomized, observer-masked, 6-month trial in pseudophakic or aphakic patients with glaucoma, CME was detected using FA in 4 of 15 latanoprost-treated eyes (27%), 1 of 16 bimatoprost-treated eyes (6%), and 1 of 17 travoprost-treated eyes (6%) up to 6 months after treatment initiation.[4] There was no statistically significant difference between the three PGAs in the incidence of CME. The mean aqueous flare values throughout follow up were significantly higher in patients receiving bimatoprost, latanoprost, and travoprost compared with unoprostone ($P < 0.02$); however, there was no difference in aqueous flare between eyes treated with bimatoprost, latanoprost, or travoprost.[4] In another study, in patients with pseudoexfoliative glaucoma, CME occurred in 3 of 69 PGA-treated eyes (4.4%) after uncomplicated cataract surgery.[32] However, the PGAs associated with CME and the time of the onset of CME after cataract surgery were not specified. CME has been reported in a patient who did not have glaucoma but who accidentally administered 6 doses of latanoprost for 7 days after uncomplicated phacoemulsification with intraocular lens implantation instead of the prescribed

tobramycin-dexamethasone drops. In this case, the CME with latanoprost was closely linked with the cataract surgery and not underlying glaucoma.[64]

Regarding data on the relationship between individual PGAs and the development of CME, most publications concern latanoprost, the first and most widely used PGA in clinical practice. The incidence of CME during latanoprost treatment is reported between 1.2 and 5% of eyes that had previously undergone cataract surgery.[61,115,128,F] CME has been reported to occur from 7 days after initiation of latanoprost treatment up to 11 months after treatment initiation[8,16,37,61,63,76,115,F]; however, it is unknown if longer duration of latanoprost treatment increases the incidence of CME. A case report has described development of CME 1 month after switching isopropyl unoprostone to latanoprost in a pseudophakic eye with a history of surgical complications.[116] Within 8 weeks of the treatment change, visual acuity decreased, and CME was detected. No association between CME and latanoprostene bunod has been reported. This may be because of a lack of experience with long-term use of this molecule in a wide population of patients, considering that it only became available at the end of 2017; however, the prescribing information states that, owing to the PGA component, it should be used cautiously in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, and in patients with known risk factors for macular edema.[A]

Two case reports have been published on two separate incidents of CME in patients who received topical tafluprost treatment after cataract surgery. It was not specified in either report whether the formulation used was preservative free or preserved. Because the preserved formulation contains a low concentration of benzalkonium chloride (BAK) (0.001%, as opposed to 0.02% in BAK-preserved latanoprost), it seems likely that these rare cases were attributable to the PGA component of the treatment rather than the preservative.[66,89] The role of BAK in the development of CME is discussed later in this review.

Despite the evidence provided for the increased risk of pseudophakic CME by treatment with topical PGAs, in some publications the authors dispute the role of PGAs in increasing this risk. In a retrospective comparative case series of patients with uveitis and raised IOP, CME occurred only in 6 of 127 eyes (5%) on PGA medication and with a history of, or high risk for, CME, and in 9 of 96 eyes (9%) that had a similar history and risk but did not receive PGAs.[19] Similar results were reported in a large retrospective database study of 3394 eyes that underwent cataract surgery. This study found that there was no statistically significant increase in the risk of clinically significant CME related to PGA use in the first 3 months after cataract surgery (relative risk to eyes that were not treated with PGAs was 1.11 [95% confidence interval 0.816–1.513]).[22] The reported retrospective studies have limitations including the nature of the retrospective study design. In addition, the studies only recorded clinically significant macular edema and have not systematically and continuously monitored patients using OCT or FA. Prospective studies on the relationship between PGAs and the development of CME are limited; however, a small, prospective, randomized controlled study has shown that treatment with latanoprost in the first month after cataract surgery (n = 76) significantly increased mean central macular thickness (±standard deviation) by 12 ± 49 μm from baseline (P = 0.03), but this returned to baseline by month 3. Changes from baseline were not significantly different from patients who discontinued latanoprost treatment after cataract surgery (n = 80).[27] Similarly, another small prospective study found that in 41 eyes of 31 patients treated with latanoprost for at least 4 months after cataract surgery, there was no significant change from baseline in central macular thickness, average macular thickness, or macular volume.[75] These data are not in agreement with most retrospective studies which found an overall association between PGA use and CME development; however, this may be explained by the findings of Wendel and coworkers,[119] who found an overall association between PGA use and CME development (N = 508) but did not observe this association with latanoprost specifically.

6.1. *PGA-timolol fixed combinations and CME*

Fixed combinations of a PGA and timolol are extensively used in clinical practice. Therefore, the relationship between the various PGA-timolol fixed-dose combinations and CME is of clinical importance. In a 6-week, prospective, randomized, open-label study, CME was not reported in patients who did not have recent cataract surgery and received a combination of latanoprost and timolol, whether taken as separate instillations (n = 58) or as a fixed-dose combination (n = 56).[12] The macula was assessed using dilated fundoscopy, but it was not stated if patients were monitored for CME or if it was diagnosed after a visual complaint. Therefore, this study suggests that the addition of timolol does not increase the risk of CME in eyes treated with latanoprost that do not have a history of recent cataract surgery or ocular inflammation.[12] In a prospective investigation of the use of latanoprost-timolol in the treatment of glaucoma or ocular hypertension, it was shown that treatment with latanoprost-timolol fixed-dose combination led to the development of CME in 8 of 974 PGA-naive patients with glaucoma (0.8%).[2] However, no information on cataract surgery or pseudophakia was reported. In a retrospective study of 508 cases of CME in patients with a history of cataract surgery, 10 of 508 cases (1.97%) had been treated with β-blocker monotherapy, 25 of 508 cases (4.92%) with PGA monotherapy, and 5 of 508 cases (0.98%) with β-blocker and PGA.[119] The risk of CME development was not statistically different for PGA monotherapy or combined PGA and β-blocker treatment. A randomized, prospective, double-masked study found significantly increased aqueous humor flare in eyes treated with timolol and fluorometholone compared with preserved vehicle in the first week after cataract surgery, and compared with preservative-free vehicle up to 2 weeks after surgery (P < 0.05 for all).[72] We found no data on CME development in eyes treated with bimatoprost-timolol, travoprost-timolol, or tafluprost-timolol fixed combinations. Overall, data regarding the risk of CME development with combined PGA and timolol treatment are lacking, and more studies are required to adequately conclude if combination treatments influence the risk of CME compared with PGA monotherapy.

6.2. The role of preservatives in the development of CME

Some published data suggest that BAK, a commonly used preservative in ophthalmic solutions, may increase the incidence of CME in pseudophakic eyes. A randomized, prospective, double-masked study found significantly increased aqueous humor flare in eyes treated with BAK-preserved vehicle and fluorometholone compared with preservative-free vehicle and fluorometholone ($P < 0.05$).[72] The incidence of fluorescein leakage into a cystic space, measured by FA, was higher in eyes treated with BAK-preserved vehicle and fluorometholone than preservative-free vehicle and fluorometholone (26 of 28 eyes and 9 of 27 eyes, respectively; $P < 0.01$). Similarly, a prospective, randomized, investigator-masked study ($N = 44$) showed that artificial tears containing BAK increased aqueous humor flare compared with preservative-free artificial tears.[1] Although there were no cases of CME in this small study, it was concluded that BAK may cause blood-aqueous barrier disruption but does not lead to blood-retinal barrier disruption. Sufficiently powered randomized investigations are necessary to clarify if BAK-preserved formulations of topical PGA and PGA-timolol fixed-dose combinations increase the risk of CME development compared with the corresponding preservative-free formulations in pseudophakic eyes.

6.3. Overall consensus on the use of PGAs after cataract surgery

Currently, there is a lack of prospective, controlled trials that investigate the risk of CME development in pseudophakic eyes. Overall, in the postoperative period, caution should be exercised in administering PGAs in eyes with risk factors for CME, and a risk-benefit analysis for the individual patient should be considered. Concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs) with PGA treatment or close monitoring of the patient for CME should be considered.[40]

7. Management of pseudophakic CME

PGA-related CME can be effectively treated with discontinuation of the PGA and appropriate treatment of the CME.[4,63] In pseudophakic CME, the most commonly used treatment strategy is to suppress postsurgical inflammation using topical NSAIDs or corticosteroids, either separately or as a combined treatment.[33,39] A summary of the medical interventions used to treat pseudophakic CME is provided in Table 3. Corticosteroids are commonly used to treat pseudophakic CME because of their well-known anti-inflammatory effects. It has been shown that within the first 2 months of treatment, intravitreal triamcinolone acetonide injection provides significant improvement in visual acuity and reduction of macular thickness compared with pars plana vitrectomy performed without the use of corticosteroids, but the differences are not sustained for 12 months.[95] It has been reported, however, that there is a risk of CME recurrence 2–4 months after intravitreal administration of triamcinolone acetonide.[11] Intravitreal triamcinolone may be beneficial in patients with long-term or persistent pseudophakic CME; however, a clinically significant sustained IOP elevation is frequently associated with this intervention.[15,23,48,54] Corticosteroid-induced elevations in IOP and inhibition of corneal wound healing have directed interest toward the use of topical NSAIDs to treat postoperative inflammation and CME.[49]

Several investigations have shown that NSAIDs are useful in the treatment of pseudophakic CME; therefore, topical formulations have been developed.[29,86,113,118] Topical application of NSAIDs leads to higher aqueous concentrations than systemic NSAID administration. The active molecules reach the retina via transvitreal diffusion from the aqueous humor.[98,99] Subsequently, topical NSAIDs are widely used to treat pseudophakic CME.[98] NSAIDs have been approved by the US Food and Drug Administration (FDA) for the treatment of postsurgical inflammation after cataract surgery; however, FDA guidance states that the use of topical NSAIDs beyond 14 days postoperatively may increase the risk of occurrence and severity of corneal abnormalities.[D,E] A topical ophthalmic solution of nepafenac has been approved in the USA and Europe for the prevention and treatment of postoperative pain and inflammation associated with cataract surgery.[B,D] In addition, it is approved in Europe for the reduction in the risk of postoperative macular edema associated with cataract surgery in patients with diabetes.[B] Both ketorolac and diclofenac have also been shown to be effective in treating chronic pseudophakic CME. In this patient population, ketorolac has been shown to significantly improve distance visual acuity within 30 days of treatment compared with placebo.[29] In a randomized, prospective study, ketorolac and diclofenac similarly improved visual acuity in patients with chronic pseudophakic CME and resolved CME within approximately 13 weeks.[86] It has also been shown that ketorolac may be effective in treating CME that develops over 24 months after cataract surgery, but it may need to be administered for longer than 3 months to get a long-term therapeutic effect.[118] A randomized study investigated the efficacy of the addition of different NSAIDs for the treatment of pseudophakic CME in 39 patients treated with intravitreal corticosteroid and VEGF. The study found that nepafenac is more effective for the treatment of chronic CME than diclofenac, ketorolac, or bromfenac.[113] Nepafenac was the only adjunctive treatment to significantly lower retinal thickness and improve visual acuity compared with placebo ($P = 0.004$ and $P = 0.02$, respectively).

In patients with PGA-related CME, it is important to discontinue the PGA treatment and to control IOP during CME treatment. NSAIDs have been demonstrated to be an effective alternative to topical corticosteroid medication in CME, and unlike topical corticosteroids, topical NSAIDs do not influence IOP. Thus, they may be the preferred treatment option in patients who are susceptible to corticosteroid-induced IOP elevations[114]; however, the currently available data are insufficient to determine whether NSAIDs as a drug class are superior to corticosteroids in treating CME. One study demonstrated that nepafenac is more effective than subtenon triamcinolone acetonide in improving visual acuity in patients with pseudophakic CME.[131] In this study, treatment with nepafenac resulted in a statistically significant improvement ($P < 0.05$) in best-corrected visual acuity at every time point (months 1, 2, 3, and 6), but treatment with triamcinolone

Table 3 – Medical treatment options for pseudophakic CME

Drug class	Molecule	Type of CME	Study design*	Time to CME reduction (weeks)	Clinical comment
NSAID	Topical diclofenac sodium 0.1%	Pseudophakic CME	Randomized prospective study (N = 18)	7.5[86]	Effective in reducing the severity and duration of CME after uneventful phacoemulsification with posterior chamber IOL implantation[86]
	Topical ketorolac tromethamine 0.5%	Pseudophakic CME	Randomized prospective study (N = 16)	8[86]	Effective in reducing the severity and duration of CME after uneventful phacoemulsification with posterior chamber IOL implantation[86]
	Topical nepafenac 0.1%	Chronic pseudophakic CME	Prospective open-label pilot study (N = 15)	4[114,†]	All patients had previously responded to steroid treatment with an increase in intraocular pressure[114]
Corticosteroid	Intravitreal triamcinolone 1 mg	Refractory chronic CME	Nonrandomized retrospective case review (N = 8)	4–6[23]	Mean duration of CME before the intravitreal corticosteroid injection was 20 months; all eyes had been resistant to topical and periocular steroids[23]
Anti-VEGF	Intravitreal bevacizumab 1.25 mg	Refractory chronic CME	Retrospective case series (N = 10)	32[10,†]	Patients had previously been treated with ketorolac alone, or with acetazolamide or prednisone. Final follow-up was at 6 months[10]
Carbonic anhydrase inhibitor	Oral acetazolamide	Inflammatory CME (uveitic and pseudophakic)	Retrospective review (N = 16; 19 eyes)	12[83,†]	Patients included were a mix of pseudophakic and uveitic CME[83]
Immunomodulator	Infliximab	Refractory pseudophakic CME	Open-label, uncontrolled, retrospective, interventional study (N = 7)	12[124]	All eyes had been treated previously with topical nepafenac 0.1%, topical prednisolone acetate 1%, intravitreal triamcinolone (4 mg), and intravitreal bevacizumab (1.25 mg)[124]
	Interferon-α 2a	Refractory chronic CME	Interventional, retrospective case series (N = 3; 4 eyes)	4[25]	This was an interventional case series[25]
	Interferon-α 2b	Refractory pseudophakic CME	Case report	4[65]	Case report of one patient resistant to topical NSAIDs and multiple intravitreal bevacizumab injections over 9 months. The patient had adverse reactions to oral acetazolamide and intravitreal triamcinolone injections[65]

CME, cystoid macular edema; IOL, intraocular lens; NSAID, nonsteroidal anti-inflammatory drug; VEGF, vascular endothelial growth factor.
* Number of eyes is equal to the patient number unless otherwise stated.
† At first follow up.

acetonide only provided a significant improvement at months 2 and 6. Regarding combined topical NSAID and corticosteroid treatment, it has been suggested that combination of NSAIDs with corticosteroids is more effective than either treatment alone.[38] In this study, the combined treatment led to significantly more patients achieving two or more lines of improvement in Snellen visual acuity compared with corticosteroid monotherapy at every monthly study visit, and versus NSAID monotherapy at months 4 and 5 ($P < 0.05$ for all analyses). However, another study has shown that there was no statistically significant difference in visual acuity between treatment with ketorolac alone and ketorolac with adjuvant prednisolone treatments (mean Early Treatment Diabetic Retinopathy Study vision was 50.0 vs 54.7, respectively; $P = 0.36$).[103] The addition of NSAIDs to a corticosteroid and anti-VEGF complex treatment regimen for chronic CME resulted in significantly lower IOP elevation than the same treatment without NSAIDs.[113]

Intravitreal anti-VEGF treatment can also be used for CME owing to its effects on reducing blood-retinal barrier permeability.[5,6] Bevacizumab, a VEGF inhibitor, reduces central macular thickness and improves visual acuity in patients with CME and has shown effectiveness in treating pseudophakic CME.[5,6,10] Although these studies do not provide information on the duration of treatment required for the resolution of CME, there has been a report of CME resolution 1 month after intravitreal bevacizumab injection and another report of substantial improvement after 1 month of intravitreal bevacizumab treatment, with complete resolution observed at a 6-month follow up after treatment initiation.[6,10] Contradictory results were reported in a retrospective case series of 16 eyes; visual acuity remained unchanged in 12 eyes which were followed up for 14–82 weeks after intravitreal injection of bevacizumab.[105] Treatment of pseudophakic CME with ranibizumab in a study of 7 eyes provided statistically significant improvements in best-corrected visual acuity and significantly decreased central retinal thickness ($P < 0.001$ for both).[69] There are no data available on the effects of aflibercept treatment of pseudophakic CME.

Where treatment with corticosteroids and NSAIDs has been unsuccessful, alternative approaches have been used. Acetazolamide is a carbonic anhydrase inhibitor that effects the elimination of fluid from the subretinal space across the retinal pigment epithelial cells, thereby lowering fluid accumulation.[98] A recent retrospective review of 4 eyes with pseudophakic CME and 15 eyes with uveitic CME showed that oral acetazolamide (500 mg twice daily) significantly reduced central macular subfield thickness and improved visual acuity within 3 months ($P = 0.002$ and $P < 0.0001$, respectively)[83]; however, systemic side effects of acetazolamide were reported in several patients; paresthesia was reported by 10 patients, dysgeusia by 6 patients, fatigue by 5 patients, and diarrhea by 3 patients. One patient had treatment-related dehydration that required hospitalization. Similarly, in a retrospective study, infliximab, a tumor necrosis factor-α inhibitor, improved visual acuity and decreased central macular thickness in 7 eyes with refractory pseudophakic CME after 6 months of treatment.[124] In this study, refractory CME was defined as persistent edema diagnosed by OCT or FA despite prior treatment of the CME. There were no systemic safety concerns reported in this study, which was underpowered for analysis of safety outcomes. One case of anterior uveitis was reported, which responded to topical steroid treatment.[124] Few case reports on the effects of interferon-α 2 on CME have been published. In 4 eyes of 3 patients with pseudophakic CME refractory to local and systemic corticosteroids, treatment with interferon-α 2a led to resolution of CME within 4 weeks, and visual acuity improved in 3 of 4 eyes. A statistically significant improvement in mean best-corrected visual acuity was observed at 3 months ($P < 0.05$). No adverse events, aside from flu-like symptoms after the first dose and relapses of flu-like symptoms, were reported during follow up at 3–11 months.[25] In another case report, when interferon-α 2b was used to treat pseudophakic CME resistant to multiple NSAIDs and corticosteroids, CME improved after 4 weeks of treatment and resolved after 12 weeks. Visual acuity and macular structure were restored, and this effect was sustained throughout a 36-week follow-up period.[65]

Where pharmacologic options fail, surgical intervention may be an alternative treatment. If vitreous loss occurs during cataract surgery, vitreous strands may adhere to structures in the anterior segment. Lysing these adhesions using lasers or vitrectomy may reduce existing CME by restoring retinal vascular stability, thereby lowering vascular leakage.[88,98] In a small study conducted on 14 eyes with CME after complicated cataract surgery with vitreous incarceration in the corneoscleral wound, the vitreous strands were cut using neodymium-yttrium-aluminum-garnet laser. This treatment improved visual acuity in all eyes, of which 11 had visual acuities of 20/40 or better after follow up at 1–9 months.[51] Conversely, in a different study carried out in 29 patients with CME, with vitreous incarceration in the corneoscleral wound, 55% of eyes achieved two or more lines of stable visual improvement, 17% improved but had fluctuating levels of vision and persistent edema, and 28% failed to improve owing to other coexisting ocular pathology.[107] In a retrospective analysis of 23 patients with pseudophakic CME without vitreous incarceration in the corneoscleral wound, but with persistent CME unresponsive to medical treatment, pars plana vitrectomy was performed.[81] Vitreomacular traction was present in 4 eyes. The median best-corrected visual acuity improved from 20/200 to 20/60 ($P < 0.0001$) after a mean follow up of 30 months, with CME resolving in a mean period of 3.3 months. In conclusion, vitrectomy may be useful for patients with CME when vitreous traction is responsible for the development of CME which does not respond to medical treatment.

7.1. *Prophylactic treatments for CME*

There is currently no official FDA- or European Medical Agency-approved strategy for the prevention of pseudophakic CME. Although most surgeons use topical steroids with or without topical NSAIDs postoperatively, prophylaxis of CME by prescribing topical NSAIDs after cataract surgery is recommended in numerous studies.[41,52,120,126] In some investigations, the authors suggest that NSAIDs are significantly more effective in preventing CME than corticosteroids, and preoperative prophylactic use may be beneficial.[52,120,127] It has also been shown that administration of NSAIDs as an

adjunctive to topical corticosteroids is more beneficial than prophylactic corticosteroids alone.[98,122] Based on the currently available data, no general conclusion on the prophylactic benefits of the different topical treatment regimens can be drawn.[33,49,60] The long-term prophylactic effects of NSAIDs for treatment periods of more than 1 year have not been investigated.[33,98] Prophylaxis using anti-VEGF treatments has also been suggested; prophylactic treatment with pegaptanib (N = 250) administered after cataract surgery together with dexamethasone-tobramycin administered 4 times daily led to a significantly lower incidence of CME (0.4%) compared with dexamethasone-tobramycin treatment alone (N = 250; 4.4%) after uncomplicated cataract surgery (P = 0.009).[31] Although there were no reported safety concerns in this study, there are added costs and risks associated with intravitreal injections. In addition, as preoperative use of PGAs has been identified as a risk factor, there is a need for guidance in clinical practice regarding possible withdrawal of PGA treatment in patients with mild glaucoma undergoing cataract surgery and the appropriate duration of this withdrawal to minimize the likelihood of postoperative development of CME.

8. Expert opinion and conclusions

Pseudophakic CME seems to be more common than previously appreciated and may be underreported after cataract surgery. In several published studies and case reports, CME was detected only upon the report of decreased visual acuity; however, advances in OCT and OCT angiography technology allow noninvasive detection, quantification, and monitoring of CME. This makes it possible to assess CME objectively, but independently from central visual function. In addition, this means that CME may be detected in high-risk populations ahead of the development of vision loss, allowing for early treatment initiation and minimizing the risk of vision loss. Although angiographic CME observed using imaging techniques may resolve without intervention, prevention of visually significant CME is clinically important in patients who are at high risk for CME, including those with underlying ocular inflammation, retinal vascular diseases, elevated IOP, or who undergo cataract surgery. As such, these imaging techniques could be used more readily in these high-risk patient populations. Although the literature is still not clear on the relationship between PGAs and the development of CME, patients who require topical PGA administration or use of fixed combinations of a PGA and a β-receptor blocker in the early postoperative period after cataract surgery, especially when the eye is inflamed, may be at increased risk for CME. Therefore, to control postoperative IOP elevation in the early postoperative period after cataract surgery, the use of non-PGA IOP-lowering topical medication should be used at the physician's discretion following a benefit-risk assessment based on available data. Carbonic anhydrase inhibitors may theoretically be an alternative hypotensive treatment, given the use of topical formulations as IOP-lowering medications and the use of oral formulations in the treatment of refractory CME[83]; however, the IOP-lowering efficacy of topical carbonic anhydrase inhibitors is considerably less than that provided by PGAs.[109] In addition, there are safety concerns associated with the use of oral formulations to treat CME,[83] and data on the use of topical ophthalmic solutions in treating pseudophakic CME are limited.

Further research is needed to provide guidance on the use of prophylactic treatment for CME. Improvements in cataract surgery technique and additional care to prevent vitreous humor loss are necessary to minimize the risk of the development of pseudophakic CME. There is significant need for new topical IOP-lowering therapy options that provide clinically significant IOP reductions comparable to PGAs but at the same time do not increase the risk of CME and do not worsen its severity even in the early postoperative period after cataract surgery. Currently, careful glaucoma and cataract surgery, prophylactic treatment with NSAIDs, and avoidance of the use of topical PGAs in patients at high risk for CME are considered important clinical factors in preventing the development of clinically significant CME and the related decrease of central vision.

9. Method of literature search

- A thorough literature search was done on Medline from 1950 to 2019 using the main search term "(cystoid macular edema) OR (cystoid macular oedema OR CME OR CMO)" AND the following terms "prostaglandin AND cataract surgery", "prostaglandin", "bimatoprost", "travoprost", "latanoprost", "tafluprost", "unoprostone", "phakic", "(phakic) AND (glaucoma)", "diagnosis", "(prostaglandin) AND (management)", "management", "(treatment) AND pseudophakic", "glaucoma filtration surgery", "glaucoma filtration surgery AND prostaglandin", "selective laser trabeculoplasty", "laser trabeculoplasty", "selective laser trabeculoplasty AND prostaglandin", "trabeculectomy AND prostaglandin", and "glaucoma AND cataract surgery".
- A narrative search was also completed on Google Scholar to substantiate some of the data discussed.
- References were also obtained from citations in papers found in the original search.

Non-English language articles were obtained if a translated version was available.

10. Disclosures

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Major review

Diabetic keratopathy: Insights and challenges

S. Priyadarsini, MS[a,†], A. Whelchel, BS[b,†], S. Nicholas, BS[a], R. Sharif, MD, PhD[c], K. Riaz, MD[a], D. Karamichos, PhD[a,c,*]

[a] Department of Ophthalmology, Dean McGee Eye Institute, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA
[b] Department of Physiology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA
[c] Department of Cell Biology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA

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ABSTRACT

Ocular complications from diabetes mellitus are common. Diabetic keratopathy, the most frequent clinical condition affecting the human cornea, is a potentially sight-threatening condition caused mostly by epithelial disturbances that are of clinical and research attention because of their severity. Diabetic keratopathy exhibits several clinical manifestations, including persistent corneal epithelial erosion, superficial punctate keratopathy, delayed epithelial regeneration, and decreased corneal sensitivity, that may lead to compromised visual acuity or permanent vision loss. The limited amount of clinical studies makes it difficult to fully understand the pathobiology of diabetic keratopathy. Effective therapeutic approaches are elusive. We summarize the clinical manifestations of diabetic keratopathy and discuss available treatments and up-to-date research studies in an attempt to provide a thorough overview of the disorder.

1. Introduction

Diabetes mellitus (DM) is one of the most common deadly metabolic disease worldwide. The incidence rate of DM has risen over the years and is expected to double by the year 2030.[147] The steep increase of the diabetic population is thought to be mainly due to the changes in lifestyle that results in elevated calorie intake and obesity. Increase in the diabetic population has led to significant financial and clinical burdens and spurs demands for effective clinical treatments.[147]

DM develops when the pancreas fails to synthesize enough insulin or the body becomes resistant to insulin, or both, leading to high levels of blood glucose. The three main types are type 1 diabetes mellitus (type 1DM), type 2DM, and gestational DM (characterized in Table 1). DM is correlated with a number of complications accounting for increased disability, morbidity,

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* Corresponding author: Dimitrios Karamichos, PhD, 608 Stanton L. Young Blvd., DMEI PA-408, Oklahoma City, OK 73104, USA.
E-mail address: Dimitrios-Karamichos@ouhsc.edu (D. Karamichos).
† These authors contributed equally.
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Table 1 – Diabetes mellitus characterization

Type of diabetes	Clinical definition	Treatment
Type 1 diabetes mellitus	Type 1 diabetes mellitus, also known as insulin-dependent diabetes, or juvenile-onset diabetes. It is a result of cellular auto-immune destruction of β cells and leads to total insulin deficiency.	• Insulin administration • Carbohydrate counting • Frequent monitoring of blood sugar level • Healthy diet • Regular exercise and healthy weight maintenance
Type 2 diabetes mellitus	Type 2 diabetes mellitus, also known as non –insulin-dependent diabetes, or adult-onset diabetes. It is caused by the progressive decline of pancreatic β-cell function leading to insulin resistance and relative insulin deficiency. The specific etiologies of this type are still not known.	• Healthy diet • Regular exercise • Insulin therapy or diabetic medication • Frequent monitoring of blood sugar level
Gestational diabetes mellitus	Gestational diabetes mellitus is a type of diabetes mostly seen during pregnancy. It is defined as any degree of glucose intolerance during first symptoms of pregnancy or onset.	• Special diet plans • Scheduled physical activities • Frequent monitoring of blood sugar level • Insulin therapy

and mortality.[209] Acute metabolic complications associated with a high mortality rate and abnormally high blood glucose concentrations (hyperglycemia) include ketoacidosis. On the other hand, extremely low blood glucose concentrations (hypoglycemia) can lead to coma. Chronic uncontrolled DM may lead to devastating consequences in the form of long-term vascular complications.[97] The hyperglycemic condition during DM has various implications on various tissues, and the most common complications witnessed during such conditions are retinopathy, nephropathy, neuropathy, and keratopathy.[11,169,171]

DM is known to cause structural and functional alterations to the human cornea. The cornea is a clear, highly organized, external layer of the eye responsible for letting in and focusing light. It has three distinct layers separated by acellular membranes. The outermost layer is the epithelium (Fig. 1), responsible for protecting the eye against various foreign particles and providing protection to the other internal structures of the eye. Below the epithelium is a tough condensed layer known as the Bowman layer (Fig. 1). The Bowman layer is acellular and composed of collagen fibers difficult to penetrate, protecting the cornea from any deeper injury. The next and the thickest layer of the cornea is the stroma (Fig. 1), which provides the cornea its structure and elastic form and is also responsible for the corneal transparency. The fourth layer lying below the stroma is the Descemet membrane (Fig. 1), a thin elastic layer of the cornea that protects the cornea against various infections. The fifth and the most posterior layer of the cornea is the neuroepithelial layer, commonly referred to as the endothelium (Fig. 1), responsible for keeping the cornea clear by controlling the hydration of the cornea. The endothelium is a single layer of hexagonal cells approximately 5 micrometers in thickness.[37] All the different layers of the cornea have their own unique functions and together support the normal functioning of the eye.

2. Clinical relevance

Diabetic keratopathy or diabetic corneal epitheliopathy[204,216] is a degenerative corneal disease seen in patients suffering from systemic DM.[49] Diabetes prevalence among adults aged between 20 and 99 years in a 2017 International Diabetes Federation census was approximately 451 million worldwide. This number is expected to increase to 693 million by the year 2045[33] and, with approximately 46–64% of diabetic patients acquiring diabetic keratopathy,[170] this is a disease that requires serious clinical attention. Most corneal pathologies observed in clinics are seen around the epithelium, but may occur through all layers of the cornea. Some of the clinical features that are exhibited in the corneas of a patient suffering from diabetic eye disease are delayed corneal re-epithelization, reduced corneal sensitivity, neurotrophic corneal ulcers, and corneal edema. Fig. 2 provides images of some of these clinical manifestations. These are mainly caused by changes within the composition of the corneal epithelial basement membrane, deposition of glycation products, damage to the corneal nerve endings, reduced tear secretion, and oxidative stress during the hyperglycemic conditions. Clinically, diabetic keratopathy can also appear as punctate keratitis, reduced adherence to the basal membrane, and corneal hypoesthesia. Diabetic keratopathy severity is exacerbated by contact lenses, leading to decreased corneal transparency and impaired vision. The primary reason for developing such corneal conditions in diabetics wearing contact lenses is the increased susceptibility to microbial keratitis and corneal ulcers. The elevated glucose levels in the tears of diabetic patients is also considered to contribute toward the development of such pathologies. Interestingly, increased lens spoliation in diabetic patients does not recover as readily from contact lens-induced corneal edema when compared to nondiabetics, which is primarily considered to be due to the abnormalities in the corneal endothelium.[44,166,185] Furthermore, hypoxia-induced corneal swelling studies on diabetic corneas have shown significantly less edema than on controls, which could be a consequence of the reduced corneal swelling effects of hyperglycemia on corneal hydration.[44,143,166,184,185,207]

Diabetic keratopathy can be generally described as a deviation from the normal wound healing mechanism

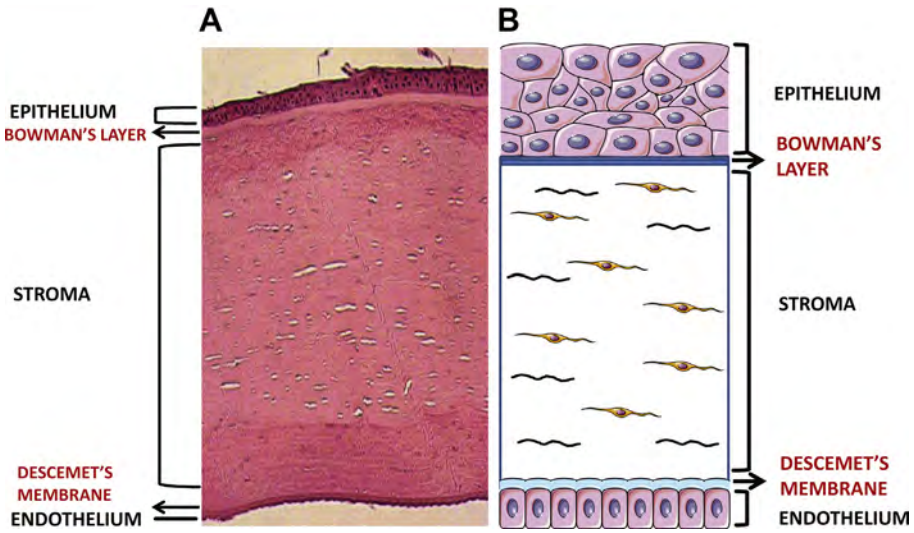

Fig. 1 – The human cornea: Five layers of the human cornea are shown: epithelium, Bowman layer, stroma, Descemet membrane, and endothelium. (A) Histology of the human cornea. (B) Representative human cornea illustration (not to scale).

leading to persistent corneal epithelial defects and unresponsiveness to treatments in the hyperglycemic environment. To date, the exact underlying mechanism behind diabetic keratopathy is not fully understood; therefore, further studies are needed to pinpoint the particular pathology underlying this disorder. While there have been several retrospective studies on corneal changes in patients with DM, clinical and laboratory studies regarding the corneal wound-healing process in patients with DM are minimal.[29,85] Corneal wound healing is a highly structured process that involves various cellular processes, including cellular migration and proliferation of epithelial cells, interactions between epithelial and stromal fibroblasts, and recruitment of various growth factors. Effective re-epithelization within a stipulated amount of time is essential to avoid potentially blinding microbial superinfection and corneal opacification. This re-epithelialization process is more difficult in patients with DM, possibly due to associated morphological changes along the epithelium which include varied number of epithelial cell layers, decrease in endothelial cell number, sectorial thinning, polymorphism, bullae, changes in the cellular coefficient of variation, and superficial debris.[163] Persistent corneal epithelial defects from diabetic keratopathy often lead to corneal scarring, corneal ulcer, decreased visual acuity or permanent vision loss, and corneal neovascularization.[211,214,222] The hyperglycemic environment of the DM cornea is also known to affect the stromal layer as well. A common stromal abnormality is increased stiffness attributed to collagen crosslinking as a result of long-term hyperglycemia. The increased corneal stiffness makes it difficult to measure the intraocular pressure (IOP), and thus, accuracy of the measurement suffers.[64,101] Endothelial dysfunction is also one of the clinical characteristics of DM. Morphological changes of the endothelial cells and alterations in cell density are some of the factors leading to an increased corneal thickness.[131] The aforementioned changes make it a complicated clinical condition that is challenging to treat.

3. Clinical manifestation

The prevalence of DM has risen exponentially over the last three decades, with a resultant increase in morbidity and mortality mainly from its complications. The most common clinical manifestations are discussed in the following sections.

3.1. *Corneal nerve density*

The cornea is the most densely innervated tissue of the human body.[176] The structure of the corneal nerves is essential in maintaining a healthy ocular surface. Perhaps the most common dysfunction experienced as a result of the hyperglycemic environment is nerve dysfunction or damage, commonly referred to as diabetic peripheral neuropathy. It is one of the most widely investigated conditions because of its frequent occurrence in patients with DM. In human beings, the corneal nerves penetrate the cornea through the stroma, further branch out, and progress anteriorly to the epithelium. These nerves appear as long bundles with fine branches and nerve endings. The nerves are involved in various corneal homeostatic functions such as blinking, the release of neuropeptides, neurotrophins, and growth factors.[72] The health and diseased conditions of the cornea greatly depend on innervation as it provides protective and trophic functions for the cornea. Several studies have shown that DM alters the corneal nerves, and this has been reviewed extensively.[12,17,71,120,125,169] Studies show significant reduction and morphological changes of the corneal subepithelial nerve fibers. During the early onset of DM, morphological changes of

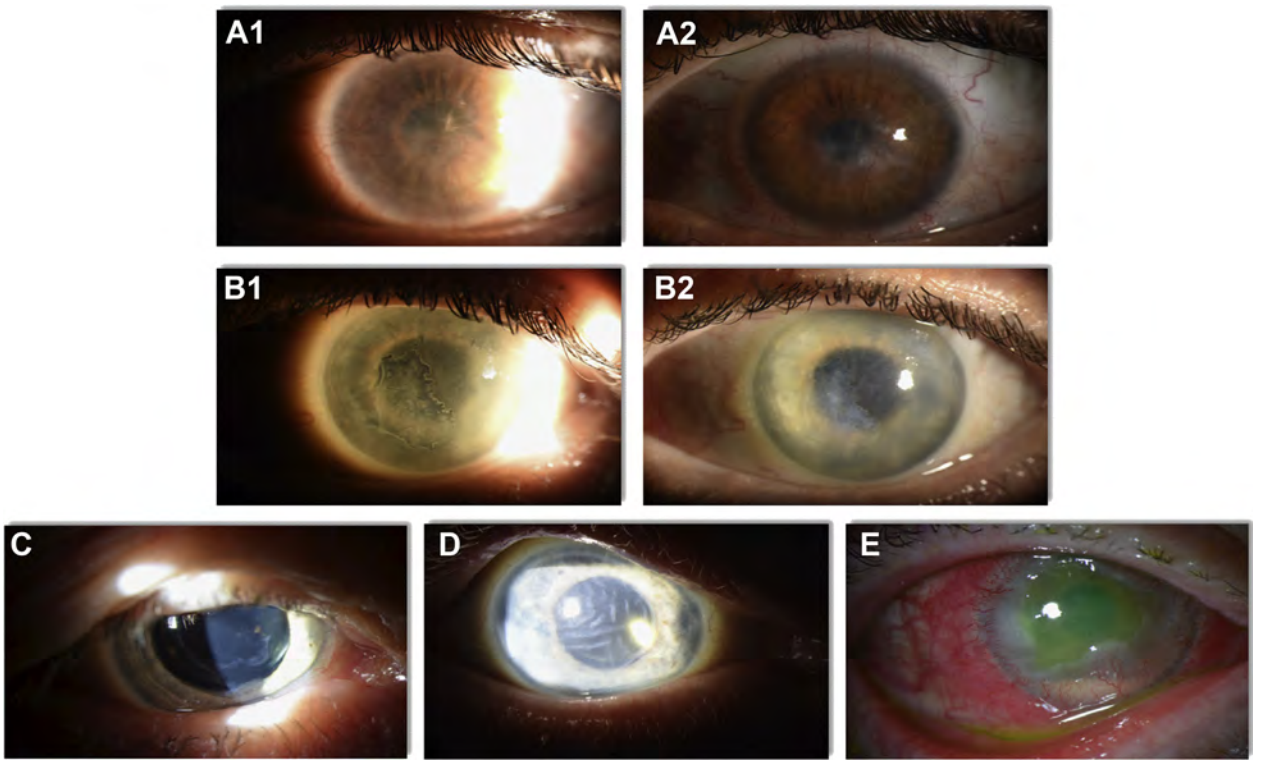

Fig. 2 – Representative images of common clinical manifestations of diabetic keratopathy. *A:* Sclerotic scatter illumination slip lamp photograph of the (*A1*) right and (*A2*) left eyes highlights areas of central stromal partial light-blocking scarring with adjacent irregular hyperplastic epithelium. Significant superior, nasal, and inferior neovascularization is present. *B:* Sclerotic scatter illumination slit lamp photograph of the (*B1*) right and (*B2*) left eye demonstrates diffuse stromal edema, Descemet folds, and microcystic edema after cataract surgery. A vertical corneal epithelial defect is also present. *C:* Slit lamp photograph of the right eye demonstrates epithelial irregularity and redundant basement membrane in a patient with diabetic keratopathy and epithelial basement membrane disease causing recurrent corneal erosions. *D:* Slit lamp photograph of the right eye demonstrates florid stromal folds and edema occupying most of the cornea with limbal sparing. Several bullae are seen superiorly. *E:* Slit lamp photograph of the right eye demonstrates 3 + conjunctival injection with significant epithelial defect occupying approximately 60–70% of the cornea with infiltrate. Prominent corneal neovascularization of 360 degrees of the cornea at multiple levels is also present. A 2-mm hypopyon is seen in the anterior chamber.

corneal nerves are observed, and prolonged exposure to such hyperglycemic conditions has been shown to lead to thicker corneal nerve fiber bundles, mainly from the accumulation of advanced glycation end-products (AGEs). The duration of DM is also known to play an important role in nerve deterioration.[71,72] Thus, corneal nerve dysfunction plays a significant role in the pathology of diabetic corneal disease.

3.2. *Corneal sensitivity*

The cornea is 300–600 times more sensitive than skin.[129] Corneal nerves serve a protective function by regulating corneal epithelial integrity and wound healing.[70,130] In DM, corneal nerve fiber loss is correlated with a significant reduction in corneal sensitivity,[135] which can lead to keratopathy.[40] In a study by Tavakoli and coworkers,[188] 147 diabetic patients with absent, mild, moderate, or severe neuropathy were compared with 18 control subjects. This study revealed that reduced corneal sensitivity in patients with DM progressed with the severity of neuropathy, suggesting that corneal nerve fiber damage accompanies somatic neuropathy, raising the possibility that corneal sensitivity could have a diagnostic value for diabetic neuropathy.

Rosenberg and coworkers[154] have reported that minimization of subbasal nerve plexus fibers correlates with loss of corneal sensitivity in patients with DM neuropathy, while tortuosity of these nerves correlated significantly with the severity of diabetic neuropathy. Another study by Hamrah et al[69] described significant morphological changes in the corneal subbasal nerve plexus in patients with herpes simplex keratitis and showed that reduction of nerve density correlated significantly with loss of corneal sensitivity in such patients. Patients with DM that have undergone intraocular surgeries are at a higher risk to develop corneal abrasions and recurrent epithelial defects. In one study, most of the 14 vitrectomy patients who exhibited corneal complications were diabetic.[185] This finding was supported by a study in which 83% of subjects who developed corneal complications including

delayed wound healing, after pars plana vitrectomies, were diabetic.[28] Another study showed that, of the patients with DM and corneal complications, 9 of 13 displayed prolonged or recurrent epithelial defects.[185] Patients with DM experience a delay in reepithelialization which is thought to be due to the presence of abnormal epithelial adhesion to the underlying basement membrane.[186] Corneal nerve abnormalities, as well as basement membrane imperfections, may justify the development of recurrent epithelial defects.[191] Studies by Göbbels and coworkers and Gekka and coworkers found that corneal epithelial barrier function is weakened in patients with DM, which is correlated with chronic disease duration and higher HbA1c levels.[61,63] Kabosova and coworkers[85] found that organ-cultured human corneas from patients with DM retinopathy exhibited delayed epithelial wound healing, in complete agreement with clinical data of patients with DM. Corneal sensitivity could potentially be used in clinics as part of the early diagnosis of diabetic peripheral neuropathy and/or keratopathy.[183]

3.3. *Epithelial defects and wound healing*

Corneal transparency and homeostasis are largely maintained by the epithelium, and in the event of injury or infection, quick epithelial resurfacing and healing is essential. Diabetes can increase susceptibility to spontaneous corneal traumas, including epithelial erosions and ulcerations.[53,54,85,204] In patients with DM, any injury/trauma to the corneal epithelium takes longer to heal, and epithelial lesions persist for a prolonged duration. Epithelial defects are usually resistant to conventional treatments.[29,218] The nonhealing epithelial defects caused by diabetic keratopathy may lead to severe visual defects.[114] Regulation of DM corneal epithelial wound healing is a cascade that is orchestrated by numerous growth factors and cytokines, leading to downstream signaling modulation. The major players include, but are not limited to, transforming growth factor beta, epidermal growth factor (EGF), human growth factor, opioid growth factor, insulin-like growth factor (IGF), nerve growth factor (NGF), keratinocyte growth factor, platelet-derived growth factor, thymosin-β4, IL-6, and IL-10. These affect cell migration, proliferation, differentiation, survival, and apoptosis, as reviewed by several recent articles, with emphasis on their importance as potential therapeutic targets to address epithelial wound healing.[36,114,221] The accumulation of AGEs observed in the diabetic cornea[85,87,179] does not support effective migration of epithelial cells essential for wound healing[85,187,222] and can, therefore, lead to delayed wound healing and recurrent erosions.[40,85,163]

Cataract and laser-assisted–*in situ* keratomileusis (LASIK) surgery are some of the high-risk surgeries for patients with DM. About 20% of cataract surgeries are performed on patients with diabetes, as these patients are 2–5 times more likely to develop lens opacity.[80] The surgery can be complicated for patients with DM, leading to often unfavorable outcomes.[67]

Glycemic changes are considered as the potential source of complications during keratorefractive and cataract procedures.[80] Corneal hypoesthesia is common in patients with diabetes, which requires special attention during surgeries to protect the epithelium. Corneal abrasions after or during surgery may lead to slow healing and thus to frequent corneal erosions.[80] Another surgery that is common among such patients is LASIK, which is considered a high-risk surgery for patients with DM.[182] Corneal complications, such as decreased corneal sensitivity and denervation, with increased risk of infections and delayed wound healing, make LASIK surgery challenging.[182] The frequency of post-LASIK complications makes it less effective in the DM population.

3.4. *Corneal erosions*

Corneal erosions are a common complication seen in patients with diabetic keratopathy. These were first reported in 1872 and were characterized by the spontaneous breakdown of the corneal epithelium.[43] Corneal erosions are difficult to treat in patients with DM because of their inherently impaired healing mechanism. Reduced reepithelization and defective epithelial barrier function make the cornea more exposed to various infections and, as a result, can lead to persistent corneal erosions and edema. Patients with DM are known to have more severe damage from corneal abrasions that, in some cases, leads to the detachment of the basement membrane and, in other cases, recurrent corneal erosions (RCEs).[185] Corneal erosions have been associated with various other corneal conditions, such as corneal epithelial dysfunctions, stromal infiltrations, epithelial basement dystrophies, and opacity. Studies have also shown corneal erosions leading to corneal thinning which is primarily due to the corneal stromal disorganization that disturbs the collagen fibrillary arrangements and thereby affects the ECM organization.[64,88,89,101,163] Thus, corneal erosion is one of the major clinical manifestations in patients with DM.

3.5. *Corneal cell density*

The balance between cell differentiation, migration, proliferation, and cell death helps maintain normal corneal epithelial cell density, thus reducing the risk of infections and erosions in the DM cornea.[152] Various studies have shown altered maturation, focal degeneration, and accumulation of glycogen granules in the DM epithelial layer.[191] Previous studies also revealed lower basal cell density in patients with DM, indicating that these epithelial pathological manifestations could be a consequence of basal cell depletion caused by a reduced level of corneal innervation.[199] Some studies reported that the endothelial cell density in patients with type 2DM is somewhat similar to that found in healthy subjects.[78] Lee and coworkers compared corneal morphology between 200 patients with DM and 100 normal control subjects. The study showed that the patients with DM had thicker corneas, less cell density, and hexagonality.[110]

3.6. *Corneal thickness*

Among the various ocular pathologies caused by DM, increased corneal thickness is one of the most well-established, thought to be the earliest detectable pathological manifestation in the diabetic eye.[26,185] Many clinical evaluations have shown increased central corneal thickness (CCT) in diabetics when compared with healthy

individuals. Stromal edema, induced by epithelial and endothelial dysfunction of the diabetic cornea, is a large contributor to the increased thickness observed.[180] Other factors that could be contributing to the increased corneal thickness are increased AGE production and glycation-induced collagen crosslinking. This is further supported by clinical studies on vascular components of the disease, which have shown that HbA1c, blood glucose levels, and severe retinal complications are associated with increased CCT in diabetic patients.[26,110,185] Interestingly, some of the studies suggest that the increased corneal thickness is linked to duration of disease being greater than 10 years.[110] Saini and Mittal[161] later established that, in type 2DM, the corneal endothelial function is significantly compromised in comparison to nondiabetic controls, and patients with diabetic retinopathy had the most adversely affected endothelial function.[185]

3.7. *Tear secretion*

An interesting relationship exists between DM and lacrimal gland dysfunctions, related to dry eye syndrome. Frequently, combined hyperglycemia, peripheral neuropathy, and reduced tear secretion induce corneal epitheliopathy accompanied by several complications including persistent epithelial defects, chronic erosions, and neurotropic keratopathy.[220] Patients with DM mostly complain of ordinary dry eye syndrome, such as foreign body sensation and burning. Altered tear film secretion may also lead to reduced lipid layer of the tear film and transient visual acuity reduction. Corneal nerve defects, as a consequence of hyperglycemia and/or microvascular damage to the tissue, lead to neurotrophic lesions and block the feedback mechanism that controls tear film secretion. These nerve defects occur late in this process; however, they play an important role in severe presentations of the diabetic dry eye. The prevalence of dry eye syndrome in DM is 15–33% in those older than 65 years and is 50% more common in women than in men. Dry eye syndrome in patients with DM can also develop after a number of ocular surgeries such as cataract surgery,[91] photorefractive keratectomy, and LASIK,[134] complicating the treatment of DM-induced corneal erosions and epithelial defects.

3.8. *Biomechanics and crosslinking*

The diabetic phenotype of the cornea can also affect its biomechanical properties. As an elastic structure containing high amounts of collagen, the cornea has an innate biomechanical structure that is a strong player in the light refraction capabilities of the cornea. Changes in corneal structure can affect biomechanical properties and, thus, vision.[175] While some research has suggested that all layers of the cornea exhibit some biomechanical properties, the stroma provides most of the biomechanical strength of the cornea. Corneal biomechanics can be measured by strip extensometry, eye inflation, Brilluoin microscopy, air-puff, ultrasound, optical coherence tomography elastography, and enzymatic digestion[99]; however, many of these measurements are taken *ex vivo*, limiting accuracy. The most common *in vivo* methods used by clinicians utilize air-puff technology to take their measurements, as they are easy to use and minimally invasive and provide very insightful measurements on corneal elasticity. Instruments of this type that have been used for diabetic studies are Corvis ST and ORA (OCULUS, Inc. Arlington, WA). Some studies have suggested that ORA has more reproducible and trustworthy results than the Corvis ST and other similar technologies[122]; however, both are still used in corneal biomechanical research. Ramm and coworkers[150] conducted a study using ORA and Corvis ST on diabetic patients with age-, CCT-, and IOP-matched controls and found statistical significance between thebiomechanical measures of the diabetics and those of the healthy controls.

There is a considerable amount of variation among different biomechanical measurements.[116] Many studies have found that corneal hysteresis (CH) values are increased in diabetic patients compared to healthy controls.[64,68,101,139,167,172] Contradictory to this, few studies have found that CH values are decreased in the diabetics.[13,146,160] Goldich and coworkers[64] observed that CH was significantly increased among 40 diabetic subjects compared to 40 healthy while accounting for CCT in the analysis. In a study of 43 diabetic patients and 61 healthy patients, Sahin and coworkers[160] found that CH was decreased in the diabetics relative to the healthy corneas, while CCT and IOP were increased. Perez-Rico and coworkers[146] showed that uncontrolled diabetics (HbA1C $>$ 7%) show significantly lower CH values than the controlled diabetics, while Scheler and coworkers[167] found significantly higher CH in uncontrolled diabetes than in controlled diabetics. The aforementioned studies highlight limitations to obtaining accurate corneal measurements from patients with DM.

While many studies on the biomechanics of the diabetic cornea have been *in vivo* in humans, Bao and coworkers[10] used rabbits with alloxan-induced diabetes, as biomechanical similarity between rabbit and human corneas has been reported. In this study, the authors used tangent modulus (Et) to define the elasticity of the rabbit corneas and took measurements including IOP, CCT, blood glucose levels, and AGE accumulation in the aqueous humor. The study found that independent evaluations of Et, IOP, and CCT were all associated with blood glucose and AGE accumulation. These results suggest that the diabetic cornea experiences increased stiffness, corneal thickness, and IOP as a result of the hyperglycemic state and/or AGEs. Increased AGEs is also known to cause oxidative stress.[84,202] Interestingly, hyperglycemia has been shown to induce collagen crosslinking *in vitro* and *in vivo*[153,157,162] by glycation of the collagen bundles.[60,123] This mechanism could play a pathogenic role in the posited protective role of diabetes on keratoconus severity.[100,105,136,173] The studies discussed here include both type 1DMs and type 2DMs. Further research needs to be carried out to understand the differences between these different pathologies.

4. Available treatments

Standard treatments for diabetic keratopathy include the use of topical lubricants,[65,92,117] topical antibiotic ointments,[18,41,45,50,66,117,196,210,213] patching, bandage soft

contact lenses (BSCLs),[51,66] tarsorrhaphy, and corneal transplants.[214] None of these methods are greatly effective, even when used in combination, especially for type 1DM, as they do not address the problem of delayed corneal healing secondary to DM.[1,107,124] Diabetic keratopathy, brought on by any form of DM, is primarily managed by addressing blood glucose control and the symptoms associated with hyperglycemia. Type 1DM is treated with insulin therapy, whereas patients with type 2DM are often prescribed drugs such as metformin that increase insulin sensitivity and lower endogenous glucose production. If insulin is gradually depleted, patients with type 2DM are shifted to insulin.[199] In the following sections, we review available treatment options for the patients suffering from diabetic keratopathy.

4.1. *Topical treatments*

Topical ointments support surface moisture in the eye and are retained longer than aqueous solutions.[58,117] With regard to diabetic keratopathy, topical ointments are generally delivered upon the appearance of corneal erosions and ulcers to provide comfort rather than actually treating the defects.

Preservative-free methylcellulose-based ointments are preferred to paraffin-based ointments as these can disrupt tear film stability and irritate the eye and are flammable. Preservative-free lubricants are recommended as preservatives can irritate the ocular surface.[58,117,181] Methylcellulose-based lubricants prolong tear breakup time and create firm adhesion between the upper and lower eyelids and help to prevent tear film evaporation.[19,117,141,168] Rebamipide, an antiulcer agent, was investigated as a potential therapeutic option, with promising results, on a 33-year-old female exhibiting corneal erosion and diagnosed with Sjögren syndrome.[92] Kashima's group[92] used topical rebamipide to treat patients and observed gradual improvement of corneal erosions that completely resolved within 4 weeks of the initial administration of the drug. Dry eye sensation was also ameliorated during the same period. The authors suggested that the drug improves ocular surface conditions and could provide a novel approach in treating dry eye–associated diseases.

Gottsch and Akpek[65] administered topical cyclosporin to five patients (7 eyes) presenting with corneal ulcers. Six of the seven eyes responded well, and after 2 weeks of treatment, reepithelialization occurred. None of the patients experienced recurrences of corneal ulceration after a mean follow-up of 28 months.

Finally, in almost every situation, topical prophylactic antibiotics can be applied in solution or ointment and are recommended in the prevention of secondary infection and/or further ulceration. These typically include erythromycin 0.5% ophthalmic ointment, polymyxin B/trimethorprim ophthalmic solution, and sulfacetamide 10% ophthalmic ointment/solution and are generally administered 4 times daily until symptoms subside for 24 hours.[18,41,45,50,117,196,210,213]

4.2. *Patch closure*

Patching the eye has been used in the past to improve discomfort by pressuring the eye and decreasing friction from blinking. It also creates a moist environment that is more beneficial for healing[214]; however, several studies have suggested that there is little benefit and can even pose harm to the cornea. Researchers found that using ointments alone improved healing significantly faster, with fewer reports of blurred vision and pain, than using same ointments with a pressure patch.[8,76,86,96,108,117,145,151,194]

4.3. *Bandage contact lenses*

BSCLs have been used to manage corneal surface disruptions and, unlike patching, can be used in congruence with topical treatments, thereby prolonging contact time of treatment with the ocular surface and serving as a reservoir that aids in the uptake and release of medications, as compared to topical treatment via ocular lubrication.[2] BSCLs also allow the patient to have usable vision and allow physicians to observe the cornea without removing the bandage. In the same way as patch closure, BSCLs further act as a barrier to reduce epithelial injury by the shearing force of eye-blinking.[90,192] Triharpini and coworkers[192] compared the use of BSCLs with pressure patching in combination with antibiotics and 0.5% tropicamide eye drops and found that the size of the corneal erosion area was reduced in the BCL group compared to the pressure patched group. In the BCL group, all the 16 eyes evaluated were healed after 72 hours, whereas only 75% of the 16 pressure-patched eyes were healed after 72 hours. The study also found that BCLs reduced pain without complications. Fraunfelder and Cabezas[51] assessed the efficacy of BCLs in 12 patients with recurrent corneal erosion. Patients were fitted with extended-wear BCLs for 3 months, and after a 12-month follow-up, 9 of the 12 patients showed no future signs of RCE.

Hadassah and coworkers[66] evaluated the efficacy of succinylated collagen bandage lenses in the context of corneal wound healing. Clinical evaluations of succinylated collagen bandage were carried out in various corneal conditions including patients with corneal ulcers. This study showed a significant reduction in symptoms, with no discomfort or changes in visual acuity. The authors concluded that the use of succinylated collagen bandages poses a promising alternative to other bandage lenses used in corneal healing.

4.4. *Corneal transplantation*

Amniotic membrane (AM) grafts have been studied for their potential of facilitating epithelial migration and healing.[42,93,149,214] Gheorghe and coworkers[62] investigated the efficacy of AM transplantation in 28 patients with ocular surface pathologies including persistent epithelial defects. During a 1-year period, all patients had necrotic and scar tissue excised before suture placement of AM graft. After a 12-month follow-up, positive results were observed in all patients, with 23 of the 28 reporting visual acuity improvements.

Vlasov and coworkers[201] conducted a study where forty PRK patients were fitted with an Acuvue Oasys lens (ACUVUE. Jacksonville, FL) on the dominant eye and a cryopreserved AM (suture less) on the nondominant eye. Patients were evaluated daily until complete corneal reepithelialization was observed in both the eyes. The study found that corneal

reepithelialization occurred faster with AM grafts but was comparable to previously reported BCLs. Researchers are currently looking to develop a type of synthetic membrane made of collagen or polymer matrices infused with growth factors and antimicrobials.[148,149] Recently, a study was conducted comparing AM grafts with lamellar corneal transplantation in treating corneal thinning. The authors found that all their patients had increased corneal thickness, but it was higher in those who underwent lamellar corneal transplantation (180 days after the operation). While AM transplantation also showed epithelialization, lamellar corneal transplantation may present a better alternative as tissue can be reabsorbed after AM transplantation surgery.[47] As a final measure, diabetic keratopathy patients may require tarsorrhaphy or corneal transplant surgery.[82,174,214]

4.5. *Growth factors*

Growth factors that have been identified in the corneal epithelium are currently being studied in the context of diabetic keratopathy. Because some were found to be effective in healing corneal ulcerations, we highlight these findings in the following sections.

4.5.1. *IGF-1 and substance P*

IGF-1 and Substance P simultaneously stimulated corneal epithelial migration, but when applied separately, the two had no detectable effects on epithelial cell migration.[138] Clinically, eye drops containing Substance P and IGF-1 were found to be effective in treating a child with neurotrophic and anhidrotic keratopathy.[23] A 55-year-old woman referred to Chikama's group[31] was experiencing corneal epithelial erosions due to hypolacrimation. The erosions did not heal after treatment with eye drops containing ofloxacin and hyaluronic acid or with therapeutic soft contact lens. Chikama's group treated the woman with eye drops containing Substance P (FGLM) and IGF-1, four times daily. Clear visible epithelial resurfacing was observed after 2 days of treatment, and within a week, defects were reduced to less than 10% of their original size. Complete resurfacing was observed within 2 weeks, and after 4 weeks, corneal transparency was satisfactory to suspend treatment. Corneal sensation was lost after treatment stopped, but no epithelial defects recurred after 5-month follow-up. Lee and coworkers[109] treated a 79-year-old monocular woman with persistent epithelial defects using eye drops containing Substance P and IGF-1 every 15 minutes for 2 hours (morning and night) for one week. During treatment, the patient was allowed to continue ocular treatment hypertension using polymyxin B and brimonidine. The authors observed complete wound healing within one week after treatment and discontinued polymyxin B and Substance P/IGF-1 after a 2-week taper. The epithelium remained intact upon examination at 3 weeks, after discontinuing therapy, and remained healed after an 8-month follow-up. Benitez-del-Castillo and coworkerrs[14] describe a 32-year-old woman suffering from RCEs who had previously been treated with eye drops and ointments containing 5% NaCl and later was given a therapeutic contact lens but saw no healing or improvement. Benitez-del-Castillo's group treated her with 20% autologous serum, 4 times daily, but saw no improvement. Eye drops containing Substance P–derived peptide and IGF-1 were then prescribed 4 times daily with complete epithelial resurfacing eleven days after the initial dose. The treatment was discontinued after 2 months when the cornea returned to normal. No recurrences were observed after an 11-month follow-up. Chikamoto and coworkers[32] used eye drops containing Substance P (FGLM-amide) and IGF-1 (SSSR) to prevent postsurgical superficial punctate keratopathy in 29 diabetic patients. Within 2 days from treatment, superficial punctate keratopathy scores were significantly lower in the FGLM-amide/SSSR group than those in the control group, as well as density scores 7 days after surgery. Eye drops containing Substance P and IGF-1 derivative tetrapeptides were effective in the treatment of persistent corneal epithelial defects associated with neurotrophic keratopathy in 19 out of 26 eyes, and complete resurfacing was observed within 4 weeks of initial treatment.[217] Nishida and coworkers[140] demonstrated that treatment with a combo of substance P–derived peptide, phenylalanine-glycine-leucine-methionine (FGLM)-amide, and IGF-1 stimulated corneal epithelial wound closure *in vivo*. Resurfacing was observed in nine out of eleven patients with no adverse effects.

4.5.2. *Epidermal growth factor*

Lou-Bonafonte and coworkers[115] concluded that EGF eye drops administered 2–3 times/day at 50–1000 ng concentrations could be effective in treating diabetic keratopathy based on data gathered from 12 articles that treated 305 eyes with EGF eye drops, 38 of which were human studies.[20] Kim and coworkers[94] used platelet-rich plasma eye drops containing high concentrations of growth factors, namely EGF, and treated patients with persistent epithelial defects. After platelet-rich plasma treatment in 11 eyes, healing rates were significantly higher than those treated with an autologous serum in 17 eyes. The authors attributed the effectiveness of the platelet-rich plasma treatment to its high concentration of EGF and stated that platelet-rich plasma could be an effective treatment for chronic ocular surface disease. More recently, Anitua and coworkers[7] evaluated biological outcomes of plasma rich in growth factors eye drops on corneal stromal keratocytes (HKs) *in vitro*. The study found that plasma rich in growth factors eye drops significantly enhanced the biological outcomes of HKs and could be used to improve corneal wound healing.

4.5.3. *Nerve growth factor*

Phase I clinical trials[48] have shown that recombinant human NGF eye drops appear to be well tolerated and safe.[6,48,118] Two phase II clinical trials tested the treatment of NGF eye drop solutions; however, one of the trials was terminated because of the inability of the drug manufacturer to supply the drug.[15] A phase III trial assessing the safety and efficacy of T4020 treatment was recently concluded.[155,190]

Lambiase and coworkers[106] found that the application of topical murine NGF eye drops daily for 4–12 weeks repaired corneal ulcers and revealed no observed negative side effects with no signs of relapse after a 4-month follow-up. Murine NGF eye drops were used in another study[21] that observed corneal epithelial healing with multiple daily treatments. Some side effects were reported during the first days of treatment, including hyperemia and ocular and periocular pain.

4.6. Aldose reductase inhibitor

Increased levels of erythrocyte aldose reductase (AR) in patients with type 2DM has been reported to cause accumulation of sorbitol and damage to the corneal epithelium.[52,81] In the polyol pathway, AR is a rate-limiting enzyme that converts glucose into sorbitol.[1,74] AR inhibitors have been studied in DM-related corneal epithelial abnormalities.[74] Nakahara and coworkers[137] evaluated the efficacy of topical AR inhibitor (CT-112) on corneal epithelial barrier function in diabetic patients and found that superficial punctate keratopathy scores did not significantly differ between the CT-112 and the placebo groups. The average fluorescein concentrations differed significantly after 4 and 8 weeks of treatment, however, and they concluded that CT-112 improved the corneal epithelial barrier function in their patients. A clinical trial[55] was conducted on diabetic patients who received oral ARI (ONO-2235; n = 12) or placebo (n = 9) for 12 weeks. The trial found that, after 12 weeks of treatment, fluorescein staining scores were reduced from 2.04 to 1.46, conjunctival sensation was increased from 1.15 to 1.36, and symptom scores were greatly reduced. The researchers concluded that oral ARI decreases ocular surface changes brought on by DM. A topical AR inhibitor (CT-112) was used by Ohashi and coworkers[144] to treat two patients with DM that had nonresolving corneal epithelial lesions. A study found that the treatments resolved the lesions, reoccurred when treatment ended, and again resolved when treatment was resumed. Tsubota and Yamada[193] treated a 41-year-old DM woman with a topical AR inhibitor and observed that the mean cell area of the corneal epithelium was decreased from 1,101 ± 275 to 723 ± 253 μm^2. This demonstrated that the application of AR inhibitor decreased the mean cell area to more physiological sizes.

5. Current research approaches and models

As DM is a highly heterogeneous disease, care must be taken when choosing a model to study diabetic complications, including those in the cornea. Many diabetic models, both *in vitro* and *in vivo*, can be/currently are being used for the study of diabetic keratopathy.[24] Applications of the models discussed in the following sections span the research field from metabolic, physiological, genetic, epigenetic, and therapeutic. It is important to note that none of these models fully recapitulate the course of the disease in humans owing to the heterogeneous nature of the disease and the marked differences in human and laboratory animal physiology; however, the use of such models is critical in understanding the different aspects of corneal DM. Animal models for DM have been reviewed extensively by others.[4,95,98] Here, we will discuss the most commonly used models in diabetes research and how they can be used to study diabetic keratopathy.

5.1. Type 1DM animal models

The most common model for diabetes is the chemically induced streptozotocin (STZ) mouse model. Type 1DM in humans is characterized by a lack of insulin production. STZ is most commonly used to induce type 1DM through high-dose administration, which results in the majority destruction of the insulin-producing beta cells, but it can also be used with a milder dose to model type 2DM characteristics.[57] This method of DM induction provided a simple and relatively inexpensive rodent DM model. It is important to note that chemical induction of DM can be toxic to other organs, so care must be taken when using this model.[38] One of the most dominant genetic models of type 1DM is the nonobese diabetic mouse, developed at the Shionogi Research Laboratories in Osaka, Japan, in 1974.[4] These mice develop insulitis at approximately 3–4 weeks of age. In this pre-DM stage, $CD4^+$ and $CD8^+$ lymphocytes infiltrate the pancreatic islets, as well as B cells and NK cells.[95] Around 10–14 weeks, approximately 90% of pancreatic insulin is lost leading to the onset of DM and rapid weight loss.[34] Wicker et al[208] showed that the class 2 major histocompatibility complex in nonobese diabetic mice are similar in structure to those in humans, making this model more attractive for this area of diabetes research. The correlation in type 1DM genes, between nonobese diabetic mice and human beings, has been critical in dissecting important signaling pathways.[189] Another commonly used genetic rodent model is the AKITA mouse, derived from a C57BL/6NSlc mouse with a spontaneous mutation in the *insulin2* gene, preventing correct processing of proinsulin[95] and resulting in a severe type 1DM state characterized by hyperinsulinemia, hyperglycemia, and polyuria by 4 weeks of age. Homozygotes left untreated rarely survive longer than 12 weeks. Mathews and coworkers[121] showed that the lack of beta cell mass, in this model, makes it an alternative to STZ-treated mice. The two main methods of inducing insulin dependence in large models are either by STZ or pancreatectomy.[142] Weiss and coworkers[206] showed that, in some animal models, a combination of a partial pancreatectomy and STZ could lower the dose of STZ and thereby reduce the toxicity levels associated with this compound.

5.2. Type 2DM animal models

Type 2DM is characterized mainly by insulin resistance of target tissues; therefore, animal models tend to include models of insulin resistance and/or models of beta cell failure. As discussed in the previous section, STZ induction of DM is also commonly used for type 2DM studies. The Goto-Kakizaki rat is a popular genetic model produced by selective breeding over many generations of the nondiabetic Wistar rats with glucose intolerance.[95] This rat serves as a spontaneous model of type 2DM, in the absence of hyperlipidemia and obesity. Diverse pathological changes in various tissues and organs of the Goto-Kakizaki rat resemble those observed in patients with DM. Moreover, Goto-Kakizaki rats also show various abnormalities of the eye, including upregulation of vascular endothelial growth factor, and increased O-GlcNAc-modified proteins in the cornea.[3,203] In addition, these rat models reveal similar corneal phenotypes to those of patients with DM, including decreased corneal sensitivity, delayed epithelial wound healing, and reduced tear secretion.[102] Other genetic models have been studied in an attempt to explore the various type 2DM complications, including the db/db mouse, KKAy

mouse, and Otsuka Long-Evans Tokushima Fatty rat.[16,164] Kleinert and coworkers[98] reviewed larger animal models that can be used for the study of T2DM development; however, these are less commonly used because of the increased life span and associated cost. Nonetheless, these animal models develop hyperglycemia and obesity, which make the attribution of pathologic changes, specifically to DM, difficult to understand. This suggests that the Goto-Kakizaki rat is currently the most suitable animal model to study the pathogenesis of diabetic keratopathy.[95]

5.3. *DM and stem cells*

Stem cells are capable of replacing damaged cells in the body, therefore offering promising treatment options; however, many diabetic patients struggle with numerous complications of protein glycosylation from chronically elevated glucose levels. Hence, exogenous insulin treatment is life redeeming but is not the ultimate cure for diabetic patients. Researchers are currently focusing on alternative therapies to solve the insulin deficiency problem in these patients, including stem cell therapy. Both embryonic stem cells and mesenchymal stem cells are able to differentiate into β cells[195]; the addition of growth factors or inhibitors can guide differentiation into β cells and mimic what happens *in vivo*. Adult stem cells can be incorporated in the treatment of DM; examples include bone marrow hematopoietic stem cells, intrapancreatic autologous bone marrow stem cells, and umbilical cord blood–derived multipotent stem cells.[77,197] In the scope of corneal diabetes, stem cells targeted by researchers include limbal epithelial stem cells,[159] mesenchymal stem cells,[39,119] embryonic stem cells,[103] and induced pluripotent stem cells.[27,119]

Stem cell treatment for diabetic keratopathy is regarded as a promising therapy that could restore stem cell loss and function. Limbal stem cell deficiency is a consequence of limbal epithelial stem cell loss, occurring from various etiologies, including DM, that can lead to vision loss.[159] Epithelial resurfacing and healing are essential in the function and homeostasis of the cornea; unfortunately, patients with DM suffer significant epithelial stem cell abnormalities that contribute to the dysfunction of wound healing and reepithelialization. As mentioned previously, DM increases the risk of various traumas and defects which may explain clinically observed diabetic wound healing delays after vitrectomy or refractive surgery.[103,114]

Clinical treatments for limbal stem cell deficiency currently include conjunctival-limbal autograft or cultured limbal epithelial stem cells by transplantation (CLET).[156,159] Limbal stem cell sheets are taken from the patient as a small biopsy and expanded *ex vivo* before transplantation. This method has a 72% success rate of reepithelialization and 63% visual acuity improvement.[79,132] Patients treated with expanded autologous limbal stem cells transplanted on human AM have a success rate of 80–100%, with improved visual acuity of 25–100%.[25,79] Blot CLET and conjunctival-limbal autograft represent the current standard in treatment in severe limbal stem cell deficiency; however, a novel alternative technique, known as simple limbal epithelial transplantation, seemingly combines the advantages of both the previously mentioned techniques.[79,165,198] Based on a recent systemic review of 22 studies on LSCT, Shanbhag and coworkers[177] conclude that each of these techniques is safe and effective and found that both simple limbal epithelial transplantation and conjunctival-limbal autograft produce more beneficial long-term anatomical and functional success rates than CLET. These studies are promising for the future of using cell therapy in treating limbal stem cell deficiency in diabetic patients.

5.4. *Hyperglycemia-induced epigenetic changes*

Epigenetic alterations in DM are especially important in a clinical aspect because patients with DM can still experience progressive complications even under glycemic control. Select components of the epigenetic modification system exhibit therapeutic potential for these persistent complications. Current treatments such as glycemic control via diet changes or therapeutics for DM can be very effective but do not address the heritable changes that patients experience as a result of diabetes onset.[30] Similarly, *ex vivo* and *in vitro*[46,148] studies exhibit that corneal cells maintain molecular alterations consistent with the diabetic corneal phenotype, suggesting the persistent complications in patients are accredited to a metabolic memory after uncontrolled hyperglycemia.[30,200] The emergence of the importance of epigenetic modification in diabetes pathogenesis has expanded the field to span *in vitro* cell culture studies up to large-scale genome-wide association studies (GWAS) and epigenome-wide association studies of human diabetic corneas.[56,104] While research has provided an abundance of insight regarding the genetics of DM, the epigenetic pathways involved in DM and its complications remain partially understood. Investigating the role of epigenetics in DM complications can add valuable new insights to define the interplay between genes and the environment in this highly heterogeneous and heritable disease and reveal new therapeutic targets for patients suffering from diabetic keratopathy. Alterations in epigenetic modifications, including histone posttranslational modifications, DNA methylation, and microRNA (miRNA) translational regulation, have been exhibited in patients with DM.[5] These epigenetic modifications affect many cellular events, including proliferation, differentiation, inflammation, and glucose metabolism, all of which play a role in the pathogenesis of diabetes progression. Studies to date on epigenetic modifications in diabetic keratopathy are summarized in Table 2.

miRNAs Have been found intracellularly, in circulating fluid, and in delivery particles such as exosomes, allowing the opportunity to serve as early biomarkers for DM onset and progression, and act as an easily accessible therapeutic target.[178] In the cornea, miRNAs have been implicated in diabetic keratopathy pathogenesis in the context of limbal epithelial wound healing, as well as corneal neuropathy.[56,75,212] A GWAS analyzing the corneal limbus of both patients with type 1DM and type 2DM demonstrated several differentially expressed miRNAs in the diabetics relative to healthy patients.[104] Human organ-cultured corneas also show upregulated miR-146a in diabetics after epithelial wounding,[212] suggesting a possible inhibitory role on

Table 2 – Studies investigating epigenetic changes in the DM cornea

First author and study period	Discovery in the cornea
Funari et al 2013[56]	Multiple differentially expressed miRNAs were found in the diabetic cornea compared to the healthy, most notably miR-146a and miR-424, which were found to significantly impair epithelial cell migration when transfected in immortalized HCECs.
Winkler et al 2014[212]	Suggests functional role and localization of miR-146a in epithelial wound healing. miR-146a is more highly expressed in the limbal region than in the central cornea, and its expression is also higher in diabetic than healthy corneas; organ-cultured diabetic corneas, treated with an miR-146a inhibitor, exhibited increased wound healing by 40%.
Gao et al 2015[59]	AKITA diabetic mice exhibit markedly increased expression of miR-204-5p; authors discovered direct inhibitory regulation of SIRT1 proliferation activity by miR-204-5p and suggest a role of miR-204-5p on epithelial wound healing dysfunction in diabetic keratopathy.
Wang et al 2016[205]	Exhibits role of miR-182 is involved in the regeneration of corneal nerves, exhibited by recovered corneal sensitivity in *db/db* mice. Suggested pathological pathways include Sirt1-induced activation and downstream inhibition of NOX4.
Kulkarni et al 2017[104]	Suggests the role of miRNAs in limbal cell differentiation in diabetic wound healing. miRNA Profiling of limbal regions of the diabetic cornea exhibited marked differences. miR-10b Transfection in organ-cultured diabetic corneas exhibit increased Ki-67 immunostaining and keratin 17 expression, and decreased PAX6 and DKK1 expression.
Herencia-Bueno et al 2018[73]	Investigates the effect of alloxan-induced hyperglycemia on histone acetylation and nuclear chromatin remodeling in the rat cornea. Diabetic rats exhibited decreased corneal sensitivity, accompanied by a decrease in histone H3 acetylation and chromatin compaction alterations in both epithelial and stromal cells.
Leszczynska et al 2018[111]	Characterization of the differences in exosome signaling in the corneal limbal region of diabetic corneas. Limbal stromal cell–derived exosomes from healthy corneas significantly increases wound healing rates of organ-cultured corneas, while the diabetic exosomes do not. Sequencing suggests a role of miRNA found inside the exosomes on regulation of Akt signaling.
Hu et al 2019[75]	Investigates the regulatory role of miRNAs on the pathological autophagy exhibited in diabetic corneal neuropathy using type 1DM STZ-induced mice. Notably, miR-34c expression was increased in the trigeminal ganglion (TG) of diabetic mice. Results suggest miR-34c stimulates autophagy in TG and inhibits epithelial healing and nerve regeneration.

DM, diabetes mellitus; HCEC, human corneal epithelial cells; miRNA, microRNA; STZ, streptozotocin.

epithelial cell migration from the limbus. Finally, miRNAs associated with SIRT1-mediated wound healing and nerve homeostasis have been implicated in diabetic keratopathy pathophysiology.[59,205]

While neither the involvement of DNA methylation nor histone modification have been investigated in the cornea as of yet, there is notable evidence in the pathogenesis of systemic DM complications. Table 3 displays various studies investigating the role of DNA methylation and histone modifications in DM. Histone modifications have most been implicated in the inflammatory genes in several DM studies.[5] One study found marked differences in histone 3 lysine 4 and 9 methylation of inflammatory genes IL-1A and PTEN in the monocytes of both patients with type 1DM and type 2DM.[128] Moreover, the knockdown of histone 3 lysine 4 histone methyltransferase SET7/9 attenuates NF-κB induction of key inflammatory genes in endothelial cells.[113] A study conducted in the alloxan-induced diabetic rat exhibited decreased histone H3 acetylation, suggesting histone modifications could play a role in the pathology of corneal diabetes, as well.[73] Differential DNA methylation has been observed in diabetic islet cells on genes responsible for insulin production and release,[35] and studies suggest that these alterations in DNA methylation are significant in the pathophysiology of persistent DM complications[9,30,133]; however, a consensus on these alterations has not been reached. These studies help shed light on the inflammatory cell epigenome under the hyperglycemic state. The data available from these studies may help generate epigenetic information as another layer of gene transcriptional regulation sensitive to environmental signals in patients with DM.

6. Future therapies

6.1. *Gene therapy*

Multiple growth factors that show promise to treat diabetic keratopathy include insulin, opioid growth factor, NGF, and substance P.[215] Nonetheless, the inhibitory growth factor (plasma Met-enkephalins) is known to be elevated in people with diabetes.[219] Corneal Met-enkephalins are blocked by topical naltrexone, simultaneously leading to corneal reepithelialization via increasing DNA synthesis of the corneal epithelium. Previous findings show that diabetic keratopathy is reversed by naltrexone *in vitro*, using human diabetic corneas as well as diabetic animal models.[124] Most of these studies revealed progress in corneal reepithelialization, tear production, corneal sensitivity, and accelerated wound healing after naltrexone administration. Previous studies by Winkler and coworkers[212] have shed light on several abnormally expressed miRNAs in diabetic corneas and their effect on wound healing *in vitro*. MiR-146a acts as a tumor suppressor and an oncogene in different types of cancers. It has a wide variety of functions and is able to target different genes in

Table 3 – Studies investigating the role of epigenetic changes in a DM hyperglycemic state

First author and study period	Epigenetic change in relation to high glucose levels
Li et al 2006[112]	An attempt to unravel the potential chromatin-based epigenetic mechanisms responsible for metabolic memory in diabetes. VSMCs from DM *db/db* mice cultured continued to exhibit increased inflammatory gene expression associated with the diabetic phenotype and complications.
Jirtle and Skinner, 2007[83]	The role of DNA methylation suggests that environment and diet may influence epigenetic modifications that predispose individuals to DM.
Miao et al 2008[127]	A subset of genes in diabetic lymphocytes was found to have increased H3K9me2; analysis linked them to immune and inflammatory pathways often associated with the development of DM and resulting complications.
Brasacchio et al 2009[22]	A role for SET7/9 in regulating NF-κB expression and inflammatory gene regulation in response to high glucose was shown in endothelial cells. In addition, DM *ApoE*$^{-/-}$ mouse model showed transient high glucose in endothelial cells was also associated with decreased H3K9me2/3 repressive marks along with an increase in LSD1 demethylase recruitment at the p65 promoter.
Miao et al 2012[126]	Dynamic changes were observed in both the H3K4me2 activation mark and H3K9me2 repressive mark at key genes in response to hyperglycemia in cultured monocytes, with relevant changes observed in monocytes from patients with DM.

DM, diabetes mellitus; VSMC, vascular smooth muscle cells.

different cell types including TRAF6, IRAK1, CXCR4, and NF-κB, which may contribute to inflammation and tumor development. MiR-146a association with Smad4 mRNA and TGF-β pathway components suggests an involvement in cell proliferation and migration, which are two critical factors in corneal epithelial homeostasis.[56] Thus, miR-146a has an inhibitory effect on corneal epithelial wound healing. As miRNAs play a role in balancing gene expression to maintain corneal homeostasis, any disruption in their function could potentially rattle this corneal balance, leading to pathological conditions such as diabetic keratopathy. Various data using *c-met* (hepatocyte growth factor receptor) gene therapy in human organ–cultured diabetic corneas stated that accelerated epithelial wound healing was dependent on p38, but not on EGFR-Akt activation.[212] At the same time, this acceleration, when achieved through silencing of the proteinase *MMP-10* and *cathepsin F* genes was via activation of the EGFR-Akt axis, but not p38, suggesting that EGFR could possibly alter corneal epithelial wound healing through the Ras-ERK-p38 pathway.[158] Nevertheless, gene therapy is emerging as a potential new treatment modality for various corneal diseases and the prevention of corneal blindness. The development of novel methods of delivering genetic material into cells has been used in preclinical studies with modest success, targeting stromal, epithelial, and endothelial corneal cells; however, various obstacles still exist, including patient safety. In the context of diabetic keratopathy, gene therapy may be beneficial and could provide solutions to the nonhealing corneal lesions in patients with DM.

7. Conclusions

Diabetic keratopathy is a significant clinical problem with no truly effective treatment available. The large number of studies published in the field, combined with the absence of a medical treatment, highlight the complexity of the disease. Focus on developing animal models for DM is certainly justified, although we are still looking for an accurate, more translational diabetic keratopathy model. As a result of anatomical differences between the mouse/rat and the human cornea, we may need to turn our attention to larger animals that better represent what is seen *in vivo*. Larger animals, of course, come with a number of limitations, including high cost and limited availability. It is a difficult decision, but one that needs to be made so that we may develop future therapeutic modalities.

8. Methods of literature search

There were no specific exclusion/inclusion criteria for our literature search. Published work written in other languages were analyzed by abstract, only, which is usually available in English language. Searches included terms similar to "diabetic keratopathy," "corneal injury treatment," and "corneal biomechanics." All articles found relevant to this article upon review were included upon the authors' discretion. Online applications used for the searches were PubMed database and clinicaltrials.gov.

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Major review

Pathophysiology and management of glaucoma and ocular hypertension related to trauma

Reza Razeghinejad, MD[a,b,*], *Michael M. Lin, MD*[a,c], *Daniel Lee, MD*[a], *L. Jay Katz, MD*[a], *Jonathan S. Myers, MD*[a]

[a] *Glaucoma Service, Wills Eye Hospital, Thomas Jefferson University, Philadelphia, Pennsylvania, USA*
[b] *Poostchi Ophthalmology Research center, Shiraz University of Medical Sciences, Shiraz, Iran*
[c] *Glaucoma Service, Massachusetts Eye and Ear, Harvard University, Boston, Massachusetts, USA*

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ABSTRACT

Ocular trauma is a significant cause of blindness worldwide, particularly if associated with glaucoma. Direct damage from blunt or penetrating trauma, bleeding, inflammation, lens-related problems, orbital and brain vascular pathologies related to trauma, and chemical injuries may increase intraocular pressure and lead to traumatic glaucoma. Treatment may be as simple as eliminating the underlying cause in some conditions or management can be challenging, depending on the mechanism of damage. If proper management is not undertaken, visual outcomes can be poor. We discuss a broad spectrum of trauma-related mechanisms of intraocular pressure elevation, as well as their management.

1. Introduction

Eye trauma is a common cause of vision loss and can lead to increased intraocular pressure (IOP). In the United States, the annual incidence of eye injury requiring treatment has been estimated at 6.98 per 1000 population, with most injuries treated in emergency departments or private physician offices.[81] Ocular injuries are most common among young white males in their 20s. The annual incidence of eye trauma as a primary admitting diagnosis to a hospital is 3 per 100,000

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* Corresponding author: Reza Razeghinejad, MD, Glaucoma Service, Wills Eye Hospital, Thomas Jefferson University, 840 Walnut Street, Suite 1140, Philadelphia, PA 19107. Tel: 215-825-9020, Fax: 215-928-3285.
E-mail address: reza@willseye.org (R. Razeghinejad).

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population, and orbital fracture is the most common diagnosis.[55] Fewer data are available about the frequency with which ocular injuries result in increased IOP and glaucoma, partially because mechanisms of trauma-related glaucoma are so heterogeneous. We will examine the wide variety of mechanisms in which trauma can lead to increased IOP and glaucoma and their management. Throughout this review, the term glaucoma is used instead of drawing a distinction between glaucoma and ocular hypertension without evidence of glaucomatous damage. This is because eye trauma can make the structural and functional assessment of the optic nerve challenging. Determining whether elevated IOP has in fact caused glaucomatous damage can be difficult because the traumatic sequelae in some cases can limit the view of the optic nerve and make visual field testing unreliable or impossible.

2. Cornea and sclera

Blunt and penetrating ocular injuries and chemical exposures to the cornea and sclera can damage ocular tissues and lead to increases in IOP.

2.1. *Corneal and scleral lacerations*

Open globe injury has been estimated to occur with an annual incidence of 4.6 per 100,000 in the US population.[101] In general, the most common patients are young men injured by projectile objects, while women with open globe injuries are generally older and have experienced falls, with one study reporting a median age of 36 years for men and 73 years for women.[67] Open globe injuries have been classified according to the anatomic location of the full-thickness injury. Zone I is limited to the cornea, zone II is the area between the limbus and 5 mm posterior to the limbus, and zone III is the region posterior to zone II.[98] The principle of primary open globe repair is almost always to close all wounds in watertight fashion, allowing time for wound healing and preparation for potential future surgeries. Widely varying incidences of ocular hypertension and glaucoma have been reported after corneal and scleral lacerations. This variation likely reflects the complex and heterogeneous nature of these injuries and concomitant hyphema, vitreous hemorrhage, lens injury, and potential development of chronic angle closure. Causes of elevated IOP after open globe include appositional or synechial angle closure, intraocular inflammation, intraocular hemorrhage, lens-related mechanisms, and epithelial or fibrous ingrowth. Thus, many different treatment approaches have been reported for elevated IOP or glaucoma after open globe injury, including topical medical treatment, laser iridotomy, cyclophotocoagulation, anterior chamber washout, trabeculectomy, and tube shunts.

Definitions of elevated IOP and glaucoma after open globe injury vary, leading to estimates ranging from 5.3% to 25%.[1,12,92,93,133] In a study of 382 eyes that suffered open globe injury, 17% developed ocular hypertension, with average maximum IOP of 33.4 mmHg occurring at a median follow-up of 21 days.[133] Increased age, hyphema, lens injury, and zone II injury were significant risk factors. The authors hypothesized that zone II injury was a risk factor because of direct injury to the trabecular meshwork (TM) and alterations to the aqueous outflow pathways. Of the eyes that developed ocular hypertension, 74% were able to be treated medically. Other factors that can contribute to elevated IOP after open globe injury include retained lens material, inflammation, hyphema, synechial angle closure, ghost cells, and angle recession.[92,93]

A lower estimate of traumatic glaucoma was reported by the United States Eye Injury Registry, which included 3627 patients who had penetrating ocular injury, finding 2.7% developed posttraumatic glaucoma, defined by physician opinion at 6-month follow-up. No details about IOP, medical and surgical glaucoma treatment, optic nerve parameters, or visual field changes were reported in the registry.[46] Given the heterogeneous nature of corneal and scleral lacerations from the widely varying nature of concomitant injuries and ocular findings, and different criteria used for definition of the condition, the estimates of the rates of traumatic ocular hypertension and glaucoma after such injury vary widely, as do the treatment and prognosis. Medical treatment generally can control IOP in such cases, and when this fails, glaucoma surgery often provides adequate IOP control.

2.2. *Chemical burn*

Chemical burns are responsible for 18% of all ocular traumas.[136] In general, alkalis tend to penetrate more effectively than acids and involve deeper intraocular tissues, including retina, because the hydroxyl in alkalis saponifies the fatty acids in cell membranes and causes cell death, while acids cause protein denaturation that forms a coagulation of proteins that serves as a barrier to deeper penetration.[136] Alkali burns are more common and severe than acid burns. Glaucoma may occur in up to 75% of eyes with severe chemical burns.[18] In a study by Cade and coworkers, 75% of patients had advanced glaucoma before vision rehabilitation surgery.[18] IOP spikes and elevation in chemical burn may be frequently overlooked because most attention is paid to the cornea and anterior segment. Also, the current chemical burn classification does not include IOP and glaucoma; prognosis is classified only based on the extent of ocular surface damage.[33]

Measuring the IOP of chemically burned eyes with distorted corneas is difficult. Rebound tonometry (e.g., iCare), transpalpebral tonometer (e.g., Diaton), and digital/tactile tonometry have been used as IOP measurement techniques. iCare and Tono-Pen rebound tonometry allow IOP assessment while contacting only a small portion of the cornea. This avoids the difficulty of distorted mires encountered when trying to applanate. In addition, multiple measurements in different areas of the cornea can be compared; in general, measuring in areas of uninjured cornea will yield more accurate results than measuring in scarred, edematous, and traumatized cornea. Transpalpebral tonometry with the Diaton also allows for IOP measurement in the setting of a traumatized cornea. In this method, the patient's head is positioned with the face upward, the patient is directed to look slightly downward, the instrument rests on the inferior portion of the upper eyelid, and a small metal rod drops onto the eyelid when the device is pressed down on the globe. While rebound and transpalpebral tonometry are helpful for

determining IOP in traumatized eyes, these devices may not always be accurate or available. In these cases, tactile tonometry is especially vital and can be performed by palpation of the upper eyelid with two index fingers while a patient looks downward. If the contralateral eye is uninvolved, it can serve for comparison of the involved eye's IOP in cases of unilateral chemical burns.

IOP may increase or decrease depending on the type of chemical agent and its intraocular penetration. The mechanisms of IOP elevation in chemical burns include collagen shrinkage and contraction, inflammation leading to posterior synechiae and subsequent pupillary block, changes in the TM, and damage to the collector channels and aqueous veins. Steroid response, whether from steroids used therapeutically or postsurgically, and damage to the TM and collector channels by non–glaucoma-related anterior segment surgeries are other causes of IOP elevation. The IOP may also decrease secondary to ciliary body damage caused by chemical agents, leading to phthisis.[76,122,131,136]

In the acute stage of chemical injury, elevated IOP may be controlled by topical glaucoma medications (beta-blockers, carbonic anhydrase inhibitors, alpha 2-agonists) and oral carbonic anhydrase inhibitors. Prostaglandin analogs and pilocarpine may not be first choices because of their proinflammatory effect. There is, however, no consensus to consider traumatic glaucoma as an absolute contraindication for prostaglandins, and they have been safely and successfully used in the management of some types of glaucoma with intraocular inflammation.[102] Retinal and optic nerve damage may also occur in early stages of chemical burns. One recommendation is to prophylactically lower the IOP to the lowest safe level with oral carbonic anhydrase inhibitors immediately after a chemical burn and after any subsequent ocular surgery.[32] In those with IOP spikes, anterior chamber paracentesis, besides lowering the IOP, removes the chemical substance and dilutes its anterior chamber concentration. This may decrease the toxic effect of the chemical agent on intraocular tissues, including the TM. Topical cycloplegic agents reduce pain from ciliary muscle spasm, prevent the development of posterior synechiae, break newly formed synechiae, help stabilize the blood aqueous barrier, and facilitate posterior segment evaluation.[137]

In eyes with persistent IOP elevation that do not respond to medical therapy, surgical procedures are required. If the superior conjunctiva is not damaged, a trabeculectomy is an option. Otherwise glaucoma drainage device (GDD) surgery or cyclophotocoagulation are the preferred surgical options. The postoperative inflammation of cyclophotocoagulation is a factor that makes this surgery less favorable in the acute stage of chemical injury.[18,85] The inflammation secondary to chemical burn may decrease trabeculectomy function, and using antimetabolites may result in further conjunctival damage and increase the risk of a bleb leak.[85]

Keratoprosthesis may be required in some chemical burn patients, and a tube shunt is often placed at the time of keratoprosthesis surgery. In a case series of 28 eyes with severe chemical burn, 75% had glaucoma before receiving a Boston keratoprosthesis.[18] The keratoprosthesis provides a clear view to a posterior segment that may have previously been obscured by corneal opacity. Postoperatively, most eyes have a cupped and pale optic nerve head with corresponding glaucomatous field defects.[91] Glaucoma is also a common complication of keratoprosthesis and one of the more common direct causes of eventual blindness. The clinical outcomes have clearly demonstrated the great importance of reducing the IOP to the lowest safe level in these patients. Therefore, if glaucoma has been diagnosed preoperatively, a tube shunt should be implanted concurrently, even if the IOP looks acceptable with medications.[32] Progression of preexisting glaucoma after keratoprosthesis has been estimated to be as high as 25%,[30] and the fastest rates occur in those who received it for corneal burns.[61] Medical treatment is limited after keratoprosthesis because of the poor topical absorption of antiglaucoma medications. Systemic carbonic anhydrase inhibitors are the mainstay of treatment.[6,91]

3. Anterior chamber

Trauma-related anterior chamber mechanisms for IOP elevation include the presence of white or red blood cells in the anterior chamber, damage to the aqueous drainage pathway, growth of abnormal tissue, and steroid use.

3.1. *Traumatic iritis*

Traumatic iritis and iridocyclitis are anterior uveitides that arise after blunt injuries to the eye. Anterior uveitis arising from trauma accounts for approximately 20% of all cases.[49] While the exact mechanism is unclear, significant trauma may result in tissue damage or necrosis triggering an innate immune response mediated by increase blood vessel permeability and inflammatory mediators.[96] IOP may be elevated or reduced depending on the ocular structures involved. Anterior chamber precipitates may cause TM obstruction, resulting in elevated IOP. Trabeculitis may result in meshwork congestion contributing to reduced aqueous outflow. On the other hand, reduced aqueous production by an inflamed ciliary body or abnormal supraciliary outflow through cyclodialysis clefts may result in low IOPs.

The mainstay of treatment is topical steroids and cycloplegic agents. Traumatic uveitis is generally self-limited in nature. Prolonged inflammation should prompt evaluation for occult systemic inflammatory conditions or occult intraocular foreign body. In a 30-year retrospective study of traumatic uveitis, 8 of 55 patients (14.8%) developed glaucoma within a mean follow-up period of 5.4 years. All cases were controlled with topical glaucoma treatments, and no patients required glaucoma surgery.[37] Prolonged steroid use may result in elevated IOPs in steroid responders.

3.1.1. *Steroid-induced IOP elevation*

Steroid-induced IOP elevation is thought to be from increased outflow resistance at the TM. Glucocorticoids have been shown to increase expression of glycosaminoglycans and extracellular matrix (ECM) proteins such as fibronectin and elastin.[60] A concomitant steroid-induced reduction in phagocytic activity has led to observations of ECM material deposition in the juxtacanalicular meshwork.[126]

Steroid-induced IOP elevations may occur in any patient. Those with primary open-angle glaucoma (POAG), family history of POAG, myopia, type I diabetes mellitus, connective tissue disease, and angle recession glaucoma are at higher than average risk.[103]

The timing of IOP elevation is related to drug potency, frequency, duration, route of administration, and susceptibility of each patient. Most studies report increased IOPs after 3–6 weeks of continuous topical steroid use. Fortunately, traumatic iritis is self-limited, and in the absence of other causes of inflammation, does not require prolonged, high potency steroid use. Engelhard and coworkers reported topical steroids were sufficient to control traumatic iritis in 77.8% of their cohort[37]; however, IOP spikes within one week of treatment have been reported, especially in pseudophakic or vitrectomized eyes.[103]

The most important step in managing steroid-induced IOP elevation is early recognition and removal of the inciting agent if possible. The steroid-induced IOP increase is usually short-lived and reversible by discontinuance of therapy if the drug has been used for less than 12 months. Being on steroid for more than 18 months could result in permanent IOP elevation. The IOP usually returns to normal within 2–4 weeks after discontinuation of the steroid.[103] Patients with predisposing risk factors should be identified before starting steroids, with treatment administered judiciously and with diligent follow-up. Lower potency steroids, steroids with less ocular penetration, and steroids associated with lower risk of IOP elevation may be helpful alternatives in the setting of persistent inflammation. Periocular steroid depots and intravitreal steroids can be surgically excised or removed by vitrectomy, respectively.[2]

Topical hypotensive medications can control the majority of cases.[113] All classes of antiglaucoma medications may be used, with a relative contraindication for prostaglandin analogs in the setting of uveitis.[90,117] There is mounting evidence for laser trabeculoplasty in the eyes with steroid-induced glaucoma in the absence of active inflammation. Rubin and coworkers described 7 patients on maximum tolerated medical therapy after intravitreal triamcinolone injections.[107] The average baseline IOP reduced from 38.4 ± 7.3 to15.7 ± 2.2 mmHg at 6 months after selective laser trabeculoplasty. Incisional surgery was avoided in 5 of 7 patients.[107] Trabeculectomy, trabeculotomy, GDD implants, and cyclodestructive procedures have been used. Fortunately, surgical intervention is required in less than 5% of intravitreal steroid injections and much less frequently in the setting of traumatic iritis.[37,56]

3.2. *Blood related*

Bleeding in the anterior chamber and vitreous cavity may lead to IOP elevation via multiple different mechanisms.

3.2.1. *Hyphema*

Hyphemas are an accumulation of blood in the anterior chamber, but may be associated with other trauma-related injuries to the anterior segment of the eye (Fig. 1). Direct, high-energy blows to the orbit are responsible for up to 66% of traumatic hyphemas. Projectile strikes account for the majority of the remaining, accounting for 30%.[15] Bleeding arises from shearing of intraocular vessels from sudden globe compression-decompression forces. While hyphemas alone seldom cause permanent vision loss, associated complications such as corneal blood staining, optic nerve atrophy, or deprivation amblyopia can lead to significant ocular morbidity. Management and treatment are therefore aimed at preventing and reducing the severity of associated complications.

On clinical history, the mechanism of traumatic hyphemas is often evident. Any personal or family history of sickle cell disease and bleeding disorders must be elicited, as these conditions may affect the clinical course and management. Sickle cell disease affects 1 in 365 African-American births. Thus, African-American patients should be screened appropriately. Sickle cell anemia patients are at increased risk for poor visual outcomes. Rigid, sickle-shaped erythrocytes are unable to easily pass through the TM, leading to an increased likelihood of elevated IOP. Furthermore, sickle cell anemia patients are susceptible to vaso-occlusive events and can experience retinal arterial occlusions and ischemic optic

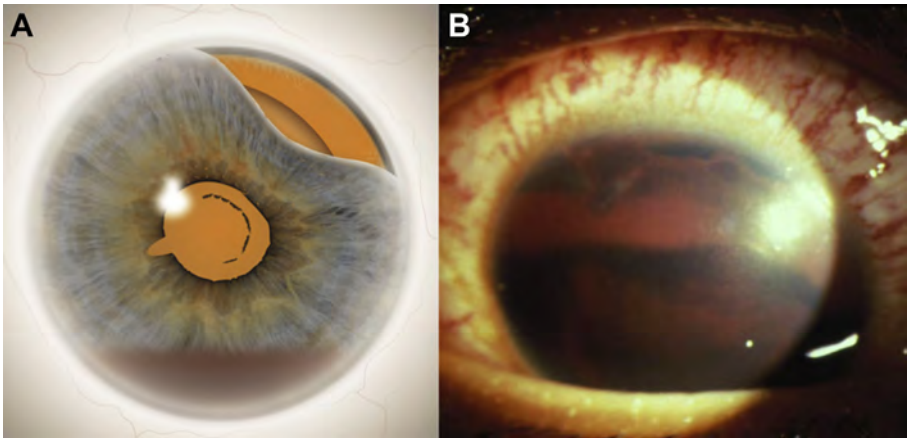

Fig. 1 – *A*: Stylized drawing shows layering hyphema at *bottom* of image, iridodialysis in *top right* of image, subluxed crystalline lens, iris sphincter tear at 8 o'clock, and Vossius ring. *B*: Anterior segment photograph shows hyphema in the anterior chamber. The blood clot occupies nearly the entire anterior chamber space. There is no corneal blood staining.

neuropathies at only modestly elevated IOPs in the 20s and low 30s, as opposed to the higher IOPs typically required in those without sickle cell anemia.

Hyphemas can be classified based on extent of anterior chamber blood fill. Grade I hyphemas fill up to a third of the anterior chamber, grade II up to half, grade III more than half, and grade IV 100% of the anterior chamber.[34] Dark-red or black grade IV hyphemas are often referred to as blackball or 8-ball hyphemas and suggest decreased aqueous circulation and oxygen concentration and are associated with a higher incidence of IOP elevation. This entity is more likely to cause pupillary block and secondary angle closure.[23]

The extent of bleeding correlates with incidence of elevated IOP, risk of secondary bleeding, and visual outcomes. Cole reported grade I and II hyphemas had 13.5% risk of elevated IOP, while grade III had 27% risk. Grade IV and rebleeds had an approximately 50% chance of elevated IOP.[28] Visual prognosis follows the same trend, with grade I and II having 75–90% and 65–70% chance of recovering to 20/50 or better, respectively. Grade III and IV have a 25–50% chance.[8] Secondary bleeding occurs in approximately a quarter of patients with grade I and two-thirds with grade III and IV hyphemas.[15]

Secondary bleeding is caused by clot lysis and retraction and typically occurs between day 2 and 7 after initial injury, during which time close monitoring is advised. Rebleeds are typically worse than the initial bleed and are associated with a worse visual prognosis.[45]

Management of traumatic hyphemas begins with supportive therapy. Head elevation at rest promotes inferior layering of the hyphema, which allows the blood to clear the visual axis sooner and allows for monitoring of secondary hemorrhages. Some advocate for eye patching with a metal shield for the duration of hyphema. Medical management includes topical corticosteroids and mydriatics to reduce associated inflammation and ciliary spasms. Elevated IOP is managed using topical, systemic, and intravenous ocular hypotensive medications. Topical and systemic carbonic anhydrase inhibitors, as well as osmotic agents, are contraindicated in sickle cell disease and trait patients, as these treatments may create an environment that promotes erythrocyte sickling.[47] A meta-analysis by Gharaibeh and coworkers indicated that aminocaproic acid and tranexamic acid reduce the likelihood of secondary hemorrhages but may be associated with significant systemic side effects.[45]

Only 5% of traumatic hyphemas result in surgical intervention. Surgery is reserved for patients at risk of developing permanent or long-term visual loss. This includes patients with IOP >50 mmHg for more than 5 days, >45 mmHg for more than 1 week, >35 mmHg for more than 2 weeks.[139] These guidelines apply to healthy, young individuals with normal optic nerves. Sickle cell disease and trait patients are at higher risk of IOP-related complications, and surgical intervention has traditionally been considered if IOP >24 mmHg for more than 24 hours.[47] Other indications for surgery include corneal blood staining, persistent grade IV for more than 10 days, and visual obstruction in children at risk for amblyopia.

If surgery is required, first-line treatment is typically anterior chamber washout, where irrigation and aspiration is performed through a small corneal incision to remove the blood. Large, adherent blood clots not amenable to simple washout or observation can be removed with the aid of viscoelastic dissection, an anterior vitrector, or a Simcoe cannula. An anterior chamber maintainer may help facilitate this process by providing constant fluid flow to encourage clot removal.[115] In cases where anterior chamber washout alone may not be enough, concurrent trabeculectomy with iridectomy provide more definitive IOP control.[62]

3.2.2. *Hemolytic glaucoma*

In the eyes that have suffered trauma, the resultant vitreous hemorrhage or anterior chamber hyphema could potentially lead to hemolytic glaucoma, an entity characterized by blockage of the aqueous outflow pathway by hemoglobin-filled macrophages and breakdown products of red blood cells, typically occurring days to weeks after a large intraocular hemorrhage.

Hemolytic glaucoma was first described in 1963 as an unusual cause of acute open-angle secondary glaucoma that developed several weeks after a vitreous hemorrhage that was likely caused by vascular malformation.[40] Histologic examination of the eye that had been enucleated for intractable pain revealed hemorrhagic debris and many large pigment-containing macrophages in the anterior chamber angle and TM. The authors speculated that the red blood cells comprising vitreous hemorrhage had disintegrated into large deposits of hemoglobin, and the iron-containing material in the vitreous converted into hemosiderin. The hemoglobin, hemosiderin, and hemoglobin-filled macrophages accumulated in the angle, mechanically blocking aqueous outflow. Given the parallel to phacolytic glaucoma caused by lenticular degenerative products and macrophages digesting these products and blocking the TM, they named this entity hemolytic glaucoma.

A case series of five additional eyes was reported by others, and the authors of this series recommended that treatment begin with standard topical medical treatment, then proceed to anterior chamber washout if necessary.[97] If vitreous hemorrhage was found to be recurrent, then they suggested vitrectomy and treating the underlying cause of hemorrhage. Trabeculectomy is a consideration for persistently uncontrolled IOP. It can be also be combined with anterior chamber washout for short-term IOP control.

Hemolytic glaucoma can clinically present in a similar manner as ghost cell glaucoma, but red-tinged instead of khaki-colored cells may be seen floating in the anterior chamber in hemolytic glaucoma, and there may be reddish brown TM coloration. Histological analysis of anterior chamber aspirate can show pigment-laden macrophages of hemolytic glaucoma and distinguish the diagnosis from ghost cell glaucoma. This may be a purely academic exercise, as medical treatment followed by possible anterior chamber washout can be effective for both entities.

3.3. *Angle recession*

Angle recession is a common finding in eyes with blunt traumatic injury associated with hyphema, iridodialysis, iris sphincter tears, and transillumination defects with pigmented dispersion. It commonly occurs with traumas leading

to retrodisplacement of the iris root (Fig. 2).[10,22] Histologically, angle recession is defined as presence of a tear between the longitudinal and circular fibers of the ciliary muscles. Clinically, the gonioscopic findings include widened ciliary body band, prominent scleral spur, and a gray to white membrane covering the angle. The clinical findings may be subtle, and examination by switching from eye to eye several times may help detect small areas of angle recession, especially in those with a widely open angle and a broad ciliary body band. Gonioscopically, cyclodialysis can appear similar to angle recession on exam. Cyclodialysis is characterized by a sector of the ciliary body becoming detached from the sclera. On examination, the cleft is recognized by the presence of an area of visible sclera posterior to the scleral spur and is associated with a low IOP.[99,109,132] If possible, avoiding steroids may be helpful, permitting inflammation can encourage cleft closure. Atropine followed by argon laser to the cleft area may close the cleft. If these fail, surgical closure of the cleft is often necessary. IOP can rapidly rise when a cyclodialysis cleft closes, whether spontaneously or surgically, as the eye may be habitually producing aqueous humor at a higher rate than usual while the cyclodialysis cleft is open.

Among patients with a hyphema, angle recession has been observed in 71–100% of eyes[10,22]; however, only 7–9% of eyes with angle recession develop glaucoma.[63] Elevated IOP results from collateral damage to the TM and possible extension of a Descemet-like membrane from the cornea over the TM.[84] Typically, patients develop glaucoma several years after the injury, but those with more than 270 degrees of recession often present earlier.[51] It has been suggested that patients with more than 180 degrees of angle recession undergo lifelong annual examination to detect late-onset glaucoma.[89] Late-onset glaucoma is glaucoma presenting 6 months after trauma and most commonly is due to angle recession.[63,132] It is likely that those who develop glaucoma after traumatic angle recession already possess other predisposing factors, and trauma may only be an initiating factor, as the risk of glaucoma development in the fellow eye is up to 50%.[51]

The initial treatment of angle recession glaucoma is medical. Medications typically used for open angle glaucoma may suffice. Cholinergic agents are better avoided as they may paradoxically increase IOP by impairing uveoscleral outflow while the trabecular outflow is compromised by angle recession.[11] The miotics increase vascular permeability and may lead to formation of a fibrin clot in the anterior chamber, which in the acute phase of trauma increases the chance of posterior synechiae formation and secluded pupil.[137] Prostaglandins may not be an ideal choice in the acute phase but can be used after resolution of inflammation.

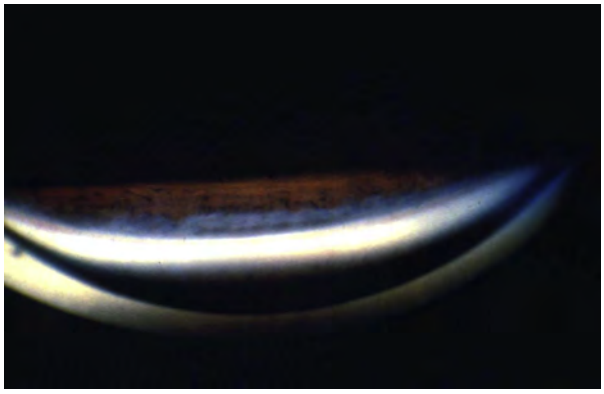

Fig. 2 – Gonioscopic photograph shows angle recession with characteristic ciliary body band widening and gray discoloration.

Laser trabeculoplasty may be less effective in this condition, but some success was observed with Nd:YAG laser trabeculopuncture. Argon laser trabeculoplasty led to failure in 7 out of 11 patients within 3 months, but patients had controlled IOP with Nd:YAG laser trabeculopuncture over 15 months of follow-up.[44] In another study, however, Nd:YAG laser trabeculopuncture was not very effective, and the authors suggested offering it only in eyes where at least part of the TM maintains its normal anatomy without angle recession on gonioscopy.[84] Studies on Nd:YAG trabeculopuncture are limited to one year follow-up, and there are no data on its long-term efficacy.

Angle recession is a risk factor for surgical failure, likely related to the younger age of patients and comorbid trauma-related eye damage. Failure rates of trabeculectomy are higher in angle recession compared to POAG, with 43% versus 74% success reported in one study.[86] The success of trabeculectomy with antimetabolite was greater than success of Molteno implantation in a group of patients with angle recession glaucoma, but there was a greater rate of bleb associated infection.[85]

3.4. *Trabecular meshwork damage*

Trauma can affect the TM in many ways. Some topics that are covered in other sections of this review include chemical injury, angle recession, blockage of the TM in phacolytic and hemolytic glaucoma, and toxicity in siderotic glaucoma. Eyes may also develop steroid-induced ocular hypertension and glaucoma from the steroids used to treat posttraumatic inflammation.

Mechanical trauma can also cause injury to the TM in the absence of angle recession. One case report of traumatic glaucoma after injury with the tip of a pool cue found features of unilateral pigment dispersion that included an abnormally deepened anterior chamber, midperipheral iris transillumination defects, and a Sampaolesi line, but there was no angle recession at presentation or on follow-up.[13] A series of closed globe injuries also reported that greater trabecular pigmentation was associated with development of traumatic glaucoma.[114] Mechanistically, liberation of pigment may be blocking the aqueous outflow pathway, and the trabecular endothelial cells phagocytizing the pigment particles could also contribute. Trabecular pigmentation has also been associated with IOP elevation in nontraumatic conditions, including pigmentary and pseudoexfoliation glaucoma.[21,105,112]

Eye trauma can also cause visible lacerations in the TM. One case report described a compressed air gun's plastic pellet causing a linear tear that split the TM and extended into Schlemm canal on ultrasound microscopy.[36] This tear was

accompanied by angle recession and persisted 2 months after injury. IOP was actually lower in the injured eye than in the fellow eye, likely from increased aqueous outflow in the area of the tear that may have functioned similar to an area of trabeculotomy. A different case report discussed how recurrent hyphema caused by laceration of the TM and Schlemm canal was resolved by argon laser photocoagulation to the traumatized area of Schlemm canal.[64]

Radiation may cause ocular hypertension and secondary angle-closure glaucoma.[122] This typically occurs in the setting of treatment for ocular melanoma, and greater radiation to the iris, ciliary body, and optic disc have been associated with higher risk of neovascular glaucoma.[52] Brachytherapy for ocular melanoma has also been shown to increase IOP from a preoperative baseline of 16.0 mmHg up to 24.3 mmHg during the time that the plaque was in place.[9] Mechanisms of radiation-induced increase in IOP include development of neovascular glaucoma, atrophy, and depigmentation of ciliary processes that lead to pigment deposits in the TM that block aqueous outflow, trabeculitis, and damage to scleral collagen that blocks episcleral venous drainage. Medical treatment may be less effective in this form of glaucoma than other types, and laser and surgical treatments such as tube shunts are preferable. Outflow procedures are often avoided in eyes with an ongoing risk of intraocular tumor dissemination. Fortunately, high levels of radiation are necessary to cause damage. Low radiation exposure to the eye such as that experienced by radiologic technologists has not been found to be associated with glaucoma development[72,73]; however, radiation exposure in survivors of atomic bombing were found to have slightly increased odds ratio for normal tension glaucoma of 1.31 per 1 Gy.[66]

3.5. *Epithelial and fibrous ingrowth*

Epithelial or fibrous ingrowths occur after perforating ocular injuries and various surgical procedures including penetrating keratoplasty, cataract extraction, and GDD implantations.[54,58,138] These create a pathway for epithelial and fibrous connective tissue to grow intracamerally (Fig. 3).[4]

3.5.1. *Epithelial ingrowth*

Epithelial ingrowth has 3 forms: epithelial pearls, epithelial cysts, and epithelial membrane. The most common and aggressive type is epithelial membrane. Epithelial pearls are rare isolated or multiple cyst-like structures implanted on the iris surface, remote from the site of the original wound. Epithelial cysts are gray or translucent cysts originating from the traumatic or surgical wound. Epithelial membranes are gray, scalloped membranes with varying thickness on the posterior surface of cornea, TM, iris, and ciliary body.[79,119] Epithelial ingrowth may masquerade as uveitis, as it can cause large anterior chamber floating deposits that may appear to be anterior chamber cell that persists despite steroid medication. This process can occur days to decades after the original surgery or trauma, but the majority present within the first year.[138] Common signs are a retrocorneal membrane, glaucoma, and corneal edema with or without a positive Seidel test. Risk factors for epithelial ingrowth include inadequate wound closure, wound fistula, iris incarceration, vitreous incarceration in a full thickness wound, and iatrogenic implantation of epithelial cells into the anterior chamber while repairing ocular lacerations.[138] In a review by Chen and Pineda, penetrating trauma was the second leading cause of

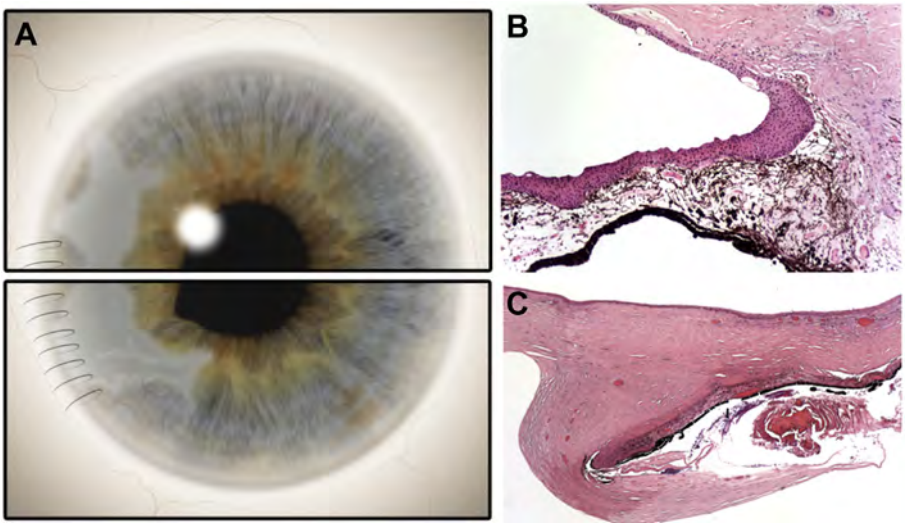

Fig. 3 – *A:* Top portion of stylized drawing shows epithelial ingrowth through surgical wound on the *left*. *Bottom* portion shows fibrous ingrowth, with a fibrovascular membrane originating from the surgical wound on the *left*. *B:* Histopathology photograph shows epithelial downgrowth. A sheet of corneal epithelial cells on the posterior cornea extends over the trabecular meshwork and onto the anterior surface of the iris. Hematoxylin & eosin, 50× magnification. *C:* Histopathology photograph shows fibrous ingrowth. Iris adheres to the posterior surface of a thick band of dense collagenous connective tissue that arises from an old corneal wound and curves around the pupillary margin into the posterior chamber. Vitreous incarcerated in the corneal wound provided a scaffold for the fibroplasia. The posterior chamber contains lens remnants. Hematoxylin & eosin, 10× magnification.

epithelial ingrowth, following cataract surgery as the most common cause.[24]

Specular microscopy may show a sharp demarcation line between the invading epithelium and endothelium in those with retrocorneal membrane[53]; however, specular microscopy is limited by the presence of corneal edema.[25] Anterior segment optical coherence tomography (OCT) is another diagnostic tool that could provide clues to the origin of epithelial ingrowth and was demonstrated to be effective in a case series of 5 patients with epithelial downgrowth after Descemet stripping automated endothelial keratoplasty.[124] Argon laser application to normal iris tissue leads to a dark brown burn area, but if epithelium is present on the iris surface, a pathognomonic fluffy white reaction is observed.[24,79] Definitive histologic diagnosis of epithelial ingrowth requires aqueous humor cytology or direct tissue biopsy.[24]

Treatment depends on the type of epithelial ingrowth. Epithelial pearls and cysts can be observed as long as there are no other complications. If epithelial pearls become large or induce uveitis and glaucoma, they can be excised with good outcomes.[119] Caution should be exercised during the excision, with a goal of performing en bloc resection of the epithelial cyst, without losing cyst contents. Treatment of epithelial ingrowth-induced glaucoma is challenging and usually associated with poor outcomes. Attempted treatments include cryotherapy, laser photocoagulation, irradiation, surgical excision, and injection of 5-fluorouracil inside the anterior chamber, although all have been associated with high failure rates.[69,111,121] The most accepted therapy is surgical resection. Glaucoma drainage devices (GDDs) are the mainstay of glaucoma management if the IOP is not controlled medically.[29] Trabeculectomy even with antimetabolites carries a high risk of failure from invasion of the ostomy, or even the bleb, with sheets of epithelial cells.[119] Cyclophotocoagulation is used when other treatment modalities fail.

3.5.2. *Fibrous ingrowth*

Fibrous ingrowth progresses more slowly and is generally more benign than epithelial ingrowth; however, aggressive cases may result in a poor outcome. Fibrous ingrowth may present with a focal, thick, vascularized membrane inside the anterior chamber or a membrane covering the entire endothelial surface of the cornea, TM, and iris surface. The exact origin of proliferating fibroblastic cells is not clear; subconjunctival connective tissue, stromal keratocytes, or metaplastic corneal endothelium are the proposed sources (Fig. 4). Fibrovascular tissue growth on the TM and cornea leads to glaucoma and corneal edema, respectively.[116]

Similar to epithelial ingrowth, fibrous ingrowth also causes glaucoma that is challenging to manage. Filtering surgeries often fail quickly because the proliferating fibrovascular tissue closes the sclerostomy. GDDs also may fail because of growth of tissue inside the lumen of the tube or because of encapsulation of the tube within the abnormal growing tissue intermixed with iris.[29] Removal of the membrane has been suggested to restore GDD function, but it is rarely effective, and cyclodestructive procedures are used as the last resort to control the glaucoma.

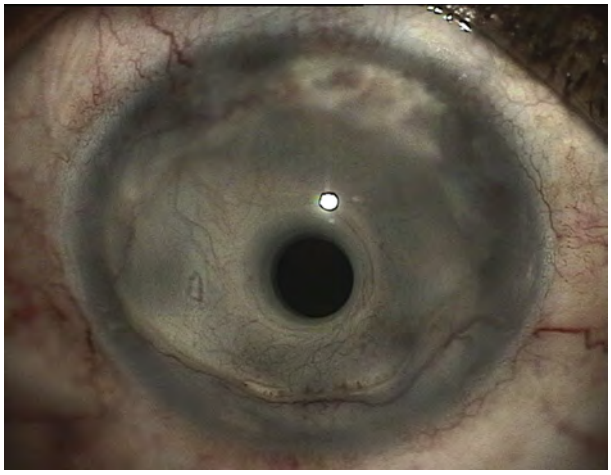

Fig. 4 – Severe fibrovascular downgrowth covering the whole iris with and sparing cornea, imitating keratoprosthesis appearance.

4. Lens

Traumatic damage to the crystalline lens or the zonular support of an intraocular lens can cause trauma-related glaucoma by a variety of mechanisms.

4.1. *Lens subluxation/dislocation*

Blunt ocular trauma causes ocular shortening in the anteroposterior dimension and elongation of the globe equatorially. This pushes the lens-iris diaphragm posteriorly and may tear the zonules and lead to lens subluxation or dislocation.

Lens subluxation typically occurs when more than 25% of zonular fibers are torn. The intact loose lens may lead to acute angle closure attack or chronic angle closure glaucoma. Slit lamp findings of lens subluxation include iridodonesis, phacodonesis, uneven depth of the anterior chamber, visibility of the lens equator on dilated exam, or the presence of a fine strand of the vitreous at the pupillary margin. In some patients, traumatic lens subluxation may be more evident in the supine position; examining these patients in both erect and supine positions is recommended.[38,74] The only imaging study that is effective in the evaluation and detection of occult zonular defects in traumatic cataracts is 50-MHz ultrasound biomicroscopy.[82]

These patients may be observed if laser iridotomy breaks the attack, IOP is controlled, and vision is good. Otherwise, lens extraction is required. Phacoemulsification and in the bag lens implantation can be successfully achieved using capsular tension rings and segments or Cionni capsular tension rings. If the intraocular lens cannot be placed safely in the capsular bag, it can be fixated to the iris or to the sclera. An anterior chamber intraocular lens may not be a good choice for these cases because the TM may have been damaged by trauma, exacerbating the risk of glaucoma.[16,50]

Lens dislocation into the anterior chamber is not common after ocular trauma in healthy subjects, but it may occur in those with spherophakia, microspherophakia, or pseudoexfoliation (Fig. 5A). In patients with microspherophakia and spherophakia, pupillary dilation and central corneal indentation in the supine position may move the lens into the posterior chamber, but in healthy subjects, this maneuver may result in lens dislocation into the vitreous cavity. Lens extraction is required to lower IOP and improve vision. Laser iridotomy is recommended to relieve pupillary block or to prevent it while awaiting surgical intervention.[27,74]

Lens dislocation into the vitreous cavity, unlike dislocation into the anterior chamber, can happen in patients without preexisting zonulopathy (Fig. 5B). Pupillary block may happen with vitreous strands. Lensectomy using vitrectomy settings combined with placement of an iris-fixated or scleral-fixated lens can be used to relieve pupillary block and restore vision.[108,125]

4.2. *Phacomorphic*

Trauma can often speed the development of cataracts, and it is important to obtain a detailed trauma history if cataract severity is highly asymmetric between a patient's two eyes. Phacomorphic glaucoma is a secondary angle closure that occurs due to the formation of a large cataract (Fig. 6). The growing intumescent lens pushes the iris forward, enhancing pupillary block and eventually leading to angle closure. The clinical presentation often mirrors acute primary angle closure (APAC). The distinguishing clinical feature is often an intumescent lens apparent on slit lamp evaluation and a uniformly shallow anterior chamber. The convex iris shape due to increased lens vault resembles a volcano on gonioscopy and is often referred to as the "Mount Fuji Sign". Anterior segment OCT shows a narrower angle, more anteriorly displaced lens, and thicker iris in the fellow eyes of APAC compared to phacomorphic glaucoma.[87]

All treatment of phacomorphic glaucoma should ultimately end with cataract extraction.[71] Initial therapy consists of topical and systemic ocular hypotensive medications for rapid IOP control of the affected eye. Laser peripheral iridotomy (LPI) and argon laser peripheral iridoplasty (ALPI) have also been advocated as a temporizing measure prior to surgical intervention. In a small retrospective study of 10 patients with phacomorphic glaucoma, LPI relieved the acute attack in all subjects.[130] ALPI has also been shown to be effective with rapid control of IOP in 17 of 21 eyes.[130] In patients with symmetrically advanced cataracts, the fellow eye should be evaluated for risk of acute glaucoma, and prophylactic laser treatment should be administered if necessary.

4.3. *Lens particle glaucoma*

With disruption of the lens capsule after trauma, cataract surgery, or release of Elschnig pearls after Nd:YAG capsulotomy, the lens material may migrate into the anterior chamber and mechanically block the aqueous outflow pathway (Fig. 7). Classic signs of lens particle glaucoma include the presence of white lens material in the anterior chamber, accompanied by an elevated IOP and open angle. Anterior chamber and vitreous tap in those with anterior chamber reaction may be necessary as initial temporizing measures. Histologic study of anterior chamber fluid specimens may demonstrate foamy macrophages intermixed with lens particles. The macrophages also contribute to TM obstruction.[35,65] In addition, the inflammatory reaction to the lens material may lead to posterior synechiae, peripheral anterior synechiae, or pupillary block. Management of lens particle glaucoma consists of topical steroids, antiglaucoma medications, and cycloplegics. Lens material removal or cataract extraction often leads to a substantial reduction of IOP, with no further glaucoma surgeries required.[95]

4.4. *Phacolytic glaucoma*

In the setting of a traumatic hypermature cataract, soluble lens particles may leak through microscopic defects in the lens capsule (Fig. 8). Similar to hemolytic glaucoma (Section 3.2.2), macrophages laden with phagocytosed lens material accumulate at the TM and block aqueous outflow. Others have observed accumulation of high-molecular-weight (HMW) proteins as an alternative explanation for the elevated IOP.[39] Cytology of aqueous humor can detect macrophages with intracellular lens material, and the presence of HMW protein in the aqueous can aid in diagnosis.

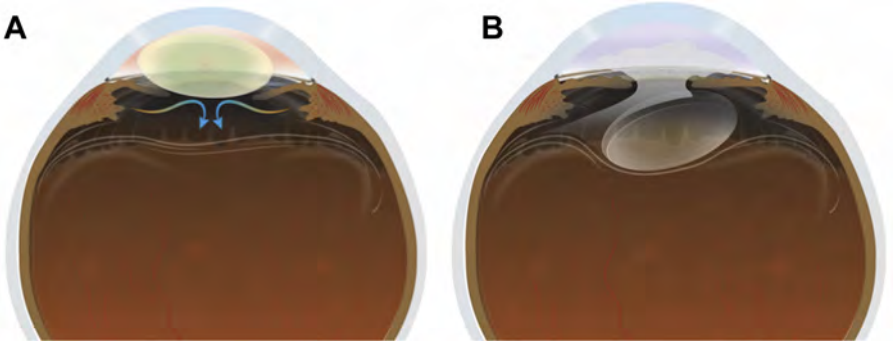

Fig. 5 – *A:* Stylized drawing of a crystalline lens dislocated into the anterior chamber. The lens is resting against the anterior aspect of the pupil margin, causing pupillary block. *B:* Stylized drawing of lens dislocation into the vitreous cavity.

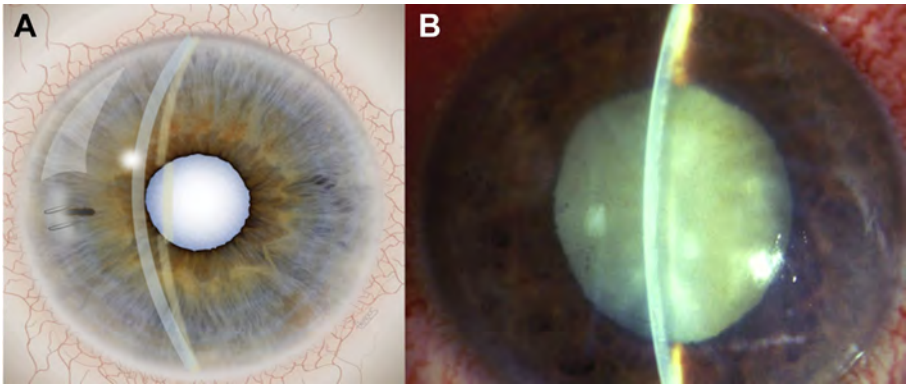

Fig. 6 – *A*: Stylized drawing of traumatic phacomorphic glaucoma. *Left* side wound has been sutured, residual conjunctival injection persists, and a large white crystalline lens is pushing the iris anteriorly and causing a narrow anterior chamber. *B*: Anterior segment slit lamp photograph shows a white traumatic cataract that is causing anterior chamber shallowing and phacomorphic glaucoma.

This entity typically has an acute presentation with a red and painful eye with a history of gradual decline of visual acuity. Examination may reveal corneal edema, anterior chamber flare, and cells that are larger than typical cells seen in uveitis. These cells are thought to be macrophages filled with lens particles. Macrophages may also present as fluffy white patches on the anterior lens surface at capsule leakage sites.[41] Free-floating clusters of macrophages may present as fluffy white material in the anterior chamber. These materials have been reported in the anterior vitreous after cataract removal with spontaneous resolution.[128] Less commonly, lens dislocation into the vitreous cavity can present with phacolytic glaucoma in a more subacute manner. A case report of phacolytic glaucoma with retinal perivasculitis after trauma found that the perivasculitis cleared after removal of the lens.[43]

Phacolytic glaucoma should be approached urgently and culminate with lens removal. Medical management of elevated IOP and inflammation should be initiated early to optimize the eye for surgical intervention. Cataract extraction with posterior chamber intraocular lens placement alone is adequate in the majority of cases, but it is important to note that these surgeries can be quite complex. In a series of 45 eyes, all patients undergoing cataract extraction alone achieved IOP <21 mm Hg without glaucoma medications.[77] Combined trabeculectomy can be considered on an individual basis, especially in patients with preexisting glaucoma or long duration of symptoms before treatment.[14] Patients with narrow angles who develop phacolytic glaucoma may have peripheral anterior synechiae (PAS). Intraoperative gonioscopy after washing out the anterior chamber and cataract surgery will determine the extent of PAS. Cataract surgery can be combined with goniosynechialysis if the optic nerve damage is not severe or with trabeculectomy in the presence of severe glaucomatous optic neuropathy. The severity of optic nerve damage can be determined from prior records or intraoperative fundoscopy after removing the cataract.

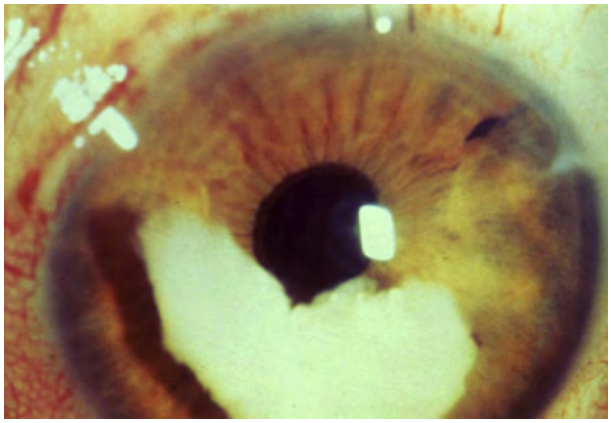

Fig. 7 – Anterior segment photograph shows a large retained lens fragment in the anterior chamber that is causing lens particle glaucoma.

4.5. *Phacoantigenic glaucoma*

Phacoantigenic glaucoma is a chronic granulomatous reaction to lens material retained in the eye (Fig. 9). This entity is no longer called phacoanaphylaxis, as it is not an allergic reaction. Instead, it is thought to be mediated by a type III hypersensitivity reaction.[95] Unlike phacolytic glaucoma, symptoms occur after a latent period during which sensitization to lens particles occurs. Inflammation typically occurs in the primary eye or in the fellow eye after lens particle exposure after cataract surgery or trauma. Keratic precipitates on the corneal endothelium is a distinguishing feature in this entity, and residual lens material is often present.[35] Initial treatment should be aimed toward IOP and inflammation control. Ultimately, surgical lens material removal is indicated if medical therapy is unsuccessful.

5. Vitreous and choroid

The mechanism of IOP elevation related to damage to these tissues is secondary to bleeding.

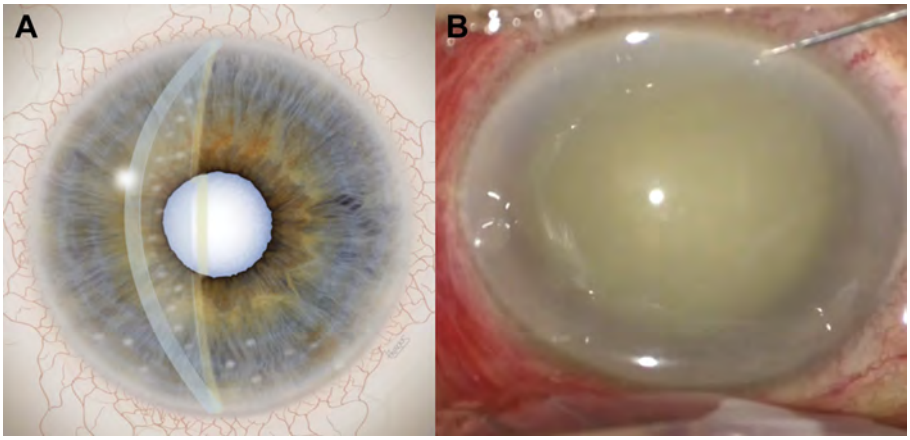

Fig. 8 – A: Stylized drawing of phacolytic glaucoma. B: Intraoperative anterior segment photograph of phacolytic glaucoma. Soluble lens particles have leaked out of a traumatic hypermature cataract and into the anterior chamber, where macrophages laden with this material clog the trabecular meshwork.

5.1. *Ghost cell glaucoma*

Ghost cell glaucoma is a secondary open-angle glaucoma caused by obstruction of the TM by aged, degenerated, spherical, rigid, depigmented red blood cells known as ghost cells (Fig. 10). The rigidity of the ghost cells is a key factor in limited their egress through the TM. Ghost cell glaucoma occurs in the setting of vitreous hemorrhage or long-standing hyphema in the absence of vitreous hemorrhage, typically after trauma or intraocular surgeries.[3,20,88,106,129] It typically is not caused by hyphema because of the rapid circulation and high levels of oxygen in the anterior chamber; in isolated hyphema, red blood cells may be cleared from the eye before they can degenerate. Vitreous ghost cells can reach the anterior chamber through a disrupted anterior hyaloid face after traumatic injury, cataract extraction, vitrectomy, or even spontaneously. Average time to onset is 1-3 months after hemorrhage, and the degree of IOP elevation correlates with the number of ghost cells in the anterior chamber.[3,20,88] The red blood cells lose their intracellular hemoglobin, and the remaining hemoglobin binds to the cell membrane, forming characteristic clumps called Heinz bodies which can be diagnostic findings of anterior chamber aspirates.[120]

Clinical findings include Khaki-colored cells in the anterior chamber and vitreous cavity, elevated IOP, and corneal blood staining. Layering of ghost cells results in pseudohypopyon, and mixture of ghost cells with layers of fresh blood gives the characteristic “candy stripe” appearance. Diagnosis is confirmed by clinical findings and demonstration of hollow erythrocytes with Heinz bodies in an aqueous aspirate specimen.[19]

Ghost cell glaucoma is often a self-limited condition and is initially managed medically. If medical therapy fails, pars plana vitrectomy and anterior chamber lavage is used.[4] Placing a pars plana tube shunt at the time of vitrectomy is a consideration to provide more definitive management. Repeated anterior chamber irrigation and trabeculectomy have been also reported as surgical management.[20,42]

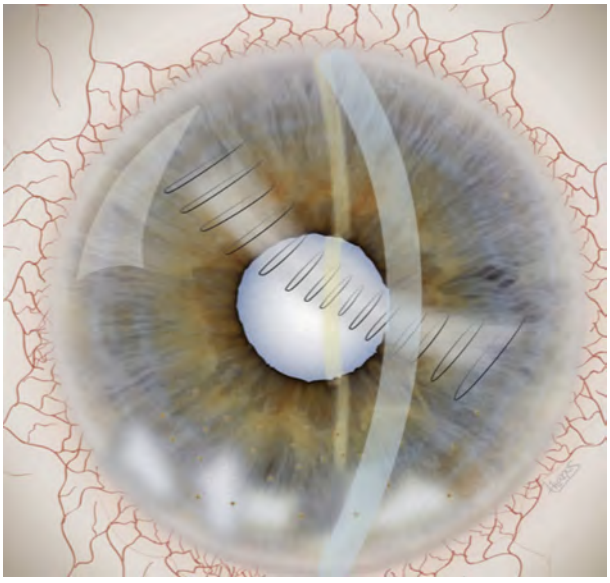

Fig. 9 – Stylized drawing of phacoantigenic glaucoma. An open globe injury that penetrated the cornea and lens capsule caused release of lens material into the anterior chamber, where a type III hypersensitivity reaction developed, resulting in keratic precipitates visualized in the lower part of the image.

5.2. *Siderotic and hemosiderotic glaucoma*

Siderosis bulbi describes a constellation of ocular toxicity findings caused by intraocular iron, which is typically introduced by trauma.[5] As early as 1894, von Hippel distinguished two distinct types of siderosis: one was hematogenous, coming from iron derived from blood, and the other was exogenous, coming from an iron-containing intraocular foreign body. While there are many publications on siderosis bulbi caused by foreign bodies, there are relatively fewer on hemosiderotic glaucoma arising from endogenous blood. Among the earliest studies of hemosiderotic glaucoma was a

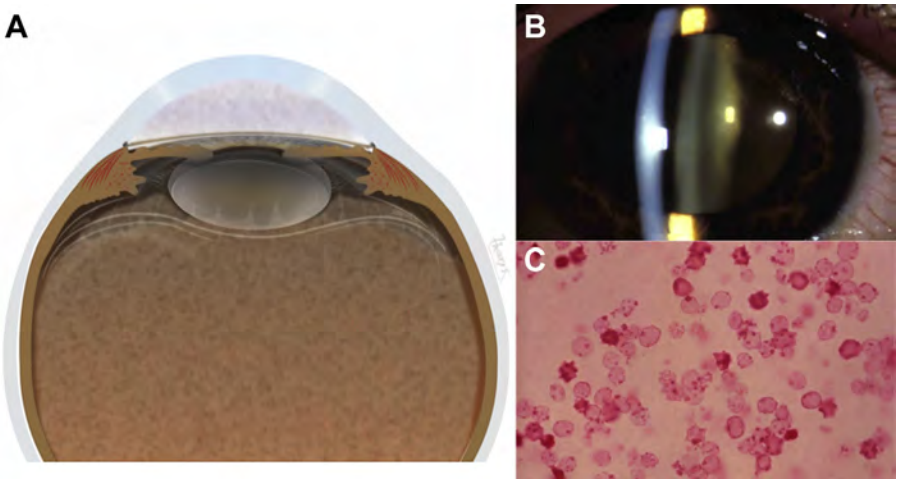

Fig. 10 – *A:* Stylized drawing of ghost cell glaucoma. The *lower* portion of the image shows dehemoglobinized vitreous hemorrhage. The *top* portion of the image shows an anterior chamber filled with aged, degenerated, spherical, rigid, depigmented red blood cells known as ghost cells. *B:* Anterior segment slit lamp photograph demonstrating old dehemoglobinized vitreous hemorrhage behind the crystalline lens. *C:* Histopathology photograph demonstrating Heinz bodies, which are characteristic clumps of hemoglobin derived from red blood cells (Hematoxylin & eosin).

series of five eyes that underwent enucleation after central retinal vein occlusion, hemorrhage after cataract extraction, or ocular contusion.[134] Another histologic study of an eye that developed hemosiderotic glaucoma two years after sudden atraumatic vision loss also demonstrated TM containing fine granular pigment, which seemed to have caused sclerosis.[140]

Secondary open-angle glaucoma from siderosis has been attributed to TM fibrosclerosis caused by a direct toxic effect of the intraocular iron.[5] When red blood cells are lysed in the anterior chamber, the hemoglobin that is released is phagocytized and degraded. Hemosiderin accumulates, and the toxic granules of inorganic iron composing the hemosiderin cause tissue degeneration and sclerosis. This can impact endothelial cells lining the TM, leading to decreased outflow facility.

Siderosis is typically a chronic process that develops slowly in the eyes with a history of recurrent intraocular hemorrhages, and it can be distinguished from hemolytic or ghost cell glaucoma by the lack of red or khaki cells in the anterior chamber and the longer timeline to development of secondary glaucoma. Other signs and symptoms that can help solidify the diagnosis include iris heterochromia, pupil dilation, pigmentation of anterior chamber structures, nyctalopia, and reduced electroretinographic responses.[118]

In two cases of ocular siderosis with secondary glaucoma, ultrasound biomicroscopy demonstrated atypically high reflectivity in the deep angular stroma, and histology of a TM sample confirmed the diagnosis.[110] A series of 20 eyes with siderosis reported a 15% rate of above normal IOP, while a 25% secondary glaucoma rate was reported in 24 eyes with intraocular foreign bodies.[5,144] A slightly lower 7.7% rate of secondary glaucoma was reported in a series of 64 patients with ocular siderosis, and 56 had intraocular foreign bodies found.[75] The most important aspect of managing siderosis is removing the iron-containing foreign body, which benefits the trabecular meshwork and the retina. A secondary glaucoma case presented greater than thirty years after initial injury, and the IOP normalized with only removal of the metallic foreign body.[31] There is little literature about management of hemosiderotic glaucoma arising from endogenous blood owing to the rarity of the condition and the fact that most publications are histologic studies of eyes that have been enucleated, but medical therapy followed by filtering surgery as needed can be a potential approach.

5.3. *Suprachoroidal hemorrhage*

Suprachoroidal hemorrhage may occur after sharp or blunt ocular trauma, although most cases occur because of either intraoperative or postoperative hypotony, which allows weakened long or short posterior ciliary arteries to rupture (Fig. 11).[78] Rapid decompression or trauma to the globe can cause the retina and choroid to shift anteriorly, stressing the posterior ciliary arteries with shearing forces that can cause suprachoroidal hemorrhage, which is typically associated with sudden onset of pain.

In large case series of suprachoroidal hemorrhage, approximately one-third of cases were associated with trauma, while most of the others were associated with surgery.[104,141] Intraoperative suprachoroidal hemorrhage is best managed with immediate wound closure, and it has a higher estimated rate of 1.8% in eyes with a history of trauma, versus a 0.12% estimated rate in nontraumatized eyes.[83]

Suprachoroidal hemorrhage is a relatively rare condition, and there are not readily available estimates of its frequency specifically in ocular trauma, but several studies estimate the risk of suprachoroidal hemorrhage in eyes undergoing glaucoma surgery. One estimated that the cumulative 3-month incidence rates of postoperative suprachoroidal hemorrhage after trabeculectomy and tube shunt were 0.6% to 1.4% and 1.2% to 2.7%, respectively.[135] A review of the literature reported an incidence of delayed suprachoroidal hemorrhage

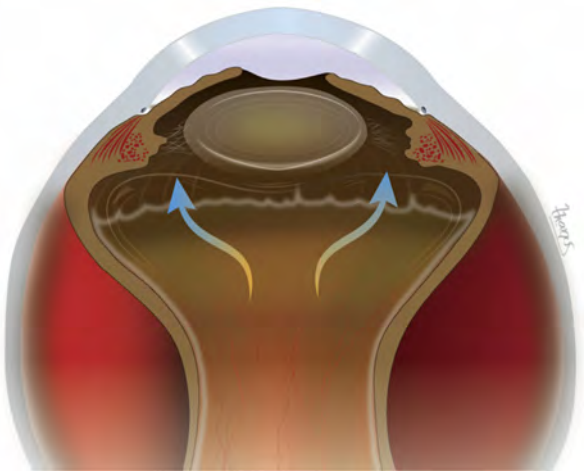

Fig. 11 – Stylized drawing of suprachoroidal hemorrhage. Hemorrhage in the *right* and *left* sides of the image causes anteriorly-directed pressure, shallowing the anterior chamber.

after trabeculectomy ranging from 0.5% to 2%, while the rate after tube shunt surgery is higher, ranging from 1.2% to 8.3%.[70] Risk factors include anticoagulation, aphakia, postoperative hypotony, atherosclerosis, axial myopia, Vasalva, and intraoperative hypertension and preoperative elevated IOP is a risk factor that is typically absent in trauma related suprachoroidal hemorrhage.

The decision to proceed to surgical drainage of suprachoroidal hemorrhage and timing of surgery remains controversial, although classic recommendations include waiting 7 to 14 days to allow liquefaction of blood, which permits more thorough drainage of the hemorrhage.[70] Ultrasound has showed complete liquefaction of the hemorrhage in an average of 14 days, with a range of 6 to 25.[26] Easy drainage has been reported in the early period in many cases.[59,70,94] Scenarios for immediate or urgent intervention include intraoperative expulsive suprachoroidal hemorrhage that prevents eye closure without drainage, concurrent retinal detachment, retina-to-retina apposition commonly called "kissing choroidals", and uncontrolled IOP or pain despite medical management. Most studies of suprachoroidal hemorrhage have not focused on IOP, but eyes can present with elevated IOP, likely caused by angle closure that results from increased posterior segment pressure. A series of 10 eyes that developed suprachoroidal hemorrhage and shallow anterior chamber, 2 of which developed after trauma, reported average IOP before treatment of 39.5 mmHg, and this decreased to 18.4 mmHg after treatment, which was drainage and/or pars plana vitrectomy within 1 to 7 days after diagnosis for 8 of the 10 eyes.[59]

6. Orbit

Bleeding in the orbital space and changes in orbital vasculature are the main mechanisms for trauma-related IOP elevation in the orbit.

6.1. *Traumatic carotid-cavernous fistula*

Carotid-cavernous sinus fistula (CCF) can develop after trauma, but also can occur spontaneously from preexisting abnormal anatomic communications between branches of the internal and external carotid arteries and the cavernous sinus (Fig. 12). Communications can be anatomically classified as direct high-flow shunts between the internal carotid artery and the cavernous sinus or lower-flow indirect dural shunts from branches of the internal and/or external carotids to the cavernous sinus.[7] Traumatic CCFs are more commonly high-flow and are more likely to require intervention such as embolization, while low flow dural fistulas are typically spontaneous and often resolve with conservative management. Causes of high-flow CCF include direct head trauma, dissection of the internal carotid artery, and rupture of an aneurysm of the internal carotid artery within the cavernous sinus.

CCF causes increased pressure in the cavernous sinus, resulting in dilation of the superior ophthalmic vein. At the same time, relative perfusion pressure of the ophthalmic artery is reduced, leading to ischemia. Clinical findings include proptosis, chemosis, dilated episcleral and conjunctival vessels, and orbital bruit.[143] Vision can be decreased, extraocular motility may be limited, and cranial nerve III–VI palsies may develop. When CCF is suspected, computed tomography or magnetic resonance imaging of brain and orbit and orbital Doppler can help confirm the diagnosis, although conventional angiography is typically needed for planning endovascular intervention.

CCF can cause elevated IOP by elevating episcleral venous pressure and is thought to lead to angle closure by causing congestion and edema of the choroid and ciliary body. Peripheral iridotomy may help in these cases if there is any pupillary block component, and argon laser pretreatment should be considered to minimize risk of hemorrhage, but closure of the fistula is more likely to be effective. CCF has also been implicated in development of hemorrhagic choroidal detachment and acute angle closure.[17] Neovascular glaucoma may develop as a result of ischemia caused by obstructed venous blood flow.[123]

In a series of 34 patients with traumatic CCF mostly related to motor vehicle accidents or falls, 33 were successfully embolized using transvascular approaches, with significant improvement in orbital congestion in all cases. Preoperative IOP was elevated in 24 cases, ranging from 24 to 60 mmHg, and normalized after surgical treatment. One patient developed central retinal artery occlusion related to IOP of 60 mmHg.[68]

In a series of 43 patients with CCF, 14 eyes showed ocular manifestations, although only 1 of these eyes was of a patient who had suffered head trauma. Elevated IOP occurred in 64.3% of the 14 eyes with ocular manifestations, with maximum IOP ranging from 22 to 55 mmHg. Successful closure of the fistula helped with IOP control, and eyes where the fistula could not be closed required trabeculectomy, cyclocryotherapy, or cyclophotocoagulation.[57]

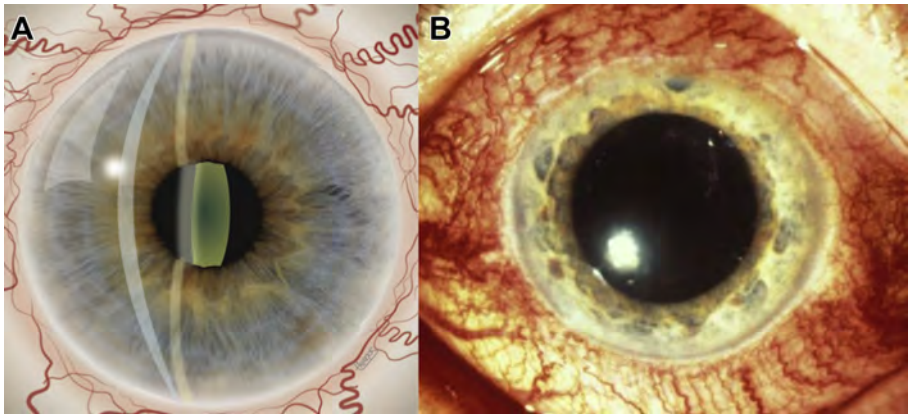

Fig. 12 – A: Stylized drawing showing dilated corkscrew conjunctival and episcleral vessels in an eye of a patient with a carotid-cavernous sinus fistula. B: Anterior segment photograph showing the same as A. In the photograph, there is also a superior iridectomy; this eye has also undergone previous filtering glaucoma surgery.

6.2. *Orbital hemorrhage*

Orbital hemorrhage can develop as a result of blunt or sharp accidental or surgical trauma. Signs and symptoms depend on the location (preseptal, intraconal or extraconal space, subperiosteal, within the optic nerve sheath, or in multiple locations) and amount of hemorrhage. Generally, owing to rapid accumulation of a significant amount of blood within the orbital tissues, acute proptosis, ecchymosis, pain, nausea, vomiting, decreased vision, and limitation in ocular motility are the presenting signs and symptoms. A marked IOP elevation occurs secondary to the elevation of intraorbital pressure.[48]

Serial ocular examinations (visual acuity, extraocular movements, pupillary reactions, and confrontational visual fields) are required to ensure there is no optic nerve dysfunction. Small hemorrhages with minimal orbital signs and moderate IOP elevation may be observed and managed medically with aqueous suppression and steroid agents. Topical medications that increase outflow may not be a good choice because the mechanism of IOP elevation is increased episcleral venous pressures.[80]

Those with IOP >40 mmHg, a relative afferent pupillary defect, worsening visual acuity, pale retina on funduscopic examination, retinal arterial pulsations, and intractable pain are candidates for lateral canthotomy with or without inferior cantholysis. The efficacy of lateral canthotomy, canthal tendon disinsertion, and inferior cantholysis in the reduction of intraorbital and IOP was compared by Yung and coworkers.[142] They concluded that inferior cantholysis resulted in significantly greater reduction in IOP than either lateral canthotomy or canthal tendon disinsertion. If lateral canthotomy and cantholysis does not help, orbital decompression is required.[100,127]

7. Conclusion

Trauma causes increases in IOP and subsequent development of glaucoma via an extremely wide variety of mechanisms. Understanding and identifying the underlying causes of IOP elevation in each scenario are important in choosing appropriate treatment approaches. In many cases, trauma-related glaucoma can be managed with topical medications, and if conservative measures fail, surgical options may provide satisfactory IOP control. Traumatic injury is highly heterogeneous, but if IOP is well controlled, visual outcomes can be good if there has not been significant concomitant anatomic damage beyond the optic nerve injury caused by elevated IOP.

8. Literature search

A comprehensive search of ophthalmology literature through the PubMed database (1960–2018) was carried out on the articles using the following search terms: angle recession, carotid-cavernous fistula, chemical burn, epithelial ingrowth, fibrous ingrowth, iritis, ghost cell glaucoma, hemolytic glaucoma, hemosiderotic glaucoma, hyphema, lens particle glaucoma, lens subluxation, open globe, orbital hemorrhage, phacoantigenic glaucoma, phacolytic glaucoma, phacomorphic glaucoma, steroid-induced glaucoma, suprachoroidal hemorrhage, trabecular meshwork damage, traumatic glaucoma, vitreous hemorrhage. Targeted searches were also performed for selected articles noted in the references of articles found with the aforementioned search terms. Non-English literature with English abstract translation was included.

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Major review

Eye involvement in primary central nervous system lymphoma

Alexandra L. Farrall, PhD, Justine R. Smith, PhD, FRANZCO**

College of Medicine and Public Health, Flinders University, Bedford Park, South Australia, Australia

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ABSTRACT

Primary central nervous system lymphoma (PCNSL) may manifest initially in the eye (termed vitreoretinal lymphoma or VRL) or in non-ocular CNS compartments, or in both. The nature of the onset of PCNSL implies two clinical specialists — ophthalmologists and neuro-oncologists — independently may assess the primary presentation of this rare malignancy. Clinically relevant perspectives on expectations of PCNSL manifestation in both ocular and non-ocular CNS compartments would help inform management practices in each specialty, which should impact clinical outcomes. A recent increase in the number of published PCNSL cohort studies provides new opportunity to review the current prevalence rates of ocular involvement, and the timing of this involvement over the course of disease. In PCNSL cohorts defined by non-ocular CNS compartment involvement, with or without ocular involvement (termed "PCNSL ± ocular involvement" cohorts), mean rates of concomitant VRL at diagnosis, or at any time during the course, are 10% and 16%, respectively. Only a few individuals within this cohort group present with exclusive eye disease (<5%), and the rate of secondary ocular involvement is only 5–9%. In PCNSL cohorts defined by the involvement of the ocular compartment, with or without non-ocular CNS involvement (termed "VRL ± non-ocular CNS involvement" cohorts), 58% of persons have a primary ocular diagnosis, which carries a 50% risk of secondary involvement in the CNS beyond the eye. Rates of non-ocular CNS involvement with VRL at diagnosis or over the course of disease are 41% and 69%, respectively.

1. Introduction

Primary central nervous system lymphoma (PCNSL) is defined by its confinement to the CNS. The CNS compartments that may be affected include the brain, spinal cord, meninges, cranial nerves, and eye. PCNSL may develop either exclusively or concomitantly within each of these compartments. The temporal onset of PCNSL in these CNS compartments, and which compartments become involved, varies between individuals. The clinical outcomes for individuals suffering from PCNSL are poor, with a 5-year overall survival rate of around 30% for immunocompetent individuals.[36,50,103,127,128,139] Without treatment, most people rapidly succumb to the disease after brain involvement. The etiology of PCNSL is poorly

* Corresponding authors: Alexandra L. Farrall, PhD & Justine R. Smith, PhD, FRANZCO, Eye and Vision Health, Flinders Medical Centre, Room 4E-431, Flinders Drive, Bedford Park, SA 5042, Australia.
E-mail addresses: alix.farrall@flinders.edu.au (A.L. Farrall), justine.smith@flinders.edu.au (J.R. Smith).
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understood, and mechanisms of PCNSL dissemination within the CNS remain an enigma.

Intraocular involvement alone is an uncommon manifestation of PCNSL. This is often referred to as primary vitreoretinal lymphoma (PVRL), given its predominant occurrence in the posterior segment of the eye; however, PCNSL in the eye may also infiltrate the anterior segment and the optic nerve. The areas of the eye affected by PCNSL represent an "ocular CNS compartment," which is distinct from other potentially involved CNS compartments (referred to here as "non-ocular CNS compartments"), and importantly do not include external eye structures such as the conjunctiva or ocular adnexa. When ocular involvement in PCNSL is not primary, the condition is termed simply vitreoretinal lymphoma (VRL). A comprehensive review of VRL, including definitions, clinical features, and diagnostic and therapeutic approaches, was recently published in this journal by Sagoo and colleagues.[122]

Typically, PCNSL is an aggressive non-Hodgkin lymphoma. At greater than 90% of cases, the most common pathological type is diffuse large B-cell lymphoma. The remaining types include Burkitt and mantle B-cell lymphomas and various T-cell lymphomas.[3,50,69,111] Recent molecular studies of diffuse large B-cell lymphoma — including gene expression and copy number profiling — are providing new pathological insights[108,145] that relate specifically to occurrence within the CNS.[16,28,83,87,112,113] Intriguingly, an understanding is emerging of cellular and molecular traits linked to its manifestation in other immune-privileged sites, such as in the urogenital tract.[17,18,22,71,98] To improve clinical outcomes for those persons suffering with the burden of PCNSL, a concerted effort is underway toward applying a standardized approach to baseline evaluations and response criteria for PCNSL[1,42,57] and toward utilizing new molecular genetic insights to aid rapid diagnosis and tailor treatment regimens to the individual.[16,51,83]

The rare nature of PCNSL hampers efforts to better define the pathology and to develop more accurate diagnostic tools and targeted therapies. The most recent population-standardized rate of PCNSL in the United States reported by the Central Brain Tumor Registry of the United States (CBTRUS) was calculated at 4.4 per million person-years between 2010 and 2014, representing approximately 2% of all brain neoplasms.[103] Other similar national population-based retrospective surveys from the United States, Europe, and Korea have revealed recent PCNSL incidence rates of 1.7 to 4.4 per million person-years.[36,52,99,128,139] Interestingly, these national studies indicate an increasing incidence of PCNSL. Subpopulation regional surveys from the United Kingdom[52] and Japan[86] also show a similar trend. PCNSL incidence has been increasing at rates of 4 to 8% per year in some places,[36,128] and has been particularly noted in people older than 70 years of age.[36,127,139,141] This widely observed recent increase in the incidence of PCNSL, particularly among immunocompetent people, appears to be independent of technological advancements in diagnostic methodology.[52,99]

2. Classification

In 1988, Hochberg and Miller reviewed the historical challenges and perceptions from the preceding 60 years that had hampered the establishment of a modern classification for non-Hodgkin lymphoma, and particularly for lymphomas of the CNS.[59] Of note was the controversy surrounding the early utilization of two terms for PCNSL, namely microglioma and reticulum cell sarcoma. Thought to be separate, albeit related, entities by different groups, this divergent nomenclature had a lasting impact on how PCNSL was interpreted and reported on within the literature. Recent studies using immunological, molecular, and genetic profiling techniques have provided valuable new insights for characterizing lymphoma subtypes at the molecular level,[28,145] which in turn has improved the classification of PCNSL. Given the recent recognition of distinct genotypic and immunophenotypic features, with reference to morphologic and clinical characteristics, PCNSL has been classified as a specific lymphoma subtype in the World Health Organization (WHO) lymphoma classification system since 2008.[15]

In the literature, PVRL may be treated as either a separate, yet related entity to PCNSL, or as a PCNSL subtype. Like PCNSL, PVRL has also been subject to attribution of differing terminology, including the now obsolete "ocular reticulum cell sarcoma," and even today, the broad term of primary intraocular lymphoma or PIOL. The treatment of any distinction between PCNSL and PVRL in the literature is varied due to differing perspectives arising from unresolved questions concerning the pathogenic mechanisms of lymphoma in the CNS.[142,147] A path toward a consistent approach to the classification of PCNSL and PVRL is being facilitated by advances in the molecular genetic profiling of this cancer. Indeed, such studies lend support to the notion that PCNSL and PVRL are the same entity. Both PCNSL and PVRL share the same unique biological and clinical features that recognize PCNSL as a specific diffuse large B-cell lymphoma subtype by the WHO.[15,28] Importantly, they both share a number of genetic aberrations: most PCNSL and PVRL are of the same activated B-cell-like (ABC) cell-of-origin subtype,[14,28] which may explain their shared poor prognostic outcomes. In particular, both PCNSL and PVRL share the same high prevalence of the L265P mutation in the myeloid differentiation factor 88 gene (*MYD88 L265P*), which is now regarded as a hallmark of PCNSL[13,94,111,113]; however, heterogeneity within PCNSL at the molecular genetic level is clearly evident in the literature.[7,28] Future work understanding the finer complexities of PCNSL oncogenic programs will help further refine PCNSL definitions and classification.

Inconsistent nomenclature and definitions have limited the facility to research and understand PCNSL, which is already limited by the rarity of the tumor itself. Herein, we take into consideration historical perceptions toward providing an inclusive overview of ocular presentation rates in PCNSL as a clinically presenting entity and irrespective of the rare pathological types that are sometimes present within this patient group.

3. Determining the prevalence of eye involvement in PCNSL

We aim to provide current estimates of the prevalence of ocular involvement, or VRL, in PCNSL.

Determining the prevalence of eye involvement in PCNSL has been problematic. Measures used in the literature have been based largely on early reports of small cohorts, and derived from settings in which the eyes were not consistently assessed, primary diagnosis was often delayed, and treatment options were few.[43,59,62,111] Historical perceptions and an evolving definition and classification of PCNSL have hampered the development of universally adopted diagnostic and follow-up practices for PCNSL. Assessment of the eye was often performed in an ad hoc or symptom-directed manner, or only at autopsy.[43,59] Even today, ocular involvement, particularly as the primary manifestation, is especially challenging to assess as it may be asymptomatic or masquerade as uveitis, thus delaying diagnosis.[27,111] Consequently, much of the published literature on the prevalence of eye involvement throughout PCNSL progression is incomplete. The most robust information addresses ocular involvement rates "at any time" throughout the course of PCNSL development. Thus, an updated perspective on the prevalence and specific timing of ocular involvement with respect to involvement of the non-ocular CNS compartments, against the backdrop of current therapeutic approaches, is warranted. This renewed perspective has important clinical implications, especially in light of recent studies that indicate overall survival is improved when primary ocular onset of PCNSL is diagnosed and treated before the onset of non-ocular CNS involvement (i.e., 60 months vs 31–35 months, respectively).[48,62] A current understanding of risk from both the ophthalmologist and neuro-oncologist perspectives would help inform the management practices required from each specialty, which in turn should impact clinical outcomes.

The literature provides two pools of cohort studies from which to assess ocular involvement in PCNSL. In one group of studies, which are predominantly neuro-oncologic in perspective, PCNSL is treated as a single whole; eye involvement is included in the definition and assessed as part of the diagnostic work-up and clinical monitoring. Ocular disease may or may not ever present in this cohort pool, but other (non-ocular) CNS compartments within the definition of PCNSL are involved, such as the brain and/or meninges. In the second group of studies, which are usually from the ophthalmic perspective, PCNSL cohorts are defined by the presence of intraocular involvement. Thus, in this review, we have applied the following definitions for lymphoma cohorts: 1) CNS disease with or without ocular involvement is termed "PCNSL ± ocular involvement" cohorts and 2) ocular disease with or without other (non-ocular) CNS involvement is termed "VRL ± non-ocular CNS involvement" cohorts. Together, these two cohort groups can be used to derive mean prevalence rates, as percentages within a 95% CI, for the expectation of eye involvement within their respective cohorts.

Despite improvements in survival of PCNSL following the introduction of combination chemotherapy–based treatments in the last 20 years, and growing evidence that those affected are living longer, there is still debate surrounding the relative effectiveness of current treatment approaches.[12,111,137,147] Analysis of the relative effectiveness of treatment types, including their impact on the onset of eye involvement in PCNSL, is beyond the scope of this review.

4. Overview of clinical studies

To capture appropriate cohort studies from the current literature to meet the aim of this systematic review, the following parameters were considered. First, to capture as many cohort reports on ocular involvement in PCNSL as possible, the literature search terms had to accommodate the limitations and complexities of historical classification approaches, and key to the aims of this review, assessment of the eye was mandatory for inclusion. Second, the emphasis of this review was to derive an understanding of expected average prevalence rates (as a percentage) of eye involvement in PCNSL within the two cohort pools presenting at the clinic: "PCNSL ± ocular involvement" and "VRL ± non-ocular CNS involvement." To this end, case reports were excluded and only published cohort groups of at least four persons were included. Cohorts contributed equally to mean prevalence rates, irrespective of size. Publications found through bibliographic database searches directed the manual curation of eligible studies from reference lists. Third, PCNSL manifests at a disproportionally higher rate in individuals who are immunosuppressed, for example, due to organ transplant or HIV infection,[59,127] than in those who are immunocompetent. The focus of this cohort review was to assess PCNSL in immunocompetent clinical cohorts. Studies were excluded from review if the immune status of the study cohort was not specified, or the study included only PCNSL in immunocompromised populations. Within the largely immunocompetent cohorts reviewed herein, no persons with positive serology for HIV were reported, as positive HIV status was a common study exclusion criterion. A few case exceptions were noted for non–AIDS-related immunosuppression due to organ transplant,[63,67] and/or due to histories of lymphoma or cancer treatment outside of the CNS, including in the testis, ovaries, cervix, breast, and heart.[11,18,29,45,64,88,97,104,116,119,133,134,138,143] These were included due to the difficulty in identifying and extracting data specific to individuals within the cohorts making it not feasible or practical to remove. These cancer histories were only reported among "VRL ± non-ocular CNS involvement" cohorts. This may likely reflect the predominantly retrospective nature of those studies versus the predominantly prospective intention-to-treat studies of "PCNSL ± ocular involvement" cohorts, in which systemic cancer was a common exclusion criterion. The studies reviewed herein were predominantly reports on newly diagnosed PCNSL cohorts. Cohort studies with patient details only pertaining to PCNSL in the context of secondary and/or relapse/refractory lymphoma were excluded if data pertaining to the initial disease presentation were absent.

Of the final 107 cohort studies found to be eligible for review, 69 were of the "VRL ± non-ocular CNS involvement" cohort type and 38 were of the "PCNSL ± ocular involvement" cohort type. This disparity in the number of eligible studies for

each cohort type reflects an inconsistent approach to routine eye assessment and reporting in the literature for PCNSL cohorts, in which eye involvement is not a focus. Indeed, on occasion, subset cohort data pertaining only to those who had eye assessments in "PCNSL ± ocular involvement" cohort studies could be extracted for use in prevalence calculations.[38,41,56,61,100,106,137] This revealed a potential bias and a systemic/inherent limitation in obtaining a full understanding of eye involvement in PCNSL due to limitations on the available data resources arising from inconsistent diagnostic, monitoring, and reporting practices still evident across the current literature. Together, the cohort studies eligible for review represent 4873 individuals with PCNSL. This value may be a slight overrepresentation as it is probable that some small level of data duplication for specific cohort individuals may have occurred across independent study reports, but not identified as such. Reports were excluded in favor of the most recent data on specific cohorts, and/or cohort individuals, where clearly identifiable, which usually equated to longer follow-up information for inclusion.

Cohort study demographics are summarized in Table 1. Studies are grouped by cohort type and listed in alphabetical order given the surname of the first author. The publication years ranged from 1983 through April, 2019, with 85% of studies published in the year 2000 or subsequently. The time periods from which the cohort data were derived were defined in 88% of the reports, half of which (50%) described cohort data collected only from the year 2000 onward, and 26% from 1999 or earlier. Only 4% included clinical cohort data from before 1980. Around 23% described cohort data bridging either side of the year 2000, from as early as 1977 up to 2018, but nearly two-thirds of these studies only used cohort data collected over various time intervals between the years 1990 and 2010 (14% of all studies). Most studies reported on local or nationally derived cohorts. However, twice as many cohorts were derived internationally for "PCNSL ± ocular involvement" cohort studies compared to "VRL ± non-ocular CNS involvement" cohort studies (18% vs 9%, respectively). Nearly all (87%) "VRL ± non-ocular CNS involvement" cohort studies were conducted in a retrospective fashion, compared to only 34% of "PCNSL ± ocular involvement" cohort studies. The size of the cohorts described in these studies ranged in size from 4 to 297 patients. The mean size of all "PCNSL ± ocular involvement" cohorts reviewed was 84 (55–123, 95% CI) (range, n = 12–297), whereas it was only 25 (18–32, 95% CI) (range, n = 4–221) for "VRL ± non-ocular CNS involvement" cohorts.

Comprehensive clinical examinations, including an ophthalmic examination, in conjunction with biopsy, were used to deduce the extent of disease involvement. Methods for the basis of PCNSL diagnosis in each cohort included confirmation by biospecimen (tissue or fluid) histopathology and/or molecular marker analysis, with or without supportive imaging (optical coherence tomography for eye involvement and computed tomography or magnetic resonance imaging for non-ocular CNS involvement). Few isolated cases were based on a clinicopathological diagnosis in the absence of a biospecimen-proven result. Only 72 studies (67%) reported data on the lymphoma pathology for their cohorts. Of these studies, 42% of tumor cohorts were all of the B-cell type, being a specific inclusion criterion for study. For the remaining studies describing pathological types, an average of 80% (±14.4% SD) (range 40% to 98%) of tumors were of the B-cell type within cohorts. Consistent with current understanding, primary onset and diagnosis usually occurred between 50 and 70 years of age, and no clear predilection of occurrence in either sex was observed.

5. Eye involvement in "PCNSL ± ocular involvement" cohorts

The "PCNSL ± ocular involvement" cohort studies (n = 38) were reviewed to obtain an updated perspective on prevalence of eye involvement in PCNSL cohorts, as would be seen by the neuro-oncologist. These data are presented in Table 2. The number of persons in each cohort ranged from 12 to 297 for all groupings. Within this clinic cohort type, 1% to 5% of patients may be expected to present with isolated eye involvement before any findings of involvement in a non-ocular CNS compartment. Around 10% of patients may be expected to have both ocular and non-ocular CNS involvement at the time of diagnosis. A mean of 16% (11–20%, 95% CI) of patients are likely to develop ocular involvement "at any time" during PCNSL burden, with follow-up periods reported ranging from 3 months to 10.3 years, and median periods of 25 to 78 months. This mean expectation of eye involvement "at any time" of around 16% is in line with previous observational reports from longitudinal clinical experience.[105] The calculated mean (95% CI) range of 11% to 20% is slightly lower than the commonly cited range of 15% to 25% in the literature that is based on historical observations in a diagnostic and treatment landscape that differs from that which exists today.[59]

6. Non-ocular CNS involvement in "VRL ± non-ocular CNS involvement" cohorts

PCNSL cohorts defined by the presence of eye involvement — "VRL ± non-ocular CNS involvement" cohorts — were reviewed to determine an updated perspective on prevalence rates of associated involvement in non-ocular CNS compartments, as the ophthalmologist would encounter in the clinic. These data are summarized in Table 3. Cohorts reviewed ranged in size from 6 to 304, where the largest cohort was delineated into two studies for reporting purposes.[48,49] Within these "VRL ± non-ocular CNS involvement" cohorts, an average of 58% of individuals may be expected to have exclusive eye involvement at first diagnosis of PCNSL. Of the 36% to 46% of persons who are expected to have concomitant lesions in non-ocular CNS compartments at VRL diagnosis, around 60% will have a known history of a PCNSL at the time VRL is first diagnosed (Table 3). The expected mean prevalence rate of 69% (64–74%, 95% CI) was calculated for non-ocular CNS involvement "at any time" in association with VRL. This prevalence value for non-ocular CNS involvement occurring in association with eye involvement remains consistent with previous assessments spanning three decades.[105,107,118]

Table 1 – PCNSL and VRL cohort demographics and study parameters

Cohort studies total = 107	Year of publication	Country/ international	Data collection sites: single or multiple	Period (years)	Study type: prospective (P) or retrospective (R)	Number of patients in cohort (n)
PCNSL ± ocular involvement cohorts (n = 38 articles)						
Abrey et al[2]	2000	US	Single	1992–1998	P	52
Balmaceda et al[8]	1995	US	Single	1983–1992	P	96
Bataille et al[9]	2000	International	Multiple	1980–1995	R	248
Batchelor et al[10]	2003b	US	Multiple	1998–1999	P	25
DeAngelis et al[34]	1990	US	Single	1985–1988	P	32
DeAngelis et al[35]	1992	US	Single	1985–1991	P	47
DeAngelis et al[33]	2002	US	Multiple	NR	P	98
Ferreri et al[40]	2001	Italy	Single	1996–1999	P	13
Ferreri et al[38]	2002	International	Multiple	1980–1999	R	170
Ferreri et al[41]	2009	International	Multiple	2004–2007	P	79
Ferreri et al[39]	2016	International	Multiple	2010–2014	P	219
Freilich et al[44]	1996	US	Single	1992–1994	R	13
Herrlinger et al[56]	1998	Germany	Single	1984–1994	R	26
Hoang-Xuan et al[58]	2003	International	Multiple	1997–1999	P	50
Hong et al[61]	2011	Korea	Single	2000–2008	R	46
Jack et al[63]	1988	US	Single	1973–1987	R	55
Karantanis et al[67]	2007	US	Single	2001–2006	R	25
Koh et al[70]	2018	Japan	Single	2005–2015	R	20
Kreher et al[72]	2015	Germany	Multiple	2000–2009	P	297
Kuker et al[76]	2005	Germany	Multiple	NR	R	100
Langer-Lemercier et al[77]	2016	France	Multiple	2011–2014	P	256
Morris et al[93]	2013	US	Multiple	2002–2009	P	52
O'Brien et al[95]	2000	International	Multiple	1991–1997	P	46
Omuro et al[102]	2005	US	Single	1990–1992	P	17
Omuro et al[101]	2015a	US	Single	2005–2011	P	32
Omuro et al[100]	2015b	France	Multiple	2007–2010	P	95
O'Neill et al[96]	1995	US	Multiple	1986–1993	P	46
Pels et al[106]	2003	Germany	Multiple	1995–2001	P	65
Peterson et al[107]	1993	US	Single	1983–1992	R	91
Poortmans et al[110]	2003	International	Multiple	1997–2002	P	52
Rubenstein et al[120]	2013	US	Multiple	2004–2009	P	44
Sandor et al[124]	1998	US	Single	NR	P	14
Sangerman et al[121]	1983	US	Single	1966–1980	R	12
Shah et al[126]	2007	US	Multiple	2002–2005	P	30
Soussain et al[131]	2012	France	Multiple	1993–2011	R	79
Thiel et al[137]	2010	Germany	Multiple	2000–2009	P	411
Wieduwilt et al[144]	2012	US	Single	2001–2006	R	31
Zhuang et al[147]	2019	China	Multiple	2009–2016	P	103
					Mean cohort size	84
					SD	90
					95% CI	55–123
VRL ± non-ocular CNS involvement (n = 69 articles)						
Abu Samra et al[3]	2018	US	Single	2005–2015	R	26
Akiyama et al[4]	2016	Japan	Multiple	2007–2013	P	18
Akpek et al[5]	1999	US	Single	1990–1995	R	10
AlQahtani et al[6]	2014	France	Single	2009–2010	R	12
Batchelor et al[11§]	2003a	US	NR	NR	P	9
Berenbom et al[12]	2007	US	Single	1995–2003	R	12
Carreno et al[18§,‡]	2018	UK	Single	NR	P	18
Casady et al[19]	2014	US	Single	NR	R	10
Cassoux et al[20]	2000	France	Single	1989–1999	R	44
Castellino et al[21§,‡]	2018	US	Single	1990–2018	R	69
Char et al[23]	1988	US	Single	1968–1986	R	20
Cheah et al[24]	2016	US	Single	2007–2015	R	11
Cho et al[25]	2018	Korea	Multiple	2000–2014	R	53
Cimino et al[26]	2016	Italy	Single	2006–2014	R	7
Coupland et al[29§,‡]	2003	Germany	Multiple	NR	R	12
Dalal et al[30]	2014	US	Single	1994–2012	R	27
de Hoog et al[31]	2019	Netherlands	Single	2012–2015	P	10
de la Fuente et al[32]	2019	US	Single	2005–2018	R	15

(continued on next page)

Table 1 – (*continued*)

Cohort studies total = 107	Year of publication	Country/ international	Data collection sites: single or multiple	Period (years)	Study type: prospective (P) or retrospective (R)	Number of patients in cohort (n)
Fardeau et al[37]	2009	France	Single	1999–2005	R	53
Freeman et al[43]	1987	US	Single	pre-1970 to 1986	R	32
Frenkel et al[45§]	2008	Israel	Single	1997–2007	R	26
Grimm et al[49]	2007	International	Multiple	1977–2005	R	83
Grimm et al[48]	2008	International	Multiple	1977–2005	R	221
Hashida et al[55]	2012	Japan	Single	2001–2010	P	13
Hashida et al[54]	2014	Japan	Single	2001–2011	R	26
Hoffman et al[60]	2003	Australia	Single	1990–2000	R	14
Hormigo et al[62]	2004	US	Single	1987–2003	R	31
Jahnke et al[64§]	2006	Germany	Multiple	2000–2005	R	22
Kaburaki et al[65]	2017	Japan	NR	2008–2015	P	17
Kakkassery et al[66]	2017	International	Multiple	NR	P	10
Kimura et al[68]	2012	Japan	Multiple	1988–2009	R	217
Klimova et al[69]	2018	Czech Republic	Single	2004–2016	R	20
Kuiper et al[74]	2015	Japan	Single	2005–2014	R	11
Kuker et al[75]	2002	Germany	Multiple	NR	R	7
Larkin et al[78]	2014	International	Multiple	NR	R	34
Lavine et al[79]	2019	US	Single	2007–2017	R	23
Lee et al[81]	2015	Korea	Multiple	2007–2014	R	20
Lee et al[80]	2018	Korea	Single	2013–2017	R	22
Levasseur et al[82]	2013	Canada	Multiple	1990–2010	R	22
Ma et al[84]	2016	Taiwan	Single	2003–2013	R	19
Mahajan et al[85]	2017	India	Single	2004–2015	R	12
Mapelli et al[88§]	2016	Italy	Multiple	2010–2013	R	10
Matsuo et al[90]	1998	Japan	Single	1981–1996	R	10
Matsuo et al[89]	2009	Japan	Single	2005–2008	R	11
Mikami et al[91]	2013	Japan	Single	1998–2010	R	22
Miserocchi et al[92]	2018	Italy	Single	2016–2017	P	8
Ohta et al[97§,‡]	2009	Japan	Single	1999–2006	R	10
Park et al[104]	2004	France	Single	1996–2002	R	10
Pochat-Cotilloux et al[109]	2018	France	Single	2009–2014	R	16
Raja et al[114§,‡]	2013	US	Single	NR	R	10
Raja et al[113]	2016	US	Single	2000–2015	R	25
Ranty et al[115]	2015	France	Single	2007–2014	R	12
Raparia et al[116§]	2009	US	Single	1999–2006	R	16
Riemens et al[117]	2015	European	Multiple	1991–2012	R	78
Rodriguez et al[119§]	2014	US	Single	2007–2011	R	20
Saito et al[123]	2016	Japan	Multiple	2010–2014	R	20
Sarafzadeh et al[125]	2010	US	Single	NR	R	7
Smith et al[129]	2002	International	Multiple	1995–2000	R	16
Sou et al[130]	2008	Japan	Single	2001–2008	R	6
Soussain et al[132]	1996	France	Single	1992–1995	P	11
Sugita et al[133§,‡]	2009	Japan	Single	2000–2007	P	22
Takeda et al[134§,‡]	2015	Japan	Single	2008–2015	R	21
Teckie and Yahalom[135]	2014	US	Single	1999–2011	R	18
Tempescul et al[136]	2011	France	Single	NR	R	4
Turaka et al[138§]	2012	US	Single	1995–2012	R	8
Verbraeken et al[140]	1997	Belgium	Single	1984–1993	R	9
Wang et al[143§]	2011	US	Single	1998–2010	R	119
Wang et al[142]	2014	Japan	Single	2005–2011	R	33
Yonese et al[146]	2018	Japan	Single	2007–2016	R	17
					Mean cohort size	25
					SD	31
					95% CI	18–32

NR, not reported; PCNSL, primary central nervous system lymphoma; VRL, vitreoretinal lymphoma.
Cohorts which include histories of systemic malignancy and/or lymphoma (§), including history of breast, ovarian, cervical, or testicular malignancy (‡).

Table 2 – Prevalence of eye involvement in "PCNSL ± ocular involvement" cohorts

"PCNSL ± ocular involvement" cohorts	Number of cohorts (n)	Mean cohort size (95% CI)	Prevalence range (%)	Mean prevalence (%) (95% CI)
Eye only (PVRL) at diagnosis	22	95 (58–132)	0–13	3 (1–5)
Non-ocular CNS and eye involvement at diagnosis	35	81 (55–107)	0–29	10 (7–12)
Non-ocular CNS and eye involvement at any time	20	68 (38–97)	3–36	16 (11–20)

PCNSL, primary central nervous system lymphoma; PVRL, primary vitreoretinal lymphoma.

7. Temporal relationships between ocular and non-ocular CNS involvement in PCNSL

When the primary onset of PCNSL occurs without eye involvement, an awareness of the risk of subsequent eye disease is important. From the review of the 18 eligible cohort studies, less than 10% of PCNSL patients with no eye involvement at diagnosis are likely to develop PCNSL in the eye (Table 4). This is a distinct and separate paradigm to the all-encompassing "at any time" expected average rate described in Table 2, which was found to be 16%. Similarly, when PCNSL onset occurs exclusively in the eye (as PVRL), it is equally important to have awareness of the risk for disease presentation in other CNS compartments. An average 50% (43–56%, 95% CI) of PVRL patients will experience cancer progression into non-ocular CNS compartments, if the full range of this outcome from 0% to 100% within the cohorts of varying sizes is considered (Table 4). The expected rate of progression beyond the eye calculated here is in line with a recent report for the largest PVRL cohort included in this review (n = 179 cases); with a mean follow-up time of 41.3 months (range 3 months to 13.5 years), in 59% of individuals in that cohort were found eventually to develop disease in the CNS beyond the eye.[68] Again, this is distinct from the assessment of non-ocular CNS compartment involvement that will be found "at any time" in a patient with VRL, which was calculated at 69% (Table 3).

From the current literature, it is not possible to calculate an average expectation of the lead time before cancer progression from the ocular to non-ocular CNS compartments, or vice versa. This is largely due to absent or inconsistent reporting on temporal relationships between cancer site presentation and disease progression within the CNS. Only one-third of the cohort studies of PCNSL without eye involvement at diagnosis provided detail regarding the time to subsequent onset of VRL. However, an understanding of this timeframe is available from a small number of "VRL ± non-ocular CNS involvement" cohort reports in which PCNSL diagnostic histories before the onset of VRL were clearly reported. When reported, timeframes for onset in the eyes after a primary diagnosis in a non-ocular CNS compartment(s) varied greatly on a case-by-case basis, from 2 weeks to up to 15 years.[20,26,40,44,45,61,89,102,107,121] Mean onset times within cohorts ranged from 7.5 months to 3 years,[29,45,61,107] and median timeframes of up to 4.5 years[20,82] have been reported. On the other hand, 67% of the PVRL cohorts, as presented in Table 4, reported data on the temporal onset of non-ocular CNS involvement after PVRL. Timeframes until non-ocular CNS involvement also ranged widely, from one week to up to 10 years. Fifty-five percent of these studies reported median and mean times to onset ranging between 8 to 41 months. Indeed, the largest of these PVRL cohorts (n = 179 persons) reported non-ocular CNS involvement developed at a mean of 21.7 months after the initial diagnosis in the eye.[68] This expected timeframe of 2 to 3 years between the initial onset in the eyes and any later cerebral involvement has remained largely unchanged for 30 years.[43] Future work assessing treatment protocol outcomes for PVRL will enlighten on how the prevalence of non-ocular CNS dissemination, found here to occur in around 50% of PVRL cases, may have been influenced in recent years.

8. Epidemiology and estimations of PCNSL vitreoretinal disease

The CBTRUS and other national and regional cancer registries worldwide utilize WHO ICD-O-3 morphology and behavior codes (International Classification of Diseases for Oncology, 3rd edition)[46] to specifically define tumor types and calculate incidence rates in the population, including for PCNSL. Population-based studies of registry meta-data of newly diagnosed PCNSL cases from around the world offer an opportunity to gain further insight on PCNSL involvement in the eyes "at any time" at a population-based level utilizing the updated prevalence rates calculated here. To this end, we conducted a second independent search of the literature

Table 3 – Non-ocular CNS involvement in "VRL ± non-ocular CNS involvement" cohorts

"VRL ± non-ocular CNS involvement" cohorts	Number of cohorts (n)	Mean cohort size (95% CI)	Prevalence range (%)	Mean prevalence (%) (95% CI)
Eye involvement only (PVRL) at VRL diagnosis	58	29 (16–41)	10–100	58 (53–63)
Eye and non-ocular CNS involvement at VRL diagnosis	57	29 (16–42)	0–90	41 (36–46)
Known history of non-ocular CNS involvement at VRL diagnosis	42	23 (13–33)	0–69	25 (20–30)
Non-ocular CNS involvement with VRL at any time	46	30 (15–45)	41–100	69 (64–74)

PVRL, primary vitreoretinal lymphoma; VRL, vitreoretinal lymphoma.

Table 4 – Prevalence of secondary ocular involvement or non-ocular CNS involvement in PCNSL or PVRL, respectively

Involvement	Number of cohorts (n)	Cohort size range (n)	Mean cohort size (95% CI)	Prevalence range (%)	Mean prevalence (%) (95% CI)
Secondary ocular involvement in PCNSL	18	11–278	64 (34–94)	0–18	7 (5–9)
Secondary non-ocular CNS involvement in PVRL	52	4–179	18 (11–25)	0–100	50 (43–56)

PCNSL, primary central nervous system lymphoma; PVRL, primary vitreoretinal lymphoma.

specifically for population-based cohort data studies reporting on incidence rates of PCNSL. These reports are summarized in Table 5. The country of origin, along with the period of years surveyed, the number of cases found, and the median age at diagnosis are shown. All eligible studies for review came from high-income countries. The ICD-O-3 codes used to encompass the capture of PCNSL cases from the national or regional registries varied between studies, and the isolated ocular manifestation of PCNSL — or PVRL — was not routinely included or considered within the curation and analysis parameters of the cancer registry meta-data. Acknowledging these limitations, the most recent age-standardized incidence rates for PCNSL reported from each study were used to extrapolate an incidence rate for eye involvement, with an average of 16% of cases expected to involve the eyes "at any time" (see Table 2). Overall, approximately 1 in 2 million person-years may be expected to have VRL "at any time" in association with PCNSL in other (non-ocular) compartments.

9. Conclusion

Awareness of the prevalence of intraocular involvement in PCNSL, with perspectives depending on the different clinical cohorts of PCNSL, is important for informing management provided by both ophthalmologists and neuro-oncologists. This information may have implications for clinical outcomes and survival. Our systematic review of 107 cohort studies on eye involvement in PCNSL was conducted to this end.

We found that within "PCNSL ± ocular involvement" cohorts, as would be primarily seen by a neuro-oncologist, an average of 1% to 4% of patients have primary onset of PCNSL exclusively in the eye, whereas approximately 10% have concomitant eye and non-ocular CNS involvement at first diagnosis (Table 2). Eye involvement is likely to develop in less than 10% of those with a primary diagnosis in a non-ocular CNS compartment (Table 4). Overall, an average of 16% with PCNSL will experience ocular involvement "at any time" during cancer development (Table 2). In light of this latter value, an approximate and generalized rate expectation of PCNSL manifesting in the eyes at approximately 1 in 2 million person-years was extrapolated from population-based PCNSL incidence rate reports from a small number of high-income countries (Table 5).

To establish the eye specialty–oriented perspective most likely experienced by an ophthalmologist in the clinic, PCNSL cohorts defined by the presence of eye involvement — "VRL ± non-ocular CNS involvement" cohorts — were also reviewed. We found that an average rate of 53% to 63% (95% CI) of those

Table 5 – Incidence estimations for ocular involvement in PCNSL calculated from population studies

Country	Data: national or regional	Period (years)	PCNSL cases (n)	Median age at diagnosis	5-year overall survival (relative rate)	Incidence of PCNSL* (ASR)	Incidence estimation of ocular involvement in PCNSL "at any time"*	Incidence estimation of primary ocular onset (PVRL) in PCNSL*
Canada[53]	Regional	1975–1996	50	NR	NR	1994–1996: 1.64	0.26	0.05
Denmark[73]	Regional	1983–1994	48	62	26%	1.56	0.24	0.05
Norway[52]	National	1989–2003	98	68	16%	1989–1993: 0.89 1994–1998: 1.74 1999–2003: 1.82	0.29	0.05
Japan[86]	Regional	1989–2004	136	NR	NR	1989–1998: 2.9 1989–2004: 4.1	0.64	0.12
Netherlands[139]	National	1989–2015	1673	65	1989–1995: 11% 2009–2015: 30%	1989–1995: 3.0 2009–2015: 4.4	0.69	0.13
Spain[47]	Regional	1994–2013	55	61	17%	4.8	0.75	0.14
Korea[128]	National	1999–2009	1062	58	29.9%	Overall: 1.77 1999: 1.1 2009: 2.5	0.39	0.08
Sweden[36]	National	2000–2013	359	66	24%	2000–2013: 2.6	0.41	0.08
US[103]	National	2010–2014	7481	66	33.5%	4.4	0.69	0.13
						Mean ± SD	0.49 ± 0.21	0.09 ± 0.04

ASR, age-standardized rate; PCNSL, primary central nervous system lymphoma; PVRL, primary vitreoretinal lymphoma.
* Incidence rates per 1 million person-years.

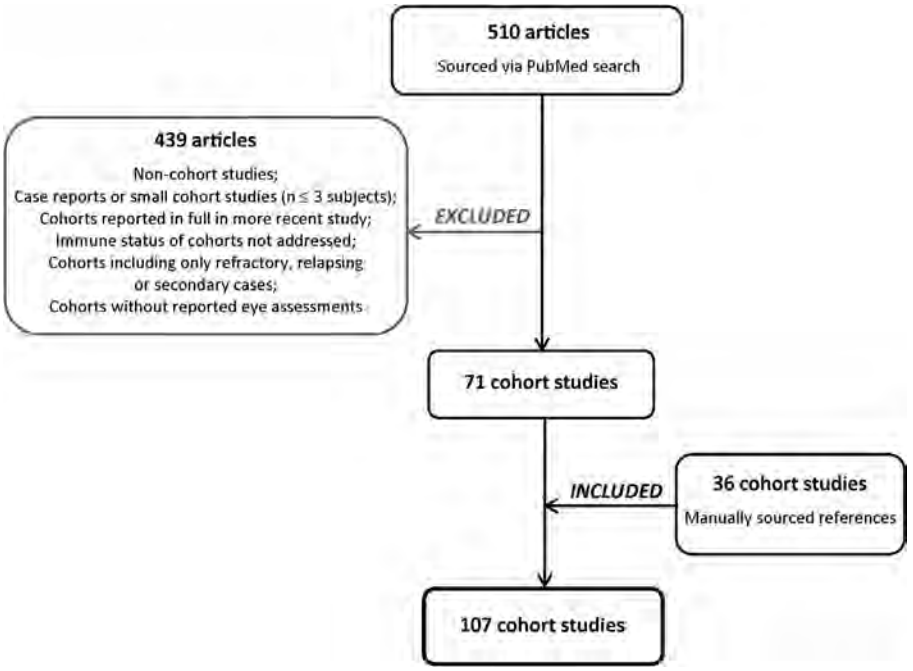

Fig. 1 – Literature search for cohort studies.

patients an ophthalmologist will see with ocular PCNSL will have their primary diagnosis established in the eye (Table 3). Of these individuals, 50% may be expected to experience lymphoma progression into other CNS compartments (Table 4). Around 25% of VRL patients are expected to have a known prior diagnosis of PCNSL at the time VRL is first identified. Overall, in a mean of 69% of those with VRL are expected to develop the cancer in a non-ocular CNS compartment "at any time" either side of their VRL diagnosis (Table 3).

The mean prevalence values calculated here may underrepresent actual rates due to limitations in the classification of PCNSL and the divergent descriptions of PCNSL as an overarching entity. This manifests in the literature as inconsistent routine screening and/or reporting practices for eye involvement in PCNSL hindered in part due to missing medical record data, which limits the pool of studies from which prevalence and expectations of risk may be derived. Inherent variation in follow-up timeframes limits the capture of site involvement and cancer progression events and may also contribute to an underrepresentation of prevalence determined here. Half of the studies we reviewed exclusively report on cohort data derived from the year 2000 onward, a time period that has seen important developments in treatment approaches. Assessing the specific impact of these various approaches on the prevalence of eye involvement in PCNSL is beyond the scope of this review; however, recently noted improvements in survival outcomes over this time period provides researchers with the opportunity to assess PCNSL progression and clinical outcomes over longer follow-up periods than were previously possible. Indeed, people with PVRL are living longer now than they did two decades ago.[111] Although yet to translate widely, there is also an emerging indication toward improved survival outcomes for people with CNS compartment involvement beyond the eye.[36,47,52,127,139,141] In light of this, the updated prevalence rates we have calculated here likely reflect an appropriate expectation of risk within current clinical care practices where a standard is yet to be universally adopted, and developing improved therapeutic approaches is being intensely pursued.

Prevalence and incidence rates of (P)VRL within PCNSL from population cohorts will be better defined given the routine use of a consistent set of diagnostic codes for PCNSL and the inclusion of criteria for eye involvement in PCNSL in any future interrogations of national and international cancer data sets. Establishing more robust clinical cohort perspectives on the rare manifestation of PCNSL in the eye, and its temporal relationship with involvement in other (non-ocular) CNS compartments, would be greatly facilitated via the unified approach to disease reporting and prospective data collection as might be provided with an international clinical registry.

10. Method of literature search

The PubMed search engine of the National Centre for Biotechnology Information (NCBI) database was used for literature searches. The English language was used as a search limit, and reviews were excluded as a source of prevalence data (date of searches, April 11, 2019).

To capture cohort studies for eye involvement in PCNSL, the search terms listed below were entered consecutively into the PubMed search engine and any new references not obtained using a previous search term were collected. Search terms separated by a forward-slash punctuation mark were used independently in conjunction with the preceding search term stem in the order shown. The primary search resulted in 510 references. Reference lists of retrieved articles were also

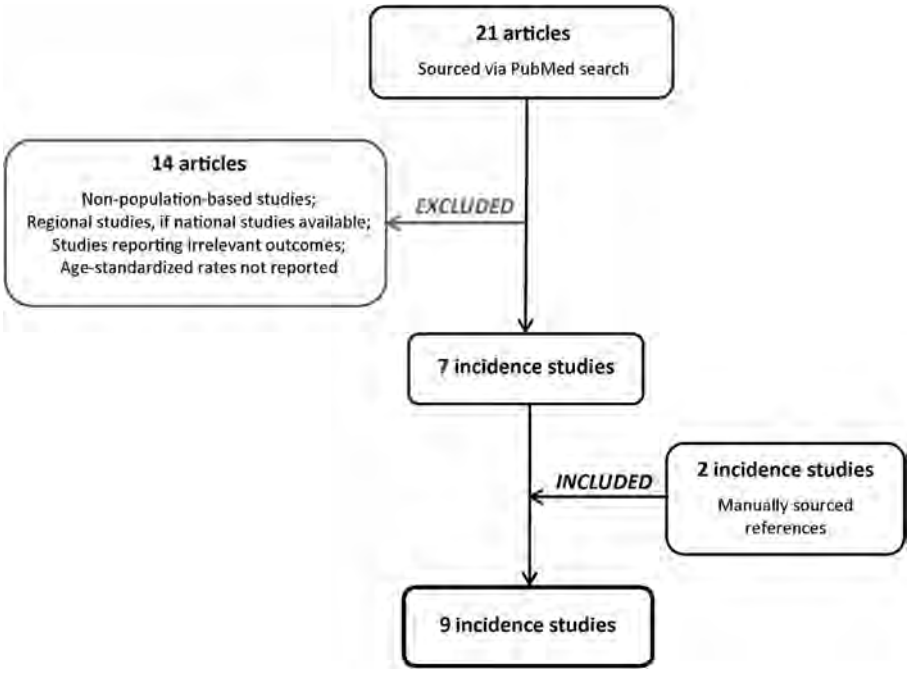

Fig. 2 – Literature search for incidence studies.

manually searched for relevant publications. In consideration of the study inclusion criteria described in detail in Section 4, 107 publications describing cohort studies were eligible for review (Fig. 1). To identify reports on PCNSL incidence rates in the population, the search term "Incidence AND Primary[Title] AND Central[Title] AND Nervous[Title] AND System[Title] AND Lymphoma" was used to search the PubMed NCBI database. Twenty-one references were retrieved. Nine studies met the inclusion criterion. Non-population studies and those in which the age-standardized rate was not reported were excluded. Only the most recent publications were included in the event that reports were retrieved for the same region or nation. Regional population reports were also excluded if national data were available. Two studies were manually curated for inclusion (Fig. 2).

10.1. *Search terms list for references pertaining to eye involvement in PCNSL*

- Non-Hodgkin lymphoma[MeSH] AND central + nervous + system AND eye/ocular/intraocular
- Non-Hodgkin lymphoma[MeSH] AND CNS AND intraocular/ocular/eye
- vitreoretinal + lymphoma
- primary + vitreoretinal + lymphoma
- primary + CNS + lymphoma AND eye/intraocular/ocular
- primary + central + nervous + system + lymphoma AND ocular/intraocular/eye
- reticulum + cell + sarcoma AND intraocular
- microglioma AND central + nervous + system

11. Disclosures

The authors report no proprietary or commercial interest in any product or concept discussed in this article.

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Genetics in ophthalmology

Psychosocial impacts of Mendelian eye conditions: A systematic literature review

Celeste S. D'Amanda, ScM[a,b,†], *Rosalie Nolen, BS*[a,†], *Laryssa A. Huryn, MD*[a], *Amy Turriff, ScM*[a,*]

[a] *Ophthalmic Genetics & Visual Function Branch, National Eye Institute, National Institutes of Health, Bethesda, MD 20892, USA*

[b] *Division of Genetics, Department of Medicine, University of Rochester Medical Center, Rochester, NY 14642, USA*

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ABSTRACT

The diagnosis of a heritable (Mendelian) eye condition can have a significant impact on patients and their families. Although a diverse group of conditions, many Mendelian eye conditions are early-onset, untreatable, progressive, and result in significant visual disability. To increase understanding of the challenges faced by this population, we review studies describing the psychosocial impacts of Mendelian eye conditions. Reduced mental health and quality of life and increased strain on relationships are common themes. We synthesize the evidence presented in this review to propose an overall model of illness factors, cultural factors, psychosocial impacts, and quality of life. Finally, we discuss implications for patient management and future research directions.

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1. Background

A large number of ophthalmic conditions have an underlying single-gene cause. These largely follow classic Mendelian inheritance patterns—autosomal dominant, autosomal recessive, and X-linked—and typically involve transmission from parent to child. Other ophthalmic conditions follow a mitochondrial inheritance pattern. Multiple members of a family may be affected. Although each condition may be rare, ophthalmic genetic disease taken as a whole is not

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* Corresponding author: Amy Turriff, ScM, National Eye Institute, NIH, 10 Center Drive MSC 1860, Building 10, Room 10N109, Bethesda, MD 20892, USA.
E-mail address: turriffa@mail.nih.gov (A. Turriff).
† These authors contributed equally to this work.

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uncommon, with approximately 30% of childhood blindness worldwide attributable to hereditary causes.[35]

Mendelian eye conditions include nonsyndromic inherited retinal degenerations (IRDs), syndromic IRDs, hereditary optic neuropathies, congenital eye abnormalities, and a rare cancer predisposition syndrome. IRDs encompass conditions such as retinitis pigmentosa (RP), Leber congenital amaurosis (LCA), and Stargardt disease (STGD). These conditions generally involve progressive vision loss, although the pattern and age of onset varies. Syndromic IRDs involve additional extraocular features and include Usher syndrome, Alstrom Syndrome, and Bardet Biedl Syndrome (BBS). Inherited optic neuropathies, including Leber hereditary optic neuropathy (LHON) and dominant optic atrophy (DOA), are typically nonsyndromic, but additional extraocular symptoms have been reported in some patients. Conditions involving congenital eye abnormalities include albinism and CHARGE (Coloboma, Heart defects, Atresia choanae, Retardation of growth, Genital abnormalities and Ear abnormalities) syndrome. Finally, retinoblastoma (RB) is a rare form of cancer that begins in the retina and presents in early childhood. Although Mendelian eye conditions range in severity of vision loss and age of onset, they are generally progressive and lack prevention or treatment. Many of these disorders present in childhood or young adulthood, leading to a lifetime of visual disability.

Vision has been described as one of the most important functions in human beings, as it critically supports daily functioning and contact with reality.[105] The diagnosis of a Mendelian eye condition is expected to have a significant impact on patients and their families. Prior research has explored psychological and social impacts of vision loss across a variety of conditions, such as diabetic retinopathy, age-related macular degeneration (AMD), and retinal detachment. This work consistently suggests that irreversible vision loss has persistent negative effects on quality of life and mental health.[25,70,79,90,91,95] Moreover, these effects can reach beyond the affected individual to family members who may struggle to adjust to new caretaking and supportive roles.[6] Individuals with Mendelian eye conditions and their families may face additional stressors related to the genetic etiology, including risk to other family members, reproductive risks, and parental guilt and blame.[9,44]

The first FDA-approved gene therapy for an early-onset inherited retinal degeneration and a growing number of clinical trials have provided new hope for families afflicted by Mendelian eye conditions.[5,50] Nevertheless, there remains no vision-restoring or preserving treatment available for the majority of affected individuals, and establishing the efficacy of experimental treatments for these conditions has proven challenging. Clinical trials have increasingly used patient reported outcome measures (PROMs) in addition to objective tests of visual function.[77] PROMs aim to assess patient perspectives of disease impact and treatment outcomes. While many PROMs for ophthalmic conditions have been developed, only a small subset is targeted toward the Mendelian eye conditions that are more recently an active area of treatment research.[72] Thus, researchers designing clinical trials must often settle on a poorly fitting PROM targeted at low vision regardless of diagnosis or created for use in evaluating the effectiveness of low vision therapy rather than potentially disease-modifying treatment. Empirical evidence describing and measuring patient reported disease impacts forms the basis for targeted PROM development.[72] Furthermore, insights gained from these data are essential to improving clinical management of patients with Mendelian eye conditions and their family members.

We provide a systematic review on the psychosocial impacts (i.e., depression, anxiety, loneliness, psychological stress, and well-being) of Mendelian eye conditions. For this, we identified all original, empirical evidence that measures or describes the effect of any Mendelian eye condition on patients' or family members' psychosocial well-being. We assessed each study's quality, synthesized evidence, and identified research gaps.

2. Methods

2.1. Study selection

Two authors (A.T. and C.S.D.) reviewed the titles and abstracts of all references returned by the literature search (see Section 7) and eliminated articles that did not fulfill the eligibility criteria. Both authors then read the full text of the remaining articles to determine final inclusion. Three authors (A.T., C.D., and R.N.) identified additional relevant articles by reference scanning and by searching Google Scholar and PubMed for additional relevant sources.

2.2. Quality appraisal

We evaluated the quality of included studies using the Mixed Methods Appraisal Tool (MMAT).[B] The MMAT, which is composed of a tutorial and checklist, primarily assesses the methodological quality of an article. It uses a modified checklist depending on the type of study being evaluated: qualitative, quantitative randomized controlled, quantitative nonrandomized (studies which use a comparison group but do not randomly assign participants to groups), quantitative descriptive (studies which do not utilize a comparison group), or mixed methods study. Each article is awarded a score from zero to four, with four being the highest, based on the fulfillment of the checklist criteria. Specific checklist items can be found in Supplementary Table 2. Two authors (C.S.D. and R.N.) independently scored each of the articles and discussed any discrepancies until agreement was reached.

2.3. Data analysis and synthesis

According to descriptive and qualitative data synthesis methodology,[D] we conducted content and thematic synthesis with all included studies, assisted by QSR International's NVivo 11 qualitative research software. We developed a preliminary codebook designed to capture study content (i.e., methodology, population, participant diagnosis) and a priori themes. Three authors (A.T., C.D., and R.N.) tested the preliminary codebook by coding the abstracts and results section of five quantitative and three

qualitative articles, resulting in minor codebook revisions. One author (C.D.) coded the abstract and results sections for the remaining articles using the revised codebook. We implemented further proposed codebook changes after discussion and consensus, and we recoded all articles with the final expanded codebook. A second author (R.N.) checked all coding for accuracy and consistency. C.D. and R.N. resolved any coding disagreements through discussion and consensus. A sample of our codebook along with selected illustrative passages from included texts can be found in Supplementary Table 3.

3. Results

3.1. Systematic review

We identified a total of 7855 articles in our literature search, 7704 from the initial database search and 151 from scanning reference lists and other sources. After elimination of duplicates (n = 583) and review of article titles and abstracts, 138 articles remained. Of the 138 articles for which the full text was reviewed, 80 were excluded, and 58 met eligibility criteria. We identified an additional 14 articles, for a total of 72 articles included in this review (Fig. 1).

3.2. Demographics of included studies

Table 1 summarizes the characteristics of the 72 included studies published between 1978 and January, 2018. Sixty-six (92%) studies were cross sectional, and 6 (8%) were longitudinal. Forty-seven (65%) had quantitative, 19 had qualitative (26%), and 6 (8%) had mixed methods methodology. Forty-four (61%) studies included adults, 4 (6%) included children, and 24 (33%) studies included both children and adults. Thirty-two (44%) studies originated in Europe, 18 (25%) in North America, 6 (8%) in Africa, 4 (6%) in Asia, 3 (4%) in the Middle East, 3 (4%) in South America, and 2 (3%) in Oceania. Four (6%) studies included samples from mixed geographic areas, including North America, South America, Europe, and Oceania. The geographic profile of one international study was unclear.

Of the 72 studies, 20 (28%) investigated RP, 12 (17%) Usher syndrome, 11 (15%) albinism, 8 (11%) RB, 3 (4%) CHARGE syndrome, 3 (4%) STGD, 3 (4%) LHON, 1 (1%) Alström syndrome, 1 (1%) BBS, and 1 (1%) DOA. Nine (13%) studies had participants with mixed Mendelian eye conditions, including LCA, cone-rod dystrophy (CRD), cone dystrophy, Best disease, neuronal ceroid lipofuscinosis (NCL), achromatopsia, and other previously mentioned and/or unspecified conditions.

The 72 studies represented approximately 7653 patients and 378 family members or support people, for a total of 8031

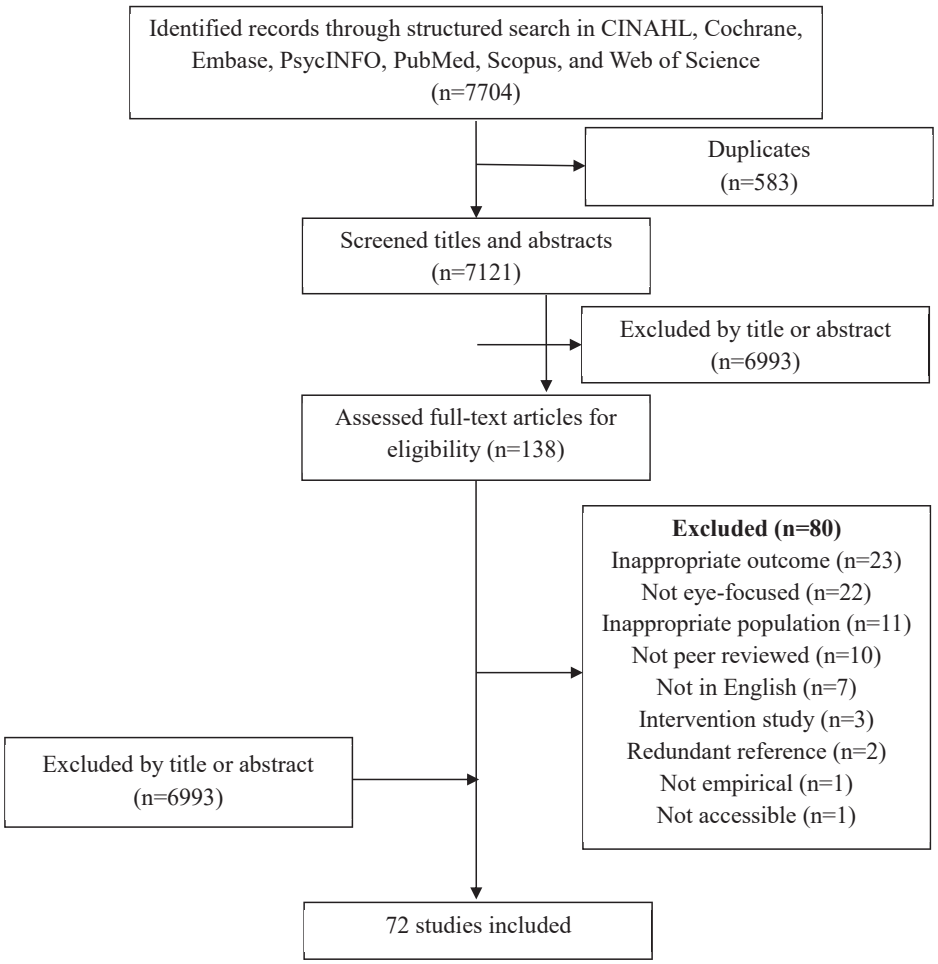

Fig. 1 – Study selection process.

Table 1 – Overview of publications meeting inclusion criteria

First author, year[ref]	Condition(s)	Geographic region (country)	Population, age group (n)	Comparison group (n)	Study design	Quantitative scale or Qualitative methodology	MMAT score
Adhami-Moghadam 2014[1]	RP	Middle East (Iran)	Patients, Adult (417)	N/A	Quantitative, CS	MMPI-2	3
Anil 2018[2]	RP	Europe (UK)	Patients, Adult (105)	N/A	Quantitative, CS	CSI-SF, MTSD, NEI-VFQ 25, WEMWBS, SHS	2
Azoulay 2015[3]	RP	Europe (France)	Patients, Adult (60)	Age-matched healthy controls (20)	Quantitative, CS	HADS, NEI-VFQ 25	2
Bailie 2013[4]	Optic Atrophy	Europe (UK)	Patients, Adult (38)	HADS normative data	Quantitative, CS	VF-14, HADS	1
Bertelsen 2015[8]	Retinal Dystrophy- Mixed	Europe (Denmark)	Patients, Adult (2285)	Randomly sampled general population controls (228,500)	Quantitative, CS	Registry data- Demographic and socio-economic characteristics	4
Bittner 2010[10]	RP	North America (USA)	Patients, Adult (8)	N/A	Qualitative, CS	Online focus groups	3
Brinkman 2015[11]	Retinoblastoma	North America (USA)	Patients, Adult (69)	N/A	Quantitative, CS	WASI-II, WJ-III, CVLT-II, Trail Making Test Part, CPT-II, Digit span forward and coding subtests of the WAIS-III, grooved pegboard, COWAT, BRIEF-A, Comprehensive health questionnaire	4
Brocco 2016[12]	Albinism	Africa (Tanzania)	Patients, Mixed ages (8), Others including relatives, NGO staff members, and religious leaders (numbers and ages unknown)	N/A	Qualitative, L	Ethnographic fieldwork: interviews, focus groups, observations	1
Bryan 2016[13]	Stargardt	International North America (USA), Europe (UK, Denmark)	Patients, Adult (22)	N/A	Qualitative, CS	Expressive writing	3
Chacon-Lopez 2013[14]	RP	Europe (Spain)	Partners or Family Members, Adult (37)	Controls (38)	Quantitative, CS	STAI, BDI	1
Chaumet-Riffaud 2017[15]	RP, Usher syndrome	Europe (France)	Patients, Adult (148)	French age adjusted socioeconomic and employment statistics NEI-VFQ normative data	Quantitative, CS	NEI-VFQ 25, HADS, Employment status questionnaire	2
Dammeyer 2012[19]	Usher syndrome	Europe (Denmark)	Patient, Pediatric (26)	SDQ normative data (900 Swedish children)	Quantitative, CS	SDQ, Retrospective chart review for psychiatric diagnoses	2
Dean 2017[20]	Usher syndrome	Europe (UK)	Patients, Adult (90)	Standardized values for SF-12 and PHQ-9	Quantitative, CS	SF-12v2, PHQ-9, ULCA-loneliness scale, mMOS-SS	3

(*continued on next page*)

Table 1 – (*continued*)

First author, year[ref]	Condition(s)	Geographic region (country)	Population, age group (n)	Comparison group (n)	Study design	Quantitative scale or Qualitative methodology	MMAT score
Decarlo 2012[21]	Mixed	North America (USA)	Patients, Pediatric (24) & Parents, Adult (23)	N/A	Qualitative, CS	Focus groups	3
Ehn 2016[24]	Usher syndrome type 2	Europe (Sweden)	Patients, Adult (67)	N/A	Quantitative, CS	HET	4
Ferguson 2016[26]	LHON	Europe (UK)	Patients, Adult (7)	N/A	Qualitative, CS	Interviews	4
Figueiredo 2013[28]	Usher syndrome	South America (Brazil)	Patients, Adult (11)	N/A	Qualitative, CS	Interviews	2
Ford 2015[29]	Retinoblastoma	North America (USA)	Patients, Adult (470)	Childhood Cancer Survivor Study sibling cohort (2820) BSI normative data	Quantitative, CS	BSI-18, IES, PTGI, FORQ, Adapted version of CCSS	3
Fourie 2007[30]	RP	Europe (Ireland)	Patients, Adult (1)	N/A	Qualitative, L	Self-Study	4
Gaigher 2002[31]	Albinism	Africa (South Africa)	Patients, Mixed ages (32)	N/A	Qualitative, CS	Interviews	2
Gale 2017[32]	LHON	International Europe (Italy, Spain, Denmark, Sweden, Germany, France), South America (Argentina)	Patients, Adult (116)	N/A	Mixed Methods, CS	Novel Graphical Online Assessment Tool	2
Garcia 2017[33]	LHON	North America (USA)	Patients, Mixed ages (103)	N/A	Quantitative, CS	SQ	0
Gavron 1995[34]	Albinism	Middle East (Israel)	Patients, Pediatric (43)	Controls (43)	Quantitative, CS	STAI, TSCS	3
Hahm 2008[37]	RP	Asia (Korea)	Patients, Adult (144)	N/A	Quantitative, CS	NEI-VFQ 25, BDI	2
Hamblion 2011[38]	Retinal Dystrophy-Mixed	Europe (UK)	Patients, Pediatric (44), Parents, Adult (44)	Unaffected siblings (34) PedsQL normative data for healthy children (665) and other systemic and ophthalmic conditions	Quantitative, CS	PedsQL	2
Hamlington 2015[39]	BBS	North America (USA)	Parents, Adult (28)	N/A	Qualitative, CS	Interviews	2
Hartshorne 2016[40]	CHARGE syndrome	North America (Canada)	Patients, Mixed ages (53)	HRQOL normative data	Quantitative, CS	Adapted HRQOL-14	0
Hayeems 2005[41]	RP	North America (USA)	Patients, Adult (43)	N/A	Qualitative, CS	Interviews, Focus Groups	3
Hogner 2015[42]	Usher syndrome type 2	Europe (Germany)	Patients, Mixed ages (262)	TICS Normative data	Quantitative, CS	SQ, TICS	2
Igarashi 2003[43]	RP	Asia (Japan)	Patients, Adult (75)	Age-matched controls (47) Patients with glaucoma (42)	Quantitative, CS	Y-G	3
Jangra 2007[45]	RP	North America (Canada)	Patients, Adult (33)	Other disease PAIS-SR published data, type 1 diabetes (99)	Quantitative, CS	PAIS-SR	3
Kim 2013[46]	RP	Asia (Korea)	Patients, Adult (194)	Matched controls (187) drawn from the KNHANES normative population	Quantitative, CS	KNHANES	2
Kromberg 1984[47]	Albinism	Africa (South Africa)	Patients, Mixed ages (35)	Matched controls (35)	Quantitative, CS	SQ pulling question from BAI, SRAYI	3

Latham 2015 "Emotional"[49]	RP	Europe (UK)	Patients, Adult (166)	N/A	Quantitative, CS	D-AI	3
Latham 2015 "Difficulties"[48]	RP	Europe (UK)	Patients, Adult (350), Support people, ages unknown (75)	N/A	Quantitative, CS	D-AI	3
Lopez-Justicia 2006[51]	RP	Europe (Spain)	Patients, Adult (22)	Randomly-selected controls (23)	Quantitative, CS	TSCS	2
Lopez-Justicia 2011[52]	RP	Europe (Spain)	Patients, Adult (35)	N/A	Quantitative, CS	TSCS	1
Lund 1998[53]	Albinism	Africa (Zimbabwe)	Patients, Adult (39)	N/A	Mixed Methods, CS	SQ	0
Lund 2001[54]	Albinism	Africa (Zimbabwe)	Patients, Mixed ages (138)	N/A	Mixed Methods, CS	SQ, Interviews (22)	1
Lund 2002[55]	Albinism	Africa (South Africa)	Patients, Pediatric (38)	N/A	Mixed Methods, CS	SQ	2
Maia 2015[57]	Albinism	South America (Brazil)	Patients, Adult (40)	Controls (40)	Quantitative, CS	WHOQOL-BREF	3
Miedziak 2000[61]	Stargardt	International	Patients, Adults, Parent Proxy for Pediatric Patients (203)	N/A	Quantitative, CS	SQ	1
Miner 1997[63]	Usher syndrome type 2	North America (USA)	Patients, Mixed ages (32)	N/A	Qualitative, L	Interviews	0
Miner 1995[62]	Usher syndrome type 1	North America (USA)	Patients, Mixed ages (39), Family members, unknown ages (unknown number)	N/A	Qualitative, L	Interviews	0
Moschos 2015[65]	RP	Europe (Greece)	Patients, Mixed ages (34)	Matched Controls (35)	Quantitative, CS	Zung SDS	1
Moschos 2016 "Evaluation"[66]	RP	Europe (Greece)	Patients, Adult (55)	Matched Controls (32)	Quantitative, CS	PHQ-9, Zung SDS	1
Moschos 2016 "Estimation"[67]	Stargardt	Europe (Greece)	Patients, Adult (39)	Matched Controls (352)	Quantitative, CS	Zung SDS, PHQ-9	1
Nagayoshi 2016[68]	Retinoblastoma	Asia (Japan)	Patients, Pediatric (17) & Parents, Adult (17)	Normative data	Quantitative, L	PSI, ESIAD, HD-KDDS, IBC-R	3
Nemshick 1986[69]	Mixed	North America (USA)	Patients, Mixed ages (307)	N/A	Mixed Methods, CS	SQ	0
Palmer 2007[71]	Albinism	Oceania (Australia)	Patients, Pediatric (10)	Controls (9)	Quantitative, CS	SEI	1
Prem Senthil 2017[73]	RP	Oceania (Australia)	Patients, Adult (23)	N/A	Qualitative, CS	Interviews	3
Reda 2008[74]	CHARGE syndrome	North America (USA)	Parents, Adult (25)	Normative data	Quantitative, CS	CHARGE history questionnaire, R-MAI, PSI-SF, SSQ, CAQ	1
Ronnasen 2016[76]	Alstrom syndrome	Europe (Sweden)	Patients, Adults (11)	N/A	Qualitative, CS	Interviews	4
Sheppard 2005[80]	Retinoblastoma	Europe (UK)	Patients, Pediatric (54) & Parents, Adult (54)	Normative data	Mixed Methods, CS	PedsQL TM 4.0, SF-36, WISC-III, Interviews	1
Spiegel 2016[83]	RP, Stargardt	North America (USA)	Patients, Adults (36)	N/A	Qualitative, CS	Interviews	4
Stogner 1980[84]	Retinal Degeneration-Mixed	North America (USA)	Patients, Mixed ages (71)	N/A	Quantitative, CS	Retrospective chart review	2
Szlyk 2000[85]	Macular Dystrophy-Mixed, Achromatopsia	North America (USA)	Patients, Adult (26), Siblings, Adult (7)	Normative data	Quantitative, CS	BSI, MMPI-2	2
Szlyk 1998[86]	Macular Dystrophy-Mixed, Achromatopsia	North America (USA)	Patients, Adults (52)	Normative data	Quantitative, CS	BABS	2
Taheri-Araghi 1994[87]	RP	North America (USA)	Patients, Mixed ages (76)	N/A	Quantitative, CS	Secondary data analysis	3
Tamayo 1997[88]	Usher syndrome	South America (Colombia)	Patients, Mixed (39), Family Members (Ages unknown, number unknown)	N/A	Qualitative, CS	Interviews	1

(continued on next page)

Table 1 – (*continued*)

First author, year[ref]	Condition(s)	Geographic region (country)	Population, age group (n)	Comparison group (n)	Study design	Quantitative scale or Qualitative methodology	MMAT score
Thurston 2014[92]	Albinism	Europe (UK)	Patients, Pediatric (2)	N/A	Qualitative, CS	Interviews	3
Torrie 1978[93]	Usher syndrome	North America (USA)	Parents, Adult (10)	N/A	Qualitative, L	Interviews	0
Van Dijk 2009[96]	Retinoblastoma	Europe (Netherlands)	Patients, Mixed ages (117)	Dutch healthy reference group	Quantitative, CS	CISS, SF-36 social functioning subscale, PCSC- social acceptance subscale, YSR/ASR	4
Van Dijk 2007[97]	Retinoblastoma	Europe (Netherlands)	Patients, Adult (87)	Dutch healthy reference group	Quantitative, CS	SF-36, Quantifiable responses from interviews	2
Van Dijk 2010[98]	Retinoblastoma	Europe (Netherlands)	Patients, Mixed ages (156)	General Population	Quantitative, CS	Quantifiable responses from interviews and focus groups	2
Wahlqvist 2016 "Implications"[100]	Usher syndrome type 3	Europe (Sweden)	Patients, Adult (15)	N/A	Quantitative, CS	HET, HADS	3
Wahlqvist 2013[99]	Usher syndrome type 2	Europe (Sweden)	Patients, Adult (96)	Swedish General Population Data (5738)	Quantitative, CS	HET	3
Wahlqvist 2016 "Physical"[101]	Usher syndrome type 1	Europe (Sweden)	Patients, Adult (60)	Normative data	Quantitative, CS	HET	3
Wan 2003[102]	Albinism	International North America (Canada, USA), Oceania (Australia)	Patients, Mixed ages (12)	N/A	Qualitative, CS	Interviews	1
Weintraub 2011[104]	Retinoblastoma	Middle East (Israel)	Patients, Pediatric (46) & Parents, Adult (46)	Normative Data	Quantitative, CS	CFFS, CASP, CAFI, CASE, CHQ-PF50, PedsQL	3
Wulffaert 2009[106]	CHARGE syndrome	Europe (Netherlands)	Parents, Adult (22)	General Population	Quantitative, CS	NPSI-S, VS 0–12, DBC-P	1
Yioti 2017[107]	Retinal Dystrophy-Mixed	Europe (Greece)	Patients, Adult (48)	Matched Controls (427)	Quantitative, CS	SCL-90-R, PHQ-9, B-IPQ, WHOQOL-BREF	3

ASY, Adult Self Report; BABS, Bradburn Affect Balance Scale; BAI, Bell's Adjustment Inventory; BBS, Bardet-Biedl Syndrome; BDI, Beck Depression Inventory; B-IPQ, Brief Illness Perception Questionnaire; BRIEF-A, Behavior Rating Inventory of Executive Function- Adult Version; BSI, Brief Symptoms Inventory; BSI-18, Brief Symptom Inventory-18; CAFI, Child and Adolescent Factors Inventory; CAQ, CHARGE Attachment Questionnaire; CASE, Child and Adolescent Scale of Environment; CCSS, Childhood Cancer Survey Study; CFFS, Child and Family Follow-Up Survey; CHQ-PF50, Children's Health Questionnaire- Generic Version; CISS, Coping Inventory for Stressful Situations; COWAT, Controlled Oral Word Association Test; CS, Cross-sectional; CSI-SF, Coping Strategies Inventory- Short Form; CPT-II, Conner's Continuous Performance Test-II; CVLT-II, California Verbal Learning Test-II; D-AI, Dutch ICF Activity Inventory; DBC-P, Developmental Behavior Checklist- Primary Carer; ESIAD, Enjoji Scale of Infant Analytical Development; FORQ, Fear of Recurrence Questionnaire; HADS, Hospital Anxiety and Depression Scale; HD-KDDS, Hiro D-K Developmental Diagnosis Scale for Visually Impaired Infants; HRQOL, Health-Related Quality of Life- 14 'Health Days Measure'; HET, Health on Equal Terms; IBC-R, Infant Behavior Checklist-Revised; IES, Impact of Events Scale; KNHANES, Korean National Health and Nutrition Examination Survey; L, longitudinal; LHON, Leber Hereditary Optic Neuropathy; mMOS-SS, Modified Medical Outcomes Study Social Support Survey; MMPI-2, Minnesota Multiphasic Personality Inventory-2; MTSD, Maryland's Trait and State Depression Scale; NEI-VFQ 25, National Eye Institute Visual Functioning Questionnaire 25; NPSI-S, Nijmegen Parenting Stress Index- Short; PAIS-SR, Psychological Adjustment to Illness Scale- Self-Report Version; PedsQL, Pediatric Quality of Life Inventory; PCSC, Perceived Competence Scale for Children; PHQ-9, Patient Health Questionnaire; PSI, Parenting Stress Index; PSI:SF, Parenting Stress Index- Short Form; PTGI, Post Traumatic Growth Inventory; QOL, quality of life; R-MAI, Revised Maternal Attachment Inventory; RP, retinitis pigmentosa; SCL-90-R, Symptom Distress Checklist-90-R; SDQ, Strengths and Difficulties Questionnaire; SEI, Self-Esteem Inventory; SF-12v2, The 12-Item Short-Form Health Survey V.2; SF-36, Short Form Health Survey; SHS, Subjective Happiness Scale; SQ, Self-Developed Questionnaire; SRAYI, Science Research Associates Youth Inventory; SSQ, Strange Simulation Questionnaire; STAI, State-Trait Anxiety Inventory; TICS, Trierer Inventory of Chronic Stress; TSCS, Tennessee Self-Concept Scale; VF-14, Visual Function Index; VS 0–12, Vineland Screener 0–12 Years; WASI-II, Wechsler Abbreviated Scale of Intelligence; WAIS-III, Wechsler Adult Intelligence Scale-III; WEMWBS, Warwick-Edinburgh Mental Wellbeing Scale; WHOQOL-BREF, World Health Organization Quality of Life Scale- Short Form; WJ-III, Woodcock-Johnson III Tests of Achievement; Y-G, Yatabe-Guilford Personality Test; YSR, Youth Self-Report; Zung SDS, Zung Self-Rating Depression Scale.

Table 2 – Themes discussed in each study

Theme	References
Coping	2,10,12,13,15,20,21,26,28,30–33,39,41,47,49,54,55,61–63,69,73,76,83,86,92,93,96,98,102
Identity	10,12,26,30,31,34,41,51,52,62,63,69,71,83,92,98,102,104
Independence	2,10,11,13,21,26,28,32,34,37,40,41,62,63,69,73,76,83,98
Mental Health	1–4,13–15,19,20,24,26,29,30,32–34,37,40–43,45–47,49,57,61–63,65–69,73,74,83–86,93,97–101,104,106,107
Quality of Life	2–4,12,15,20,21,26,29–31,37,38,40,47,48,53,54,57,61,73,76,80,97–101,104,107
Relationships	2,10–13,20,21,26,28,30–33,37–40,42,45,47,48,51,53–55,57,62,63,69,71,73,74,76,80,83,86,88,92,93,96–98,100–102,104
Socioeconomics: Trends and Impacts	8,11–13,15,21,24,28–33,40,42,45,47,48,53–55,61–63,69,73,76,80,83,84,86–88,92,98,100–102
Stigma	12,13,21,26,30,31,39,41,47,53–55,62,63,69,71,76,80,83,92,97,98,100,102

participants from 23 countries. The number of included patients may be an overestimate as we cannot exclude the possibility that some cohorts overlap, and the number of included family members may be an underestimate, as several articles mentioned interviewing relatives without providing specific numbers. Unaffected siblings who served as controls are not included in this statistic.

3.3. *Critical appraisal*

Of the 72 included studies, approximately half were quantitative nonrandomized (n = 34, 47%), followed by qualitative (n = 19, 26%), quantitative descriptive (11, 15%), and mixed methods (n = 6, 8%) studies. The included studies received mean and median MMAT scores of 2.14 and 2, respectively, but varied greatly in quality and comprehensiveness of reporting. Seven (10%) studies received a score of 0, 15 (21%) studies received a score of 1, 19 (26%) received a score of 2, 23 (32%) received a score of 3, and 8 (11%) received a score of 4 (Table 1). The 47 total quantitative articles received an average MMAT score of 2.23, while the 19 qualitative articles received an average score of 2.26 and the 6 mixed methods studies received an average score of 1.00.

A common point deduction across all study types related to recruitment methods, as many studies recruited from charities, advocacy organizations, or support groups. These methods of recruitment, although understandable because of the rarity of many Mendelian eye conditions, were deemed to produce nonrepresentative samples. Another common deduction was a failure to provide adequate demographic information on sample groups, and studies were only determined to have provided adequate information if they included details about socioeconomic status, such as education and income level. Several quantitative studies received deductions due to utilization of novel, invalidated measures; however, any attempts by the authors to pilot or validate a novel measure were also considered positively. A common deduction among qualitative studies was a failure to discuss sufficiently context and reflexivity of findings. In addition to these issues, many mixed-methods studies received deductions due to a lack of discussion of the reasons for choosing a mixed-methods design to address the research question. Detailed scoring and comments on methodological weaknesses can be found in Supplementary Table 1.

3.4. *Themes*

We identified the following eight themes in the 72 studies: coping, identity, independence, mental health, quality of life, relationships, socioeconomics, and stigma (Table 2). These themes are categorized into three key domains: psychological impacts, social impacts, and quality of life.

3.4.1. *Psychological impacts*

3.4.1.1. Mental health: depression, suicidality, anxiety. Across the 72 studies, mental health was the most commonly addressed psychosocial impact (n = 49, 68%). Twenty-eight of these studies evaluated mental health of adult patients only, and 2 reported on pediatric patients only. Nine studies included both pediatric and adult patients, 4 included only unaffected family members, and 6 studied a mixture of patients and family members. Participants with a variety of conditions were represented, including RP (14 studies),[1–3,30,37,41,43,45,46,49,65,66,69,73] Usher syndrome (10 studies),[19,20,24,42,62,63,93,99–101] mixed sample conditions (7 studies),[14,15,83–86,107] RB (5 studies),[29,68,97,98,104] albinism (3 studies),[34,47,57] CHARGE syndrome (3 studies),[40,74,106] STGD (3 studies),[13,61,67] LHON (3 studies),[26,32,33] and DOA (1 study).[4] Mental health constructs were measured quantitatively using 26 different scales, and qualitatively using self-study,[30] interviews and focus groups,[26,41,62,63,73,83,97,98] and analysis of patient expressive writing pieces.[13] The two most frequently used quantitative scales were the Hospital Anxiety and Depression Scale (HADS)[3,4,15,99] and the Patient Health Questionnaire (PHQ-9).[20,65–67,107] Many studies developed novel scales to assess mental health constructs[19,32,33,42,47,61,69,93] or used subscales of broader scales (i.e., quality of life scales, public health surveys, and personality tests) to evaluate mental health concerns.[2,20,24,38,40,43,46,49,57,99–101,104]

The prevalence, nature, or predictors of depression within these patient populations was a frequent area of study among the articles included in our review, with 29 (40%) of the 72 studies focused on this central theme. Eleven studies suggested the prevalence of depression for adult patients with DOA,[4] Usher syndrome,[15] and macular dystrophies of mixed etiologies[5] and patients of mixed ages with RP,[1,15,37,46,65,66] LHON[33] and STGD[61,67] to exceed that of the general population or the included control group. Those studies that calculated specific prevalence statistics reported depressive symptoms in 25.7%,[37] 31.2%,[1] 34.8%,[46] and 64.7%[65] of adult RP patients, 51.7% of STGD patients of mixed ages,[61] 26% of adult patients with mixed macular dystrophies,[85] 49.5% of LHON patients of mixed ages,[33] and 18.4% of adult DOA patients.[4] Two studies (one including adult RB survivors[29] and one including adults with mixed retinal degenerations[107]) found no significant difference or a significant reduction in the prevalence of depressive symptoms in their patient group compared to control groups. Significant predictors of depressive symptoms included the use of disengaging coping strategies for adults with RP,[2] older age at symptom-onset for

patients with LHON of mixed ages,[33] and receiving disability pension for adults with Usher syndrome.[24] There were mixed results as to whether visual function, including visual acuity and visual field, predicted depressive symptoms in patients with RP[3,37,65] and STGD.[67]

Several additional articles discussing adults with STGD,[13] RP,[30,73] and LHON[32] and patients of mixed ages with Usher syndrome[62,63,99] discussed depression without quantifying prevalence, typically through qualitative methods. For example, one participant in a study of expressive writing pieces by adults with STGD commented that, in response to receiving his/her diagnosis, "I felt hopeless and depressed. I had already started having panic attacks and rather than my world expanding with boundless opportunity, it was shrinking by the day".[13]

Nine studies included in our review revealed suicidality (encompassing attempts and/or ideation) within their patient sample.[24,26,32,46,62,63,99–101] Strikingly, six of these studies were concerning pediatric and adult patients with Usher syndrome.[24,62,63,99–101] The remaining three were of adults with LHON[26,32] and RP.[46] One such study of adults with Usher syndrome type 1 found that suicide attempts were over five times more common within their patient group than their general population reference group.[101] Two qualitative studies of individuals with Usher syndrome types 1[62] and 2[63] provided context for participants' suicidality, for example, "… aged 20, told the group… that he would shoot himself when he lost his vision because he could not imagine how he would live with deaf-blindness."[62] A study of adults with RP found that 38.5% of patients and 12.9% of controls in their sample reported suicidal thoughts,[46] and two studies of adults with LHON qualitatively described suicide attempts or suicidal thoughts.[26,32]

There were nearly as many studies discussing concerns for stress and anxiety as there were for depression, with 25 studies (35%) focusing on this mental health concern. Several studies explored mental health for their participants generally and thus collected data about both depression and anxiety. Anxiety was elevated in this population compared to general population frequency or the included control group in six studies of adults with DOA,[4] RP,[15,46] Usher syndrome,[15,100] mixed macular dystrophies,[85] and mixed retinal dystrophies.[107] Symptoms of anxiety were present among 50.0% of DOA patients,[4] 36.5% of patients with RP and Usher syndrome,[15] and 23% of patients with mixed macular dystrophies.[85] A Korean study of adults with RP observed 51.9% of patients to have stress, compared to 29.4% for controls.[46] Similar to what was reported for depression, one study found that there was not a significantly higher rate of anxiety for adult RB survivors compared to controls.[29] Another study of adult RB survivors described anxieties regarding reproductive risks for 68% of hereditary RB survivors and 32% of non-hereditary RB survivors.[98]

Several studies have evaluated predictors of anxiety and found that decreased visual function in adults with RP,[3] legal-disability status in adults with Usher syndrome,[24] and identity concealment behaviors in adults with RP and STGD[83] were associated with anxiety. Three studies measured or explored parenting stress among parents of individuals with CHARGE syndrome[40,106] and Usher syndrome,[93] and all suggested parents to experience increased stress attributed to their child's diagnosis. Another study showed that mothers of infants with RB did not have significantly different parenting stress compared to normative data.[68]

Several studies qualitatively explored stress, fears, worries, and anxiety of adult participants with STGD,[13,83] Usher syndrome,[24,99,101] and RP,[41,49,73,83] participants of mixed ages with LHON,[33] mixed conditions[69] and CHARGE Syndrome,[40] and parents of children with Usher syndrome.[93] One study described adults with RP feeling anxious due to "vague" language used by physicians; "He told me I had RP but did not tell me I would likely go blind. I did not know what it was… I went through a lot of anxiety attacks because I had no knowledge of what was actually going to happen…"[41] Another study of adults with RP described patients' fears associated with their vision loss, for example, "There's fear of being in a place, that catches fire or in an accident or something and not being able to get yourself to safety because you cannot see, so that's quite frightening."[73]

3.4.1.2. Coping: vision aid uptake, religion and prayer, humor, maintaining perspective, and hope for treatment. Thirty-two of the included studies (44%) addressed the ways that affected individuals or their family members cope with Mendelian eye conditions, primarily through exploring common "coping strategies" used by study participants. Studies included participants or family members with RP, (8 studies)[2,10,30,41,48,49,69,73] albinism (7 studies),[12,31,47,54,55,92,102] Usher syndrome (5 studies),[20,28,62,63,93] mixed conditions (4 studies),[15,21,83,86] LHON (3 studies),[26,32,33] RB (2 studies),[96,98] STGD (2 studies),[13,61] BBS (1 study),[39] and Alström syndrome (1 study).[76] These included 19 qualitative, 10 quantitative, and 3 mixed methods studies.

Although a wide variety of coping strategies were identified, the most commonly discussed was the use of vision aids such as white canes, guide dogs, braille, and magnifiers. Fifteen studies discussing pediatric and adult patients with RP,[10,15,30,41,49,69,73] LHON,[26,32,33] and Usher syndrome,[28,62,63,101] and adults with Alström syndrome[76] discussed vision aid uptake as a critical coping strategy utilized by their participants. Several studies, including adults with LHON[26] and RP,[41] and patients of mixed ages with Usher syndrome,[28,62,63] discussed the challenges of learning and incorporating these new skills in adulthood. Two studies involving adults with RP[41] and patients with Usher syndrome of mixed ages[63] discussed the barrier of perceived risk of stigmatization to using vision aids when needed. Studies including adults with RP,[15,49] mixed macular dystrophies,[86] and Usher syndrome,[15] and patients of mixed ages with LHON[33] and mixed conditions[69] described vision aids to be underutilized in their cohort. For example, in one study of adults with RP, 90% were registered as sight impaired or severely sight impaired, but only 49% used vision aids. Older age, length of visual impairment, and severity of visual impairment increased the likelihood of vision-aid use for patients.[49] Despite difficulties cited by patients in the process of incorporating vision aids into their daily lives, the use of these practical strategies was repeatedly found to benefit patient well-being, sense of independence, and to facilitate overall coping for patients with RP,[10,30,73] Alström syndrome,[76] mixed macular dystrophies,[86] and LHON.[32,33]

Fourteen articles, including adults with RP,[10,30,73] STGD,[13] and Alström syndrome,[76] and patients of mixed ages with albinism,[12,92,102] LHON,[26,32,33] Usher syndrome,[62,63] and mixed conditions,[69] described coping through obtaining social support from other affected individuals. These relationships, whether online or in person, were key sources of emotional support. One participant described the benefit of connecting with other people with RP by saying, "Knowing that you're not alone is one of the most important things."[10] Social support was also derived from other relationships, which we address further Section 3.4.2.1.

Religion and prayer (in patients of mixed ages with albinism,[12,47,55,102] children with mixed conditions and their parents,[21] adults with RP,[41] and parents of children with Usher syndrome[93]) humor (in adults with RP,[10,30] STGD,[13] and LHON[26]), maintaining perspective (in adults with RP[10,30,73]), and hope for a treatment (in adults with RP[10] and children with mixed conditions and their parents[21]) were additional coping strategies identified across studies. Studies of albinism in Africa discussed the ways that affected children and adults use a religious framework to conceptualize their condition positively as a part of God's plan to cope with experiences of stigmatization.[12,47,55] One study including parents of children with a variety of diagnoses described prayer and hope for a cure as a "big thing that gets [them] through,"[21] while another study including parents of children with Usher syndrome discussed the ways that their religious faith has enabled them to "take the new tragedy [of vision loss after hearing loss] in stride…"[93] Humor was mentioned as a coping strategy in 4 studies.[10,13,26,30] Specifically, it was described as a distraction and defense mechanism for adults with RP,[10,30] and as a tool in reframing embarrassing moments and alleviating stress and anxiety for adults with LHON[26] and RP.[30] Three studies of adults with RP found that participants cope by maintaining perspective in considering "worse things" and experiencing gratitude that their condition is not life threatening.[10,30,73]

3.4.1.3. Identity: self-esteem and concept, normality, sighted to blind, disability. Identity was a theme in 18 studies (25%), which included participants with albinism (6 studies),[12,31,34,71,92,102] RP (5 studies),[10,30,41,51,52] Usher syndrome (2 studies),[62,63] RB (2 studies),[98,104] mixed conditions (2 studies),[69,83] and LHON (1 study).[26] Many studies of patients of mixed ages and a variety of conditions (albinism,[12,31,92,102] RP,[30,83] mixed conditions,[69] STGD,[83] and RB[98]) emphasized the importance of feeling normal and not standing out; however, in one mixed-age study of patients with albinism, some participants expressed the opposite sentiment, such as one participant who "reveled in her conspicuousness and publicly revealed her uniqueness."[102]

Several studies including children with albinism[34] and adults with RP[51,52] explored self-concept. Additional studies of pediatric and adult patients with albinism,[31,71] Usher syndrome,[63] and RB,[98,104] and of adults with RP[41,83] and STGD,[83] evaluated self-esteem. According to Baumeister, self-concept can be defined as "how a person thinks of him- or herself, that is, the person's own beliefs and ideas about this self."[7] It is distinguished from identity in that it is only comprised of a person's own ideas and no external input.[7] Self-esteem, on the other hand, is a subset of self-concept in which individuals judge these beliefs and ideas as "good" or "bad."[7] Three studies[34,51,52] used the Tennessee Self-Concept Scale and found that children with albinism[34] and adults with RP[51] had similar self-concept to controls. Among adults with RP, moral self-concept increased with age, family self-concept decreased with age, and female sex and higher education were associated with higher physical self-concept.[52]

Reports of self-esteem were mixed. Four studies, including participants of mixed ages with albinism,[31] Usher syndrome,[63] and RB,[98] and adults with RP,[41] qualitatively described struggles with self-esteem in their samples. For example, one participant with RP said, "Sure I've had my inferiority problems… I've been ashamed that I could not be the one to drive and macho stuff like that… that was a low point for me."[41] On the other hand, one qualitative study of adults with RP and STGD described self-esteem benefits.[83] For instance, one participant indirectly described self-esteem benefits by saying, "People are more comfortable sharing information with me quicker than they may if I did not have this disability … I've become a better listener by not being able to see well. I've become a better problem-solver. I've become more, let's say, empathetic. And there's probably a laundry list of other things."[83] A quantitative study of children with RB found that enucleation of the eye was associated with significantly lower self-esteem.[104] Finally, a quantitative study of children with albinism in Australia found that 80% had high self-esteem.[71]

Other facets of identity explored included disability identity in patients of mixed ages with albinism[12,31] and Usher syndrome,[62,63] and the transition between sighted and blind identities among adult patients with RP[10,41] and LHON,[26] and mixed-age patients with Usher syndrome.[63] For example, one study of adults with RP stated that "for most participants, resolving personal identity as a sighted versus a visually impaired person posed an early and pivotal challenge."[41] The transition between sighted and blind identities also appeared to be connected to the decision to use assistive technology, which was often viewed as a visible signal of blind identity for adults with LHON[26] and RP.[41] One study of adults with RP described that some participants chose to self-identify as sighted and "[resisted] using assistive devices and making lifestyle changes," while some self-identify as visually impaired and chose to integrate assistive technology into their lives.[41] In addition, two studies of pediatric and adult patients with Usher syndrome discussed the difficulties that can be encountered when people identifying as members of the Deaf community begin to lose their vision.[62,63]

3.4.2. *Social impacts*

3.4.2.1. Relationships: family, friends and peers, professionals, romantic, work-setting. Relationships were the second most discussed psychosocial impact, with 46 (64%) of the included studies covering this theme. These studies included adult and pediatric participants with albinism (10 studies),[12,31,47,53–55,57,71,92,102] RB (6 studies),[11,80,96–98,104] mixed conditions (5 studies),[21,38,69,83,86] LHON (3 studies),[26,32,33] CHARGE syndrome (2 studies),[40] and Usher syndrome (9 studies),[20,28,42,62,63,88,100,101] adults with RP (8 studies),[2,10,30,37,45,48,51,73] Alström syndrome (1 study),[76] and STGD (1 study).[13]

Twenty-two studies explored family relationships, and reports varied greatly within and across these studies. For example, two studies of patients with albinism reported largely positive family relationships,[53,102] whereas three studies including pediatric and adult patients reported both positive and negative family relationships.[12,54,55] Family relationships were also mixed among people of mixed ages with Usher syndrome.[62,63,88,93] Notably, two studies including both adult and child participants discussed communication as a challenge in family relationships and emphasized the importance of family members using sign language.[62,63] Other studies explored family relationships for adults with STGD,[13] RP,[45] and Alström syndrome,[76] participants of mixed ages with RB,[104] LHON,[33] and mixed conditions,[38,69] and parents of children with BBS[39] and CHARGE syndrome.[74] Two studies investigated the influence of vision impairment on family relationships, and found that increased visual impairment negatively impacted attachment in infants with CHARGE syndrome[74] and family functioning among children with mixed retinal dystrophies.[38] Three qualitative studies of adult patients with Usher syndrome[28] and RP,[30,73] discussed family relationships only in terms of "friends and family." They described a negative impact on relationships with friends and family[28,73] as well as feeling misunderstood.[30,73]

Twenty-two studies discussed friend and peer relationships among individuals with LHON,[26,33] Usher syndrome,[28,62,63] RP,[30,73] albinism,[31,47,54,55,71,92,102] BBS,[39] CHARGE syndrome,[40] Alström syndrome,[76] RB,[80,97,98] and mixed conditions.[21,69] Of these, 7 and 3 studies included only adult and pediatric participants, respectively, while 12 had mixed populations. Studies focusing on albinism,[31,54] BBS,[39] Alström syndrome,[76] RB,[80] and mixed conditions[21] all mentioned incidences of bullying, teasing, or name-calling in childhood. However, these were countered by several positive reports of peer relationships during childhood among studies of people with mixed conditions[21] and albinism.[54,92,102] One study found that bullying worsened future quality-of-life outcomes in RB survivors.[97] Studies of both pediatric and adult participants affected by CHARGE syndrome,[40] albinism,[47,55,71] Usher syndrome,[62,63] and RB[80,98] reported difficulty in forming or maintaining friendships; however, in studies which measured this quantitatively, the prevalence of such difficulties varied greatly, from 15% for patients (of mixed ages) with RB[80] to 86.8% for children with albinism.[55]

Relationships with professionals such as ophthalmologists, other doctors, and teachers were described in 11 articles, including patients of mixed ages with LHON,[33] Usher syndrome,[62,63] mixed conditions,[69] and albinism,[92,102] adults with Alström syndrome,[76] RP,[45,73] and mixed macular dystrophies,[86] and parents of children with BBS.[39] Both positive and negative experiences with professionals were reported. For example, one study of patients with LHON found that 52.4% of participants reported receiving emotional support from an ophthalmologist[33]; however, a study of people with albinism from North America and Australia reported that "doctors and nurses were found to be excessively ignorant and insensitive toward the respondents. As albinism is a rare condition, doctors and nurses very seldom meet patients with albinism. The respondents reported that when doctors received a patient with albinism, the doctors seized the opportunity to examine them."[102] Other relationships explored included romantic relationships (17 studies)[10–13,31,32,47,53,62,63,69,73,76,86,88,98,102] and work-setting relationships (10 studies).[13,28,30,33,45,53,63,69,83,102]

Eight studies indicated that children and adults with Usher syndrome[20,28,42,62,100,101] and CHARGE syndrome[40] and adults with RP[30] and Alström syndrome[76] experience loneliness and isolation. Six studies of adults with STGD,[13] LHON,[26] mixed conditions,[69] and RP[30,37,73] specifically described the impact of visual function on social interactions. For example, participants with STGD[13] and RP[30] expressed concerns about difficulty seeing faces, and participants with LHON[26] and RP[30,73] cited trouble picking up on nonverbal cues. One study of mixed conditions described challenges in participating in social activities due to "difficulty in dark places such as bars, theaters, and in night activities;"[69] however, adults with STGD in one study found benefits in these challenges, mentioning increased verbal communication ability.[13]

3.4.2.2. Socioeconomics: trends and impacts: Employment, finances, education, accommodations. Thirty-eight studies (53%) discussed the impact of Mendelian eye conditions on socioeconomic factors. These included adult and pediatric participants with Usher syndrome (8 studies),[24,28,42,62,63,88,100,101] albinism (8 studies),[12,31,47,53–55,92,102] mixed conditions (7 studies),[8,15,21,69,83,84,86] RP (5 studies),[30,45,48,73,87] RB (4 studies),[11,29,80,98] LHON (2 studies),[32,33] STGD (2 studies),[13,61] CHARGE syndrome (1 study),[40] and Alström syndrome (1 study).[76] Prominent subthemes were employment and finances (33 studies) and education (18 studies). Two studies[8,86] found a significantly lower employment rate in adults with mixed conditions in reference to a comparison group, while a third found a nonsignificant trend toward lower employment for patients with RP and Usher syndrome.[15] A study on RB survivors of mixed ages found no differences in employment compared to the general population.[98] However, a separate study of adult RB survivors found that bilateral disease was related to lower employment compared with unilateral.[29] Several additional studies of patients of mixed ages with RB,[11] albinism,[53] STGD,[61] RP,[87] and mixed conditions[69] reported employment rates without the use of a comparison group. Both employed and unemployed people often reported that their vision influenced their career. For example, in the previously referenced study which found no employment differences for RB survivors of mixed ages, 26% said that RB had influenced their career choice.[98] In a study in adults with mixed macular dystrophies, 66% of unemployed people referenced their vision as the reason for unemployment.[86]

Only two studies measured education levels against a comparison group. One study found that significantly fewer adults with mixed retinal dystrophies had completed higher levels of education as compared to the control group,[8] while another found that more blind adults with RP or Usher syndrome had completed higher education than controls.[15] Two studies of adults with Usher syndrome[101] and mixed retinal dystrophies[8] compared patients' financial statuses to controls or the general population and both identified a significantly worse financial situation. Other related concepts explored quantitatively included vocational adjustment for adults with RP,[45] beliefs about the ability to obtain a job for children and

adults with albinism,[47] percentage of children with CHARGE syndrome[40] and RB[80] attending mainstream school, and vocational and educational success for children and adults with mixed retinal degenerations, as judged by the authors.[84]

Several articles also discussed employment, finances, and education in a qualitative manner. Many adults with RP[13,30,83] and STGD[83] reported concerns about whether to disclose vision limitations to employers. Adults with RP[13] and patients of mixed ages with albinism[102] cited difficulty in obtaining necessary accommodations. Adults with RP[13,30,83] and STGD[83] were concerned by decisions to adjust educational and career plans. Psychological issues resulting from unemployment, retraining, or problems in school were cited by adults with LHON[32] and patients with Usher syndrome of mixed ages.[62] One mixed methods study cited obtaining employment as a key issue in adjusting to vision loss in adults with LHON,[32] and two quantitative studies also associated employment with increased wellbeing for patients with Usher syndrome of mixed ages.[24,42] Issues with stigma and discrimination both while searching for a job and once working were prominent for people with albinism across time periods and geographic locations.[12,53,102] In addition, several studies of primarily pediatric patients with syndromic and non-syndromic conditions explored participation in special education programs[29,31,40,55,63,76,80,98] or use of accommodations in school.[21,54,55,63,69,76,92] Accommodation use in the workplace was also examined for adults with STGD,[13,83] RP,[15,30,83] Usher syndrome,[15,30] mixed conditions,[69,83,86] and mixed macular dystrophies.[86] While utilization of low vision accommodations in school appeared to have a positive impact on learning for patients with mixed conditions,[21,69] albinism,[92] and Alström syndrome,[76] it was also noted to have difficult social consequences for children with albinism in one study.[92]

3.4.2.3. *Stigma: albinism, cane-use, violence, vulnerability*. The impact of stigma on people with Mendelian eye condition was addressed in 24 studies (33%), including participants with albinism (9 studies),[12,31,47,53–55,71,92,102] mixed conditions (3 studies),[21,69,83] Usher syndrome (3 studies),[62,63,100] RB (3 studies),[80,97,98] RP (2 studies),[30,41] STGD (1 study),[13] LHON (1 study),[26] BBS (1 study),[39] and Alström syndrome (1 study).[76] Among the 9 articles covering stigma in people with albinism, 6 took place in African countries, including South Africa,[31,47,55] Zimbabwe,[53,54] and Tanzania.[12] Each of these articles reported extreme stigma or misconceptions surrounding albinism, most often related to differences in appearance, including a belief that people with albinism are cursed,[12] fear of close proximity or physical contact with people with albinism,[12,31,53,55] and a belief that albinism is caused by a misdeed committed by relatives.[12,31] Incidents of offensive or threatening name-calling were common.[12,31,53,55] Stigmatization affected many aspects of people with albinism's lives, including social relationships,[12,47] employment,[12,53] marriage,[31] and education.[12,54,55] One study of students with albinism in South Africa described that they undergo, "a constant battle to come to terms with a body that does not meet social expectations for role compliance or appearance."[31] The other three studies of albinism included studies based in the UK[92] and Australia,[71] as well as one international study with participants from Canada, the US, and Australia.[102] These studies also revealed significant stigma faced by people with albinism impacting education,[92,102] childhood social relationships,[71] and employment.[102]

Patients with other syndromic conditions also reported stigmatization due to various features of their condition, including vision loss. This was illustrated by a study of parents of children with BBS, who reported stigmatization due to various symptoms, especially obesity, but also due to vision loss.[39] For example, one parent said, "I have been looked at as a parent who maybe cannot control [my] children because with their vision they cannot see where they are going sometimes and they will knock into somebody or, you know, they will trip over something or they will knock against something in a store and, you know, you get these looks as in, you know, 'Gosh, you know, you do not teach your children where to go.'"[39]

Studies of nonsyndromic Mendelian eye conditions, including adults with LHON,[26] RP,[30,41,83] and STGD,[83] identified use of a cane or mobility equipment as one of the most common sources of stigmatization. Many participants in these studies felt conflicted between the practical benefits of using mobility equipment and the perceived stigmatization that would occur.[26,30,41,83] Several studies of adults with STGD,[13] RP,[30] and LHON[26] also reported that participants felt misunderstood due to society's tendency to dichotomize people as sighted or blind, without understanding the varying degrees of vision loss in between. For example, one person with RP expressed worries about not appearing "blind enough" to use a cane.[30]

Six studies[12,31,54,55,100,102] reported experiences of physical violence. Five of these studies included individuals of mixed ages with albinism in Africa,[12,31,54,55,102] and one study concerned adults with Usher syndrome type 3.[100] A seventh article reporting on adults with LHON did not directly reference experiences of violence but described the feeling of vulnerability experienced by people with a vision impairment by quoting one participant who said, "If you are out and the long and short of it is that it is not a very nice world out there, and there are places that are not very nice, and I would probably prefer to struggle than walk down the road with a long cane saying 'Hey I am blind, come and mug me.'"[26]

3.4.2.4. *Independence: driving, independent-living*. Independence was a theme in 19 (26%) articles. These included participants with RP (5 studies),[2,10,37,41,73] Usher syndrome (3 studies),[28,62,63] mixed conditions (3 studies),[21,69,83] RB (2 studies),[11,98] LHON (2 studies),[26,32] STGD (1 study),[13] CHARGE syndrome (1 study),[40] Alström syndrome (1 study),[76] and albinism (1 study).[34] Most of these studies included only adult populations[2,10,11,13,26,28,32,37,41,73,76,83] or mixed-populations[62,63] but focused primarily on independence in adulthood. A major challenge for adult participants with RP,[10,73] STGD,[13] and Usher syndrome[62] was losing the ability to drive. One study of adults with RP reported that, "participants continued driving with their vision loss well beyond when they should have stopped, and eventually only gave it up after having an accident or very close call."[10] Utilization of mobility training and aids and other assistive technology had a positive impact on independence for patients with RP[10,41] and LHON.[26,32] Despite concerns about driving or having to rely on

others, one study of adults with RP described most participants as "very independent."[73]

For syndromic conditions (CHARGE syndrome,[40] Usher syndrome,[62] and Alström syndrome[76]) independent living was an important theme. Completion of activities of daily living was addressed for patients of mixed ages with CHARGE syndrome[40] and adults with Alström syndrome.[76] One study of people with CHARGE syndrome found that 23% of adults included in the study lived independently.[40] Another study of adults with Alström syndrome qualitatively described that many individuals required a great deal of family support to accomplish certain tasks like cooking, cleaning, taking public transportation, or using the internet.[76] For people of mixed ages with Usher syndrome, one study reported that deteriorating vision led to loss of the ability "to drive, read regular or large print, enjoy their hobbies, go to the deaf club, or walk around their communities alone."[62] Finally, for younger patients with mixed conditions[21] and RB,[98] independence in school work was a focus. For example, one study indicated that children who had survived RB felt that dependency negatively influenced their educational attainment,[98] while a separate study of children with mixed conditions and their parents suggested that using assistive technology positively affected ability to complete schoolwork independently.[21]

3.4.3. *Quality of life (QoL)*

The World Health Organization (WHO) defines quality of life (QoL) as a "broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships, and their relationships with salient features of their environment."[F] QoL includes several key subdomains, such as physical, psychological, emotional, spiritual, socioeconomic, and social QoL.[17,27] These subdomains overlap with many of the themes discussed in the previous sections of this review. In this section, we focus on studies that explored the more encompassing concept of QoL, rather than its individual subdomains.

Thirty (42%) studies evaluating QoL were identified. These articles included participants with RP (6 studies),[2,3,30,37,48,73] albinism (6 studies),[12,31,47,53,54,57] RB (5 studies),[29,80,97,98,104] mixed conditions (4 studies),[15,21,38,107] Usher syndrome (4 studies),[20,99–101] LHON (1 study),[26] DOA (1 study),[4] CHARGE syndrome (1 study),[40] STGD (1 study),[61] and Alström syndrome (1 study).[76] There were 19 quantitative, 8 qualitative, and 3 mixed methods studies. Quantitative studies used a variety of validated QoL measures including the National Eye Institute Visual Function Questionnaire (NEI-VFQ),[2,3,15,37] Visual Function Index (VF-14),[4] 12-Item Short-Form Health Survey V.2 (SF-12v2),[20] Pediatric Quality of Life Inventory (PedsQL),[38,80,104] Health Related Quality of Life-14 'Health Days Measure' (HRQOL-14) (adapted),[40] World Health Organization Quality of Life Scale-Short Form (WHOQOL-BREF),[57,107] Children's Health Questionnaire (CHQ),[104] and Short Form Health Survey (SF-36).[80,97] Five such studies of adults with RP,[3,15] Usher syndrome,[15,20] and mixed retinal dystrophies,[38] and children with RB[80] found that affected individuals had reduced overall QoL when compared to healthy controls, reported normative values, other disease populations, or unaffected siblings. Six studies[40,57,97,104,107] reported reduced QoL only on certain subscales. Two studies evaluated QoL in mothers of children with RB[80] and siblings of children with mixed retinal dystrophies[38] and found QoL to be comparable to normative data.

An additional seven[29,47,48,61,99–101] studies investigated concepts that we considered conceptually similar to QoL but did not use QoL-specific scales. Five used validated measures, including "Health on Equal Terms" (HET),[99–101] the Dutch ICF Activity Inventory (D-AI),[48] and an adapted version of the Childhood Cancer Survey Study (CCSS)[29]; two[47,61] used novel measures. Three studies, including participants of mixed ages with albinism in South Africa[47] and adults with Usher syndrome[99,101] indicated that affected individuals had reduced quality of life compared to healthy controls or the general population. One study of adult RB survivors showed similar quality of life to population norms and increased quality of life compared to another disease population.[29]

Many of the qualitative studies described the impact of visual function on QoL.[12,21,26,30,53,54,73,76,98] Participants described the impact of their vision on global functioning and experience, as well as on many different aspects of life, including school (for patients of mixed ages with albinism,[12] children with mixed conditions,[21] and adults with Alström syndrome[76]), employment (for adults with albinism[53] and RP),[73] and relationships (for adults with RP).[73] One person with RP described his experience, saying, "I am blind in the day even under very bright light except in the center and some patches on the side. My reading vision is fine still, and I can see people's faces if they are across the room, but I cannot see a whole face close to me even in bright light. My RP is no longer a night thing."[30]

Several studies explored predictors of QoL, such as visual function[3,21,37,107] and coping methods.[2,73] Interestingly, there were different results regarding visual function and QoL for different measures. For example, while the NEI-VFQ scores seemed to correlate with measures of visual function such as visual field[3] and visual acuity levels for adults with RP,[3,37] the WHOQOL-BREF did not correlate with visual acuity or visual field for adults with mixed retinal dystrophies.[107]

4. Discussion

The literature on psychological and social impacts of Mendelian eye conditions on patients has explored constructs of mental health, coping, identity, relationships, socioeconomic trends and impacts, stigma, independence, and quality of life. Across studies, these conditions were found to have negative effects on patient psychological and social well-being, with more severe impacts reported in individuals with syndromic diagnoses. Literature on family impacts was limited but focused primarily on family relationships and parenting stress.

Mental health was the most commonly studied impact, with numerous studies reporting increased rates of depression and anxiety among adult patients. Reports of reduced quality of life, an overlapping yet more general construct, substantiate these mental-health specific findings. Individuals with chronic medical conditions are known to be at increased risk for developing depression and anxiety[82,94] over the general population estimated prevalence of 7.1% for major depressive disorder[C] and 5.7% for generalized anxiety

disorder.[E] For example, people with type 2 diabetes, cancer, rheumatoid arthritis, chronic pain, and AMD have reported rates of depression of approximately 25%,[78] 22%,[60] 16.8%,[59] 13–42%,[58] and 11–44%,[89] respectively. The studies included in this review revealed prevalence of depression to range between 18.4–65%, and anxiety to range between 23–52%, suggesting that progressive Mendelian eye conditions may impart a particularly negative impact on patients' mental health, even when compared to other chronic illnesses. Interestingly, the relationship between mental health and visual function remains unclear, as studies report mixed results. Even if a correlation is present, individuals with comparatively good visual function may still have increased rates of anxiety and depression, as was shown by one study.[3] This evidence indicates that people with Mendelian eye conditions, regardless of visual function, may be at risk for reduced mental health and/or quality of life. Additional research is needed to illuminate whether screening for depressive symptoms and anxiety in ophthalmic genetics clinics improves detection and treatment of clinically significant depressive symptoms and anxiety within this population.

This work also reveals concerns for suicidality, particularly among patients with Usher syndrome. This observation reinforces the added complexity and increased psychosocial impacts of syndromic conditions. Several prior studies have revealed increased suicidality in populations with chronic illnesses,[22] particularly among adolescents and young adults.[36] Chronic illness is associated with as high as a 3.5- to 4.5-times increased rate of suicide attempts in this population.[16,56] The high prevalence of suicidality among "healthy" adolescents and young adults is an established public health concern, as it is the second leading cause of death in this population.[A] The findings of reported suicidality and increased rates of anxiety and depression, in conjunction with the natural history of Mendelian eye conditions with disease onset often occurring in young adulthood, make a concerning case for increased suicidality within this patient population, with particular concerns for patients with syndromic diagnoses. This evidence supports mental health screening and robust mental health referral processes in clinical practices caring for individuals within this vulnerable subpopulation of patients.

Emerging research relating to patient coping strategies was also an important topic among the reviewed studies. The use of vision aids was the most commonly studied coping strategy in this review. Most studies cited positive effects, but underutilization, of vision aids. A major barrier to the use of low vision aids was patient-perceived risk of stigmatization. Ophthalmologists and other eye care professionals should be aware of these critical resources for patients with low vision, barriers to utilization, and mechanisms to refer for evaluation when appropriate. In the current era of readily accessible technology in the developed world, some assistive devices and technologies have become more discreet and may lessen some of the stigmatization that occurs. While improving the social acceptability of low vision aids is a continued effort, patients may not be aware of technical developments and may imagine out-of-date interventions. Health-care providers can play an important role in both educating patients and facilitating access to modern low vision aids.

In addition to perceptions of stigmatization, there is evidence in this review of actual stigmatization, including reports of physical violence directed at individuals with albinism and Usher syndrome. This again highlights the observation that patients with multisystemic diagnoses experience greater psychosocial impacts. Stigmatization of affected individuals likely contributed to identified sociodemographic trends and impacts across conditions and societal contexts. Reports of physical violence most often occurred among individuals with albinism in Africa due to differences in their physical appearance and may not be generalizable to individuals with Mendelian eye conditions in other geographic regions; however, fears of stigmatization, vulnerability, and violence were barriers to visual aid utilization among individuals with nonsyndromic Mendelian eye conditions. Patients may benefit from sharing their concerns and experiences with health-care providers, as well as from peer support from other patients and patient advocacy organizations. Research aimed at designing interventions to help patients effectively manage stigmatization is needed.

This review adds to a growing body of literature on the negative impacts of chronic disease on personal relationships.[18,23,103] Many Mendelian eye conditions are both invisible and unfamiliar to the general population. Decisions around disclosure are often a source of stress for patients. While our included studies did not frequently discuss patient experiences with verbal disclosure, the use of the white cane appears to be perceived by patients as a form of "passive disclosure," and discomfort with this is another likely explanation for reduced utilization. Effects of vision loss on perception of nonverbal social cues, navigating dimly lit environments, and driving were also discussed. These concerns may be particularly relevant in this population of patients, as many present in young adulthood, a life-stage characterized by developmental tasks surrounding fitting in and feeling normal.[89] In contrast, the immediate visibility and complexity of syndromic diagnoses appear to create particularly complex social and relational impacts, such as parenting stress and communication challenges. Social isolation and loneliness were reported frequently across conditions. Relationships with other affected individuals were repeatedly found to enhance coping and address this social isolation, a finding which is supported by past research.[81] Health-care providers can play a key role in connecting patients with the same diagnosis or similar symptoms.

Overall, these findings are largely consistent with prior studies of patients with non-Mendelian eye conditions, such as AMD,[91] glaucoma,[79] and diabetic retinopathy,[25] although concerns for depression, suicidality, and stigmatization appear to possibly exceed what has been reported previously. Rolland's Family Systems-Illness Model[75] is a useful framework for understanding the numerous external and internal factors impacting patients with these conditions. This model highlights the role of belief systems and culture, family dynamics, and specific disease characteristics (onset, course,

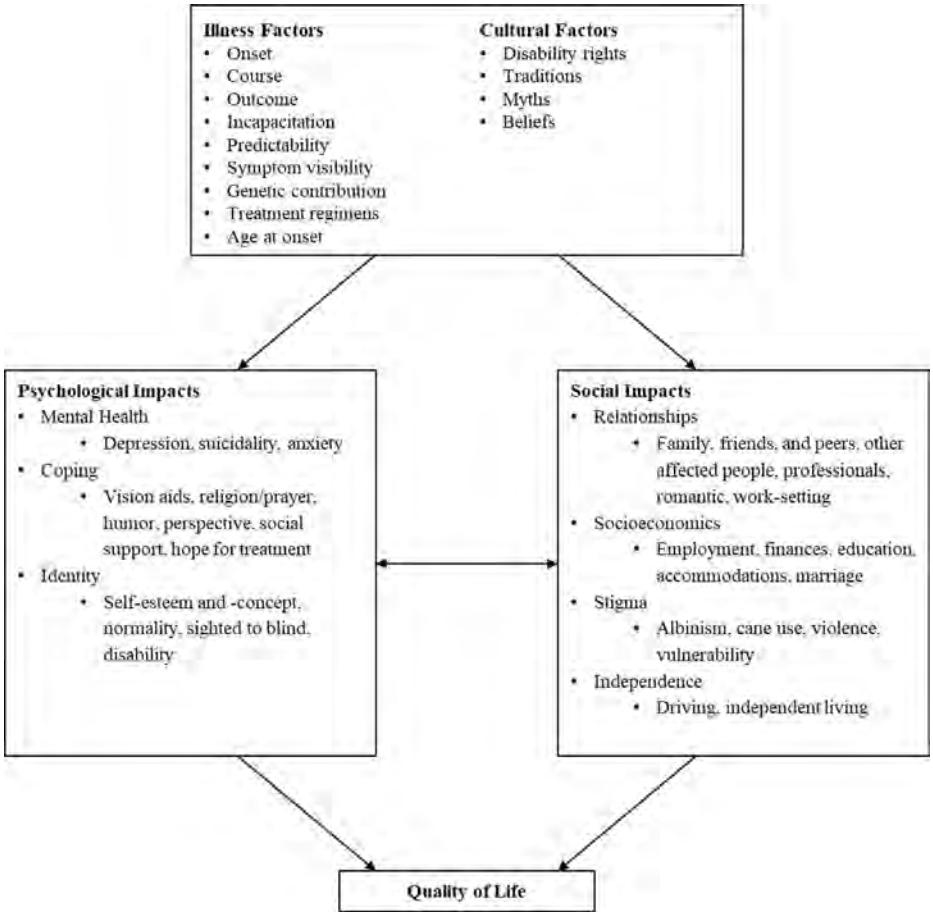

Fig. 2 – Psychosocial impacts of Mendelian eye conditions.

outcome, incapacitation, level of uncertainty) in a family's process of coping and adaptation.[75] Fig. 2 applies this bio-psychosocial typology and summarizes a proposed model derived from the results of this review.

5. Future research and developments

Methodological challenges encountered by many of the included studies and our exclusion of studies not available in English should be considered when assessing the generalizability of the findings. The rarity of many of the included conditions is a likely contributing factor to the lack of statistical power or biased recruitment strategies that were noted for several included studies within the MMAT quality appraisal process. In addition, qualitative studies would benefit from the use of more robust methodology and reporting, such as including descriptions of the treatment of data, and context and reflexivity. Furthermore, future studies should continue to explore understudied conditions, themes, and populations. For example, only four studies focused on STGD, despite the fact that this is one of the more prevalent conditions included in this review. In addition, few studies report on disclosure decisions, family functioning, and the impact of genetic etiologies on the family system. Lastly, only four studies included in this review focused on purely pediatric patients. Given the overwhelming evidence suggesting negative psychosocial impacts, future research may evolve from evaluating the presence or prevalence of various psychosocial impacts to exploring psychotherapeutic or social interventions aimed at improving well-being in this population. These interventions have particular importance in this disease context where medical treatment remains largely unavailable. Finally, the impacts revealed in this review may be incorporated into further development or selection of PROMs in this disease group. Although numerous disease-specific PROMs exist, most assess mobility only.[72] Development of more multidimensional PROMs and/or supplementing existing PROMS with additional measures is needed to adequately assess the wide variety of impacts reported by patients.

6. Conclusions

We have reviewed the evidence regarding the lived experiences and needs of patients and families with Mendelian eye conditions. These data shed light on the challenges and priorities of those affected. Patient management and clinical care may be improved by incorporating assessment and support around the impacts identified in this review. Patients may also benefit from evaluation in multidisciplinary clinics

specializing in the care of patients with these diagnoses.[64] These synthesized data should be a critical resource for researchers selecting or creating PROMS relevant to this patient group.

7. Method of literature search

7.1. *Eligibility*

We included references that met the following predetermined criteria:

- Original research articles (qualitative or quantitative design), including empirical evidence
- Study participants are either patients with a diagnosis of a Mendelian eye condition or their family members
- Effect of Mendelian eye condition on participants' psychosocial well-being is measured or described
- Written in English
- Full article accessible
- Published any time up to March 2018

Studies that only evaluated the visual function domain of quality of life were excluded, as were studies that evaluated the psychosocial impact of an intervention on people with Mendelian eye conditions.

7.2. *Search methods*

We searched for relevant references in CINHAL, Cochrane, Embase, PsychInfo, PubMed, Scopus, and Web of Science. Search terms were chosen to be as inclusive as possible of all psychosocial impacts and Mendelian eye conditions. Two authors (A.T. and C.S.D.) developed the list of psychosocial impacts, while three authors (A.T., C.S.D., and L.A.H.) developed the list of Mendelian eye conditions. The following search terms were used: oguchi disease OR optic atrophies OR optic atrophy OR wolfram syndrome OR retinal degeneration OR cohen syndrome OR knobloch syndrome OR norrie disease OR retinal degeneration OR spinocerebellar ataxia type 7 OR retinitis pigmentosa OR alstrom syndrome OR bardet biedl syndrome OR mckusick-kaufman syndrome OR meckel syndrome OR mitochondrial encephalopathy OR joubert syndrome OR usher syndrome OR zellweger syndrome OR retinoblastoma OR rod-cone dystrophies OR newfoundland OR vitelliform OR best disease OR waardenburg syndrome OR walker-warburg syndrome OR weill-marchesani syndrome OR macular dystrophy OR stargardt disease OR fundus flavimaculatus OR macular dystrophy OR macular dystrophy OR macular dystrophy, occult OR macular dystrophy OR macular dystrophy OR malattia leventinese OR x linked retinoschisis OR gelatinous corneal dystrophy OR fuchs endothelial dystrophy OR epithelial basement membrane corneal OR granular corneal dystrophy OR lattice corneal dystrophy OR schnyder crystalline corneal dystrophy OR enhanced s cone syndrome OR familial exudative vitreoretinopathy OR gyrate atrophy OR leber congenital amaurosis OR senior-loken syndrome OR reis-bucklers corneal dystrophy OR meesmann OR posterior polymorphous corneal dystrophy OR posterior polymorphous corneal dystrophy OR cone dystrophy OR achromatopsia OR blue cone monochromat OR cone rod dystrophies OR jalili syndrome OR neuronal ceroid lipofuscinosis OR congenital stationary night blindness OR corneal dystrophies, hereditary OR corneal dystrophy, juvenile epithelial of OR congenital hereditary endothelial dystrophy OR congenital stromal corneal dystrophy OR "Aicardi Syndrome" OR "Albinism" OR "Chediak-Higashi Syndrome" OR "Aniridia" OR "Aniridia cerebellar ataxia mental deficiency" OR "Axenfeld-Rieger syndrome" OR "Bietti Crystalline Dystrophy" OR "Choroideremia" OR "Coloboma" OR "CHARGE Syndrome" OR "Kahrizi Syndrome" OR "Mandibulofacial Dysostosis" OR "Aicardi Syndrome" OR "Albinism" OR "Chediak-Higashi Syndrome" OR "Aniridia" OR "Axenfeld-Rieger syndrome" OR "Bietti Crystalline Dystrophy" OR "Choroideremia" OR "Coloboma" OR "CHARGE Syndrome" OR "Kahrizi Syndrome" OR "Mandibulofacial Dysostosis" OR cone dystrophy OR achromatopsia OR blue cone monochromat OR cone rod dystrophies OR jalili syndrome OR neuronal ceroid lipofuscinosis OR congenital stationary night blindness OR corneal dystrophies, hereditary OR corneal dystrophy, juvenile epithelial of OR congenital hereditary endothelial dystrophy OR congenital stromal corneal dystrophy AND psychosocial OR psychological OR "quality of life" OR qol OR "Health related quality of life" OR coping OR adaptation OR adjustment OR well-being OR "family functioning" OR depression OR "depressive symptoms" OR distress OR stigma OR anxiety OR emotional OR stress OR social OR "mental health" OR relationships OR "real world visual ability" OR expectations OR disability OR "health status" OR "functional status" OR "activities of daily living" OR "self-concept" OR "personal satisfaction" OR "patient satisfaction" OR worry OR cognitive OR behavior OR discrimination OR support OR mood OR friends OR identity OR "self-image" NOT 'therapy' NOT clinical AND trial NOT 'gene' NOT 'phase 2 clinical trial' NOT 'phase 1 clinical trial' NOT 'age related macular degeneration' NOT 'history' NOT 'incidence.'

8. Disclosures

The authors report no commercial or proprietary interest in any product or concept discussed in this article.

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Supplementary data

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Viewpoints

Modern vitreolysis—YAG laser treatment now a real solution for the treatment of symptomatic floaters

*Inder Paul Singh, MD**

President, The Eye Centers of Racine and Kenosha, Racine, Wisconsin, USA

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ABSTRACT

I review the background of laser floater treatment and address the differences between the old technology and the new technology of YAG lasers. I also review some recent publications and discuss the importance of careful patient selection, some of the adverse events, and patient outcomes.

Historically, the only treatment offered for symptomatic vitreous floaters has been pars plana vitrectomy. This procedure works well to eliminate the symptoms associated with floaters, but there are risks involved with the procedure, such as cataract progression and the possibility of a retinal detachment.[5] Although recent advances in technology have significantly improved the safety profile of vitrectomy, there still is a postoperative recovery period, which may result in time away from work. For some patients, the potential cost of pars plana vitrectomy also remains an issue. Therefore, most doctors decide to observe many of the common types of floaters, such as a Weiss ring or other solitary vitreous opacities. Unfortunately, these floaters can sometimes negatively affect patients' daily functioning and quality of life.

A study by Wagle and coworkers addressed the impairment on functional quality associated with floaters in 311 outpatients.[9] The utility values of floaters were equal to those of age-related macular degeneration and similar to those of glaucoma, mild angina, stroke, and asymptomatic HIV. This demonstrates that floaters do have a similar impact on quality of life as other ocular and systemic diseases.

* Corresponding author: Dr Inder Paul Singh, MD, President, The Eye Centers of Racine and Kenosha, 3805B Spring Street, Suite 140, Racine, WI 53405, USA.
E-mail address: ipsingh@amazingeye.com.
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Furthermore, a study by Webb and coworkers demonstrated that floaters are common in the general population, irrespective of age, race, gender, and eye color.[10] In a review of 603 smartphone users, 76% (n = 458) indicated that they notice floaters, with 199 of these individuals citing noticeable vision impairment as a result of their floaters. Furthermore, myopes and hyperopes were 3.5 and 4.4 times, respectively, more likely to report moderate severe floaters. A 2016 study by Garcia and coworkers[2] showed that there was a 52.5% reduction in contrast sensitivity function after posterior vitreous detachment.

Recent advances in laser technology has improved the adverse event profile associated with laser-based floater treatment. The procedure also offers the potential benefit of a simplified postoperative course. Smaller floaters, such as Weiss rings and other types of floaters (amorphous clouds and strings), that are often considered to be not clinically significant to warrant surgery may now be treated. It is important to note that laser floater treatment (LFT) is not intended to replace or compete with vitrectomy. The ideal patient for LFT is quite different from a vitrectomy patient. Laser vitreolysis may be a reasonable option in select group of pseudophakic and phakic patients.

LFT for symptomatic floaters, also known as vitreolysis, was first introduced in 1993 by Tsai and coworkers.[8] Older data sets suggested only modest efficacy and possible safety concerns that led many doctors to be skeptical about the procedure. It is important to note these older studies were using laser technology not optimized for LFT. Furthermore, the treatment protocol was not optimized. The reason for the variable outcomes in some of the earlier studies was the limitations of traditional YAG lasers. There were three main limiting factors when performing LFT with traditional YAG lasers: 1) lack of visualization of the entire vitreous and mandatory spatial awareness between lens and retina; 2) suboptimal power usage during the procedure thus limiting vaporization of the floater; 3) inability to apply sufficient number of laser because of older cooling cavities and thus the instability/inconsistency of energy delivery through the entire procedure.

So, how has technology changed to now allow us to perform LFT with better safety and efficacy?

1. Visualization

Optimal visualization is key to performing LFT. Appreciating spatial context is crucial for safety and efficacy. The illumination systems on traditional YAG lasers were not optimized to visualize and treat floaters in the middle or posterior vitreous, as they have primarily devised for capsulotomies and laser peripheral iridotomy, procedures requiring visualization of the anterior chamber only. These YAG lasers use noncoaxial illumination towers, in which the illumination is coming from one pathway of the optical system and the laser and oculars are coming from a different optical pathway, converging at the posterior capsule. Therefore, one could not see beyond a few millimters behind the posterior capsule. This limited the ability of the surgeon to view or identify floaters in the middle and posterior vitreous. In addition, surgeons need to be able to determine where they are within the vitreous in relation to other ocular structures, such as retina and lens. This limitation of visualization is a reason why some of the earlier studies demonstrated variable efficacy and safety (Fig. 1).

Owing to the limitations of previous YAG lasers, a new YAG laser illumination system in the form of True Coaxial Illumination™ (TCI™; Ellex Medical, Adelaide, Australia) has been developed. Using new midvitreous contact lenses, this illumination system provides surgeons with full visualization of the entire vitreous cavity from the lens to the retina. This is achieved by using a retractable, reflecting mirror designed to move out of the laser pathway during the treatment. The laser, the oculars, and the illumination tower use the same

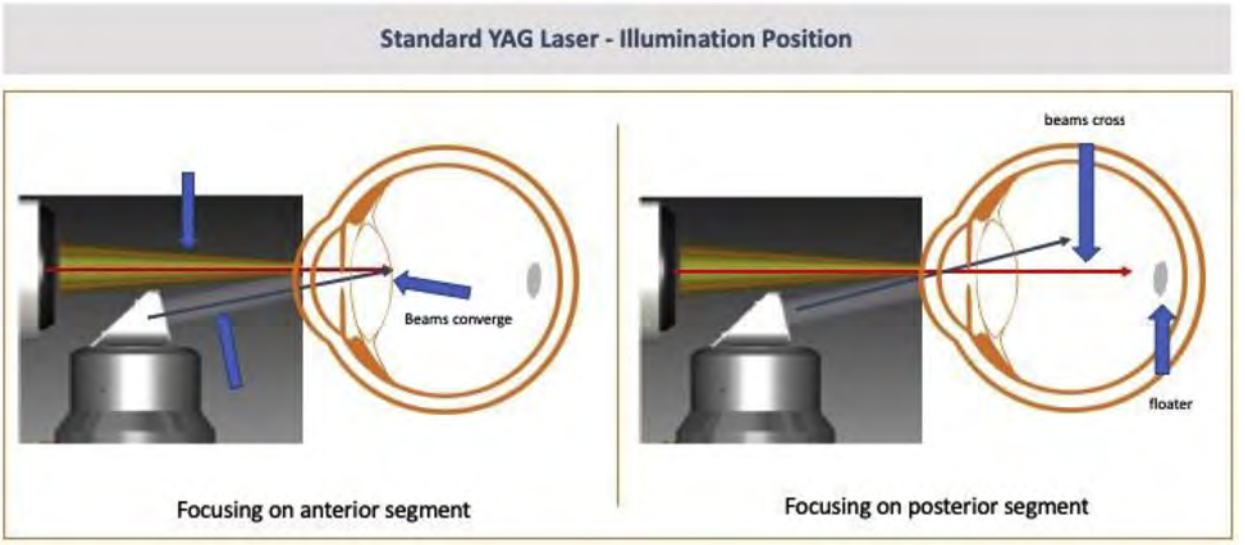

Fig. 1 – *Left*: Standard YAG laser tower; the laser beam and the illumination beam converge when focused on the posterior capsule. *Right:* The laser beam and illumination beam cross when attempting to focus on a floater in the posterior vitreous, thus not allowing a view of the floater and the relationship between the floater and the retina.

optical pathway, allowing for simultaneous visualization of both the retina and the floater. This is important to minimize the risk of inadvertent damage to the retina (Fig. 2).

The True Coaxial illumination design also enables titration of the red reflex by moving the slit lamp obliquely or off axis because the laser can be applied at any position of the slit lamp. For example, a floater in the middle of the vitreous that is seen using coaxial positioning with a full red reflex can occasionally have a lot of glare (Fig. 3). To maximize the contrast in the vitreous to best visualize this type of floater, while maintaining adequate coaxial illumination to also locate the retina, the surgeon can titrate the degree of illumination by moving the slit lamp slightly oblique, around 10° to 15°. This allows for optimal visualization and identification of the location of the floater. This technique is not possible with standard YAG lasers (Fig. 4).

An important clinical pearl: If the floater is in focus and retina is out of focus, you have enough spatial distance from the retina to apply the laser (Fig. 5).

It is critically important for the surgeon to understand how far behind the lens one can treat, which is of great importance when treating phakic patients. The on-axis slit lamp position can be used to visualize the floater against the red-glow background (to help visualize floaters in the middle and posterior vitreous), then advance further off-axis to determine how far behind the lens it is. If the floater is difficult to see in the off-axis position, then it is safe to treat because the off-axis position only allows for visualization a few millimeters behind the lens. Using off-axis slit lamp position allows the surgeon to identify the posterior capsule with better clarity than when the slit lamp is the center on-axis position (Figs. 6 and 7).

1.1. *Energy delivery*

Previous studies that reported marginal results with YAG laser vitreolysis often set the energy level to 1–2 millijoules, which is much less than the 4–8 millijoules typically required to vaporize floaters. I conducted a study using a B-scan probe to view the behavior of the vitreous during LFT. At an energy setting of 7 mJ, I did not see movement of the vitreous 1 mm or greater from the plasma creation. There was also no movement seen of the posterior hyaloid face. (This study was accepted and presented at American Society of Cataract and Refractive Surgery 2019 in San Diego.[C])

Fig. 3 – Full coaxial illumination with slit lamp in the center position. Red reflex demonstrating retina is not in focus, but floater is slightly obscured by the glare of the red reflex.

Recent refinements in YAG laser technology have resulted in less energy required to achieve the optical breakdown necessary to vaporize the floater(s) (Fig. 8). There is a non linear rise in dispersion of energy in the vitreous (convergence zone) with energy setting on the laser (see Fig. 9). At 1 mJ, the movement of fluid was 110 microns, and only increased to 220 microns at 10 mJ.

Plasma is the fourth state of matter; solid is being transformed into gas which is then absorbed by the tissues. Therefore, during LFT, there is both vaporization and fractionation. Owing to the short duration of the pulse (4 ns), heat is

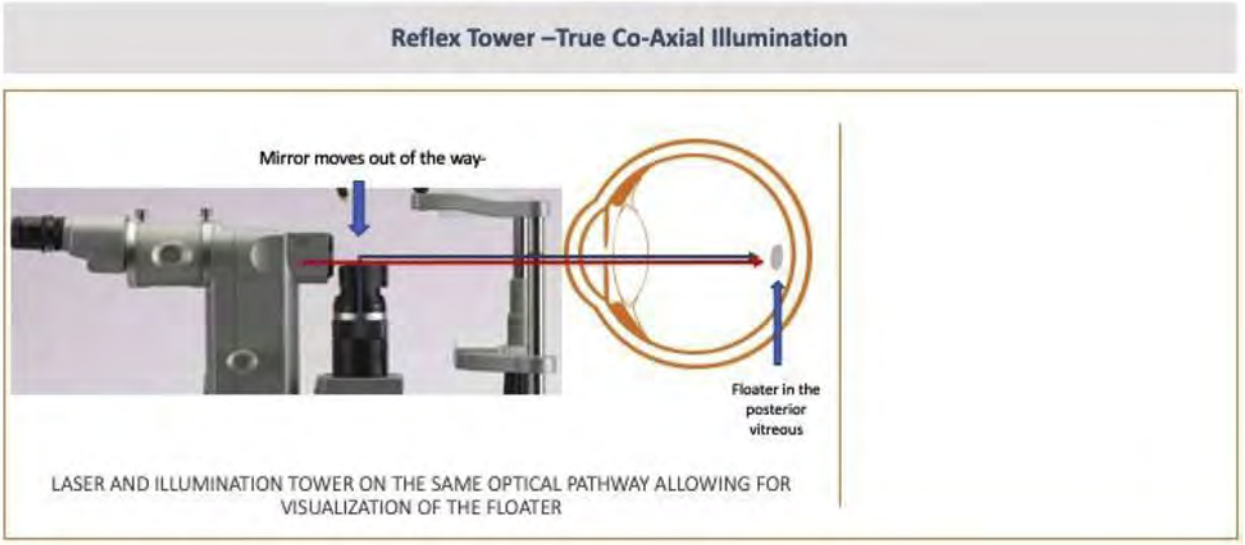

Fig. 2 – Reflex laser lower—the mirror moves out of the way of the laser beam allowing for coaxial illumination—laser, aiming beam, and illumination tower on the same optical pathway, thus allowing for visualization of the floater in the posterior vitreous.

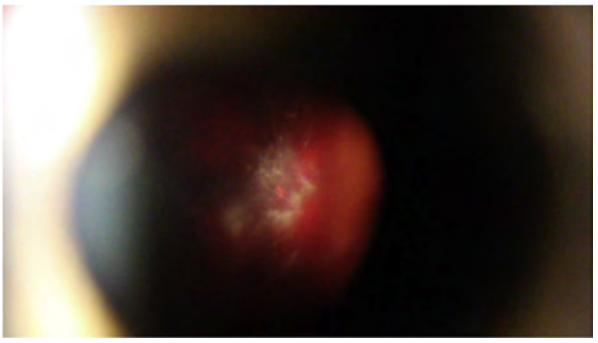

Fig. 4 – Slit lamp moved 10° oblique (off axis). This titrates some of the anterior illumination but keeps adequate posterior illumination to assess the retina. This maximizes contrast with the floater and still provides spatial context.

Fig. 6 – A rope like floater is seen behind the lens. Owing to full red glow of the coaxial beam (slit lamp in the center position), it is hard to tell where the posterior capsule is located. Not recommended to fire until the surgeon identifies the posterior capsule.

dissipated before the next shot is fired. Therefore, treatment is doing more than merely breaking up floaters; the laser actually removes some of the solid matter, and heat does not build up because of the short duration. These new advanced YAG lasers also feature a specially designed active cooling cavity.

1.2. *Recent publications*

Shah and Heier were the first to conduct a randomized placebo-controlled trial evaluating the safety and efficacy of LFT using advanced YAG technology specifically designed for laser-based floater treatment.[6] This study involved 52 eyes treated with the Reflex Technology™ platform (Ellex Medical, Adelaide, Australia). The study concluded that 54% of patients in the YAG laser group experienced symptomatic improvements compared with 9% of patients in the control group. The YAG laser group also showed greater improvement in the 10-point visual disturbance score than the control group.

This study also demonstrated no retinal adverse events in the treatment group, although a retinal defect was seen in the control group. This is an important point because the cause of retinal defects is often the result of vitreous traction. According to the American Academy of Ophthalmology, the definition of YAG vitreolysis is the "severing of vitreous strands and opacities with a laser." One cannot assume the traction on the retina is the same or more than a vitrector. This study was not designed for a follow-up treatment session. Multiple sessions are common with LFT as it is not always possible to vaporize the entire floater in one session.

In 2016, we presented an article at American Society of Cataract and Refractive Surgery that investigated patient satisfaction, complication rates and treatment specifics associated with LFT in a prospective review of patients undergoing the procedure.[D] This observational study included 130 patients (mean age, 61 years [range, 28–92 years]) who underwent LFT with the Ultra Q Reflex system (Ellex Medical, Adelaide, Australia). Patient satisfaction was assessed with a 1–10 self-rated scale, with higher values indicating greater patient satisfaction as well as a "Yes" or "No" indicating whether they were satisfied with improvement in daily functioning. Information on complications was recorded for all patients. We found 91% of patients stated that they were

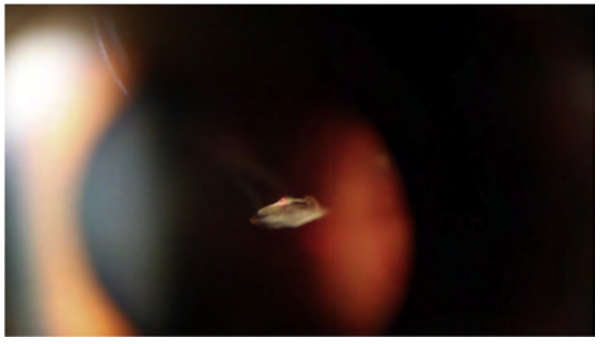

Fig. 5 – Photo demonstrates a Weiss ring using the reflex tower with true coaxial illumination. Slight titration maximizes the view of the opacity and provides spatial context as to where the retina is located. In this picture, the floater is in focus but retina is not seen, indicating safe distance to initiate laser treatment fire.

Fig. 7 – Photo demonstrates the view when the laser slit lamp is in a slightly oblique (off-axis) position thus decreasing the glare, also allowing for visualization of the posterior capsule and the floater. In this case, the floater is too close to the posterior capsule to treat.

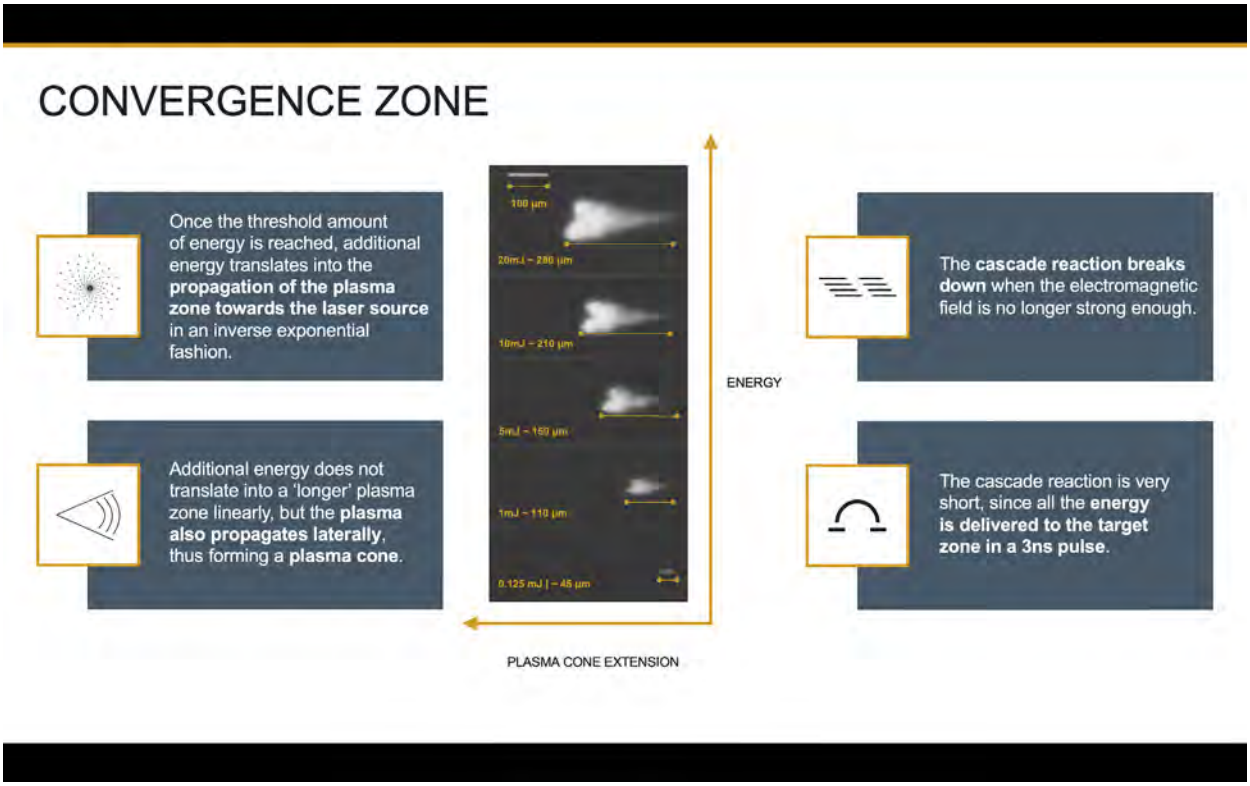

Fig. 8 – *Arrows point* to the narrow Gaussian curve of the energy delivery using the new reflex cavity. There is a sharper rise and fall of the energy with limited waste.

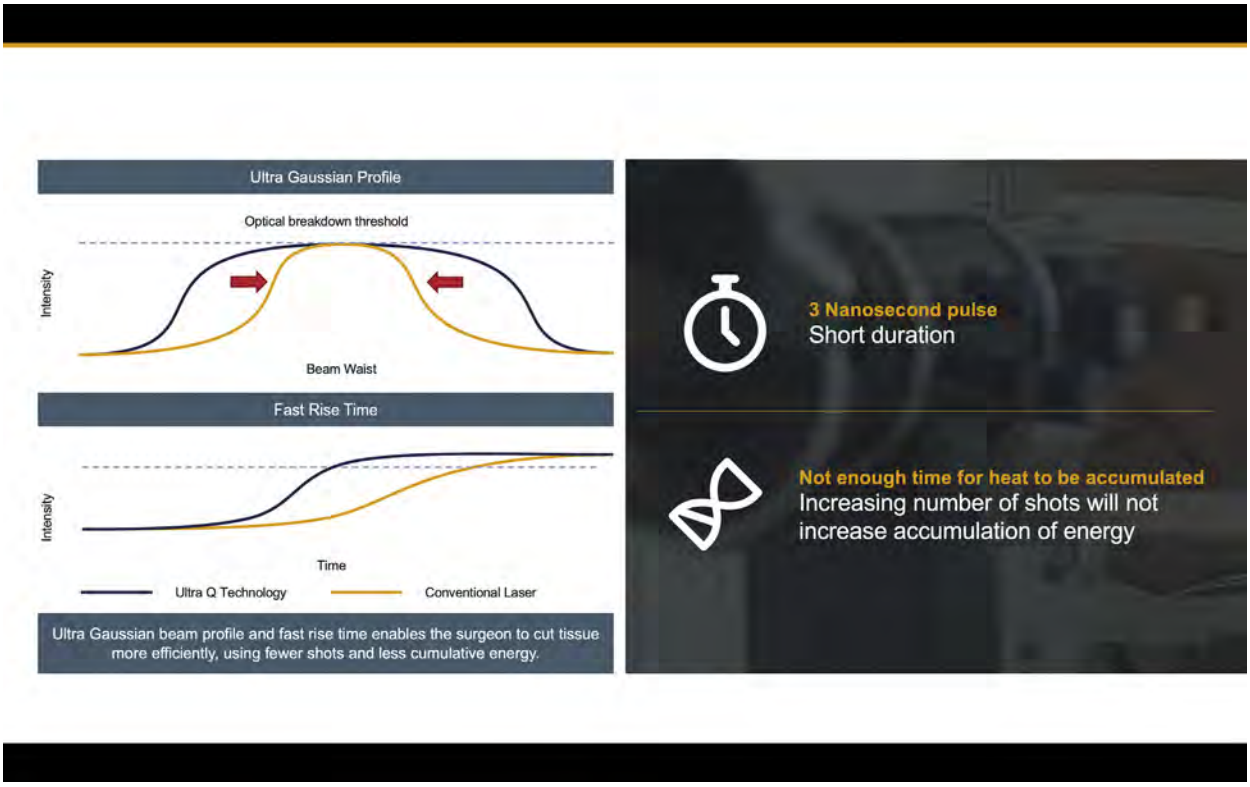

Fig. 9 – The size of the convergence zone increases in a nonlinear fashion as the power on the laser is increased. At 1 mJ, the size of the convergence zone is 110 microns, and increasing power to 10 mJ increases the size to 210 microns (less than 50% increase).

satisfied with their improvement in daily visual functioning. The noted average degree of improvement was 8.5 out of 10 (after multiple sessions in some patients). Patients with a Weiss ring required 1.3 sessions as compared to 3.2 sessions in patients with amorphous clouds. The number of laser shots to sufficiently vaporize floaters amorphous clouds was 568 shots (vs. 186 for Weiss rings). Power settings also varied depending on floater type, with the average setting at 5.8 mJ (range, 2.9–9 mJ). Best results and higher patient satisfaction scores were notably seen with solitary Weiss rings versus amorphous clouds. The adverse event profile included 2 lenticular damage, 3 intraocular pressure (IOP) spikes, and one retinal hemorrhage. The 2 cases of lenticular damage (both in the first 50 cases) were before we appreciated the importance of using the laser slit lamp in the oblique position to view the posterior capsule and properly gauge the distance of the floater from the lens. The retinal hemorrhage occurred when the retina was in focus at the same time as the floater. The 3 IOP spikes occurred in the post YAG cap patients where the amorphous clouds were right behind the lens. Now we decrease the number of shots to 300 or less if the floaters are close to the lens in a post YAG laser capsulotomy patient.

At American Society of Cataract and Refractive Surgery 2017, I also presented my analysis of all consecutive patients who underwent YAG laser vitreolysis for the treatment of symptomatic floaters and had at least 1–4 years of follow-up. This retrospective study included 1,272 procedures performed in 680 patients.[B] In all cases, the Ellex Ultra Q Reflex YAG laser was used to vaporize floaters; an average power of 6 mJ per laser shot was used with an average of 564 shots per treatment session. Patients with both amorphous and solitary Weiss ring type of floaters were included. Ten adverse events were recorded, comprising 7 cases of IOP spikes, two cases of native lens damage (Fig. 10), and 1 retinal hemorrhage (this included the adverse events from the 130 cases in the 2016 prospective article), representing a total adverse event rate of 0.8%. Patients with IOP spikes were placed on topical antihypertensive medications (average postmedication IOP, 19 mm Hg). One of the phakic patients subsequently required cataract surgery and achieved a corrected visual acuity of 20/20. The other patient, where the lenticular burn was in the periphery, is still being observed. The case of retinal hemorrhage resolved in 3 months with no long-term negative effects. There was no ocular inflammation, exacerbation of diabetic retinopathy, progression of epiretinal membrane, or cystoid macular edema. Postoperative regimen for all cases included IOP checks immediately after the procedure, at 1 week, and 1 month. No antiinflammatory drops used. Topical IOP-lowering agents were used in cases with IOP spikes. Preoperative, 1-month, and 3-month macular optical coherence tomography was obtained for all patients (Fig. 11).

Qualitative analyses of the effects of LFT have been performed with spectral domain optical coherence tomography and scanning laser ophthalmoscopy by comparing shadows on the retina created by floaters before and after treatment. A recent study published in *OSLI Retina* October, 2018, on novel optical coherence tomography applications, including shadow changes on a 5-line raster scan after vitreolysis, described cases with persistent scotoma.[7] Once initial testing did not reveal a clear etiology, further evaluation using spectral domain-optical coherence tomography demonstrated a large floater overlying the macula. After YAG vitreolysis, patients described resolution of the symptoms, and the spectral domain-optical coherence tomography scans revealed resolution of the shadow that was cast on the retina (Fig. 12).

The utilization of ray-tracing aberrometry beyond anterior segment needs further investigation before one can claim that

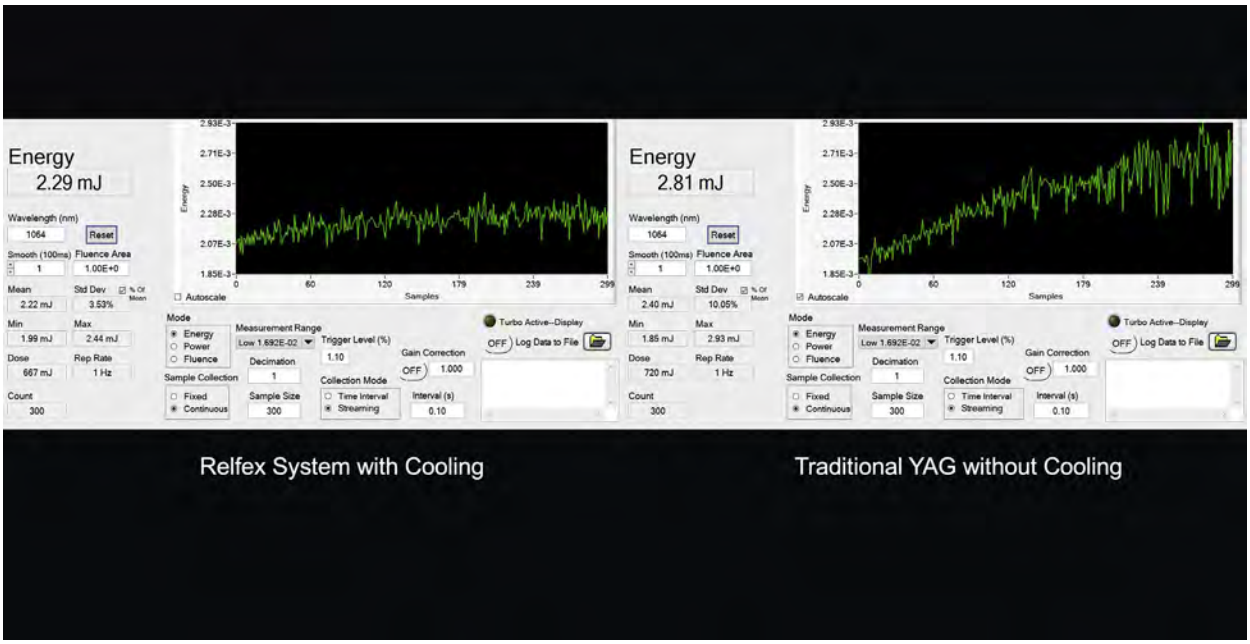

Fig. 10 – *Left*: Graph demonstrates a stable delivery of energy over hundreds of shots when using active cooling cavity. *Right*: Graph demonstrates the same when using a passive cooling cavity, the delivery of energy is not stable over hundreds of shots fired. (Poster presented at American Society of Cataract and Refractive Surgery 2019).

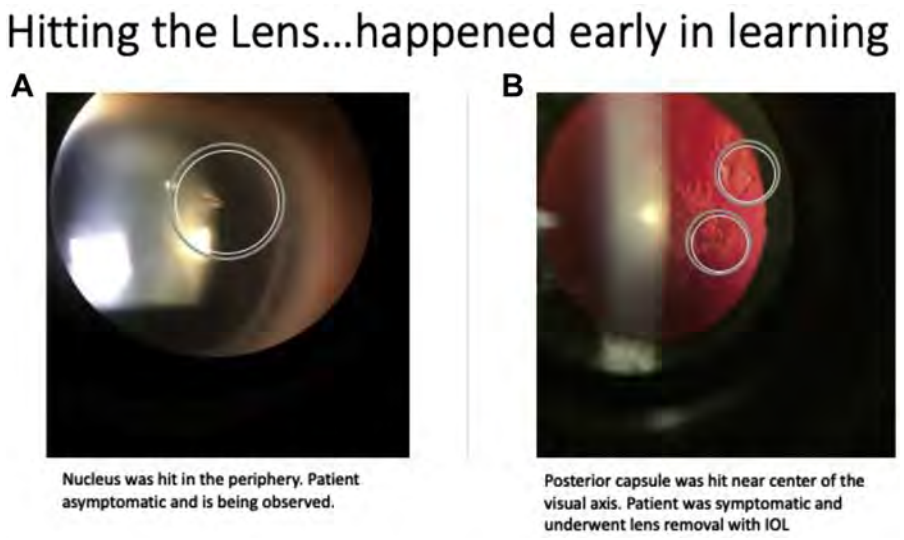

Fig. 11 – Two cases of phakic lens damage with the laser. *A*: Patient is asymptomatic and being observed. *B*: The patient was symptomatic and required cataract removal with IOL.

it "offers true analysis and objective benefits." I would still include the discussion (Ray tracing has been well established to analyze the entire optical system). Since 256 beams reach the retina, they have to pass through the entire optical system, including the vitreous. The difference between the iTrace (Tracey Technologies LLC, Houston Texas, USA) and other aberrometers is the ability of the iTrace to separate the corneal contribution versus intraocular contributions to higher order aberrations, such as the lens and vitreous. In fact, there are studies that have shown significant improvement in

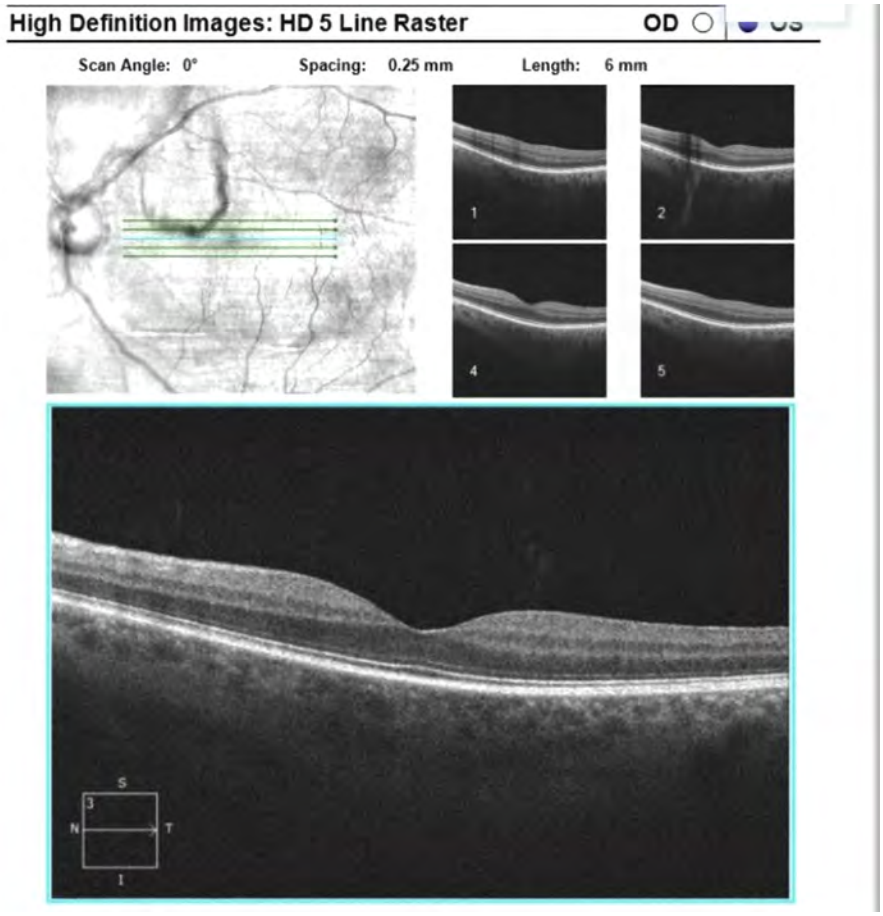

Fig. 12 – Vitreous opacity overlying the macula (*arrow A*). Presumed floater shadow on raster scans (*arrow B*).

higher order aberrations after pars plana vitrectomy, as well as using the same device. Our study demonstrated no change in topography, and patient lens status did not change after vitreolysis; therefore, the improvement in higher order aberrations could only be the vitreous opacity.

Ray-tracing aberrometry offers a potential objective measurement of the effect floaters have on quality of vision. This device fires 256 laser beams parallel to the line of sight, distributed over the entrance pupil, and images where these lasers hit the retina. The laser beams are fired one at a time, in quick succession so that high levels of aberrations or scatter that might be caused by floaters does not cause confusion in the detection system. The pattern where the lasers hit the retina allows an accurate calculation of the point spread function of the eye to be determined, therefore an MTF can be calculated. Furthermore, the device measures the topography of the anterior surface of the cornea. Any aberrations that are not explained by the anterior surface topography must have been created inside the eye.

The iTrace software characterizes the effect of these internal aberrations on quality of vision with a single number called dysfunctional lens index. This dysfunctional lens index score has excellent correlation with visual acuity loss due to cataract formation.[1,11] The internal aberrations have also been used to characterize the aberrations induced by tilted IOLs[3] and the improved quality of vision after Nd:YAG capsulotomy.[4] A comparison of preoperative and postoperative internal aberrations obtained from ray tracing aberrometry should provide a good objective measure of quality of vision improvements after LFT. I presented an article on this topic at American Society of Cataract and Refractive Surgery 2017,[A] demonstrating a significant improvement higher order aberrations, MTF area under the curve, and dysfunctional lens index score after LFT.

1.3. *Patient selection*

Patient selection is extremely important. Like any other procedure, not all patients are good candidates or qualify for the procedure. For LFT, solitary opacities may be the best candidates. If the floater is too close to the lens or retina, or if the patient has new onset of floaters and/or flashes suggestive of recent posterior vitreous detachment, observation remains the best option. Patients also need to be informed of the possible need for multiple sessions and/or possible failure to resolve symptoms completely.

2. Conclusion

The new illumination design, coupled with the modified laser energy delivery system, may represent an alternative option to vitrectomy in management of clinically significant floaters in carefully selected patients; however, randomized, controlled clinical trials with large cohorts and long-term follow-up are necessary to optimally assess the efficacy and safety of laser vitreolysis.

3. Disclosure

I.P.S. is a speaker and consultant for Ellex, Zeiss, and Tracey Technologies.

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Laser vitreolysis for symptomatic floaters is not yet ready for widespread adoption

Daniel Su, MD[a], *Chirag P. Shah, MD, MPH*[b], *Jason Hsu, MD*[a,*]

[a] *The Retina Service of Wills Eye Hospital, Mid Atlantic Retina, Philadelphia, PA, USA*
[b] *Ophthalmic Consultants of Boston, Boston, MA, USA*

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ABSTRACT

Vitreous floaters are common, related to age, myopia, genetic predisposition, and infiltration of the vitreous body. A subset of patients report symptoms impacting their quality of vision. Treatment with laser vitreolysis, the use of an Nd:YAG laser to vaporize the collagenous vitreous opacities appears to be used more frequently; however, data regarding long-term safety and effectiveness are lacking. We present currently available data regarding efficacy and safety, as well as additional considerations. Laser vitreolysis of symptomatic floaters should not be routinely performed without additional studies documenting its safety and long-term efficacy. Ideally, the procedure would be effective in most patients and be approved by the Food and Drug Administration based on the results of a Food and Drug Administration registration trial before widespread adoption.

1. Introduction

Opacities in the vitreous cavity are perceived as floaters, which can cause significant visual symptoms in some patients.[6,10,17] The most common cause of vitreous floaters is age-related posterior vitreous detachment (PVD). A PVD is present in approximately 65% of patients by the age of 65.[2] Clinically often marked by the presence of a Weiss ring floating over the optic nerve, a PVD allows increased movement of the vitreous body with head or eye movements. Floaters can also be a result of myopic vitreopathy, which is caused by vitreous gel liquefaction with collagen aggregation.[6,7] Other causes of floaters include retinal tears, often associated with vitreous hemorrhage, and uveitis.

For most patients, symptoms from floaters improve with time due to gravity and neuroadaptation. Such patients are best managed with observation alone; however, a subset of patients report a significantly lower quality of life and can even be psychologically distressed by vexing visual phenomena and degraded contrast sensitivity from floaters.[4,10,18] Current options for treating symptomatic floaters are YAG laser vitreolysis and vitrectomy.[6,13]

While laser vitreolysis has been described since the 1980s,[9,16] anecdotal reports suggest that the use of this procedure may be increasing.[3] This may be attributed in part to the marketing of laser systems optimized for vitreolysis. We will argue that laser vitreolysis is not yet ready for widespread adoption because of lack of data and concerns with its safety profile. Some additional practical considerations will also be discussed.

1.1. *Limited data*

Currently published studies on the outcome of laser vitreolysis for treating symptomatic floaters are limited. There are several uncontrolled case series assessing the effect of laser vitreolysis on subjective symptoms, which may be confounded by placebo effect.[1,16] Singh presented a poster of a large retrospective series at the 2017 AAO Annual Meeting. This study of nearly 1,300 patients treated with laser vitreolysis reported low rates of adverse events (0.8%).[15] These included intraocular pressure spikes (7 cases), lens damage (2 cases), and retinal hemorrhage (1 case); however, related to the retrospective nature, there was no standardized follow-up, and potentially not all complications were captured during the follow-up period. Furthermore, this study has yet to be published in a peer-reviewed journal. Hahn and coworkers, on behalf of the American Society of Retina Specialists research and safety in therapeutics committee, compiled complications after laser vitreolysis that were voluntarily reported by

* Corresponding author: Jason Hsu, MD, Retina Service, Wills Eye Hospital, Suite 1020, 840 Walnut Street, Philadelphia, PA 19107, USA.
E-mail address: jhsu@midatlanticretina.com (J. Hsu).
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practitioners throughout the United States from September, 2016, to March, 2017.[3] A total of 16 complications were reported during this 6-month period, which included elevated intraocular pressure leading to glaucoma, cataracts, and posterior capsule defects requiring surgery, retinal tear, retinal detachment, retinal hemorrhages, scotomas, as well as an increased number of floaters. This collection of complications is fairly broad, but likely not comprehensive, and may have been subject to underreporting. In addition, because it is unknown how many laser vitreolysis procedures were performed, the analysis cannot estimate complications rates or their relative frequencies. It is worth noting that retinal tears and detachments were reported to the American Society of Retina Specialists research and safety in therapeutics committee, but were not part of the large retrospective study by Singh. Prospective controlled longitudinal studies would be best suited to determine such complication rates.

To date, there is only one published randomized clinical trial on laser vitreolysis by Shah and Heier.[14] Fifty-two patients with symptomatic Weiss rings were randomized to either treatment with YAG laser vitreolysis or sham laser. Patients were assessed with questionnaires assessing subjective response and by masked grading of floater appearance based on wide-angle fundus photography. Subjects reported a 54% improvement in floater symptoms after laser vitreolysis, compared to 9% among controls at 6 months' follow-up. This does speak to an element of placebo effect in the control arm or to the effect of time and gravity. About half of the patients (53%) reported significant or complete resolution of their symptoms after treatment, compared with none in the control arm. A large majority of those in the laser group (94%) had significantly improved or completely resolved floaters based on photographs graded by a masked observer, compared with none in the sham group. This pivotal study demonstrated efficacy of laser vitreolysis in about half of treated patients, and there were no differences in adverse events between the two groups. It is important, however, to note that this study had stringent inclusion criteria to minimize complications. Symptomatic Weiss ring floaters were required to diagnose a PVD, which was corroborated by 3 separate modalities: clinical examination, optical coherence tomography, and ultrasound B-scan. In addition, the Weiss ring needed to be located at least 3 mm anterior to the retina and 5 mm posterior to the lens capsule as measured on B-scan in an effort to maximize safety. The results of this study do not necessarily translate to other floater types, as the researchers only included eyes with Weiss ring floaters in patients with longstanding PVDs.

At the 2018 Retina Subspeciality Day, Shah presented long-term follow-up data on 35 patients enrolled initially in the YAG vitreolysis randomized clinical trial.[12] Patients originally in the control arm were offered treatment at 6 months, so all 35 patients received treatment. At 2.3 years after the last YAG vitreolysis, 3 of 35 patients had retinal tears (One had a cuff of subretinal fluid that was pigmented.). These findings were not present at the 6-month examination, indicating that they occurred sometime between 6 months and 2.3 years after YAG vitreolysis. Because there was no control arm observed to this duration, it remains unclear whether these 3 late tears were related to YAG vitreolysis, or whether they were due to the natural history of PVDs in eyes with prominent Weiss rings. This uncertainty further supports the need for a large multicentered controlled trial with long-term follow-up.

The alternate treatment option for visually significant floaters is a vitrectomy, which is the more definitive treatment for vitreous opacities by removal of the vitreous gel through surgical intervention. In a retrospective study of 168 eyes of 143 consecutive patients who underwent vitrectomy for persistent symptomatic floaters, Mason and coworkers reported a high satisfaction rate of 95%.[5] Furthermore, the advent of small-gauge vitrectomy with 25- and 27-gauge incisions has reduced the threshold for offering vitrectomy to patients with debilitating floaters. Sebag and coworkers reported good safety profile after limited vitrectomy with 25-gauge instrumentation.[11] In this retrospective study of 195 eyes with a mean follow-up of 32 months, macular pucker and vitreous hemorrhage developed in 1% of eyes, and retinal tear and retinal detachment occurred in 1.5% of eyes. Despite the high success rate, complications secondary to vitrectomy such as retinal detachment can be devastating, resulting in loss of vision in an otherwise healthy eye.[8] In addition, phakic eyes will almost invariably develop a cataract, requiring a second surgical intervention. Nevertheless, vitrectomy remains the most definitive option for patients willing to undertake the small but potentially blinding risk of surgery. The role of laser vitreolysis and its complication rates as compared with vitrectomy will need to be assessed in future prospective studies.

2. Currently no Food and Drug Administration approval or CPT code

Laser vitreolysis is currently not an approved procedure by the US Food and Drug Administration because of a lack of an Food and Drug Administration registration trial. Such trials are important to answer many important questions regarding this procedure. How do different floater types respond to treatment? What is the optimal number of treatment sessions? What are the effects of vaporizing vitreous floaters with laser energy on the subsequent behavior of the vitreous and its liquefaction? Could there be long-term consequences and what are the risks and adverse events? These questions may first need to be addressed by a registration trial—or at least a large multicenter trial—before many physicians feel confident about performing this procedure on patients.

An additional concern with laser vitreolysis currently is the lack of a dedicated CPT billing code. Some physicians are using the code 67031, which is technically intended for "severing of vitreous strands, vitreous face adhesions, sheets, membranes, or opacities"; however, this is not the same as laser vitreolysis, which uses laser energy to vaporize vitreous opacities. Whether this is an acceptable use of this specific CPT code and whether an increase in its use will result in increased scrutiny for both the code and the physician is unclear. In Australia, the National Health Service scrutinized this code and revoked its use for YAG vitreolysis.

Alternatively, physicians may pursue a cash model similar to the reimbursement for refractive surgery; however, as only half of patients may notice subjective improvement after one treatment session as seen in the prospective trial by Shah and Heier,[14] far less than the level seen in refractive surgery, it is

unclear how this model deals with the unimproved or even unhappy patient and may portend unwanted liability from a clinician's perspective.

2.1. *Practical considerations*

Patients who are debilitated from symptomatic vitreous floaters may be more observant and have high expectations and demands in regard to their quality of vision. Because of this, there may be a selection bias toward patients who would be more critical of less than expected outcomes (particularly if they are paying cash for the procedure). This can be unsatisfying for the physician, especially when the vitreous opacities are improved objectively by the treatment. The study by Shah and Heier reinforces the apparent disconnect between the objective (94%) and the subjective response (53%).[14] Another consideration is the amount of chair time that is required to adequately counsel patients regarding the possibility of limited improvement with laser vitreolysis, as well as potential posttreatment dissatisfaction may not fit into the existing practice model of the treating physician.

3. Conclusion

Patients who are severely symptomatic from floaters are often some of the unhappiest patients we encounter. In this setting, it may be tempting to offer laser vitreolysis as a treatment that promises to improve this condition with minimal side effects; however, given the currently available data, YAG vitreolysis may not be beneficial, and we may in fact be doing our patients a disservice if we proceed without demanding more evidence for its long-term safety and efficacy. As with any new procedure, a healthy dose of skepticism is warranted. The commitment to first do no harm should be the guiding principle until further studies clearly demonstrate a favorable risk/benefit ratio.

4. Disclosures

D.S. and J.H. have no financial interest in the content of this article. C.P.S. has received speakers' fees and research funding from Ellex Lasers.

5. Literature Search

Literature search was performed using PubMed Medline using the following terms: laser vitreolysis, YAG vitreolysis, vitreous floaters, and vitreous opacities. References not included in the electronic database were identified from the selected articles. Included abstracts were obtained from the American Academy of Ophthalmology website (www.aao.org).

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Clinical challenges

Beware of the sneeze

Patrick Yang, MD[a], *Christopher B. Toomey, MD, PhD*[a], *Jonathan Lin, MD, PhD*[c], *Don O. Kikkawa, MD*[a,b], *Bobby S. Korn, MD, PhD*[a,b,*], *Andrew Harrison, MD*[d]

[a] *Division of Oculofacial Plastic and Reconstructive Surgery, Viterbi Family, Department of Ophthalmology, University of California, San Diego, California, USA*
[b] *Division of Plastic Surgery, Department of Surgery, University of California, San Diego, California, USA*
[c] *Division of Pathology, University of California, San Diego, California, USA*
[d] *University of Minnesota Departments of Ophthalmology and Visual Neurosciences and Otolaryngology, University of California, San Diego, California, USA*

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(In keeping with the format of a clinical pathologic conference, the key words and abstract appear at the end of the article.)

1. Case report

A 61-year-old Caucasian woman presented to a community emergency room with left periocular fullness and pain behind the left eye characterized as the "worst headache of my life." Her past medical history was remarkable for hypertension and a 40+ pack year history of smoking. She denies any history of trauma or surgery.

Ophthalmic examination by the emergency room physician revealed normal visual acuity in each eye, no pupillary abnormalities, and intraocular pressures of 15 mm OD and 22 mm OS. Left upper and lower eyelid ecchymoses were noted.

What is the differential diagnosis in this patient with acute pain, periocular ecchymosis, and elevated intraocular pressure? What is the next step in management?

2. Comments

2.1. *Comments by Andrew Harrison, MD*

The differential of an acute orbital process includes infectious, inflammatory, and vascular etiologies, as well as neoplasm. Periocular ecchymosis may occur as a result of a vascular event or process such as a spontaneous orbital hemorrhage or a neoplastic process. In the acute setting, the next step in management is orbital imaging. Computed tomography of the orbits would be the quickest and easiest study to obtain in this setting.

3. Case report (continued)

Computed tomography of the orbits revealed a mass lesion in the left ethmoid sinus with extension into the medial orbit (Fig. 1A). Axial cuts through the optic nerve showed no globe

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* Corresponding author: Bobby S. Korn, MD, PhD, UC San Diego Shiley Eye Institute, 9415 Campus Point Drive, La Jolla, CA 92039.
E-mail address: bkorn@ucsd.edu (B.S. Korn).

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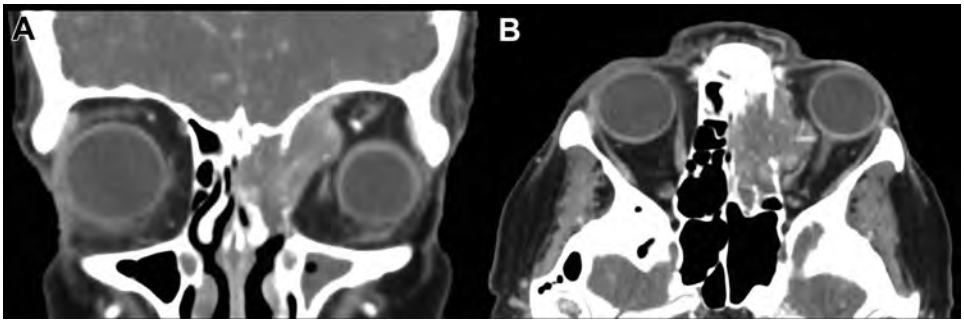

Fig. 1 – CT scans on initial presentation showing left ethmoidal mass with extension into the orbit but no significant globe tenting. *A:* Coronal. *B:* Axial.

tenting (Fig. 1B). Bedside examination showed no epistaxis or visible intranasal extension. Imaging of the brain (not shown) disclosed no pathology. The patient was discharged home and advised to follow up with otolaryngology for workup of the ethmoid sinus mass.

Does this change your differential diagnosis after review of the imaging?

4. Comments (continued)

4.1. *Comments by Dr. Harrison continued*

The patient clearly has a neoplastic process involving the ethmoid sinus with extension into the orbit. The most common sinus tumor that invades the orbit is squamous cell carcinoma, although it typically arises from the maxillary sinus. Other invasive sinus tumors include sinonasal undifferentiated carcinoma, small-cell neuroendocrine tumors, osteosarcomas, and rhabdomyosarcoma.

5. Case report (continued)

Two days later, the patient returned to the same emergency room eight hours after the onset of acute orbital pain, epistaxis, worsening proptosis, and decreased vision in the left eye after sneezing. She said her vision dimmed over the ensuing hour. She also had persistent headaches, nausea, and bouts of emesis. On examination, she had no light perception vision in her left eye and an intraocular pressure of 36 mmHg; her right eye was unremarkable. She also had a left afferent pupillary defect and diffusely limited extraocular movements in the left eye.

What are some causes for acute vision loss in this setting? What is the next immediate step in the management of this patient?

6. Comments (continued)

6.1. *Comments by Dr. Harrison continued*

The patient has a rapidly progressive orbital process now with acute vision loss. The most likely etiology is an orbital compartment syndrome with secondary optic nerve ischemia due to the prolonged stretching of the optic nerve. Other etiologies of vision loss in this setting include central retinal artery occlusion and secondary invasion of the nerve by the tumor. The next step in management of this patient is emergent lateral canthotomy with inferior and superior cantholysis.

7. Case report (continued)

An orbital compartment syndrome was diagnosed by the emergency physician, and an emergent lateral canthotomy with cantholysis was performed that decreased the intraocular pressure to 26 mmHg; however, the vision remained no light perception. The patient was transferred to our institution.

On presentation, the patient noted continued, severe orbital pain. Examination of the left eye revealed no light perception vision and an intraocular pressure of 21 mmHg. There was diffuse periorbital edema, ecchymosis, and chemosis (Fig. 2). Dilated fundus examination revealed no disc edema or pallor. There was low lying exudative fluid in the posterior pole with a preretinal hemorrhage in the nasal macula and loss of detail of the choroidal vasculature. An urgent computed tomography scan was performed that revealed a new left superior orbital mass suspicious for hemorrhage (Fig. 3A, red arrow). Furthermore, there was further infiltration of the mass into the orbit causing tenting of the globe with a critical angle less than 120° (Fig. 3B, yellow arrow).

What is the significance of a critical angle less than 120°? How would you manage the patient at this time?

Fig. 2 – External photo of the left eye after lateral canthotomy and cantholysis. There is diffuse periocular ecchymosis and chemosis.

8. Comments (continued)

8.1. *Comments by Dr. Harrison continued*

The posterior globe angle is measured by drawing tangents to the medial and lateral sclera at the optic nerve insertion. The normal globe has an angle of 150°. With progressive proptosis, the optic nerve becomes stretched, the tethered globe begins to tent posteriorly, and the critical angle becomes smaller. Tenting is considered significant when the angle is less than 130°, and a posterior globe angle less than 120° is a surgical emergency. A delay in surgical decompression in these patients may result in permanent loss of vision. Given that this patient has a critical angle less than 120°, this patient should undergo emergent decompression of the orbit with tumor debulking and biopsy of the mass.

9. Case report (continued)

An emergent orbitotomy was performed to decompress the orbit by debulking the mass and to obtain a tissue diagnosis with an incisional biopsy. The orbitotomy was performed through a retrocaruncular incision. Upon dissection in the subperiosteal plane along the medial orbit, a white, gelatinous mass was encountered in the medial orbit, and further exploration along the orbital roof revealed an organized hemorrhage corresponding to the new superior orbital mass (Fig. 3A, red arrow). Further tumor debulking was performed to decompress the orbit, and meticulous hemostasis was achieved. After orbitotomy, the patient had immediate relief of her orbital pain and stabilization of the intraocular pressure; however, her vision did not recover.

Pathology (Fig. 4) showed a poorly differentiated carcinoma with multiple mitotic figures as well as positive staining for cytokeratin AE1/AE3, suggestive of an epithelial origin. There was loss of integrase interactor 1 protein expression, which is part of the switch/sucrose nonfermentable adenosine triphosphate–dependent chromatin remodeling complex found on chromosome 22.127.[1,2,5] Tissue was further sent for cytogenetic analysis which showed homozygous loss of 22q11.23 (SMARCB1, BCR) and loss/absence of heterozygosity of chromosome 22, which favored the diagnosis of SMARCB1 (integrase interactor 1)-deficient sinonasal undifferentiated carcinoma.[1,2] The case was presented at a multidisciplinary tumor board meeting. The tumor was deemed inoperable, and the patient was referred to oncology for chemotherapy and radiation.

10. Discussion

We present the first case of SMARCB1 (integrase interactor 1)-deficient sinonasal undifferentiated carcinoma associated with valsalva-induced acute orbital hemorrhage and compartment syndrome, resulting in vision loss.

Although urgent canthotomy with cantholysis was performed at the community hospital emergency department with resultant lowering of intraocular pressure to 21 mmHg,

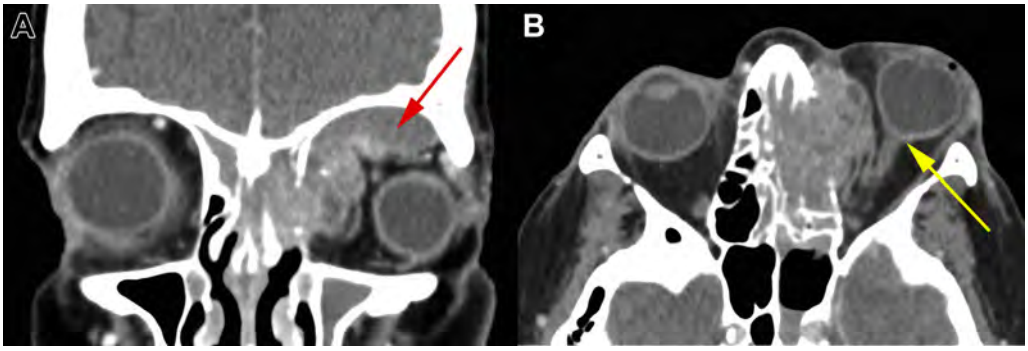

Fig. 3 – CT scans after presentation with vision loss after an episode of sneezing. *A:* Coronal. *B:* Axial. A new mass is noted in the superior subperiosteal plane consistent with hemorrhage (*red arrow*, panel A). Globe tenting subtending an angle less than 120° is noted on the axial slice (*yellow arrow*, panel B).

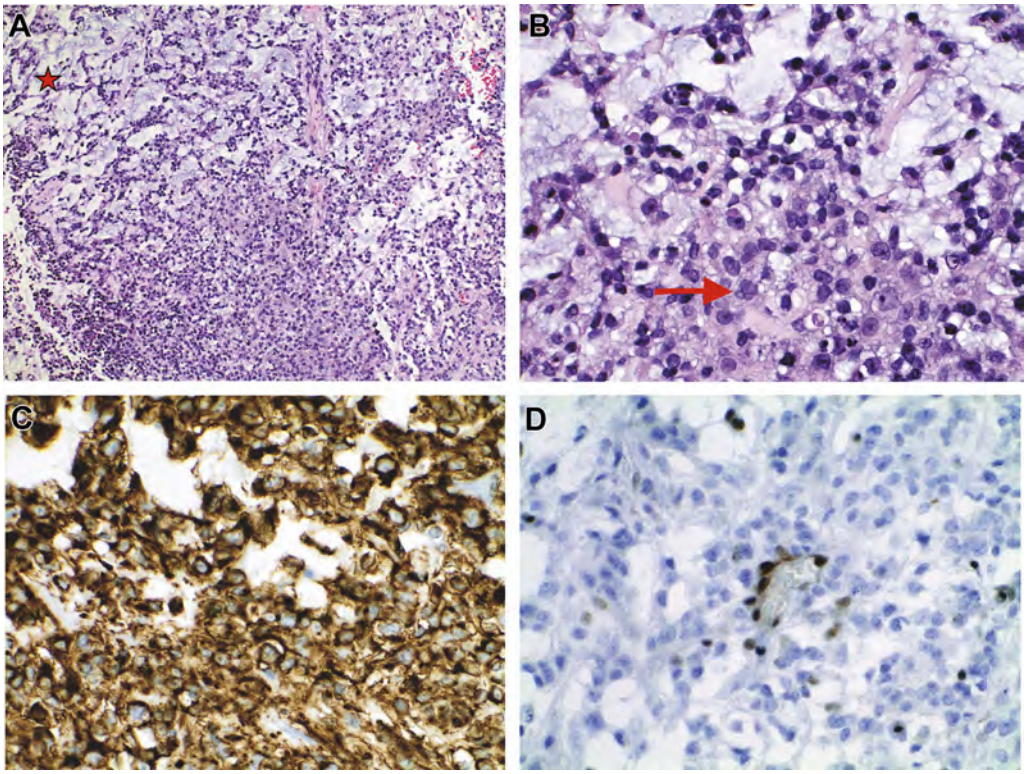

Fig. 4 – Histopathology of biopsy. *A:* Low-power H&E image shows hypercellular lesion with areas of myxoid change (*red star*). *B:* High-power H&E image shows basaloid tumor cells with high nuclear:cytoplasmic ratios and nonspecific vacuoles (*red arrow*). *C:* Pan-cytokeratin immunostain highlights all tumor cells. *D:* SMARCB1 (INI-1) immunostain reveals loss of SMARCB1 (INI-1) protein expression in tumor cells (see loss of brown chromagen).

the patient sustained permanent vision loss. This is likely explained by the prolonged time (8 hours) between onset of symptoms from the spontaneous orbital hemorrhage and presentation to the emergency room. Vision loss in the setting of acute orbital hemorrhage is likely due to prolonged stretching of the nerve by severe proptosis, resulting in ischemia of the optic nerve head, a mechanism previously described in orbital compartment syndrome.[3]

Subconjunctival hemorrhages are frequently observed after coughing, secondary to valsalva maneuvers. A similar pathophysiologic mechanism likely occurred in this patient. Stimulation of angiogenesis is a well-known pathway for enriching vascular supply by tumors.[4] These nascent vessels are often fragile and leaky similar to those seen with choroidal neovascularization in neovascular age-related macular degeneration. With the patient's acute sneezing episode, valsalva-induced hemodynamic changes likely caused increased leakage and rupture of these nascent tumor vessels, leading to rapid accumulation of blood in the orbit, resulting in acute orbital compartment syndrome.

It is unclear if SMARCB1 (integrase interactor 1)-deficient sinonasal undifferentiated carcinoma is a specific risk factor for hemorrhage. It is possible that this rapidly growing sinus carcinoma has prominent neovascularization prone to hemorrhage, but more likely, any potential rapidly growing sinus or orbital mass could present with an acute valsalva-induced hemorrhage, leading to orbital compartment syndrome. The clinician should have a high index of suspicion for the possible development of orbital compartment syndrome with any sinus mass and discuss warning signs with patients.

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ABSTRACT

Switch/sucrose non-fermentable-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (SMARCB1), also known as integrase interactor 1 –deficient sinonasal carcinoma, is a rare entity that was first described in 2014. Since then, there have been 39 cases published in the literature, with basaloid or plasmacytoid/rhabdoid morphology being the most common pathological subtype. We report a patient with switch/sucrose non-fermentable-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (integrase interactor 1)-deficient sinonasal carcinoma who had permanent vision loss after valsalva-induced acute hemorrhage and resultant orbital compartment syndrome.